Nicotine Psychopharmacology: Addiction, Cognition and Neuroadaptation

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I. INTRODUCTION

Understanding of tobacco use and of how nicotine acts in the central nervous system has been transformed as a result of knowledge gained over the last two decades. As late as 1970, the dominant view in the smoking research field portrayed tobacco use as a habit, not an addiction, and assumed that it had little to do with the psychopharmacology of nicotine. In addition, many neuropharmacologists had concluded that there were few nicotinic receptors in the brain and interest in central cholinergic mechanisms was focused squarely upon muscarinic receptors. Indeed, when around 1970 one of us (IPS) discussed with a colleague an interest in shifting from the opioid to the nicotine field, he received the following advice (that had better remain unattributed): "Don't waste your time with that rubbish."

The literature of the next 10 years yielded numerous studies that supported the view that one of the main reasons for the smoking of tobacco was to obtain the effects of

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nicotine and thus there was a sea-change in the majority view of the nature of tobacco use. Earlier reviews[1–3] have documented in great detail this material that will not be reiterated here. During the same period, the then new approach of ligand-binding methodology was applied to the identification of brain nicotinic receptors, and evidence on the reality of such receptors proliferated with the number of ligands used (including radiolabeled forms of nicotine, acetylcholine, α-bungarotoxin, neuronal bungarotoxin, tubocurarine, and dihydro-β-erythroidine). Although much discussion took place over the relative merits of these different binding sites as candidates for receptors, it became increasingly difficult to maintain that there were no brain nicotinic receptors of any consequence. Previous reviews have considered the functional roles of these binding sites.[4] The present article deals with three selected topics and reviews advances made in about the last 5 years from a predominantly behavioral viewpoint; there is no attempt made to catalog the field in a comprehensive and exhaustive manner.

This article takes up the story of the relationship between, on the one hand, binding sites for nicotinic ligands and, on the other hand, behavioral effects that may help to explain why smokers seek nicotine. It will be argued that mediation of the behavioral effects through multiple subtypes of nicotinic receptor is a possibility, but it is necessary to admit at the outset that there is no generally accepted classification of these receptors and that knowledge is still rudimentary in comparison with that pertaining to multiple muscarinic receptors. Following upon the binding studies of the late 1970s and early '80s, the striking advances of the last 5 years in understanding the molecular structure of nicotinic receptors has given a further impetus to research that attempts to relate structure to binding and function. Thus, an action of nicotine at nicotinic cholinoceptors will be presented as the origin of the drug's effects. However, nicotine, like many other addictive drugs, acts on the dopamine system, and evidence will be reviewed that facilitation of dopamine release is the next step in the chain of events that ultimately leads to addiction. Recent studies implicating some excitatory amino acid receptors will also be considered.

The second main theme of the present review is the effect of nicotine and related substances on cognition. Historically, pharmacological studies have suggested that nicotine may be able to improve some aspects of cognitive processes such as attention, learning, and memory. Up to about 1980, a dozen or so studies supported such a view,[5]

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but evidence was sparse and few findings had been replicated. Such data are, of course, consistent with the self-reports of some smokers, who have claimed that smoking helps them to concentrate, especially on tasks requiring sustained attention over long periods of time; thus cognitive effects of nicotine may contribute to the positive reinforcing effects of nicotine that maintain tobacco smoking and thus, to nicotine addition. In the last 5 years, interest in such effects has grown enormously because of the possibility that nicotine might have some therapeutic value as a symptomatic treatment for the cognitive impairments of dementia. This trend has been strengthened by evidence that there was a loss of nicotinic receptors in the cerebral cortex of patients with Alzheimer's disease.[6]

Although the ability of nicotine to serve as a positive reinforcer can be seen as the major psychopharmacological effect that underlies nicotine-seeking behavior, it may be simplistic to assume that the addicted organism is merely one that has learned to self-administer the drug. According to such a view, the only relevant neuroadaptations in the dependent organism would be the neural correlates of the learning involved in self-administration. However, repeated exposure to nicotine, as to many other psychoactive substances, can under appropriate circumstances result in neural adaptations that are reflected in nicotine tolerance, sensitization (reverse tolerance), and withdrawal. There have been many assumptions about the roles of these adaptations in tobacco dependence and the third main section of this review will deal with the neuropharmacological mechanisms that may underlie some of them, and it will emphasize the possible role of glutamate. It will be suggested that these adaptations contribute to the transition between initial nicotine-seeking behavior and the development of an addicted state with a more compulsive character. This work, like the studies on dopamine mentioned earlier, developed from the core construct of nicotine as an addictive drug that is amenable to study by the methods used for classical drugs such as heroin and cocaine.

II. MULTIPLE NICOTINIC MECHANISMS

A. Background

Nicotine has a wide range of behavioral and physiological effects; only rarely have studies of these effects in intact organisms been interpreted in terms of multiple nicotinic receptors, although studies of the binding of nicotinic ligands and molecular studies of the structure of nicotinic receptors have often resorted to discussion of putative multiple types of receptor. The present article deals mainly with behavioral effects and for full discussion of neurochemical and molecular studies, readers are referred to several excellent recent reviews.[4,7–9] Several putative types of nicotinic receptor have emerged from this work, such as (1) the high-affinity binding site for [^{3}H] nicotine (corresponding to the α_4 subunit of receptors proposed from molecular studies, (2) the lower affinity binding site for [^{125}I]α-bungarotoxin (corresponding to the α_7 subunit), and (3) the binding site for neuronal bungarotoxin (related to the α_3 subunit). The binding site for [^{3}H]nicotine also appears to serve as the main binding site for some other nicotinic ligands such as cytisine[10] and acetylcholine in the presence of a muscarinic antagonist.[11]

The behavioral effects of nicotine include changes in the rates of conditioned and unconditioned behaviors, a variety of stimulus properties, and possible influences on cognitive functions. The changes in rates of behavior such as locomotor activity and rewarded responses show a complex pattern, including both decreases and increases in rate depending on (1) the dose and time after administration of nicotine, (2) the amount of previous exposure to nicotine and the test situation, (3) the schedule of reinforcement that may be used to maintain the behavioral baseline.[12] Nicotine can also decrease food

consumption and affect the startle response to sudden loud acoustic stimuli.[13,14] The stimulus properties of nicotine include the ability (1) to maintain self-administration behavior by serving as a positive reinforcer (reward), (2) to generate distinctive discriminative stimuli that can be used by trained organisms to identify the drug, and (3) to produce aversive effects that may oppose the tendency to self-administer nicotine.[1,12] Nicotine also seems to improve the performance of certain tasks involving learning in ways that cannot be explained by changes in rates of behavior. Nicotine also brings about a wide range of well-known physiological effects in the intact organism, including changes in heart rate, respiratory rate, and body temperature. The questions at issue are whether these diverse effects of nicotine are brought about through actions at a single type of nicotinic receptor and whether the central effects are mediated through actions on nicotinic receptors in different parts of the brain.

