Pharmacology Biochemistry and Behavior, Vol. 66, No. 1, pp. 47–64, 2000

0091-3057/00/$–see front matter

ELSEVIER

PII S0091-3057(00)00234-3

# Alteration of the Behavioral Effects of Nicotine by Chronic Caffeine Exposure

GIANLUIGI TANDA* AND STEVEN R. GOLDBERG†*

*Department of Pharmacology, Georgetown University School of Medicine, Washington, DC 20007-2195, and
†National Institutes of Health, National Institute on Drug Abuse, Intramural Research Program,
Preclinical Pharmacology Section, Baltimore, MD 21224

Received 22 October 1999; Revised 31 January 2000; Accepted 02 February 2000

TANDA, G. AND S. R. GOLDBERG. *Alteration of the behavioral effects of nicotine by chronic caffeine exposure.* PHARMACOL BIOCHEM BEHAV **66**(1)47–64, 2000.—The prevalence of tobacco smoking and coffee drinking place nicotine and caffeine among the most used licit drugs in many societies and their consumption is often characterised by concurrent use. The pharmacological basis for any putative interaction between these drugs remains unclear. Some epidemiological reports support anecdotal evidence, which suggests that smokers consume caffeine to enhance the effects of nicotine. This paper reviews various aspects of the pharmacology of caffeine and nicotine, in humans and experimental animals, important for the understanding of the interactions between these drugs. In particular, recent experiments are reviewed in which chronic exposure to caffeine in the drinking water of rats facilitated acquisition of self-adminstration behavior, enhanced nicotine-induced increases in dopamine levels in the shell of the nucleus accumbens and altered the dopaminergic component of a nicotine discrimination. These studies provide evidence that the rewarding and subjective properties of nicotine can be changed by chronic caffeine exposure and indicate that caffeine exposure may be an important environmental factor in shaping and maintaining tobacco smoking. © 2000 Elsevier Science Inc.

Caffeine Nicotine Schedule-controlled behavior Drug Self-administration Drug discrimination
Dopamine microdialysis Nucleus accumbens Tobacco Coffee Drug abuse Cigarettes

CAFFEINE and nicotine are among the most frequently self-administered licit psychoactive drugs in western countries. Caffeine is the main psychoactive ingredient of several different drinks, foods and over-the-counter drugs. Nicotine is the main pharmacologically active ingredient in tobacco and its presence in smoke is recognized as fundamental to the initiation and subsequent persistence of smoking habits and addiction (15,62). Over the past twenty years, a number of epidemiologic studies have documented a positive correlation between caffeine consumption and the use of psychomotor stimulant drugs (30,121,202,217,225). This correlation was strongest for nicotine in the form of tobacco smoke (30,121) and supported anecdotal evidence and some human studies indicating that caffeine can interact with nicotine's pharmacologic effects and modify the frequency of tobacco smoking and the subjective reports of positive effects (35,76). In the present paper different aspects of the pharmacologic effects of caffeine and nicotine are reviewed, with a focus on recent findings indicating that long term exposure to caffeine may alter the behavioral and neuropharmacologic effects of nicotine and other psychomotor stimulant drugs.

## CAFFEINE

The major dietary intake of caffeine is from coffee or tea, but caffeine is also present in a large number of foods, beverages and over-the-counter drugs. Among these products coffee has the highest, although variable, content of caffeine, which ranges from 21 to 128 mg/150 ml of drink, depending on the source of coffee and the brewing technique (12,136). Tea also has a high but variable content of caffeine, ranging from 8 to 81 mg/150 ml (12). Other important sources of caffeine are cocoa and chocolate products (5 to 20 mg/100 g in chocolate candy), soft drinks, especially cola beverages (15 to 24 mg/180 ml/serving), and both prescription and non-prescription drugs that can contain from 15 to 200 mg per tablet

Requests for reprints should be addressed to Steven R. Goldberg, PhD, NIH, NIDA, IRP, Preclinical Pharmacology Section, 5500 Nathan Shock Drive, Baltimore, MD 21224; Tel.: 410-550-1522; Fax: 410-550-1563/1648; E-mail: sgoldber@intra.nida.nih.gov

or capsule (12). Human consumption of caffeine is variable among populations; on average it is estimated to be between 70 and 76 mg/person/day worldwide (93,94). The highest consumption of caffeine from all sources is found in the Scandinavian countries, about 400 mg/person/day, while in the US it reaches 210 mg/person/day (12,60,228).

After oral ingestion, caffeine is quickly and completely absorbed by the gastrointestinal tract (10,24,25) without any significant first-pass effect. Plasma levels of caffeine peak 30 to 120 min. after ingestion, depending on dose, the characteristics of the drink (volume, pH, etc.) or the food (fatty or not) (25,88,133) and on the status of the gastrointestinal tract (i.e., empty or not). Ingestion of caffeine from different dietary products can lead to human plasma levels in the range of 5 to 20 μM concentration that are able to produce pharmacologic effects in the majority of the population. The plasma half-life of caffeine in healthy people is in the range of 2.5 to 4.5 h (54,73,98). The half-life of caffeine is about the same for monkeys, but is shorter in rats and mice (10,26).

### *Caffeine Intake in Children*

Caffeine is generally considered a safe drug. For this reason, and due to its widespread and ubiquitous presence in different drinks and foods, caffeine is likely to be the only psychotropic drug easily available to children. Caffeine, moreover, is the most used psychoactive drug during pregnancy and breastfeeding. For this reason, humans are exposed to active concentrations of caffeine during fetal life and all later stages of life, including breastfeeding, childhood and adulthood. Caffeine crosses the placenta and enters the fetal circulation; it is important to recognize that no physiologic barriers limit the diffusion of caffeine and that a rapid equilibrium is reached between mother and fetus (31). Moreover, during fetal life and during the first 7 to 9 months after birth, there is a lack of the enzymes needed to demethylate caffeine (54,73), so its plasma half-life can range from 32 to 149 h (4,5,135,165). At least 77% of children ingest caffeine in their diet (10,11) with a trend toward increases in recent years.

### *Behavioral Pharmacology*

Caffeine's popularity is likely due to its mild central stimulant properties (42). It is able to increase vigilance, elevate mood, and delay onset of sleep (139,197). Also, it is easily available at a low cost. Caffeine ingestion can be viewed as the most frequent form of drug self-administration behavior in humans (104). Because there appear to be only minor, if any, negative health consequences from acute or chronic ingestion of regular doses of caffeine (41,124), and because reports of loss of control over caffeine intake in people are infrequent compared with the large number of people that regularly drink caffeine without problems (1), it is generally viewed as a safe drug with a low dependence potential (102,103,110,215,216). In fact, there is no government restriction or regulation on the use of caffeine, and the drug is not classified as a drug of dependence in the DSM-IV (62). Health concerns with acute or chronic use of caffeine and its correlation with different diseases that have arisen have not been clearly demonstrated nor reproduced (41). On the other hand, over consumption of caffeine is harmful and can lead to so-called "caffeinism." Due to the biphasic action of caffeine on behavior, however, people tend to self-limit its dose in order to obtain the desired stimulant effects and avoid unpleasant symptoms (87). Also, although many effects of caffeine undergo tolerance with repeated use (117,183), this does not appear to be the case with its reinforcing and aversive effects, when observed, for which tolerance appears to be weak (87).

Behavioral effects of caffeine are biphasic in both humans and animals (56,57). In humans caffeine elicits pleasurable effects at low doses, while it produces unpleasant effects at higher doses (56,57). In rats and mice low doses of caffeine increase locomotor activity and, over the same range of doses, produce conditioned place-preference (28,40,157), while higher doses of caffeine are depressant and inhibit motor activity (40,157). These high doses of caffeine can also produce conditioned-place aversion in rodents (28). Animals and humans can be trained to discriminate caffeine from saline or placebo in drug-discrimination studies (101,102,230). Mumford and Holtzmann (150) showed that if rats are trained to discriminate a low dose of caffeine (10 mg/kg) from saline, adenosine-receptor antagonists and dopaminergic compounds, such as cocaine and amphetamine, produce generalization to the caffeine-training stimulus. When rats were trained to discriminate a higher dose of caffeine (56 mg/kg) from saline, however, generalization to the caffeine-training stimulus was found only with theophylline, a nonselective antagonist of the adenosine receptors (150). Finally, caffeine can function as a reinforcer of human drug-taking behavior under certain circumstances (100,104,105), but its reinforcing effects are small compared to other abused stimulants such as cocaine and amphetamine (102,110). Results from animal drug self-administration studies have been limited and often inconsistent (102,105,172).

Pharmacologic effects of caffeine are mediated by its ability to mobilize intracellular calcium (119,144), inhibit phosphodiesterase (14,84), antagonize the effects of adenosine on adenosine receptors (196), and to interact with $GABA_A$ receptors (55,86). Among these actions, antagonism of adenosine receptors seems the best candidate for mediation of caffeine's effects when caffeine intake is in the dose range of its regular use, 5 to 20 μM plasma concentration (87). Higher plasma concentrations of caffeine appear necessary to obtain the other actions (e.g., inhibition of phosphodiesterase), requiring caffeine doses in the range that can produce toxic effects (87). Adenosine receptors are divided into several subtypes, including $A_1$, $A_{2A}$, $A_{2B}$, and $A_3$ receptors (87). Caffeine is a non-selective antagonist at the level of $A_1$ and $A_{2A}$ receptors, showing a much lower affinity at $A_{2B}$ and $A_3$ receptors (128,56,87).

## NICOTINE

Nicotine is the major psychoactive alkaloid present in tobacco, and its presence in cigarette smoke is fundamentally important for the initiation and persistence of smoking behavior in people, which occurs despite abundant evidence of its harmful effects (15,58,62,199,214). Nicotine is distilled from burning cigarettes. The smoke contains gaseous and particulate phases in which about 3500 different compounds are present (113). During smoking, nicotine is inhaled and carried together with tar in the particulate phase. It reaches the alveoli of the lung, where it is rapidly absorbed, then enters the arterial circulation and reaches the brain in about 20 s (106,111). Plasma nicotine levels vary greatly across smokers and depend on the intensity and number of cigarette puffs and on the nicotine content of the particular cigarette (16,19). During the day, plasma nicotine values of smokers generally range between 20 and 40 ng/ml (20,112). Smokers are able to change their pattern of smoking in order to elevate and then sustain their levels of nicotine. After absorption nicotine is mainly

metabolized to cotinine by the liver. Its half-life is about 2 to 4 h, but smokers (compared with nonsmokers) have an average lower nicotine clearance (16,17,19,134). Non-therapeutic sources of nicotine, other than cigarette smoke, include moist snuff and pipe, cigar and chewing tobacco. Nicotine gums are intended as therapeutic tools for the treatment of nicotine dependence resulting from cigarette smoking [see (20) for a review of pharmacokinetics and pharmacodynamics data for these products].

### *Behavioral Pharmacology*

The main pharmacologic sites of action of nicotine are nicotinic-cholinergic receptors that are present in the brain and periphery (11,38,46,223). The central actions of nicotine are mediated by neuronal nicotinic-acetylcholine receptors that are expressed in different brain regions (46). Eleven nicotinic-acetylcholine-receptor subunit genes have been identified in the vertebrate central nervous system (39); eight of them are $\alpha$ subunit genes and three are $\beta$ subunits. Each receptor is a combination of 5 subunits either $\alpha$ or $\beta$. Because each subunit has different subtypes, it is possible to have a large number of different subtypes of these receptors and, effectively, each brain region possesses nicotine receptors that differ in their agonist affinity and their electrophysiologic properties (61, 229). Also, nicotinic receptors can exist in different functional states after being occupied by an agonist (11) and this may play a role in the addictive properties of nicotine (58).

There is a large body evidence that the mesolimbic dopaminergic system plays an important role in mediating the reinforcing and rewarding effects of psychoactive drugs abused by humans (66,68,129). Different types of nicotine-acetylcholine receptors are present in mesolimbic pathways (140,143) and ventral tegmental area (VTA) neurons are excited by agonists for these receptors (32). Stimulation of VTA dopamine neurons induces the release of dopamine in mesolimbic terminal areas, especially in the shell of the nucleus accumbens (13,52,147,159,160,175,218) in rats. Moreover, both dopamine antagonists and lesions of the nucleus accumbens can decrease nicotine self-administration behavior in rats (53,214).

In smokers, nicotine produces pharmacologic effects that can result in reports of pleasurable subjective feelings, such as increased mental alertness, relaxation or anxiety reduction, and positive reports of mood. These subjective effects are thought to be an important factor in maintaining motivation for smoking (123). We can speculate that, as for the administration of nicotine in animals, when a human smoker inhales nicotine from cigarette smoke, it passes through the arterial blood, reaches the brain and, after activation of nicotinic-acetylcholine receptors, stimulates the release of dopamine in mesolimbic terminals (52). Each inhalation of smoke from a cigarette can contain from about 30 to 250 $\mu$g of nicotine [a cigarette contains on average 8.4 mg of nicotine but only an average intake of 1.0 mg, ranging from 0.3 to 2.5 mg, per cigarette is described (7,18,20)] which can induce a small increase in dopamine release in brain areas thought to mediate the reinforcing and addictive properties of drugs (52,175).

After contact with an agonist such as nicotine, nicotinic acetylcholine receptors become inactive for a certain period of time (48,137). Chronic exposure to low levels of nicotinic agonists, as in the case of plasma levels of nicotine in smokers, can lead to inactivation of most of these receptors (137). It has been shown, moreover, that long-term exposure to a low steady-state level of a nicotinic agonist can result in an increased number of nicotinic acetylcholine receptors (21,140, 232), most of which are in the inactive state, as would be the case with nicotine in smokers (137,166,232,233). An interesting hypothesis for the persistent use of nicotine was proposed by Dani and Heinemann (58). They suggested that when a smoker remains abstinent from nicotine, for example, during the night while sleeping, plasma levels of nicotine decrease and the receptors can slowly recover their active functional state. In the morning, a smoker will not only have an increased number of nicotinic-acetylcholine receptors but also an increased number of these receptors in the active responsive conformation. This might contribute to development of withdrawal symptoms and, perhaps, craving, that would be alleviated by smoking. Thus nicotine could interact with a larger number of active acetylcholine receptors during the first part of the day, at a time when craving for a cigarette would be most intense due to development of withdrawal symptoms. This would allow nicotine to more efficiently function as a reinforcer of smoking behavior mediated through the final pathway of increased dopamine transmission. Thus, a smoker would repeatedly experience a heightened response to the subjective effects of nicotine with the first few cigarettes of the day. At the same time, nicotine would relieve unpleasant symptoms of withdrawal. Russell (195) found that smokers report the first few cigarettes as the most pleasurable of the day.

