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The Role of Dopamine in the Behavioral Effects of Caffeine in Animals and Humans

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GARRETT, B. E. AND R. R. GRIFFITHS. *The role of dopamine in the behavioral effects of caffeine in animals and humans.* PHARMACOL BIOCHEM BEHAV **57**(3) 533–541, 1997.—Dopamine has been proposed to mediate some of the behavioral effects of caffeine. This review discusses cellular mechanisms of action that could explain the role of dopamine in the behavioral effects of caffeine and summarizes the results of behavioral studies in both animals and humans that provide evidence for a role of dopamine in these effects. Caffeine is a competitive antagonist at adenosine receptors and produces a range of central and physiological effects that are opposite those of adenosine. Recently, caffeine has been shown to enhance dopaminergic activity, presumably by competitive antagonism at adenosine receptors that are colocalized and interact functionally with dopamine receptors. Thus, caffeine, as a competitive antagonist at adenosine receptors, may produce its behavioral effects by removing the negative modulatory effects of adenosine from dopamine receptors, thus stimulating dopaminergic activity. Consistent with this interpretation, preclinical behavioral studies show that caffeine produces behavioral effects similar to classic dopaminergically mediated stimulants such as cocaine and amphetamine, including increased locomotor activity, increased turning behavior in 6-hydroxydopamine-lesioned animals, stimulant-like discriminative stimulus effects, and self-administration. Furthermore, caffeine potentiates the effects of dopamine-mediated drugs on these same behaviors, and some of caffeine's effects on these behaviors can be blocked by dopamine receptor antagonists. Although more limited in scope, human studies also show that caffeine produces subjective, discriminative stimulus and reinforcing effects that have some similarities to those produced by cocaine and amphetamine. © 1997 Elsevier Science Inc.

Caffeine Psychomotor stimulants Adenosine Dopamine Mechanisms of action Behavioral methods Rats Nonhuman primates Humans

STUDIES conducted in humans show that caffeine produces subjective and behavioral effects that are similar to those of typical psychomotor stimulant drugs that are known to be dopaminergically mediated (e.g., amphetamine and cocaine). Caffeine, like amphetamine and cocaine, enhances feelings of well-being, motivation for work, energy, and concentration (50,52), delays sleep (75,106), and enhances vigilance performance on psychomotor tasks (78). As with other psychomotor stimulants, termination of dosing after chronic daily administration with caffeine produces a withdrawal syndrome, thus providing evidence of physical dependence. The major components of caffeine withdrawal are increased fatigue and sleepiness (47,51,53,110), which are also prominent symptoms in the withdrawal syndrome following chronic administration of amphetamine and cocaine (2,101,119,120). The behavioral stimulant profile of caffeine, in combination with its ability to produce physical dependence, may help account for its widespread use throughout the world (4,44).

As with human studies, preclinical studies show the behavioral profile of caffeine to be similar to those of amphetamine and cocaine. Like cocaine and amphetamine, caffeine increases locomotor activity (87,113), may produce stimulant-like discriminative stimulus effects (43,124), may be self-administered by rats and nonhuman primates (49,51), and can produce withdrawal effects upon termination of chronic administration, as demonstrated by a disruption in operant responding (9) and decreases in spontaneous locomotor activity (27,61).

Although the behavioral effects of caffeine have been well documented, the cellular mechanisms of action that underlie these effects are unclear. The behavioral effects of caffeine are thought to be mediated primarily through competitive blockade of adenosine receptors (15,33,107). Dopamine has also been proposed to mediate the behavioral effects of caffeine because caffeine induces several behaviors that are similar to those of amphetamine and cocaine, whose actions are known to be dopaminergically mediated. It is thought that caffeine's dopamine agonist-like effects are due to an indirect action on dopamine receptors that is secondary to antagonism of adenosine receptors. The present review will summarize mechanisms of action that could possibly explain the role of dopamine in the behavioral effects of caffeine, with emphasis on the adenosine–dopamine interaction. In addition, this pa-

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per will summarize the results of behavioral studies in both animals and humans that provide evidence for a role of dopamine in the behavioral effects of caffeine.