The approaches to this question have included classical pharmacological studies that attempt to use nicotinic agonists and antagonists to demonstrate selectivity of actions.[15,16] The behavioral approaches to the same problem are exemplified by work using different nicotinic agonists[17,18] and complementary studies using behavioral genetics to dissociate the effects of a single agonist (nicotine) by comparisons across different strains of inbred mice.[19,20]

B. Behavioral Studies with Nicotinic Agonists and Antagonists

Some experiments have used measures of drug discrimination and locomotor activity in rats in attempts to dissociate the effects of nicotinic agonists. The discriminative stimulus effect of a drug relates to an ability of an individual to recognize its pharmacological actions in the body, and it may therefore play a significant role in the addiction process. It was possible to develop a discrimination based upon subcutaneous doses of nicotine as small as 0.1 mg/kg[21] and dose-response effects for several nicotinic agonists were compared. Two related series of experiments employed changes in the locomotor activity of rats. The first set of data defined the ability of the nicotinic agonists to decrease locomotor activity in experimentally naive rats whereas a second set of results described the ability of the same compounds to increase in locomotion in rats that had been previously exposed repeatedly to both nicotine and the test apparatus.[18] The ability of the same series of agonists to inhibit the high affinity binding of [^{3}H](−)-nicotine to rat brain membranes *in vitro* was also determined.[22]

1. Drug Discrimination

The natural (−)-nicotine produced a steep dose response curve with an ED_{50} value that was typically about 0.04 mg/kg, and the full discriminative stimulus effect was seen in the absence of any reduction in the overall rate of responding. The other nicotinic agonists that were tested could be placed into three groups. Appropriate doses of some compounds produced a full nicotine-like discriminative effect without change in response rate (i.e., were indistinguishable from (−)-nicotine except in potency). The compounds in this group were (+)-nicotine, N-(3-pyridylmethyl)pyrrolidine (PMP), and nornicotine. A second group of compounds produced a maximal or nearly maximal nicotine-like discriminative stimulus effect, but less consistently and often only at doses that markedly reduced overall rates of responding; the compounds in this group were anabasine, cytisine, isoarecolone, and 1-acetyl-4-methyl-piperazine (AMP). Other compounds produced either no or a very weak nicotine-like discriminative effect, even when overall response rate was reduced (lobeline and (+)-anatoxin). These results, some of

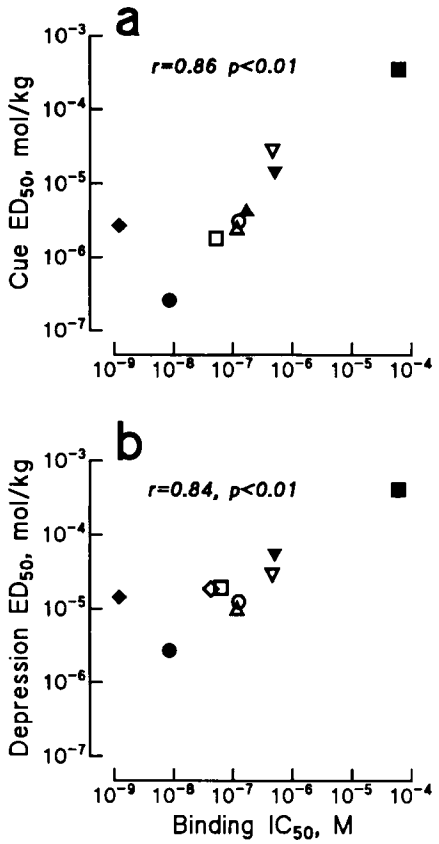

Figure 1. Compilation of results from several studies on correlation between the ability of nicotinic agonists to inhibit the binding of [^{3}H]nicotine to rat brain synaptosomes *in vitro* and to produce two behavioral effects in rats, the nicotine discriminative stimulus (upper section) and decreases of locomotor activity (lower section).[22,23,25,30] Key: (−)-nicotine, ●; (+)-nicotine, ○; cytisine, ◆; (+)-nornicotine, △; PMP, □; (−)-nornicotine, ▲; isoarecolone, ▼; anabasine, ▽, AMP, ■.

which confirmed findings of previous work from other laboratories, have been described fully.[18,21,23–25]

All compounds tested in this series of studies inhibited nicotine binding *in vitro* and it was established that some of the compounds lacking full-nicotine like potency *in vivo* (i.e., cytisine and lobeline) penetrated into the brain easily.[17] The IC_{50} values varied over a range of 50,000:1 and Figure 1 shows that when the seven compounds that produced nicotine-like discriminative effects *in vivo* were considered, there was an overall correlation between potency in inhibiting binding and that for producing the discriminative response ($r = 0.86$, $p < 0.01$). However, as noted above, some, such as lobeline and anatoxin, were potent inhibitors of binding but produced no or weak discriminative effect. The novel nicotine analogue ABT 418 [(*S*)-3-methyl-5-(1-methyl-2-pyrrolidinyl] isoxazole also inhibits nicotine binding but is weakly active in a nicotine discrimination procedure (Brioni, personal communication). Very few other nicotinic compounds have been tested in the drug discrimination procedure; a rigid analogue of nicotine described by Glassco *et al.*[26] appears interesting because it augmented the response to nicotine without itself producing a nicotine-like discriminative stimulus. Non-nicotinic com-

pounds were almost invariably inactive both as inhibitors of binding and in the drug discrimination procedure (but see below for consideration of dopamine agonists).

The nicotinic antagonist mecamylamine administered subcutaneously can fully block the discriminative effects of nicotine and those of the other nicotinic agonists (e.g., cytisine, anatoxin) upon which it has been tested:[25,27,28] however, after intracerebroventricular injection, the nicotinic antagonists mecamylamine and chlorisondamine blocked the response to nicotine fully, whereas pentolinium was only partly effective and hexamethonium was inactive.[28,29]

2. Decreases in Locomotor Activity

In one series of studies, all nicotinic agonists tested decreased locomotor activity in a dose-related manner, including substances that produced clear nicotine-like discriminative effects [(+)-nicotine, nornicotine, isoarecolone, etc.)] and substances (anatoxin, lobeline) that failed to produce full nicotine-like discriminative stimulus effects[18,24,25,30] (and Garcha and Stolerman, unpublished data). Mecamylamine (1.5 mg/kg s.c.) attenuated the locomotor depressions produced by approximately equally effective doses of (−)-nicotine and of nearly all the agonists; the only exceptions were lobeline and anatoxin, the responses to which were unchanged by mecamylamine[24,25] (and Mirza and Stolerman, unpublished data).

There was an overall correlation between the potencies of the compounds as inhibitors of binding and in depressing locomotor activity ($r = 0.81$, $p < 0.01$), as shown in Figure 1; this correlation was not greatly different from that between the discriminative effect and inhibition of binding (see above). A correlation has also been reported between the inhibition of [^{3}H]nicotine binding and a behavioral effect, prostration produced by administering nicotinic compounds into the fourth ventricle of rats.[31] Prostration was accompanied by a marked depression of locomotor activity, but the change in activity was not very susceptible to the development of tolerance or to blockade by mecamylamine.[32] Therefore, the pharmacological characteristics of superficially similar effects of nicotine administered systemically or directly into the fourth ventricle seem to be very different; the relevance of the fourth ventricle effects to those of systemic administration can be questioned.

3. Increases in Locomotor Activity

The various nicotinic agonists may be subdivided into two groups according to their resemblance to (−)-nicotine which reliably increased rates of locomotion of 2–5 times above control rates. The first group of compounds also increased locomotor activity above control rates and these compounds were (+)-nicotine, PMP, nornicotine, and anabasine. The second group of compounds failed to increase locomotor activity significantly at any dose, despite the use of a wide range of doses; these compounds were cytisine, lobeline, isoarecolone, AMP, and (+)-anatoxin[17,23,25,30] (and Garcha and Stolerman, unpublished data). Thus, it was not possible to demonstrate a correlation between increases in locomotor activity and inhibition of [^{3}H]nicotine binding. Other studies have suggested a role of the binding site for [^{3}H]nicotine in the locomotor activating effect of nicotine because the onset of upregulation of nicotinic binding sites occurs in parallel with the development of the sensitized locomotor response;[33] however, the two phenomena do not always covary.[34] It follows that the high affinity binding site plays a less important role in the locomotor activating response to nicotine that it does in the discriminative stimulus and locomotor depressant effects. Figure 2 illustrates the behavioral profiles of four nicotinic

