Actions of Caffeine in the Brain with Special Reference to Factors That Contribute to Its Widespread Use

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This paper is available online at http://www.pharmrev.org

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I. Introduction

Caffeine is the most widely consumed behaviorally active substance in the world. Almost all caffeine comes from dietary sources (beverages and food), most of it from coffee and tea. Acute and, especially, chronic caffeine intake appear to have only minor negative consequences on health. For this reason and because few caffeine users report loss of control over their caffeine intake, governmental regulatory agencies impose no restrictions on the use of caffeine. Ordinary caffeine use has generally not been considered to be a case of drug abuse, and is indeed not so classified in DSM-IV (Diagnostic and Statistical Manual of Mental Disorder).[3] However, some years ago it was pointed out that caffeine may be a potential drug of abuse (see Gilliland and Bullock, 1984), and more recently caffeine has been described as "a model drug of abuse" (Holtzman, 1990) and the possibility that caffeine abuse, dependence, and

[3] Abbreviations: AP-1, activator protein 1; APEC, 2-[(2-aminoethylamino)carbonylethylphenylethylamino]-5′-N-ethylcarboxamidoadenosine; CGS 15943, 9-chloro-2-(2-furanyl)-5,6-dihydro-[1,2,4]-triazolo[1,5]quinazolin-5-imine; CGS 21680, 2-[p-(2-carbonylethyl)phenylethylamino]-5′-N-ethylcarboxamidoadenosine; CHO, Chinese hamster ovary; CNS, central nervous system; CREB, cyclic AMP response element-binding protein; CRE, cyclic AMP response element; DA, dopamine; DPCPX, 1,3-dipropyl-8-cyclopentylxanthine; DSM, Diagnostic and Statistical Manual of Mental Disorders; EEG, electroencephalogram; ICD, International Classification of Diseases; IEG, immediate early gene; MK-801, (+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]-cyclohepten-5,10-imine; NGFI-A/B, nerve growth factor-induced genes A and B (NGFI-A is also called *zif/268* and *egr1*); NMDA, N-methyl-D-aspartate; PCP, phencyclidine; REM, rapid eye movement; SCH 58261, 5-amino-2-(2-furyl)-7-phenylethylpyraxolo[4,3-*e*]-1,2,4-triazolo[1,5-*c*]pyrimidine; SKF 38393, 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine; VTA, ventral tegmental area.

withdrawal should be added to diagnostic manuals has been seriously considered (Hughes et al., 1992b; Strain et al., 1994; Pickworth, 1995; Hughes et al., 1998)

In the present review we discuss the evidence regarding caffeine and dependence in light of increasing knowledge regarding the actions of caffeine on specific neuronal brain substrates. Because the use of caffeine is probably related to its diverse effects on several brain functions, these are also briefly presented. Even though we have attempted to cover many of the aspects that are relevant to this complex issue, we are aware of several omissions and we also realize that the complex—often somewhat contradictory—literature lends itself to more than one interpretation.

II. Consumption and Metabolism of Caffeine

A. Sources of Caffeine

Although coffee and other caffeine-containing beverages were introduced in Europe only a few hundred years ago, consumption of these beverages now occupies a significant place in our national cultures. The same can be said for most nations of the world (see Table 1). The national consumption of caffeine summarized in this table relies heavily on official statistics, which are notoriously unreliable. It is, for example, possible that the rather low figures for caffeine consumption in countries that produce the relevant plants may partly be due to the fact that not all the production has entered into the official statistics. In addition, Table 1 does not include soft drinks, although they are a major source of caffeine for example for children in Western society.

Caffeine is present in a number of dietary sources consumed worldwide, i.e., tea, coffee, cocoa beverages, chocolate bars, and soft drinks. The content of caffeine of

TABLE 1
Consumption of caffeine from coffee, tea, maté, and cocoa[a]

Country	Population (1995)	Coffee consumed		Caffeine from coffee	Tea consumed		Caffeine from tea	Maté consumed		Caffeine from maté	Cocoa consumed		Caffeine from cocoa	Caffeine from all these sources
	1000 pers[b]	*kton*	*kg/pers/yr*	*mg/pers/day*	*kton*	*kg/pers/yr*	*mg/pers/day*	*kton*	*kg/pers/yr*	*mg/pers/day*	*kton*	*kg/pers/yr*	*mg/pers/day*	*mg/pers/day*
Algeria	28,109	54	1.92	79	4	0.12	5	0.0	0.00	0	4	0.14	1	85
Angola	10,816	1	0.09	4	0	0.00	-	0.0	0.00	0	0	0.00	0	4
Argentina	34,768	36	1.04	43	1	0.02	1	220.0	6.33	52	29	0.83	5	100
Australia	17,862	88	4.93	202	13	0.72	29	0.1	0.01	0		0.00	0	232
Austria	8,045	54	6.71	276	2	0.19	8	0.0	0.00	0	24	2.98	16	300
Brazil	159,015	100	0.63	26	2	0.02	1	191.6	1.20	10	110	0.69	4	40
Canada	29,402	129	4.39	180	13	0.44	18	0.1	0.00	0	62	2.11	12	210
China	1,220,224	53	0.04	2	407	0.33	14	0.0	0.00	0	39	0.03	0	16
Colombia	35,814	110	3.07	126	0	0.00	0	0.0	0.00	0	60	1.68	9	136
Denmark	5,223	45	8.62	354	2	0.36	15	0.0	0.00	0	20	3.83	21	390
Egypt	62,096	7	0.11	5	80	1.29	53	0.0	0.00	0	7	0.11	1	58
Finland	5,107	40	7.83	322	1	0.16	6	0.0	0.00	0	1	0.20	1	329
France	58,104	304	5.23	215	11	0.20	8	0.0	0.00	0	171	2.94	16	239
Germany	81,594	580	7.11	292	18	0.22	9	0.5	0.01	0	181	2.22	12	313
Guatemala	10,621	6	0.56	23	0	0.04	2	0.0	0.00	0	4	0.38	2	27
Honduras	5,654	22	3.89	160	0	0.00	-	0.0	0.00	0	2	0.35	2	162
Hungary	10,106	34	3.36	138	1	0.08	3	0.0	0.00	0	16	1.58	9	150
India	929,005	16	0.02	1	589	0.63	26	0.0	0.00	0	8	0.01	0	27
Ireland	3,546	7	1.97	81	11	3.10	127	0.0	0.00	0	3	0.85	5	213
Italy	57,204	276	4.82	198	5	0.08	3	0.0	0.00	0	82	1.43	8	210
Ivory Coast	13,694	2	0.15	6	0	0.03	1	0.0	0.00	0	32	2.34	13	20
Japan	125,068	362	2.89	119	135	1.08	44	0.0	0.00	0	119	0.95	5	169
Kenya	27,150	5	0.18	8	28	1.03	42	0.0	0.00	0	1	0.04	0	50
Kuwait	1,691	2	1.18	49	5	2.72	112	0.0	0.00	0	4	2.37	13	173
Malaysia	20,140	24	1.19	49	13	0.67	27	0.0	0.00	0	16	0.79	4	81
Netherlands	15,482	139	8.98	369	14	0.93	38	0.0	0.00	0	18	1.16	6	414
Nicaragua	4,123	22	5.34	219	0	0.00	-	0.0	0.00	0	1	0.24	1	221
Nigeria	111,721	4	0.04	1	5	0.04	2	0.0	0.00	0	14	0.13	1	4
Norway	4,332	40	9.23	379	1	0.18	8	0.0	0.00	0	10	2.31	13	400
Paraguay	4,828	6	1.24	51	0	0.02	1	59.2	12.26	101	3	0.62	3	156
Poland	38,557	94	2.44	100	31	0.81	33	0.0	0.00	0	54	1.40	8	141
Russian Fed	148,460	94	0.63	26	143	0.96	40	0.0	0.00	0	182	1.23	7	72
Saudi Arabia	18,255	6	0.33	14	6	0.32	13	0.0	0.00	0	5	0.27	2	28
South Africa	41,465	15	0.36	15	24	0.57	23	0.0	0.00	0	10	0.24	1	40
Sweden	8,788	83	9.44	388	3	0.28	12	0.0	0.00	0	11	1.25	7	407
Switzerland	7,166	48	6.70	275	2	0.28	11	0.0	0.00	0	1	0.14	1	288
Syria	14,208	12	0.84	35	23	1.62	67	8.0	0.56	5	6	0.42	2	108
Tanzania	30,026	2	0.07	3	3	0.10	4	0.0	0.00	0	0	0.00	0	7
United Arab Emirates	2,210	4	1.81	74	5	2.13	87	0.0	0.00	0	2	0.90	5	167
United Kingdom	58,301	131	2.25	92	137	2.34	96	0.0	0.00	0	147	2.52	14	202
United States	267,115	931	3.49	143	80	0.30	12	0.4	0.00	0	596	2.23	12	168
Venezuela	21,844	72	3.30	135	0	0.00	0	0.0	0.00	0	14	0.64	4	139

[a] The data on which this table is based are taken from the 1995 food balance sheets of the Food and Agriculture Organization of the United Nations (FAO), which allow a very rough estimate of average consumption of foodstuffs in a population. Individual consumption will of course depend on whether a person consumes a certain product at all and, if so, how much. Another uncertainty inherent in food balance sheets is that they do not correct for waste (e.g., losses in processing, coffee brewed but not drunk, etc.). One major advantage of food balance sheets is that data are available for all the countries of the world. *Coffee:* Caffeine content in coffee beans varies depending on the species. *Arabica* coffees contain about 1.1% caffeine and *Robusta* about 2.2% dry weight (Gilbert, 1984; Viani, 1993). The amount of caffeine extracted varies with preparation technique used, ranging from 75% in boiled coffee, 80% in espresso, and 85% in percolated coffee, to nearly 100% in filtered coffee (D'Amicis and Viani, 1993). Tastes differ in different countries, and the relative proportions of *Robusta* and *Arabica* (and hence caffeine content) in the coffee blends vary. In Scandinavia, *Arabica* is used almost exclusively; in Southern Europe and North America, the proportion of *Robusta* can be 50 to 60% (D'Amicis and Viani, 1993). There is a tendency that preparation techniques with a greater caffeine extraction efficiency are used in countries that consume mainly *Arabica* coffee (e.g., filtered coffee in Sweden) and techniques with a lower extraction efficiency in countries where more *Robusta* is consumed (e.g., espresso coffee in Italy). For these calculations the caffeine content is taken as 1.6%, and the extraction efficiency is taken as 95%. *Tea:* The caffeine content in tea leaves depends on age of leaf (young leaves have about 4% by dry weight, old leaves contain less than half that), amount of fertilization (as fertilization increases caffeine content) season, and treatment after harvest (Graham, 1984b). About half the caffeine in tea leaves can be extracted, but the caffeine content in the beverage itself is strongly dependent on the brewing time (Graham, 1984b; IARC Working Group, 1991). For these calculations the caffeine content of tea is taken as 3% and the extraction efficiency as 50%. *Maté:* The caffeine content of maté ranges from 0.9 to 2.2% (dry weight) in a fresh leaf (Graham, 1984a). As usually prepared, 50 g of maté yields 1 liter of beverage containing a total of 160 mg of caffeine. The extraction figure used here is 0.3% of the total weight of the maté leaves. *Cocoa:* The caffeine content varies considerably in beans from different varieties of cacao trees: it is low in some (around 0.2% w/w in dry, defatted beans) but can be quite high in certain experimental clones (as much as 1%) (Shively and Tarka, 1984). For these calculations, the amount of caffeine consumed is assumed to correspond to 0.2% of the total domestic consumption of cocoa products.

[b] pers, persons.

these various food items ranges from 40 to 180 mg/150 ml for coffee to 24 to 50 mg/150 ml for tea, 15 to 29 mg/180 ml for cola, 2 to 7 mg/150 ml for cocoa, and 1 to 36 mg/28 g for chocolate (Barone and Roberts, 1996; Debry 1994; see also Table 2). Difficulties in taking all the sources into account may partly explain the consid-erable differences, such as in the estimates of caffeine consumption in the United Sates [from 196 to 423 mg/24 h; Weidner and Istvan (1985)] or in the UK [from 359 to 621 mg/24 h; Bruce and Lader (1986)].

Caffeine consumption from all sources can be esti-mated to around 70 to 76 mg/person/day worldwide (Gil-

TABLE 2
Content of caffeine of various foods and beverages[a]

Product	Volume or weight	Caffeine content
		mg
Roasted and ground coffee		
Percolated	150 ml	40–170
Drip	150 ml	60–180
Decaffeinated	150 ml	2–5
Instant coffee		
Caffeinated	150 ml	40–180
Decaffeinated	150 ml	2–8
Tea		
Bagged	150 ml	28–44
Leaf	150 ml	30–48
Instant	150 ml	24–50
Iced	150 ml	28–32
Cocoa	150 ml	2–7
Chocolate bar		
Milk	28 g	1–15
Sweet	28 g	5–36
Dark	28 g	5–35
Baking chocolate	28 g	18–118
Soft drinks		
Regular cola	180 ml	15–24
Caffeine-free cola	180 ml	0
Diet cola	180 ml	13–29

[a] Data from Debry (1994) and Barone and Roberts (1996).

bert, 1981, 1984) but reaches 210 to 238 mg/day in the US and Canada and more than 400 mg/person/day in Sweden and Finland, where 80 to 100% of the caffeine intake comes from coffee alone (Debry, 1994; Barone and Roberts, 1996; Viani, 1996). In the UK, the consumption is as high as in Sweden and Finland, but 55% comes from tea, 43% from coffee, and 2% from colas (Barone and Roberts, 1996). According to the recent survey of Barone and Roberts (1996), the daily intake of caffeine from all sources in the US is estimated at 3 mg/kg/ person, two-thirds of it coming from coffee in subjects more than 10 years old. If only consumers are taken into account, the daily caffeine consumption reaches a value of 2.4 to 4.0 mg/kg (170–300 mg) in a 60- to 70-kg individual. In 7- to 10-year-old children, the daily consumption of caffeine ranges from 0.5 to 1.8 mg/kg. The soft drinks represent 26 to 55%, chocolate foods and beverages 17 to 40%, tea 6 to 34%, and coffee 0 to 22% of the total caffeine intake (Morgan et al., 1982; Arbeit et al., 1988; Ellison et al., 1995). It is also clear from the data given below that the amounts of caffeine ingested via these sources are biologically active. This emphasizes that caffeine is indeed the most widely used of all psychoactive drugs.

B. Caffeine Absorption, Distribution, and Pharmacokinetics

Caffeine absorption from the gastrointestinal tract is rapid and reaches 99% in humans in about 45 min after ingestion (Marks and Kelly, 1973; Bonati et al., 1982; Blanchard and Sawers, 1983a,b; Arnaud, 1993). Caffeine absorption is also complete in animals (Arnaud, 1976, 1985). Pharmacokinetics are comparable after oral or i.v. administration of caffeine in humans and animals, leading to superimposable plasma curves (Arnaud,

1993). Absorption is, however, not complete when the substance is taken as coffee (Morgan et al., 1982). It is also known that when very large doses of caffeine are accidentally ingested, toxic effects appear, with an LD_{50} of about 200 mg/kg in rats (see Eichler, 1976). In patients who have been admitted to hospital due to acute caffeine poisoning, levels of a few hundred micromoles per liter have been recorded.

The hydrophobic properties of caffeine allow its passage through all biological membranes. There is no blood-brain barrier to caffeine in the adult or the fetal animal (Lachance et al., 1983; Tanaka et al., 1984), and the blood-to-plasma ratio is close to unity (McCall et al., 1982), indicating limited plasma protein binding and free passage into blood cells. In newborn infants, caffeine concentration is similar in plasma and cerebrospinal fluid (Turmen et al., 1979; Somani et al., 1980). There is no placental barrier to caffeine (Ikeda et al., 1982; Kimmel et al., 1984) and unusually high levels of caffeine have been reported in premature infants born to women who are heavy caffeine consumers (Khanna and Somani, 1984). Finally, saliva concentrations of caffeine, which are considered to be a reliable index of plasma caffeine levels, reach 65 to 85% of plasma concentrations (Cook et al., 1976; Khanna et al., 1980).

Peak plasma caffeine concentration is reached between 15 and 120 min after oral ingestion in humans and equals 8 to 10 mg/l for doses of 5 to 8 mg/kg (Arnaud and Welsch, 1982; Bonati et al., 1982). Ingestion of a single cup of coffee provides a dose of 0.4 to 2.5 mg/kg. It can therefore be estimated that this gives a peak concentration of 0.25 to 2 mg/l or approximately 1 to 10 μM.

For doses lower than 10 mg/kg, caffeine half-lives range from 0.7 to 1.2 h in rat and mouse, 3 to 5 h in monkey (Bonati et al., 1984–1985) and 2.5 to 4.5 h in humans (Arnaud, 1987). There are no differences in caffeine half-life in young and elderly humans (Blanchard and Sawers, 1983b). Conversely, caffeine half-life is increased during the neonatal period due to lower activity of cytochrome P-450 (Aranda et al., 1979) and to the relative immaturity of some demethylation and acetylation pathways (Aranda et al., 1974; Carrier et al., 1988). The half-life of caffeine is about 80 ± 23 h for the full-term newborn infant (Aranda et al., 1977; Le Guennec and Billon, 1987) and can be over 100 h in premature infants (Parsons and Neims, 1981). Thereafter, the half-life of caffeine decreases exponentially with postnatal age to 14.4 and 2.6 h in 3- to 5- and 5- to 6-month-old infants, respectively (Aldridge et al., 1979; Parsons and Neims, 1981; Paire et al., 1988; Pearlman et al., 1989). The clearance of caffeine is low in 1-month-old infants (31 ml/kg/h), increases to a maximal value of 331 ml/kg/h at 5 to 6 months, and is 155 ml/kg/h in adult humans (Aranda et al., 1979). In adult males, caffeine half-life is reduced by 30 to 50% in smokers compared with nonsmokers (Hart et al., 1976; Joeres et al., 1988; Murphy et al., 1988), whereas it is approximately doubled in

women taking oral contraceptives (Patwardhan et al., 1980) and greatly prolonged (up to 15 h) during the last trimester of pregnancy (Aldridge et al., 1981; Knutti et al., 1981; Brazier et al., 1983).

C. Caffeine Metabolism

Caffeine is metabolized by the liver to form dimethyl- and monomethylxanthines, dimethyl and monomethyl uric acids, trimethyl- and dimethylallantoin, and uracil derivatives (Arnaud, 1987, 1993). The demethylation, C-8 oxidation, and uracil formation occur mostly in liver microsomes. The major metabolic difference between rodents and humans is that, in the rat, 40% of the caffeine metabolites are trimethyl derivatives as compared with less than 6% in humans (Arnaud, 1985, 1993). Metabolism in humans is characterized by the quantitative importance of the 3-methyl demethylation leading to the formation of paraxanthine. This first metabolic step represents up to 72 to 80% of caffeine metabolism (Arnaud and Welsch, 1982; Arnaud, 1993). Many of the metabolic steps may be saturable in humans as the elimination half-time for not only caffeine, but also some of its metabolites, is dose-dependent (Kaplan et al., 1997).

Some metabolites of caffeine also have marked pharmacological activity. Thus, 1,3-dimethylxanthine (theophylline) and 1,7-dimethylxanthine (paraxanthine) must be taken into account when considering the biological actions of caffeine-containing beverages. In rodents, paraxanthine is the major metabolite in plasma, but levels of theophylline are also high. The metabolism of caffeine to paraxanthine can be used to phenotype individuals with regard to one subform of cytochrome P-450, CYP1A2 (Fuhr et al., 1996; Miners and Birkett, 1996). By contrast, the formation of theophylline from caffeine does not correlate with any specific subform.

It has recently been shown that, after long-term caffeine ingestion, the levels of theophylline in the mouse brain may be higher than those of caffeine during a substantial part of the day and almost always higher than the levels of paraxanthine (Johansson et al., 1996a). This could mean that caffeine in the brain is metabolized partly via specific, local enzymatic pathways and that caffeine administration leads to high central nervous system (CNS) concentrations of theophylline, whereas peripheral theophylline levels are kept low. It is possibly relevant that demethylation of caffeine to paraxanthine in rats appears to be predominantly catalyzed by cytochrome P-450, whereas demethylation to theophylline and theobromine may also take place via flavin-containing monooxygenases (Chung and Cha, 1997). Future studies will have to be performed to determine if the situation is similar in humans. It is, however, clear that the contention that most of the effects of caffeine in the CNS are direct or indirect consequences of adenosine receptor blockade (see Section III below) increases in strength if local CNS concentrations of theophylline and/or paraxanthine are high after caffeine ingestion. Theophylline is some three to five times more potent than caffeine as an inhibitor of both adenosine A_1 and A_{2A} receptors, and paraxanthine is also at least as potent as caffeine. Indeed it has been shown that, in humans, some tested effects of caffeine are readily mimicked by paraxanthine (Benowitz et al., 1995).

Because so much of the background information is derived from animal experiments, we must try to extrapolate the data to humans. However, it is not a trivial task to compare doses of caffeine in animals and humans. For example, it must be kept in mind that in most experiments on rodents, one single high dose of caffeine is administered, whereas human consumption of coffee is divided up during the day. Gilbert (1976) suggested the use of a metabolic body weight correction factor when comparing the effect of a given dose of caffeine in animals and humans. However, not everyone agrees that such a correction based on the metabolic body weight should be applied. Indeed the LD_{50} of caffeine is fairly consistent across species, including *Homo sapiens* (Dews, 1982). The plasma level resulting from 1.1 mg/kg caffeine (a single cup of coffee containing 80 mg of caffeine ingested by a 70-kg human) ranges from 0.5 to 1.5 mg/l. A similar dose-concentration relationship is found in many species, including rodents and primates (Hirsh, 1984). However, because the metabolism of caffeine differs between rodents and humans and the half-life of the methylxanthine is much shorter in rats (0.7–1.2 h) than in humans (2.5–4.5 h) (Morgan et al., 1982), it seems reasonable to correct for the metabolic body weight when comparing animal and human doses. Thus, it is generally assumed that 10 mg/kg in a rat represents about 250 mg of caffeine in a human weighing 70 kg (3.5 mg/kg), and that this would correspond to about 2 to 3 cups of coffee.

III. Molecular and Cellular Action of Caffeine in the Brain

A. Fundamental Biochemical Actions

The biochemical mechanism that underlies the actions of caffeine at doses achieved in normal human consumption must be activated at concentrations between the extremes (between barely effective doses and doses that produce toxic effects; see Fig. 1). This tends to rule out the direct release of intracellular calcium [probably via an action on ryanodine receptors (McPherson et al., 1991)], which occurs only at millimolar concentrations. Also the inhibition of cyclic nucleotide phosphodiesterases (Smellie et al., 1979; see Fredholm, 1980; Nehlig and Debry, 1994) occurs at rather higher concentrations than those attained during human caffeine consumption. Xanthines can influence 5′-nucleotidase and alkaline phosphatase, but these actions are also exerted only at millimolar concentrations (Fredholm et al., 1978; Fredholm and Lindgren, 1983). In fact,
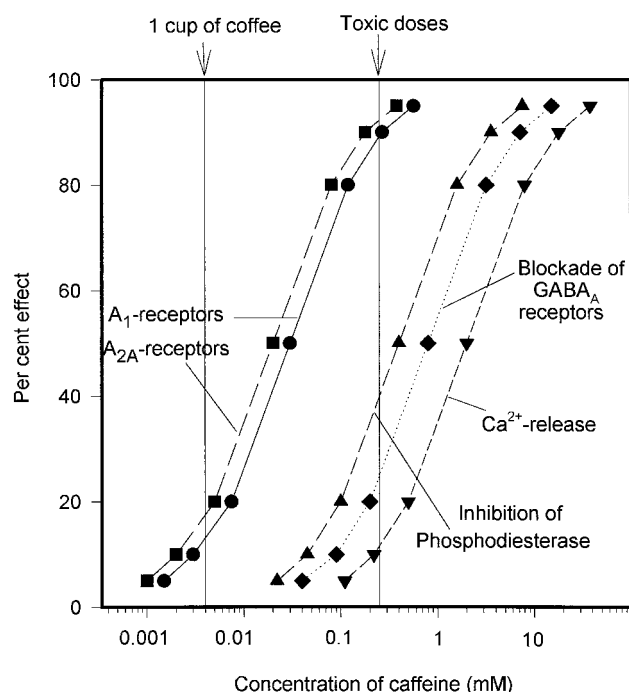
FIG. 1. Effect of caffeine on different biochemical targets in relation to its levels in humans. Note that caffeine is able to significantly block adenosine effects on A_{2A} (most potent) and A_1 receptors already at the low concentrations achieved after a single cup of coffee. To inhibit cyclic nucleotide breakdown via inhibition of phosphodiesterase, 20 times higher concentrations are required; to block $GABA_A$ receptors, 40 times higher concentrations; and to mobilize intracellular calcium depots, concentrations of 100 times higher are needed. These latter levels are unlikely to be reached in humans by any form of normal use of caffeine-containing beverages (modified from Fredholm, 1980).

the only known mechanism that is significantly affected by the relevant doses of caffeine is binding to adenosine receptors and antagonism of the actions of agonists at these receptors (see Fredholm, 1980, 1995). Thus, in the remainder of this section, adenosine receptor antagonism is taken to be *the* mechanism of action of caffeine even though there are data, especially from behavioral experiments, that could be interpreted as evidence for some other, as yet unidentified mechanism of action (see, e.g., Garrett and Holtzman, 1995).

B. Adenosine Levels in Brain and Other Tissues

The hypothesis that we consume coffee because it blocks the actions of endogenous adenosine at its receptors is only tenable if adenosine is present in sufficient concentrations to activate the adenosine receptors already under basal conditions. We must therefore critically assess this postulate.

Adenosine is a normal cellular constituent. The intracellular level is regulated by the balance of several enzymes. Adenosine is formed by the action of an AMP-selective 5'-nucleotidase, and the rate of adenosine formation via this pathway is mainly controlled by the amount of AMP. Therefore, the important factor determining the rate of adenosine formation via this pathway is the relative rates of ATP breakdown and synthesis.

These are in turn determined by the rate of energy utilization and the availability of metabolizable substrate.

There are two enzymes that constitute the major pathways of adenosine removal: adenosine kinase and adenosine deaminase. The latter enzyme is present mostly intracellularly but is also found in some extracellular compartments. The preferred substrate of the enzyme is not adenosine but 2-deoxyadenosine (Fredholm and Lerner, 1982). The K_m for adenosine is well above 5 μM and adenosine deaminase is therefore of particular importance when adenosine levels are high (Arch and Newsholme, 1978). Adenosine kinase, by contrast, has a K_m level in the range of physiological intracellular adenosine concentrations. Indeed, blockade of adenosine kinase has a much larger effect on the rate of adenosine release than does blockade of adenosine deaminase (Lloyd and Fredholm, 1995). Another enzyme of importance is S-adenosylhomocysteine hydrolase. This enzyme sets the equilibrium between S-adenosylhomocysteine and adenosine + L-homocysteine. When the level of the amino acid is low, this enzyme serves to generate adenosine. On the other hand, when the level of L-homocysteine is raised, it can trap adenosine formed via AMP breakdown as S-adenosylhomocysteine inside the cell. This reaction has been used to demonstrate that the bulk of the adenosine formed by energy deprivation or electrical field stimulation in hippocampal slices is formed intra- rather than extracellularly (Lloyd et al., 1993).

