Caffeine

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20 Caffeine

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20.1 INTRODUCTION

Caffeine is the most widely consumed behaviorally active substance in the world. The behavioral effects of caffeine have been reviewed many times (e.g., Lieberman, 1992; Fredholm et al., 1999; Smith, 2002) and this chapter overviews the main findings and provides an update of recent research. Caffeine produces its behavioral effects through adenosine receptor antagonism and subsequent changes in many neurotransmitter systems. This results in increased alertness, and caffeine may be especially beneficial in low arousal situations (e.g., working at night, prolonged work, or sleep deprivation). It improves performance on tasks that are impaired when alertness is low (vigilance and sustained response). Such effects largely reflect increased turnover of central noradrenaline. In addition, it increases the speed of encoding and response to new stimuli, an effect that probably reflects changes in cholinergic functioning. More complex cognitive tasks show less consistent effects of caffeine, which is again consistent with its arousal-increasing effect. Beneficial effects have been observed in simulations of real-life activities such as driving and in interpolated tasks

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used in the field. Similarly, there is some evidence that regular consumption of caffeine has benefits, although this may depend on age. In terms of negative effects, there is little convincing evidence that caffeine produces major health problems. Sleep may be impaired if large doses are ingested late at night. Mental health problems (e.g., anxiety) have also been observed when very large doses are consumed or caffeine is given to those with existing psychopathology. Caffeine is not a typical drug of dependence and many of the withdrawal effects appear to be weak or transient. Overall, evidence shows that levels of caffeine consumed by most people have largely positive effects on behavior. The next section briefly describes sources of caffeine, metabolism of caffeine, results from animal studies, and our knowledge of underlying CNS mechanisms.

20.2 SOURCES OF CAFFEINE

Caffeine occurs naturally in dietary sources (food and drinks), is added to a number of products, and is present in certain medications. The major sources of caffeine vary from country to country and across different age groups. For example, in many Asian countries tea is the caffeine-containing beverage of choice, whereas in North America and many European countries coffee is the major source of caffeine. Cola beverages and energy drinks also contain caffeine and are popular worldwide and are often the major source of caffeine in younger groups. Caffeine is also added to many analgesics, and caffeine pills are sold in pharmacies as stimulants. Small amounts are also present in chocolate products (both drinks and chocolate bars). When caffeine is added to a product, the amount that is present is constant. However, where caffeine occurs in natural products, such as coffee or tea, the growing conditions, plant variety, processing and storage, and the method of preparation increase variability in the caffeine concentration of the final beverage. For example, coffee prepared by the drip method may contain more than 100 mg caffeine per cup, whereas instant (soluble) coffee contains ca. 60 mg per cup. Tea contains less caffeine than coffee (ca. 40 mg of caffeine) and most colas have 30 to 40 mg caffeine.

20.3 PATTERNS OF CONSUMPTION

Caffeine consumption from all sources has been estimated to be 70–75 mg/person/day worldwide (Gilbert, 1984), but reaches 210–238 mg/day in the U.S. and Canada and more than 400 mg/day in Scandinavia, where 80–100% of caffeine intake comes from coffee alone (Debry, 1994; Barone and Roberts, 1996). A recent study in the U.K. (Brice and Smith, 2002a) reported an average caffeine intake of about 220 mg/day, with about two third coming from coffee. It is also important to emphasize the large individual variation in consumption, with some individuals never drinking caffeinated beverages and a small minority ingesting more than 1000 mg/day.

20.4 CAFFEINE ABSORPTION, DISTRIBUTION, AND PHARMACOKINETICS

Caffeine (1,3,7-trimethylxanthine) is one member of a class of naturally occurring substances termed methylxanthines. Absorption from the gastrointestinal tract is rapid and reaches 99% in humans ca. 45 min after ingestion. The hydrophobic properties of caffeine allow its passage through all biological membranes and there is no blood-brain barrier to caffeine. The time for peak plasma concentration is variable (15 to 120 min) and caffeine half-lives range from 2.5 to 4.5 h. Caffeine half-life is reduced by 30 to 50% in smokers and is approximately doubled in those taking oral contraceptives.

20.5 CENTRAL NERVOUS SYSTEM (CNS) MECHANISMS

CNS mechanisms have been reviewed in detail by Fredholm et al. (1999). 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. 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, acetylcholine, dopamine, serotonin, glutamate, and GABA (Daly, 1993). Such effects show that caffeine has the ability to increase alertness, a possible reason why people consume caffeine-containing beverages. There are other effects of caffeine on the CNS (e.g., direct release of intracellular calcium and effects on alkaline phosphatase), but many of these only occur at doses well above the range of human consumption.

20.6 ANIMAL STUDIES

Much of our knowledge of the CNS mechanisms of caffeine comes from animal studies. It is difficult to extrapolate these findings to humans because of the issue of comparing doses in different species. This topic is discussed in detail in Fredholm et al. (1999), and it is generally assumed that 10 mg/kg in a rat represents ca. 250 mg of caffeine in a 70-kg human (3.5 mg/kg).

The effect of caffeine on locomotor behavior of animals has been widely studied. The threshold for such effects is 1 to 3 mg/kg and the peak effect between 10 and 40 mg/kg. Above 50 mg/kg there is evidence of reduced responding (see Fredholm et al. 1999). Caffeine has also been shown to increase cortical and hippocampal activity, which provides a plausible basis for examining cognitive effects of caffeine. Indeed, evidence from animal studies suggests that caffeine improves maze learning and visual discrimination (Daly, 1993). It has been suggested that blockade of the A_{2a} receptors may underlie the effects of caffeine on locomotion whereas blockade of adenosine A_1 receptors may be responsible for the effects of caffeine on cognitive tasks.