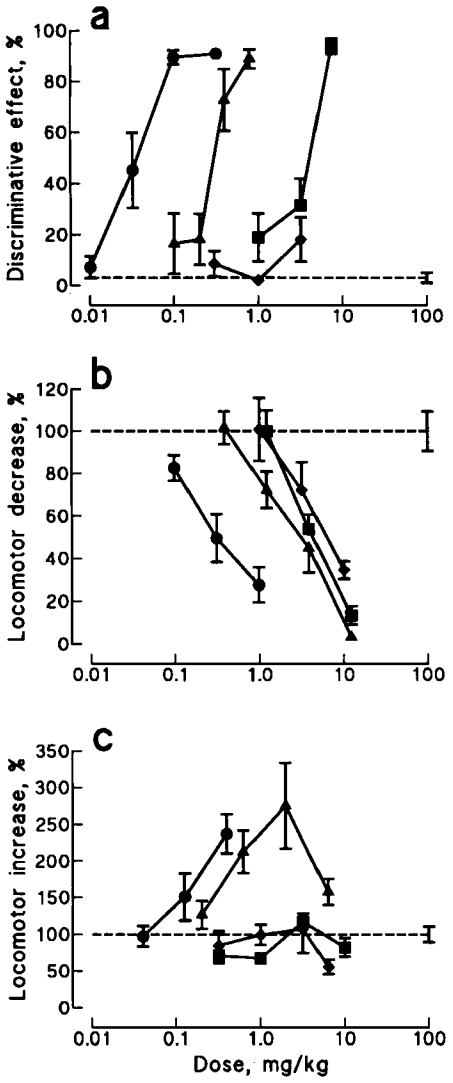

Figure 2. Dose-response curves for nicotinic agonists in three behavioral procedures [(−)-nicotine, ●; PMP, ▲; isoarecolone, ■; lobeline, ◆]. Upper section shows percentage of drug-appropriate responding in rats trained to discriminate nicotine from saline; center section shows locomotor activity (cage crosses) in experimentally naive rats; lower section shows locomotor activity in rats with extensive previous exposure to nicotine and the test apparatus.[17,18,185]

agonists in three behavioral tests, illustrating how it is possible to develop provisional groupings of compounds according to these criteria. These groupings of compounds may reflect actions at slightly different subpopulations of nicotinic receptor subtypes, although other explanations are also possible. For example, the substances may all act at the same receptor and the response profiles found may reflect partial rather than full agonist activity, or different degrees of receptor desensitization. Regardless of which of these explanations is correct, the results show unequivocally that nicotinic agonists with greater functional selectivity than nicotine itself can be identified.

C. Behavioral Genetics of Nicotine Responses in Mice

Another approach to the possible multiplicity of nicotinic mechanisms has used inbred strains of mice in attempts to dissociate different effects of nicotine. In this series of studies, dose-response curves for nicotine on a range of behavioral and physiological responses were determined in male mice from 19 inbred strains.[19,35] Considerable variability between strains was found in the magnitude of responses to nicotine. For example, the dose of nicotine required to reduce locomotor activity in a Y-maze varied from 0.51 mg/kg for C57BL/6 mice to 1.89 mg/kg for BUB mice; although some strains differed from each other with respect to activity in the undrugged state, this was not so in all cases and differences in baselines could not, therefore, account for all the variability in drug response. The strains were also assessed for acoustic startle response, seizure liability, heart rate, respiratory rate, and body temperature, and for the binding of nicotinic radioligands to synaptosomes prepared from different regions of the brains of mice of each species. Different strains of mice did not show simply a greater or lesser sensitivity to nicotine; sensitivity depended on the response measured and principal components factor analyses were carried out to determine whether particular sets of responses covaried in a systematic manner.

The factor analyses suggested that two main variables contributed to the expression of sensitivity to nicotine for almost all the responses measured. One variable seemed to affect primarily the body temperature and locomotor activity responses, whereas the second variable influenced primarily seizure sensitivity.[19,35] However, both variables influenced respiratory rate and acoustic startle. For example, the results showed that the strains of mice that were either the most or least sensitive to seizures were of only average sensitivity to the locomotor activity and heart rate effects. Similarly, the mice that showed the extremes of sensitivity to the locomotor and cardiac effects did not show corresponding variation in response to seizures. It was suggested that at least part of the expression of the major subgroups of responses may be controlled by a common mechanism.

Studies with the nicotinic antagonist mecamylamine supported a similar grouping of responses; seizure and startle responses were most sensitive to antagonism by mecamylamine, whereas ten-fold large doses of mecamylamine were needed to block effects of nicotine on locomotor activity, heart rate, temperature, and respiration.[14] A subdivision of responses based on adaptations to the chronic administration of nicotine in DBA mice also has some similarity to that based on the acute responses examined across the 19 different strains.[19] The grouping of the *in vivo* responses to nicotine suggests that each group of responses may be associated with actions at slightly different subpopulations of nicotinic receptors, perhaps reflecting the sites labeled by different radioligands.

In a parallel study, variations in the binding of two nicotinic radioligands, [^{3}H]nicotine and α-bungarotoxin, were examined in the same 19 inbred strains of mice.[20] As noted above, these ligands appear to label very different populations of putative nicotinic receptors. The affinity of the ligands did not vary significantly between strains or drain regions, but there were marked differences in the numbers of binding sites. In general, those strains that had large numbers of binding sites in one region had large numbers of binding sites in other regions, but there was no correlation between binding of the two ligands.

Interestingly, the binding of each ligand correlated with different physiological and behavioral responses. Figure 3 shows scattergrams relating ligand binding to "test battery" responses (locomotor activity and body temperature) and overall seizure sensitivity. Negative correlations were found between the numbers of nicotine binding sites and ED_{50} values for nicotine in the test battery ($r = 0.62$, $p = 0.005$), and between the

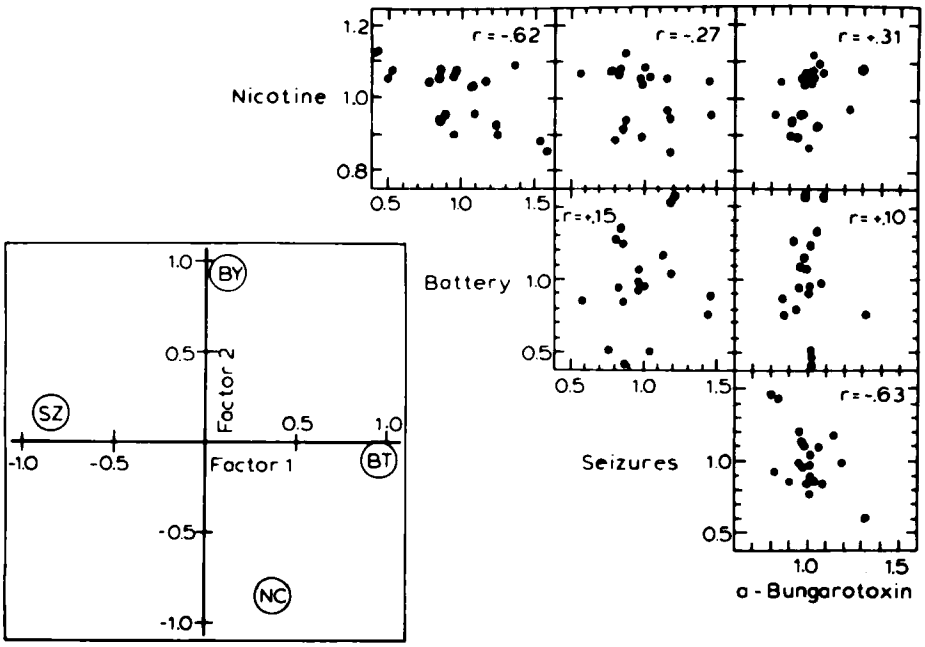

Figure 3. Global factor analysis relating nicotinic binding to functions. The panels in the upper right show scattergrams correlating overall brain nicotine and α-bungarotoxin binding with behavioral and physiological responsiveness (test "battery"), seizure sensitivity for 19 inbred strains of mice. Correlation coefficients are shown in panels. The panels in the lower left of the figure represent the factor loadings for each of the global measures.[20]

numbers of toxin binding sites and ED_{50} values for nicotine in tests of seizure sensitivity ($r = -0.63$, $p = 0.0004$). No other correlations were significant. Thus, the larger the number of nicotinic binding sites, the smaller the dose of nicotine needed to produce the responses. This analysis is suggestive of different functional significance for the two types of nicotinic binding site. The elegantly stated and cautious conclusions of Marks *et al.*[20] explain that "these relationships are expressed in the most general of terms since the variables used in the factor analysis were obtained by combining many, albeit related, variables. Nevertheless, the intriguing suggestion of a relationship between two independent types of nicotinic receptors and two different types of *in vivo* responses provides a basis to investigate further the role of nicotinic receptors in controlling these responses in mice." As was the case for studies discussed above that evaluated different nicotinic agonists in rats, it appears that different effects of nicotine do not always covary; responses are dissociable, suggesting the involvement of different mechanisms and a potential for novel compounds with greater selectivity and unique profiles of action.