Extracellular ATP is very rapidly hydrolyzed to adenosine and other metabolites. Thus, if ATP is released from neuronal (or glial) cells, e.g., as a transmitter or an intercellular signal, it will provide a source of extracellular adenosine. It seems likely that this may be significant in some circumstances and in some locations. However, extracellular ATP is not the major source of adenosine released from brain slices during field stimulation (at least when relatively low frequency stimulation is used) or following hypoxia/hypoglycemia. This is shown by the fact that agents that block extracellular AMP hydrolysis fail to affect the rate of adenosine release significantly (Lloyd et al., 1993). Thus, intracellular adenosine formation is quantitatively most important.

Intra- and extracellular adenosine concentrations are kept in equilibrium by means of equilibrative transporters. These transporters are blocked by several agents such as nitrobenzylthioinosine, propentofylline, dipyridamole, and dilazep. In addition there are sodium-dependent, concentrating transporters that move extracellular adenosine into cells. These latter transporters are not blocked by the above agents, and their precise role in the CNS is unknown. When inhibitors of equilibrative transport are given, the levels of adenosine rise in the CNS despite a decrease in the release of adenosine metabolites such as inosine and hypoxanthine (Andiné

et al., 1990; Fredholm et al., 1994b). The reason for this has been discussed elsewhere (see Fredholm et al., 1994b). Adenosine, once released, can secondarily be taken up by cells and metabolized to inosine and hypoxanthine. It should, however, be pointed out that transport inhibitors block the overall release of adenine nucleotide breakdown products (Jonzon and Fredholm, 1985), as expected for a model where equilibrative transporters are critically important. Furthermore, the addition of L-homocysteine in the presence of transport inhibitors leads to a very substantial reduction in the efflux of adenosine. The reason is that an excess of L-homocysteine forces the S-adenosylhomocysteine hydrolase reaction to occur in reverse and intracellular adenosine levels are very much reduced. When intracellular levels are decreased the extracellular levels also go down.

From these facts it can be deduced that adenosine levels in the extracellular fluid should be raised whenever there is a discrepancy between the rate of ATP consumption and ATP synthesis. In addition, it is expected that drugs that interfere with the key enzymes and with the transporters should affect adenosine levels. Extracellular adenosine levels have been measured using microdialysis. In the first paper using this method it was shown that the level of adenosine, while initially high, stabilized at about 1 μM within a few hours of implantation of the dialysis probe (Zetterström et al., 1982). It was also shown that the level of adenosine was raised about 3-fold following a mild hypoxia. The level of adenosine can increase dramatically to 10 μM or more following ischemia (Andiné et al., 1990; Dux et al., 1990). However, a later study showed that it took much longer to reach the true equilibrium level and that consequently the disturbance produced by the microdialysis probe lasted for perhaps 24 h (Ballarin et al., 1991). Our current best estimate of the basal level of adenosine in the brain of awake, unrestrained rats is between 30 and 300 nM. Interestingly, these levels are close to the estimated levels of adenosine in plasma (Reid et al., 1991). There is one report to the effect that caffeine, particularly prolonged administration of caffeine, increases the levels of adenosine in plasma dramatically (Conlay et al., 1997) at least in rats, and that this effect is receptor-mediated. This finding clearly needs to be reproduced—especially in humans.

We turn now to the question of whether there are adenosine receptors that are activated not only by the high adenosine levels seen in ischemia, but also by the low (high nanomolar concentrations) physiological levels.

C. Adenosine Acts on Several Types of G-Protein-Coupled Receptors

1. Receptor Subtypes. At present four distinct adenosine receptors, A_1, A_{2A}, A_{2B}, and A_3, have been cloned and characterized in several species (Fredholm et al., 1994a; Table 3). Of these subtypes, the rat A_3 receptor was originally shown to be but little affected by many methylxanthines, including caffeine. In humans, the A_3 receptor is blocked by caffeine with a K_D of close to 80 μM. Therefore, this receptor is not the best target for caffeine actions in humans. The A_{2B} receptor has been shown to require higher concentrations of adenosine for activation than those found in resting animal tissues. Thus, inhibition of adenosine actions at this receptor is similarly unlikely to provide an explanation for the actions of caffeine under physiological conditions. Under pathophysiological conditions, however, A_{2B} receptors are likely to be activated by endogenous adenosine and caffeine may then very well act also on these receptors.

Although A_3 and A_{2B} receptors are unlikely to be important, A_1 and A_{2A} receptors are activated at the low basal adenosine concentrations measured in resting rat brain. Thus, these receptors are likely to be the major targets for caffeine and theophylline. A_1 and A_{2A} receptors are both G-protein-coupled. The A_1 receptor is coupled to the pertussis toxin-sensitive G-proteins G_{i-1}, G_{i-2}, G_{i-3}, G_{o1}, and G_{o2}. In agreement with this, activation of A_1 receptors can cause inhibition of adenylyl cyclase and of at least some types of voltage-sensitive Ca^{2+}-channels such as the N- and the Q-channels, and activation of several types of K^+-channels, phospholipase C and phospholipase D. Consequently, a host of different cellular effects can ensue (see Fredholm et al., 1994a,1995). A_{2A} receptors associate with G_s-proteins; therefore, activation of these receptors causes the activation of adenylyl cyclase and perhaps also activation of some types of voltage-sensitive Ca^{2+}-channels, especially the L-channel. Thus, A_1 and A_{2A} receptors have partly opposing actions at the cellular level. This is interesting because the two types of receptor are sometimes coexpressed in the same cell. It is therefore important to consider where these two adenosine receptors are located.

2. Receptor Distribution. A_1 and A_{2A} receptors in the brain can be localized by receptor autoradiography with radioactive ligands. In addition, the sites of receptor synthesis can be determined using in situ hybridization. Adenosine A_1 receptors are present in almost all brain areas, with the highest levels in hippocampus, cerebral and cerebellar cortex, and certain thalamic nuclei (Goodman and Snyder, 1982; Fastbom et al., 1987). Only moderate levels are found in caudate-putamen and nucleus accumbens. The corresponding mRNA shows a somewhat different distribution (Mahan et al., 1991; Reppert

TABLE 3
Potency of caffeine at rat and human adenosine receptor subtypes

Receptor subtype	Rat (K_D)	Human (K_D)
	μM	
A_1 receptors	20	12
A_{2A} receptors	8.1	2.4
A_{2B} receptors	17	13
A_3 receptors	190	80

et al., 1991), indicating that some of these receptors are located on nerve terminals rather than cell bodies (Johansson et al., 1993a). Indeed, the presence of presynaptic adenosine A_1 receptors mediating inhibition of transmitter release has been demonstrated on virtually all types of neurons [for review see Fredholm and Dunwiddie (1988)]. In the caudate-putamen, adenosine A_1 receptor mRNA was found to be present, albeit in low abundance, on all the major types of neurons (Ferré et al., 1996).

Adenosine A_{2A} receptors are found to be concentrated in the dopamine-rich regions of the brain, irrespective of whether ligand binding or mRNA is used for the localization (Fig. 2). This association was in fact noted a long time ago when it was shown that in cell-free homogenates from these regions, and only from these regions, adenosine stimulated adenylyl cyclase activation (Fredholm, 1977; Premont et al., 1979). In the first direct studies on the localization of A_{2A} receptors, a number of radiolabeled agonists were used. One of the agonists used most frequently was [^{3}H]CGS 21680 (Jarvis and Williams, 1989; Parkinson and Fredholm, 1990). More recently it has become apparent that CGS 21680 is not an optimal ligand. For example, it has been found to have a relatively low affinity for A_{2A} receptors in non-rodent species. At human A_{2A} receptors for example those expressed in Chinese hamster ovary cells, CGS 21680 has an affinity close to 100 nM, whereas its affinity at rat A_{2A} receptors is closer to 10 nM (see Ongini and Fredholm, 1996). A second factor that limits its usefulness as a radioligand is that it is an *agonist* and that its affinity consequently depends on the association of the receptor with G-proteins. This association is highly variable between preparations and methods used. Finally, it has been found that CGS 21680 binds to sites that are clearly different from A_{2A} receptors (Johansson et al., 1993b; Johansson and Fredholm, 1995). These sites are present in cortex and hippocampus and can be clearly differentiated from the A_{2A} receptors by the use of selective antagonists (Lindström et al., 1996). In fact, in many respects these non-A_{2A}-receptor binding

sites for [^{3}H]CGS 21680 show many characteristics of an A_1 receptor (Cunha et al., 1996). It has recently been shown that [^{3}H]SCH 58261, a nonxanthine antagonist, can be used successfully to study the distribution of A_{2A} receptors (Ongini and Fredholm, 1996). When this radioligand is used there is little evidence for significant A_{2A} receptor binding outside striatum, nucleus accumbens, and tuberculum olfactorium.

In situ hybridization, using either oligodeoxynucleotide probes or riboprobes, similarly reveals a very selective localization of A_{2A} receptor mRNA to the same dopamine-rich regions of the brain. Very little mRNA is detected in other regions of the brain. This is somewhat surprising given the amount of functional data that clearly suggests the presence of functionally important A_{2A} receptors in hippocampus and cortex.

The in situ hybridization technique makes it possible to determine which cells express A_{2A} receptor mRNA. It was observed that A_{2A} receptor mRNA was colocalized with dopamine D_2 receptors in enkephalin-expressing, medium-sized spiny neurons in the dorsal striatum (Schiffmann et al., 1991; Fink et al., 1992; Johansson et al., 1993a). It has later become clear that this colocalization of A_{2A} and D_2 receptors extends also to the core and shell regions of the nucleus accumbens and to the tuberculum olfactorium (Svenningsson et al., 1997b) (Fig. 3). On the other hand, the neurons that express dopamine D_1 receptors and Substance P do not express adenosine A_{2A} receptor mRNA. Furthermore, none of the above reports detected any significant expression of A_{2A} receptor mRNA in the large aspiny cholinergic neurons. One group did report A_{2A} receptor mRNA in cholinergic neurons using in situ hybridization (Dixon et al., 1996) as well as functionally important A_{2A}-like receptors regulating acetylcholine release from cholinergic synaptosomes (Kirk and Richardson, 1994; Kurokawa et al., 1994). As shown in Fig. 3, this finding could not be replicated in studies using riboprobes for both the A_{2A} receptor and choline acetyl transferase despite the fact that these probes show a much higher sensitivity and specificity (Svenningsson et al., 1997b). The reason for

Adenosine A$_{2A}$ Dopamine D$_2$ Dopamine D$_1$

mRNA Binding mRNA   Binding mRNA Binding
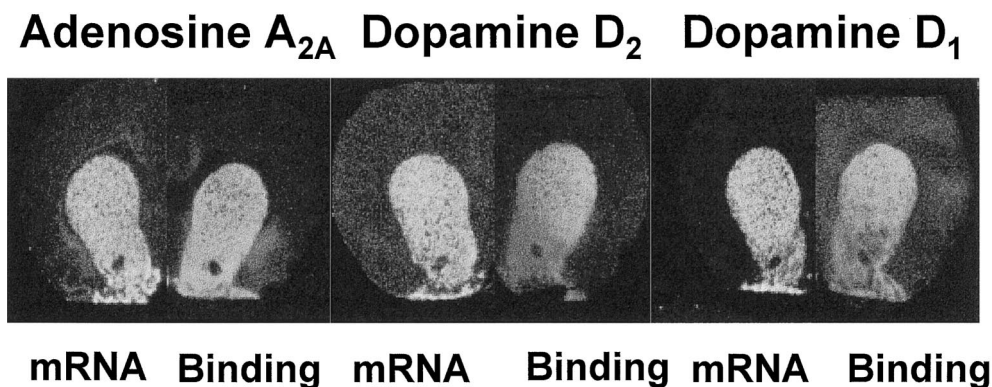
FIG. 2. The similarity in the distribution of adenosine A_{2A}, dopamine D_2, and dopamine D_1 receptors in rats. These film autoradiograms (negatives) show the distribution of mRNA (in situ hybridization) or protein (receptor autoradiography with antagonist radioligand) for the three types of receptors in coronal sections of rat brain. Note the excellent colocalization.
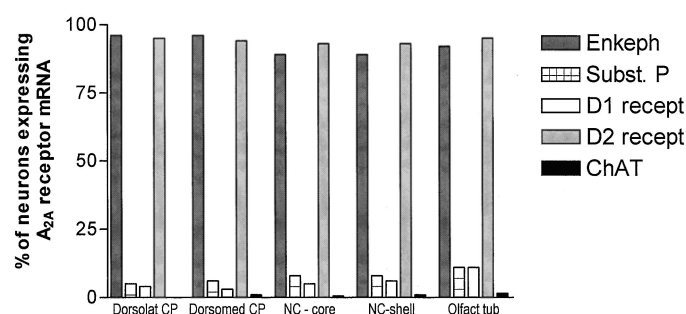
FIG. 3. A_{2A} receptor mRNA is specifically associated with D_2, but not with D_1 receptors, with enkephalin, but not with Substance P, and is essentially absent from large aspiny cholinergic neurons. In situ hybridization experiments were carried out using two separate probes in each experiment. A radioactive probe for the adenosine A_{2A} receptor was combined with a nonradioactive probe for preproenkephalin, preprotachykinin, dopamine D_1 and D_2 receptors, or choline acetyl transferase. Using an image analysis system, the number of cells expressing mRNA for the A_{2A} receptor was calculated as a percentage of the total number of cells expressing mRNA for the other probes. Cells were counted in several areas of the brain, including dorsolateral and dorsomedial caudate putamen (CP), nucleus accumbens (NC) core and shell, and in the olfactory tubercle. Data are from Svenningsson et al. (1997b).

this discrepancy between the results of different studies is unclear.

D. Caffeine Affects Transmitter Release and Neuronal Firing Rates via Actions on Adenosine A_1 Receptors

The inhibitory effect of adenosine on transmitter release was first noted in the peripheral nervous system, but similar effects in the CNS were soon demonstrated (see Fredholm and Hedqvist, 1980; Fredholm and Dunwiddie, 1988). There is some evidence that the release of excitatory transmitters is more strongly inhibited by adenosine than that of inhibitory neurotransmitters (Fredholm and Dunwiddie, 1988). This would be in keeping with a proposed role of adenosine as a homeostatic regulatory factor that serves to match the rate of energy consumption to the rate of substrate supply. The receptors involved are similar to adenosine A_1 receptors.

As discussed previously (Fredholm and Dunwiddie, 1988), adenosine appears to use several mechanisms in order to produce inhibition of transmitter release. The electrically evoked release, but not the spontaneous release of neurotransmitter, is strongly dependent on the concentration of calcium in the extracellular environment (see Fredholm and Hu, 1993). On the other hand, the electrically evoked release is poorly affected by buffers of intracellular calcium, whereas the spontaneous transmitter release is strongly affected. This supports the contention that calcium entering via voltage-dependent calcium channels and acting on docked vesicles in the neighborhood of the channel is important. It is interesting to note that adenosine acting on A_1 receptors has been shown to decrease calcium entry via N-type channels in hippocampal CA1 and CA3 neurons (Scholz and Miller, 1992; Mogul et al., 1993). However, in some types of neurons the effect of adenosine is only moderately or not at all affected by ω-conotoxin, a selective

inhibitor of N-type channels (Fredholm, 1993). This could mean that adenosine acts either on some other type of calcium channel (Takahashi and Momiyama, 1993), perhaps the putative Q-type channel (Sather et al., 1993; Takahashi and Momiyama, 1993). Another possibility is that adenosine affects, directly, a calcium-sensitive member of the release machinery, a contention for which there is some support (Silinsky, 1984; Scholz and Miller, 1992; Thompson et al., 1992). However, when it has been possible to actually measure Ca^{2+} influx, the reduction has been found to adequately account for the decrease in transmitter release (Yawo and Chuhma, 1993; Wu and Saggau, 1994). There is also some evidence that increases in cyclic AMP in nerve endings are associated with an increase in transmitter release (Chavez-Noriega and Stevens, 1994). Because activation of adenosine A_1 receptors is known to cause a decrease in cAMP formation, it is conceivable that this may also be a mechanism of decreased transmitter release—at least under some circumstances.

There is also considerable evidence that adenosine acts to decrease the rate of firing of central neurons (Phillis and Edstrom, 1976). This effect appears to be quite general and is due to an activation of potassium channels via adenosine A_1 receptors (Dunwiddie, 1985). When the effect of endogenous adenosine at these receptors on glutamatergic neurons is blocked by caffeine, it leads to epileptiform activity in vitro (Dunwiddie, 1980; Dunwiddie et al., 1981), and this could be the mechanism by which methylxanthines produce seizures in vivo.

It is also known that caffeine increases the turnover of several monoamine neurotransmitters, including 5-hydroxytryptamine (5-HT) dopamine, and noradrenaline (Fernström and Fernström, 1984; Bickford et al., 1985; Fredholm and Jonzon, 1988; Hadfield and Milio, 1989). There is evidence that methylxanthines increase the rate of firing of noradrenergic neurons in the locus ceruleus (Grant and Redmond, 1982). The increase in noradrenaline turnover is probably the explanation for the fact that methylxanthines also reduce the number of β-adrenoceptors in rat brain (Fredholm et al., 1984; Shi et al., 1993a). It has also been shown that the mesocortical cholinergic neurons are tonically inhibited by adenosine and that caffeine consequently increases their firing rate (Rainnie et al., 1994). It was postulated that this effect is of importance in the electroencephalogram (EEG) arousal following caffeine ingestion. Because dopamine and noradrenaline neurons also are involved in arousal, there is ample neuropharmacological basis for assuming that central stimulatory effect of caffeine could be related to inhibition of adenosine A_1 receptors. Also there are increases in 5-hydroxytryptamine receptors, muscarinic receptors, and δ-opioid receptors following higher doses of caffeine (Shi et al., 1993a, 1994). The functional relevance, if any, of these changes remains to be elucidated.

There is considerable evidence for a link between adenosine A_1 receptors and dopamine D_1 receptors (see Ferré et al., 1997). Thus, blockade of adenosine A_1 receptors enhances motor effects of D_1 receptor agonists. Infusion of an adenosine A_1 receptor agonist into the caudate-putamen does not per se modify the levels of GABA in the entopeduncular nucleus, the output structure of the dopamine D_1 receptor-expressing, medium-sized GABAergic neurons, but blocks the stimulatory effect of a D_1 receptor agonist (Ferré et al., 1996). There are several possible mechanisms that could underlie these behavioral and neurochemical effects. It has been shown that activation of adenosine A_1 receptors influence the binding of dopamine D_1 agonists (Ferré et al., 1994, 1996, 1998). There are also more indirect interactions, and an involvement of N-methyl-D-aspartate (NMDA) receptors has been implicated. It is interesting to note that a recent study (Harvey and Lacey, 1997) presented strong evidence that combined dopamine D_1 and NMDA receptor stimulation increases the release of adenosine, which then acts at adenosine A_1 receptors to decrease the release of the excitatory neurotransmitter. Some of these interactions between A_1, D_1, and NMDA receptors are schematically represented in Fig. 4. In addition, D_1 receptors in the ventral tegmental area (VTA) interact with adenosine A_1 receptor effects (Bonci and Williams, 1996).

E. Caffeine Effects on Dopaminergic Transmission Are Exerted Mainly via Actions on Adenosine A_{2A} Receptors

As noted above A_{2A} receptors are located preferentially in the subpopulation of the medium sized spiny GABAergic neurons that project to globus pallidus, a subpopulation in which they are colocalized with dopamine D_2 receptor mRNA. These colocalized receptors have been shown to interact functionally. Thus, activation of A_{2A} receptors has been shown to decrease the affinity of dopamine binding to D_2 receptors (Ferré et al., 1991), but not antagonist binding affinity. This type of change mimics that observed following the addition of sodium ions. However, the effect of the A_{2A} receptor agonist was at least as large in the presence as in the absence of sodium ions. The interaction could not be observed when high levels of dopamine D_2 and adenosine A_{2A} receptors were transiently expressed in Cos-7 cells (Snaprud et al., 1994). In these cells the receptors were not functionally coupled to an effector response. This suggests that the interaction may not occur between the receptor molecules only but that some interactions with other membrane components are also necessary. Conversely, in fibroblasts stably transfected with both A_{2A} and D_2 receptors there was a clear-cut interaction at the binding level despite the fact that the A_{2A} receptors in these cells were very poorly coupled to adenylyl cyclase (Dasgupta et al., 1996). This indicates that the interaction at the level of binding does not require the full effector response. The latter contention is also supported by the fact
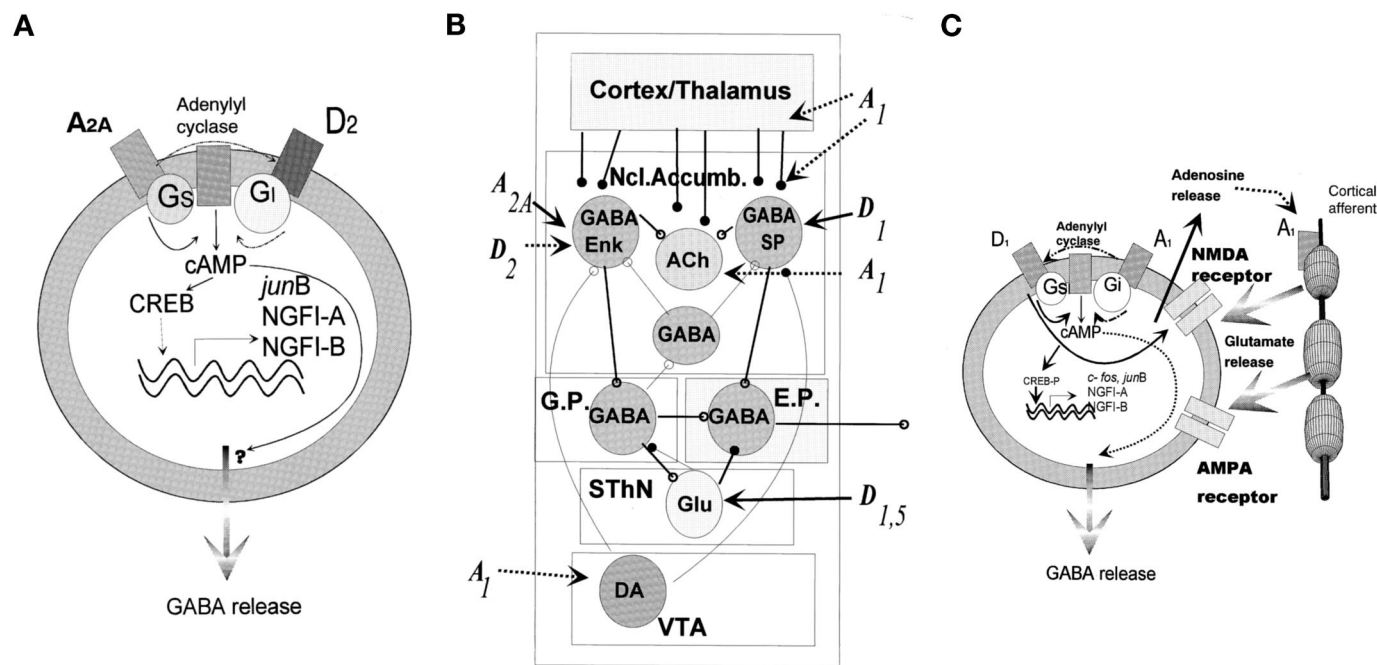

FIG. 4. Schematic illustration of the effect of caffeine on striatopallidal and striatonigral neurons. A, potential interactions between A_{2A} and D_2 receptors in the GABAergic neurons that comprise the so-called indirect pathway and project to the ventral pallidum. B, a simplified wiring diagram of the nucleus accumbens and some of its input and output structures. Synapses are shown as stimulatory (●) or inhibitory (○). In this part of the figure are also indicated areas where adenosine and dopamine receptor subtypes are enriched. C, the interactions between A_1, D_1, and glutamate receptors in neurons that comprise the so-called direct pathway. In particular, it should be noted that activation of dopamine D_1 receptors can enhance the actions mediated via NMDA receptors. This causes release of adenosine, which activates A_1 receptors located on the terminals of the excitatory input. Hereby the release of glutamate is reduced.

that the binding studies were conducted on broken cell preparations and under conditions when adenylyl cyclase activity and protein phosphorylation can be expected to proceed at negligible rates. More recently this binding interaction was observed in Chinese hamster ovary cells cotransfected with A_{2A} and D_2 receptors, and in this cell type there were also very clear-cut interactions at the second messenger level and beyond.

There is evidence that these interactions between adenosine A_{2A} and dopamine D_2 receptors observed in vitro have functional correlates in intact striatum. Thus, it is interesting that dopamine administered in the striatum has been shown to block the release of GABA in the globus pallidus (Ferré et al., 1993) and that this effect is reduced by endogenous adenosine. Furthermore, activation of adenosine A_{2A} receptors increases GABA release from pallidal slices (Mayfield et al., 1993). The effects of adenosine on striatal GABA release are much more complex, possibly indicating a complex interaction between different neuronal populations. In slices of striatum, adenosine A_{2A} receptor agonists do not directly influence the release of dopamine or acetylcholine (Jin and Fredholm, 1997), but adenosine A_{2A} receptor stimulation has been shown to block the inhibitory effect of a dopamine D_2 receptor agonist on acetylcholine release from striatal slices (Jin et al., 1993). This could indicate that part of the dopamine D_2 receptor-mediated control of acetylcholine release from striatal slices is indirect and mediated via actions exerted at GABAergic neurons.

F. Identifying the Neuronal Substrates For Caffeine by Examining Changes in Immediate Early Genes—High Dose Effects

An increased neuronal activity is often accompanied by an expression of so-called immediate early gene (IEGs) such as c-fos, c-jun, junB, junD, NGFI-A (also called zif/268), and NGFI-B. Thus it is possible to determine which neuronal pathways are activated by caffeine by examining the effect of caffeine on immediate early gene expression. Caffeine causes a concentration-dependent increase in c-fos expression, which is confined to the striatum (Johansson et al., 1994). However, the increase does not become apparent until caffeine doses exceed 50 mg/kg, i.e., doses clearly higher than those required to elicit behavioral stimulation (see below). This could mean that the caffeine-induced increase in immediate early genes is related to the second phase of caffeine action, which involves a behavioral depression. Alternatively, the dose-response relationship could indicate that substantially higher concentrations are required to observe a generalized c-fos increase than are needed to activate a sufficient number of neurons to produce a behavioral stimulation. Some support for the latter contention is provided by the finding that other central stimulants, including amphetamine and cocaine,

have to be given in very much higher concentrations to induce c-fos than to cause behavioral stimulation.