## BEHAVIORAL INTERACTIONS BETWEEN CAFFEINE AND NICOTINE

### *Locomotor Activity*

As noted above, caffeine's effects on locomotor activity are biphasic in nature; it is a stimulant at low doses and a depressant at higher doses (57). The stimulant effects of caffeine on locomotion rapidly undergo tolerance after chronic administration (116,117,157). Holtzman (114) found that the tolerance that develops in rats to the locomotor stimulant effects of caffeine was reversed 3 weeks after removal of caffeine from the drinking water. Stimulant effects of caffeine on locomotion are mediated by antagonism at the level of adenosine receptors (154). After chronic treatment with caffeine, there is evidence for an increased number of adenosine receptors in the brain (55) and their sensitization (99,109,151,152). This, however, does not explain the apparently insurmountable tolerance to the stimulant effects of caffeine after chronic treatment (83). Nicodijevic et al. (157) suggest that tolerance to the stimulant effects of caffeine might be due to an enhanced activity of a neurotransmitter that in normal conditions is under the inhibitory control of adenosine receptors. The increased release of such a neurotransmitter might result in a down regulation of the receptors mediating its effects and, in turn, to an insurmountable tolerance to the stimulatory actions of caffeine. Indeed, chronic caffeine exposure is able to modify the function of different neurotransmitter systems and to change the density of different receptors in the brain (85,203,204). Nicodijevic et al. (157) also found that chronic treatment with caffeine (1.0 mg/kg in the drinking water) led to a depression of locomotor activity in mice. This depression of locomotor activity appeared to be due to increased central cholinergic activity, since scopolamine, an antagonist of muscarinic receptors, was less potent in increasing locomotor activity in caffeine-exposed mice than in caffeine-free control mice.

A frequently described effect of the acute administration of low-to-intermediate doses of nicotine in naive rats is depression of locomotor activity (43,44,45). This effect under-

goes tolerance with repeated administration of nicotine (43,44,45). In nicotine-tolerant rats, administration of nicotine consistently results in stimulation of locomotor activity (43,44). This stimulant effect of nicotine in rats continues to be seen with acute injections of the drug for several weeks after the end of chronic treatment (211,212). In other studies, however, it has been shown that acute administration of nicotine in naive rats can produce stimulation of locomotor activity (145,167,180). These discrepancies could result from the different procedures used to test for locomotor activity or from differences in the baseline levels of locomotor activity in the animals. Cohen et al. (47) reported that acute administration of caffeine to naive rats abolished the depressant effect of a co-administered dose of nicotine. In contrast, when caffeine and nicotine were coadministered to nicotine-tolerant rats, locomotor activity increased above control levels, whereas, administration of either caffeine or nicotine alone resulted in lower and nonsignificant increases in activity. Finally, Nicodijevic et al. (157) found that chronic treatment of mice with caffeine abolished the depressant effect of a single acute dose of nicotine on locomotor activity.

*Schedule-Controlled Behavior*

Both caffeine and nicotine, when administered alone, produce biphasic changes in response rates in animals responding for food under fixed-interval (FI) schedules of food reinforcement (65,230). White (230) found that both nicotine and caffeine dose dependently increased rates of FI responding for food by rats, with maximum increases at a 0.3 mg/kg dose of nicotine and a 3.0 mg/kg dose of caffeine. Higher doses of either drug decreased response rates. In the same report, White (230) found that co-administration of graded doses of nicotine with a 3.0 mg/kg dose of caffeine produced increases in FI rates of responding. Higher doses of caffeine, which were ineffective in altering FI response rates by themselves, diminished or eliminated the rate-increasing effects of nicotine on FI responding. White (230) also noted that even when caffeine had little effect on nicotine's effects on average rates of FI responding, it appeared to have a considerable effect on the temporal patterns of responding, suggesting that caffeine could be used to magnify some effects of nicotine. White (230) speculated that these interactions could be part of the pharmacologic basis for the high incidence of coffee drinking in smokers (121).

Acute interactions between caffeine and nicotine are not the best way to study the influence of caffeine on the behavioral actions of nicotine. Humans consume caffeine on a daily basis and regular consumption of pharmacologically active doses of caffeine results in the development of tolerance to many of its effects (117,183). With this in mind, Jaszyna et al. (126) examined the behavioral effects of nicotine and caffeine under a FI schedule of food reinforcement in rats chronically exposed to caffeine in their drinking water. Rats were given access to caffeine only after they developed a characteristic pattern of responding under the FI schedule of food reinforcement (82), which consisted of few responses early in the interval and gradually increasing responding as the interval progressed. Once characteristic FI responding was maintained, rats were divided into two groups, with one group of rats receiving caffeine in their drinking water while a control group of rats continued to drink tap water. With a 3 mg/ml concentration of caffeine in their drinking water, rats consumed about 90 mg/kg/day of caffeine and this daily intake did not change significantly over the entire course of the experiment. After an additional 20 or more daily sessions, to allow baseline responding to adjust to chronic caffeine exposure, different doses of caffeine, nicotine, amphetamine and cocaine were tested.

In water-drinking rats, caffeine produced dose-dependent biphasic changes in mean response rates, with a maximum increase at a dose of 10 mg/kg and decreases in response rates at doses of 30 to 56 mg/kg. In caffeine-drinking rats, however, there was complete tolerance to the rate-increasing, but not the rate-decreasing, effects of caffeine (see Fig. 1). In contrast, nicotine produced dose-dependent biphasic changes in mean response rates in both water- and caffeine-drinking rats, with a maximum increase at a dose of 0.17 mg/kg nicotine and a decrease in response rates at a high dose of 1.0 mg/kg. No significant differences in response rates after nicotine were found in caffeine-drinking, as compared to water-drinking rats. Nicotine also dose-dependently modified the pattern of FI responding in both water- and caffeine-drinking rats, as measured by changes in average quarter-life values (expressed as the percentage of the 5-min interval within which 25% of the total number of responses during the interval had been emitted). This effect was significant at doses higher than 0.17 mg/kg in water-drinking rats and 0.3 mg/kg in caffeine-drinking rats. Doses of nicotine of 0.17 mg/kg or higher produced significant decreases in quarter-life values. As in the case with rates of responding, no significant differences were found between water- and caffeine-drinking rats. In the same study, Jaszyna and coworkers (126) found that there was a marked and significant enhancement of the rate-increasing effects of both amphetamine and cocaine in caffeine-drinking as compared to water-drinking rats. Thus in this study, chronic caffeine exposure resulted in development of complete tolerance to the stimulant acute effects of caffeine itself, but there was no cross tolerance to the stimulant effects of nicotine on FI rates of responding. Finally, potentiation, rather than cross tolerance, to the stimulant effects of cocaine and amphetamine on FI responding, was found in caffeine-drinking rats.

The tolerance observed in these experiments to the acute effects of caffeine on FI responding for food was likely due to a change in sensitivity of central adenosine receptors after long-term blockade by an antagonist such as caffeine (116, 122), but interaction with other neurotransmitter systems or receptors cannot be excluded (85,203,204). Because chronic caffeine exposure did not alter the behavioral effects of nicotine on FI responding for food (126), neither alterations in the numbers or sensitivity of adenosine receptors nor modification of other neurotransmitter systems after long-term administration of caffeine appear to play an important role in nicotine's effects on FI schedule-controlled behavior. On the other hand, potentiation of the stimulant effects of cocaine and amphetamine in caffeine-drinking rats suggests differences in the neurochemical mechanisms underlying the actions of commonly abused psychomotor stimulant drugs, such as cocaine and amphetamine, which act primarily through direct stimulation of dopamine transmission, and other psychomotor stimulants, such as nicotine and caffeine (126).

*Drug Discrimination*

Drug-discrimination procedures in animals are a reliable tool to study and identify the receptor systems involved in mediating the subjective effects of various psychoactive drugs (115). With these procedures, animals and humans are trained to discriminate a particular drug from saline or placebo and

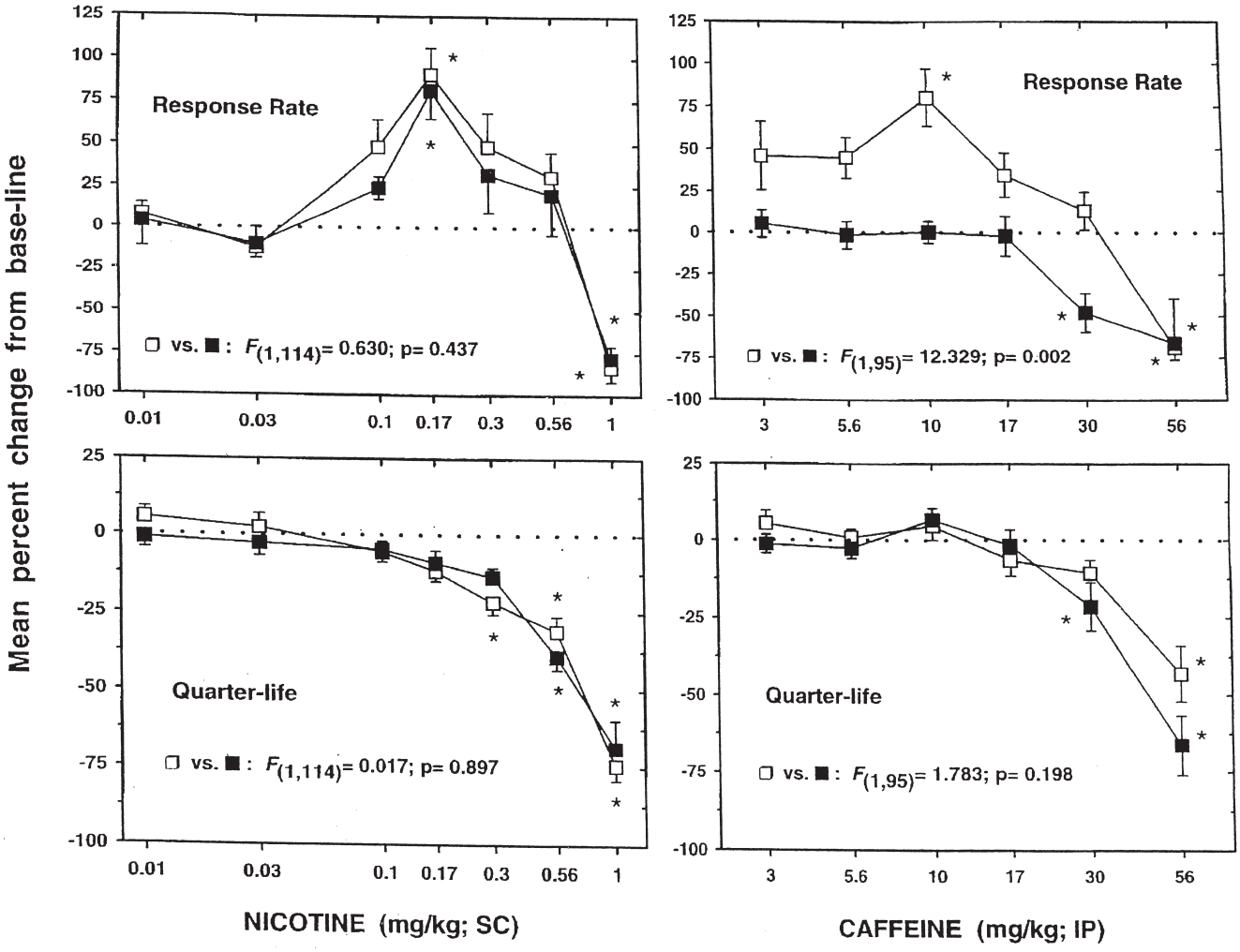


FIG. 1. Effects of graded doses of nicotine or caffeine on response rates and quarter-life (QL) values in water- and caffeine-drinking rats. Nicotine was injected SC and caffeine IP. Each data point represents mean percentage change (± SEM) from individual baseline levels of responding in water-drinking rats (●) and caffeine-drinking rats (•). The individual baseline level of responding consisted of mean response rates and QL values recorded during all vehicle sessions that separated treatments with nicotine or caffeine. F-ratios and *p*-values in each plot represent the outcome of the between-group comparisons of the effects of nicotine or caffeine upon the rates and patterns of responding in water- and caffeine-drinking rats (two-way, random measure ANOVA on one factor). Asterisks represent performance significantly ($p < 0.05$) different from vehicle. From (126) with permission.

other drugs, belonging to the same or to other specific pharmacologic classes, are then tested by substitution. Nicotine has been frequently studied with drug-discrimination procedures and has been found to possess well-defined stimulus properties that can be recognized by animals and humans (167). It has long been known that rats can be trained to discriminate nicotine from saline (149,163) and generalization and pretreatment tests can subsequently be performed to determine the pharmacologic characteristics of the nicotine discriminative stimulus (190,191,192,213). Drugs that have been reported to fully generalize to a nicotine discriminative stimulus are usually nicotinic-acetylcholine receptor agonists (37,89,146, 193,213). Pretreatment with antagonists of these receptors in appropriate doses fully blocks the nicotine discriminative stimulus (163,190,191,213). Caffeine generally produces no nicotine-appropriate responding in rats trained to discriminate nicotine from saline (37,149) [in one study performed in human subjects caffeine produced nicotine-appropriate responses (75). See the "Interaction of caffeine with nicotine's effects in humans" section, below]. In contrast, abused psychomotor stimulants, such as amphetamine, usually produce some nicotine-appropriate responding but do not fully generalize to a nicotine-training stimulus (36,213). Finally, caffeine is also able to potentiate the discriminative stimulus effects of cocaine (92,108) and amphetamine (132,198).

Recently Gasior et al. (91) studied both the rate of acquisition of a nicotine drug discrimination and the subsequent discriminative-stimulus properties of nicotine, caffeine, amphetamine and cocaine, in rats chronically exposed to caffeine in their drinking water. Rats were first trained to press a lever under a 10-response fixed-ratio (FR) schedule of food reinforcement and were then divided into groups, with one group of rats receiving caffeine (3 mg/ml) in their drinking water and the other group continuing to drink plain tap water. After an

additional two weeks under the FR schedule of food reinforcement, rats were trained to discriminate nicotine (0.4 or 0.1 mg/kg) from saline. Rats trained with the highest dose of nicotine met the criteria for discriminative-stimulus control in a shorter period of time than rats trained with the lower dose. The rate of acquisition of the nicotine discrimination in the caffeine-drinking rats was not significantly different from the rate of acquisition in the water-drinking rats, although, there was a non-significant trend for a slower rate of acquisition for the caffeine-drinking versus water-drinking rats at the lower nicotine training dose. When graded doses of nicotine were substituted for the training dose, there was no difference in the nicotine dose-response curves for generalization in caffeine- and water-drinking rats, regardless of the training dose of nicotine. Caffeine exposure also did not change the effects of nicotine on response rates. Further, no significant differences were found in either the potency or efficacy of the nicotinic antagonist mecamylamine in blocking the discriminative stimulus effects of nicotine between caffeine- and water-drinking rats. However, there was a qualitative change in the discriminative stimulus effects of nicotine in the caffeine-drinking rats. Amphetamine, cocaine, apomorphine, and GBR 12909, all psychomotor stimulants with pronounced dopaminergic actions, generalized to the nicotine-training stimulus in the water-drinking rats but not in the caffeine-drinking rats. For example, a dose of 1.0 or 1.7 mg/kg of d-amphetamine produced complete generalization to both the 0.4 and 0.1 mg/kg nicotine training stimuli in the water-drinking rats but produced only saline-appropriate responding in the caffeine-drinking rats (Fig. 2). Also, pretreatment with CGS 10746B, a dopamine-release inhibitor, attenuated nicotine-appropriate responding only in the water-drinking rats.