III. COGNITIVE EFFECTS OF NICOTINE

A. Studies in Humans

1. Background

Nicotine's effects on cognition have been extensively studied in human smokers. It has been proposed to affect attention and vigilance, rapid information processing, and

both short-term and long-term memory. These studies are difficult to assess for a number of reasons: (1) smokers chronically take nicotine making interpretation of acute effects of the drug difficult, (2) individuals may have different tissue concentrations of nicotine, (3) it is a self-selected subpopulation of all potential human subjects. All these factors may influence results. Furthermore, nicotine has psychomotor and physiological effects that may influence assessment of cognitive effects. It is still being debated whether or not the purported enhancements in cognitive functions contribute to the motivation for the use of tobacco.[37] Nevertheless, some conclusions may now be possible in the light of the extensive recent work reviewed below.

2. Attention

Although many smokers report that smoking helps them to concentrate, tobacco contains numerous substances apart from nicotine and it cannot be assumed that it is exclusively the nicotine that is responsible for any effect. In order to overcome this problem, nicotine has been administered in tablets or chewing gum. For example Wesnes and colleagues showed that nicotine from either tablets or tobacco smoking was able to maintain target detection in a monotonous task.[38–40] Parrott and Winder[41] directly compared the effects of smoking and nicotine gum on a rapid visual information processing (RVIP) task in which subjects had to detect sequences of three odd and/or even numbers presented on a computer screen. Both smoking and nicotine tablets improved target detection which otherwise deteriorated over time.[39,41] There was also a decrease in reaction time, but a general increase in activity could not have accounted for the improvement because there was no increase in "false positive" responses. However, the improvement with even the 4-mg nicotine gum was only 50% of that seen with smoking. Revell also found a clear effect of smoking with a rapid onset.[42] However, some studies have found that the RVIP task is insensitive to nicotine.[43] Greater effects of smoking than of nicotine gum may be expected because smoking usually produced larger plasma concentrations of nicotine.

Attention is a diverse phenomena which can be assessed in a number of ways. Keenan *et al.*[44] compared deprived and nondeprived chewers of tobacco for their ability to respond to a bright square presented for 100 msec at the 12 o'clock position on a computer screen. They were also required not to respond to the same stimulus presented at the 6 o'clock position during the 23-min sessions (interstimulus interval = 2 sec). Reaction time deteriorated in deprived but not nondeprived subjects but there were no differences between errors made by the two groups. Thus, unlike the RVIP task, there was only an improvement in reaction time and no real improvement in the cognitive aspect of the task. When subjects were required to detect a change in a single item in a set of visual items, nonsmokers outperformed both active and deprived smokers.[45] Importantly, active smokers performed better than deprived smokers implying that smoking may have been correcting a deficiency associated with tobacco deprivation.

Quite a large number of studies, such as that of Peters and McGee[46] comparing active and deprived smokers have been interpreted in terms of effects of smoking deprivation. Snyder and Henningfield[47] used the smoking condition as the baseline in a battery of cognitive tasks; when given placebo gum, deprived smokers took longer to complete the tasks, whereas nicotine gum dose-dependently restored performance back to baseline. Similarly, Parrott and Roberts[48] have shown that smoking when deprived returns performance of a letter cancellation task back to baseline (smoking). Convincingly, Hatsukami *et al.*[49] showed that withdrawal from nicotine gum resulted in an impairment in perfor-

mance of a sustained attention task, albeit to a lesser extent than smoking withdrawal. However, Wesnes and Warburton[40] have reported that nicotine tablets can improve RVIP performance in nonsmokers, although Wesnes and Revell[50] did not demonstrate the effect clearly. Nicotine tablets can also reduce the vigilance decrement in nonsmokers and light and heavy smokers tested on the Mackworth clock task.[39] Other studies are also consistent with the idea that nicotine improves performance of tasks requiring sustained attention more markedly than that of divided attention tasks;[51] these distinctions are in need of further clarification.

3. Memory

Improvements in both immediate and delayed recall have been reported, with some inconsistencies that may be related to factors such as dose of the drug, whether it was administered before or after learning, and whether subjects were required to perform a distracter task before recall.[52–55] Nicotine administered in tablets can enhance short-term memory,[58] but this improvement may have been due to a greater burden put on attentional resources by use of a longer word list (48 words) than in earlier studies[52] that showed impairment of short-term memory using shorter lists. The authors proposed that nicotine was facilitating the storage of information under conditions of high arousal induced by a difficult task. However, nicotine also impaired short- and long-term recall of a list of 75 words.[57]

Although nicotine may improve certain types of memory, much of the literature has been interpreted in terms of attentional effects of the drug. Spilich *et al.*,[45] using a range of tasks from simple repetitive perceptual tasks to complex dynamic tasks, have shown that smoking impaired performance of complex tasks but had no effect on simple tasks (although it is surprising that these authors did not find an effect on a simple perceptual task or an attentional task). The idea that nicotine may enhance performance under conditions of high arousal or stress is consistent with reports from smokers that smoking helps them to concentrate and deal with stress. In addition, Mangan showed that smoking impeded learning of a paired-associate task under conditions of low interference but improved learning under high interference conditions.[58]

It has also been suggested that nicotine may have a direct effect on memory. Smoking improved recall of words at the beginning of a list after a delay, and it was argued that this was due to a direct effect in memory since nicotine was taken *after* the input of information.[59] However, immediate recall of words late in the list (i.e., when attention span wanes) was also improved. Therefore, nicotine may enhance memory directly or via attentional means. Other studies have shown that smoking or nicotine can improve long-term memory tested at one week to one month after learning.[53,58,60,61]

4. The Confounding Influence of Withdrawal

In many of the preceding studies, the baseline was the deprived condition and reversal of withdrawal decrements may have been the reason for reported improvement. For example, increases in response times and decreased accuracy have been reported with as little as 4 h deprivation, and maximal impairments were seen 24–48 h after deprivation, after which performance began to recover.[62] All measures returned to baseline within 24 h of resuming smoking. These and other studies suggest that in deprived smokers, nicotine is simply reinstating a "normal" state.[47,62] However, the subjects were all long-term heavy smokers and tolerance may have developed to enhancing effects of nicotine.[47]

West and Hack[63] compared occasional smokers showing no withdrawal symptoms and regular smokers on memory search rate. Neither group was asked to abstain from their normal smoking pattern. Both groups were tested when smoking normal and nicotine-free cigarettes. There were equivalent improvements in memory search rate in both groups after smoking of the nicotine-containing cigarette. This study appeared to have shown a real enhancing effect of nicotine, over and above any effect that was easily attributable to withdrawal. Other studies have included nonsmoker groups to ascertain whether alleviation of withdrawal symptoms can account for some of the effects seen. Hindmarch *et al.*[64] compared smokers with nonsmokers on a number of tests. Smokers given nicotine gum showed improvement on the motor aspects of some of the tasks but no effect on memory per se. There were no effects of nicotine gum in nonsmokers although there was some doubt about the adequacy of plasma concentrations of nicotine. Similarly, nicotine gum improved psychomotor performance in nonsmokers and in smokers under conditions designed to minimize any role for relief from withdrawal.[65,66] These studies seem to demonstrate that withdrawal relief cannot totally account for the cognitive effects of smoking. However, other experiments showed that while there was no difference between active smoking and deprivation on performance and retention of maze and word recognition tasks, there were important differences depending upon the daily pattern of smoking.[67] People who smoked early in the day performed better when smoking, whereas "late" smokers performed better when deprived; these results may be interpreted as evidence that the enhancing effects of nicotine are mainly due to termination of withdrawal since "early" smokers may be more heavily dependent.