20.7 STUDIES IN HUMAN VOLUNTEERS

20.7.1 Caffeine and Mental Performance

This section is subdivided into two parts: research before 1990 [reviewed in detail by Lieberman (1992)] and research before 2000 [reviewed by Smith (2002)]. Recent developments in the topic are covered at the end of the chapter.

20.7.1.1 Research before 1990

When caffeine is consumed in moderate amounts, it is often regarded as a mild stimulant, a view suggested more than 400 years ago by Pietro della Vale [cited in Tannahill (1989)]. Reviews written in the 1980s (e.g., Dews, 1984) suggested that the effects were highly variable, which probably reflects the numerous problems associated with early studies of caffeine (e.g., use of insensitive tests and designs). Later reviews (e.g., Lieberman, 1992) argued that effects are task or situation specific and the following section considers results from studies using different types of task.

20.7.1.1.1 Sensory Functions

Lieberman (1992) stated, "there is no evidence to suggest that moderate doses of caffeine have direct effects on sensory function, although well controlled studies using state-of-the-art methods have not been conducted."

20.7.1.1.2 Reaction Time

A number of studies have shown beneficial effects of caffeine on simple reaction time (e.g., Clubley et al., 1979) and choice reaction time (e.g., Lieberman et al., 1987). Other research has demonstrated such effects in some groups but not others (e.g. the elderly but not the young — Swift and Tiplady, 1988) and with some doses but not others (e.g., Roache and Griffiths, 1987).

20.7.1.1.3 Sustained Attention

Several studies have shown that caffeine improves sustained attention (e.g., Clubley et al., 1979). Other researchers (e.g., Loke and Meliska, 1984) have failed to demonstrate significant effects of caffeine on vigilance, but there is little evidence to suggest that it may actually lead to impairments of performance of tasks requiring sustained attention.

20.7.1.1.4 Memory and Cognition

Effects of caffeine on memory are less evident, with most studies finding that it has no effect (e.g., Fine et al., 1982; Loke, 1988). This may, at least in part, reflect the limited number of studies of the topic and the restricted tasks investigated.

20.7.1.1.5 Simulation of Real-Life Tasks

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Regina et al. (1974) examined the effects of caffeine on a simulated driving task. The results showed beneficial effects of caffeine and confirmed findings by using laboratory vigilance tasks. Studies conducted by the military [cited by Lieberman (1992)] have also shown that caffeine can improve a critical military task, namely, sentry duty.

20.7.1.1.6 Caffeine and Reduced Alertness

A major research issue has been whether caffeine can remove impairments produced by fatigue or drugs. A number of studies from the late 1980s and early 1990s show that caffeine removes performance impairments produced by sleep loss, fatigue, working at night, or sedative drugs (File et al., 1982; Nicholson et al., 1990; Johnson et al., 1990, 1991; Zwyghuizen-Doorenbos et al., 1990; Roache and Griffiths, 1987; Rogers et al., 1989). These findings have important implications for safety-critical jobs and for maintaining operational efficiency when arousal is reduced.

20.7.1.1.7 Caffeine, Personality, and Time of Day

Revelle and his colleagues [see Revelle et al. (1987) for a review] showed that caffeine improved the performance of high impulsive individuals and impaired the performance of low impulsive individuals doing complex cognitive tests in the morning. In the evening, the opposite pattern of results was observed. This has been interpreted in terms of relationships between optimum levels of arousal and complex task performance. Such effects do not appear with simple tasks, in which even high levels of alertness usually facilitate performance.

20.7.1.1.8 Adverse Effects of Caffeine on Performance

Fine motor performance: Anecdotally, it has been suggested that the increased arousal induced by consumption of caffeine impairs hand steadiness. However, early studies failed to demonstrate such effects (e.g., Lieberman et al., 1987).

Caffeine withdrawal: Lieberman (1992) discusses the effects of caffeine withdrawal on headache and mood but cites no evidence to suggest that it influences performance.

20.7.1.1.9 Cost–Benefit Analysis of Early Studies on the Behavioral Effects of Caffeine

Lieberman (1992) reaches the following conclusions about the beneficial and adverse behavioral effects of caffeine. “When caffeine is consumed in the range of doses found in many foods, it improves the ability of individuals to perform tasks requiring sustained attention, including simulated automobile driving. In addition, when administered in the same dose range, caffeine increases self-reported alertness and decreases sleepiness. Adverse behavioral effects occur when caffeine is consumed in excessive doses or by individuals who are overly sensitive to the substance."

20.7.1.2 Research after 1990

20.7.1.2.1 Confirmation of Earlier Findings

More recent studies of effects of caffeine on performance have confirmed many of the earlier results. For example, the beneficial effects of caffeine on psychomotor speed and vigilance have been replicated (e.g., Fine et al., 1994; Frewer and Lader, 1991). Similarly, the absence of effects in episodic memory tasks has also been confirmed (e.g., Loke, 1990; Smith et al., 1997a).

20.7.1.2.2 Consideration of Other Aspects of Memory

The effects of caffeine on other aspects of memory have also been investigated. For example, components of Baddeley's working memory model have been examined and the results show no effects of caffeine on the articulatory loop (Smith et al., 1999) or the visuospatial sketchpad (Warburton, 1995) but improved central executive function as shown by improved speed and accuracy of performing a logical reasoning task (Smith et al., 1992, 1994). Semantic memory has also been studied and results show that caffeine improves the speed of retrieval of semantic information. This effect appears to be very consistent with the majority of studies showing improved performance after caffeine (Smith et al., 1992, 1994, 1999).