CENTRAL MECHANISMS OF ACTION OF CAFFEINE

The central mechanisms of action of caffeine have been reviewed elsewhere (3,87,97,113). The complexity of this extensive literature suggests that no single cellular mechanism can possibly explain all the effects of caffeine. This section will briefly discuss several of the most prominent cellular mechanisms often proposed to account for the behavioral effects of caffeine. In keeping with the focus of this paper on the similarities of caffeine to classical psychomotor stimulant drugs, this section will then review the newly emerging literature that provides compelling evidence for the role of dopamine, which is known to mediate the effects of psychomotor stimulant drugs such as amphetamine and cocaine, in the behavioral effects of caffeine.

Mobilization of Intracellular Calcium

Caffeine mobilizes intracellular calcium in neurons by reducing calcium uptake in microsomal vesicles (114) and stimulating calcium release from the endoplasmic reticulum (80). Because increases in intracellular calcium concentrations are important for the release of neurotransmitters (e.g., dopamine), mobilization of intracellular calcium has been proposed as a possible mechanism underlying the behavioral effects of caffeine [cf. (14) for review]. This action of caffeine could explain caffeine's dopamine agonist-like effects. However, previous results suggest that mobilization of intracellular calcium by caffeine is unlikely to account for its behavioral effects after normal dietary doses in humans because the concentrations of caffeine required to mobilize intracellular calcium are achieved only at toxic caffeine levels [i.e., millimolar concentrations; Table 1; (114)].

Inhibition of Phosphodiesterase Activity

Caffeine inhibits cyclic nucleotide phosphodiesterase activity, an action that results in an accumulation of cyclic adenosine monophosphate [cyclic AMP; (112)]. Cyclic AMP is a prototypical second messenger that mediates the cellular events required to achieve the physiological and behavioral effects produced by the activation of several neurotransmitter systems. Caffeine's dopamine agonist-like behavioral profile has been attributed to its ability to inhibit phosphodiesterase activity (34) because caffeine may stimulate the release of catecholamines via potentiation of cyclic AMP. However, there is some controversy regarding the concentrations of caffeine required to inhibit phosphodiesterase activity. Previous results suggest that the behavioral effects of caffeine are not attributable to inhibition of phosphodiesterase because concentrations of caffeine required to do so are extremely high [Table 1; (5,8,115,121)]. Furthermore, a compelling reason to doubt the role of phosphodiesterase inhibition in the behavioral stimulant effects of caffeine comes from studies conducted with xanthines, which have various degrees of potency as phosphodiesterase inhibitors. These studies show that the more potent inhibitors of phosphodiesterases are not associated with increased stimulant potency. In fact, methylxanthines, which are potent inhibitors of phosphodiesterase activity, produce marked reductions in locomotor activity in mice (13) and decrease scheduled-controlled responding in nonhuman primates (63,64). In contrast to these findings, more recent studies conducted in nonhuman primates suggest that the respiratory stimulant effects of caffeine are mediated by inhibition of phosphodiesterase activity. Pronounced respiratory stimulant effects are observed in monkeys after the administration of nonselective phosphodiesterase inhibitors (including caffeine) and Type IV-selective phosphodiesterase inhibitors. Their potencies in increasing respiratory stimulation correspond with their potencies as phosphodiesterase inhibitors (63). On the other hand, CGS-15943, a very potent and selective adenosine antagonist without phosphodiesterase inhibitory effects, produces only modest respiratory stimulant effects (63). These findings suggest that the respiratory stimulant effects of caffeine are mediated through inhibition of phosphodiesterase activity. Although previous results suggest that inhibition of phosphodiesterase activity occurs at extremely high concentrations of caffeine, the phosphodiesterase-mediated respiratory stimulant effects of caffeine occur at much lower doses, similar to those that produce behavioral stimulation.

TABLE 1

RELATIONSHIP AMONG CELLULAR MECHANISM OF ACTION, PLASMA CONCENTRATION, AND CAFFEINE DOSE

Mechanism	Molar Plasma Concentration[a]	Caffeine Dose[b]
Mobilization of intracellular calcium	5–15 mM	76,000–228,000 mg (500–1500 cups of brewed coffee)
Inhibition of phosphodiesterase activity	0.1–1 mM	1520–15,200 mg (10–100 cups of brewed coffee)
Antagonism of adenosine receptors	10–100 μM	152–1520 mg (1–10 cups of brewed coffee)

[a]Plasma concentration required to produce the corresponding cellular effect.