B. Studies in Animals

1. Background

The older literature reviewed was suggestive of nicotine's potential as a cognitive enhancer.[5] Nicotine was reported to improve learning or performance in several procedures, including complex mazes, shock avoidance, and attentional tasks. Recent studies have been more systematic in their approach and have been re-assessing the effects of the drug in the light of current concepts of learning and memory. Effects of nicotine can be defined in terms of biological processes (attention, reference memory, working memory) or with regards to task-related criteria (attentional tasks, spatial tasks, nonspatial tasks). Sarter and Dudchenko have provided critical reviews of tasks for assessing cognitive effects of drugs.[68,69]

2. Spatial Tasks

Effects of Agonists in Normal Animals. Several studies have shown that nicotine can enhance acquisition of spatial radial maze and water maze tasks in normal animals;[70–74] in these studies nicotine was administered continually over the period of acquisition. This was a surprising result since the beneficial effects of many drugs are apparent only after learning has been compromised by age, drugs, or brain damage. Some studies also showed that the enhancement persisted after termination of treatment. Rats trained 1 week after chronic treatment was stopped also acquired the task faster than controls.[75] Also, when rats were injected repeatedly with nicotine before commencing training, they learned the water maze task faster than controls.[76]

Mirza and Stolerman[77] have confirmed that nicotine can enhance water maze acquisition and that the enhancement persists during a retention test in the undrugged state.

The nicotinic agonist isoarecolone had similar effects.[77] There is some consistency in these reports most of which have suggested that nicotine can facilitate acquisition of spatial tasks but there are some puzzling exceptions; nicotine injected prior to daily training impaired radial maze learning, but had no effect when injected after training.[78] Welzl *et al.*[79] also obtained negative results in a study where nicotine was administered chronically in drinking water. However, their six-arm maze task was rather insensitive to the effects of age and this lack of sensitivity may also have extended to drugs. Furthermore, rats were not tested on this task until 120 days after nicotine treatment had begun. Tolerance to positive effects on cognition may already have developed by this stage.

Nicotine can also facilitate the performance of spatial tasks when injected acutely. Even after rats had been trained in a radial maze, nicotine decreased errors.[80] However, although a counterbalanced design in which all rats received each treatment was used,[80] there was little indication that a stable baseline of performance in the undrugged state had been attained. On the other hand, Mundy and Iwamoto[78] detected no change after acute injections of nicotine in rats with a demonstrably stable baseline that may, however, have been close to a ceiling level.

Studies of Agonists in Aged Animals. Arendash and Sengstock have observed that daily injections of nicotine can alleviate age-related deficits of reference memory in Sprague–Dawley rats tested in a 17-arm maze.[81] Nicotine also reversed the deficits seen in aged Long–Evans rats on a test of spatial working memory in a T-maze.[82] Similar effects were not observed in aged Sprague–Dawley rats[79] but, as noted above, the task in this study was insensitive to age. Aged Fisher rats were impaired on the spatial water maze task and CA1 pyramidal neurons in the same strain of rats showed an age-related increase in responsiveness to nicotine.[83] The authors tentatively suggested that nicotine antagonists may alleviate the spatial learning deficit observed. This would be a remarkable finding since chronic nicotine atypically up-regulates nicotine receptors in various brain regions[33,84] and enhances spatial learning, whereas mecamylamine has been reported to impair learning in normal animals (see below).

Studies with Agonists and Brain Lesions. Levin *et al.* demonstrated that chronic infusion of nicotine could reverse an impairment of spatial radial maze learning produced by knife cut lesions of the fimbria.[85] This lesion truncated neural connections with the hippocampus, a system consistently associated with learning of spatial tasks. A lesser impairment, also reversed by nicotine, was found after a basalo-cortical lesion. Decker *et al.* showed that nicotine reversed deficits during acquisition of a water-maze task produced by electrolytic lesions of the septum[86]; this effect persisted during retention tests 24 h and 2 weeks after training had ceased. The nicotine agonist lobeline showed a similar profile in septal-lesioned rats.[87]

Combined lesions of the nucleus basalis, medial septal nucleus, and diagonal band of Broca produced by the excitotoxin ibotenic acid[88] or by the chronic administration of alcohol[89] caused impairments of working and reference memory in a radial maze; these impairments were reversed by acute injections of nicotine. Similar lesions also caused deficits in water maze acquisition, retention, reversal learning, and working memory[73]; nicotine reversed all these deficits. Lesioning the nucleus basalis with colchicine impaired radial maze acquisition and increased performance errors; large doses (1.5 mg/kg) of nicotine decreased the number of errors.[90]

Studies with Antagonists in Normal Animals. The muscarinic antagonist scopolamine has consistently produced amnestic effects in both animals and humans. The effects of nicotinic antagonists such as mecamylamine have been more variable. Mecamylamine increased errors made by rats trained on a radial maze task.[80,91] Furthermore, if rats were

simultaneously treated chronically with mecamylamine and nicotine, the improvement of acquisition and retention of radial maze performance otherwise produced by the nicotine was eliminated.[72] However, the nicotine antagonist chlorisondamine (administered intracerebroventricularly) failed to impair T-maze alternation performance or acquisition in radial and water mazes.[92,93]

Rats treated chronically with nicotine were more sensitive than controls to the impairing effects of mecamylamine and scopolamine and to mecamylamine's sedative effect.[70] This last effect of mecamylamine suggests that nicotine may not be acting simply as an agonist because an attenuated effect of mecamylamine would have been expected; instead, the effects may have resulted from the up-regulation of nicotine receptors that nicotine can produce.[84] Interestingly, chronic treatment with mecamylamine alone produced a transient improvement in radial maze performance.[72] Studies with a T-maze test of working memory showed that mecamylamine could either increase or decrease errors, depending on whether a delay of 30 s occurred between forced and choice runs.[94] It has also been reported that mecamylamine impairs working memory more than reference memory.[95]

In many studies, large doses of mecamylamine, typically 10 mg/kg (s.c.), were required to produce cognitive impairments, raising the possibility of nonspecific effects. The doses of mecamylamine required to block behavioral effects of nicotine in rats are rarely larger than 1 mg/kg, whereas 5 mg/kg has been the smallest dose reported to produce cognitive impairments in normal rats.[94,96] The most probable alternative explanation for the effects of mecamylamine would be based on its ability to block the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptors, as reported in some *in vitro* systems.[97,98] The ability of NMDA antagonists to produce cognitive deficits[99] supports this interpretation. However, the concentrations required for the effects of mecamylamine at NMDA receptors *in vitro* were quite large and the doses needed to produce them *in vivo* are not known. Mecamylamine was shown to antagonize the lethal effect of NMDA in mice only when administered in very large doses (ED_{50} = 19 mg/kg), although this effect had some selectivity since there was no protection from the lethal effect of kainic acid.[100] These studies do not support the view that doses of mecamylamine that produce cognitive impairments block NMDA receptors, but more direct evidence is needed.

Studies with Antagonists and Brain Lesions. Small doses of mecamylamine (1–2 mg/kg) exacerbated the deficits in radial maze performance of rats produced by combined lesions of the nucleus basalis, medial septal nucleus, and diagonal band of Broca.[88] A smaller impairment was seen in normal animals and in both cases, the impairment of working memory was more pronounced than that of reference memory. Mecamylamine (2.5 mg/kg) exacerbated impairments in the radial maze produced by lesions of the fornical projections to the hippocampus.[101] However, both scopolamine and mecamylamine impaired working memory in a radial maze[102]; lesions of nonhippocampally projecting forebrain cholinergic pathways reversed the deleterious effects of mecamylamine but not those of scopolamine.

3. *Nonspatial Tasks*

Studies with Agonists. The extent to which delayed matching and non matching to sample or position tasks and conditional discrimination tasks can be defined as spatial is debatable. For present purposes they will be considered as nonspatial to distinguish them from the maze tasks discussed above.