Because amphetamine and cocaine are known to act by releasing dopamine and because caffeine is presumed to act in part by increasing dopaminergic transmission, it is of interest to compare the effects of these three agents. A recent study revealed a gross morphological difference in the pattern of c-fos induction: cocaine and amphetamine increase the c-fos mRNA expression throughout the striatum, not least in the nucleus accumbens; caffeine, on the other hand, increases c-fos mRNA expression primarily in dorsolateral striatum (Johansson et al., 1994). Furthermore there is a marked difference at the cellular level. Amphetamine and cocaine primarily increase c-fos in the cells that express dopamine D_1 receptors and Substance P, but not in those that express D_2 receptors and met-enkephalin. By contrast, caffeine increases c-fos expression in both types of cells (Johansson et al., 1994). These data point to differences between the two types of agents, differences that could have some bearing on the question of whether caffeine is an addictive drug much like cocaine and amphetamine (Griffiths and Woodson, 1988a–c), but, as noted, the doses used to elicit IEG expression are high and not necessarily relevant in discussing behavioral stimulation.

The effect of an increase in the release of dopamine on IEG expression in the nucleus accumbens was directly studied by electrical activation of the medial forebrain bundle (Chergui et al., 1996). Burst activation of these neurons causes a marked increase in the evoked release of dopamine in the nucleus accumbens as assessed by voltametry. It is also associated with a marked increase in the expression of several IEGs, including c-fos, jun-B, NGFI-A, and NGFI-B. This increase can be blocked by dopamine D_1 receptor antagonists and is confined to the striatonigral neurons that express D_1 receptors. This shows that increased dopamine release—whether brought about by nerve activation or by pharmacological means—causes a D_1 receptor-mediated increase in IEG expression. Because high doses of caffeine increase c-fos both in D_1- and D_2-expressing neurons, the mechanism underlying its actions cannot be explained solely by an increase in dopamine.

As noted above, there are adenosine A_1 receptors on virtually all types of neurons that have the ability to decrease transmitter release. They are certainly present on the dopaminergic neurons (see Jin et al., 1993; Jin and Fredholm, 1997). However, they are also present on glutamatergic neurons. The striatum receives a strong glutamatergic input from both cortex and thalamus (see Gerfen, 1992), and part of the caffeine-induced increase in c-fos could be due to elevated release of glutamate. Indeed, at least part of the elevation in c-fos could be blocked by NMDA receptor antagonists (Svenningsson et al., 1996). Because the blockade was not complete, it is clear that additional mechanisms are also operative, but it may be relevant that the largest effect of NMDA

receptor antagonism was observed in nucleus accumbens.

Caffeine injections lead to an increased expression not only of c-*fos* but also of other members of the same family of IEGs, notably c-*jun* and *jun*-B. Furthermore, there is an increased expression of the AP-1 transcription factor (Svenningsson et al., 1995b). Moreover, there are later changes in the expression of neuropeptides that are known to have AP-1-sensitive regulatory elements, notably preproenkephalin. These results suggest that even a single, albeit high, dose of caffeine can induce changes in gene expression that could lead to adaptive changes in the brain. The mRNA for four different neuropeptides, dynorphin, enkephalin, neurotensin/neuromedin, and Substance P, is elevated in the striatum by high doses of caffeine (Svenningsson et al., 1997a). Two of these, neurotensin/neuromedin and Substance P, are dependent on a rise in c-Fos as evidenced by the effect of a specific antisense oligonucleotide. By contrast, mRNA for dynorphin and enkephalin, were unaffected by blocking c-Fos increases, suggesting that other transcription factors are more important. Cyclic AMP response element-binding protein (CREB) is a likely candidate.

G. Low Doses of Caffeine Selectively Decrease the Activity of Striatopallidal Neurons in the Striatum and Their Counterparts in the Nucleus Accumbens

The high doses of caffeine used in these previous studies lead to a behavioral depression in experimental animals (see Daly, 1993). Therefore the induction of IEG expression might reflect behavioral depression rather than the behavioral stimulation that is the basis for the widespread human use of caffeine. It is known that the basal expression of mRNA for NGFI-A (Milbrandt, 1987) and NGFI-B (Milbrandt, 1988) is relatively high in striatum (Watson and Milbrandt, 1990; Schlingensiepen et al., 1991; Worley et al., 1991; Bhat et al., 1992). Several studies have shown that the striatal levels of NGFI-A mRNA can be regulated via dopaminergic transmission and an increase in the expression of the gene is seen following treatment with D_1 agonists, D_2 antagonists, and indirect dopamine agonists like cocaine and amphetamine (Cole et al., 1992; Moratalla et al., 1992; Nguyen et al., 1992). In addition, it has been reported that a significant reduction of NGFI-A mRNA occurs following chronic treatment with cocaine (Bhat et al., 1992).

Two recent studies examined the expression of mRNA for NGFI-A and NGFI-B in an attempt to reveal effects of low, behaviorally relevant doses of caffeine (Svenningsson et al., 1995a, 1997c). They showed that lower doses of caffeine (7.5–25 mg/kg) decrease the expression of mRNA for NGFI-A and NGFI-B in striatum (see Fig. 5). Indeed, the effect seen at the lowest dose was almost 75% of that maximally observed, suggesting that the threshold effect may be on the order of a few milligrams

per kilogram. This may be the first evidence for direct neurochemical changes induced by such low, clearly stimulant doses of caffeine. As noted above, the only known biochemical action of caffeine, in the concentrations reached following administration of doses similar to those attained during normal human caffeine consumption, is blockade of adenosine receptors. Because the effect was most clear-cut in the striatum, where A_{2A} receptors are abundant, the data suggest that antagonism at adenosine A_{2A} receptors plays an important role in mediating the effects of caffeine. This is further supported by the finding that the caffeine-induced changes are located specifically to the striatopallidal neurons, which express A_{2A} receptors in high abundance. It has also been shown that the effect of a low dose of caffeine can be mimicked by the selective adenosine A_{2A} receptor antagonist SCH 58261, but not by the selective adenosine A_1 receptor antagonist 1,3-dipropyl-8-cyclopentylxanthine (DPCPX; Fig. 5) (Svenningsson et al., 1997c).

There is a parallelism between caffeine (or SCH 58261)-induced increase in locomotion and a decrease in the expression of the mRNA for some IEGs in the striatum (Svenningsson et al., 1995a, 1997c). The parallelism does not necessarily imply a direct causal relationship. Clearly the fall in mRNA cannot be the cause of the altered motor behavior since the latter occurred very rapidly. Conversely, the alteration in locomotor behavior is unlikely to cause the change in mRNA expression, because other drugs such as amphetamine cause an increase in locomotor behavior and an increase in the expression of mRNA for NGFI-A (Svenningsson et al., 1995a). The possibility exists, however, that the parallelism may be due to the fact that a single mechanism is the cause of a change both in mRNA and in locomotion after caffeine.

There is reason to believe that a reduction of intracellular levels of cyclic AMP is important for the observed decrease in the expression of the IEGs, because both NGFI-A and NGFI-B have CRE-like binding sites in their 5′ flanking sequence (Watson and Milbrandt, 1989; Sheng and Greenberg, 1990). Adenosine A_{2A} receptors are coupled to G-proteins that activate adenylyl cyclase. By antagonizing the actions of adenosine at these receptors, caffeine would decrease intracellular cyclic AMP levels. Dopamine D_2 receptors are coupled to G_i-proteins, and decrease the levels of cyclic AMP. It should be pointed out that a D_2 agonist will be able to depress cyclic AMP formation only if there is a high basal rate of cyclic AMP generation. Adenosine acting on A_{2A} receptors is a probable mediator of such basal cyclic AMP generation (see Fig. 4).

These considerations focus the attention on the cyclic AMP system in the basal ganglia. Indeed, there is evidence that cAMP-dependent protein kinase is very important in the acquisition of cocaine self-administration and also in relapse into cocaine-seeking behavior (Self et al., 1998). As illustrated in Fig. 4, cAMP formation is
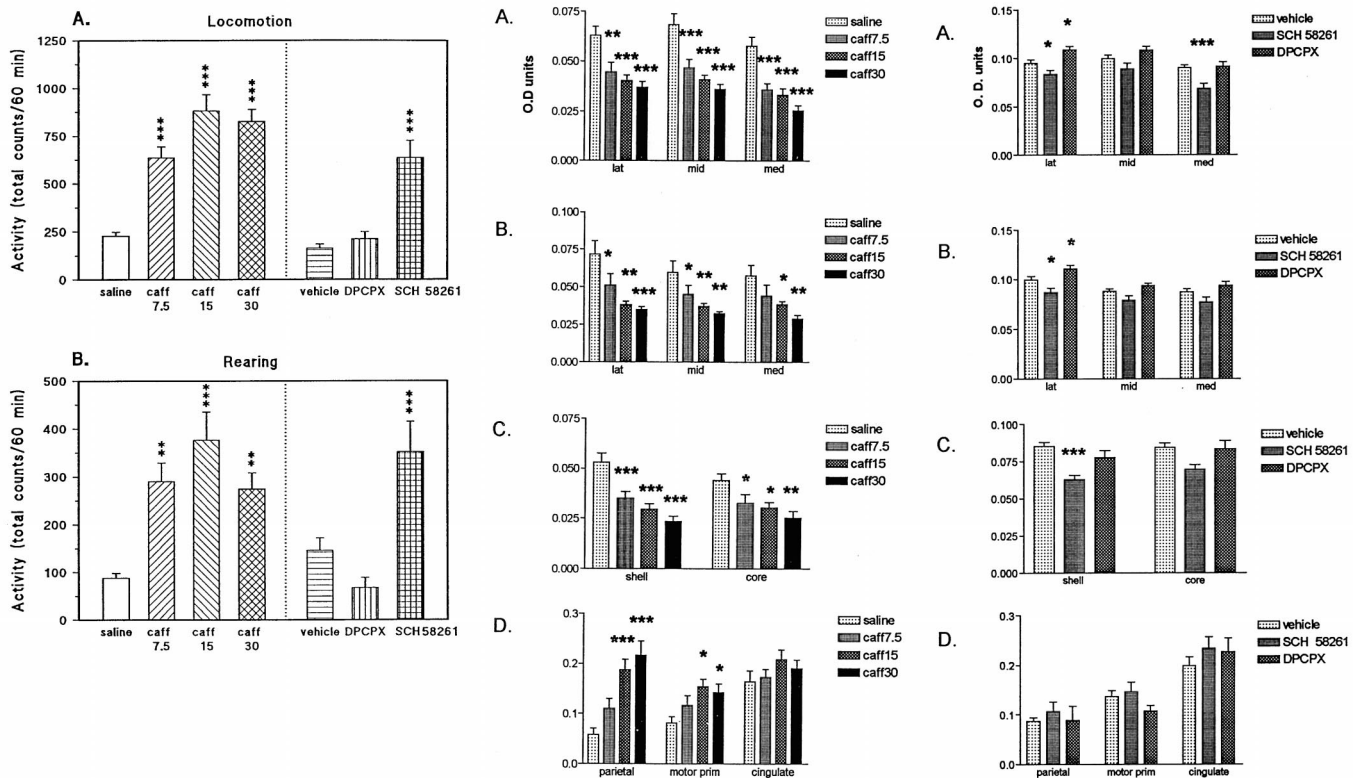
FIG. 5. The effect of low doses of caffeine, of SCH 58261, and of DPCPX on NGFI-A expression in striatum and cortex. Left, the effect of increasing doses of caffeine (7.5, 15, or 30 mg/kg i.p.) on locomotion and rearing. Middle, the effect of caffeine on the expression of NGFI-A (measured in arbitrary optical density units; O.D.) in the same animals in the dorsal caudate putamen (upper panel–A), ventral caudate putamen (upper middle panel–B), nucleus accumbens (lower middle panel–C), and in several areas of cortex (lower panel–D). Right, the NGFI-A expression (in optical density units; O.D.) in the animals given the adenosine A_{2A} antagonist SCH 58261 or the A_1 antagonist DPCPX in the same brain regions. $*p < .05$; $**p < .01$; $***p < .001$. Reprinted with permission from Elsevier Science [Svenningsson P, Nomikos GG, Ongini E and Fredholm BB (1997c) Antagonism of adenosine A2A receptors underlies the behavioural activating effect of caffeine and is associated with reduced expression of messenger RNA for NGFI-A and NGFI-B in caudate-putamen and nucleus accumbens. *Neuroscience* **79:**753–764].

stimulated via D_1 receptors in the GABAergic neurons of the direct pathway, whereas adenosine A_{2A} receptors mediate the important cAMP-raising signal in the neurons of the indirect pathway. Additional support for this scheme has recently been provided by the observation that D_1 agonists and A_{2A} agonists cause additive effects on striatal cAMP and on cAMP-dependent phosphorylation of DARPP-32 (Svenningsson et al., 1998a).

Bidirectional changes in gene expression following low and high doses of caffeine were also found for *jun*-B. The basal expression of *jun*-B is known to be relatively high in striatum (Mellstrom et al., 1991), and it has been reported that the expression of this IEG increases markedly following administration of a high dose of caffeine (Svenningsson et al., 1995b). Interestingly, it has been reported that cyclic AMP can regulate also the expression of *jun*-B (de Groot et al., 1991).

A working hypothesis is illustrated in Fig. 4. It is assumed that the level of cyclic AMP is important to determine the expression of mRNA for NGFI-A, NGFI-B, and Jun B in striatopallidal neurons. It is further assumed that the rate of cyclic AMP production is importantly controlled by adenosine, acting on A_{2A} receptors to stimulate adenylyl cyclase, and by dopa-

mine, acting on D_2 receptors to inhibit the enzyme. In agreement with this basic hypothesis, the D_2 receptor agonist quinpirole was found to induce a marked reduction of the expression of mRNA for NGFI-A and NGFI-B. Quinpirole does not alter the expression of c-*fos* (Paul et al., 1992) unless c-*fos* expression is enhanced, e.g., by reserpine treatment (Cole and Di Figlia, 1994). Caffeine (7.5–25 mg/kg) had an effect of equal magnitude, and its effect was not clearly additive to that of quinpirole. Because the effect of caffeine was confined to the striatopallidal neurons, the data suggest that these neurons are the target also for quinpirole.

It is known that neuroleptic drugs with D_2 antagonistic properties cause a rapid and transient increase in IEG expression; this effect has been attributed to a removal of an inhibitory D_2 receptor tone (Robertson et al., 1992; Merchant and Dorsa, 1993). In one study (Svenningsson et al., 1998b), haloperidol was given with or without caffeine and the animals were sacrificed 30 min later. Under these circumstances the expected increase in IEGs was observed after the D_2 antagonist. The effect of the D_2 antagonist was reduced by caffeine in the dorsomedial striatum and nucleus accumbens, but it was increased in the caudal part of striatum (Sven-

ningsson et al., 1998b). This suggests that caffeine not only acts on the basal ganglia neurons but also affects the striatal inputs. In another study (Svenningsson et al., 1995a) the D_2 receptor antagonist raclopride was given 4 h before sacrifice, and then there was no significant effect of the antagonist per se, probably because IEG levels had returned to control by this time. Furthermore, raclopride did not inhibit the depressant effect of caffeine given simultaneously with raclopride (Svenningsson et al., 1995a). These findings can be explained if adenosine and dopamine are both tonically active at their respective receptors. Thus, when dopamine receptors are blocked with raclopride, the stimulatory effect of adenosine is unhampered, leading to a transient increase in the IEG expression; when the adenosine receptors are also blocked, gene expression is brought down to essentially normal levels. The finding is less easy to explain if it is assumed that the major effect of adenosine A_{2A} receptor stimulation is to regulate signaling via the D_2 receptors. Thus, we have to assume that adenosine plays an important role in regulating gene expression in striatopallidal neurons that is independent of its established ability to influence the affinity of dopamine as an agonist at D_2 receptors (Ferré et al., 1992). The scheme in Fig. 4 also indicates that GABA release in the pallidum may be regulated by adenosine and dopamine in opposite directions, and as noted above, studies of GABA release support this proposal.

Given that adenosine acting on A_{2A} receptors is expected to increase the release of GABA in globus pallidus, caffeine is expected to decrease it. As a consequence of the decreased release of the inhibitory transmitter, caffeine is then also expected to increase activity in this brain area. This contention has been borne out in studies examining the expression of IEGs in globus pallidus following caffeine or selective adenosine A_{2A} receptor antagonists (Le Moine et al., 1997; Svenningsson and Fredholm, 1997). Furthermore, there are important synergistic effects of adenosine A_{2A} receptor antagonism and stimulation of dopamine D_1 receptors (Pinna et al., 1996; Le Moine et al., 1997). It is also of potential relevance that the human adenosine A_{2A} receptor gene has been linked to a potential schizophrenia locus on chromosome 22 (Deckert et al., 1997). If this tentative identification holds up, the link between adenosine and dopamine-related functions would be strengthened.

The link between adenosine A_{2A} receptors and dopamine-related effects in the striatum is further supported by the finding that a selective adenosine A_{2A} receptor agonist, 2-[(2-aminoethylamino)carbonylethylphenylethylamino]-5′-N- ethylcarboxamido adenosine (APEC), can antagonize the motor stimulant effects of amphetamine. The A_{2A} agonist also reduced the effects of amphetamine on c-Fos in nucleus accumbens core and shell (Turgeon et al., 1996). These authors also demonstrated effects of an A_1 receptor agonist and thus supported several previous reports that not only A_{2A} but also A_1 receptors are important in the regulation of striatal function (Ferré et al., 1997). Indeed, blockade of adenosine A_1 receptors has been shown to potentiate the motor stimulation afforded by a dopamine D_1 receptor agonist (Popoli et al., 1996b). Conversely, stimulation of A_1 receptors blocks the EEG arousal afforded by D_1 receptor stimulation (Popoli et al., 1996a).

IV. Actions of Caffeine on Brain Functions and Behavior

Having discussed the molecular and neuronal actions of caffeine, especially as they relate to a primary effect on adenosine receptors, it is important to consider some actions at a more integrated level. Even though the primary action of caffeine may be to block adenosine receptors this leads to very important secondary effects on many classes of neurotransmitters, including noradrenaline, dopamine, serotonin, acetylcholine, glutamate, and GABA (Daly, 1993). This in turn will influence a large number of different physiological functions. It would clearly be outside the scope of this review to cover all aspects of caffeine action in the CNS. Nonetheless, some specific aspects need to be brought forward as they relate directly or indirectly to the issue at hand. Below we will briefly consider a set of such responses and attempt to relate them to the primary actions of caffeine. Finally, we will briefly comment upon the similarities and dissimilarities between caffeine and known addictive drugs such as cocaine, morphine, and nicotine.

A. Activation of Dopaminergic Transmission and Effects on Motor Behavior

The interaction between adenosine A_{2A} and dopamine D_2 receptors highlighted above could provide a mechanism for several actions of caffeine and some of its metabolites on dopaminergic activity. Thus, an inhibition of A_{2A} receptors by caffeine would be expected to increase transmission via dopamine at D_2 receptors (Ferré et al., 1992). There is indeed ample evidence that caffeine (and other adenosine receptor antagonists) can increase behaviors related to dopamine. The first demonstration of an adenosine-dopamine interaction on behavior was the finding that several adenosine receptor antagonists, including caffeine, theophylline, and isobutyl-methylxanthine, could increase dopamine receptor-activated rotation behavior (Fredholm et al., 1976). This finding was preceded by the observation that theophylline could enhance such rotation behavior (Fuxe and Ungerstedt, 1974), but in that study the authors proposed that the mechanism was phosphodiesterase inhibition. In the later study (Fredholm et al., 1976) this possibility was discounted. This type of finding has since been repeatedly confirmed and elaborated (see Daly, 1993; Ferré et al., 1992; Ongini and Fredholm, 1996). Indeed, dopamine receptor antagonists can inhibit the stimulatory effects of caffeine on motor behavior (Fredholm et al., 1983; Herrera-Marschitz et al., 1988; Garrett and Holtzman, 1994b), and long-term treatment of rats with caffeine re-

duces the effects of both caffeine and dopamine receptor agonists (Garrett and Holtzman, 1994a).

Besides the direct effects on striatopallidal neurons mediated via an antagonism of A_{2A} receptors, caffeine—at least at high doses—has been reported to influence the turnover of dopamine [for review see Nehlig and Debry (1994)]. Adenosine A_1 receptors (in contrast to adenosine A_{2A} receptors) have been shown to influence dopamine release in slices of the striatum (Jin et al., 1993; Jin and Fredholm, 1997). Caffeine has been reported to cause a dose-dependent (30–75 mg/kg) increase in dopamine in the striatum (Morgan and Vestal, 1989). In that study electrochemistry was used, which presents a potential problem since caffeine itself appears to influence the response of the recording electrode (F. Gonon, personal communication). In a recent study, microdialysis techniques were used to study this question (Okada et al., 1997). Perfusion with a solution containing caffeine (5–50 μM in perfusate, probably corresponding to a five times lower level in brain) caused a time- and concentration-dependent increase in dopamine levels. This was mimicked by the selective adenosine A_1 receptor antagonist cyclopentyltheophylline. Both drugs caused a 30 to 40% increase. Adenosine A_1 agonists, but not adenosine A_{2A} agonists, depressed the dopamine levels (Okada et al., 1997). Because the drugs were administered locally in the striatum, the effects are probably exerted at the presynaptic A_1 receptors. In addition to these presynaptically located adenosine A_1 receptors, A_1 receptors are also present in the substantia nigra and in the VTA (Fastbom et al., 1987; Johansson et al., 1993a), where they regulate the firing of dopamine (DA) neurons (Ballarin et al., 1995). In these regions of the brain there is a marked discrepancy between the distribution of the receptor and the corresponding mRNA. This suggests that many of the adenosine A_1 receptors in the area of the DA cell bodies are located not on the dopaminergic neurons, but on the terminals of the input neurons. There, they could negatively influence excitatory input to these nuclei.

Caffeine has been shown to decrease the activity of dopaminergic neurons in the VTA (Stoner et al., 1988), but not the dopaminergic neurons in substantia nigra. This was interpreted as evidence that caffeine increased the release of DA, which in turn acted on DA receptors to depress firing of the neurons. However, a direct injection of caffeine into the VTA does not increase release of DA in the nucleus accumbens (Gonon and Svenningsson, unpublished data). Furthermore, the reported effect of caffeine on VTA neurons (Stoner et al., 1988) was observed only when excessively high concentrations of caffeine were used—concentrations that as we will see below do not stimulate motor behavior or produce reinforcement, but instead have the opposite effect. Thus, caffeine may not act to stimulate motor behavior by regulating firing of DA neurons. This conclusion is reinforced by a comparison of the effects of caffeine in low,

behaviorally stimulant doses of caffeine (Svenningsson et al., 1995a, 1997c) and of an electrical activation of the dopaminergic neurons from VTA to nucleus accumbens (Chergui et al., 1996, 1997). The latter is accompanied by an increase in the DA levels in accumbens and with an increase in several IEGs in the nucleus accumbens. The IEG increases are confined to the dopamine D_1 receptor-containing cells and are blocked by D_1 receptor antagonists (Chergui et al., 1996, 1997). By contrast, in the dopamine D_2 receptor-expressing cells, caffeine does not increase IEGs and in fact decreases the expression of constitutively active IEGs. This effect is uninfluenced by D_1 antagonists. Hence, caffeine differs in important respects from other stimulant drugs such as cocaine and amphetamine.

It can be concluded that the only important interaction between caffeine in relevant doses and the dopaminergic transmission is based on enhancement of postsynaptic dopamine D_2 receptor transmission and of the glutamatergic input. The previously emphasized enhancement of dopamine release occurs only at high doses of caffeine and is therefore unrelated to the stimulant effects of caffeine, which occur only at low doses.

It is well known that the striatum is strongly involved in the regulation of motor behavior in animals, and presumably in humans, and the ability of caffeine to stimulate motor behavior is well documented and summarized (see Waldeck, 1975; Nehlig et al., 1992; Daly, 1993). Here it will suffice to point out a few relevant facts. Motor stimulation has been studied either by examining spontaneous locomotion or by examining the rotation behavior that can be elicited by, for example, dopamine receptor agonists in animals with unilateral lesions of the nigrostriatal dopamine pathway. The data in those two models are not exactly analogous and we will deal with them separately.

In both rats and mice the effect of caffeine on spontaneous locomotion is markedly biphasic (see Fig. 6). The threshold effect is 1 to 3 mg/kg and the peak effect is seen between 10 and 40 mg/kg (see Nikodijeviç et al., 1993; Garrett and Holtzman, 1994b). As in the case of cocaine, stimulation of motor behavior occurs at roughly similar doses as those needed for reinforcement (Bedingfield et al., 1998). In the case of cocaine the two effcts are positively correlated, but this is not the case for caffeine, suggesting differences in mechanism of action (Bedingfield et al., 1998). The effect of caffeine is shared by several other xanthines, and their potency is much better correlated with adenosine receptor blockade than with phosphodiesterase inhibition (Choi et al., 1988). Several adenosine analogs are motor depressants when given systemically or locally into the striatum (see Daly, 1993). The effect of caffeine is shared by the nonxanthine, nonselective adenosine receptor antagonist, CGS 15943, but not by the selective adenosine A_1 receptor antagonist DPCPX (Griebel et al., 1991). Locomotor stimulation is also brought about by the nonxanthine,
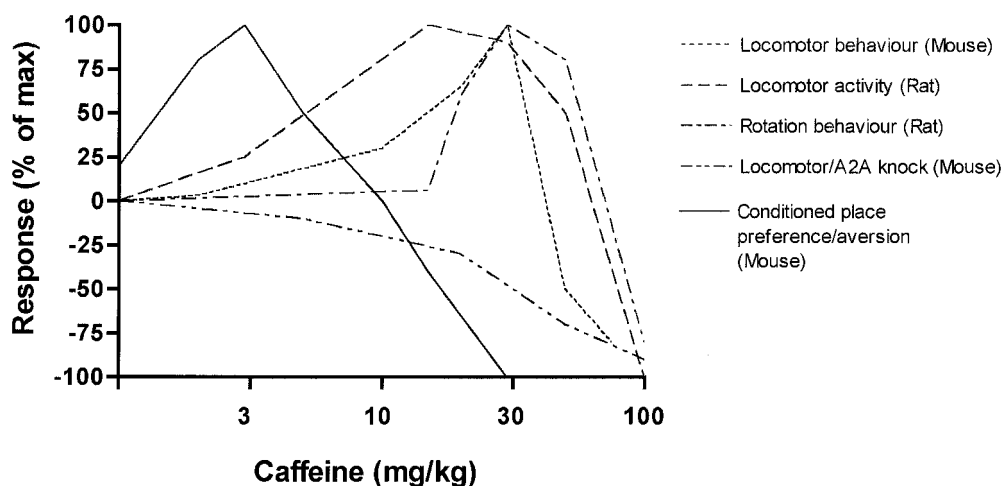
FIG. 6. Biphasic effects of caffeine on rodent behavior. For further details, see text.

selective, adenosine A_{2A} receptor antagonist SCH 58261 (Svenningsson et al., 1997c). The direct injection of an adenosine A_{2A} receptor agonist into the nucleus accumbens leads to a decreased locomotion (Barraco et al., 1993; Hauber and Münkle, 1997). The effects of caffeine are synergistic with actions of dopamine or dopaminergic drugs injected into the nucleus accumbens (Andén and Jackson, 1975; Garrett and Holtzman, 1994b). Both selective dopamine D_1 and dopamine D_2 receptor antagonists reduced locomotion, the former being more efficacious (Garrett and Holtzman, 1994b). Under these circumstances an effect of an adenosine A_1 antagonist is also revealed and is manifested as a selective enhancement of locomotion induced by a D_1 receptor agonist (Popoli et al., 1996b).