[b]Estimated human caffeine dose necessary to produce molar plasma concentration. Caffeine dose is expressed in milligrams and in number of cups of brewed coffee (150 mg/cup).

Competitive Antagonism of Adenosine Receptors

Caffeine is a competitive antagonist at adenosine receptors (96), and produces a range of central and physiological effects that are opposite those of adenosine (Table 2). For example, adenosine constricts bronchial smooth muscle, produces negative inotropic/chronotropic effects on the heart, and inhibits lipolysis, renin release, and gastric secretions. All of these effects are opposite those produced by caffeine. In the central nervous system, adenosine produces depressant effects, some of which are antagonized by and opposite those of caffeine. Furthermore, behavioral studies suggest that adenosine receptor antagonism is a primary mechanism of action underlying the behavioral effects of caffeine. For example, the behavioral stimulant effects of a series of adenosine antagonists (including caffeine) in rodents and nonhuman primates correlate with their potencies as adenosine antagonists (107,108). Unlike concentrations of caffeine that are required to mobilize intracellular calcium and inhibit phosphodiesterase activity, concentrations required to antagonize adenosine receptors occur with dietary doses of caffeine [10–100 μM; Table 1; (87,97)]. As described in more detail below, adenosine recep-

TABLE 2
OPPOSING PHARMACOLOGICAL ACTIONS OF CAFFEINE AND ADENOSINE ANALOGS

	Caffeine	Adenosine
CNS	Increases spontaneous electrical activity	Decreases spontaneous electrical activity
	Enhances neurotransmitter release	Inhibits neurotransmitter release
	Convulsant activity	Anticonvulsant activity
	Stimulates locomotor activity	Depresses locomotor activity
	Increases operant response rates	Decreases operant response rates
Heart	Positive inotropic/chronotropic effects	Negative inotropic/chronotropic effects
Renal	Diuresis; stimulates renin release	Antidiuresis; inhibits renin release
Vasculature		
Peripheral	Dilation	Constriction
Central	Constriction	Dilation
Gastrointestinal	Increases gastric secretions	Inhibits gastric secretions
Respiratory	Relaxes bronchial smooth muscle	Constricts/dilates bronchial smooth muscle
Adipose	Stimulates lipolysis	Inhibits lipolysis

Portions of this table are adapted from Daly (14).

tor antagonism has also been implicated in caffeine's indirect action on dopamine receptors.

Indirect Action on Dopamine Receptors via Antagonism of Adenosine

Various findings suggest an involvement of dopamine systems in the central effects of caffeine (14,21), but the cellular mechanisms for these effects remain ambiguous (14,87). Although caffeine does not bind directly to dopamine receptors (118), a number of conflicting reports suggest that caffeine can either decrease or increase dopamine release. These discrepancies are probably due to the complex nature of caffeine's effects on dopamine release. For example, caffeine has various effects on dopamine release in different brain regions: caffeine significantly decreases dihydroxyphenylacetic acid (DOPAC) levels in the striatum, hypothalamus, and frontal cortex, but increases DOPAC levels in the nucleus accumbens (45). Another study showed that caffeine produces significant decreases in caudate dopamine release (82). In contrast, this same study showed that a low dose of caffeine decreases and higher doses of caffeine increase caudate dopamine release. According to this study and concordant with caffeine-induced locomotor stimulant effects, caffeine's effects on dopamine release appear to be biphasic (i.e., low doses increase and high doses decrease both locomotor activity and dopamine release).