Elrod *et al.* showed an impressive effect of nicotine on delayed matching to sample in adult macaques, notably when the interval between sample and choice was long and working memory was heavily taxed.[103] This reproducible effect was abolished by mecamylamine which alone impaired accuracy on the task at short delays when basal levels of accuracy were high. Subsequently, this effect was confirmed in young and aged monkeys and the enhancement was maintained for 24 h after the last dose of nicotine.[104] In contrast, Sahgal *et al.* were unable to show any effect of nicotine in rats trained on either delayed matching or nonmatching to position tasks, and actually found small impairments in the nonmatching task.[105] Hudzik and Wenger showed that nicotine slightly impaired accuracy in a three-level, delayed matching to sample task in squirrel monkeys.[106] Dunnet and Martel found that nicotine impaired delayed matching to position performance, but only on trials in which the previous response had been on the side opposite the current response.[107] They suggested nicotine increased proactive interference; as in the study by Hudzik and Wenger,[106] the impairment may have been due to nicotine enhancing a competing memory process. Thus, task structure can be a crucial determinant of nicotine's effects. Several psychostimulants, including nicotine, were able to improve certain aspects of a visual tracking task in rats while simultaneously inducing behaviors which impaired other aspects of the task.[108] It was suggested that enhancement may only be seen when there is a "clear goal and a structured form of behaviour to reach that goal."[108]

Mundy and Iwamoto found that nicotine impaired acquisition of an autoshaped lever-touch response task in rats, an effect which they attributed to disruption of memory consolidation.[109] Furthermore, they showed the impairment only in naive or partially trained rats, but not in fully trained animals. Interestingly, many of the negative findings with nicotine have been observed using nonspatial tasks in which subjects were trained to a high level of performance.[105–107] The nature or structure of these tasks may render them insensitive to enhancing effects of drugs. In one study, oxotremorine and physostigmine, drugs which have been shown to enhance cognition in various other tasks, were also without effect.[105] There may also be species differences; nicotine has been found to improve memory in primates more frequently than in rats.

Studies with Antagonists. Large doses of mecamylamine alone were required to impair delayed matching to sample performance in rats, but combinations of subthreshold doses of mecamylamine plus scopolamine were able to impair accuracy without motor side effects.[110] Similarly, large, 3–8 mg/kg doses of mecamylamine were needed to impair time-discrimination and lever-alternation tasks.[111,112] It appears that usually, large doses of mecamylamine are needed to produce impairing effects, although the hints of interactions with non-nicotinic neurotransmitter systems are intriguing.

Avoidance Tasks. The limitations of passive and active avoidance tasks as methods for assessing cognitive functions have been noted before.[68,69] Nevertheless, they are still used and need to be considered. Haroutunian *et al.* showed that in normal rats, nicotine and some other cholinomimetics improved retention of a passive avoidance task.[113] Nicotine also improved learning of passive avoidance in rats fed on a choline-deficient diet that impaired learning ability on the task.[114] The nicotinic agonist cytisine has also been found to improve retention of passive avoidance in mice, whereas the effects of lobeline were inconsistent.[115] However, Lobeline penetrates to the CNS and binds potently to nicotinic receptors.[17,116]

Attentional Tasks. Studies in animals that examine the effects of nicotine on vigilance and attention have been surprisingly rare. An early study in rats by Nelsen and Goldstein suggested that nicotine may enhance attentional abilities, paralleling results in

humans.[117] Few subsequent studies have looked at this possibility, although many authors have given attentional explanations for the cognitive effects of nicotine that they report.[88,89,108]

4. Nicotine and Alzheimer's Disease

Human and animal data both suggest that nicotinic mechanisms may have a significant role in cognition. Following findings of losses of central nicotinic receptors in psychiatric illnesses including Alzheimer's disease,[118–120] and the lack of therapeutic success with muscarinic drugs, clinical trials with nicotine have been carried out. A pilot study with a small number of Alzheimer patients showed that nicotine (administered intravenously) decreased intrusion errors in a free recall task.[121] Later studies compared the effects of nicotine injected subcutaneously in demented patients with age-matched and young controls and showed that in the former group, nicotine improved sustained attention, reaction time and perception, but not short-term memory.[122,123] Mecamylamine slowed learning, increased intrusion errors and reaction time in healthy young adults.[124] However, there have been concerns about psychological (anxiety, fear, and depression) and physiological (cardiovascular) side effects of nicotine, particularly in demented patients.[125] However, the different behavioral profiles of a number of nicotine agonists (see above) in animals studies suggest that it may eventually be possible to develop nicotinic agonists with greater selectivity of action.

IV. NICOTINE, DOPAMINE, AND ADDICTION

In preceding sections it was noted that many effects of nicotine, involving both conditioned and unconditioned behavior, were mediated through actions at CNS nicotinic–cholinergic receptors. In fact, the great majority of the behavioral effects of nicotine have proved susceptible to blockade by the nicotinic–cholinergic antagonist mecamylamine, including its positive reinforcing and discriminative stimulus effects that are thought to be central to the maintenance of the drug-seeking behavior that characterizes nicotine addiction. For many years it was suspected that dopamine was also involved in behavioral responses to nicotine because of evidence that nicotinic receptors were located on parts of the dopamine system, and because nicotine potently facilitated the release of dopamine in a variety *in vitro* and *in vivo* preparations.[126] These effects of nicotine show some selectivity for the mesolimbic as compared with the nigrostriatal branch of the dopamine system.[127,128] Behavioral studies with procedures such as drug discrimination revealed evidence for similarities between the effects of nicotine and those of drugs that were known to act as direct or indirect dopamine agonists.[126] Dopamine antagonists can also attenuate some of the behavioral effects of nicotine, including stimulation of locomotor activity, nicotine self-administration, and the nicotine discriminative stimulus.[129–131] Nevertheless, to some observers, the magnitude of this literature was impressive but individually, few studies had yielded compelling evidence of a dopaminergic mechanism in nicotine addiction.

Clearer evidence implicating dopamine in behavioral effects of nicotine and in nicotine addiction has come from studies utilizing the neurotoxin 6-hydroxydopamine to produce lesions of forebrain dopamine systems. In 1982, Singer *et al.* examined the effects of 6-hydroxydopamine infusions into the nucleus accumbens on the acquisition of nicotine self-administration.[132] Although there was a decrement in responding, the behavioral baselines had not been very strong and there was no control for any motor deficit that the lesions may have produced. However, subsequent studies have confirmed that

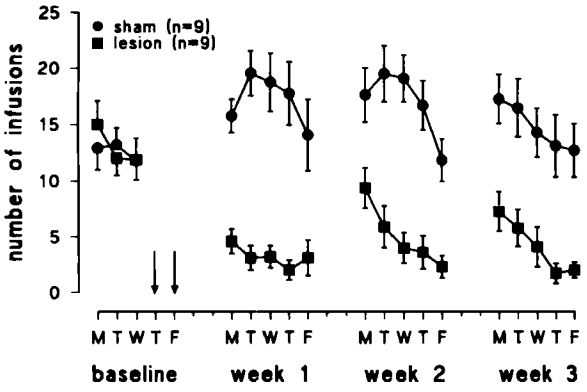

Figure 4. Study of Corrigall and colleagues of effects on the intravenous self-administration of nicotine of lesions of the mesolimbic dopamine system made by infusing the neurotoxin 6-hydroxydopamine bilaterally into the nucleus accumbens (n = 9). Each rat was lesioned on one of two days (arrows). Response rates of lesioned rats (■) may be compared with those of controls (●) infused with ascorbate.[135]

similar lesions can markedly attenuate both the locomotor activation produced by nicotine[133,134] and nicotine self-administration in a procedure that generates a more robust behavioral baseline.[135] In the study by Corrigall *et al.*, rats were trained to self-administer nicotine intravenously under a fixed ratio schedule of reinforcement. The experimental group then received infusions of 6-hydroxydopamine into the nucleus accumbens. Figure 4 shows that in these animals, nicotine self-administration was markedly attenuated during the subsequent 3-week period of testing, whereas sham-lesioned rats continued to show a stable pattern of behavior. Histochemical evaluations showed that the lesions produced about 90% depletion of dopamine in the nucleus accumbens and olfactory tubercle, but only 23% depletion in the caudate nucleus.[135] This study also included a control for motor deficits that the lesions may have produced; the lesions reduced responding for food reinforcers as well as for nicotine, but the response rates of lesioned rats for food were greater than the response rates of unlesioned rats for nicotine. For this and other reasons, it seems unlikely that a motor deficit explained the results, and it is becoming widely accepted that the mesolimbic dopamine system is involved in the proclivity to self-administer nicotine. The dopamine antagonist haloperidol has been found to increase blood nicotine levels in cigarette smokers, an effect interpreted as a compensatory increase in smoking to obtain the rewarding effect of nicotine (Dawe *et al.*, personal communication); this finding seems to resemble the effect of mecamylamine on smoking.[136]

V. ADAPTATIONS TO NICOTINE

A. Background

Understanding the mechanisms of adaptation to chronic drug administration could open new opportunities for the management of disorders related to chronic drug intake. Most proposed pharmacotherapies for addictions aim to provide either substitutes for or antagonists of the target drug and do not attempt to moderate the adaptive processes that lead to dependent states.