As noted above caffeine can also induce contraversive rotation in animals with unilateral nigrostriatal lesions and it thus mimics the effects of dopamine receptor agonists (Fuxe and Ungerstedt, 1974; Fredholm et al., 1976). The effect is dose-dependent (Fredholm et al., 1983; Herrera-Marschitz et al., 1988; Garrett and Holtzman, 1995). If the total number of rotations is recorded over a fixed time period, the curve shows the inverted U-shape with a maximum close to 30 mg/kg (Garrett and Holtzman, 1994b). However, the effect of the high doses is very protracted, and, if rotation is recorded over a longer period, say 12 h, the maximum is seen at over 50 mg/kg (Herrera-Marschitz et al., 1988). The rotational behavior induced by caffeine varied between animals, but there was a strong correlation between rotation induced by the dopaminergic agonist apomorphine and that produced by caffeine (Casas et al., 1989). All these findings give good reason to assume a close relationship between the mechanisms that underlie caffeine-induced rotation and dopaminergic rotation. Several studies have tried to pinpoint the mechanism further.

Intrastriatal injection of an adenosine analog produces rotation in the opposite direction (Green et al., 1982; Brown et al., 1991) to an injection of caffeine (Herrera-Marschitz et al., 1988; Josselyn and Beninger, 1991). Drugs that raise the level of adenosine, including adenosine transport inhibitors and inhibitors of adenosine deaminase, reduce the rotation response induced by dopaminergic drugs (Fredholm et al., 1976, 1983). These data have been taken as support of the general idea that rotation behavior induced by caffeine is related to adenosine receptor blockade. The systemic administration of an adenosine analog also reduces rotation behavior (Fredholm et al., 1983). Furthermore, potent phosphodiesterase inhibitors that do not act as adenosine receptor antagonists reduce rather than enhance rotation behavior (Fredholm et al., 1976, 1983). The effect of caffeine is shared by some other xanthines, including its metabolites theophylline and paraxanthine (Fredholm et al., 1976; Garrett and Holtzman, 1995). However, isobutylmethylxanthine produces limited (Fredholm et al., 1976) or no (Garrett and Holtzman, 1995) effect despite the fact that it is a potent adenosine receptor antagonist. Perhaps this could be accounted for by its high potency as a phosphodiesterase inhibitor. However, 8-phenyltheophylline produced only limited rotation despite the fact that it lacks appreciable phosphodiesterase inhibitory effect but is a potent adenosine receptor antagonist. The reason may instead be that it penetrates only poorly into brain (Fredholm et al., 1983). Although the nonselective nonxanthine antagonist CGS 15943 mimics caffeine actions on spontaneous locomotor behavior, it is much less potent than caffeine in inducing rotation behavior (Garrett and Holtzman, 1994b; Pinna et al., 1996). This was taken as evidence that adenosine receptor antagonism may not be the only mechanism by which caffeine causes an increased rotation behavior (Garrett and Holtzman, 1994b). CGS 15943 did, however, potentiate the effect of a D_1 receptor agonist (Pinna et al., 1996). Further studies of CGS 15943, including an examination of its pharmacokinetics, are warranted.

More recent studies have tried to examine the roles of specific adenosine and dopamine receptors by using se-

lective agonists and antagonists. The adenosine A_1-selective antagonists 8-cyclopentyltheophylline and DPCPX potentiate the response to amphetamine (Popoli et al., 1994) and to the selective dopamine D_1 agonist SKF 38393 (Pinna et al., 1996; Pollack and Fink, 1996). The selective adenosine A_{2A} receptor antagonist SCH 58261 also potentiates the response to a D_1 agonist (Pinna et al., 1996), as does the somewhat A_{2A}-selective antagonist 3,7-dimethyl-1-propylargylxanthine (Pollack and Fink, 1996). The enhancement of the behavioral response was mirrored by an effect on IEGs in the striatum and globus pallidus (Pinna et al., 1996; Pollack and Fink, 1996; Fenu et al., 1997). The response to dopamine agonists is blocked by adenosine A_{2A} and A_1 agonists (Morelli et al., 1994; Popoli et al., 1994). Neither the selective A_1 antagonist DPCPX nor the selective A_{2A} receptor antagonist SCH 58261 had any effect per se (Pinna et al., 1996).

It is clear that particularly adenosine A_{2A} receptor-blocking drugs can enhance the activity of dopaminergic drugs in the rotation model (see Ongini and Fredholm, 1996; Ferré et al., 1997; Richardson et al., 1997). This is important since it suggests the possibility of novel therapy in Parkinson's disease. It is, however, also clear that adenosine A_1 receptor modulates the response. Furthermore, there are several discrepancies in the literature concerning the ability of adenosine receptor antagonists to produce rotation per se. It is conceivable that some of this variability relates to the extensiveness of the lesions and also to the tone of the dopaminergic innervation on the contralateral side. Finally, it must be borne in mind that the rotation behavior to both dopaminergic drugs and adenosine receptor antagonists requires priming of the system by a drug that activates D_1 receptors. The effect is long-lasting and is blocked by NMDA receptor antagonists (Morelli et al., 1996).

B. Caffeine and Mood

Mood is a complex and poorly defined psychic phenomenon. This holds for the underlying psychological and behavioral functions as well as for the difficulties of assessment. Recently, standardized instruments such as the Profile of Mood States (POMS), the Drug-Effect Questionnaire for the assessment of liking a medication, different Visual Analog Scales for rating different aspects of the subjective state have been used increasingly for the study of mood.

The effects of caffeine on mood have been studied in human subjects. There is ample evidence that lower doses (20–200 mg) of caffeine are reliably associated with "positive" subjective effects even in the absence of acute withdrawal effects. The subjects report that they feel energetic, imaginative, efficient, self-confident, and alert; they feel able to concentrate and are motivated to work but also have the desire to socialize (see Griffiths et al., 1990; Silverman et al., 1994; Griffiths and Mumford, 1995). Schoolchildren consuming more that 50 mg of caffeine per day, mainly from soft drinks, report higher wakefulness than a control group consuming less than 10 mg per day (Goldstein and Wallace, 1997). The relative failure to demonstrate such effects in subjects that regularly consume coffee contrasts with the common perception of regular caffeine consumers (Goldstein and Kaizer, 1969). The apparent discrepancy may be related to the importance that investigators and normal consumers place on the small performance benefits discussed elsewhere. Another aspect is that the caffeine user may especially appreciate performance benefits when he or she is less alert than usual. For example, in a recent study subjects with upper respiratory tract illness ("common cold") were not only feeling more alert after consuming caffeine but were also performing better in a reaction time task, something they did not do when they were feeling well (Smith et al., 1997).

There are well-documented effects of caffeine on anxiety in humans: these have recently been summarized (Hughes, 1996). There is much less information on the effects of caffeine on anxiety in animals. In particular, we do not know much about the possible mechanism(s) involved. It is known that high concentrations of caffeine can decrease the binding of benzodiazepines, but it is generally believed that this effect on the $GABA_A$ receptor is not directly involved in producing anxiety (see Daly, 1993). There are, however, effects of caffeine on $GABA_A$ receptor channels (Lopez et al., 1989) observed at doses above 20 mg/kg, in the absence of effects on diazepam binding. Thus, further studies to explain this observation are needed. Caffeine might affect $GABA_A$ receptors indirectly. It is known that adenosine, acting via A_1 receptors, can regulate the release of many different neurotransmitters, including glutamate. If the effect of adenosine is blocked, excitatory transmission would be enhanced, which could directly or indirectly influence GABAergic transmission.

About 25 years ago Greden (1974) noted that outpatients undergoing treatment for psychiatric disorders who consumed more than 1000 mg of caffeine per day had symptoms of generalized anxiety. This was denoted caffeinism and was suggested to present some diagnostic problems. Indeed caffeinism has been added to DSM-III and DSM-IV. In intervention studies the administration of high (but not low) doses of caffeine leads to a clear increase in measures of anxiety (Stern et al., 1989), which, however, are not accompanied by changes in noradrenaline turnover (Charney et al., 1984). The anxiogenic effects were greater in patients with panic disorders (Boulenger et al., 1984; Charney et al., 1985; DeMet et al., 1989), and patients who report being anxious in response to caffeine had higher prestudy anxiety scores (Lee et al., 1985). Patients with high anxiety scores due to depression do not appear to be supersensitive to caffeine (Boulenger et al., 1984). An increased anxiogenic response to caffeine was related to an increased sensitivity to caffeine as an enhancer of gustatory signals

(DeMet et al., 1989). This was interpreted as evidence that patients with panic disorders have an altered sensitivity of A_1 receptors, because previous data had implied a role for adenosine receptors in this response (Schiffman et al., 1985). There is no independent evidence that this is the case.

Despite all the cited evidence for an effect of caffeine on anxiety, in a rather large population study there was no clear relationship between reported caffeine intake and anxiety (Eaton and McLeod, 1984). Furthermore, there was no relationship to the intake of caffeine in patients with anxiety. In fact, subjects with high anxiety scores tended to have a lower caffeine intake (Lee et al., 1985; Rihs et al., 1996). Thus the preferred caffeine dose was negatively related to prestudy anxiety scores (Griffiths and Woodson, 1988a). Nonetheless, a subpopulation of patients with anxiety do improve when they abstain from caffeine. Thus, it seems clear that high doses of caffeine can induce a state of anxiety and that there are considerable differences between individuals in what constitutes a high, anxiogenic dose of caffeine. Most individuals seem to adapt their caffeine intake to, e.g., their susceptibility to its anxiogenic effects.

The anxiogenic effects of caffeine are related not only to the dose of caffeine but also to plasma levels (Boulenger et al., 1987), but the level of anxiety was not related to measured plasma levels of adenosine. This does not, however, mean that adenosine receptors are not involved. In the study mentioned, adenosine levels were very high, probably indicating formation of adenosine during sampling, and moreover there is no clear relationship between brain and plasma adenosine levels. The recent demonstration that mice with a targeted disruption of adenosine A_{2A} receptors exhibit increased anxiety (Ledent et al., 1997) instead provides good evidence that adenosine receptors are involved in the anxiogenic effects of caffeine. Precisely how these effects are brought about is not known, but it is known that caffeine produces anxiety via a mechanism that is quite different from that used by the α_2 adrenoceptor antagonist yohimbine, because the two drugs antagonize each other via complex paradigm-dependent interactions (Baldwin et al., 1989).

The possible link between caffeine intake and other psychiatric diagnoses is less evident. Among psychiatric patients, caffeine consumption is highest among diagnosed schizophrenics and lowest among depressed patients and those with anxiety disorders (Rihs et al., 1996). In view of the interactions between adenosine and DA receptors, it is possible that the intake of caffeine represents an attempt to counteract the actions of the neuroleptic medication. Indeed there are reports that high caffeine intake can exacerbate the symptoms of schizophrenia (Mikkelsen, 1978). The relationship between caffeine intake and depression is also poorly understood and poorly studied. Sleep disorders constitute a major predictor for depression (Chang et al., 1997), and

caffeine is known to affect sleep. However, the relationship between poor sleep and subsequent depression holds, even after correction for the intake of caffeine (Chang et al., 1997). Among hospitalized patients there was a correlation between symptoms of depression and caffeine intake (Rihs et al., 1996). Again it is difficult to know if this related to the actions of the antidepressant medication: some of the side effects can probably be counteracted by caffeine. In a study of Japanese medical students, caffeine intake was associated with fewer depressive symptoms among female, but not male students, and in a large prospective study, coffee drinking was negatively correlated with suicide (Kawachi et al., 1996). These findings can be interpreted in two diametrically different ways: 1) caffeine decreases symptoms of depression, including the risk of suicide or 2) individuals with depressive symptoms choose to take less caffeine (in much the same way as anxious patients do). Only a carefully controlled intervention study could possibly elucidate these questions.

C. Effects of Caffeine in the Cortex and Hippocampus— Information Processing and Performance

In the rat, cortical electrical activity is stimulated by caffeine (Phillis and Kostopoulos, 1975; Arushanian and Belozertsev, 1978). In the cat, caffeine produces an activation of the cortical EEG similar to the activity recorded at the time of physiological awakening or to the activity produced by direct stimulation of the reticular formation (Jouvet et al., 1957), a structure which plays an important role in vigilance and awakening.

Methylxanthines elevate the excitability of rat hippocampal slices by antagonizing the actions of adenosine (Dunwiddie et al., 1981; Greene et al., 1985) and activate the theta rhythm of the EEG in rabbit hippocampus (Popoli et al., 1987). Adenosine depresses the development of long-term potentiation (Arai et al., 1990), whereas xanthines with adenosine receptor antagonistic effects have been reported to have the opposite effect (Arai et al., 1990; Tanaka et al., 1990). Caffeine lengthens the postfiring duration in the hippocampus, and this effect lasts longer than the changes induced by caffeine on the EEG (Dunwiddie et al., 1981; Greene et al., 1985; Popoli et al., 1987). High doses (100 mg/kg or above) of caffeine provoke electrical modifications in the hippocampus similar to those that are recorded during generalized seizures.

The effects of caffeine on cortical and hippocampal activity provide a basis for examining possible cognitive effects of caffeine. There are a few animal studies that report improved performance in a water Y-maze model or a visual discrimination task after caffeine (see Daly, 1993). Later studies have indicated that blockade of adenosine A_1 receptors is more important than blockade of A_2 receptors to produce this effect (Suzuki et al., 1993; Von Lubitz et al., 1993a; Ohno and Watanabe, 1996). The effect of a direct intrahippocampal injection of an A_1

receptor agonist is to increase the number of errors related to working memory (Ohno and Watanabe, 1996). Interestingly, there was a major difference in the effect of chronic treatment. If an A_1 receptor antagonist was injected daily, the beneficial effect decreased and a slight deterioration was observed (Von Lubitz et al., 1993a). Conversely, long-term treatment with an agonist actually improved performance dramatically (Von Lubitz et al., 1993a).

The effects of caffeine on human information processing have been well reviewed (van der Stelt and Snel, 1993). A large number of studies has been performed on human subjects (Estler, 1976; Daly et al., 1993). As for most effects of caffeine, the dose-response curve is U-shaped—doses of 500 mg causing a decrease in performance although lower doses have positive effects (Kaplan et al., 1997). Despite this, increases in caffeine consumption over an already high normal level (400–1000 mg/day) did not impair performance even in a complex setting (Streufert et al., 1997). Revelle and coworkers (1980) showed a complex interaction between the effects of caffeine on performance and parameters such as personality and time of day. Thus, the effects of caffeine are related to a level of arousal (Anderson and Revelle, 1982) and largely follow the so-called Yerkes-Dodson law that postulates that the relationship between arousal and performance follows an inverted U-shape curve. An increase in arousal improves performance of tasks where relatively few sources of information have to be monitored, particularly under conditions when the need for selective attention is stressed by time pressure. When, on the other hand, multiple sources of information or working memory have to be used, an increase in arousal and attention selectivity has no apparent beneficial effect on performance, which may consequently even decrease (see Kenemans and Lorist, 1995). Thus, it was concluded that caffeine 1) increases cortical activation, 2) increases the rate at which information about the stimulus accumulates, 3) increases selectivity particularly with regard to further processing of the primary attribute, and 4) speeds up motor processes via central and/or peripheral mechanisms (Kenemans and Lorist, 1995). In a study where caffeine significantly improved performance in a vigilance test, caffeine neither increased nor decreased the mood changes that occur after such stressful tasks (Temple et al., 1997).

Therefore it can probably be concluded that caffeine in doses that correspond to a few cups of coffee "improves behavioral routine and speed rather than cognitive functions" (Bättig et al., 1984). This probably indicates that many animal models test for psychomotor function rather than cognition, but it is of course very different from claiming that "caffeine bestows little if any benefit on... psychomotor performance" (James, 1991). The small benefits that can be shown may be considered of value by some caffeine users, and it can be expected from the above considerations that, particularly, individuals with a low level of arousal (high scores on the impulsivity subscale of Eysenck) should experience such a beneficial effect. Indeed, such individuals appear to consume more caffeine (Rogers et al., 1995). Conversely, in situations with a high level of stress, caffeine might prove detrimental, but there is no evidence that this is the case (Smith et al., 1997).

In order to perform adequately, an animal (or human) must be able to filter out irrelevant sensory input. A deficiency in this regard is believed to be a characteristic of schizophrenic subjects (Koch and Hauber, 1998). Filtering ability can be assessed by so called prepulse inhibition of the acoustic startle response (see Hauber and Koch, 1997; Koch and Hauber, 1998). Such prepulse inhibition can be attenuated by systemic or intra-accumbens administration of apomorphine, and this is counteracted by an injection of the adenosine A_{2A} agonist CGS 21680 into the nucleus accumbens (Hauber and Koch, 1997). These results suggest that caffeine might, via an action on adenosine receptors, influence sensorimotor gating and, in this way, performance.

D. Effects on Sleep

It is well established that caffeine delays the onset of sleep (see Eichler, 1976; Snel, 1993). It can first be noted that effects on sleep are quite variable. It has been suggested that the subjects most sensitive to the effects of coffee on sleep might metabolize caffeine more slowly than the others (Levy and Zylber-Katz, 1983). Indeed, for the same amount of caffeine ingested, the plasma concentration of the methylxanthine can vary among individuals by a factor of 15.9 (Birkett and Miners, 1991). However, as discussed elsewhere in this review, there are also major differences in the sensitivity to caffeine.

Caffeine in doses corresponding to one cup of coffee taken at bedtime increases sleep latency and decreases the reported quality of sleep in parallel with small changes in the EEG pattern during sleep, especially in the non-REM deep sleep (Landolt et al., 1995a). However, also a dose of caffeine taken in the morning can have such effects the following night (Landolt et al., 1995b). Thus, in humans, concentrations of caffeine as low as 3 μM can influence sleep. Indeed sleeping problems is one of the major reasons why people, on their own initiative, cease drinking coffee (Soroko et al., 1996). There is, however, no evidence that the effects of caffeine are different in subjects with poor sleep and in those with normal sleep (Tiffin et al., 1995). Indeed, there is no clear evidence that stopping caffeine intake can eliminate the problems of poor sleep (Curless et al., 1993; Searle, 1994; Tiffin et al., 1995). It is often remarked that some people seem to have no sleep problems despite taking a regular evening dose of caffeine. This clearly emphasizes that caffeine interferes with a modulatory mechanism in sleep regulation, not with a

fundamental sleep regulatory brain circuit. It probably also reflects on the fact that regular sleeping habits are of fundamental importance in ensuring satisfactory sleep (Manber et al., 1996). If a regular caffeine intake is part of such a normal diurnal pattern, it is easy to understand how it could contribute to satisfactory sleep.

Performance, such as when driving a car, appears to be improved by caffeine in doses corresponding to 1 to 2 cups of coffee (Horne and Reyner, 1996). There is, however, some evidence to suggest that one may "pay" for this benefit with a lower restorative capacity of a nap after sleep deprivation (Bonnet and Arand, 1996). There is also evidence that caffeine improves work performance during night shift work, without severely compromising daytime sleep (Muehlbach and Walsh, 1995). The combination of a prophylactic afternoon nap and caffeine appears to maintain performance at a high level even for prolonged periods without sleep (Bonnet and Arand, 1996). Also some of the negative mood effects of prolonged sleep deprivation are reduced by caffeine (Penetar et al., 1993). The effects of caffeine on several different measures of performance after prolonged (45 h) sleep deprivation were additive to the effect of bright light (Wright et al., 1997). Because bright light is believed to reduce sleepiness by reducing melatonin, this finding indicates that caffeine acts independently of melatonin.

There is a link between adenosine and the sleep-wake cycle in rodents. Initial studies by Radulovacki and co-workers (see Radulovacki, 1985) showed that adenosine agonist increased sleep and altered the EEG pattern in a manner different from that brought about by barbiturates. The effect of adenosine analogs is mimicked by drugs that decrease adenosine elimination (O'Connor et al., 1991). Caffeine had effects opposite to those of adenosine on EEG (Yanik et al., 1987).

There are important circadian rhythms in adenosine receptors (Virus et al., 1984), adenosine-metabolizing enzymes (Chagoya de Sanchez, 1995), and in adenosine itself. Thus, in cortical areas of rat brain, including the hippocampus, adenosine levels were high during the active (dark) period (Chagoya de Sanchez et al., 1993; Huston et al., 1996), but they were also much increased in the beginning of the inactive (light) part of the diurnal cycle (Chagoya de Sanchez et al., 1993). The levels in the dopamine-rich areas of the brain decreased during the active period and increased transiently toward its end (Huston et al., 1996). This could mean that adenosine acts as a transient signal to go to sleep. More recently it has been shown that the levels of adenosine progressively increase in the cat basal forebrain with increasing sleep deprivation and then return toward basal during sleep (Porkka-Heiskanen et al., 1997).

Probably adenosine A_1 and A_{2A} receptors are involved in producing the sleep-promoting effects of adenosine, but these effects appear to be exerted in different parts of the brain. Local injections of adenosine A_1 receptor agonists in the preoptic area of the rat produced sleep, whereas an A_{2A} agonist did not (Ticho and Radulovacki, 1991). The administration of the adenosine A_1 receptor-selective agonist cyclopentyladenosine mimicked the EEG effects of sleep deprivation (Benington et al., 1995) and non-REM sleep (Schwierin et al., 1996). Systemic administration of the relatively A_1-selective antagonist 8-cyclopentyltheophylline mimicked the effect of caffeine (O'Connor et al., 1991). It has also been reported that REM sleep deprivation increases the number of A_1 receptors (O'Connor et al., 1991), even though this finding is somewhat difficult to reconcile with the ability of adenosine to decrease A_1 receptors and with the reported increase in adenosine. The site at which adenosine (and caffeine) exert these A_1 effects related to sleep is not known, but the mesopontine cholinergic neurons that are under tonic adenosine A_1 receptor control are likely candidates (Rainnie et al., 1994). Indeed, it is well established that acetylcholine turnover is increased by theophylline (Murray et al., 1982) and that caffeine can affect acetylcholine levels and metabolism in the brain (Phillis et al., 1980; Murray et al., 1982; Katsura et al., 1991; Carter et al., 1995). The caffeine-induced increase of cortical acetylcholine is dose-dependent, and the increased cholinergic activity at doses of caffeine relevant to those encountered in humans may provide a basis for the psychostimulant effects of caffeine (Carter et al., 1995). Thus, there is good evidence that adenosine acting at A_1 receptors might promote sleep, perhaps in part by decreasing activity in cholinergic neurons.

On the other hand, injection of the selective adenosine A_{2A} receptor agonist CGS 21680 into the subarachnoid space underlying the rostral basal forebrain mimicked the sleep-promoting effects of prostaglandin D_2, whereas an A_1 agonist did not (Satoh et al., 1996). Furthermore, in this study an A_{2A} receptor antagonist attenuated the sleep induced by PGD_2. It has also been shown that the selective adenosine A_{2A} receptor antagonist SCH 58261 is at least as potent as the A_1 receptor antagonist DPCPX in increasing wakefulness and in increasing the latency to REM sleep in rats (Bertorelli et al., 1996). The adenosine A_{2A} receptors in the tuberculum olfactorium/ventral nucleus accumbens are a likely site of action (Satoh et al., 1996).

From the above brief summary it is evident that the ability of caffeine to increase wakefulness is an important reason why people consume caffeine-containing beverages. It is also evident that unsatisfactory sleep is one of the reasons why individuals wish to curtail their habitual caffeine intake. Hence, effects on sleep and wakefulness are intimately linked to the way that caffeine is rated in the DSM-IV scale. It is also clear that caffeine's effects on sleep are probably related to adenosine receptor antagonism, because adenosine is likely to be one of the factors that acts as endogenous sleep promoters. It is, however, less clear precisely where in the brain these effects are exerted and whether the

receptors involved are A_1 receptors, A_{2A} receptors, or (possibly) both.

E. Effects of Caffeine on Cerebral Blood Flow and Metabolism

Caffeine given as an acute dose of 10 mg/kg increases the rates of cerebral energy metabolism in the rat. Increases are significant in all monoaminergic cell groupings, in structures of the extrapyramidal motor system, in thalamic relay nuclei, and in the hippocampus (Nehlig et al., 1984, 1986). These increases correlate well with the known effects of caffeine on locomotor activity and on the sleep-wake cycle. Moreover, caffeine-induced increases in the rates of cerebral glucose utilization are of the same amplitude and occur in the same brain regions whether caffeine (10 mg/kg) is given as the first acute dose or after a previous 2-week chronic exposure to the methylxanthine. Thus, cerebral energy metabolism does not seem to develop tolerance to the stimulant effects of caffeine. Moreover, the structures in which cerebral energy metabolism remains increased even 5 to 6 h after the last chronic i.p. administration of caffeine are the caudate nucleus and the substantia nigra pars compacta as well as the locus ceruleus and the dorsal raphe nucleus, i.e., the structures regulating motor activity as well as the sleep-wake cycle (Nehlig et al., 1986).

Conversely to its stimulant effects on brain energy metabolism, caffeine has central vasoconstrictive properties that lead to a 20 to 30% decrease in cerebral blood flow in humans [for review see Nehlig and Debry (1994)]. In newborns treated with methylxanthines for apnea, cerebral blood flow decreases of up to 21% have been reported, that can be avoided if methylxanthine-induced hypocapnea is corrected [for review see Nehlig and Debry (1994)]. In rats, the caffeine-induced decrease in cerebral blood flow is especially marked in the regions where cerebral energy metabolism increases (Nehlig et al., 1990). Thus, caffeine is one of the rare substances able to reset the level of coupling between cerebral blood flow and metabolism in favor of an increased metabolic rate at a given rate of perfusion. However, these changes are moderate and the decrease in blood flow could be compensated for by an increase in oxygen and glucose extraction, because the consumption of moderate amounts of caffeine has positive effects on alertness. The other alternative is that the metabolic increase related to caffeine exposure might only activate the anaerobic pathway of glucose degradation, as seen in several situations of physiological activation in which metabolic increases are not coupled with a commensurate increase in oxygen consumption (Fox and Raichle, 1986; Fox et al., 1988). In the latter case, metabolic activation would rely primarily on glucose whose entry into brain is always in large excess, whereas the decrease in blood flow could reflect the decrease in oxygen needs. However, this hypothesis needs to be tested.

The acute administration of 10 mg/kg caffeine leads to widespread increases in the rates of cerebral glucose utilization in the nucleus accumbens, both the shell and the core as well as in most structures of the extrapyramidal motor system, and in many limbic regions and cortices (Nehlig et al., 1984, 1986). Conversely, amphetamine, cocaine, and nicotine increase rates of cerebral glucose utilization primarily in the nucleus accumbens (Porrino et al., 1984, 1988; Stein and Fuller, 1992; Porrino, 1993; Pontieri et al., 1996), with a specific metabolic activation only in the shell and not in the core of the nucleus accumbens, as shown in some of these studies. These effects are quite specific and occur already at rather low doses (Porrino et al., 1988; Stein and Fuller, 1992; Pontieri et al., 1996). On the other hand, one of the structures most sensitive to caffeine appears to be the caudate nucleus whose metabolic activity is increased after the injection of a very low dose of caffeine (1 mg/kg) and remains increased at 5 to 6 h after the last chronic i.p. injection of 10 mg/kg caffeine in the rat (Nehlig et al., 1984, 1986). Conversely, with cocaine, amphetamine, and nicotine, increases in cerebral glucose utilization in the dorsal caudate nucleus usually appear at doses higher than those needed to induce increases in the shell of the nucleus accumbens (Porrino et al., 1984, 1988; Orzi et al., 1993; Pontieri et al., 1996).