Caffeine has also been proposed to indirectly enhance dopaminergic activity by competitive antagonism of adenosine receptors that are colocalized and functionally interact with dopamine receptors. Several lines of evidence support this proposed mechanism. The A2 adenosine receptor appears to be colocalized postsynaptically with the D2 dopamine receptor on striatal neurons [cf. (21) for review]. In situ hybridization techniques show the expression of D2 dopamine and A2 adenosine receptor mRNA in GABAergic-enkephalin striatal neurons (77,100). In addition, biochemical evidence suggests that functional interactions exists between the A2 adenosine and D2 dopamine receptors in the striatum. For example, studies conducted with the highly selective A2 adenosine receptor agonist CGS 21680 demonstrate that stimulation of the A2 adenosine receptor decreases the affinity of the D2 dopamine receptor for dopamine and decreases the transduction of the signal from the D2 dopamine receptor to the G-protein (26). Interestingly, induction of dopamine supersensitivity by dopamine denervation with 6-OHDA (20) or by chronic treatment with the D2 dopamine receptor antagonist haloperidol (25) appears to result in an increased interaction between the A2 adenosine and D2 dopamine receptors. Specifically, findings from these studies show that a low dose of the selective A2 adenosine receptor agonist CGS 21680, which is ineffective in striatal membranes of naive nontreated rats, is effective in decreasing the affinity of the D2 dopamine receptor for dopamine in denervated striatal membranes or in striatal membranes from haloperidol-treated rats.

Additional evidence providing support for the A2 adenosine–D2 dopamine receptor interaction comes from studies on early gene expression. An increase in neuronal activity is often accompanied by the expression of what is commonly termed immediate early genes such as c-fos, c-jun, junB, junD, NGF-A, and NGF-B (35). The A2 adenosine receptor agonist CGS 21680 induces c-fos expression in the 6-OHDA-lesioned striatum that can be blocked by the selective D2 dopamine receptor agonist quinpirole (83).

There is also evidence for a postsynaptic colocalization and functional interaction between the A1 adenosine and the D1 dopamine receptors. In situ hybridization techniques show the colocalization of A1 adenosine and D1 dopamine receptors on medium-sized striatal neurons (23). Functional evidence shows that A1 adenosine receptor agonists inhibit D1 dopamine receptor-mediated increases in adenylate cyclase activity (1). In addition, radioligand competitive binding studies suggest that stimulation of A1 adenosine receptors produces an uncoupling of D1 dopamine receptors from the G-protein of rat striatal neurons (24). These findings suggest that A1 adenosine and D1 dopamine receptors are colocalized on striatal neurons, where they negatively interact with each other.

THE ROLE OF DOPAMINE IN THE BEHAVIORAL EFFECTS OF CAFFEINE IN ANIMALS

Preclinical studies with caffeine (Table 3) are consistent with molecular and biochemical evidence demonstrating a role for dopamine in the behavioral effects of caffeine. As in the case of classic dopaminergically mediated drugs (e.g., amphetamine and cocaine), low to intermediate doses of caffeine produce increases in spontaneous locomotor activity [cf. (87) for review]. This effect can be blocked by selective D1 and D2 dopamine receptor antagonists (38,74). Dopamine has also been proposed to play a role in the development of tolerance to the locomotor stimulant effects of caffeine (39). Rats that are tolerant to these effects exhibit cross-tolerance to selective D1 and D2 dopamine receptor agonists (39). These findings suggest that the locomotor stimulant effects of caffeine, and tolerance to these effects, are mediated by both D1 and D2 dopamine receptor subtypes. Other findings suggesting an involvement of dopamine in the locomotor stimulant effects