Several behavioral procedures yield evidence of adaptations to chronic nicotine exposure in rats. The effects of acute and chronic administration of nicotine on locomotor

activity have been extensively studied. Administration of nicotine to experimentally naive rats can depress locomotor activity, an effect to which acute and chronic tolerance can develop, associated with a 2–3 fold shift to the right in the dose-response curve.[137,138] In rats previously exposed to the test apparatus, nicotine can produce moderate increases in activity and with repeated exposure to the drug, sensitisation occurs to this effect as shown by an upward shift of the dose-response curve.[34] Other effects of nicotine can also show adaptations, as reviewed by Swedberg *et al.*[30] For example, in a conditioned taste aversion (CTA) paradigm, rats learn to avoid consuming distinctively flavored solutions that have previously been paired with nicotine injections.[139] Repeated administration of nicotine over 4 days before conditioning can attenuate nicotine-induced CTA.[140] However, in recent studies, previous exposure to nicotine has produced a moderate degree of sensitization to its ability to support conditioned place preferences.[141]

The mechanisms underlying chronic tolerance and sensitization to nicotine are not known. However, biochemical studies have consistently shown that chronic treatment with nicotine can increase the number of nicotine binding sites.[33,84,142] It is widely assumed that these upregulated receptors are desensitized rather than fully functional, although more direct evidence on this issue is needed. As noted above, both *in vivo* and *in vitro* studies have shown that nicotine can release dopamine, but only a few studies have examined the effects of chronic nicotine treatment on this measure. Damsma and colleagues found no tolerance to nicotine-induced dopamine release in the nucleus accumbens, with treatments lasting up to 15 days.[143] In contrast to this finding, Benwell and Balfour found that subchronic nicotine treatment consisting of injections over a period of 6 days sensitized dopamine release in the nucleus accumbens; these findings correlated well with the sensitization of locomotor activity increases.[144] It is difficult to explain such results if the effect of chronic treatment with nicotine is invariably to desensitize nicotinic receptors.

B. Role of NMDA Receptors

After the identification of MK-801 (subsequently called dizocilpine) as a noncompetitive antagonist at the NMDA receptor,[145] it was used in a large number of studies to test the physiological and behavioral significance of the receptors. Evidence is accumulating that suggests a possible role for endogenous glutamatergic systems in the development of sensitization and tolerance to several different abused drugs. There are reports that dizocilpine weakens or prevents the development of adaptations to diverse drugs, including CNS stimulants such as amphetamine, methamphetamine, and cocaine;[146–148] opioids such as morphine;[149,150] and alcohol.[151] Dizocilpine is not the only NMDA antagonist that has this effect; competitive antagonists of the NMDA receptor such as D-CPPene[152] and LY274614[153] are also effective at weakening tolerance to nicotine and morphine, respectively. DNQX, a kainate/AMPA, receptor antagonist can block the development of sensitization to amphetamine.[154] Collectively, these studies have suggested a critical role for glutamate in development of behavioral adaptation to psychoactive compounds.

Behavioral studies suggest that NMDA receptors may play a role in the adaptive responses to nicotine. The sensitization that develops to the locomotor stimulants effects of nicotine in rats can be prevented by administering dizocilpine before the daily nicotine injections during chronic treatment.[155] Figure 5 shows the activity scores for doses of nicotine in four groups of rats. As shown previously,[34] chronic treatment with nicotine

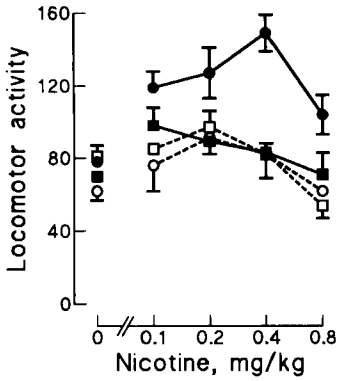

Figure 5. Effects of nicotine on locomotor activity assessed in photocell cages (means ± s.e.m.) in four groups of rats (n = 8). Rats were given daily chronic treatment of two injections 30 min apart; saline + saline (○); saline + nicotine (●); dizocilpine + saline (□); and dizocilpine + nicotine (■). Following 14 days of chronic treatment, each rat was tested with the doses of nicotine shown and locomotor activity was recorded over 60 min.[155]

shifted the dose-response curve for nicotine upwards. Dizocilpine administered 30 min before each chronic treatment with nicotine completely blocked this sensitization, whereas it did not influence locomotor activity during tests with rats that had not received chronic treatment with nicotine.[155] Under different experimental conditions, dizocilpine weakened the development of tolerance to the locomotor depressant effect of nicotine.[156] This effect was not restricted to dizocilpine, since D-CPPene, a competitive NMDA antagonist, was also effective.[152] However, neither of these antagonists completely prevented tolerance to the effect of nicotine on locomotor activity. Complete abolition of tolerance has been observed to the ability of nicotine to support conditioned taste aversions in rats. Pre-exposure to nicotine attenuated the taste aversions, and this pre-exposure effect was completely prevented in rats treated with dizocilpine prior to each injection of nicotine during the chronic treatment phase of the study.[156]

Studies using *in vivo* microdialysis to assess extracellular concentration of dopamine in the nucleus accumbens have shown that dizocilpine can also affect adaptation to neurochemical effects of nicotine. Treatment with nicotine lasting for 7 days sensitized its dopamine-releasing property. Figure 6 shows concentrations of dopamine in dialysates of extracellular fluid from four groups of rats. Dizocilpine administered 30 min before nicotine administration during the chronic treatment phase prevented the development of sensitization to nicotine-induced dopamine release in the nucleus accumbens.[152] The sensitization of locomotor activity in these rats was also attenuated (Fig. 6). The competitive NMDA antagonist D-CPPene similarly attenuated the neurochemical sensitization, but the behavioral results with D-CPPene were equivocal because pretreatment with D-CPPene alone influenced the response to a subsequent acute challenge with nicotine.[152] Nevertheless, these results suggest that nicotine-induced sensitization of the mesolimbic dopamine response may be mediated at least in part by activation of NMDA receptors.

Many reports suggest that learning plays a role in the development of tolerance to psychoactive drugs,[157,158] and NMDA antagonists may impair learning in various procedures.[99,159] However, some studies examining the effects of dizocilpine on tolerance to drug action have used experimental procedures that minimize the role of learning fac-