Taken together, these data show that caffeine has rather widespread effects on cerebral functional activity in contrast to the specific effects of amphetamine and cocaine on the neural substrates believed to underlie addiction. In fact, caffeine primarily acts on the extrapyramidal motor system and on cerebral structures related to the sleep-wake cycle such as the reticular formation, raphe nuclei, and locus ceruleus (Nehlig et al., 1984, 1986). These data are in agreement with the facilitated motor output (James, 1991; Lorist et al., 1994) and the increase in wakefulness reported in humans after caffeine ingestion (James, 1991). Caffeine is also able to increase cerebral energy metabolism in the shell of the nucleus accumbens. However, these effects occur only at doses that already increase functional activity throughout the brain and that are effective both on the shell and the core part of the nucleus accumbens (Nehlig, unpublished data). Therefore, although caffeine acts on the neural substrates of addiction, these effects are not specific, compared to those of the drugs of addiction, and occur at rather high doses, which induce the activation of other numerous brain structures and are already probably close to aversive doses in humans.

F. Other Effects

Caffeine is present in several analgesic preparations. To the extent that this is at all rational it may be related to the presence of adenosine A_{2A} receptors in or close to sensory nerve endings that cause hyperalgesia (Ledent et al., 1997). Indeed, caffeine does have hypoalgesic effects in certain types of C-fiber-mediated pain (Myers et

al., 1997). The analgesic effects are small (Bättig and Welzl, 1993). Under conditions of pain, however, caffeine could have an indirect beneficial effect by elevating mood and clear-headedness (Lieberman et al., 1987). In this study it was found that both mood and vigilance were more improved by aspirin in combination with caffeine than by aspirin given alone or by placebo.

It cannot be excluded that caffeine might have analgesic properties for specific types of pain, which may be the case for headache (Ward et al., 1991), which is significantly and dose-dependently reduced by caffeine under double-blind conditions. The effect was similar to that of acetaminophen, which is frequently combined with caffeine, and showed no relation to the effects on mood or to self-reported coffee drinking. As reviewed (Migliardi et al., 1994), patients rate caffeine-containing analgesics as superior to caffeine-free preparations for the treatment of headache. In addition, caffeine may exert an antinociceptive effect in the brain, because it can antagonize pain-related behavior in the mouse following i.c.v. injection (Ghelardini et al., 1997). Moreover, this effect may be related to antagonism of a tonic inhibitory activity of adenosine A_1 receptors that reduce cholinergic transmission (cf. Rainnie et al., 1994; Carter et al., 1995).

Many central stimulants reduce appetite, via mechanisms that are incompletely understood. Caffeine appears to have a small reducing effect on caloric intake (Tremblay et al., 1988; Racotta et al., 1994; Comer et al., 1997). This effect is similar to, although less marked than, that seen after amphetamine (Foltin et al., 1995). For both stimulant drugs the effect is on the number of meals consumed rather than on meal size.

Given that many caffeine-containing drinks are typically consumed in social settings, surprisingly little is known about the possible effects of caffeine on social behavior (see Bättig and Welzl, 1993). In male rats caffeine causes a dose-dependent (10–40 mg/kg) increase in social investigation (Holloway and Thor, 1983). This was observed not only after injection of single doses but also after the addition of caffeine to the drinking water. The effect was dose-dependent from 0.12 to 0.5 g/l in the water. Finally, the effect of injecting caffeine on social investigation did not decrease in animals exposed to caffeine in the drinking water (Holloway and Thor, 1983). The recent finding that male mice—but not female mice—whose A_{2A} receptors have been knocked out exhibit increased aggressive behavior (Ledent et al., 1997) suggests that caffeine might have similar effects in this species, but this has not been studied. In an experimental study in humans, caffeine was reported to decrease aggressive responses (Cherek et al., 1983), but the aggressive behavior was very artificial and involved push-button punishment of fictitious individuals. Reintroduction of caffeine after a brief abstinence does not significantly affect human social behavior (Comer et al.,

1997). However, more information on the effect of caffeine on social behavior is clearly needed.

V. Addiction and Drug Dependence

A. Definitions

Drug dependence may be used to denote "a state of affairs when administration of the drug is sought compulsively, leading to disrupted behavior if necessary to secure its supply. Use continues despite the adverse psychological or physical effects of the drug" (Rang et al., 1995).

Drug (or substance) abuse "are general terms, meaning the use of illicit substances" (Rang et al., 1995), whereas the term drug addiction is older and focused on physical dependence. In popular usage, addiction is a term indiscriminately used to describe all sorts of habits from relatively harmless ones to openly dangerous ones. A stricter usage emphasizes that addiction refers to compulsive drug use (O'Brien, 1995). Up until the late 1960s separate definitions for "addictions" and "habits" as proposed by the World Health Organization (1957) were used in the scientific and medical world. *Drug-addiction as a state of periodic or chronic intoxication* was then characterized by four criteria: 1) An overpowering desire or compulsive need to obtain the substance by any means. 2) A tendency to increase the dose progressively. 3) A psychic and generally a physical dependence on the effects. 4) Detrimental effects on the individual and the society. This concept of addiction would fit the opiates and alcoholism but not necessarily cocaine, which does not create any clear physiological withdrawal.

Drug-habit consisting of the repeated (not intoxicating) consumption of a substance was also characterized by four criteria which contrast with those of addiction: 1) A strong but not compulsive desire to take the substance for the sense of improved well being. 2) A moderate or no tendency to increase the dose. 3) A psychic dependence but no physiological abstinence syndromes. 4) Detrimental effects, if any, primarily on the individual but not on the society. This latter set of criteria was considered at that time to fit coffee-drinking

As pointed out by O'Brien (1995), "abuse and addiction are behavioral syndromes that exist along a continuum from minimal use, to abuse, to addictive use". The modern diagnostic manuals of the World Health Organization (WHO, 1992) and the American Psychiatric Association (APA, 1992, 1994) no longer use the terms addiction or habit. These terms have been given up for their "lack of precision" and their "discriminating connotation". The more recent manuals instead formulated a set of criteria for "substance dependence". This construct differs in very important aspects from the older concepts. It combines the old criteria of habit and addiction into a single list, and it does not rely on quantitative (often value-based) aspects of the criteria, but rather on

qualitative "Yes or No" statements. Furthermore, it requires only that three (nonspecified) of the six (WHO, 1992) or seven (APA, 1987, 1994) criteria be fulfilled for the diagnosis "dependence". The old definitions of addiction and habit required the fulfillment of all four respective criteria.

The seven criteria of dependence as proposed by the APA (1987) in DSM-III are: 1) Tolerance (not specified for severity). 2) Substance-specific withdrawal syndrome (psychic or physiological, not specified for severity). 3) Substance is taken in greater amounts or over longer periods than intended. 4) Persistent desire or unsuccessful attempts to cut down or control use. 5) A great deal of activity and time spent in order to obtain the substance or recover from its effects. 6) Important social, occupational, or recreational activities given up or reduced because of substance use. 7) Use despite knowledge of persistent or recurrent physical or psychological problems likely to be caused or exacerbated by the substance. Although a new revised version appeared as DSM-IV (APA, 1992), the older DSM-III version is still in use and served as the basis for most of the recent discussions and controversies about substance use.

The six criteria as proposed by the WHO (1992) in ICD-10 differ only modestly from those of the APA, mainly by a different sequence, slightly different formulations, and the combination of the two DSM criteria 5 and 6 into a single item.

Accordingly, all nonmedical and more or less regular use of any psychoactive substance can be considered as "dependence", which is seen further by DSM-IV as a "substance related disorder". The only possibility to differentiate between substances that remains is, therefore, to locate them within a continuum of the number of criteria that are met and to specify the severity and frequency of occurrence. DSM-IV does not consider caffeine as a substance of dependence on the basis of such evaluations, but this is, as noted above, contentious. Furthermore, it lists intoxication and anxiety disorders as possible substance disorders.

Central to all the above attempts to define drug dependence is the concept of drug *reinforcement*. This has been defined as "a form of behavioral plasticity in which behavioral changes occur in response to some exposure to a reinforcing drug. Drugs are classified as reinforcers if the probability of a drug-seeking response is increased when the response is temporarily paired with drug exposure" (Self and Nestler, 1995). The drug somehow utilizes the brain's intrinsic motivational systems that are involved in maintaining various behaviors necessary for the survival of the individual or species.

"Chronic exposure to reinforcing drugs can lead to addiction, which is also characterized by an increase in drug-seeking behavior" (Self and Nestler, 1995). Thus a sustained increase in drug-seeking behavior (i.e., *craving*) is a core feature of clinical drug addiction. Importantly, addicted subjects usually exhibit a sustained increase in drug-seeking even when the drug has been withdrawn. Sometimes, the withdrawal is associated with negative affective states (i.e., dysphoria) and the drug can relieve these symptoms. Indeed, drug dependence can be defined as the need to sustain drug intake to eliminate the risk of *withdrawal symptoms*. Both craving and withdrawal effects are related to a process of *habituation* to the drug. The sometimes severe withdrawal symptoms are generally possible to limit and the physical dependence is not the reason why many subjects revert to drug use after being drug-free for long periods (O'Brien, 1995; Rang et al., 1995).

Koob (1996) has recently discussed the transition that occurs from a controlled drug use to the lack of control that is characteristic of drug dependence. A priori one can outline four types of *reinforcement*: positive reinforcement, negative reinforcement, conditioned positive reinforcement, and conditioned negative reinforcement (Wikler, 1973). Because a positive reinforcement is clearly of fundamental importance in establishing a drug-taking behavior, it has been hypothesized to be the key process (Wise, 1988). However, others have emphasized withdrawal as the driving force of addiction, and argued that the defining characteristic of drug dependence is the establishment of a negative affective state (see Koob, 1996). Such a state may on the one hand have a basis in the neurobiological setup of the individual—genetic and environmental factors both playing a role—and on the other in changes brought about by the long-term drug use itself. Furthermore, other cues—internal as well as external—may become associated by processes known as classical conditioning to both the positive and the negative affective states related to the presence or absence of the drug (Wikler, 1973). These theories thus invoke a critically important role of the basic neuronal circuitry that is involved in motivation and also postulate that drugs can induce important adaptive changes in these mechanisms.

B. On the Neuronal and Molecular Basis of Drug Reinforcement and Addiction

In pioneering studies, Olds and Milner (1954; see Wise, 1996) showed that electrical stimulation of certain brain areas can induce a learned place preference and that stimulation of these brain areas was rewarding in the sense that it could act as an operant reinforcer (see Wise, 1996). It was soon realized that this could best be explained if the electrical stimulation of these brain areas activated brain circuitry relevant to the pursuit of natural incentives (Olds and Milner, 1954; Olds, 1956). It is now clear that many brain areas, from the olfactory bulb and frontal cortex in the rostral part of the brain all the way to the nucleus tractus solitarii in the caudal brain can serve as substrates for such rewarding stimulation (see Wise, 1996). Drugs with habit-forming properties act through these same incentive-forming brain circuits (Wise and Bozarth, 1987; Koob, 1992, 1996).

Over the past several years our knowledge about the neuronal and molecular substrates underlying reinforcement and drug dependence has increased substantially. The molecular mechanisms were recently reviewed (see Self and Nestler, 1995) and the critical role of the mesolimbic dopamine system emphasized (Wise and Bozarth, 1987; Di Chiara, 1995; Koob, 1996). The mesolimbic dopamine system consists of the dopaminergic neurons that originate in the VTA and terminate in the nucleus accumbens. Two drugs, cocaine and amphetamine, target this system directly. Cocaine is known to exert its primary effect by blocking the sodium-dependent dopamine reuptake transporter (Kilty et al., 1991; Shimada et al., 1991). Amphetamine acts both by inhibiting the transporters and by releasing dopamine from intracellular stores. In animals with a targeted disruption of the dopamine transporter, amphetamine does not increase dopamine levels (Giros et al., 1996). This may be due in part to the fact that amphetamine needs to be transported via this system to exert its actions. It is known that rats will self-administer amphetamine and dopamine directly into the nucleus accumbens. By contrast, cocaine is not readily self-administered into the accumbens, but lesions of the dopamine neurons or drugs that attenuate dopamine actions will substantially reduce the reinforcing properties of cocaine (see Self and Nestler, 1995). Opiates also interact with the mesolimbic dopamine system. They are self-administered not only when given systemically, but also when injected into the VTA, where they act by disinhibiting the dopaminergic neurons (Johnson and North, 1992).

Drugs that enhance dopaminergic transmission tend to enhance an animal's response to brain self-stimulation, for example by reducing the reward threshold, whereas dopamine receptor antagonists have the opposite effect (see Wise, 1996). Reward thresholds are also decreased by cocaine, heroin and morphine, nicotine, phencyclidine, cannabis, and possibly ethanol (see Wise, 1996). Many of the same drugs, including ethanol (Rossetti et al., 1992) and cannabinoids also increase dopamine levels in the nucleus accumbens.

Phencyclidine (PCP) is also self-administered in humans, monkeys, and rodents (see Carlezon and Wise, 1996). In rodents, self-administration is erratic when the drug is given systemically but reliable when it is injected into the nucleus accumbens (Carlezon and Wise, 1996). The effect of PCP was shared by other inhibitors of NMDA receptors including MK-801, and was not influenced by DA receptor antagonists. The latter finding indicates that it is not the DA neuron per se that is important to induce self-administration but rather the activity of the neurons activated by both DA and NMDA receptors.

The nucleus accumbens is functionally and morphologically divided into a core and a shell part. The medioventral (shell) part is related to the limbic "extended amygdala" assumed to play a role in emotional and motivational functions, whereas the laterodorsal (core) part is viewed as a part of the striatopallidal complex and to be concerned with motor functions (see Heimer et al., 1985). The extended amygdala receives input from basolateral amygdala, frontal cortex, and hippocampus and sends efferents to the medial part of the ventral pallidum as well as the lateral hypothalamus.

Interestingly, i.v. administration of recognized drugs of abuse such as cocaine, morphine, and amphetamine, and even nicotine, increases the extracellular levels of DA specifically in the shell part of the accumbens (Pontieri et al., 1995). Nicotine has the same ability to increase DA specifically in the shell as compared to the core part of the nucleus accumbens (Pontieri et al., 1996). This is also manifested as a selective increase in glucose utilization in the shell part of the nucleus accumbens. Quite recently, cannabinoids were shown to have a similar effect (Tanda et al., 1997). There is also evidence that direct injection of drugs into the shell part of nucleus accumbens is much more efficacious in inducing drug-related behavior than is an injection into the core part of nucleus accumbens (see Ikemoto et al., 1997).

The regulation of the mesolimbic DA system was recently reviewed (White, 1996). The midbrain DA neurons with cell bodies in VTA respond with an increase in firing or even with burst activity to novel, unexpected events (Schultz, 1992). In particular, primary rewards such as food and water, when presented in an unexpected manner, are among the most effective stimuli for VTA DA neurons (Mirenowicz and Schultz, 1994). Furthermore, it is possible to condition the activation of these neurons by traditional methods (Schultz, 1992). Thus there is excellent evidence that the VTA DA neurons are deeply involved in reward-driven learning of the type that seems a priori to be involved in drug addiction.

In nonhuman primates, Schultz and coworkers (1997) have identified dopaminergic neurons whose fluctuating output appears to signal changes or errors in predictions concerning future salient and rewarding events. The neurons were suggested to provide information about appetitive stimuli, but not about aversive stimuli, which might mean that the absence of an expected reward is interpreted as "punishment" (Schultz et al., 1997). Moreover, the information would include a value component that if, and only if, combined with specific information about the nature of the specific stimulus, would provide an excellent basis for decisions. Indeed, in the basal ganglia, there are tonically active neurons that develop a response to conditioning that is spatially distributed, temporally coordinated, predictive of reward, and dependent on DA (Graybiel et al., 1994). Furthermore, in some of the output structures from the basal ganglia, the morphological distinguishing criteria of such integration have been detected (Bevan et al., 1997).

The VTA DA neurons receive a major *excitatory input* from prefrontal cortex, but also excitatory inputs from amygdala, and possibly the entopeduncular nucleus and the pedunculopontine region (see White, 1996). Many, but perhaps not all, of these inputs use an excitatory amino acid as the major transmitter, and NMDA receptors have been particularly implicated in producing the bursting type of activity (Johnson et al., 1992; Gonon and Sundström, 1996). Several lines of evidence indicate the presence of a major *GABAergic inhibitory* input from the nucleus accumbens (see White, 1996). There is also evidence for control by nicotinic receptors (Calabresi et al., 1989), but the localization of these receptors is unclear. There is some as yet incomplete evidence for control of VTA neuronal activity by 5-HT and noradrenaline. Finally, adenosine A_1 receptors are present in VTA and regulate the firing of the dopaminergic neurons and thereby the release of DA in the nucleus accumbens (Ballarin et al., 1995). Thus, several neuronal pathways and transmitter and modulator systems act in concert to modulate the activity of the critically important DA neurons in the VTA, but their relative roles under in vivo conditions and how they interact is still incompletely known (White, 1996). Although it seems clear that habit-forming drugs do not all activate the reward systems in the brain in the same way, it is nonetheless established that several of the more addictive substances synergize with endogenous rewarding mechanisms involving the medial forebrain bundle, and that they directly or indirectly elevate DA levels in the nucleus accumbens (Wise, 1996).

Given that many drugs of abuse interact with the VTA DA neurons (Koob, 1992; Self and Nestler, 1995) it is obviously interesting to examine if such drugs produce lasting effects on these neurons. At least for some drugs such adaptive changes have been shown to occur. For example, amphetamine was shown to decrease the sensitivity of the DA D_2 receptors on VTA neurons (Seutin et al., 1991). The subsensitivity probably does not involve any significant decrease in the number of D_2 receptors (Peris et al., 1990), but it may involve a decreased ability of the receptors to couple to the relevant G-proteins (Nestler et al., 1990). The decreased sensitivity of soma-dendritic D_2 receptors in VTA may provide a partial explanation for the long-term increases in drug-induced release of DA in the nucleus accumbens (see Self and Nestler, 1995). However, additional mechanisms are probably involved, including changes in the glutamatergic transmission. Thus, NMDA receptor antagonists prevent the development of drug-induced sensitization of dopaminergic transmission (Karler et al., 1989; Wolf et al., 1994). It should also be pointed out that the two mechanisms, i.e., a desensitization of D_2 receptors and a sensitization to glutamatergic input, may be closely linked at the cellular level. Thus, the role of DA may be predominantly to regulate the efficiency of the glutamatergic neurotransmission (Gonon and Sundström, 1996).

The release of DA in the nucleus accumbens depends not only on the overall rate of firing of the VTA DA neurons, but it is also critically dependent on the firing pattern. The levels of DA are much higher when the neurons fire in a burst mode, probably because under those circumstances the inactivation mechanisms cannot keep up with the release (Chergui et al., 1994, 1997). Burst stimulation of the medial forebrain bundle leads to changes in the expression of NGFI-A (*zif/268*) mRNA in the nucleus accumbens. Specifically, this is seen in the GABAergic medium-sized spiny neurons that also express Substance P mRNA (Chergui et al., 1997). These neurons are known to express most of the D_1 receptors in the nucleus accumbens, and indeed the change in the expression of the IEGs following burst stimulation of the medial forebrain bundle is inhibited by dopamine D_1 receptor antagonists (Chergui et al., 1996, 1997). These data thus indicate that burst firing of VTA DA neurons causes an increase in the free extracellular DA level in the nucleus accumbens and that this, in turn, leads to an activation of DA D_1 receptors that is manifested in an altered gene expression.

It is known that different individuals are differently susceptible to drug dependence. Among the many factors that might predispose an individual to drug dependence, animal experiments have identified stress as one (see Piazza and Le Moal, 1998). As discussed, several types of stressors can facilitate acquisition, maintenance, and reinstatement of self-administration of drugs such as heroin and cocaine (Piazza and Le Moal, 1998). The mechanism may be related to an effect of glucocorticoids on drug-induced release of DA.

Much of the above discussion centers on the idea that alterations in the DA neurons themselves or in the levels of the transmitter is the important factor. However, it is obvious that the effect of an alteration in the amount of DA at a relevant target neuron might be mimicked by a stimulus that enhances the actions of a normal level of DA. Such plastic changes may be brought about via multiple mechanisms as exemplified in other well-studied cases of plasticity of central synapses. As will be obvious from the discussion in Section III, there is good evidence that caffeine could do just this by interacting with receptors that coexist with DA receptors.

Dopamine acts on two classes of receptors: D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, D_4), which differ in their G-protein coupling and distribution in the brain (see Jaber et al., 1996). Both these classes of receptors may be involved in the motivational symptoms of drug addiction (see Self and Nestler, 1995). It has been shown that D_1 receptor agonists delay the initiation of cocaine self-administration, whereas D_2 agonists have no such effect (Self, 1992). However, in other studies, the relative potency of agonists was suggested to reflect an importance of D_3 receptors (Caine and Koob, 1993). The dopamine

D_4 receptor may also play a role because motor behavior responses to cocaine, ethanol, and methamphetamine are enhanced in mice lacking this receptor (Rubinstein et al., 1997). Furthermore, D_1 agonists decrease reinstatement of cocaine-seeking behavior, whereas D_2 agonists enhance it (Self et al., 1996). Moreover, in mice with a targeted disruption of the dopamine D_2 receptor, opiates did not have a rewarding effect (Maldonado et al., 1997), even though the rewarding effect of food was maintained. Any attempt to associate a given behavior, short- or long-term, to a single dopamine receptor subtype is complicated by the fact that D_1-like and D_2-like receptors functionally interact in a highly complex manner. Although either a D_1-like or a D_2-like agonist may under some circumstances have rewarding properties per se, a combination of the two produces much larger effects (see Ikemoto et al., 1997).

Dopamine D_1 receptors appear to be important for the motor effects of cocaine (Xu et al., 1994). These receptors are also important in the phenomenon of sensitization (see Self and Nestler, 1995; Hyman, 1996). A single dose of a drug that activates dopamine receptors can sensitize an animal for months to the locomotor effect of amphetamine or cocaine and this is blocked by D_1 antagonists and correlated with an increased responsiveness of D_1 receptors in the nucleus accumbens (Henry and White, 1995). D_1 receptors are known to interact with NMDA receptors to phosphorylate CREB and this leads to an increased expression of several IEGs that act as transcription factors (see Konradi et al., 1994; Hyman, 1996). These molecular events have been hypothesized to lead to behavioral sensitization. In particular, changes in dynorphin might provide a mechanism for producing dysphoria when the drug is discontinued (see Hyman, 1996). Part of the sensitization to both cocaine and morphine may be exerted at the level of the dopaminergic cell bodies in the VTA (Bonci and Williams, 1996). Whereas activation of dopamine D_1 receptors normally augments the $GABA_B$ receptor-mediated inhibitory postsynaptic potentials, D_1 receptor stimulation given after chronic cocaine or morphine inhibits these responses. Interestingly, the mechanism appears to involve release of adenosine that acts on adenosine A_1 receptors (Bonci and Williams, 1996).

According to the model of Schultz et al. (1997) signaling via the dopaminergic neurons would provide a type of general value-related information that only provides a basis for decisions about specific actions if combined with specific information about different types of stimuli. Therefore, a very general activation or inactivation of parts of this dopaminergic signaling machinery would theoretically generate information that is too unspecific to be of use in decision-making by rats or humans. If, however, the adaptive processes require not only the activation of dopamine receptors, but also activation of a glutamatergic input, as postulated above, we could have a mechanism that would allow for a synthesis of nonspecific motivational input and specific information

about drug-related cues—exactly as postulated by the psychological theories of drug dependence.

For obvious reasons there is much less information about the neuronal substrates for drug dependence in humans. In a recent study using functional magnetic resonance imaging, the brain regions activated by cocaine in humans were studied (Breiter et al., 1997). In agreement with the extensive literature on rodents and subhuman primates, cocaine (0.6 mg/kg) caused a clearcut increase in the signal in nucleus accumbens/subcallosal cortex (Breiter et al., 1997). These changes could be correlated to the craving, but not to the "rush". The latter, which by definition occurred very rapidly, correlated better with changes in activity in caudate-putamen, thalamus, posterior hippocampus, insula, cingulate, and parahippocampal gyri. The widespread sustained changes after cocaine could indicate that the sustained behavior changes, including craving, reflect a change in the overall pattern of brain activity rather than a focused alteration in one or more specific regions or brain nuclei (Breiter et al., 1997).

VI. Caffeine Withdrawal and Relief of Abstinence Symptoms by Caffeine

A. Animal Studies on Caffeine Withdrawal

There are few animal studies on caffeine withdrawal. Caffeine withdrawal induces a 2-fold decrease in rat locomotor activity. This effect lasts for about 4 days and is dose-dependent and maximal on the second day (Griffiths and Woodson, 1988c; Nehlig and Debry, 1994). Caffeine withdrawal also affects the effect of caffeine on cerebral electrical stimulation in the rat (Mumford et al., 1988). Withdrawal of chronic caffeine intake in rats results in disruptions in operant responding (Carney, 1982; Mumford et al., 1988) and decreases in locomotor activity (Holtzman, 1983; Finn and Holtzman, 1986), effects that last from one to several days. The magnitude and duration of caffeine withdrawal appears to be a direct function of the amount of caffeine that has been consumed daily. Disruption of operant behavior is also observed in the monkey after caffeine deprivation but is less pronounced than after phencyclidine or cocaine deprivation (Carroll et al., 1988). Withdrawal of caffeine after continuous infusion at the level of 190 mg/kg/day to mice caused a marked decrease in locomotor behavior, which gradually returned to normal after the first few days (Kaplan et al., 1993; Nikodijeviç et al., 1993). In the withdrawal phase, the peak stimulatory effect was slightly shifted from 30 to about 20 mg/kg (Nikodijeviç et al., 1993) indicating a supersensitivity to the depressant actions of caffeine. Low doses of caffeine also restored the lowered locomotion to normal.

B. Human Studies

Humans can experience a variety of withdrawal symptoms. These include weariness, apathy, weakness and

drowsiness, headaches, anxiety, decreased motor behavior, increased heart rate, and increased muscle tension and, occasionally, tremor, nausea, vomiting, and flu-like feelings (Griffiths et al., 1990; Silverman et al., 1992; Nehlig and Debry, 1994; Höfer and Bättig, 1994a,b; Strain et al., 1994; Griffiths and Mumford, 1995; Schuh and Griffiths, 1997). There are also several reports on caffeine abstinence and postoperative headaches (Fennelly et al., 1991; Weber et al., 1993; Nikolajsen et al., 1994). Mathew and Wilson (1985) reported that, in high but not in low caffeine consumers, abstinence was followed by marked increases of blood flow in the frontal lobes. Two studies insisted that caffeine withdrawal should be included in the list of diagnoses recognized by the American Health System (DSM-IV and ICD-10) (Hughes et al., 1992b; Strain et al., 1994).