TABLE 3

PRECLINICAL FINDINGS SUPPORTING THE INVOLVEMENT OF DOPAMINE IN THE BEHAVIORAL EFFECTS OF CAFFEINE

Behavioral Measure	Findings[a]
Locomotor activity	Caffeine, like classic dopaminergically mediated drugs such as amphetamine and cocaine, increases locomotor activity (87) Caffeine-induced locomotor stimulation is blocked by selective D1 and D2 dopamine receptor antagonists (38,74) Rats that are tolerant to caffeine show cross-tolerance to selective D1 and D2 dopamine receptor agonists (39) Caffeine potentiates the locomotor stimulant effects of dopamine agonists (20,73,81,84,98,111,122) Inhibition of dopamine synthesis attenuates the locomotor stimulant effects of caffeine (28,74,123)
Rotational behavior	In rats with unilateral 6-OHDA-induced lesions of the nitrostriatal dopamine pathway, caffeine produces long-lasting turning when adminstered alone (10,40,59,117) In rats with unilateral 6-OHDA-induced lesions of the nigrostriatal dopamine pathway, caffeine and other methylxanthines potentiate dopamine agonist-induced rotational behavior (36,37,67) In rats with unilateral 6-OHDA-induced lesions of the nigrostriatal dopamine pathway, caffeine-induced rotational behavior can be blocked by dopamine receptor antagonists (40,59,70)
Drug discrimination	Cocaine and other dopamine receptor agonists occasion caffeine-appropriate responding in rats trained on a low dose of caffeine but not in those trained on a high dose of caffeine (86) Selective D1 and D2 dopamine receptor antagonists block the discriminative stimulus effects of a low dose of caffeine but not those of a high dose of caffeine (7,91,124) Caffeine produces partial generalization to the discriminative stimulus effects of cocaine and amphetamine (42,57,72) Caffeine potentiates the discriminative stimulus effects of cocaine and amphetamine (41,57,98)
Drug self-administration	Caffeine increases rates of low-dose cocaine self-administration behavior (99) Caffeine preexposure enhances the rate of acquisition of subsequent cocaine self-administration behavior (62) Caffeine reinstates self-administration responding that was previously maintained by cocaine (125) Caffeine reinstatement of cocaine self-administration behavior can be blocked by a selective D1 dopamine receptor agonist (79)

[a]Numerals indicate literature citations. All studies were conducted in rodents.

of caffeine come from studies conducted in short-term reserpinized mice in which caffeine potentiates the locomotor stimulant effects of selective D2 dopamine receptor agonists (22). Consistent with these findings, caffeine potentiates the locomotor activity effects that are produced by the indirectly acting dopamine receptor agonists amphetamine (98,122), methamphetamine (73), and cocaine (81) and by the directly acting dopamine receptor agonist L-dopa (84,111). Finally, blockade of dopamine synthesis with alpha-methyl-*para*-tyrosine attenuates the locomotor stimulant effects of caffeine (28,74,123) as well as those of amphetamine (28).

Rotational behavior is a useful model for studying drug interactions with the nigrostriatal dopamine system. In rats with unilateral 6-OHDA-induced lesions of the nigrostriatal dopamine pathway, caffeine produces long-lasting turning when administered alone (10,40,59,117); in addition, caffeine and other methylxanthines potentiate dopamine agonist-induced rotational behavior (36,37,67). Selective D2 and nonselective dopamine receptor antagonists block caffeine-induced rotational behavior (40,59,70). In contrast, selective D1 dopamine receptor antagonists either do not (40) or only partially antagonize caffeine-induced rotational behavior (21). Based on the latter findings, it appears that the D2 but not the D1 dopamine receptor is involved in caffeine-induced rotational behavior.

Dopamine may also mediate some of the discriminative stimulus effects of caffeine. For example, rats trained to discriminate a low (10 mg/kg) but not a high (56 mg/kg) dose of caffeine from placebo generalize completely to amphetamine and cocaine, but do not generalize to drugs from other pharmacological classes (i.e., ethylketocyclazocine, pentylenetrazol, yohimbine, phencyclidine, etc.) that have no apparent dopamine-mediated effects (86). In line with these findings, the discriminative stimulus effects of low doses of caffeine as well as those of amphetamine and cocaine are blocked by selective D1 and D2 dopamine receptor antagonists (7,91); however, the discriminative stimulus effect of a high training dose of caffeine (60 mg/kg) is not blocked by dopamine receptor antagonists (91,124). These findings suggest that dopamine may mediate the discriminative stimulus effects of a low, but not a high, caffeine training dose. Other findings implicating a role for dopamine in the discriminative stimulus effects of caffeine include studies showing that caffeine produces partial generalization to the discriminative stimulus effects of cocaine (42,43,57) and amphetamine (60,72) and can potentiate the discriminative stimulus effects of both amphetamine (98) and cocaine (41,57).