An alternative research strategy has been to consider memory processes (speed of retrieval, recognition vs. Recall, levels of processing and implicit memory). Speed of retrieval has been studied by using the memory scanning paradigm and the effects of caffeine have been inconsistent (Kerr, 1991; Hindmarch et al., 1998; Hogervorst et al., 1998). Recognition memory, whether immediate or delayed, also shows few effects of caffeine except in cases in which word lists are long (e.g., Anderson and Revelle, 1994; Bowyer et al., 1983), a situation wherein caffeine might reduce attentional lapses during encoding. Implicit memory has received little attention and the one study on the effects of caffeine showed no effect (Turner, 1993), although this might reflect the methods used. Research on effects of caffeine on memory following different levels of encoding has shown consistent interactions among caffeine, impulsivity, and level of processing (Gupta, 1991, 1993). These results have been interpreted in terms of arousal level, with high arousal facilitating the processing of physical features of verbal stimuli and low arousal improving memory following processing of semantic information. Interactions between caffeine and impulsivity are less consistent in other types of tasks. About half the studies investigating this topic have failed to obtain significant interactions and only one (Anderson and Revelle, 1994) has verified the predictions made by the model of Humphreys and Revelle (1984).

20.7.1.2.3 Stages of Processing

Research has continued to study the effects of caffeine on attention tasks, with one aim being to identify mechanisms underlying the effects of caffeine. For example, Lorist and Snel (1997) have shown that target detection and response preparation are enhanced by caffeine, and Ruijter et al. (1999) have demonstrated that the quantity of information processed is higher after caffeine. Smith et al. (1999) showed that caffeine increases the speed of processing new stimuli, confirming results reported by Streufert et al. (1997). In contrast to its effects on encoding and sustained attention, caffeine not been shown to reduce resistance to distraction (Kenemans and Verbaten, 1998). Similarly, caffeine appears to have little effect on output processes (e.g., movement time — Lorist, 1998), although occasional reports of caffeine-induced impairments on hand steadiness can be found (e.g., Bovim et al., 1995).

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20.7.1.2.4 Caffeine and Low Levels of Alertness

Research has shown that the decreased alertness produced by consumption of lunch can be eliminated by consuming caffeinated coffee (Figure 20.1; Smith et al., 1991; Smith and Phillips, 1993). Furthermore, alertness is often reduced by minor illnesses such as the common cold, and caffeine can remove the impaired performance and negative mood associated with these illnesses (Smith et al., 1997a). The ability of caffeine to counteract the effects of fatigue has been confirmed by using simulations of driving (Horne and Reyner, 1996; Reyner and Horne, 1997). A study of simulated assembly-line work (Muehlbach and Walsh, 1995) also demonstrated significant improvements after caffeine on five consecutive nights and showed no decrements when caffeine was withdrawn.

Some of these studies allow one to assess the magnitude of the effects of caffeine. For example, Smith et al. (1993) found that consumption of caffeine at night maintained individuals at the levels seen in the day. Another approach has been to compare the effects of caffeine with other methods aimed at counteracting sleepiness. Bonnet and Arand (1994a, 1994b) report that the combination of a prophylactic nap and caffeine was more effective in maintaining nocturnal alertness than was the nap alone. Other studies have continued to demonstrate that caffeine can remove impairments produced by sedative drugs (e.g., alcohol, Hasenfratz et al., 1993; scopolamine, Riedel et al., 1995; lorazepam, Rush et al., 1994a; triazolam, Rush et al., 1994b).

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One issue is whether positive effects of caffeine are largely restricted to low alertness situations. Battig and Buzzi (1986) argued that caffeine can improve performance beyond a mere restoration of fatigue. Other studies have shown that fatigued subjects show larger performance changes after caffeine than do well-rested volunteers (Lorist et al., 1994a, 1994b). Another issue is whether caffeine exacerbates negative effects produced by stressful conditions (e.g., electrical shocks, Hasenfratz and Battig, 1992; noise, Smith et al., 1997b) and results suggest that it does not.

20.7.1.2.5 Different Doses of Caffeine

A number of studies (e.g., Lieberman et al., 1987; Durlach, 1998; Smith et al., 1999) have shown that beneficial effects of doses of caffeine typically found in commercial products can now be demonstrated in both measures of mood and performance. A linear dose–response curve has also been shown in a number of studies (Amendola et al., 1998; Smith, 1999) although, like the animal literature, beneficial effects often disappear at very high doses.

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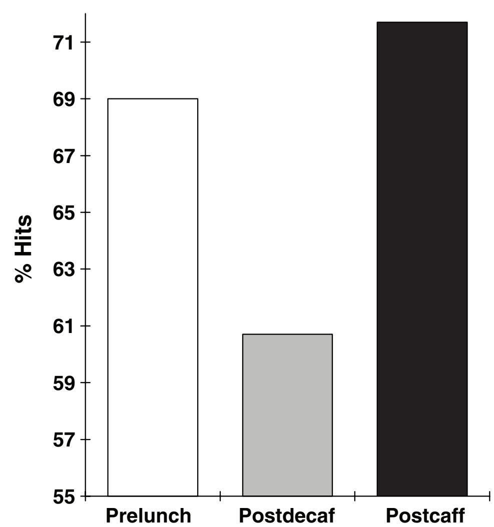

FIGURE 20.1 Effects of caffeine on the postlunch dip in sustained attention (Smith and Miles, 1987). Prelunch, performance before lunch; post-de-caff, performance after lunch and decaffeinated coffee; post-caff**,** performance after lunch and caffeinated coffee)**.**

20.7.1.2.6 Expectancy Effects

Fillmore and colleagues (e.g., Fillmore, 1994, 1999) have demonstrated that effects of caffeine depend on a person's expectations. These expectations can generalize to placebo conditions if individuals are led to expect that they are consuming a caffeinated beverage. In many experiments, the role of expectations has not been assessed and these could account for at least some of the conflicting results in the caffeine literature.