Anecdotal reports on complaints induced by caffeine withdrawal go far back into the last century. The first controlled study was carried out by Dreisbach and Pfeiffer (1943), who gradually increased the dose of caffeine across 7 days up to 850 mg/day and then substituted this medication with placebo capsules. Fatigue, disinclination to work, mental depression, and headache appeared in most subjects. Headache was alleviated by reinstitution of caffeine but hardly by conventional analgesics. This may be related to changes in blood flow. Caffeine has central vasoconstrictive properties, which lead to a 20 to 30% decrease in cerebral blood flow in humans and in animals. This decrease can be achieved in humans after the absorption of 250 mg of caffeine (Mathew and Wilson, 1985; Cameron et al., 1990). Thus, blood flow velocity in the middle cerebral, posterior cerebral, and basilar arteries is increased during withdrawal, and decreased within 30 min after intake of caffeine, returning to baseline values after 2 h (Couturier et al., 1997).

Withdrawal symptoms generally begin about 12 to 24 h after sudden cessation of caffeine consumption and reach a peak after 20 to 48 h. However, in some individuals, these symptoms can appear within only 3 to 6 h and can last for 1 week (Barone and Roberts, 1984; James, 1991; Nehlig and Debry, 1994; Phillips-Bute and Lane, 1998). Thus, even a short abstinence, equivalent to missing the morning cup of coffee, can lead to significant unpleasant effects (Phillips-Bute and Lane, 1998). There were generally more complaints in the afternoons than in the mornings. All complaints tended to be as severe or even more severe on the second than on the first day of abstinence, but had nearly vanished by the third day. Most complaints were correlated with the headache reports, suggesting that they were secondary to headache. Furthermore, in a group that alternated between 1 day of caffeine consumption and 2 caffeine-free days, the complaints decreased from the first period of abstinence to the next and vanished almost completely by the third one, demonstrating that more than 1 day of previous caffeine exposure is needed to induce

withdrawal symptoms (Höfer and Bättig, 1994a,b). The syndrome is further probably specifically due to the discontinuation of caffeine intake, because it persisted regardless of the increased consumption of over-the-counter analgesics that closely paralleled the intensity of the headache complaints.

A great number of laboratory studies, particularly by the Griffiths group (Griffiths and Woodson, 1988a; Griffiths and Mumford, 1995; Schuh and Griffiths, 1997), has since then confirmed the withdrawal syndrome using doses of caffeine ranging from 0.2 to 1 g daily. There are no reliable effects on social behavior during withdrawal (Comer et al., 1997). This can be contrasted to the major effect on performance and social behavior upon withdrawal from other drugs.

Warburton and Thompson (1994) analyzed data from a life-style survey on 9000 subjects with respect to a number of different behavioral and personality attributes, including coffee drinking and headache. Headache was reported more frequently by women than men and less with increasing age. The relation to coffee drinking was biphasic with the fewest reports by moderate drinkers (3–4 cups/day) and more reports by both drinkers of more and of less coffee. On the other hand, headache was positively related to alcohol consumption. One might expect, from the animal data cited above, that heavy caffeine users would experience stronger withdrawal symptoms than light users. In a field study including 60 males and 40 females (Höfer and Bättig, 1994a,b) about half of the subjects subjected to withdrawal experienced moderate headache and about 20% more severe headache. However, the subjects with headache did not differ from those without headaches with respect to the magnitude of their caffeine consumption.

A lack of relationship between withdrawal symptoms and the quantity of caffeine ingested daily is also reported in another study: withdrawal symptoms were found in subjects with a daily caffeine intake ranging from 129 mg (1–2 cups of coffee) to 2548 mg (20–30 cups of coffee) (Strain et al., 1994).

Several investigators studied the effects of caffeine withdrawal on objective measures of performance, such as speed of finger tapping (Bruce et al., 1991; Strain et al., 1994) or reaction times (Rizzo et al., 1988) in users and nonusers of coffee, and failed to see differences, although performance decreased in the users when they abstained from coffee. In a more recent study, however, brief deprivation of caffeine did not affect psychomotor performance in several tests despite the fact that there were major effects on activity and many subjects experienced headaches (Lane, 1997).

Withdrawal symptoms have been reported in newborns whose mothers were heavy coffee drinkers during pregnancy. These infants display irritability, high emotivity, and even vomiting. Symptoms begin at birth and spontaneously disappear after a few days (McGowan et

al., 1988). Caffeine withdrawal may also occur in school-children who largely obtain their caffeine from soft drinks (Goldstein and Wallace, 1997). Furthermore, these effects tended to be larger in children with a high consumption, even though this high consumption would correspond to consumption of only a few cups of coffee daily by adults (Goldstein and Wallace, 1997).

C. Effect of Caffeine on Withdrawal Symptoms

In their pioneering study on caffeine withdrawal, Dreisbach and Pfeiffer (1943) observed that caffeine was highly efficient in relieving withdrawal headache. The same observation has since been made in many other studies. This raises the question: To what extent do people consume coffee in order to avoid or terminate headache? Cines and Rozin (Cines and Rozin, 1982) did a study on the different aspects of liking coffee in 180 adult coffee drinkers. Liking coffee flavor was linked mostly to the hot coffee and correlated with the pharmacological effects of the morning coffee. Coffee liking was scored higher by those subjects who indicated that coffee gives a good feeling, calms the nerves, stimulates, helps thinking and vigilance, and last but not least reduces or prevents headache. Volunteers asked to discriminate between caffeine and placebo mentioned tiredness and headache as the most important cues for the detection of placebo (Evans and Griffiths, 1992).

It has been suggested that the studies showing an improved psychomotor performance following caffeine are all flawed because they have not taken caffeine withdrawal into account (James, 1994, 1995). Whereas the point is well taken, it may not explain all the data. For example, it has been pointed out 1) that caffeine withdrawal of the magnitude usually seen in the cited studies above does not lead to a marked decrease in psychomotor performance (Rogers et al., 1995) and 2) that caffeine appears to have effects in such tasks even in the absence of any real withdrawal (Rogers et al., 1995; Warburton, 1995).

Heavy consumers of coffee show a preference for coffee containing caffeine if they have been drinking this type of coffee for 1 week or more, whereas subjects who have been drinking decaffeinated coffee will choose either decaffeinated or caffeine-containing coffee (Griffiths et al., 1986a; Stern et al., 1989). Indeed, caffeine content influences coffee drinking (Kozlowski, 1976; Griffiths et al., 1986b) and caffeine alone is able to reverse withdrawal syndromes induced by caffeinated coffee cessation (Goldstein and Kaizer, 1969; Goldstein et al., 1969; Griffiths et al., 1986a). Caffeine doses as low as 100 mg were associated with alertness, well-being, sociability, willingness to work, energy, and self-confidence (Griffiths et al., 1990). The beneficial effects, derived or expected, of caffeine consumption on mood or performance would indeed seem to incite people to drink coffee or caffeine-containing beverages (Kuznicki and Turner, 1986; Richardson et al., 1995).

The risk of caffeine withdrawal headache has recently also been recognized for hospitalized patients who are required to fast before operations. Nikolajsen et al. (1994) examined perioperative headache in 219 patients who fasted from midnight before the surgical intervention. The odds ratio for patients to develop postoperative headache amounted to 5.0 for those consuming more than 400 mg/day caffeine and to 3.7 for those operated after noon on the following day. The frequency of pre- and perioperative headaches is strongly correlated with the duration of fasting and the daily consumption of caffeine (Fennelly et al., 1991; Nikolajsen et al., 1994) and is reduced in individuals who drank caffeine or got substitutive caffeine tablets on the day of the surgery (Weber et al., 1993; Hampl et al., 1995). Therefore, it was supported by three studies that the numerous healthy patients who drink caffeine beverages daily and are undergoing minor surgical procedures should be permitted to ingest preoperative caffeine (Weber et al., 1993; Nikolajsen et al., 1994) or even be given prophylactic i.v. caffeine (Weber et al., 1997).

Subjects who had withdrawal headaches and drowsiness were 2.3 to 2.6 times more likely to self-administer caffeinated coffee (Hughes et al., 1993). Several variables (e.g., average caffeine intake) did not predict caffeine self-administration or withdrawal. In another study (Mitchell et al., 1995), the effects of complete or partial caffeine deprivation on withdrawal symptomatology and self-administration of coffee in caffeine-dependent coffee drinkers were examined. Caffeine deprivation was manipulated by administering capsules containing 0%, 50%, or 100% of each subject's daily caffeine intake (complete, partial, and no deprivation conditions). Caffeine withdrawal symptomatology was measured using self-report questionnaires. Caffeine self-administration was measured using: 1) the amount of coffee subjects earned on a series of concurrent random-ratio schedules that yielded coffee and money reinforcers; 2) the amount of earned coffee they consumed. Caffeine withdrawal symptoms occurred reliably following complete caffeine deprivation, although not in the partial deprivation condition. Caffeine self-administration was not related to deprivation condition, indicating that caffeine withdrawal symptomatology is not necessarily associated with increased caffeine consumption.

A different conclusion was, however, drawn from a recent study on 20 subjects who were moderate consumers of caffeine (average daily intake 379 mg) (Schuh and Griffiths, 1997). Using saliva measurements, it was ascertained that the subjects generally complied with an admonition to refrain from caffeine during the study. They were then asked to rate their subjective impression of the of randomly assigned placebo or caffeine capsules and to assign a cash value to receiving the same type of capsule again. The symptoms of headache, feeling "worn out" and experiencing "flu-like symptoms" were, as expected, higher in the subjects that received placebo than

in those that received caffeine. Conversely, caffeine capsules were associated with subjective alertness, well-being, and symptoms of stomach upset (Schuh and Griffiths, 1997). Importantly, the subjects chose caffeine and were willing to forfeit money to avoid receiving placebo. Because this behavior correlated with the symptom of headache, the authors conclude that choice of coffee is potently controlled by avoiding withdrawal. In fact, in this study, avoiding withdrawal was a stronger controller of caffeine intake than were the positive effects of caffeine.

This conclusion was later confirmed in another well-controlled study (Garrett and Griffiths, 1998).

VII. Tolerance to the Effects of Caffeine

It is known that tolerance develops to some, but not to all effects of caffeine in humans and experimental animals (Robertson et al., 1981; Holtzman and Finn, 1988). The precise mechanism underlying these effects is not known. In animals, attempts to relate this to receptor changes were made. The number of adenosine A_1 receptors is increased following long-term caffeine treatment (Fredholm, 1982). This effect appears to be due to the blockade of a down-regulation induced by the endogenous agonist adenosine but not to changes at the level of gene transcription (Johansson et al., 1993a). There are much smaller effects, if any, on A_{2A} receptors. This agrees with the reports from in vitro experiments that A_1 receptors are readily down-regulated, whereas A_{2A} receptors are not. Responses to A_{2A} receptors are decreased following changes in G_s-proteins or adenylyl cyclase but not by changes in receptor levels (Chern et al., 1993). It must be pointed out that a change in adenosine A_1 receptors occurs when animals are fed or injected with higher doses of caffeine, but not when lower doses are given (<50 mg/kg/day), doses that are still able to produce tolerance (Bona et al., 1995; Johansson et al., 1996a). The changes in the number of adenosine A_1 receptors are not the cause of the tolerance (Holtzman et al., 1991), which may instead be due to other types of adaptive changes, perhaps at the level of gene transcription, as noted above.

A. Cardiovascular Effects

It is generally agreed that high coffee intake causes tachycardia, palpitations plus a rapid rise in blood pressure, and a small decrease in heart rate. However, the tolerance to the effects of caffeine on blood pressure and heart rate usually develops within a couple of days (Colton et al., 1968; Robertson et al., 1981; Ammon, 1991; Denaro et al., 1991; Shi et al., 1993b). The tolerance to cardiovascular effects of caffeine is paralleled by a decrease in caffeine-induced increase in plasma adrenaline, noradrenaline, and renin levels (Robertson et al., 1981). Tolerance to caffeine pressor effects is lost after relatively brief periods of caffeine abstinence and depends on how much caffeine is consumed, the schedule of

consumption, elimination half-life of caffeine, and possible saturation of caffeine metabolism (Denaro et al., 1991; Shi et al., 1993b). Furthermore, tolerance to the blood pressure-raising effects might not be complete (Höfer and Bättig, 1993). Whereas blood pressure at rest tends to be negatively correlated with self-reported coffee drinking, actual blood pressure readings within less than 3 h after the last coffee tend to be elevated. On the other hand, some field studies (van Dusseldorp et al., 1989; Höfer and Bättig, 1994a) reported increases of heart rate upon caffeine abstinence. It was, however, not examined whether this could be attributed to some of the more subjective changes discussed below.

It should be pointed out that caffeine could elevate catecholamines and renin both by peripheral and central actions. The release of noradrenaline from sympathetic nerves could be regulated by methylxanthines by a presynaptic mechanism at the sympathetic nerve terminal (Hedqvist and Fredholm, 1976; Hedqvist et al., 1978). It has, however, been shown that this action, which depends on the antagonism of adenosine acting at A_1 receptors, does not appear to be physiologically important in comparison to the much more important autoreceptor control via noradrenaline acting on α_2 adrenergic receptors (Sollevi et al., 1981; Fredholm, 1995). It is therefore likely that the most important mechanism underlying increases in catecholamines is a rise in the sympathetic outflow and that this is centrally regulated.

B. Effects on Sleep

As noted above, sleep seems to be one of the physiological functions most sensitive to the effects of caffeine in humans. It is well known that caffeine taken at bedtime affects sleep negatively (see Snel, 1993). Generally, more than 200 mg of caffeine is needed to affect sleep significantly. The most prominent effects are shortened total sleep time, prolonged sleep latency, increases of the initial light sleep EEG stages, and decreases of the later deep sleep EEG stages, as well as increases of the number of shifts between sleep stages. Subjective sleep quality decreases in parallel to the lengthening of sleep latency, the duration and number of periods of wakefulness, and the shortening of total sleep time. REM sleep is hardly decreased in relation to total sleep time, but the latency to the first REM period is shortened. However, the practical importance of these findings is limited by the fact that most coffee is consumed in the morning and by the question as to what extent tolerance might develop to the sleep-disturbing effects, particularly in heavy consumers.

The results of the few studies comparing sleep problems between heavy and light consumers are equivocal. In general, coffee abstainers who drink coffee experience a longer delay before the onset of sleep as well as more disturbances in the different sleep phases and a shortening of the total time of sleep (Curatolo and Robertson, 1983), while habitual coffee drinkers seem to be rather immune to the effects of coffee on sleep (Colton et al.,

1968). Although caffeine use is higher in poor than in good sleepers, caffeine use in insomniacs is lower, perhaps because they tend to decrease their caffeine consumption to limit their poor sleep nights (Edelstein et al., 1984). In two studies, self-reported caffeine consumption was unrelated to sleep problems (Broughton and Roberts, 1985; Lack et al., 1988). In two other studies, consumption of caffeine was correlated inversely with total sleep time after controlling for age and cigarette smoking, even in drinkers of only two cups of coffee per day (Hicks et al., 1983; Levy and Zylber-Katz, 1983).

Likewise, the relation between the time of coffee drinking and sleep disturbances is not clear. After analysis of the relation between caffeine consumption and sleeping habits in 140 students separately for caffeine consumed during the last 4 h before bedtime and during the whole day, Pantelios et al. (1989) found that sleep onset was delayed in association with coffee before bedtime but not with total daily consumption. On the other hand, Landolt et al. (1995b) reported that in modest coffee drinkers (1.5 cups/day, n = 9) 200 mg of caffeine given in the morning reduced sleep efficiency for the subsequent night. Total sleep time was reduced by about 10 min, the latency to stage 2 sleep was prolonged by a similar interval, and sleep efficiency (time asleep/time in bed) was reduced by about 3%.

It is not clearly established yet whether the difference in the sensitivity to the effects of coffee on sleep could be attributable to tolerance. Some authors consider that the difference rather reflects interindividual variations in sensitivity to the effects of caffeine as well as variability in the subject's response from one night to the next (Goldstein et al., 1965; Lieberman et al., 1987), whereas other studies show the development of tolerance to the effects of caffeine on sleep (Colton et al., 1968; Curatolo and Robertson, 1983; Zwyghuizen-Doorenbos et al., 1990; Bonnet and Arand, 1992). Recently, two field studies were carried out controlling for sleep duration objectively with portable actometers. In the first study, sleep duration decreased and the latency to sleep onset increased after the intermittent caffeine days in a group given regular and decaffeinated coffee for alternating 2-day periods, whereas subjective sleep quality and nightly awakenings were unaffected by switching from regular to decaffeinated coffee. No significant differences were seen between the group with continued caffeine abstinence and the control group (Höfer and Bättig, 1994a). In a second study, an initial 3-day period of habitual coffee drinking was followed either by 3 days of consuming caffeine tablets (50 mg) or by consumption of decaffeinated instead of regular instant coffee. Saliva caffeine decreased by about 50% with the tablets and 90% with decaffeinated coffee, whereas sleep duration remained unaffected with the tablets but increased by about 30 min with decaffeinated instant (Höfer and Bättig, 1994b).

Taken together, the results suggest that habitual daily coffee drinking does not strongly modify caffeine effects on total sleep time, and the exact role of tolerance remains to be determined. Despite the fact that heavy consumers of caffeine tend to have smaller effects of caffeine on sleep (see Snel, 1993), tolerance is probably incomplete, particular regarding the effect of caffeine late during the day on the ease of falling asleep.

C. Effects on Mood

As discussed above (Section IVB), the reports on acute effects of caffeine on mood are somewhat equivocal. To the extent that positive changes were observed, they were described as feelings of being more active, awake, clearheaded, calm and attentive, and less fatigued. Negative changes obtained, particularly with higher doses or in nonusers, include having the jitters, nervousness, anxiety, tension, restlessness, and sleeplessness. Several different aspects have been proposed in the past to explain the differences in the findings, and habituation and tolerance might be decisive factors (Estler, 1982). The majority of 10 early studies revealed no significant effects (Estler, 1982), but a more recent review concludes that there is a clear deterioration of mood even after overnight caffeine deprivation (Rogers et al., 1995).

Some attempts have been made to study tolerance with appropriate experimental protocols. Evans and Griffiths (1992) studied 32 subjects who had to abstain for the 32 days of the study from all dietary caffeine. During an initial choice phase of 3 days, the subjects were tested with the technique of color-cued capsules as to whether they preferred capsules containing caffeine (300 mg) or placebo. Around one third of the subjects chose caffeine, but this was not related to gender, age, smoking status, prestudy caffeine consumption, or years of coffee drinking. However, anxiety scores on the Spielberger State-Trait Inventory (STAI) index correlated with not choosing caffeine. This initial screening was followed by an 18-day treatment period for which the subjects were split into a placebo and a caffeine group, balanced for caffeine choosers and nonchoosers. Three capsules were given per day, the caffeine capsules containing increasing amounts of caffeine with 100 mg at the start and 300 mg at the end of the treatment phase. During this phase no subjective ratings differed between the caffeine and the placebo group. The study was then continued with a second choice period with the same procedure as the first one. In this period the placebo-caffeine differences of the subjective ratings varied considerably between the subjects who received placebo and those who received caffeine during the preceding chronic treatment phase. In the chronic placebo-pretreated group, caffeine produced in comparison to placebo strongly increased ratings of tension and anxiety, having the jitters, nervousness, and having shakes, a feeling of "different from normal" and stronger "drug action". On the other hand, no such placebo-caffeine differences

appeared in the caffeine-pretreated group, although the choices of the subjects between placebo and caffeine were hardly different from the first choice period and were not affected by the nature of the previous treatment, placebo or caffeine. The caffeine choosers showed additional preference to caffeine, and a reduction of tension, anxiety, headache, confusion and bewilderment, and fatigue. In contrast, the nonchoosers revealed more tension and anxiety and more nervousness. During the final withdrawal period, the withdrawal effects, in particular headache, were limited to the subjects who were pretreated chronically with caffeine. However, the severity of withdrawal was not related to the caffeine chooser status.

This study provides good evidence that tolerance develops to some of the negative effects of caffeine on the subjective state, but it gives less information with respect to possible tolerance for the positive effects of the substance. In the two field studies by Höfer and Bättig (1994a,b) subjective wakefulness increased significantly and clearly above preabstinence baseline levels upon resumption of caffeine intake, suggesting that tolerance to this positive parameter develops. A recent experiment closely related to everyday conditions was carried out by Warburton (1995). He assessed mood ratings and performance data in subjects who were minimally deprived from caffeine by 1 h only. Under this condition, the low doses of 75 and 150 mg of caffeine still produced significant increases of clearheadedness, happiness, calmness, and decreases in tenseness. These data are interpreted as an argument against tolerance for the positive effects and also for the possibility that the habitual coffee drinking might do no more than reverse withdrawal.

Thus, it appears that some tolerance to the effects of coffee on mood probably develops, but also that more experimentation would be needed to delineate the phenomenon more quantitatively.

D. Other Central Effects

There is no difference in the effect of an acute dose of 10 mg/kg caffeine on deoxyglucose uptake, when caffeine is given to naive or chronically caffeine-exposed rats (Nehlig et al., 1986). By contrast, animal studies on mice and rats demonstrate a marked tolerance to the behaviorally stimulant effect of caffeine. In the rotation model in rats, the stimulant effects of both caffeine and theophylline are virtually eliminated in animals that consumed 75 mg/kg/day of caffeine orally (Garrett and Holtzman, 1995). In mice that consumed oral caffeine (1 g/l in the drinking water) there was a marked increase in locomotion during the first day, but this subsided during continued treatment, and during the third week of treatment the animals actually showed a lower locomotion (Nikodijeviç et al., 1993). The response to injected caffeine was altered in that the depressant phase was shifted to lower doses. Possibly this is related to the

sum of the effects of oral and injected caffeine. The effect of dopaminergic drugs was little altered (Nikodijeviç et al., 1993), suggesting that the tolerance is not nonselective. In another study, long-term infusion of caffeine tended to reduce the locomotor response to 20 mg/kg (Kaplan et al., 1993), but it is not certain if this represents tolerance or a shift of the entire inverted U-curve toward the left so that lower doses produce depressant effects. However, virtually complete tolerance to the increase of locomotor activity was observed in rats consuming approximately 40 mg/kg caffeine per day via their drinking water (Finn and Holtzman, 1986), and this was accompanied by a downward displacement and flattening of the dose-response curve.

Oral intake appears more efficacious than systemic injection in producing motor stimulation, judging by the relationship between plasma caffeine levels and forward locomotion (Lau and Falk, 1994), but both systemic and oral administration of caffeine can produce tolerance, albeit at slightly different rates (Lau and Falk, 1994). There was little evidence for any change in the amount of xanthine in plasma during daily i.p. injections, indicating that altered metabolism plays a minimal role in tolerance development in rats (Lau and Falk, 1994). Because brain caffeine levels do not completely match plasma levels especially following ingestion of the drug (Fredholm et al., 1983; but see Kaplan et al., 1990), this may represent differences in brain levels of caffeine and its behaviorally active metabolites. There is a cross-tolerance to the activity-stimulating effect of theophylline (Finn and Holtzman, 1987). Tolerance appears more marked to high doses than to low doses of caffeine (Lau and Falk, 1995). All these results suggest that part of the "tolerance" may be related to a sensitization to the aversive/motor depressant effects of caffeine and not only to a decrease in the stimulant effects. Nonetheless these animal results are in apparent contrast to the human data summarized above, which instead tended to suggest that there is tolerance to the negative effects of caffeine.

Caffeine disrupts operant responding in rats trained to press levers for food rewards, but tolerance develops to this effect: the dose-response curve was shifted to the right by a factor of 6 (Carney, 1982). This could indicate that the decrease in caloric intake noted above (Section IVF) might be an effect of acute rather than long-term caffeine use.

Caffeine's effects on psychomotor and cognitive performance have been investigated in innumerable studies. Hand steadiness, reaction times, and tapping rate have been altered mostly in the positive direction by caffeine insofar as any changes were observed at all (James, 1991). The situation is similar for tests of different types of cognitive performance, including mental arithmetic, learning, and information processing.

As discussed above, information processing has often been studied under the condition of maintaining vigilance. Koelega (1993), who recently reviewed such experiments, came to the conclusion that improvements do

not depend on fatigue induced by protracted sessions and that they represent more than a mere recovery from a previously withdrawal-induced impairment. Systematic analysis of the different components of such tasks indicates that it is more likely that caffeine acts by facilitating the sensory input and motor output rather than the central processing functions (Lorist et al., 1994). In a study of reaction times, "users" and "non-users" of coffee did not differ when tested without previous abstinence in the users (Rizzo et al., 1988). However, when the users had to abstain for 2 days, their reaction time performance was inferior to that of the nonusers. This result is not surprising, because withdrawal symptoms culminate on the second day of abstinence and are often accompanied by headache. However, as mentioned earlier, even a minimal abstinence duration of 1 hour affects mental performance, and a low dose of caffeine after this brief abstinence gives improvements in attention, problem solving, and delayed recall compared to the control condition (Warburton, 1995).

E. Differences between Acute and Long-Term Administration—Effect Inversion

The adaptive changes to long-term caffeine are very dramatic, being not only quantitatively different from but often opposite to the acute effects of caffeine in normal and pathological conditions. Thus, a long-term treatment with caffeine causes a decrease in locomotor activity (Nikodijeviç et al., 1993), whereas, as noted above, acute treatment stimulates locomotor behavior in rodents. Likewise, long-term treatment with caffeine leads to an improved capacity for spatial learning (Von Lubitz et al., 1993a), whereas acute treatment does not.

In pathological conditions, the first example is the finding that long-term caffeine treatment leads to decreased susceptibility to ischemic brain damage (Rudolphi et al., 1989), whereas acute treatment with caffeine and other methylxanthines instead exacerbates the damage (Dux et al., 1990). One of the most dramatic effects is shown in very young animals. When pregnant and lactating rat dams are treated with caffeine in their drinking water (0.3 g/l), caffeine is absorbed by the fetuses and the pups through the placenta and maternal milk, respectively, leading to very low levels of caffeine in the serum of the pups (about 1 μM). Rat pups subjected to hypoxia-ischemia at 7 days suffered significantly less brain damage when previously treated with caffeine than the untreated controls (Bona et al., 1995). This protective effect of low doses of caffeine over a long period of time has been repeatedly confirmed and there is good evidence that it cannot be attributed to changes in adenosine receptor number (Jacobson et al., 1996).

Some of the most dramatic effects have been noted on seizures. It is known that high doses of caffeine can precipitate seizures in humans and animals. However, long-term treatment leads to decreased seizure susceptibility whether the seizures are induced by the glutamatergic

agonist NMDA (Georgiev et al., 1993; Von Lubitz et al., 1993b) or by GABA$_A$ receptor antagonists such as bicuculline or pentylenetetrazol (Johansson et al., 1996a). These data indicate that the chronic caffeine effect is not related to any specific form of seizure but is more general and occurs in the complete absence of any change in the number of adenosine A$_1$ receptors (Georgiev et al., 1993) or GABA$_A$/benzodiazepine receptors (Johansson et al., 1996a). Furthermore, the effects were most marked during the ongoing treatment with caffeine, not after it, as would be expected had an increased transmission through adenosine receptors been the mechanism (Georgiev et al., 1993). Long-term treatment with the adenosine A$_1$ receptor agonist cyclohexyladenosine actually increased susceptibility (Von Lubitz et al., 1993b), in complete contrast to the acute treatment with such agonists.