The role of dopamine in the reinforcing effects of caffeine is less clear, because caffeine is erratically self-administered in animal models of drug self-administration (51). However, there appears to be a functional interaction between the reinforcing effects of caffeine and cocaine. Caffeine increases rates of self-injection of a low dose of cocaine (99), and caffeine preexposure enhances the rate of acquisition of subsequent cocaine self-injection behavior and potentiates extracellular dopamine levels after an acute cocaine injection (62). Furthermore, caffeine pretreatment reinstates responding in rats with a prior history of cocaine self-injection behavior that has been extinguished by substituting saline (125). This effect is blocked by a selective D1 dopamine receptor antagonist but not by selective A1 and A2 adenosine receptor agonists (79).

THE ROLE OF DOPAMINE IN THE BEHAVIORAL EFFECTS OF CAFFEINE IN HUMANS

Low to intermediate doses of orally administered caffeine produce various mood changes (e.g., increased feelings of well-being, energy, and alertness) and a stimulant profile of positive subjective effects (Table 4) that are qualitatively similar to the effects of classic psychomotor stimulants such as amphetamine and cocaine (32). Consistent with these findings, Rush and colleagues (95) showed that the intravenous administration of low to intermediate doses of caffeine to subjects with histories of stimulant drug abuse produces a profile of subjective effects similar to those produced by intravenously administered cocaine (29–31,92,93,116). In the Rush study, caffeine increased subject ratings of drug liking and high, and increased the frequency of stimulant identifications (e.g., amphetamine-like and cocaine-like; Fig. 1) on a pharmacological class identification questionnaire. In contrast to the profile of positive subjective effects that emerges at low to intermediate doses, high doses of caffeine increase subject-reported feelings of anxiety, nervousness, and being jittery (52). Increases in anxiety and dysphoric effects also occur at high doses of amphetamine and cocaine (32). The mechanism by which caffeine and other psychomotor stimulant drugs produce their subjective effects is unknown. However, limited evidence suggests a role for dopamine in the subjective effects of amphetamine and cocaine in humans. The dopamine receptor antagonist haloperidol does not attenuate the initial "rush" induced by intravenous cocaine. However, haloperidol attenuates other euphorigenic effects of intravenous cocaine such as subject-reported good feelings and high (103). Haloperidol also attenuates intravenous amphetamine-induced excitation (88). Other findings implicating a role for dopamine in the subjective effects of psychomotor stimulants come from studies using the selective D2 dopamine receptor antagonist pimozide. Pimozide decreases the euphoria produced by high doses of intravenous amphetamine in heavy amphetamine users (55,69). However, pimozide has minimal effects on the subjective effects of modest doses of amphetamine in normal subjects (6,66). Although the role of dopamine in the subjective effects of caffeine has not been studied directly, the amphetamine-like subjective profile of low doses of caffeine suggests that dopamine could possibly be involved in these effects.

Human drug discrimination procedures are widely used to determine the pharmacological profile of various psychoactive drugs (71). Caffeine serves as a discriminative stimulus at both low and high doses (52). However, the discriminative stimulus profile of a low caffeine dose appears to be different from that of a high caffeine dose. For example, subjects who can discriminate a low caffeine dose (20–200 mg) from a placebo usually report increases in positive mood effects (e.g., increased well-being, energy, and alertness) as the basis by which they make their drug discrimination (50,85,104), whereas subjects discriminating a high dose (200–800 mg) of caffeine from placebo usually report negative subjective effects (e.g., increased anxiety, jitteriness, and upset stomach) as the basis for the discrimination (18,89). Similar to low doses of caffeine, there is a close relationship between amphetamine-induced positive mood effects and discriminative stimulus effects in volunteers trained to discriminate amphetamine vs. placebo (11,12). These findings suggest that drug-induced positive subjective effects are the underlying basis for both amphetamine and low-dose caffeine-induced discriminative stimulus effects. Although the discriminative stimulus profiles of caffeine and amphetamine are similar, the pharmacological specificity of the discriminative stimulus effects of caffeine remains unclear. To date, only two cross-generalization studies have investigated the pharmacological specificity of the discriminative stimulus effects of caffeine in humans. In one study, the discriminative stimulus effects of caffeine and benzphetamine were investigated in subjects trained to discriminate amphetamine from placebo (11). Caffeine only partially generalized to the amphetamine discriminative stimulus cue: the mean amphetamine-appropriate responding was 42% and 58% after 100 and 300 mg of caffeine, respectively. In another study (90), subjects were trained to discriminate caffeine from placebo. Cross-generalization tests with theophylline and methylphenidate revealed that both drugs occasioned caffeine-