20.7.1.2.7 Habitual Consumption

There has been far less research on the effects of regular caffeine consumption than on acute effects. However, a number of papers suggest that high consumers demonstrate better performance (e.g., Loke, 1988, 1989). The strongest evidence for beneficial effects of regular caffeine consumption comes from a study by Jarvis (1993). He examined the relationship between habitual coffee and tea consumption and cognitive performance by using data from a cross-sectional survey of a representative sample of more than 9000 British adults. Subjects completed tests of simple reaction time, choice reaction time, incidental verbal memory, and visuospatial reasoning, in addition to providing self-reports of usual coffee and tea intake. After controlling extensively for potential confounding variables, a dose–response trend to improved performance with higher levels of coffee consumption (best performance associated with ca. 400 mg caffeine/day) was found for all tests. Estimated overall caffeine consumption showed a dose–response relationship to improved cognitive performance that was strongest in those who had consumed high levels for the longest time period (the 55 years plus age group). Studies by Hogervorst et al. (1998) and Rogers and Dernoncourt (1998) failed to replicate these effects by using acute caffeine challenges, which suggests that these effects reflect regular consumption patterns rather than recent intake of caffeine.

20.7.1.2.8 Beneficial Effects of Caffeine or Removal of Negative Effects of Withdrawal

Overall, studies discussed in the preceding sections confirm that the effects of caffeine on performance are largely beneficial. However, this view has been questioned by James (1994), who argues that the beneficial effects of caffeine are really only removal of negative effects produced by caffeine withdrawal. Smith (1995) argued against this general view of caffeine effects on a number of grounds. First, it cannot account for the behavioral effects seen in animals or nonconsumers (see later), in which withdrawal cannot occur. Second, caffeine withdrawal cannot account for behavioral changes following caffeine consumption after a short period of abstinence (Warburton, 1995; Smith et al., 1994) or the greater effects of caffeine when arousal is low. Finally, claims about the negative effects of caffeine withdrawal require closer examination as they can often be interpreted in ways other than caffeine dependence (e.g., expectancy, Smith, 1996; Rubin and Smith, 1999). In most studies that have demonstrated increases in negative effects following caffeine withdrawal, the volunteers were not blind but were told or even instructed to abstain from caffeine. This is clearly very different from the double-blind methodology typically used to study effects of caffeine challenge.

The view that beneficial effects of caffeine reflect degraded performance in caffeine-free conditions (James, 1994) crucially depends on the strength of the evidence for withdrawal effects. James (1994) states, "there is an extensive literature showing that caffeine withdrawal has significant adverse effects on human performance." If one examines the details of the studies cited to support this view, one finds that some of them do not even examine performance, and when they do, any effects are selective, not very pronounced, and largely unrelated to the beneficial effects of caffeine reported in the literature.

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Rogers et al. (1995) reviewed a number of studies of caffeine withdrawal and performance. They concluded, "in a review of recent studies we find no unequivocal evidence of impaired psychomotor performance associated with caffeine withdrawal." They found that caffeine improved performance in both deprived volunteers and nonconsumers (Richardson et al., 1994). Furthermore,

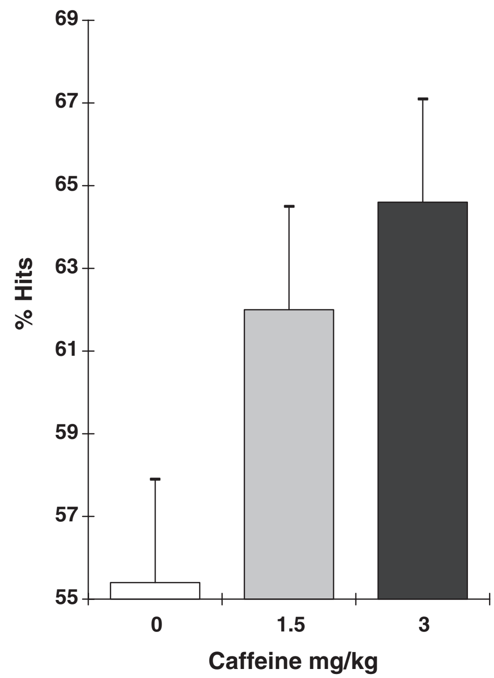

FIGURE 20.2 Effects of caffeine in volunteers deprived of caffeine for 7 days: hits in cognitive vigilance task (Smith, 1999).

other studies which suggest that withdrawal may impair performance (e.g., Bruce et al., 1991; Rizzo et al., 1988) can be interpreted in other ways than deprivation (e.g, changes in state).

The effects of caffeine withdrawal are still controversial. James (1998) showed that caffeine withdrawal impaired short-term memory performance but caffeine ingestion had no effect. In contrast, Smith (1999) reported that caffeine improved attention in both those who had been deprived of caffeine for a short period and those who had had no caffeine for 7 days (Figure 20.2).