These results indicate that long-term treatment with caffeine, in doses similar to those habitually used by humans, can induce important adaptive changes in the brain (Jacobson et al., 1996). Furthermore, these adaptive changes may be beneficial rather than detrimental.

VIII. Caffeine Discrimination and Dose Adjustment in Animals and Humans

A. Caffeine Discrimination in Animals

Several studies have examined the discriminative stimulus properties of caffeine in rats. In most of the early studies (Modrow et al., 1981; Winter, 1981; Carney et al., 1985; Holloway et al., 1985; Modrow and Holloway, 1985) animals were trained on 30 to 60 mg/kg caffeine, and as noted repeatedly above, this dose is definitely on the downward slope of the inverted U-shaped dose–response curve. Animals trained on a high dose of caffeine generalized to papaverine (Holloway et al., 1985), and papaverine depresses motor behavior as do very high doses of caffeine (Fredholm et al., 1983). This suggests that the high dose cue is not related to stimulation. This conclusion was supported in a later study where it was shown that the discriminative effect of a low-caffeine training dose (10 mg/kg) exhibits more commonalties with those of amphetamine-like drugs than do the discriminative effects of a higher training dose (30 mg/kg) (Holtzman, 1986). In a follow-up study, Mumford and Holtzman (1991) trained rats to discriminate 10 and 56 mg/kg caffeine over saline. Rats required a large number of training sessions (average 93) to discriminate the lower dose. However, then they generalized completely to dopaminergic drugs, including amphetamine, but also to several adenosine receptor antagonists, including the nonxanthine CGS 15943 (Mumford and Holtzman, 1991). By contrast, animals required fewer training sessions (average 43) to learn to discriminate the high dose of caffeine over saline. Then they generalized to a completely different set of drugs, including benzodiazepine inverse agonists, pentylenetetrazol, and phencyclidine (Mumford and Holtzman, 1991).

These data indicate that a low, stimulatory dose of caffeine gives a cue that resembles a weak dopaminergic stimulus and that a high dose provides a strong cue that is difficult to define in terms of a single precise mechanism. This interpretation is reinforced by the meta-analysis of Griffiths and Mumford (1996), where an inverse relationship between the caffeine training dose and generalization to cocaine is demonstrated. The interactions between caffeine and cocaine were investigated by Harland and coworkers (1989). Animals trained to discriminate cocaine (10 mg/kg) generalized to caffeine, but only at rather high doses. However, caffeine in doses of 10 mg/kg markedly enhanced responding to low doses of cocaine, even though it reduced cocaine-induced responding when given at high doses. These findings may have a bearing on the interaction between caffeine and cocaine discussed below (Section XIB). Here it may suffice to say that these results suggest that caffeine and cocaine interact at neuronal targets, but that they probably do not share mechanism of action.

The observation that low stimulatory doses of caffeine have discriminative stimulus properties is largely in agreement with the idea that the effects are mediated by adenosine receptor antagonism and that adenosine A_{2A} receptors may be particularly important. Recently, Holtzman (1996) has specifically addressed this question in a series of experiments in monkeys. He trained them to discriminate between the nonxanthine, nonselective adenosine receptor antagonist and its vehicle. All monkeys generalized dose-dependently to a series of xanthine derivatives. There was no linear relationship to their potency in vitro as either A_1 or A_{2A} receptor antagonists. However, these potency determinations have not been performed in monkeys and, furthermore, the relationship between the dose administered and the levels of these xanthines in brain has not been determined. Holtzman (1996) also found that the adenosine analog CGS 21680 blocked the effect of CGS 15943, indicating a role of A_{2A} receptors. However, the agonist was not able to block the effects of caffeine and theophylline. This was taken as evidence against a role of the adenosine receptor in mediating the actions of the xanthines. Before this conclusion is accepted the pharmacokinetics of these compounds in monkeys must be determined. It should also be remembered that CGS 21680 is not a potent or highly selective adenosine A_{2A} receptor agonist in humans (Kull et al., 1999), and the same may apply to monkeys.

B. Caffeine Discrimination in humans

Several studies show that humans discriminate caffeine (for references see Griffiths and Mumford, 1995, 1996). In one of the first studies (Chait and Johanson, 1988), the subjects were first trained to discriminate the effects of 10 mg of amphetamine and 12.5 and 50 mg of benzphetamine against placebo and then tested whether they would generalize this discrimination to 100 and 300

mg of caffeine. The subjects learned the initial task, but the generalization to caffeine was poor and hardly exceeded chance. In a study with a different design, the initial training with a classical stimulant was omitted (Griffiths et al., 1990). Instead, two differently colored capsules were given each day at intervals of 1.5 h, and the task was to detect which color marked caffeine. The dose levels were decreased stepwise from an initial 178 mg as soon as the criterion of successful discrimination was reached. The subjects were also the authors of the study and, as such, experienced psychopharmacologists and informed about the research goal. All seven recognized 178 mg, three detected 56 mg and 18 mg, and one subject even 10 mg after training periods lasting from a minimum of 10 to a maximum of 50 days. However, mood changes were observed only with doses of 100 mg or more, leaving open the question of which stimulus properties allowed the detection of the doses below 100 mg.

A later study (Evans and Griffiths, 1991) tested a number of moderate caffeine users who were first trained to discriminate 0 and 300 mg of caffeine and then tested as to which other doses they might generalize this discrimination to. Training to criterion took the shortest time (6 sessions) in the subject with the lowest habitual caffeine consumption and longest (16 sessions) in the subject with the highest habitual consumption. Doses of 300 mg or more were more easily detected than the lower doses, and the data suggest that the higher doses were mainly recognized by their negative effects (e.g., the subjects felt jittery, anxious, or nervous), whereas the lower doses were detected by feelings of "no effect at all" or by the negative feelings of caffeine withdrawal such as tiredness, sluggishness, or headache. Quite strikingly, however, doses in the middle range of around 100 mg, which closely approach the caffeine content of a normal serving of coffee, were detected poorly or at chance level only.

Such doses, which neither induce feelings of withdrawal nor of overdose, were shown by Hughes et al. (1992a) to be preferred by moderate coffee drinkers. Subjects were tested for their preference under blind conditions across a range from 25 to 200 mg of caffeine added to decaffeinated coffee. Out of eight subjects, two preferred coffee with 25 mg, four preferred coffee with 50 mg, two coffee with 150 mg, and none coffee with 200 mg. In one study it was shown that subjects involved in a discrimination study were able to make an accurate choice of caffeine or placebo (Silverman et al., 1994). After subjects had established an ability to discriminate caffeine (100 mg) from placebo, they were able, reliably, to choose letter-coded caffeine capsules when aiming for vigilance, and letter-coded placebo capsules when the aim was relaxation. This finding could possibly relate to the question of caffeine reinforcement (see below).

As already noted, psychomotor stimulants do not readily generalize to caffeine (Chait and Johanson,

1988). The reverse experiment was tried by Oliveto et al. (1993). Healthy volunteers were trained to discriminate between caffeine (320 mg/70 kg, p.o.) and placebo, using monetary reinforcement of correct letter code identification. After four training sessions, subjects were tested with the training conditions until they were >80% correct on four consecutive sessions. As expected, theophylline (56–320 mg/70 kg) produced 100% appropriate responding, albeit with interindividual differences in the doses required, whereas buspirone (1–32 mg/70 kg) did not. The psychostimulant methylphenidate (10–56 mg/70 kg) produced increases in caffeine-appropriate responding in most but not all subjects, and only at the highest dose. Together, these two studies indicate that in humans psychostimulants and caffeine are experienced in similar, but not identical manner.

As discussed by Griffiths and Mumford (1996) the available evidence does not favor the view that caffeine discrimination in humans requires that the subjects be in a state of withdrawal. Indeed this is what should be expected from the animal data.

C. Dose Adjustment

It is a characteristic of several substances of abuse, including morphine and cocaine, that the intake is adjusted so that a relatively constant plasma or brain concentration is achieved: this can be called *dose adjustment* or *drug titration*. In animals, such dose titration can readily be studied provided that a sustained and relatively constant rate of a drug-induced behavior can be maintained. However, as discussed below (Section IX) such constant and regular intake has not been possible to achieve with caffeine in animals and hence there are no reliable animal data relating to this point. In the case of humans, dose adjustment could be assumed if subjects would increase coffee drinking when offered coffee containing less caffeine and vice versa. Griffiths and co-workers (1986) switched subjects with drug abuse histories and self-reported caffeine consumption of 100 mg or more per day under blind conditions to decaffeinated coffee. However, the number of daily cups of coffee remained practically unchanged. On the other hand, clear evidence of avoidance was obtained, when coffee with increased and nonhabituated amounts of caffeine was offered.

In two similarly designed field studies, there were no differences in the daily consumption between the groups offered regular or decaffeinated coffee (Höfer and Bättig, 1994a,b). In addition, none of the subjects were able to tell at the end of the experiments exactly on which days they had consumed regular or decaffeinated coffee. Similar results were also obtained in one laboratory experiment in which the subjects had to perform the Stroop task before and after drinking coffee containing either 250 mg or only traces of caffeine (Hasenfratz and Bättig, 1992). Thus, there is no evidence in support of caffeine dose adjustment in human and animals.

IX. Reinforcing Effects of Caffeine

The literature on the reinforcing effects of caffeine has been excellently summarized (Griffiths and Mumford, 1995, 1996). In particular, the earlier article clearly summarizes the salient findings of all the relevant studies before 1995. Here we will focus on certain aspects of this phenomenon.

A. Reinforcement in Animals

1. Intravenous and Oral Self-Administration. Reinforcing efficacy of a drug refers to the relative efficacy in establishing or maintaining behavior on which the delivery of the drug is dependent. The most widely used technique in animals is i.v. self-administration. The reinforcing efficacy of caffeine has been studied after the implantation of venous catheters allowing the animals to self-administer the drug by pressing a lever or some other means, such as poking the nose at an appropriate target.

In nonhuman primates, caffeine can act as a reinforcer in some conditions (see Griffiths and Mumford, 1995; Howell et al., 1997). The results range from no reinforcement at all at a low dose of caffeine (0.2 mg/kg) (Hoffmeister and Wuttke, 1973), to maintenance of self-administration in a minority (25–33%) of the animals (Atkinson and Enslen, 1976; Collins et al., 1984), to an effect observed in all the animals (Deneau et al., 1969; Griffiths et al., 1979; Dworkin et al., 1993). The self-administration of caffeine in nonhuman primates is quite irregular, with periods of relatively high rates alternating with periods of low rates of caffeine self-administration (Deneau et al., 1969; Griffiths et al., 1979; Griffiths and Mumford, 1995), and, under conditions when cocaine and amphetamine act reliably as reinforcers, caffeine cannot consistently be shown to be self-administered. In particular, the fact that there is no maintenance of a regular rate of caffeine self-administration means that it is impossible to examine questions of dose titration, although this is readily done with drugs such as cocaine.

In the early studies in rats, only some rats showed a response, and the overall effect was small (Atkinson and Enslen, 1976; Collins et al., 1984). Although rats respond at higher rates for caffeine than they will for saline (Deneau et al., 1969; Griffiths and Woodson, 1988b), the level of responding maintained by caffeine is far less than that maintained by nonxanthine psychomotor stimulants, such as cocaine and amphetamine and other phenethylamines. In a recent series of experiments on mice (Kuzmin et al., unpublished data) caffeine infusion was induced by nose-poke responses. The total number of nose pokes during a 30-min session in the "active" mouse (response-contingent caffeine infusion) was higher than that of the "passive" mouse (response-noncontingent infusion for the control of caffeine effect on nose-poke behavior). In this mouse model, ac-

quisition could thus be demonstrated, as has previously been done in rats. To our knowledge, this is a first demonstration of caffeine i.v. self-administration in mice. The efficacy of the model may be related to the fact that nose poking is a form of spontaneous natural orienting behavior in the mouse; this might facilitate learning of positively reinforced responding. In fact, spontaneous nose poke activity is usually quite high, favoring the self-infusion of the drug under investigation in pharmacologically active bolus doses which are at the same time not too high to disrupt association between nose poke and drug psychotropic effect. Moreover, the partial immobilization limits the behavioral repertoire, favoring nose pokes. Because locomotor activity is relatively high in mice, the probability of spontaneous nose pokes, with the contingent infusions of the drug, is higher than in the classical models of the acquisition of i.v. self-administration in rats. It is important that the nose-poke model makes it possible to compare reinforcing potencies and efficacy values of different compounds. For example, cocaine had a higher potency (lower EC_{50}) and efficacy (maximal values of reinforcing criteria) than caffeine. Hence, despite the fact that caffeine can, under some experimental circumstances, support initiation of i.v. self-administration, it is markedly less efficacious than drugs such as cocaine. Just as in the case of nonhuman primates, acquisition of the drug-related behavior can be demonstrated, but it is poorly and irregularly maintained.

The interpretation of the above data is also limited by the fact that all these animal studies concern i.v. self-administration, whereas human caffeine consumption is always by the oral route. This point is particularly relevant because the effects of the drug of abuse, cocaine,

differ with the route of administration—i.p. or i.v. (Porrino, 1993).

In oral self-administration studies in rats, preference for caffeine solution over water was demonstrated only at extremely low concentrations that resulted in very low intake (Heppner et al., 1986). Preference for caffeine in such high concentration in drinking water that behaviorally active amounts are ingested was demonstrated only after a 14-day period of forced exposure (Vitiello and Woods, 1977). Oral self-administration may be increased by food deprivation or chronic nicotine exposure (Heppner et al., 1986). Using a fixed-time schedule for presentation of a food pellet, it was possible to demonstrate more drinking of a caffeine solution than of water (Falk et al., 1994).

2. Reinforcing Effects of Caffeine: Place Conditioning. An animal placed in an experimental box with two identifiable compartments can be given drugs when it is in one of the compartments. If this is repeated the animal will, by a variant of classical conditioning, associate that compartment with the effects of the drug. In a test session one can then determine if the animal prefers the drug-associated compartment (conditioned place preference) or avoids it (conditioned place aversion). Conditioned place preference occurs with a low dose of caffeine (3 mg/kg) in rats (Brockwell et al., 1991). At a dose of 30 mg/kg or higher, place preference was replaced by place aversion. The nonselective adenosine receptor antagonist CGS 15943, but not the A_1 antagonist DPCPX, produced a significant conditioned place preference, suggesting that adenosine A_{2A} receptors are particularly important in mediating the response. A study (Patkina et al., unpublished data; see Fig. 7) investigating the
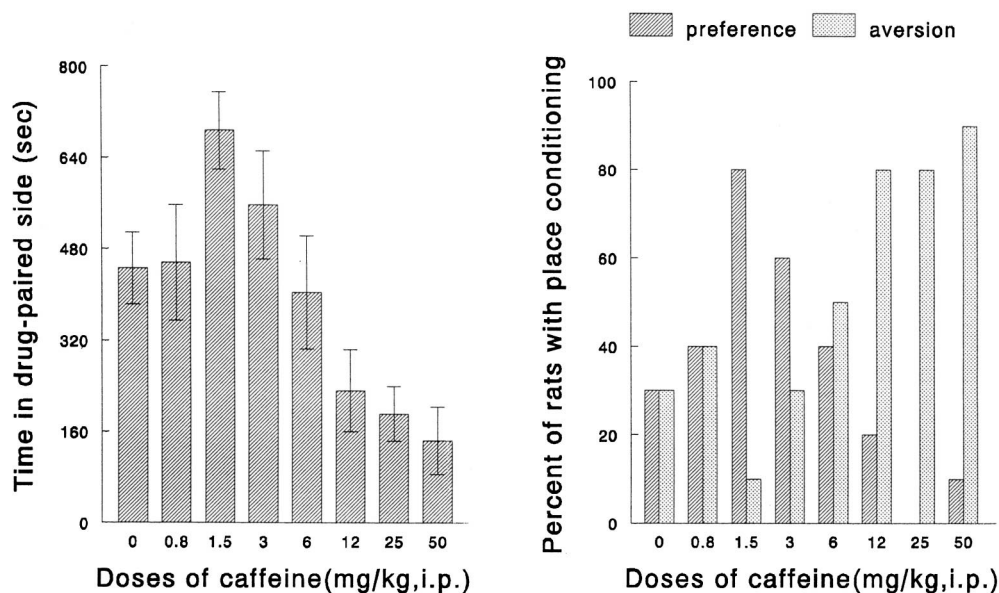

FIG. 7. Caffeine place conditioning in rats (Patkina and Zvartau, unpublished data). Left, scores of place conditioning (time spent in drug-paired side) across doses of caffeine (mg/kg, i.p.). Rats were allowed to freely investigate a shuttle box. Rats that spent approximately equal amounts of time in the two compartments were, in a second phase, injected with caffeine while in one of the compartments on four consecutive days. To evaluate the preference, the animals were then allowed, in a drug-free state, to freely investigate the shuttle box. Right, score of place conditioning (percentage of animals with place preference/aversion) across doses of caffeine.

place conditioning effects of caffeine over a wider range of doses (0.8–50 mg/kg, i.p.) demonstrated the ability of caffeine, depending on the dose given, to establish both conditioned place preference and place aversion. The maximal conditioned place preference effect of caffeine was seen at the dose of 1.5 mg/kg, and significant conditioned place aversive effect was seen at the dose of 25 mg/kg.

The possible involvement of adenosine receptors was tested in mice. Low doses of theophylline (<25 mg/kg) showed conditioned place preference, whereas doses higher than 50 mg/kg produced conditioned place aversion. 8-Phenyltheophylline, a nonselective adenosine receptor antagonist with a low ability to block phosphodiesterases, also produced conditioned place preference (Zarrindast and Moghadamnia, 1997). These authors also used adenosine receptor agonists, but the interpretation of these findings is complicated by the known effects of such drugs on, for example, the circulatory system.

In another study (Patkina and Zvartau, unpublished data) the place conditioning technique was used to compare the rewarding potential of caffeine with that of cocaine, nicotine, and ethanol. Caffeine (1.5 mg/kg, i.p.), cocaine (5 mg/kg, i.p.), nicotine (0.6 mg/kg, s.c.), and ethanol (1.5 g/kg, i.g.) did produce comparable reinforcing effects in an unbiased place conditioning paradigm in rats. The animals then had the opportunity to "compare" the rewarding effects of two drugs. All the animals preferred cocaine over caffeine, but there were no significant differences between the other three drugs.

Caffeine is thus able to act as a reinforcer in several animal species under a certain range of conditions but is unable to maintain self-administration behavior, in contrast to what is seen after other psychostimulant drugs. These data point out a marked difference between caffeine and drugs such as amphetamine and cocaine that maintain self-administration across species and conditions (Griffiths et al., 1979; Pontieri et al., 1995). The inconsistency between the data of the different studies seen with caffeine is similar to that seen in nicotine self-administration studies (Goldberg and Henningfield, 1988; Dworkin et al., 1993). The fact that regular caffeine intake is very difficult to maintain in animals also means that it has not been possible to study caffeine in reinstatement paradigms. Thus, it has been difficult to experimentally address the question of whether caffeine "craving" exists. Caffeine has, however, been shown to affect cocaine reinstatement (see below Section XIIB).

B. Reinforcement in Humans

In humans, the widely recognized behavioral stimulant and mildly reinforcing properties of caffeine are probably responsible for the maintenance of caffeine self-administration, primarily in the form of caffeinated beverages, such as coffee, tea and cola (for review see Nehlig and Debry, 1994; Griffiths and Mumford, 1995). All in all, Griffiths and Mumford in their review (Griffiths and Mumford, 1995) concluded that caffeine reinforcement occurred in about 45% of moderate or heavy caffeine users.

Most of the animal studies discussed above were performed using injection of caffeine, whereas most human studies examined oral caffeine. In a recent study (Rush et al., 1995) i.v. caffeine (37, 75, 150, or 300 mg/70 kg) was given twice with at least 24 h delay. The subjects reported a dose-dependent, rapid drug effect that was described as "a high". They liked the drug and reported overwhelmingly positive effects. Importantly, these effects were very transient: with the lower doses the effects were over within 10 min and only when the highest i.v. dose was given did the effect last for 20 to 40 min. At the highest dose, virtually all the subjects identified the drug as a stimulant (Rush et al., 1995).

Also in studies with oral intake, the reinforcing effect of caffeine varies with the dose. It has been pointed out that the dose-response relationship in humans may resemble that in animals: an inverted U-shape, with high doses sometimes associated with aversion (Griffiths and Mumford, 1995; Garrett and Griffiths, 1998). Doses of caffeine encountered in tea and coffee are high enough to act as reinforcers, but as pointed out above, a significant factor appears to be avoidance of withdrawal effects (Schuh and Griffiths, 1997). The relationship between pre-exposure to caffeine and caffeine reinforcement requires further study (Griffiths and Mumford, 1995). Caffeine users, but not people who do not consume caffeine, showed a preference for a fruit juice drink containing caffeine (100 mg) as a postlunch beverage (Richardson et al., 1996). This provides, according to the authors, evidence for the existence of a reinforcing effect of caffeine, which requires prior exposure to caffeine-containing drinks. The consumption of the caffeine-containing drink prevented a postlunch dip in mood in the habitual caffeine consumers. This is compatible with prevention of a slight withdrawal effect, but also with the effects of caffeine on blood flow distribution. A similar study (Rogers et al., 1995) investigated caffeine reinforcement by assessing changes in preference for a novel drink consumed with or without caffeine. Caffeine had no significant effects on drink preference in subjects with habitually low intakes of caffeine, whereas users of higher doses of caffeine developed a relative dislike for the drink lacking caffeine. This could be related to a lowered mood following overnight caffeine abstinence, which was significantly improved by caffeine. However, another study (Brauer et al., 1994) found that subjects' ratings of the pleasantness of the coffee taste were not significantly altered by caffeine deprivation. In several studies, only 10 to 50% of the individuals reliably chose caffeine over placebo [for review see Silverman et al., 1994] and subjects do not always show a clear caffeine withdrawal syndrome under a placebo condition (Grif-

fiths and Mumford, 1995). One problem is that the ability to discriminate between caffeine and placebo is acquired slowly, another is that the behavioral requirements following caffeine ingestion, such as tasks requiring enhanced vigilance, can affect caffeine reinforcement (for review see Silverman et al., 1994). Therefore, many different aspects of caffeine reinforcement remain to be explored.

The reinforcing effect of any given substance can be assessed by determining how much work would be performed or money spent in order to get access to it. A series of earlier studies (in part not very systematic) documenting reinforcement through caffeine in humans and animals was reviewed by Griffiths and Woodson (1988). Griffiths et al. (1989) used more stringent conditions in a group of six consumers with excessively high caffeine intake (>1000 mg/day) by requiring ergometer cycling for getting either decaffeinated coffee with 100 mg or no caffeine or capsules with 100 mg or no caffeine. The subjects took 10 servings per day when only a few minutes of cycling were required, but this decreased to about two servings per day when the price, in minutes of cycling, was gradually increased to 32 min. Decaffeinated coffee was almost as valuable to the subjects as caffeinated coffee or caffeine capsules and it was only the placebo capsules that were not deemed worth any cycling work at all. In a later study from the same laboratory (Evans et al., 1994), caffeine reinforcement was demonstrated in a majority of moderate caffeine users. A mutually exclusive choice procedure was used to evaluate the reinforcing effects of caffeine in subjects with histories of regular caffeine consumption (256 mg/day). Subjects participated for 24 weeks; each week consisted of three consecutive daily sessions (two sampling days followed by a choice day) during which subjects were required to abstain from dietary sources of caffeine. On each sampling day, subjects ingested four capsules, one every 2 h. Capsules contained placebo on one sampling day and caffeine (50 or 100 mg/capsule) on the other sampling day. Placebo and caffeine were associated with different color-coded capsules. At the beginning of the choice day, subjects chose one of the two color-coded capsules they wished to take on that day; they were required to ingest one capsule and, thereafter, they could ingest up to six additional capsules of the same color throughout the day. Across subjects and dose, caffeine was chosen over placebo on 80% of choice occasions; nine of 11 subjects chose caffeine on more than 70% of choice occasions and caffeine choice was replicable despite changes in capsule colors across blocks.

Another study from the same laboratory (Silverman et al., 1994) revealed that situational conditions might have a substantial effect on caffeine reinforcement. Subjects previously trained to discriminate caffeine from placebo, after being given the choice between caffeine and placebo, were engaged either in relaxation or in vigilance. All six subjects chose caffeine before vigilance and four of the six consistently chose placebo before relaxation. Furthermore, six of seven subjects were ready to spend money to receive caffeine when vigilance rather than relaxation was the aim.

Another approach is to test whether consumption of a fixed-price item increases, decreases, or remains unchanged when the price of another item increases. Several studies using this technique for pharmacological questions have been reviewed (Bickel et al., 1995). Increasing consumption of a fixed-price item when the other one became more expensive, indicating thus a substitute function, was particularly apparent for different preparations of opiates, cocaine, phencyclidine, and pentobarbital. Independence of two rewards was seen between phencyclidine and saccharine, between morphine or heroin and food, between alcohol and cigarettes, and in several studies between caffeine and cigarettes. Using this method, the reward values of cigarettes and coffee were compared (Bickel et al., 1992).

When the price of coffee increased in terms of the number of responses required, coffee drinking decreased and the consumption of fixed-price cigarettes remained unchanged. On the other hand, both coffee and cigarette consumption decreased when the cigarettes became more expensive and the price of coffee remained fixed. This suggests not only a complementary function for the two rewards but also that the interaction between two substances can be asymmetrical.

In theory one might also use data on consumption versus price in the entire community. This was done by Olekalns and Bardsley (1995, 1996), and they found a high degree of price sensitivity, which in economic terms was described as rational and also forward looking.

X. Possible Reinforcing Effects of Coffee, Independent of Caffeine Content

Even though there has been no demonstration yet of the possible reinforcing effects of coffee that are unrelated to caffeine, the smell and flavor of coffee and the social environment that usually accompanies a coffee break or an after-dinner coffee should not be totally neglected as factors in everyday coffee drinking. The possible effect of some other constituents of coffee has not been extensively explored, but there are some suggestive data.

Similar amounts of work on an ergometer were spent for caffeine capsules, regular and decaffeinated coffee and only the placebo capsules were considered not to be worth any effort (Griffiths et al., 1989). In a field study, a switch from filter coffee, to which the subjects were accustomed, to decaffeinated instant coffee supplemented with different amounts of caffeine, decreased the number of cups of coffee consumed per day slightly but significantly, regardless of the amount of caffeine (Höfer and Bättig, 1994a). In parallel, the ratings for the pleasantness of these substitutes for the habituated fil-

ter coffee decreased strongly but also independently of the caffeine content.

In another field study, this general finding was confirmed (Höfer and Bättig, 1994a). Two groups of 21 female regular coffee drinkers participated in the experiment. Both groups started with a 3-day baseline period with drinking of filter coffee. After this initial period one group obtained 50 mg of caffeine in tablets, whereas the other group received decaffeinated instant coffee for the following 3 days. As in the first study, less instant coffee was consumed than filter coffee, but the number of tablets taken instead of coffee decreased even more, resulting in a decrease of saliva caffeine by about 50%. During the second 3 days, the subjects had to rate six times per day their desire for coffee. This desire increased considerably and in a highly significant manner in the group given caffeine tablets but remained unchanged in the group given decaffeinated instant coffee, although this group, in contrast to the group consuming the caffeine tablets, experienced considerable symptoms of caffeine withdrawal. All measures returned to baseline values on a 7th day of the experiment when the subjects were allowed to drink again the filter coffee they were accustomed to.