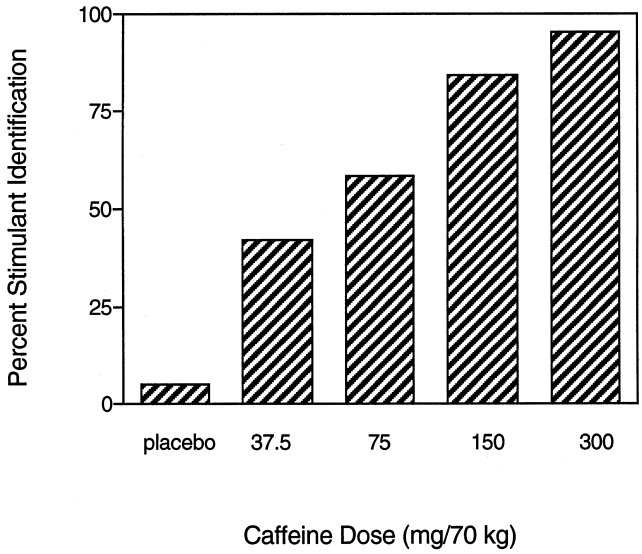

FIG. 1. Identification of caffeine (double-blind IV administration) as a stimulant (e.g., cocaine, amphetamine) by subjects with histories of stimulant abuse. Subjects were told that they could receive a wide range of drugs; 60 min after an injection of caffeine, they were required to identify the drug effect as being most similar to one of 10 categories of psychoactive drugs. Doses were generally administered twice to each of 10 subjects. Bars show the percentage of the total number of occasions caffeine was identified as a stimulant. Adapted from Rush et al. (95).

TABLE 4

LOW TO INTERMEDIATE DOSES OF CAFFEINE (18–178 mg) PRODUCE A VARIETY OF POSITIVE SUBJECTIVE EFFECTS

Subjective rating	Effect	References
Well-being	+	(50,85,104)
Energy/active/vigor	+	(50,65,76,78,85,104,105)
Alert/clear-headed	+	(50,65,78,85,104,105)
Concentration	+	(50,85)
Self-confidence	+	(50,85,104)
Motivation for work	+	(50,85,104,105)
Desire to talk/social	+	(50,85,104)
Imaginative	+	(76)
Efficiency	+	(76,78)
Sleepy	−	(50,65,85,104,105)

Results of group statistical analyses comparing caffeine and placebo.

appropriate responding. In contrast, the nonstimulant anxiolytic buspirone did not exhibit caffeine-appropriate responding (90). Although this study concluded that noradrenaline is involved in the discriminative stimulus effects of caffeine, a role of dopamine cannot be ruled out because methylphenidate produces its stimulant effects through both noradrenergic and dopaminergic-mediated mechanisms.

A drug is considered to be reinforcing if it maintains behavior on which the delivery of the drug is dependent (49). The reinforcing effects of drugs in humans have been extensively examined by using drug self-administration and choice procedures (46,48, 51,58). Using such methods, 12 studies provide clear evidence that caffeine can function as a reinforcer in humans (51,54,56,65). In choice studies, for example, subjects typically first sample two different drug conditions (e.g., caffeine and placebo) and later have the opportunity to choose to self-administer one of the two conditions. Such studies demonstrate caffeine reinforcement under double-blind conditions when caffeine is available in coffee, soda, or capsules and when subjects either have or do not have immediate histories of chronic caffeine exposure (51). Caffeine reinforcement has been demonstrated in 100% of subjects with histories of heavy caffeine use and abuse of alcohol or drugs, and in a somewhat lower proportion (about 45%) of subjects with histories of moderate and heavy caffeine use alone (51). A repeated finding is that qualitative ratings of subjective effects generally covary with measures of reinforcement and choice (51). An example of this covariance is provided by choice studies that measured subjective effects of caffeine and placebo on sampling days prior to choice opportunities. When the data were retrospectively categorized into caffeine choosers (those who chose caffeine over placebo) and nonchoosers (those who chose placebo over caffeine), it showed that caffeine choosers reported positive stimulant mood effects of caffeine (e.g., increased alertness, energy, and drug liking), whereas nonchoosers reported negative mood effects of caffeine [e.g., increased anxiety, mood disturbance, and being jittery (19,109)]. Analogous findings have been reported in choice studies with amphetamine (16,68). Although avoidance of placebo-associated headache or fatigue may also play a role in choice of caffeine (17,51,94,102), studies do show that caffeine can function as a reinforcer in the absence of physical dependence (51). For example, Silverman and colleagues (105) studied subjects who were not physically dependent on caffeine because all dietary sources of caffeine were eliminated throughout the study, which was more than 6 weeks in duration. In this study, 100 mg of caffeine served as a reinforcer when subjects were required to perform a computer vigilance performance task. Under these conditions, caffeine produced a typical profile of positive subjective effects (i.e., increased ratings of energy/activity, alertness, and motivation for work; decreased ratings of sleepiness).