Other studies (e.g., Comer et al., 1997) suggest that effects of withdrawal are restricted to mood and that performance is unaltered. Like many areas of caffeine research, some of the effects that have been attributed to withdrawal are open to other interpretations. For example, Lane (1997), Phillips-Bute and Lane (1997), and Lane and Phillips-Bute (1998) compared days when mid-morning coffee was either caffeinated or decaffeinated. Caffeine consumption was associated with better performance and mood. The authors interpret this as a negative effect of caffeine withdrawal, whereas one could interpret it as a positive effect of caffeine. Other studies of caffeine withdrawal effects have methodological problems such as the lack of predrink baselines (e.g., James, 1998; Robelin and Rogers, 1998) or failure to consider possible asymmetric transfer when using within-subject designs (e.g., James, 1998). This topic is dealt with again when very recent research is considered.

Literature suggests that caffeine often has alerting effects. This may be beneficial in many circumstances, but it can be an unwanted effect when the person is trying to sleep. This issue is covered in the next section.

20.7.2 Effects of Caffeine on Sleep

Much of the research on caffeine and sleep has been concerned with removing unwanted sleepiness either when persons are working at night or when they are sleep deprived. The fact that caffeine can remove sleepiness means that it can interfere with normal sleep. However, patterns of consumption suggest that individuals usually control their caffeine intake to prevent interference with sleep. If large amounts of caffeine are consumed shortly before trying to sleep, then it will undoubtedly disturb sleep. The experimental evidence for such effects is well established and is briefly summarized next.

A number of studies have shown that caffeine increases sleep latency (e.g., Zwyghuizen-Doorenbos et al., 1990) and reduces sleep duration (Hicks et al., 1983). Caffeine often produces its effects by increasing latencies in the first half of the night (Bonnet and Webb, 1979), which is different from the insomnia seen in hypnotic withdrawal (Brezinova et al., 1975). It would not appear, therefore, that caffeine-induced insomnia acts as a good general model of insomnia, as suggested by some researchers (Alford et al., 1996).

There are large individual differences in the effects of caffeine on sleep. For example, one study showed that caffeine given even in the early morning can influence the subsequent night's sleep (Landolt et al., 1995), whereas other individuals report that they can consume caffeine-containing beverages before bedtime with no adverse impact on their sleep (Colton et al., 1967; Levy and Zylber-Katz, 1983). There are probably many reasons for these differences, but it appears to be established that high consumers appear less likely to report sleep disturbance than those who consume caffeine only infrequently (Snyder and Sklar, 1984). Indeed, other results suggest that tolerance develops to effects of caffeine on sleep (Zwyghuizen-Doorenbos et al., 1990), but there are no withdrawal effects on sleep when caffeine is no longer given (Searle, 1994). It is also unclear whether the sleep disturbance produced by caffeine has an impact on behavior the next day, with one study showing no changes in mood and performance following caffeine-disturbed sleep (Smith et al., 1993b).

It is quite easy to demonstrate effects of late-night caffeine on sleep, but it is much harder to find evidence that high levels of consumption per se will affect sleep. Hicks et al. (1983) conducted a survey to examine the associations between daily caffeine consumption, habitual sleep duration, and sleep satisfaction. The results showed an inverse relationship between level of daily consumption of caffeinated drinks and habitual sleep duration, but no significant association between caffeine consumption and sleep satisfaction. Dekker et al. (1993) examined the impact of caffeine consumption on the sleep of locomotive engineers and their spouses. For the engineers only, caffeine consumption was correlated with longer sleep latency. The effect was not apparent in their spouses.

Other surveys have found little evidence of associations between caffeine consumption and sleep. For example, Lee (1992) examined data from 760 nurses. The results showed that age and family factors contributed to differences in sleep much more than caffeine did. Similarly, Greenwood et al. (1995) found no effect of caffeine consumption on the sleep of 72 rotating-shift workers. Finally, a study of sleep in elderly women found no differences in level of caffeine consumption in good and poor sleepers (Bliwise, 1992).

Overall, the research on the effects of caffeine on sleep leads to three main conclusions. First, large amounts of caffeine (e.g., more than 3 mg/kg in a single beverage) consumed in the late evening prevent individuals from going to sleep and reduce sleep duration. Effects of smaller doses show large individual variation, with high consumers being more resistant to effects of caffeine on sleep. Second, the impact of caffeine-induced changes in sleep on behavior the next day and long-term health is not known. Finally, high levels of caffeine consumption do not appear to be strongly related to sleep parameters. This again suggests that consumption is usually controlled to avoid any potential adverse effects on sleep.

20.7.3 Effects of Caffeine on Mood

20.7.3.1 Increases in Alertness and Hedonic Tone

Many studies have shown that consumption of caffeine leads to increased alertness (or reduced fatigue) that may or may not be accompanied by an increase in hedonic tone (feeling happier or more sociable). These effects have often been demonstrated by using paradigms involving low alertness situations, but beneficial effects of caffeine have also been demonstrated in individuals in an alert state (e.g., Leathwood and Pollet, 1982; Rusted, 1994, 1999; Smith et al., 1994; and Warburton, 1995). Many of these studies have used quite high doses of caffeine that would not be typically consumed in a single drink in real-life situations. However, other studies have demonstrated similar effects with realistic doses (e.g., Leathwood and Pollet, 1982; Warburton, 1995). Many of the studies have administered caffeine in coffee and it is unclear whether it is the caffeine aloneor caffeine in combination with other compounds in the coffee that underlies the behavioral effects. Recent research (Smith et al., 1999) has shown that it is the caffeine rather than a combination of the caffeine and the type of drink in which it is presented that is important. Similar results have also been demonstrated with caffeine given as a capsule and in a drink.