The main finding of the study by Gasior et al. (91) was that chronic caffeine exposure selectively blunted a dopaminergic component of the nicotine discriminative stimulus without affecting its nicotinic component. As noted above, nicotinic-acetylcholine receptors are the main pharmacologic target through which nicotine exerts its behavioral effects (11,210). The presence of a dopaminergic component in the discriminative stimulus of nicotine has been previously reported (36,213) and might be explained by neuroanatomic studies showing that nicotinic-acetylcholine receptors can be presynapticly localized on dopamine-containing neurons in brain regions potentially involved in mediating the discriminative stimulus effect of nicotine (58,129,206,233). Activation of these receptors can facilitate dopamine release in dopaminergic terminals (159,160,175). Chronic caffeine exposure has been shown to produce an alteration in the number and function of central adenosine receptors (55). Adenosine, acting as an agonist at $A_1$ and $A_2$ receptors, can modulate in an inhibitory fashion the effects mediated by $D_1$ and $D_2$ dopamine receptors (79,80,81). $A_1$ receptors are colocalized with $D_1$ receptors and can antagonize $D_1$-induced increases in cAMP levels in the striatum, while $A_2$ receptors are colocalized with $D_2$ receptors in the striatum where they can inhibit the decrease of cAMP levels induced by dopamine acting on $D_2$ receptors (81,90). Caffeine, acting as a non-selective antagonist at $A_1$ and $A_2$ adenosine receptors (56), can reduce or remove the endogenous inhibitory tone of adenosine on dopaminergic receptors (81,90). This effect can potentiate dopaminergic neurotransmission. Chronic administration of caffeine may induce an overstimulation of dopaminergic neurotransmission that might mask the dopaminergic component of training doses of nicotine during the acquisition of a nicotine discrimination and throughout the entire course of the experiments. It is interesting to note that the effects of chronic caffeine exposure on nicotine's discriminative stimulus effects were long-lasting. When the caffeine solution was replaced with tap water in the caffeine-drinking rats for three weeks, and the amphetamine dose-response curve was then redetermined, the rats continued to show no generalization to the nicotine-training stimulus with *d*-amphetamine.

*Self-Administration*

The drug self-administration procedure is an exceptionally useful tool for evaluating the effectiveness of different psychoactive drugs as reinforcers of drug-seeking behavior. The ability of nicotine to function as a reinforcer to maintain drug-taking behavior was in question until the 1980s because of difficulties in obtaining consistent nicotine self-administration behavior in experimental animals. As a result there was continuing debate about the extent to which nicotine was important in initiating and subsequently maintaining self-administration of tobacco products by humans (184). Reports of powerful effects of IV nicotine as a reinforcer of self-administration behavior by Goldberg and colleagues (96,97,181,209) in squirrel monkeys and dogs focused attention on tobacco use as a form of nicotine self-administration. Until recently, however, experiments in rodents had failed to convincingly demonstrate that nicotine can serve as a reinforcer (107). This was done successfully by Corrigal and Coen (51), and since then other investigators have successfully replicated the findings (74,205,206).

In a recent series of experiments by Shoaib et al. (207), the effects of chronic exposure to caffeine on intravenous nicotine self-administration behavior in rats were investigated. Rats were divided into two groups with one group being given access to caffeine in their drinking water (3 mg/ml) for 7 days before the start of self-administration experiments and the second group continuing to drink plain tap water. Intake of caffeine in the caffeine-drinking rats ranged from 150 to 180 mg/kg/day. Daily self-administration sessions lasting 2 h were then initiated. There were two nose-poke holes with photocells in each experimental chamber, one active and one inactive. Initially, each nose poke in the active hole produced an IV injection of 0.03 mg/kg nicotine accompanied by a brief feedback tone and each injection was followed by a 20-s time-out period. Once the rats showed reliable accuracy in responding and a stable intake of nicotine for two days, the number of responses required to produce an injection was increased progressively from two to five (fixed-ratio 5 schedule of drug injection; FR 5). Significant differences between responding in the active and inactive hole appeared after 14 sessions. Half of the rats in the water-drinking group were then changed to caffeine in their drinking water starting on day 15. Within four sessions this group of rats showed a marked increase in the number of active-hole responses and the number of nicotine injections self-administered as compared to the control group of rats that continued to drink tap water (Fig. 3). Rats exposed to caffeine in their drinking water for 7 days before the start of self-administration sessions showed an accelerated pattern of acquisition over the first 14 days that led to a 50% increase in their intake of nicotine compared to water-drinking rats. Withdrawal of caffeine in half of these rats on day 15 resulted in a marked decrease in both the number of active nose-poke responses and the number of injections of nicotine self- administered. However, responding for nicotine recovered to pre-withdrawal levels in about 5 sessions (Fig. 3). These results suggest that chronic exposure to caffeine can potentiate the reinforcing properties of nicotine, thus acceler-

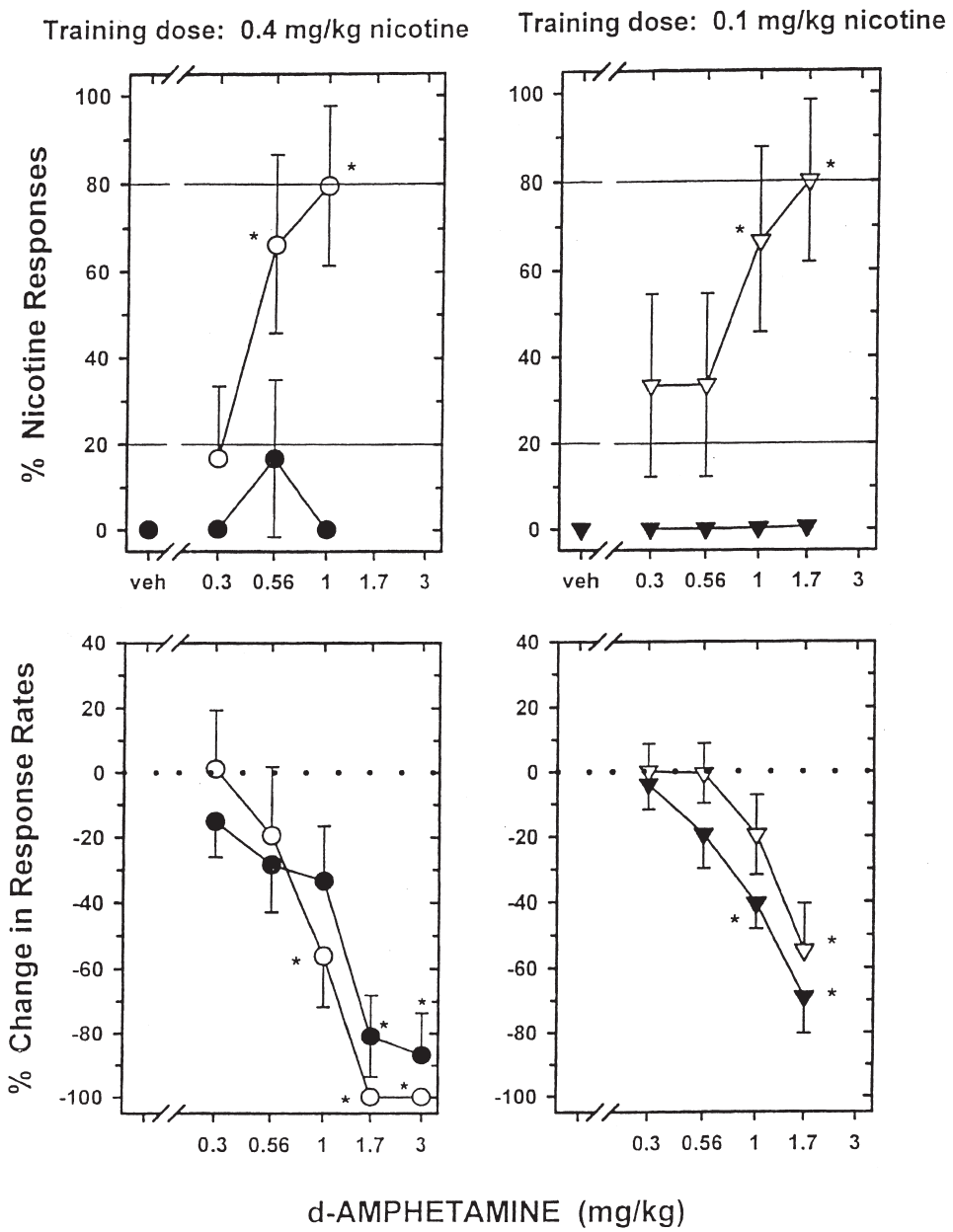


FIG. 2. Dose-response functions for the discriminative-stimulus generalization of amphetamine to the nicotine cue in water- and caffeine-drinking rats. Circles represent water (○)- and caffeine (●)-drinking rats trained to discriminate 0.4 mg/kg of nicotine from saline. Triangles represent water (▽)- and caffeine (▼)-drinking rats trained to discriminate 0.1 mg/kg of nicotine from saline. Top, mean percentage of nicotine-appropriate responses (± SEM; $n = 5$ to 6 rats) after injections with increasing doses of amphetamine or control vehicle (IP 10 min before test session). Bottom, mean percentage of change (± SEM) from the individual baseline rates of responding after different doses of amphetamine. Asterisks represent performance significantly ($p < 0.05$) different from vehicle. From (91) with permission.

ating the rate of acquisition of self-administration and markedly increasing the moderate rates of self-administration responding normally maintained by nicotine in rats. These findings parallel results from our and other laboratories in which chronic caffeine exposure potentiated the reinforcing effects of nicotine in squirrel monkeys (177,235) and of cocaine in rats (33,49,110,200) and reinstated extinguished cocaine-taking behavior in rats (201,234).

*Neurochemical Correlates*

Caffeine, nicotine, amphetamine and cocaine act on different pharmacologic targets. Caffeine is an antagonist of adenosine $A_1$ and $A_2$ receptors (87,196) and its behavioral effects appear to be mediated mostly by blockade of $A_1$ and/or $A_2$ receptors (87). Acute administration of behaviorally active doses of caffeine selectively and significantly increases dopa

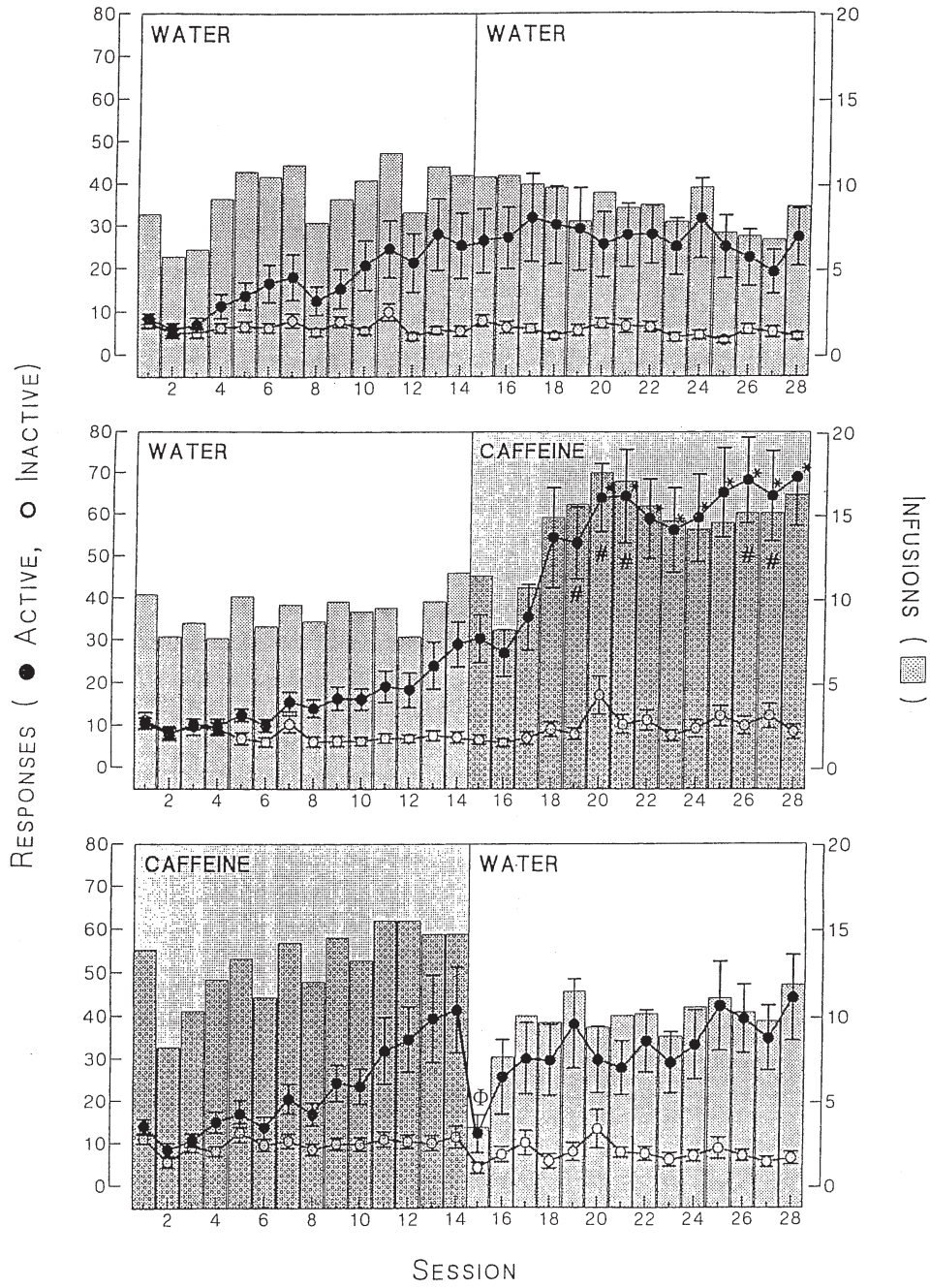


FIG. 3. Acquisition of nicotine self-administration in Sprague-Dawley rats. The mean ± SEM ($n$ = 17 to 20) number of nose pokes in the active and inactive holes for three groups of rats are shown. The bars represent the total number of nicotine infusions delivered during the 2-h session. The top panel represents data from rats that had access only to water at all times during the entire 28-day testing period. The middle panel shows data for rats that had access to water for the first 14 days following by access to caffeine (shaded region) for the latter 14 days. The bottom panel represents data from rats habituated on caffeine in their drinking water for 7 days before training and then trained with caffeine in their drinking water for the first 14 days (shaded region). Caffeine was then removed from the drinking water in this group and the rats were trained for a further 14 days. Statistical differences are indicated by the appropriate symbols following Tukey-Kramer post hoc procedure analysis. Asterisks represent significant differences ($p < 0.05$) in active nose-pokes of caffeine-drinking rats (middle panel) from those of water-drinking control rats (top panel). The hatch symbols (#) represent significant differences ($p< 0$ .05) in the number of nicotine infusions self-administered by caffeine-drinking rats (middle panel) from those of water-drinking control rats (top panel). The omega (φ) symbol in the bottom panel represents a significant reduction ($p < 0.01$) in the number of nose-poke responses and nicotine infusions following the removal of caffeine from the rats' drinking water (comparison of session 14 versus 15). From (207) with permission.

mine release in the medial prefrontal cortex of the rat (71,219). This might be the result of caffeine's antagonistic actions at adenosine $A_1$ receptors in the VTA (78); these receptors might, in turn, modulate the firing activity of dopaminergic mesocortical neurons projecting also to the medial prefrontal cortex. Nicotine is an agonist at nicotinic-acetylcholine receptors, (11) and its reinforcing and other behavioral effects appear to be mediated by activation of these receptors, which can, in turn, facilitate dopamine release preferentially in the shell of the nucleus accumbens, an area that plays an important role in the motivational properties of drugs abused by humans (175).