All these results suggest that the type of drink, and even the type of coffee, is a significant factor in the subject's preference for coffee. In particular, coffee drinkers were not attracted by caffeine capsules, except, possibly, to relieve withdrawal effects. It is conceivable that the low liking of the capsules can in part be related to the fact that a warm drink in itself produces a number of physiological effects (Quinlan et al., 1997). Interestingly, some of the effects of hot water are influenced by caffeine, but the type of beverage and the presence or absence of milk modifies the overall response (Quinlan et al., 1997). For example, the addition of milk appeared to have positive mood effects and to cause reduced anxiety. Conversely, liking for the taste and aroma of coffee might be acquired through the process of classical conditioning, involving association of these orosensory cues with the psychopharmacological consequences of caffeine ingestion.

XI. Comparisons with Known Addictive Compounds and Interactions between Caffeine and Addictive Drugs

A. General Considerations

It is generally admitted that even though important variations in individual sensitivity to the effects of caffeine exist, abuse of caffeine represents a minimal risk, particularly when compared with other stimulant drugs (Griffiths et al., 1986a). Recently, the effects of an i.v. administration of caffeine were tested in 10 subjects with histories of stimulant drug abuse. In that study, caffeine dose-dependently increased ratings of positive mood, and the higher doses of caffeine were more fre-

quently identified with other stimulant drugs like amphetamine and cocaine. While the effects of i.v. administration of caffeine on mood were similar to those previously reported for cocaine in the same subjects, the physiological effects were different (Rush et al., 1995). In other respects as well, caffeine differs from drugs that are typically abused (Heishman and Henningfield, 1994). Thus, there is little evidence for compulsive use of caffeine. Hence, the great majority of consumers drink caffeinated beverages in a controlled manner, although a small minority use caffeine compulsively, such that they have difficulties in reducing or stopping intake.

B. Interactions between Caffeine and Cocaine or Amphetamine

To compare caffeine with other substances, effects on mood (POMS scale) and euphoric and dysphoric effects (using several different scales) of placebo, caffeine base (50–800 mg) and amphetamine (25 mg) were measured (Chait and Griffiths, 1983). Caffeine and amphetamine produced markedly different subjective and behavioral effects. Amphetamine produced a prominent increase in the MBG scale (euphoria), whereas caffeine gave only very modest dose-related increase in euphoria in the range of 200 to 800 mg.

Caffeine is able to sensitize rats to the reinforcing effects of cocaine (Horger et al., 1991) in that self-administration was acquired more rapidly and the cocaine-induced increases in dopamine release were stronger. Caffeine also enhanced cocaine-induced conditioned place preference (Tuazon et al., 1992), but it is unclear whether we are dealing with true synergy or only with additivity (Bedingfield et al., 1998). In some rhesus monkeys trained to self-administer smoked cocaine base, pretreatment with oral caffeine increased the number of smoke deliveries using a high dose (1.0 mg/kg per delivery) but not a low dose (0.25 mg/kg per delivery) of cocaine. The authors concluded that caffeine pretreatment can produce small, but statistically significant increases in smoked cocaine self-administration in rhesus monkeys, but the interpretation of this finding is not straightforward. Essentially similar results were obtained in a rat study where rats self-administering cocaine were treated with caffeine either as an i.p. injection (20.0 mg/kg) before each self-administration test or the caffeine was coadministered with cocaine in the infusion syringe (0.25 mg/kg per infusion). Both of these routes of administration of caffeine increased the intake of low doses of cocaine (Schenk et al., 1994). An increased self-administration of cocaine could easily be construed as evidence of a blockade of the action of cocaine.

In drug discrimination studies, cocaine substituted for the caffeine-discriminative stimulus in rats trained to discriminate caffeine from saline (Holtzman, 1986), whereas caffeine only partially substituted for the cocaine-discriminative stimulus in rats trained to discrim-

inate cocaine from saline (Gauvin et al., 1989, 1990; Harland et al., 1989). Similarly, the potentiation by caffeine of the effects of low doses of dopaminergic agonists has been observed in the tests of the discriminative stimulus properties of both amphetamine (Schechter, 1977) and apomorphine (Schechter, 1980).

These studies have thus shown caffeine effects on acquisition of cocaine-related behavior, interaction with the maintenance of such behavior, and a partial overlap in drug discrimination. It was also demonstrated that caffeine dose-dependently reinstated extinguished cocaine-taking behavior in rats, indicating that nondopaminergic agonists can also provide an effective prime to reinstate responding (Worley et al., 1994). Although caffeine was an effective cue for reinstatement of extinguished cocaine taking, the effect was reduced when repeated exposures occurred in the test environment (Schenk et al., 1996). In rats trained to press a lever to self-administer cocaine, substitution of saline for cocaine leads to a progressive decline in lever pressing. In such animals a priming dose of 10 mg/kg caffeine, given s.c., reinstated the lever pressing to an extent resembling that achieved by the dopamine $D_{2/3}$ agonist 7-OH-dopamine (Self et al., 1996). By contrast, a dopamine D_1 agonist reduced the priming effect of cocaine in this paradigm.

It has been suggested that caffeine may be capable of priming reward-relevant circuitry that is used by cocaine. In an unpublished study, Kuzmin, Johansson, Zvartau, and Fredholm used a mouse model that tests whether drug-seeking behavior can be reinstated by noncontingent drug primes. Naive DBA/2 mice were trained to self-administer cocaine i.v. (bolus dose 0.04 mg/kg) in a single initiation session. Cocaine exhibited a distinct reinforcing effect, which manifested itself as a higher level of nose-poke responding in "active" mice (response-contingent injections) when compared with "passive" mice (yoked control). Forty-eight hours later the mice were placed again in the operant boxes but without i.v. infusions. Groups of mice were treated i.p. with saline, low or high doses of cocaine (5 and 20 mg/kg) or caffeine (3 and 30 mg/kg). In saline-treated animals a time-dependent extinguishing of the drug-related behavior was found. Administration of both caffeine and cocaine in the high doses produced immediate elimination of the cocaine reward-associated behavior. Conversely, noncontingent priming injections of the low doses of cocaine and caffeine were found to have a priming effect, i.e., they reinstated the extinguished cocaine-seeking pattern despite the absence of contingent infusions of cocaine. This effect of caffeine could be partly mimicked by DPCPX, an adenosine A_1 receptor antagonist, but not by the A_{2A} receptor antagonist SCH 58261. This is surprising because evidence was recently presented that acute disruption of cAMP generation in the nucleus accumbens might provide a stimulus for drug relapse (Self et al., 1998). The adenosine A_{2A} receptor

antagonist would be expected to do this directly, but the A_1 antagonist only indirectly.

These findings may be taken as evidence that caffeine use is a risk factor for individuals who have been cocaine abusers. This conclusion is, however, not necessarily warranted. Normal caffeine use in humans is long-term, oral use, whereas the experiments in rodents used single parenteral administrations. As noted elsewhere in this review, there can be major differences between acute and long-term caffeine use. As yet unpublished data from our groups suggest that this may be true in this context.

It has been found that caffeine use is less prevalent among cocaine users than among age-matched controls, and that the amount of cocaine is reduced among the cocaine users who do consume caffeine (Budney et al., 1993). However, much more research on humans is needed. Recently, it was found that, in a small group (11 subjects) of former cocaine users, caffeine did not produce cocaine-like effects and it did not increase the desire for cocaine (Liguori et al., 1997). Nonetheless, the majority of the subjects preferred caffeine-containing coffee over decaffeinated. This suggests that there may be major differences between current cocaine users (Rush et al., 1995) and ex-cocaine users (Liguori et al., 1997).

C. Interactions between Caffeine and Ethanol

There is a weak association between caffeine and alcohol consumption, which is stronger if the drugs are used heavily (Istvan and Matarazzo, 1984). At least part of the association may be related to a factor denoted *polysubstance use* (Swan et al., 1996).

There is some evidence for a causal link between caffeine and ethanol use from animal studies, and this relates to effects of ethanol on adenosine. Thus, there is evidence that ethanol can increase adenosine levels by decreasing adenosine uptake (Diamond and Gordon, 1994) or secondarily to acetate metabolism (Carmichael et al., 1991). Indeed, there is good evidence that the increase in portal blood flow that is observed following a meal with ethanol is due to acetate-induced formation of adenosine, which dilates the portal vessels (Carmichael et al., 1988). Therefore, caffeine can reduce this vasodilatation and redirect blood flow to other areas, including the brain. This may be one physiological basis for the marked alerting effect of a cup of coffee after a meal with ethanol intake.

The magnitude of the ethanol-induced increase in adenosine may be smaller in brain than in liver (Brundege and Dunwiddie, 1995; Fredholm and Wallman-Johansson, 1996). Nonetheless, there is some evidence that adenosine may contribute to the behavioral effects of ethanol (Dar, 1990). It has also been shown that mice bred for increased ethanol sensitivity also exhibit increased sensitivity to behavioral effects of adenosine analogues (Proctor et al., 1985), and this is related to the number of adenosine A_1, but not A_2, receptors (Fredholm et al., 1985). Furthermore, ethanol-

tolerant rats have been shown to be tolerant also to behavioral effects of adenosine (Dar and Clark, 1992). Some of the motor-incapacitating effects of ethanol have been suggested to depend on adenosine-related mechanisms in the basal ganglia (Meng and Dar, 1995). Part of this might be explained by an adenosine A_1 receptor-mediated modulation of ethanol-induced changes in striatal chloride ion flux (Meng et al., 1997). Based on studies using an antisense approach, it was suggested that adenosine A_1 receptors in this region are not important (Biggs and Myers, 1997). However, it was not shown that the antisense oligonucleotide altered A_1 receptor expression in this region and furthermore, as discussed above, many of the A_1 receptors in this region are present on nerve terminals and thus cannot be modified by local antisense injection. Acute administration of ethanol may also cause an increase in the number of adenosine A_1 receptors (Clark and Dar, 1991), but it is not known if long-term exposure has similar effects. A recent study using a rat model of alcoholism showed that life-long ethanol intake does not significantly affect the age-dependent changes in A_1 or A_{2A} receptors (Fredholm et al., 1998).

It is obvious that ethanol has a large number of effects that are unrelated to adenosine and that the interactions with caffeine will be complex. This is further underscored by the fact that the behavioral effects of both ethanol and caffeine are strongly dose- and time-dependent. Consequently, it is not surprising that a complex picture arises from the numerous animal studies (see White, 1994).

The literature on alcohol–caffeine interactions in humans is relatively modest despite the importance of the issue: we are dealing here with interactions between the two most widely used psychoactive compounds. One review (Fudin and Nicastro, 1988) mentioned among 20 studies a single study (Franks et al., 1975) that documented a significant antagonism between the two substances. All other considered studies differed widely in their methods and compared mostly the effect of alcohol alone versus the combination with caffeine, without ensuring that caffeine alone was able to affect the experimental variables in a direction opposite to that of alcohol. Thus, the fundamental question—if caffeine specifically antagonizes ethanol effects or if one is considering the joint effects of a stimulant and a depressant drug—has often not been addressed. Several newer studies that included this necessary control condition were successful in demonstrating a significant antagonism in several test models, including compensatory tracking of a moving target with a joystick (Kerr et al., 1991), a digit-symbol substitution task (Rush et al., 1993), and a subject-paced rapid information processing task (Hasenfratz et al., 1993). In these three experiments caffeine was given not after alcohol, as was done in most earlier studies, but rather some time before or at the latest together with alcohol. One investigation of this dimension even suggested that it may be more helpful to drink a few cups of coffee before rather than after a party (Hasenfratz et al., 1994). There thus appears to be a negative interaction between caffeine and alcohol in humans. It appears to be at least as complex as in animals, and to depend on the doses, the considered variables, and the order and time interval between the intake of the two substances, to mention but a few aspects.

D. Interactions between Caffeine and Nicotine

There is a positive correlation between drinking coffee and smoking (Istvan and Matarazzo, 1984; Puccio et al., 1990; Swanson et al., 1994), which is stronger and more consistent than that between drinking coffee and alcohol. In addition, it is well known that smokers are particularly liable to smoke when drinking coffee, whereas, on the other hand, coffee is consumed more in the morning and alcohol in the evening. In twin studies, a heritability for caffeine consumption (36%) was detected, but this was lower than for smoking (56%) or alcohol consumption (50%) (Swan et al., 1996). Furthermore, multivariate analysis showed that about 10% of the total variance in caffeine consumption could be related to a common factor related to drug use, but in the case of nicotine the contribution of this factor was more than one third of the total variance (Swan et al., 1996). According to an extensive review by Swanson et al. (1994), all considered studies reported smokers to drink more coffee, on an average of about 50% more. There is also a larger proportion who do not consume caffeine among nonsmokers than among smokers. The review also cites several studies showing that the typical desire of smokers to smoke while drinking coffee is independent of the caffeine dose. There is, however, no evidence that caffeine intake increases the number of cigarettes smoked or the amount of smoke inhaled (Chait and Griffiths, 1983; Rose, 1987). In this respect, caffeine differed from amphetamine, which did increase both parameters. The amounts of nicotine and its metabolites in blood are also unchanged by caffeine intake at several dose levels for several days (Brown and Benowitz, 1989). In another study (Lane, 1996) it was found that the rate of smoking was higher during such periods of the day when caffeine-containing beverages were consumed than during other parts of the day. However, only a minimal part of the total number of cigarettes consumed were associated with caffeine intake, and at least half of the caffeine intake occurred without smoking. This suggests that other variables than caffeine are of overriding importance.

There is ample evidence that smokers metabolize caffeine by approximately 50% more rapidly than nonsmokers (Benowitz et al., 1989). Exsmokers consume somewhat less caffeine than smokers (although more than nonsmokers), but they also metabolize the drug more slowly (Swanson et al., 1994). Thus, the levels of caffeine may be at least as high. As we noted above, the effects of caffeine are probably due to a mixture of caffeine,

theophylline, and paraxanthine, and the changes in the total amount of active drug are not known. Therefore, the speculation (Swanson et al., 1994) that lowered metabolism of caffeine in exsmokers may lead to increased toxicity remains unsubstantiated.

Both nicotine and caffeine are minor stimulants and one might expect that these effects would be additive. This appears to be the case for the cardiovascular actions and the effects on plasma catecholamines (Smits et al., 1993; Perkins et al., 1994) and EEG (Hasenfratz and Bättig, 1992). There appear to be no additive effects on subjective arousal and mental performance. There was no additive effect for the beneficial actions of the two substances on rapid information processing (Hasenfratz et al., 1991) or on the Stroop task (Hasenfratz and Bättig, 1992). Interestingly, an increase of subjective arousal with either caffeine or nicotine alone but an antagonistic effect with the two in combination has been reported (Rose, 1987).

It has also been reported (Rush et al., 1995) that, among stimulant abusers, those who do not smoke report a higher reinforcing effect of caffeine than do the smokers. If such results were confirmed, they would suggest that the coconsumption of the two substances might not be pharmacologically based.

XII. Possible Harmful Effects of Caffeine at the Individual or Social Level—Abuse or Misuse

Negative social consequences of coffee drinking are not claimed, but DSM-IV (1994) lists caffeine intoxication, caffeine-induced anxiety, and sleep disorders as caffeine-induced disorders.

Despite its wide availability, caffeine intoxication occurs rarely. The lethal dose has been estimated to be in the range of 10 g (Ritchie, 1975), which would correspond to about 100 strong coffees. Provided adequate emergency measures are taken, patients appear to survive levels up to 1 mM or even slightly above, but still higher levels are fatal (Rivenes et al., 1997). Among the 3749 cases of "caffeine exposure", registered during 1 year by the American Association of Poison Control Centers, there were only three fatalities (Litovitz et al., 1987).

Although caffeine overdoses can induce anxiety, there is little and in part controversial evidence as to whether coffee might play a significant role in this disorder (see above Section IVB). No significant association between anxiety and coffee or tea consumption was seen in a US nationwide sample of 3854 subjects (Eaton and McLeod, 1984) or in an English sample of 9003 individuals (Warburton and Thompson, 1994). The same negative result holds also for depression (Warburton and Thompson, 1994), confirming the results of an earlier larger study (Jacobsen and Hansen, 1988). One possible explanation for this failure to find relationships between coffee drinking and anxiety may be that anxious subjects avoid coffee. In fact, avoidance of coffee by anxious subjects

has been reported repeatedly over the last decades (Boulenger et al., 1984; Uhde et al., 1984; Lee et al., 1985). A review on putative correlations between sleep disorders or insomnia and caffeine consumption would yield a similarly controversial picture, as discussed above in the chapter on tolerance for the sleep-disturbing effects of caffeine. As in the case of anxiety, it appears that by far the most consumers of coffee adapt their intake both with respect to time of day and dosage so as to avoid acute sleep disturbance or chronic insomnia.

When people are interviewed about psychoactive substance use disorders, seven criteria are used: 1) tolerance; 2) withdrawal; 3) substance often taken in larger amounts or over a longer period than intended; 4) persistent desire or unsuccessful efforts to cut down or control use; 5) a great deal of time spent in activities necessary to obtain, use, or recover from the effects of the substance; 6) important social, occupational, or recreational activities given up or reduced because of substance use; 7) use continued despite knowledge of a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by substance use. Because coffee or caffeine-containing nutrients or drinks are widely available and culturally accepted, their consumption does not usually have negative social consequences. Indeed, in the studies on caffeine dependence, criteria 3, 5, and 6 are usually excluded. Especially in the US there is no doubt that many individuals reduce or try to reduce their caffeine intake due to perceived health problems (see Hughes and Oliveto, 1997). Indeed, not less than 14% of all erstwhile consumers in Vermont had stopped the intake of all caffeine-containing beverages largely for this reason (Hughes and Oliveto, 1997). This relates to criterion 7 if these individuals have difficulties in reducing intake. One interesting question is therefore if caffeine poses a real health hazard or if the negative association between health and caffeine is a perceived one.

Considering the individual consequences, caffeine-induced dysphoria and nervousness could negatively influence the relationship of some individuals in the society. However, this aspect of caffeine consumption does not seem very pertinent.

The possibility that caffeine consumption may pose major health risks has been widely discussed (see James, 1991). Caffeine does raise mean arterial blood pressure by a few millimeters of mercury; this has been suggested to pose a health risk by some (James, 1991), but not by others (Tuomilehto and Pietinen, 1991). More recently, greater concern has been voiced about the ability of caffeine to raise plasma cholesterol (Thelle et al., 1983, 1987). It is now known that the increase in plasma cholesterol is due to two diterpenes: cafestol and kahweol (see Urgert and Katan, 1997). These compounds are largely eliminated when coffee is prepared by filtration or percolation or from instant coffee. By contrast, boiled coffee and Turkish coffee, and to a lesser extent

espresso and mocha coffee, do contain these diterpenes and have been shown to raise cholesterol levels by some 0.1 to 0.5 mM during prolonged use (see Urgert and Katan, 1997). The rather low intake of these brews suggest that coffee contribution to overall cardiovascular risk is small (Myers and Basinski, 1992; Greenland, 1993; Kawachi et al., 1994; Willett et al., 1996), even though it has been calculated that the large-scale switch from boiled to filtered coffee might have contributed to a third to half of the 10% reduction in serum cholesterol noted in Scandinavia since 1970 (Johansson et al., 1996b; Pietinen et al., 1996).

Another potential factor in predicting cardiovascular risk is plasma homocysteine. It was recently shown that, although coffee drinking per se has a limited effect on this variable, combined smoking and high coffee drinking was associated with an increased number of subjects with very high plasma homocysteine levels (Nygård et al., 1998). It is, however, too early to decide on the importance of these findings, particularly because the relevant intervention studies have not been performed.

There are several reports showing that very high doses of caffeine can have mutagenic or carcinogenic effects (see Mohr et al., 1993). This has raised concerns about cancer risks following normal caffeine consumption, but a careful consideration of the evidence "provides further reassuring information on the absence of any meaningful association of coffee with most common cancers" (La Vecchia, 1993).

Although there is a public perception (especially in the US) that caffeine is detrimental to one's health, this has a surprisingly weak basis in reality. On the other hand, health problems from other causes might provide an incentive to cease caffeine consumption, especially in the form of coffee. If this is true, then ex-caffeine consumers may constitute a subgroup with more health problems than the average population. This could be a concern in the interpretation of some epidemiological studies.

XIII. Conclusions

Caffeine is widely consumed throughout the world in behaviorally active doses. Most of the data suggest that caffeine, in the doses that are commonly consumed, acts primarily by blocking adenosine A_1 and A_{2A} receptors. The possibility that some, as yet unidentified, additional mechanism contributes, cannot be excluded, however. Caffeine thus has a unique mechanism of action among all centrally stimulating drugs. It does interact with the dopaminergic transmission, but the mechanism is very different from that of other drugs such as cocaine and amphetamine. Caffeine does not markedly increase the release of dopamine, and it does not lead to any substantial increase in activation of D_1 dopaminergic neurotransmission in nucleus accumbens, in contrast to the other central stimulants. Instead it increases transmission via cells equipped with dopamine D_2 receptors in this nucleus as well as elsewhere in the basal ganglia.

The effect of caffeine in nucleus accumbens is manifested as a *decrease* in activity of the cells involved, whereas the effects of cocaine and amphetamine are associated with an *increased* activity of the relevant cellular targets. Accordingly, the overall activity of the nucleus accumbens is much less affected by caffeine than by cocaine, nicotine, and amphetamine. Furthermore, the cells activated by cocaine possess particularly dopamine D_1 receptors, whereas those affected by caffeine possess D_2 and adenosine A_{2A} receptors. There is, however, very good evidence that D_1 and D_2 receptor-stimulating drugs interact and potentiate each other's actions. Thus, the unique molecular and cellular actions of caffeine in the brain do not a priori rule out a potential as an addictive drug, they only indicate that its stimulant effects are different from those exerted by drugs such as cocaine and amphetamine.

There is good experimental evidence that i.v. caffeine can act as a reinforcing agent in several paradigms. The reinforcing properties of caffeine are, however, very much weaker and less consistent than those of cocaine and amphetamine. In some studies, the effects of caffeine are even weaker in this regard than those of nicotine, which is notoriously unreliable as a reinforcing drug.

Another important issue relates to the mode of administration. The studies concerning caffeine reinforcement in animals have generally examined the effect of i.v. administered drug, despite the fact that this mode of administration is hardly ever used by humans. If caffeine is administered i.v., human subjects report a higher liking than after oral use.

One important aspect of caffeine use is that the margin for dose increases may be limited by the biphasic effects of the drug. It is important to remember that the doses of caffeine that cause reinforcement in animals are low and that high doses are aversive. Thus, reinforcement is observed with doses even below 1 mg/kg, and doses above 10 to 15 mg/kg are usually aversive. Similarly, doses that are behaviorally stimulant (increasing motor behavior) are below about 30 mg/kg, and doses above 50 mg/kg are generally depressant in these paradigms. A similar biphasic dose-response curve is observed in humans, with low doses being perceived as stimulant and pleasant, whereas higher doses frequently are associated with dysphoria or in extreme cases with clear-cut toxic effects. The exact reasons for these biphasic responses are unknown (even though some possibilities are outlined above), but the fact that the response curve is inverted U-shaped has very important implications for the possibilities of dose increases.

Caffeine has important effects on alertness, and there is no doubt that caffeine is widely consumed by subjects who need to stay awake. Caffeine also has some poorly investigated analgesic actions that contribute to its use. In some contexts there are performance-enhancing actions.

Tolerance develops to some caffeine effects but not to others. For example the blood pressure increase that is observed with acute administration of caffeine, and which is most likely centrally mediated, shows a rapid tolerance development. Other effects, including susceptibility to seizures and ischemic brain damage, actually demonstrate a complete effect reversal. By contrast, tolerance to discriminative stimulant effects, motor stimulant effects, and alerting actions develops more slowly and to a variable extent.

Withdrawal effects are observed after long-term caffeine use. The exact frequency may be debatable, but most studies indicate that the majority of subjects exhibit some withdrawal symptoms after acute discontinuation of caffeine. Withdrawal symptoms typically characterize physical drug dependence. It is, however, less clear if these withdrawal effects are a significant factor in continued caffeine use, at least for the majority of subjects (but see Garrett and Griffiths, 1998). The available evidence should probably be interpreted to indicate that, for some individuals and in some circumstances, caffeine can be used to alleviate withdrawal symptoms, but this is not the case for all subjects and the urge to re-administer caffeine is nowhere near as strong as in several other cases of drugs of addiction. Hence, despite the fact that individuals exist who profess a wish to stop using caffeine because of real or perceived detrimental effects and who yet persist in their caffeine use, the continued use "despite adverse psychological or physical effects" (Rang et al., 1995) does not appear to be a major issue in caffeine use (but see Hughes et al., 1998).

This leads naturally to another major consideration, namely, if caffeine use leads to major negative consequences. Because the drug is consumed by a majority of the adult population in most countries, it is clear that caffeine use does not introduce major social problems. In fact, there is even some, albeit weak, evidence to suggest that caffeine can improve social interactions. It is also widely accepted that compared with other widely used drugs such as nicotine (in smoked tobacco) or alcohol the social consequences of caffeine use are negligible. Thus, caffeine does not impose a potential health hazard or a polluted environment on fellow citizens as does smoking. Similarly, the behavioral changes are not nearly as great as those seen after use of ethanol.

Also there really is very little evidence that caffeine used in moderation leads to any significant negative effects on the health of the individual. Thus, initial concerns that coffee drinking may lead to increases in cancer incidence have now largely vanished. Similarly, concerns that coffee use is a cardiovascular risk factor have lessened. Instead there has been an increasing realization that some of the effects of caffeine use may be beneficial. The alerting actions, for example, have been shown to be important in reducing accidents during driving or night time work. There is accumulating evidence that caffeine use may reduce suicidal tendencies,

perhaps by being antidepressant. And performance of some types of activities is facilitated by caffeine use. For other stimulant drugs such as amphetamine and cocaine, as well as for opiates, the reason why many subjects eventually relapse into drug use is not the physical withdrawal effects (even though they may be more severe than observed with caffeine) but rather is brought about by drug-associated cues (O'Brien, 1995; Rang et al., 1995). We have found little evidence that this is a major factor in continued caffeine use.

From the above considerations it is clear that caffeine cannot really be considered a "model drug of dependence" (Holtzman, 1990), at least not if by "model" is meant "typical". Its weak reinforcing properties are due to a unique and atypical mechanism of action. The drug is self-limiting and subjects do not gradually increase the dose, because tolerance development to both the reinforcing and aversive effects is limited. There are few negative consequences of caffeine use in moderation and the withdrawal affects are modest and transient in the individuals that experience them. Because caffeine will, according to current drug classification schemes, be designated a drug of dependence, and that it will not, in this respect, be different from drugs such as amphetamine, morphine, ethanol, or nicotine, it is possible that, in addition to the qualitative criteria, some quantitative criteria of relative abuse potential and negative health consequences would be useful in a modified drug classification scheme. This is particularly true for a drug whose use is so entrenched in normal societal activities.

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