One must now consider why some studies (e.g., Svensson et al., 1980; Swift and Tiplady, 1988) have failed to find effects of caffeine on alertness. This lack of effect could possibly, in some studies, reflect sample size or other details of the methodology. Lieberman (1992) suggests that beneficial effects of caffeine on alertness are most easily demonstrated when circadian alertness is low and mood is measured in the context of doing demanding performance tasks. Rusted (1999) also suggests that mood effects occur after changes in performance and this may account for the absence of effects in certain studies. Smith et al. (1997) demonstrated that caffeine reduced the drop in alertness seen over the course of performing a battery of tests. Another possible explanation of the failure to find positive mood changes in certain studies is that they are masked by increases in negative mood. A number of results suggest that caffeine may increase anxiety and these are reviewed next.

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20.7.3.2 Increases in Anxiety

Anecdotal evidence suggests that when individuals have an excessive amount of caffeine they may become anxious. Similarly, some psychiatric patients attribute their problems to consumption of caffeine, which has led to a diagnosis of "caffeinism." Other patients, especially those with anxiety disorders, report that caffeine may exacerbate their problems. The validity of these statements is assessed by considering the literature on these topics.

Lieberman (1992) stated, "it appears that caffeine can increase anxiety when administered in single bolus doses of 300 mg or higher, which is many times greater than the amount present in a single serving of a typical caffeine-containing beverage. However, in lower doses it appears to have little effect on this mood state or, under certain circumstances, it may even reduce anxiety levels. It has also been observed that caffeine reduces self-rated depression when administered in moderate doses" (Lieberman, 1988).

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The literature supports Lieberman's view, because only a small proportion of the studies reviewed show increases in anxiety following administration of caffeine. Loke (1988) found that caffeine reduced fatigue but also led to increased tension and nervousness. Loke et al. (1985) reported increased anxiety following caffeine when the doses were high (either 3 or 6 mg/kg). Green and Suls (1996) also found that caffeine increased anxiety and again the volunteers had consumed very high amounts (125 mg caffeine per cup of coffee over the day). Similarly, Sicard et al. (1996) found increased anxiety following consumption of 600 mg of caffeine. Stern et al. (1989) found that individuals who chose a high dose of caffeine reported positive mood changes whereas nonchoosers reported anxiety and dysphoria. Overall, these results suggest that increases in anxiety following caffeine are often only found following consumption of amounts that would rarely be ingested by the majority of people.

It is important to assess whether caffeine leads to mood problems when the person ingesting it already has a high level of anxiety. It has been claimed that some people abstain from caffeinated drinks because of the accompanying jitteriness and nervousness (Goldstein et al., 1969). Other authors have even gone as far as to suggest that caffeine acts as a "fairly convincing model of generalised anxiety" (Lader and Bruce, 1986). Caffeinism refers to a constellation of symptoms associated with very high caffeine intake that are virtually indistinguishable from severe chronic anxiety (Greden, 1974). Caffeinism is usually associated with daily intakes of between 1000 and 1500 mg. However, it appears to be a rather specific condition and there is little evidence for correlations between caffeine intake and anxiety in either nonclinical volunteers (Lynn, 1973; Hire, 1978) or psychiatric outpatients (Eaton and Mcleod, 1984). Other research has investigated whether caffeine is capable of increasing the anxiety induced by other stressors. Shanahan and Hughes (1986) found that 400 mg of caffeine increased anxiety when paired with a stressful task. However, other research (e.g., Hasenfratz and Battig, 1992; Smith et al., 1997b) has not been able to provide any evidence of interactive effects of caffeine and stress. The next section considers another area in which caffeine is claimed to be associated with adverse effects, namely, when it is withdrawn.

20.7.3.3 Caffeine Withdrawal and Mood

Caffeine withdrawal has been widely studied because it is meant to provide crucial evidence on whether caffeine is addictive or leads to some kind of dependence. The most frequent outcome measure has been reporting of headache, but mood has been examined in other studies. Ratcliff-Crain et al. (1989) reported that caffeine deprivation led to increased reporting of stress by heavy coffee drinkers. This has been confirmed by Schuh and Griffiths (1997), who found that caffeine withdrawal was associated with feelings of fatigue and decreased feelings of alertness. Silverman et al. (1992) found that ca. 10% of volunteers with a moderate daily intake (235 mg/day) reported increased depression and anxiety when caffeine was withdrawn.

Richardson et al. (1995) examined the effects of varying time periods of caffeine deprivation (90 min, overnight, and 7 days) on mood. They report that overnight caffeine deprivation produced dysphoric symptoms and these mood effects were reduced but still present after longer-term abstinence. However, close examination of the results does not support this conclusion, with only 1 of the 17 mood scales showing a significant effect.

20.7.4 Reinforcing Effects of Caffeine

Caffeine acts as a reinforcer in several animal species but is unable to maintain self-administration behavior, which contrasts with other psychostimulant drugs (Fredholm et al., 1999). The reinforcing effects of caffeine in human volunteers appear to vary with dose, with high doses sometimes associated with aversion (Garrett and Griffiths, 1998). The relationship between the reinforcing properties of caffeine and preexposure to caffeine has also been studied. 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 preferences of low habitual caffeine consumers, but the high caffeine consumers developed a relative dislike for drinks lacking caffeine. However, another study (Brauer et al., 1994) found that ratings of the pleasantness of a coffee taste were not significantly altered by caffeine deprivation. In studies assessing preference by choice of caffeinated or placebo beverages, only 10 to 50% of participants reliably chose caffeine over placebo (Silverman et al., 1994). Other studies have assessed the reinforcing effects of caffeine by determining how much work would be performed or money spent in order to get access to caffeine. Griffiths et al. (1989) found that decaffeinated coffee was as valuable to volunteers as caffeinated coffee and that it was it was only placebo capsules that were not deemed worthy of any work at all. Situational factors also have a substantial effect on caffeine reinforcement. Silverman et al. (1994) found that volunteers chose caffeine before doing a vigilance task, whereas placebo was chosen before relaxation. This confirms the view that the great majority of consumers drink caffeinated beverages in a controlled manner, although a small minority may use caffeine compulsively, which could lead to problems when intake is stopped.