The reinforcing and addictive effects of cocaine and amphetamine are mediated by direct actions on mesolimbic dopaminergic terminals (174), with amphetamine serving as a dopamine releaser and cocaine as a dopamine-reuptake blocker (179). Thus nicotine, amphetamine and cocaine share, with other drugs abused by humans, the property of preferentially increasing dopamine release in the shell of the nucleus accumbens (174,175, 221). In contrast, intravenous administration of caffeine, at doses that are behaviorally active, does not stimulate dopamine release in the shell or the core of the nucleus accumbens (71,219). These findings, together with the inability of caffeine to change the pattern of glucose utilization in brain (153), which is a characteristic of almost all drugs abused by humans (174), suggest that caffeine would be a weak reinforcer when compared to cocaine and other abused psychomotor stimulant drugs (102,110).

Cocaine and amphetamine are able to increase dopamine levels in the medial prefrontal cortex more efficiently than in the nucleus accumbens shell (220), but this effect seems secondary to the ability of these drugs to block the noradrenaline reuptake transporter (179). This transporter is able to take up dopamine from the extracellular space more efficiently than it takes up noradrenaline itself (179). Blockade of the noradrenaline transporter by cocaine and amphetamine in the medial prefrontal cortex would increase dopamine levels in the extracellular space (220). It is not likely, however, that this effect of cocaine and amphetamine is related to their abuse liability. GBR 12909, a selective blocker of the dopamine but not of the noradrenaline transporter (3), does not significantly increase dopamine output in the prefrontal cortex at doses which do increase dopamine output in the nucleus accumbens shell (220). Nonetheless, GBR 12909 is self-adminstered by rats, although not as consistently as cocaine and amphetamine (182,224). Also nicotine, and other nonpsychomotor stimulant drugs of abuse, such as alcohol and morphine, do not significantly increase dopamine release in the prefrontal cortex at doses that are effective in increasing dopamine levels in the shell of the nucleus accumbens (13), whereas caffeine increases dopamine release selectively in the prefrontal cortex (71,219).

The neurochemical mechanisms that mediate alterations in the behavioral actions of nicotine and psychomotor stimulant drugs after acute and chronic exposure to caffeine appear to be complex. Using microdialysis techniques, Horger et al. (118) found that the elevation in dopamine levels in the ventral striatum induced by cocaine, was enhanced in rats that had been chronically exposed to caffeine and suggested this might be due to a "sensitization" of the neurochemical response to cocaine. In our laboratory, we have used microdialysis techniques [see Tanda et al. (220,221) and Di Chiara et al. (72) for details of methods] to compare the effects of subcutaneous administration of nicotine (0.2 and 0.4 mg/kg) in rats that had been chronically exposed to caffeine (3 mg/ml) in their drinking water for three weeks and control rats that continued to drink plain tap water (Fig. 4). In both caffeine-drinking and water-drinking control rats, nicotine produced a significant and dose-related increase in dopamine levels in the shell of the nucleus accumbens. This effect with nicotine, as was the case with cocaine (118), was significantly enhanced in caffeine-drinking rats, compared to water-drinking rats. Thus chronic exposure to caffeine appears to interact with the functional responsivity of the mesolimbic dopamine transmission. Acute administration of caffeine can facilitate dopamine neurotransmission by antagonizing the inhibitory tone of adenosine acting at presynaptic $A_1$ and $A_2$ receptors which are colocalized with dopamine $D_1$ and $D_2$ receptors (81,176), thus allowing more efficient transduction of the dopaminergic signal. We can speculate, however, that rats might develop tolerance to this effect after chronic caffeine exposure. Thus the effect of chronic caffeine exposure in enhancing nicotine- and cocaine-induced release of dopamine might be mediated by an altered, possibly reduced, ability of dopamine receptors to transduce the dopamine signal. For example, the negative feedback on dopamine firing, dopamine release, and possibly dopamine synthesis might be reduced in caffeine-exposed rats compared to control rats. Additional experiments are needed to test this possibility. Further studies are also needed to determine whether this effect is specific to the mesolimbic dopamine system or if it is a more general effect of chronic caffeine exposure on dopaminergic systems throughout the brain.

Another possible different explanation for this effect might be found in the potential anxiogenic effects of caffeine (22,120,161,197). Caffeine shares with other anxiogenic drugs the property of selectively increasing dopamine release in the prefrontal cortex, as compared to the shell of the nucleus accumbens (13,71,219). The medial prefrontal cortex appears to be a focus for the influence of stress on dopaminergic systems (63,64,70,194). In rats, forced to drink water containing 3 mg/ml caffeine, long-term exposure to such active doses of caffeine might induce a stressful state. Moreover there is evidence suggesting that elevated stress can contribute to individual vulnerability to the reinforcing and other behavioral effects of psychomotor stimulant drugs of abuse (169,170). For example, glucocorticoid activation by stress appears to play a direct role in the process of sensitization to the locomotor stimulant effects of psychomotor stimulant drugs (171).

A third possible explanation for the alteration of the behavioral and neurochemical effects of nicotine by chronic caffeine exposure comes from studies of the prefrontal cortex as a modulator of the activity of subcortical brain areas (23,222,227). After chronic caffeine exposure, it is possible that there is a decreased influence of the prefrontal cortex on subcortical areas. Because acute administration of caffeine can increase dopamine release in the prefrontal cortex, (71,219), thus decreasing the activity of subcortical areas, we can speculate that chronic exposure to caffeine might result in the development of tolerance to this effect, with a subsequent facilitation of dopaminergic subcortical functioning. This might contribute to increased dopamine output in subcortical mesolimbic areas after administration of psychomotor stimulant drugs, such as nicotine, amphetamine, or cocaine, in caffeine-drinking rats.

Although the prefrontal cortex does not appear to play a major role in the addictive properties of psychomotor stimulant drugs and opiates (13,60,220), it may provide attentional and motor resources for active responding to drug-related

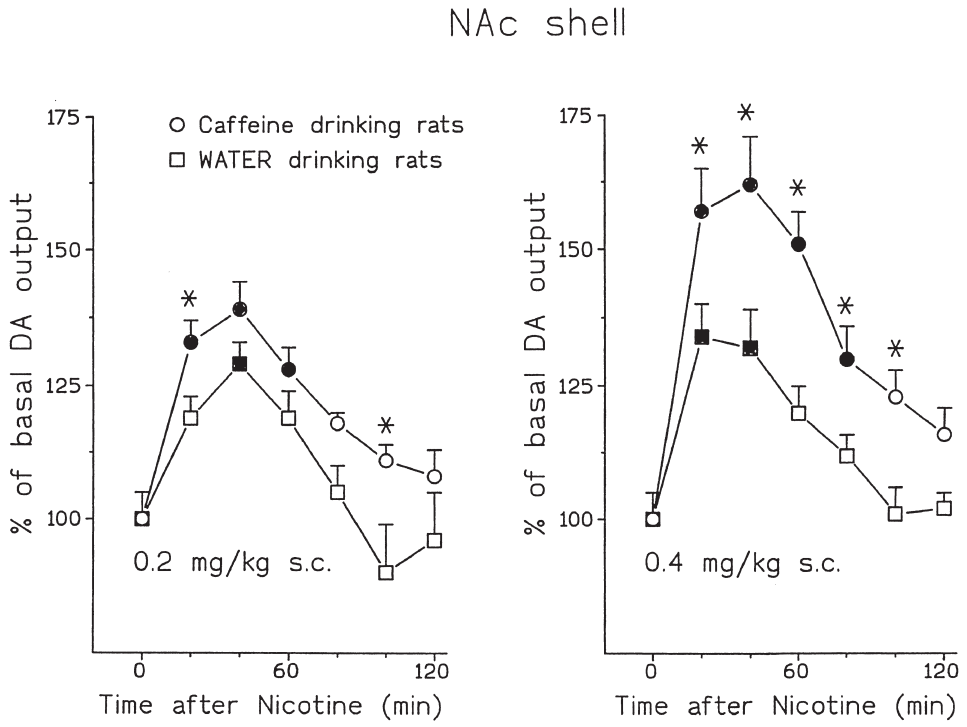


FIG. 4. Effects of administration of nicotine, 0.2 and 0.4 mg/kg (free base) SC, on dopamine output from dialysates of the nucleus accumbens (NAc) shell, in caffeine-drinking (3.0 mg/ml) rats (○) or water-drinking (□) rats. Results are means ± SEM ($n = 4$) of the amount of dopamine in a 20-min dialysate sample, expressed as percent of basal values. Basal values of dopamine were not significantly different between groups and were as follows (means ± SEM, fmoles/sample): water drinking, 73 ± 9, 0.2 mg/kg, 0.2 mg/kg nicotine-treated group; 78 ± 11, 0.4 mg/kg nicotine-treated group; caffeine drinking, 77 ± 8, 0.2 mg/kg 0.2 mg/kg nicotine-treated group; 80 ± l0, 0.4 mg/kg nicotine-treated group. Filled symbols $p < 0.05$ compared with basal values. Asterisks: $p < 0.05$ as compared to the corresponding value obtained in water-drinking control rats. Methods and statistical analysis as described (72,220,221).

stimuli. Thus the mesolimbic dopaminergic system, whose major terminal area, the nucleus accumbens shell, is an integral part of the so-called "extended amygdala" and the mesocortical dopaminergic system, whose major terminal area is the prefrontal cortex, may interact to integrate responses to emotional stimuli and learned strategies acquired from past experience so that the resulting behavior is directed toward obtaining the desired reinforcing event.

### INTERACTION OF CAFFEINE WITH NICOTINE'S EFFECTS IN HUMANS

In a number of different studies positive correlations in the concurrent use of nicotine and caffeine have been found. There have been reports that heavy smokers tend to drink more caffeine than nonsmokers (30,121,188,131). Also, anecdotal and scientific reports show that smokers smoke more cigarettes while drinking coffee (76,121,141,156,164). Emurian and coworkers (76) found that a cigarette-smoking event occurred more often during the 20 min after drinking a cup of coffee than in the 20 min before. On the other hand, there have been other reports that the administration of caffeine had no or a small effect on smoking behavior or nicotine consumption. For example, Kozlowsky (130) reported that coffee-drinking smokers took in more nicotine during periods of no-caffeine drinking than during drinking of beverages containing 75 to 300 mg of caffeine. Chait and Griffiths (35) found that caffeine did not increase the number of cigarettes smoked or the amount of smoke inhaled by smokers who smoked cigarettes ad libitum in a naturalistic laboratory environment. Brown and Benowitz (29) tested the hypothesis that increasing the duration of exposure to caffeine in relation to its dose, could modify the intake of nicotine from cigarette smoking in smokers. They suggested that results from previous studies might not be relevant for coffee and nicotine consumption because the behavior was examined only over brief intervals. As a result their study was conducted over a 4-day interval. Brown and Benowitz (29) found a trend toward an increase in cigarette consumption during caffeine consumption. They also found a tendency toward higher plasma nicotine levels in the lower dose caffeine group compared to the no-caffeine group. Marshall et al. (141,142) also reported that caffeine consumption, in the form of coffee drinking, increased the number of cigarettes smoked, but they found this effect did not appear to be entirely due to the pharmacologic effects caffeine, because water and Postum (a noncaffeinated beverage) drinking influenced the cigarettes smoked.

Because there are epidemiologic as well as clinical studies suggesting that coffee drinking and cigarette smoking are not causually related (30,76,121,156,217), it is possible that other internal or external factors can link the consumption of these two drugs, with consumption of one drug functioning as a trigger to elicit consumption of the other. One of these factors

is that both caffeine drinking and smoking are behaviors that often occur during breaks from worktime or as habits after lunch or during breakfast. Nicotine can function as a calming drug during stressful situations (125) while caffeine can increase anxiety levels in humans (120,161,197) and trigger the consumption of nicotine to relieve this unpleasant state. In this respect, Conway and coworkers (50) investigated the impact of occupational stress on the consumption of alcohol, caffeine and nicotine in a longitudinal field study performed in 34 men over an 8-month period. They reported that during periods of high stress there was more cigarette smoking and, interestingly, more caffeine drinking but less alcohol consumption than during periods without stress.

In another series of studies, Rose (185) and Rose and Behm (187) reported no interaction between caffeine and nicotine on anxiety levels, while they found a significant effect of nicotine in decreasing the arousal induced by caffeine. Pritchard and coworkers (178) also found no interaction between caffeine and nicotine on anxiety levels. In contrast, Perkins et al. (168) found that the combined effect of both caffeine and nicotine was additive, or greater than additive, for anxiety and the same additive effect was found with arousal levels. However, with studies of cognitive performance there were no clear interactive effects of combined administration of nicotine and caffeine (127,178,208). Perkins et al. (168) explained differences between their study and other studies on the basis of differences in the baseline of subjective and activity states of subjects during the tests. It should be noted that Perkins et al. (168) used controlled nasal-spay doses of nicotine in their study instead of cigarette smoking nicotine as in the previously cited studies.