As is the case with amphetamine, there are no direct human experimental data that demonstrate a role for dopamine in the reinforcing effects of caffeine. No studies, for example, have attempted to block the reinforcing effects of amphetamine or caffeine with a dopamine receptor antagonist. However, changes in positive mood effects are often assumed to underlie the reinforcing effects of drugs. Because caffeine and amphetamine produce similar profiles of subjective effects in the context that they function as reinforcers, and because some data (previously discussed) implicate dopamine in the subjective effects of amphetamine, a similar role for dopamine in the subjective effects and consequently the reinforcing effects of caffeine appears plausible.

CONCLUSIONS AND FUTURE DIRECTIONS

This review describes evidence supporting the hypothesis that some of the behavioral effects of caffeine are mediated by dopaminergic mechanisms. It is well established that caffeine is a competitive antagonist at adenosine receptors and produces a range of central and physiological effects that are opposite those of adenosine. Caffeine enhances dopaminergic activity, presumably by competitive antagonism of adenosine receptors that are colocalized and functionally interact with dopamine receptors. Specifically, as a competitive antagonist at adenosine receptors, caffeine may remove the negative modulatory effects of adenosine from dopamine receptors, thus stimulating dopaminergic activity. Consistent with this interpretation, preclinical behavioral studies show that caffeine produces behavioral effects similar to classic dopaminergically mediated stimulants such as cocaine and amphetamine, including increased locomotor activity, increased rotational behavior in 6-hydroxydopamine-lesioned rats, stimulant-like discriminative stimulus effects, and self-administration. Furthermore, caffeine potentiates the effects of dopaminergically mediated drugs on locomotor activity, rotational behavior, drug discrimination, and self-administration. Finally, some of caffeine's effects on these behaviors can be blocked by dopamine receptor antagonists.

In comparison with the preclinical research, human data supporting the hypothesis that the behavioral effects of caffeine are mediated by dopaminergic mechanisms are more limited. Human studies show that caffeine produces subjective, discriminative stimulus and reinforcing effects that have some similarities to those produced by classic dopaminergically mediated stimulants such as cocaine and amphetamine. However, neither the potentiation of the effects of dopaminergically mediated stimulant drugs by caffeine nor the antagonism of caffeine's effects by dopamine antagonists has been studied. Indeed, antagonism of the subjective effects of amphetamine by dopamine antagonists has not been reliably demonstrated.

Although the present review has focused on the competitive blockade of adenosine receptors as a primary cellular mechanism of action accounting for caffeine's dopamine agonist-like behavioral effects, there are other actions of caffeine that should also be considered. Reports suggesting the release of dopamine by caffeine are inconclusive. Although some studies suggest that mobilization of intracellular calcium and inhibition of phosphodiesterase activity only occur at toxic concentrations of caffeine and therefore cannot explain caffeine's behavioral effects, it may be premature to conclude that these actions of caffeine do not play a role in its central nervous system effects (14). For example, Howell (63) showed that the phosphodiesterase-mediated respiratory stimulant effects of caffeine occur at relatively low doses, similar to those that produce behavioral stimulation. Future research strategies for elucidating the mechanisms underlying the behavioral effects of caffeine should consider other central mechanisms of caffeine, particularly those that are linked to dopamine systems.

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