20.7.5 Recent Developments

20.7.5.1 Methodological Issues

20.7.5.1.1 Consumption Regime

Most studies of the effects of caffeine have administered a single large dose, often equivalent to the person's total daily consumption level. Caffeine is usually ingested in a number of smaller doses and it is unclear whether effects observed after a single large dose are the same as those produced by an identical level produced by consuming several caffeine containing drinks over a longer time period. Brice and Smith (2002b) examined this issue and found that the improved mood and enhanced performance found after a single dose of 200 mg were also observed following four doses of 65 mg given at hourly intervals (which resulted in a final level identical to the single 200-mg dose).

20.7.5.1.2 Effects of Single Doses Typically Found in Commercial Beverages

Smit and Rogers (2000) examined the effects of 0, 12.5, 25, 50, and 100 mg of caffeine on cognitive performance and mood. They concluded that all doses of caffeine affected cognitive performance and that the dose–response relationships were rather flat. The effects were also more marked in individuals with higher levels of habitual caffeine consumption. Unfortunately, the order of the caffeine conditions was not included in the analyses and the similar effects of different caffeine doses may reflect transfer effects across conditions. Subjective alertness was only significant in the 100-mg condition and the benefits of this dose became greater over the test session.

20.7.5.1.3 Metabolism of Caffeine and Behavior

Most of the beneficial effects of caffeine show a linear dose–response relationship up to ca. 300 mg, which is then followed by either a flattening of the curve or, sometimes, impaired performance at higher doses. Brice and Smith (2001a) examined the relationship between metabolism of a fixed dose of caffeine (as indicated by saliva levels) and mood and performance changes and found that there was no strong association between the two. This is not too surprising in that it is not caffeine levels in the periphery per se but secondary CNS mechanisms that produce the behavioral changes. The individual differences in the metabolism of the caffeine may be very different from the individual differences in the CNS mechanisms, which plausibly accounts for the lack of a strong association between plasma or saliva levels and behavioral changes.

20.7.5.2 Caffeine Withdrawal

Recent research in this area has been concerned with two main topics: (1) what underlies the increase in symptoms following caffeine withdrawal and (2) whether the effects of caffeine reflect removal of negative effects of withdrawal. Dews et al. (2002) considered factors underlying caffeine withdrawal and concluded, "non pharmacological factors related to knowledge and expectation are the prime determinants of symptoms and their reported prevalence on withdrawal of caffeine after regular consumption."

In contrast, some researchers still suggest that caffeine only has beneficial effects on performance when the person has been caffeine withdrawn. Yeomans et al. (2002) reported that caffeine improved performance on a sustained attention task and increased rated alertness when volunteers had been caffeine deprived but had no such effects when they were no longer deprived. However, the results showed an effect of order of treatments with those who received caffeine first continuing to show better performance even when subsequently given placebo.

Smith et al. (submitted a) examined effects of caffeine in the evening after a day of normal caffeine consumption. Caffeine improved performance (Figure 20.3), which casts doubt on the view that reversal of caffeine withdrawal is a major component underlying effects on performance.

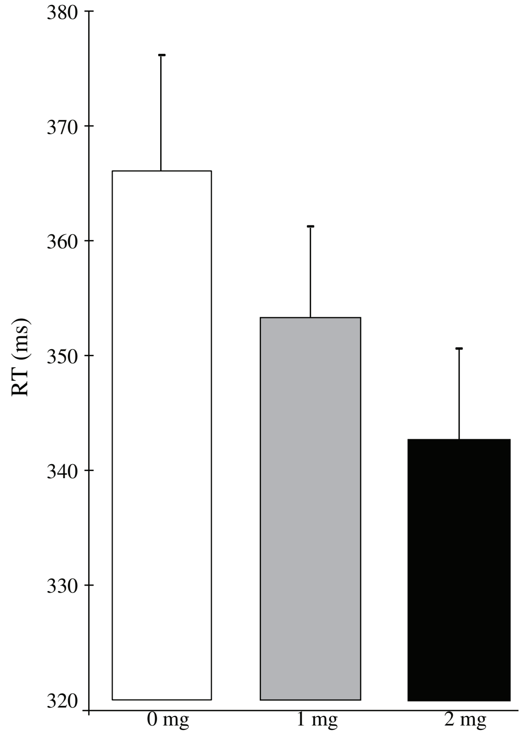

FIGURE 20.3 Effects of caffeine on simple reaction time of fatigued volunteers following a day of normal caffeine consumption (Smith et al., submitted a).

Further evidence against the caffeine withdrawal explanation comes from recent studies of nonconsumers (Smith et al., 2001). These studies not only detected few negative effects of withdrawal (Figure 20.4) but also showed that caffeine improved the performance of both withdrawn consumers and nonconsumers (Figure 20.5), a finding that argues strongly against the withdrawal reversal explanation.