In a drug discrimination study by Duka et al. (75) with 20 human subjects, the discriminative-stimulus properties of low doses of nicotine (0.25, 0.75, and 1.0 mg) in the form of chewing gum were evaluated when given in combination with 50 mg oral caffeine tablets or placebo tablets. Caffeine produced nicotine-appropriate responses in human subjects trained to discriminate nicotine from placebo, suggesting that in humans this dose of caffeine shares with 1.0 mg of nicotine common interoceptive stimulus properties. Another finding was that subjects reported that significant factors in their discrimination of nicotine were "sensation in mouth" and "taste," which further supports the importance of peripheral sensory stimuli in nicotine's subjective effects in humans.

## GENERAL SUMMARY AND CONCLUSIONS

The findings reviewed in this paper demonstrate that both acute and chronic exposure to caffeine can modify some, but not all, of the pharmacologic and behavioral actions of nicotine. In particular, caffeine appears able to alter the behavioral actions of nicotine, not simply in terms of nicotine's actions as a stimulant or depressant of motor activity, but more importantly in terms of nicotine's subjective and reinforcing effects and, thus, its addictive potential. This is an important issue, not only because caffeine is the most widely consumed psychotropic drug, but because it is generally considered safe and is the only licit drug regularly ingested by children and by women during pregnancy and breastfeeding. In humans, caffeine exerts positive feelings of alertness, increased performance and enhanced cognitive functioning at lower doses, but at very high doses it can have unpleasant, anxiogenic effects (56,101,104,120). Tolerance develops readily to some behavioral effects of caffeine after chronic ingestion (117) and withdrawal symptoms that ensue after cessation of chronic caffeine consumption are well recognized (77,105). Dependence on caffeine, both physical and psychologic, has also been described (105), but the small number of people involved in such effects with documented deleterious consequences, as compared to the hundreds of million individuals that drink coffee regularly without showing significant problems, allows caffeine to stay free of the regulatory control for drugs with DMS-IV abuse liability (2). Caffeine does not share with other psychomotor stimulant drugs the property of selectively or preferentially increasing dopamine release and cerebral glucose utilization in the shell of the nucleus accumbens at doses that have stimulant effects on behavior (71,153,155, 175,218,219), but over this range of doses there is increased dopamine release in the medial prefrontal cortex. This is consistent with the modest reinforcing properties of caffeine reported in humans and animals (87,102,110,112). In a recent review on the animal and human data on caffeine dependence, Nehlig (155) concluded that although caffeine fulfilled some criteria for drug dependence, the risk of addiction is not only relatively low, but the lowest in the drug classes considered.

Although caffeine alone does not appear to resemble other psychomotor stimulants in terms of addictive potential (71,155,218), it does appear able to alter the reinforcing and addictive properties of other psychoactive drugs as shown by Shoaib et al. (207) with nicotine and Horger et al. (118) with cocaine. However, in an epidemiologic study of a cocaine-user population, ingestion of caffeine was not correlated with heavy use of cocaine. It appeared, instead, that cocaine users that drank caffeinated beverages showed a lower intake of cocaine than users that did not consume caffeine (30). Alcohol consumption is correlated with caffeine intake, but this correlation is robust only if either drug is used heavily (121). It is possible that heavy alcohol users drink more caffeine only to counteract behavioral depressant effects of alcohol or to antagonize an increased level of adenosine in the brain induced by alcohol ingestion (59,121). Epidemiologic studies do indicate a strong positive correlation between caffeine consumption and smoking habits (121,217). Interestingly, coffee consumption has been noted as an important factor in prediction of plasma nicotine and cotinine levels in smokers by Bridges et al. (27). In other studies, however, caffeine intake did not correlate with an increase in cigarette smoking or to increases in plasma levels of nicotine (34,130,158,162). In contrast, Kozlowski (130) found that in a population of coffee-drinking smokers, abstinence from caffeine produced an increase in smoking behavior (nicotine consumption).

The studies of Shoaib et al. (207) and Horger et al. (118) indicate that caffeine exposure can increase the rate of acquisition of nicotine and cocaine self-administration in rats. These findings suggest that caffeine might serve as an environmental factor capable of influencing the behavior of rats during the initial stage of drug use. The neurochemical mechanism underlying such an effect needs to be clarified. Our preliminary data, and that of Horger (118), suggest an increased sensitivity of mesolimbic dopamine transmission after chronic exposure to caffeine. To better understand and clarify this important issue, it would be helpful to have more extensive epidemiologic data on environmental factors, such as caffeine, that can contribute to the acquisition of smoking habits and nicotine addiction (62) or other forms of drug use. For example, from the available data it is not known if people that start smoking tend to have an intake of caffeine greater than the average, or if they increase their drinking of caffeine after starting to smoke. The importance of this issue can be understood in terms of prevention, due to the high percentage of

children and adolescents that consume caffeine on a regular basis (138,148, 226). If caffeine is an important environmental factor in animals for the initiation and subsequent maintenance of drug-taking behavior with nicotine (and other drugs abused by humans), its heavy use in youth might play a role in the high incidence of cigarette smoking in youth and its frequent correlation with the use of other drugs.

There are important differences between experimental studies in animals, such as these by Shoaib et al. (207), and the human situation. In the rat studies, caffeine was given only one or few weeks before the first nicotine exposure. In humans caffeine is considered a safe drug and for this reason it is possible that the majority of the population is exposed to caffeine from their birth and very often also during prenatal life. Such differences should be studied and addressed. Also, the forced drinking of caffeine solution in rats might have a stronger impact on subsequent behaviors and neurochemical responses than voluntary drinking by humans. Moreover, in preliminary studies in our laboratory on the ability of caffeine to potentiate the discriminative stimulus properties of methamphetamine and the increase in dopamine output produced by methamphetamine in dialysates from the nucleus accumbens shell (Munzar, Tanda and Goldberg, unpublished observations) we found that tolerance appears to develop to these effects after 12 to 15 weeks of exposure to caffeine in the drinking water. It is possible that longer (e.g., 12 to 15 weeks) exposure to caffeine in the drinking water would result in tolerance to the potentiation of nicotine's effects on self-administration and dopamine transmission by caffeine.

It should also be noted that although chronic exposure to caffeine in the drinking water facilitated the acquisition of nicotine self-administration behavior and altered the qualitative nature of the nicotine discriminative stimulus in the experiments reviewed (91,207), it was ineffective in changing the rate of acquisition of nicotine-discrimination performance (91) and did not alter the rate-increasing effect of nicotine on food-maintained responding under a FI schedule (126). An explanation for these discrepancies might be found in the different brain regions that are involved in the discriminative and reinforcing properties of nicotine (206). Nicotine's discriminative-stimulus effects appear to be mediated by the dorsal hippocampus, while its effects as a reinforcer appear to be mediated by the mesolimbic dopamine system (52,175, 206). It is likely that chronic caffeine exposure differentially affects different brain areas, thus resulting in different interactions depending on the function of these particular areas and on the transmitter systems innervating these brain areas. Moreover, recent preliminary data obtained by Goldberg et al. (95) showed that a lower concentration of caffeine in the drinking water (0.25 mg/kg caffeine) did increase the rate of acquisition of a nicotine discrimination in caffeine-drinking compared with water-drinking rats.

From data obtained in human studies it seems that the positive correlation between caffeine and nicotine described in epidemiologic studies is more complex than a simple pharmacologic interaction between drugs. Many other factors appear to be involved in such an interaction, starting from an interaction between the sensory stimuli produced by beverages containing caffeine (for example: taste, smell and, possibly, temperature of the drink) and the pleasurable sensations induced by cigarette smoke. Moreover sensory stimuli appear to have an important role in the maintenance of smoking behavior in humans (186,188,189). In this respect, the pharmacologic effects of nicotine, that elicit increased levels of dopamine in the nucleus accumbens shell, are repeatedly associated with the sensory properties of nicotine, and might induce a kind of associative learning. In this situation, sensory stimuli surrounding nicotine self-administration via tobacco smoking can acquire motivational values, an effect that is typical of conventional reinforcers (69,71). In the case of nicotine, as with other drugs abused by humans, it is possible that the non-decremental increase in dopamine output in the shell, subsequent to intake of active doses of the drug, can pathologically strengthen this association. Thus, the sensory stimuli associated to cigarette smoking may acquire excessive motivational value and became able to facilitate the occurrence of smoking and retard attempts at cessation of smoking.

In conclusion, the experiments reviewed demonstrate that caffeine can alter some of the behavioral and pharmacologic effects of nicotine. These interactions appear complex, since caffeine is able to magnify some important aspects of nicotine's actions, as in the case of self-administration or dopamine release in the shell of the nucleus accumbens, while within the same time period caffeine exposure appeared to be either ineffective or decreased the effects of nicotine in other behavioral tests. Thus the end result of caffeine-nicotine interactions can be qualitatively different depending on the particular aspects of behavior taken into consideration. From this point of view, self-administration data are strongly in agreement with epidemiologic data and give a pharmacologic counterpart to the strong correlation between caffeine and nicotine consumption in humans.

ACKNOWLEDGEMENTS

Animals used in the studies described in Figs. 1–4 were maintained in facilities fully accredited by the American Association for the Accreditation of Laboratory Animal Care (AAALAC) and all experimentation was conducted in accordance with the guidelines of the Institutional Care and Use Committee of the Intramural Research Program, National Institute on Drug Abuse, NIH, and the Guide for Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council, Department of Health, Education and Welfare, Publication (NIH) 85-23, revised 1985. We wish to thank Drs. Jame Goldberg, Sergi Ferre, Wallace Pickworth, Steven Heishman, Patrik Munzar, and Gaetano DiChiara for helpful comments about the manuscript.

## REFERENCES

1. Adams, D.: Ditzler, T.: Haning, W.F.: Primary caffeine dependence: a case report. Hawaii Med. J. 52:190–194; 1993.
2. American Psychiatric Association: Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
3. Andersen, P.H.: The dopamine inhibitor GBR 12909: selectivity and molecular mechanism of action. Eur. J. Pharmacol. 66:493–504; 1989.
4. Aranda, J.V.; Collinge, J.M.; Zinnian, R.; Watters, G.: Maturation of caffeine elimination in infancy. Arch. Dis. Child 54:946–949; 1979.
5. Aranda, J.V.; Gorman, W.; Bergsteinson, H.; Gunn, T.: Efficacy