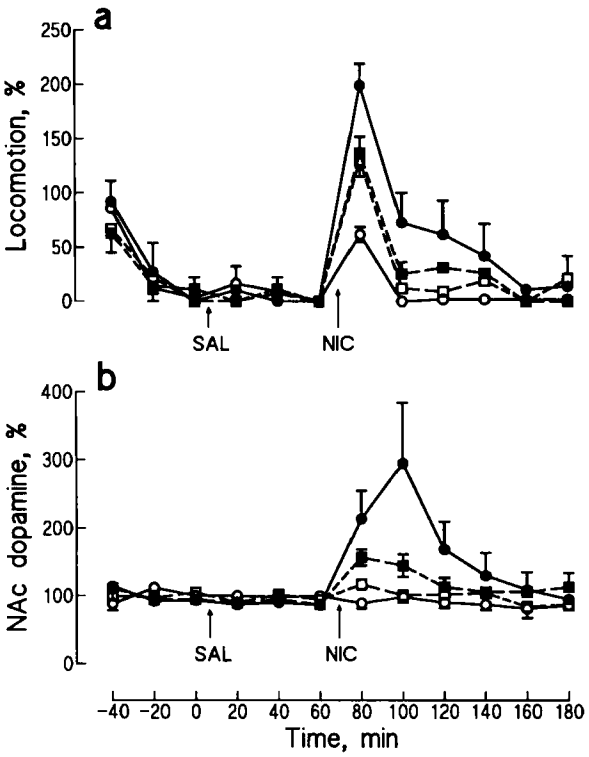

Figure 6. Locomotor activity and dopamine levels in nucleus accumbens (NAc) following saline and nicotine (0.4 mg/kg s.c.) challenges in four groups of rats (n = 4–6). Rats were pretreated for 7 days with dizocilpine (0.3 mg/kg i.p.) and nicotine (0.4 mg/kg s.c.) and were tested for locomotor activity recorded simultaneously with collection of dialysate for successive 20-min periods (pretreatments: saline + saline, ○; saline+ nicotine, ●; dizocilpine + saline, □; dizocilpine + nicotine, ■). Saline and nicotine were injected at times shown. (A) locomotor activity (means ± s.e.m.) in photocell cages and (B) dopamine as a percentage of means ± s.e.m. for the three samples collected prior to the injection of saline.[152]

tors.[146,159,161] For example, dizocilpine can prevent the tolerance that sustained release of morphine produces in rats.[150] However, Stewart and Druhan have shown that dizocilpine can inhibit adaptations to amphetamine both when associative factors are involved, and when they are not involved.[162] With nicotine, reports suggest that conditioning may be important in development of tolerance to some, but not all, effects.[163–166] No studies seem to have distinguished between the effects of dizocilpine or other NMDA antagonists on associative and nonassociative adaptations to nicotine.

Microinjections of noncompetitive and competitive NMDA antagonists into the ventral tegmental area and the ventral amygdala suggest that these structures are target areas of action in behavioral sensitization to cocaine.[167] Similar studies with nicotine seem not to have been reported. Nevertheless, given these findings, it is not surprising to find that local applications of nicotine can release glutamate *in vivo*.[168]

There are two ways to interpret the interactions occurring between NMDA antagonists and nicotine-induced adaptations of behavior. The first interpretation is that dizocilpine may be acting like mecamylamine, a noncompetitive antagonist of the nicotinic receptor; biochemical and electrophysiological studies show some effects of dizocilpine at nicotinic receptors[169,170] and there are similarities between the molecular structure of the ion

channels of nicotinic and excitatory amino acid receptors.[171] Alternatively, dizocilpine may indeed be acting selectively at NMDA receptors. There are several lines of evidence suggesting that this is the correct explanation. Firstly, dizocilpine is more potent at the NMDA than the nicotinic receptor[169] and thus, it may not attain large enough concentration *in vivo* to block nicotincic sites. Secondly, the discriminative stimulus effects of mecamylamine are different from those of dizocilpine and D-CPPene, suggesting differences between the dominant mechanisms of action of these drugs at behaviorally active doses.[172] Thirdly, it seems unlikely that the competitive NMDA antagonist D-CPPene also acts on nicotinic receptors in the way reported for channel-blockers such as mecamylamine and dizocilpine. Fourthly, as noted above, it is not adaptations to nicotine upon which NMDA antagonists act; they influence adaptations to a wide range of drugs from different classes and indeed, neuronal plasticity that is not produced by administering a drug; this broad spectrum of action cannot be explained by an action at nicotinic receptors.

In view of evidence that many drugs, including but not limited to nicotine, share the ability to increase the extracellular concentration of dopamine in the nucleus accumbens, an interaction between the glutamate and the dopamine systems may explain the effects of NMDA antagonists on adaptation to drug action. It may be the case that NMDA antagonists prevent development of sensitization or tolerance to nicotine via a mechanism "downstream" of the primary site of action of nicotine at nicotinic–cholinergic receptors. For example, there are dopamine-containing neurons that respond to glutamate in the prefrontal cortex and the nucleus accumbens.[174] Similarly, kynurenic acid and dizocilpine can prevent excitation of locus coeruleus neurons produced indirectly by applications of nicotine.[174]

The glutamatergic system is not the only mechanism involved in adaptation to nicotine, as has become apparent from studies implicating corticosteroids in both the acute response to nicotine and in nicotine tolerance. Pauly *et al.* have shown that administration of nicotine can produce a centrally mediated increase in plasma concentrations of corticosterone, a hormone that can attenuate some behavioral and physiological effects of nicotine in mice.[175,176] In contrast, adrenalectomy can increase the sensitivity of mice to nicotine in a strain-dependent manner that suggests an important genetic influence.[177] These observations lead to the hypothesis that tolerance to nicotine may be a consequence of the increases in corticosterone concentrations that it produces when administered chronically.[178] Findings that adrenalectomy attenuated the development of tolerance supported the involvement of corticosterone.[179] Marked tolerance to injected nicotine was apparent in the absence of changes in the numbers of binding sites for nicotinic ligands. Thus, evidence reviewed above suggests the involvement of multiple mechanisms in nicotine tolerance, including associative factors, glutamatergic systems, and glucocorticoids. The ways in which these different mechanisms interact and jointly control sensitivity to the drug remain to be determined.

C. Therapeutic Significance

It is tempting to suggest that the involvement of excitatory amino acids in behavioral and neurochemical effects of nicotine may lead to a novel approach to manage problems associated with chronic nicotine intake. However, it has not been established that NMDA antagonists influence dependence on nicotine, although the adaptations studied to date may be part of the dependence process. Nevertheless, nothing is known about the effects of the antagonists on nicotine self-administration or discrimination, or wheth-

er they influence the nicotine withdrawal syndrome. In addition, it is likely that dizocilpine and closely related compounds have phencyclidine-like psychotomimetic effects and abuse potential.[180] For example, dizocilpine can serve as a reinforcer in monkeys with a history of phencyclidine self-administration.[181] Studies need to be conducted with other excitatory amino acid antagonists, such as compounds that bind to the strychnine-insensitive glycine modulatory site of the NMDA receptor complex. For example, (+)-HA966 and L687,414 are anticonvulsant and neuroprotective and are thought not to have the side effects associated with the other types of NMDA antagonists.[182] These compounds have not yet been examined for their effects on adaptations occurring with chronic exposure to drugs. Preliminary evidence suggests that (+)-HA966 and 7-chlorokynurenic acid, another partial agonist at the glycine site, can block activation of the mesolimbic dopaminergic system induced by psychostimulants in rodents.[183,184]

VI. CONCLUSIONS

Studies in recent times show advances in areas of nicotine psychopharmacology, including knowledge of the nature of its effects on behavior and cognition, the receptors at which the effects originate, and the subsequent steps in the chain of events that leads to the observed responses. Evidence that nicotine can produce beneficial effects on some cognitive functions has become firmer and there can now be little doubt that some such effects do occur and that they are not invariably confounded with suppressions of deficits present during the nicotine withdrawal syndrome. However, the beneficial effects are generally small and limited to very specific tests; whether any clinically relevant benefit can be obtained either by tobacco users or by patients with senile dementia is not known yet. Evidence that behavioral effects of nicotine are mediated through more than one subtype of receptor is beginning to emerge, although such conclusions are very speculative at present and few functional correlates have yet emerged of the putative multiple receptors suggested by molecular studies. A clearer picture has been revealed regarding what happens beyond the nicotinic receptor. For some time it was suspected that an action on the dopamine system constituted an important second link in the chain, following upon the primary action at nicotinic–cholinergic receptors. Recent evidence discussed in this review has confirmed the importance of the dopaminergic link, an important mechanism of addiction shared by drugs from several other classes. Finally, attention is being turned towards mechanisms of adaptations seen when organisms are chronically exposed to nicotine and the studies have implicated a number of possible mechanisms, including those involving the dopamine system, its interconnections with glutamate, and the role of corticosteroids. Many questions remain unanswered but some of the tools needed to attack them are available and a continuing growth of the field can be anticipated.

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