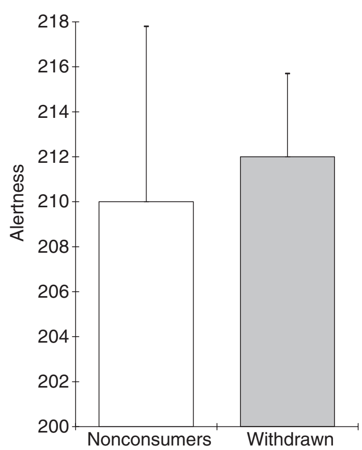

FIGURE 20.4 Alertness ratings given before caffeine ingestion by nonconsumers of caffeine and withdrawn consumers (Smith et al., 2001). High scores = greater alertness; the two groups do not differ.

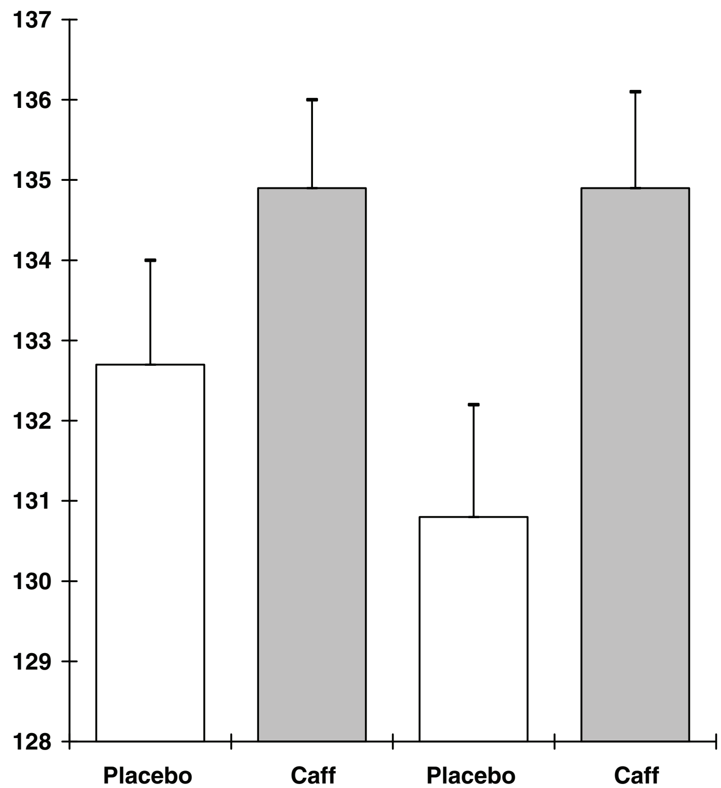

FIGURE 20.5 Effects of caffeine (4 mg/kg) on the number of items completed in a semantic processing task by nonconsumers and withdrawn consumers (Smith et al., 2001). Both groups show improved performance after caffeine.

20.7.5.3 Real-Life Performance

Recent research has shown that caffeine can have beneficial effects on performance in real-life situations. Lieberman et al. (2002) investigated whether caffeine would reduce the adverse effects of sleep deprivation and exposure to severe environmental and operational stress. They studied U.S. Navy Sea-Air-Land trainees and found that even in the most adverse circumstances moderate doses of caffeine improved vigilance, learning, memory and mood state. A dose of 200 mg appeared to be optimal under such conditions. Lieberman et al. (2002) concluded, "when cognitive performance is critical and must be maintained during exposure to severe stress, administration of caffeine may provide a significant advantage." Such beneficial effects of caffeine have been reported in many real-life activities (Weinberg and Beale, 2002) and a recent study suggests that performance at work may be improved (Brice and Smith, 2001a).

20.7.5.4 Underlying CNS mechanisms

Animal studies of the CNS effects of caffeine show that it can potentially influence behavior through a number of mechanisms. In contrast to this, research with human volunteers is often based on the assumption that all the observed changes can be accounted for by a single mechanism. Evidence for distinct effects of caffeine comes from pharmacological challenge studies. Low states of alertness can be induced by reducing the turnover of central noradrenaline by giving clonidine. In a recent study (Smith et al., submitted b), we have shown that caffeine can reverse the effect of clonidine (Figure 20.5).

However, certain types of tasks (e.g., a cognitive vigilance task) were not impaired by clonidine yet showed significant improvements following ingestion of caffeine. These tasks are known to be sensitive to cholinergic challenges and prior research has shown that caffeine can reverse these (Riedel et al., 1995). These cholinergic effects reflect an increase in the speed of encoding of information and a reduction in variability in performance (Warburton et al., 2001) and are not restricted to low-alertness situations. This dual mechanism model is clearly an oversimplification of the effects of caffeine, but it represents a move toward mapping the behavioral effects with the underlying neurotransmitter changes.

20.8 CONCLUSIONS

This chapter has reviewed the effects of caffeine on mood, mental performance, and sleep. In all areas it is apparent that there is a big difference between the effects of amounts of caffeine that are normally consumed and those observed when excessive amounts are ingested or when very sensitive individuals are studied. Most of the research has examined acute effects of single doses, and further studies are needed to produce a more detailed profile of effects of regular levels of consumption. However, the general picture to emerge is that when caffeine is consumed in moderation by the majority of the population there are unlikely to be many negative effects. The positive effects may be important in maintaining efficiency and safety at both the workplace and other environments. Excessive consumption of caffeine produces problems, and appropriate information should be given to minimize effects in psychiatric patients and other sensitive groups. It is important to balance this with information on the benefits of caffeine, for most consumers can usually control their intake to maximize the beneficial effects and reduce or prevent adverse effects due to overconsumption or consumption at inappropriate times. The behavioral effects of caffeine may reflect a variety of different neurotransmitter changes, and further research is needed to identify the mechanisms underlying specific effects. Future studies must use appropriate designs and tasks so that development of the topic is not slowed by the methodological problems frequently seen in the existing literature.

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