of caffeine in treatment of apnea in the low-birth-weight infant. J. Pediatr. 90:467–472; 1977.
6. Arbeit, M.L.; Nicklas, T.A.; Frank, G.C.; Webber, L.S.; Miner, M.H.; Berenson, C.S.: Caffeine intakes of children from a biracial population: The Bugaluse Heart Study. J. Am. Diet Assoc. 88:468–471; 1988.
7. Armitage, A.K.; Dollery, C.T.; George, C.F.; Houseman, T.H.; Lewis, P.J.; Turner, D.M.: Absorption and metabolism of nicotine from cigarettes. Br. Med. J. 8:313–316; 1975.
8. Arnaud, M.J.: The pharmacology of caffeine. Prog. Drug Res. 31:273–313; 1987.
9. Arneric, S.P.; Sullivan, J.P.; Williams, M.: Neuronal nicotinic acetylcholine receptors: Novel targets for central nervous system therapeutics. In: Bloom, F.E.; Kupfer, D.J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press, Ltd.; 1995.
10. Axelrod, J.; Reichenthal, J.: The fate of caffeine in man and a method for its estimation in biological material. J. Pharmacol. Exp. Ther. 107:519–523; 1953.
11. Baer, R.A.: Effects of caffeine on classroom behavior, sustained attention, and a memory task in preschool children. J. Applied Behav. Anal. 20:225–234; 1987.
12. Barone, J.J.; Roberts, M.R.: Caffeine consumption. Food Chem. Toxicol. 34:119–129; 1996.
13. Bassareo, V.; Tanda, G.; Petromilli, P.; Giua, C.; DiChiara, G.: Non-psychostimulant drugs of abuse and anxiogenic drugs activate with differential selectivity dopamine transmission in the nucleus accumbens and in the medial prefrontal cortex of the rat. Psychopharmacology 124:293–299; 1996.
14. Beavo, J.A.; Rogers, N.L.; Crofford, O.B.; Hardman, J.G.; Sutherland, E.W.; Newman, E.V.: Effects of xanthine derivatives on lipolysis and on adenosine 3',5'-monophosphate phosphodiesterase activity. Mol. Pharmacol. 6:597–603; 1970.
15. Benowitz, N.L: Drug therapy: Pharmacological aspects of cigarette smoking and nicotine addiction. N. Engl. J. Med. 319:1318–1330; 1988.
16. Benowitz, N.L.; Kuyt, F.; Jacob III, P.: Circadian blood nicotine concentration during cigarette smoking. Clin. Pharmacol. Ther. 32:758–764; 1982.
17. Benowitz, N.L.; Jacob III, P.: Nicotine and cotinine elimination pharmacokinetics in smokers and nonsmokers. Clin. Pharm. Ther. 53:316–323; 1993..
18. Benowitz, N.L.; Jacob III, P.: Daily intake of nicotine during cigarette smoking. Clin. Pharmacol. Ther. 35:499–504; 1984.
19. Benowitz, N.L.; Jacob III, P.; Jones, R.T.; Rosenberg, J.: Interindividual variablity in the metabolism and cardiovascular effects of nicotine in man. J. Pharmacol. Exp. Ther. 221:368–372; 1982.
20. Benowitz, N.L.; Porchet, H.; Jacob III, P.: Pharmacokinetics, metabolism and pharmacodynamics of nicotine. In: Wannacott; Russel; Stolerman, eds. Nicotine psychopharmacology. Oxford: Oxford University Press; 1990:112–157.
21. Benwell, M.E.; Balfour, D.J.; Anderson, J.M.: Evidence that tobacco smoking increases the density of (-)-[$^3$H]nicotine binding sites in human brain. J. Neurochem. 50:1243–1247; 1988.
22. Bhattacharya, S.K.; Satyan, K.S.; Chakrabarti, A.: Anxiogenic action of caffeine: an experimental study in rats. J. Psychopharmacol. 11:219–24; 1997.
23. Blanc, G.; Trovero, F.; Vezina, P.; Herve, D.; Godeheu, A.M.; Glowinski, J.; Tassin, J.P.: Blockade of prefronto-cortical alpha 1-adrenergic receptors prevents locomotor hyperactivity induced by subcortical D-amphetamine injection. Eur. J. Neurosci. 6:293–298; 1994.
24. Blanchard, J.; Sawers, S.J.A.: The absolute bioavailability of caffeine in man. Eur. J. Clin. Pharmacol. 24:93–98; 1983.
25. Bonati, M.; Latini, R.; Galetti, F.; Young, J. F.; Tognoni, G.; Garattini, S.: Caffeine disposition after oral doses. Clin. Pharmacol. Ther. 32:98–106; 1982.
26. Bonati, M.; Latini, R.; Tognoni, G.; Young, J.F.; Garattini, S.: Interspecies comparison of in vivo caffeine pharmacokinetics in man, monkey, rabbit, rat and mouse. Drug Metab. Rev. 15:1355–1383; 1984–5.
27. Bridges, R.B.; Combs, J.G.; Humble, J.W.; Turbek, J.A.; Rehm, S.R.; Haley, N. J.: Population characteristics and cigarette yield as determinants of smoke exposure. Pharmacol. Biochem. Behav. 37:17–28; 1990.
28. Brockwell, N.T.; Eikelboom, R.; Beninger, R.J.: Caffeine-induced place and taste conditioning: production of dose-dependent preference and aversion. Pharmacol. Biochem. Behav. 38:513–517; 1991.
29. Brown, C.R.; Benowitz, N.L.: Caffeine and cigarette smoking: Behavioral, cardiovascular, and metabolic interactions. Pharmacol. Biochem. Behav. 34:565–570; 1989.
30. Budney, A.J.; Higgins, S.T.; Hughes, J.R.; Bickel, W.K.: Nicotine and caffeine use in cocaine-dependence individuals. J. Subst. Abuse 5:117–130; 1993.
31. Burg, A.W.: Physiological disposition of caffeine. Drug Metab. Rev. 4:199–228; 1975.
32. Calabresi, P.; Lacey, M.G.; North, R.A.: Nicotinic excitation of rat ventral tegmental neurons in vitro studied by intracellular recording. Br. J. Pharmacol. 98:135–140; 1989.
33. Carroll, M.E.; Lac, S.T.: Dietary additives and the acquisition of cocaine self-administration in rats. Psychopharmacology 137:81–89; 1998.
34. Chait, L.D.; Griffiths, R.R.: Effects of caffeine administration on human cigarette smoking. Clin. Pharmacol. Ther. 34:612–622; 1982.
35. Chait, L.D.; Griffiths, R.R.: Effects of caffeine on cigarette smoking and subjective response. Clin. Pharmacol. Ther. 34: 7612–622; 1983.
36. Chance, W.T.; Murfin, D.; Krynock, G.M.; Rosecrans, J.A.: A description of the nicotine stimulus and tests of its generalization to amphetamine. Psychopharmacology 55:19–25; 1977.
37. Chance, W.T.; Kallman, M.D.; Rosecrans, J.A.; Spencer, R.M.: A comparison of nicotine and structurally related compounds as discriminative stimuli. Br. J. Pharmacol. 65:609–616; 1978.
38. Changeux, J.-P.; Devillers-Theiry, A.; Chemouilli, P.: Acetylcholine receptor: an allosteric protein. Science 225:1335–1345; 1984.
39. Chavez-Noriega, L.: Characterization of recombinant human neuronal acetylcholine receptors. 2nd International Symposium on: Nicotinic acetylcholine receptors. Annapolis, MD; May 13–14; 1999.
40. Choi, O.H.; Shamim, M.T.; Padgett, W.L.; Daly, J.W.: Caffeine and theophylline analogues: Correlation of behavioral effects with a activity as adenosine receptor antagonists and as phosphodiesterase inhibitors. Life Sci. 43:387–398; 1988.
41. Chou, T.: Wake and smell the coffee: Caffeine, coffee and the medical consequences. West. J. Med. 157:544–553; 1992.
42. Cines, B.M.; Rozin, P.: Same aspects of the liking for hot coffee and coffee flavor. Appetite 3:23–24; 1982.
43. Clarke, P.B.S.; Kumar, R.: The effects of nicotine on locomotor activity in non-tolerant and tolerant rats. Br. J. Pharmacol. 78:329–337; 1983.
44. Clarke, P.B.S.; Kumar, R.: Characterization of the locomotor stimulant action of nicotine in tolerant rats. Br. J. Pharmacol. 80:587–594; 1983.
45. Clarke, P.B.S.; Kumar, R.: Nicotine does not improve discrimination of brain stimulation reward by rats. Psychopharmacology 79:271–277; 1983.
46. Clarke, P.B.S.; Schwartz, R.D.; Paul, S.M.; Pert, C.D.; Pert, A.: Nicotinic binding in rat brain autoradiographic comparison of [$^3$H]-acetylcholine, [$^3$H]-nicotine, and [$^{123}$I]-L-Bungarotoxin. J. Neurosci. 5, Suppl:1307–1315; 1985.
47. Cohen, C.; Welzl, H.; Batig, K.: Effects of nicotine, caffeine, and their combination on locomotor activity in rats. Pharmacol. Biochem. Behav. 40:121–123; 1991.
48. Collins, A.C.; Luo, Y.; Selvaag, S.; et al.: Sensitivity to nicotine and brain nicotinic receptors are altered by chronic nicotine and mecamylamine infusion. J. Pharmacol. Exp. Ther. 271:125–133; 1994.
49. Comer, S.D.; Carroll, M.E.: Oral caffeine pretreatment produced modest increases in cocaine administration in rhesus monkeys. Psychopharmacology 126:281–285; 1996.
50. Conway, T.L.; Vickers, R.R. Jr; Ward, H.W.; Rahe, R.H.: Occu-

pational stress and variation in cigarette, coffee, and alcohol consumption. J. Health. Soc. Behav. 22:155–165; 1981.
51. Corrigall, W.A.; Coen, K.M.: Nicotine maintains self-administration in rats on a limited-access schedule. Psychopharmacology 99:473–478; 1989.
52. Corrigall, W.A.; Coen, K.M.; Adamson, K.L.: Self-administered nicotine activates the mesolimbic dopamine system through the ventral tegmental area. Brain Res. 653:278–284; 1994.
53. Corrigall, W.A.; Franklin, K.B.; Coen, K.M.; Clarke, P.B.: The mesolimbic dopaminergic system is implicated in the reinforcing effects of nicotine. Psychopharmacology 107:285–289; 1992.
54. Curatolo, P.W.; Robertson, D.: The health consequences of caffeine. Ann. Intern. Med. 98:641–653; 1983.
55. Daly, J.W.: Mechanism of action of caffeine. In: Garattini, S., ed. Caffeine, coffee and health. New York: Raven Press; 1993: 97–150.
56. Daly, J. W.: Pharmacology of caffeine. In: Tarter, et al., eds. Handbook of substance abuse: Neurobehavioral pharmacology. New York: Plenum Press; 1998.
57. Daly, J.W.; Fredholm, B.B.: Caffeine—an atypical drug of dependence. Drug Alcohol Dep. 51:199–206; 1998.
58. Dani, J.A.; Heinemann, S.: Molecular and cellular aspects of nicotine abuse. Neuron 16:905–908; 1996.
59. Dar, M.S.: Central adenosinergic system involvement in ethanol-induced motor incoordination in mice. J. Pharmacol. Exp. Ther. 255:1202–1209; 1990.
60. Debry, G.: In: Debry, G., ed. Coffee and health. Paris: John Libbey; 1994: 1–538.
61. Deneris, E.S.; Connolly, J.; Rogers, S.W.; Duvoisin, R.: Pharmacological and functional diversity of neuronal nicotinic acetylcholine receptors. Trends Pharmacol. Sci. 12:34–40; 1991.
62. Department of Health and Human Services; Public Health Service: The health consequences of smoking: Nicotine addiction: A report of the Surgeon General. Washington, DC: Government Printing Office. 1988: DHHS Publication No. (CDC) 88-8406.
63. Deutch, A.Y.; Roth, R.H.: The determinants of stress-induced activation of the prefrontal cortical dopamine system. Prog. Brain Res. 85:367–403; 1990.
64. Deutch, A.Y.; Lee, M.C.; Gillham, M.H.; Cameron, D.A.; Goldstein, M.; Iadarola, M.J.: Stress selectively increases fos protein in dopamine neurons innervating the prefrontal cortex. Cereb. Cortex 1:273–292; 1991.
65. Dews, P.B.: The theory of fixed-interval responding. In: Schoenfeld, W.N., ed. The theory of reinforcement schedules. New York: Appleton-Century-Crofts; 1970: 43–61.
66. DiChiara, G.: The role of dopamine in drug abuse viewed from the perspective of its role in motivation. Drug Alcohol Depend. 38:95–137; 1995.
67. Di Chiara, G.: Cortical and limbic dopamine (on opiate addiction): do not mix before use! Trends Pharmacol. Sci. 18:77–78; 1997.
68. DiChiara, G.: A motivational learning hypothesis of the role of mesolimbic dopamine in compulsive drug use. J. Psychopharmacol. 12:54–67; 1998.
69. Di Chiara, G.: Drug addiction as dopamine-dependent associative learning disorder. Eur J. Pharmacol. 375:13–30; 1999.
70. Di Chiara, G.; Loddo, P.; Tanda, G.: Reciprocal changes in prefrontal and limbic dopamine responsiveness to aversive and rewarding stimuli after chronic mild stress: implications for the psychobiology of depression. Biol. Psychiatry 46:1624–1633; 1999.
71. DiChiara, G.; Tanda, G.; Bassareo, V.; Pontieri, F.; Acquas, F.; Fenu, S.; Cadoni, C.; Carboni, E.: Drug addiction as a disorder of associative learning. Role of nucleus accumbens shell/extended amygdala dopamine. Ann. NY Acad. Sci. 877:461–485; 1999.
72. DiChiara, G.; Tanda, G.; Carboni, E.: Estimation of in-vivo neurotransmitter release by brain microdialysis: The issue of validity. Behav. Pharmacol. 7:640–657; 1996.
73. Dipalma, J.R.: Caffeine. Am. Fam. Physician 25:206; 1982.
74. Donny, E.C.; Caggiula, A.R.; Knopf, S.; Brown, C.: Nicotine self-administration in rats. Psychopharmacology 122:390–394; 1995.
75. Duka, T.; Tasker, R.; Russell, K.; Stephens, D.N.: Discriminative stimulus properties of nicotine at low doses: the effects of caffeine preload. Behav. Pharmacol. 9:219–29; 1998.
76. Emurian, H.H.; Nellis, M.J.; Brady, J.V.; Ray, R.L.: Event time-series relationship between cigarette smoking and coffee drinking. Addict. Behav. 7:441–444; 1982.
77. Evans, S.M.; Griffiths, R.R.: Low-dose caffeine physical dependence in normal subjects: Dose-related effects. In: Harris, L.S., ed. Problems of drug dependence 1990. NIDA Research Monograph No. 105, DHHS Publication No. (ADM)91-1753. Washington, DC: US Government Printing Office; 1991:446.
78. Fastbom, J.; Pazos, A.; Palacios, J.M.: The distribution of adenosine A1 receptors and 5'-nucleotidase in the brain of some commonly used experimental animals. Neuroscience 22:813–826; 1987.
79. Ferre, S.; Fuxe, K.; von Euler, G.; Johansson, B.; Fredholm, B.B.: Adenosine-dopamine interactions in the brain. Neuroscience 51:501–512; 1992.
80. Ferre, S.; O'Connor, W.T.; Fuxe, K.; Ungerstedt, U.: The striopallidal neuron: a main locus for adenosine-dopamine interactions in the brain. J. Neurosci. 13:5402–5406; 1993.
81. Ferre, S.; Fredholm, B.B.; Morelli, M.; Popoli, P.; Fuxe, K.: Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. Trends Neurosci. 20:482–487; 1997.
82. Fester, C.B.; Skinner, B.F.: Schedules of reinforcement. New York: Appleton-Century-Crofts; 1957.
83. Finn, I.B.; Holtzman, S.G.: Tolerance to caffeine-induced stimulation of locomotor activity in rats. J. Pharmacol. Exp. Ther. 238:542–546; 1986.
84. Fredholm, B.B.: Are methylxanthine effects due to antagonism of endogenous adenosine? Trends Pharmacol. Sci. 1:129–132; 1980.
85. Fredholm, B.B.: Adenosine actions and adenosine receptors after 1 week treatment with caffeine. Acta Physiol. Scand. 115:283–286; 1982.
86. Fredholm, B.B.; Arslan, G.; Johansson, B.; Kull, B.; Svenningsson, P.: Adenosin $A_{2A}$ receptors and the actions of caffeine. In: Okado, Y., ed. The role of adenosine in the nervous system. Amsterdam: Elsevier Science; 1997:51–74.
87. Fredholm, B.B.; Battig, K.; Holmen, J.; Nehlig, A.; Zvartau, E.E.: Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol. Rev. 51:83–133; 1999.
88. Garattini, S.; Bonati, M.; Latini, R.: Studies on the kinetics and metabolism of caffeine: In: Proceedings of First International Caffeine Committee Workshop. November 8-10; 1978, Kesuhou-Kona, Hawaii; 1979.
89. Garcha, H.S.; Goldberg, S.R.; Reavill, C.; Stolerman, I.P.: Behavioral effects of the optical isomers of nicotine and nornicotine, and of cotinine, in rats. Br. J. Pharmacol. 88:298P; 1986.
90. Garrett, B.E.; Griffiths, R.R.: The role of dopamine in the behavioral effects of caffeine in animals and humans. Pharmacol. Biochem. Behav. 57:533–541; 1997.
91. Gasior, M,: Shoaib, M,: Yasar, S,: Jaszyna, M,: Goldberg, S.R.: Acquisition of nicotine discrimination and discriminative stimulus effects of nicotine in rats chronically exposed to caffeine. J. Pharmacol Exp. Ther. 288:1053–1073; 1999.
92. Gauvin, D.V.; Criado, J.R.; Moore, K.R.; Holloway, F.A.: Potentiation of cocaine's discriminative effects by caffeine: A time-effect analysis. Pharmacol. Biochem. Behav 36:195–197; 1990.
93. Gilbert, R.M.: Caffeine: Overview and anthology. In: Miller, S., ed. Nutrition & behavior. Philadelphia: The Franklin Institute; 1981:146–266.
94. Gilbert, R.M.: Caffeine consumption. In: Spiller, G.A., ed. The methylxanthine beverages and foods: Chemistry, consumption and health effects. New York: Liss; 1984: 185–213.
95. Goldberg, S.R.; Jaszyna, M.J.; Gasior, M.; Yasar, S.; Tanda, G.: Alteration of the behavioral response to nicotine by caffeine

exposure. Abstract in Proceedings of the 6th Annual Meeting of the Society for Research on Nicotine and Tobacco. Arlington, VA, February 18–20, 2000.
96. Goldberg, S.R.; Spealman, R.D.; Goldberg, D.M.: Persistent behavior at high rates maintained by intravenous self-administration of nicotine. Science 214:573–575; 1981.
97. Goldberg, S.R.; Spealman, R.D.; Risner, M.E.; Henningfield, J.E.: Control of behavior by intravenous nicotine injections in laboratory animals. Pharmacol. Biochem. Behav. 19:1011–1020; 1983.
98. Graham, D. M.: Caffeine—Its identity, dietary sources, intake and biological effects. Nutr. Rev. 36:97–102; 1978.
99. Green, R.M.; Stiles, G.L.: Chronic caffeine ingestion sensitizes the $A_1$ adenosine receptor-adenylate cyclase system in rat cerebral cortex. J. Clin. Invest. 77:222–227; 1986.
100. Griffiths, R.R.; Bigelow, G.E.; Liebson, I.A.: Human coffee drinking: Reinforcing and physical dependence producing effects of caffeine. J. Pharmacol. Exp. Ther. 239:416–425; 1986.
101. Griffiths, R.R.; Evans, S.M.; Heishman, S.J.; Preston, K.L.; Sannerud, C.A.; Wolf, B.; Woodson, P.P.: Low-dose caffeine discrimination in humans. J. Pharmacol. Exp. Ther. 252:970–978; 1990.
102. Griffiths, R.R.; Mumford, G.K.: Caffeine—A drug of abuse? In: Bloom, F. E.; Kupfer, D. J., eds. Psychopharmacology: The fourth generation of progress. New York: Raven Press Ltd.; 1995.
103. Griffiths, R.R.; Mumford, G.K.: Caffeine reinforcement, discrimination, tolerance and physical dependence in laboratory animals and humans. In: Schuster, C.R.; Kuhar, M.J., eds. Pharmacological aspects of drug dependence: Toward an integrated neurobehavioral approach. Handbook of experimental pharmacology. New York: Springer-Verlag; 1996:315–341.
104. Griffiths, R.R.; Woodson, P.P.: Reinforcing effects of caffeine in humans. J. Pharmacol. Exp. Ther. 246:21–29; 1988.
105. Griffiths, R.R.; Woodson, P.P.: Caffeine physical dependence: A review of human and laboratory animal studies. Psychopharmacology 94:437–451; 1988.
106. Gourlay, S.G.; Benowitz, N.L.: Arteriovenous differences in plasma concentration of nicotine and catecholamines and related cardiovascular effects after smoking, nicotine nasal spray, and intravenous nicotine. Clin. Pharmacol. Ther. 62:453–463; 1997.
107. Hanson, H.M.; Ivester, C.A.; Morton, B.R.; Krasnegor, N.A.: Cigarette smoking as a dependence process. In: Nicotine self-administration in rats. Rockville, MD, NIDA Monograph, US Department of Health, Education and Welfare; 1979: 70–90.
108. Harland, R.D.; Gauvin, D.V.; Michaelis, R.C.; Carney, J.M.; Seal, T.W.; Holloway, F.A.: Behavioral interaction between cocaine and caffeine: A drug discrimination analysis in rats. Pharmacol. Biochem. Behav. 32:1017–1023; 1989.
109. Hawkins, M.; Dugich, M.M.; Porer, N.M.; Urbancic, M.; Radulovacki, M.: Effects of chronic administration of caffeine on adenosine $A_1$ and $A_2$ receptors in rat brain. Brain Res. Bull. 21:479–482; 1988.
110. Heishman, S.J.; Henningfield, J.E.: Stimulus functions of caffeine in humans: relation to dependence potential. Neurosci. Biobehav. Rev. 16:273–287; 1992.
111. Henningfield, J.E.; Stapleton, J.M.; Benowitz, N.L.; Grayson, R.F.; London, E.D.: Higher levels of nicotine in arterial than in venous blood after cigarette smoking. Drug Alcohol Depend. 33:23–29; 1993.
112. Herning, R.I.; Jones, R.T.; Benowitz, N.L.; et al.: How a cigarette is smoked determines blood nicotine levels. Clin. Pharmacol. Ther. 33:84–90; 1983.
113. Hoffmann, D.; Hoffmann, I.: The changing cigarette, 1950–1995. J. Toxicol. Environ. Health 50:307–364; 1997.
114. Holtzman, S.G.: Complete, reversible, drug-specific tolerance to stimulation of locomotor activity by caffeine. Life Sci. 33:779–787; 1983.
115. Holtzman, S.G.: Discriminative effect of drugs: Relationship to potential for abuse. In: Alder and Cowan, eds. Testing and evaluation of drug of abuse. Modern methods in pharmacology, vol. 6. 1990:193–210.
116. Holtzman, S.G.: CGS 15943, a nonxanthine adenosine receptor antagonist: Effects on locomotor activity of nontolerant and caffeine-tolerant rats. Life Sci. 49:1563–2570; 1991.
117. Holtzman, S.G.; Finn, I.B.: Tolerance to behavioral effects of caffeine in rats. Pharmacol. Biochem. Behav. 28:411–418; 1988.
118. Horger, B.A.; Wellman, P.J.: Morien, A.; Davies, B.T.; Schenk, S.: Caffeine exposure sensitizes rats to the reinforcing effects of cocaine. Neuroreport 2:53–56; 1991.
119. Huddart, H.; Bayton, E.; Shanklin, J.: Influence of some common methylxanthines on contractile responses and calcium mobilization of ileal, vas deferens and bladder smooth muscle. J. Exp. Bio. 107:73–93; 1983.
120. Hughes, R.N.: Drugs which induce anxiety: Caffeine. N Zeal. J. Psychol. 25:36–46; 1996.
121. Istvan, J.; Matarazzo, J.D.: Tobacco, alcohol, and caffeine use: A review of their interrelationships. Psychol. Bull. 95:301–326; 1984.
122. Jacobson, K.A.; von Lubitz, D.K.; Daly, J.W.; Fredholm, B.B.: Adenosine receptor ligands: Differences with acute versus chronic treatment. Trends Pharmacol. Sci.. 17:108–113; 1996.
123. Jaffe, J.H.; Jarvik, M.E.: Tobacco use and tobacco use disorder. In: Lipton; Di Mascio; Killam, eds. Psychopharmacology: A generation of progress. 1978: 1665–1676.
124. James, J.E.: Caffeine and health. San Diego: Academic Press Ltd.; 1991.
125. Jarvik, M.E.; Caskey, N.H.; Rose, J.E.; Herskovic, J.E.; Sadeghpour, M.: Anxiolytic effects of smoking associated with four stressors. Addict. Behav. 4: 379–386; 1989.
126. Jaszyna, M.J.; Gasior, M.; Shoaib, M.; Yasar, S.; Goldberg, S.R.: Behavioural effects of nicotine, ampehtamine and cocaine under a fixed-interval schedule of food reinforcement in rats chronically exposed to caffeine. Psychopharmacology 140:257–271; 1998.
127. Kerr, J.S.; Sherwood, N.; Hindmarch, I.: Separate and combined effects of the social drugs on psychomotor performance. Psychopharmacology 104:113–119; 1991.
128. Koltz, K-N.; Hessling, J.; Hegler, J.; et al.: Comparative pharmacology of human adenosine receptor subtypes—characterization of stably transfected receptors in CHO cells. Naunyn-Schmiedeberg's Arch. Pharmacol. 357:1–9; 1997.
129. Koob, G.F.: Drugs of abuse: Anatomy, pharmacology and function of reward pathways. Trends Pharmacol. Sci. 13:177–184; 1992.
130. Kozlowski, L.T.: Effects of caffeine consumption on nicotine consumption. Psychopharmacologia, 47:165–168; 1976.
131. Kozlowski, L.T.; Henningfield, J.E.; Keenan, R.M.; Lei, H.; Leigh, G.; Jelinek, L.C.; Pope, M.A.; Haertzen, C.A.: Patterns of alcohol, cigarette, and caffeine and other drug use in two drug abusing populations. J. Subst. Abuse Treat. 10:171–179; 1993.
132. Kuhn, D.M.; Appel, J.B.; Greenberg, I.: An analysis of some discriminative properties of d-amphetamine. Psychopharmacologia 39:57–66; 1974.
133. Latini, R.; Bonati, M.; Castelli, D.; Garattini, S.: Dose-dependent kinetics of caffeine in rats. Toxicol. Lett. 2:267–270; 1978.
134. Lee, B.L.; Benowitz, N.L.; Jacob III, P.: Influence of tobacco abstinence on the disposition kinetics and effects of nicotine. Clin. Pharmacol.Ther. 41:474–479; 1987.
135. Le Guennec, J.C.; Billon, B.: Delay in caffeine elimination in breast-fed infants. Pediatrics 79:264–268; 1987.
136. Lelo, A.; Miners, J.O; Robson, R.; Birkett, D.J.: Assessment of caffeine exposure: Caffeine content of beverages, caffeine intake, and plasma concentration of methylxanthines. Clin. Pharmacol. Ther. 39:54–59; 1986.
137. Lester, R.A.J.; Dani, J.A.: Time dependent changes in central nicotinic acetylcholine channel kinetics in excised patches. Neuropharmacology 33:27–34; 1994.
138. Liebman, B.: The changing American diet. Nutrition Action Newletter 1997:8–9.
139. Lieberman, H.R.; Wurtman, R.J.; Emde, G.G.; Roberts, C.; Coviella, I.L.G.: The effects of low doses of caffeine on human performance and mood. Psychopharmacology 92:308–312; 1987.
140. Marks, M.J.; Pauly, J.R.; Gross, S.D.; Deneris, E.S.; Hermans-Borgmeyer, I.; Heinemann, S.F.; Collins, A.C.: Nicotine binding

and nicotinic receptor subunit RNA after chronic nicotine treatment J. Neurosci. 12:2765–2784; 1992.
141. Marshall, W.R.; Green, S.B.; Epstein, L.H.; Rogers, C.M.; McCoy, J.F.: Coffee drinking and cigarette smoking: II. Coffee, urinary pH and cigarette smoking behavior. Addict. Behav. 5:395–400; 1980.
142. Marshall, W.R.; Epstein, L.H.; Green, S.B.: Coffee drinking and cigarette smoking: I. Coffee, caffeine and cigarette smoking behavior. Addict. Behav. 5:389–94; 1980.
143. McGehee, D.S.; Role, L.W.: Physiological diversity of nicotinic acetylcholine receptors expressed by vertebrate neurons. Ann. Rev. Physiol. 57:521–546; 1995.
144. McPherson, P.S.; Kim, Y.K.; Valdivia, H.; Knudson, C.M.; Takekura, H.; Franzini-Armstrong, C.; Coronado, R.; Campbell, K.P.: The brain ryanodine receptor: A caffeine-sensitive calcium release channel. Neuron 7:17–25; 1991.
145. Meliska, C.J.; Loke, W.H.: Caffeine and nicotine: Differentail effects on ambulation, rearing and wheel-running. Pharmacol. Biochem. Behav. 21:871–875; 1984.
146. Meltzer, L.T.; Rosecrans, J.A.; Aceto, M.D.; Harris, L.S.: Discriminative stimulus properties of the optical isomers of nicotine. Psychopharmacology 68:283–286; 1980.
147. Mitchell, S.N.; Smith, K.M.; Joseph, M.H.; Gray, J.A.: Acute and chronic effects of nicotine on catecholamine synthesis and release in the rat central nervous system. In: Lipiello, P.M.; Collins, A.C.; Gray, J.A.; Robinson, J.H., eds. The biology of nicotine: Current research issues. New York: Raven Press; 1992:97–119.
148. Morgan, K.J.; Stults, V.J.; Zabik, M.E.: Amount and dietary sources of caffeine and saccharin intake by individuals ages 5 to 18 years. Regul. Toxicol. Pharmacol. 2:296–307; 1982.
149. Morrison, C.F.; Stephenson, J.A.: Nicotine injections as the conditioned stimulus in discrimination learning. Psychopharmacologia 15:351–360; 1969.
150. Mumford, G.K.; Holtzman, S.G.: Qualitative differences in the discriminative stimulus effects of low and high doses of caffeine in the rat. J. Pharmacol. Exp. Ther. 258:857–865; 1991.
151. Murray, T.F.: Up-regulation of rat cortical adenosine receptors following chronic administration of theophylline. Eur. J. Pharmacol. 82:113–114; 1982.
152. Murray, T.F.; Blaker, W.D.; Cheney, D.L.; Costa, E.: Inhibition of acetylcholine turnover rate in rat hippocampus and cortex by intraventricular injection of adenosine analogs. J. Pharmacol. Exp. Ther. 222:550–554; 1982.
153. Nehlig, A.; Daval, J.L.; Boyet, S.; Vert, P.: Comparative effects of acute and chronic administration of caffeine on local cerebral glucose utilization in the conscious rat. Eur. J. Pharmacol. 129:93–103; 1986.
154. Nehlig, A.; Daval, J.L.; Debry, G.: Caffeine and the central nervous system: Mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain Res. Rev. 17:139–170; 1992.
155. Nehlig, A.: Are we dependent upon coffee and caffeine? A review of human and animal data. Neurosci. Biobehav. Rev. 23:563–576; 1999.
156. Nellis, M.J.; Emurian, H.H.; Brady, J.V.; Ray, R.L.: Behavior analysis of cigarette smoking. Pavlov. J. Biol. Sci. 17:140–149; 1982.
157. Nikodijevic, O.; Jacobson, K.A.; Daly, J.W.: Locomotor activity in mice during chronic treatment with caffeine and withdrawal. Pharmacol. Biochem. Behav. 44:199–216; 1993.
158. Nil, R.; Buzzi, R.; Battig, K.: Effects of single doses of alcohol and caffeine on cigarette smoking puffing behavior. Pharmacol. Biochem. Behav. 20:583–590; 1984.
159. Nisell, M.; Nomikos, G.G.; Svensson, T.H.: Systemic nicotine-induced dopamine release in the rat nucleus accumbens is regulated by nicotinic receptors in the ventral tegmental area. Synapse 16:34–44; 1994.
160. Nisell, M.; Nomikos, G.G.; Svensson, T.H.: Nicotine dependence, midbrain dopamine systems and psychiatric disorders. Pharmacol. Toxicol. 76:157–162; 1995.
161. Orlikov, A.; Ryzov, I.: Caffeine-induced anxiety and increase of kynurenine concentration in plasma of healthy subjects: a pilot study. Biol. Psychiatry 29: 391–396; 1991.
162. Ossip, D.J.; Epstein, L.H.: Relative effect of nicotine and coffee on cigarette smoking. Addict. Behav. 6:35–39; 1981.
163. Overton, D.A.: Control of T-maze choice by nicotinic, antinicotinic and antimuscarinic drugs. Proceedings 77th Annual Convention, American Psychological Association. 1969: 869–870.
164. Parsons, W.D.; Neims, A.H.: Effect of smoking on caffeine clearance. Clin. Pharmacol. Ther. 24:40–45; 1978.
165. Parsons, W.D.; Neims, A.H.: Prolonged half-life of caffeine in healthy term newborn infants. J. Pediatr. 98:640–641; 1981.
166. Peng, X.; Gerzanich, V.; Anand, R.; Whiting, P.J.; Lindstrom, J.: Nicotine induced increase in neuronal nicotinic receptors result from a decrease in the rate of receptor turnover. Mol. Pharmacol. 46:523–530; 1994.
167. Perkins, K.A.; Stitzer, M.: Behavioral pharmacology of nicotine. In: Tarter, et al., eds. Handbook of substance abuse: Neurobehavioral pharmacology. New York: Plenum Press; 1998.
168. Perkins, K.A.; Sexton, J.E.; Stiller, R.L.; Fonte, C.; DiMarco, A.; Goettler, J.; Scierka, A.: Subjective and cardiovascular responses to nicotine combined with caffeine during rest and casual activity. Psychopharmacology 113:438–444; 1994.
169. Piazza, P.V.; Deroche, V.; Rouge-Pont, F.; Le Moal, M.: Behavioral and biological factors associated with individual vulnerability to psychostimulant abuse. NIDA Res. Monogr. 169:105–33; 1998.
170. Piazza, P.V.; Le Moal, M.: The role of stress in drug self-administration. Trends Pharmacol Sci 19:67–74; 1998.
171. Piazza, P.V.; Le Moal, M.: Glucocorticoids as a biological substrate of reward: physiological and pathophysiological implications. Brain Res. Rev. 25:359–72; 1997.
172. Pickworth, W.B.: Caffeine dependence. Lancet 345:1066; 1995.
173. Pontieri, F.E.; et al.: Mapping of functional changes associated with administration of substances of abuse in the rat. Funct. Neurol. 13:311–326; 1998.
174. Pontieri, F.E.; Tanda, G.; DiChiara, G.: Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the 'shell' as compared with the 'core' of the rat nucleus accumbens. Proc. Natl Acad. Sci. USA 92:12304–12308; 1995.
175. Pontieri, F.E.; Tanda, G.; Orzi, F.; DiChiara, G.: Effects of nicotine on the nucleus accumbens and similarity to those of addictive drugs. Nature 382:255–257; 1996.
176. Popoli, P.; Pezzola, A.; Scotti De Carolis, A.: Modulation of striatal adenosine A1 and A2 receptors induces rotational behaviour in response to dopaminergic stimulation in intact rats. Eur. J. Pharmacol. 257:21–25; 1994.
177. Prada, J.A.; Goldberg, S.R.: Effects of caffeine on nicotine pretreatments on nicotine self-administration by the squirrel monkey. Pharmacologist 27:226; 1985.
178. Pritchard, W.S.; Robinson, J.H.; deBethizy, J.D.; Davis, R.A.; Stiles, M.F.: Caffeine and smoking: subjective, performance, and psychophysiological effects. Psychophysiology 32:19–27; 1995.
179. Raiteri, M.; Del Carmine, R.; Bertollini, A.; Levi, G.: Effects of sympathomimetic amines on the synaptosomal transport of noradrenaline, dopamine and 5-hydroxytryptamine. Eur. J. Pharmacol. 41:133–143; 1977.
180. Reavill, C.; Stolerman, I.P.: Locomotor activity in rats after administration of nicotinic agonists intracerebrally. Br. J. Pharmacol. 99:273–278; 1990.
181. Risner, M.E.; Goldberg, S.R.: A comparison of nicotine and cocaine self-administration in the dog: Fixed-ratio and progressive-ratio schedules of intravenous drug infusion. J. Pharmacol. Exp. Ther. 224:319–326; 1983.
182. Roberts, D.C.: Self-administration of GBR 12909 on a fixed ratio and progressive ratio schedule in rats. Psychopharmacology 111:202–206; 1993.
183. Roberton, D.; Wade, D.; Workman, R.; Woosley, R.L.; Oates, J.A.: Tolerance to the humoral and hemodynamic effects of caffeine in man. J. Clin. Invest. 67:1111–1117; 1981.
184. Robinson, J. H.; Pritchard, W. S.: The role of nicotine in tobacco use. Psychopharmacology 108:397–407; 1992.
185. Rose, J.E.: Cigarette smoking blocks caffeine-induced arousal. Alcohol Drug Res. 7:49–55; 1987.

186. Rose, J.E.: The role of upper airway stimulation in smoking. Prog. Clin. Biol. Res. 261:95–106; 1988.
187. Rose, J.E.; Behm, F.M.: Psychophysiological interactions between caffeine and nicotine. Pharmacol. Biochem. Behav. 38:333–337; 1991.
188. Rose, J.E.; Behm, F.M.; Levin, E.D.: Role of nicotine dose and sensory cues in the regulation of smoke intake. Pharmacol. Biochem. Behav. 44: 891–900; 1993.
189. Rose, J.E.; Corrigall, W.A.: Nicotine self-administration in animals and humans: similarities and differences. Psychopharmacology 130: 28–40; 1997.
190. Rosecrans, J.A.; Chance, W.T.: Cholinergic and non-cholinergic aspects of the discriminative stimulus properties of nicotine. In: Lal, H., ed. Discriminative stimulus properties of drugs. New York: Plenum Press; 1977: 155–185.
191. Rosecrans, J.A.; Chance, W.T.: The discriminative stimulus properties of N- and M-cholinergic receptor stimulants. In: Ho, B.T.; Richards, D.W.; Chute, D.L, eds. Drug discrimination and state dependent learning. New York: Academic Press; 1978: 119–130.
192. Rosecrans, J. A.; Kallman, M. J.; Glenon, R.: The nicotine cue: An overview. In: Colpaert, F.C.; Rosecrans, J.A., eds. Stimulus properties of drugs: Ten years of progress. Amsterdam: Elsevier; 1978:69–81.
193. Romano, C.; Goldstein, A.; Jewell, N.P.: Characterization of the receptor mediating the nicotine discriminative stimulus. Psychopharmacology 74:310–315; 1981.
194. Roth, R.H.; Tam, S.Y.; Ida, Y.; Yang, J.X.; Deutch, A.Y.: Stress and the mesocorticolimbic dopamine systems. Ann. NY Acad. Sci. 537:138–147; 1988.
195. Russell, M.A.: Subjective and behavioural effects of nicotine in humans: some sources of individual variation. Prog. Brain Res. 79:289–302; 1989.
196. Sattin, A.; Rall, T.W.: The effect of adenosine and adenine nucleotides on the cyclic adenosine 3'5'-phosphate content of guinea pig cerebral cortex slices. Mol. Pharmacol. 6:13–23; 1970.
197. Sawyer, D.A.; Julia, H.L.; Turin, A.C.: Caffeine and human behavior: Arousal, anxiety and performance effects. J. Behav. Med. 5:415–439; 1982.
198. Schechter, M.D.: Caffeine potentiation of amphetamine: Implication for hyperkinesis therapy. Pharmacol. Biochem. Behav. 6:359–361; 1977.
199. Schelling, T.C.: Addictive drugs: the cigarette experience. Science 255:430–433; 1992.
200. Schenk, S.; Valadez, A.; Horger, B.A.; Snow, S.; Wellman, P.J.: Interactions between caffeine and cocaine in tests of self-administration. Behavioural Pharmacology 5:153–158; 1994.
201. Schenk, S.; Worley, C.M.; McNamara, C.; Valadez, A.: Acute and repeated exposure to caffeine: Effects on reinstatement of extinguished cocaine-taking behavior in rats. Psychopharmacology 126:17–23; 1996.
202. Schubert, D.S.P.: Arousal seeking as a central factor in tobacco smoking among college students. Int. J. Soc. Psychiat. 11:221; 1965.
203. Shi, D.; Nikodijevic, O.; Jacobson, K.A.; Daly, J.W.: Chronic caffeine alters the density of $A_1$-adenosin, β-adrenergic, serotonin, cholinergic and $GABA_A$ receptors and L-type calcium channels in mouse brain. Cell. Mol. Neurobiol. 13:247–261; 1993.
204. Shi, D.; Nikodiijevic, O.; Jacobson, K.A.; Daly, J.W.: Effects of chronic caffeine on adenosine, dopamine and acetylcholine systems in mice. Arch. Pharamcodyn. Ther. 328:261–287; 1994.
205. Shoaib, M.; Schindler, C.W.; Goldberg, S.R.: Nicotine self-administration in rats: Strain and nicotine pre-exposure effects on acquisition. Psychopharmacology 129:35–43; 1997.
206. Shoaib, M.; Stolerman, I.P.: Brain sites mediating the discriminative stimulus effects of nicotine in rats. Behav. Brain Res. 78:183–188; 1996.
207. Shoaib, M.; Swanner, L.S.; Yasar, S.; Goldberg, S.R.: Chronic caffeine exposure potentiates nicotine self-administration in rats. Psychopharmacology 142:327–333; 1999.
208. Smith, D.L.; Tong, J.E.; Leigh, G.: Combined effects of tobacco and caffeine on the components of choice reaction-time heart rate and hand steadiness. Percept. Mot. Skills 45:635–9; 1977.
209. Spealman, R.D.; Goldberg, S.R.: Maintenance of schedule-controlled behavior by intravenous injections of nicotine in squirrel monkeys. J. Pharmacol. Exp. Ther. 223:402–408; 1982.
210. Stolerman, I.P.: Behavioural pharmacology of nicotine: implications for multiple brain nicotinic receptors. Ciba Found. Symp. 152:3–16; discussion 16–22; 1990.
211. Stolerman, I.P.; Bunker, P.; Jarvik, M.E.: Nicotine tolerance in rats: Role of dose and dose interval. Psychopharmacologia 34:317–324; 1974.
212. Stolerman, I.P.; Fink, R.; Jarvik M.E.: Acute and chronic tolerance to nicotine measured by activity in rats. Psychopharmacologia 30:329–342; 1973.
213. Stolerman, I.P.; Carcha, H.S.; Pratt, J.A.; Kumar, R.: Role of the training dose in discrimination of nicotine and related compounds by rats. Psychopharmacology 84:413–419; 1984.
214. Stolerman, I.P.; Shoaib, M.: The neurobiology of tobacco addiction. Trends Pharmacol. Sci. 12:466–473; 1991.
215. Strain, E.C.; Griffiths, R.R.: Caffeine dependence: fact or fiction? J. R. Soc. Med. 88:437–40; 1995.
216. Strain, E.C.; Mumford, G.K.; Silverman, K.; Griffiths, R.R.: Caffeine dependence syndrome. Evidence from case histories and experimental evaluations. JAMA 5;272:1043–1048; 1994.
217. Swanson, J.A.; Lee, J.W.; Hopp, J.W.: Caffeine and nicotine: A review of their joint use and possible interactive effects in tobacco withdrawal. Addict. Behav. 19:229–256; 1994.
218. Tanda, G.; DiChiara, G.: A dopamine-mu1 opioid link in the rat ventral tegmentum shared by palatable food (Fonzies) and non-psychostimulant drugs of abuse. Eur. J. Neurosci. 10:1179–1187; 1998.
219. Tanda, G.; Loddo, P.; Frau, R.; Acquas, E.; Di Chiara, G.: Effect of intravenous caffeine on limbic and cortical dopamine transmission in the rat: A microdialysis study. Proceedings of the 6th International Symposium on Adenosine and Adenine Nucleotides, Ferrara, Italy, May 19–24; 1998.
220. Tanda, G.; Pontieri, F.E.; Frau, R.; Di Chiara, G.: Contribution of blockade of the noradrenaline carrier to the increase of extracellular dopamine in the rat prefrontal cortex by amphetamine and cocaine. Eur. J. Neurosci. 9:2077–85; 1997.
221. Tanda, G.; Pontieri, F. E.; DiChiara, G.: Cannabinoid and heroin activation of mesolimbic dopamine transmission by a common $\mu_1$ opioid receptor mechanism. Science 276:2048–2050; 1997.
222. Tassin, J.P.; Vezina, P.; Trovero, F.; Blanc, G.; Herve, D.; Glowinski, J.: Cortico-subcortical interactions in behavioral sensitization: differential effects of daily nicotine and morphine. Ann. NY Acad. Sci. 654:101–16; 1992.
223. Taylor, P.: Agents acting at the neuromuscular junction and autonomic ganglia. In: Goodman and Gilman's The pharmacological basis of therapeutics, 8th ed. New York: Pergamon Press; 1990:166–186.
224. Tella, S.R.; Ladenheim, B.; Andrews, A.M.; Goldberg, S.R.; Cadet, J.L.: Differential reinforcing effects of cocaine and GBR-12909: Biochemical evidence for divergent neuroadaptive changes in the mesolimbic dopaminergic system. J. Neurosci. 16:7416–27; 1996.
225. Thomas, C.B.: The relationship of smoking and habits of nervous tension. In: Dunn, W., ed. Smoking behavior: Motives and incentives. Washington: V.H. Winston & Sons; 1973.
226. US Department of Agriculture: 1994 Continuing survey of food intakes by individuals (CD-ROM). Accession PB96-501010. Springfield, VA: National Technical Information Service 1996.
227. Vezina, P.; Blanc, G.; Glowinski, J.; Tassin, J.P.: Blockade of D-1 dopamine receptors in the medial prefrontal cortex produces delayed effects on pre- and postsynaptic indices of dopamine function in the nucleus accumbens. Synapse 16:104–112; 1994.
228. Viani, R.: Caffeine consumption. In: Proceedings of the Caffeine Workshop, Thai FDA and ILSI, Bangkok; 1996.
229. Wada, E.; Waka, K.; Boulter, J.; Deneris, E.; Heinemann, S.; Patrik, J.; Swanson, L.W.: Distribution of alpha 2, alpha 3, alpha

4 and beta 2 neuronal nicotinic receptor subunit mRNAs in the central nervous system: a hybridization histochemical study in the rat. J. Comp. Neurol. 284:314–335; 1989.
230. White, J.M.: Behavioral interactions between nicotine and caffeine. Pharmacol. Biochem. Behav. 29:63–66; 1988.
231. Winter, J.C.: Caffeine-induced stimulus control. Pharmacol. Biochem. Behav. 15:157–159; 1981.
232. Wonnacott, S.: The paradox of nicotinic acetylcholine receptor upregulation by nicotine. Trends Pharmacol. Sci. 11:216–218; 1990.
233. Wonnacott, S.; Soliakov, L.; Wilkie, G.; Redfern, P.; Marshall, D.: Presynaptic nicotinic acetylcholine receptors in the brain. Drug Dev. Res. 38:149–159; 1996.
234. Worley, C.M.; Valadez, A.; Schenk, S.: Reinstatement of extinguished cocaine-taking behavior by cocaine and caffeine. Pharmacol. Biochem. Behav. 48:217–221; 1994.
235. Yasar, S.; Shoaib, M.; Gasior, M.; Jaszyna, M.; Goldberg, S.R.: Facilitation of IV nicotine self-administration in squirrel monkeys by caffeine. J. Psychopharmacol. 11(suppl):A14; 1997.