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Discriminative effects of CGS 15943, a competitive adenosine receptor antagonist, have a dopamine component in monkeys

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Abstract

9-Chloro-2-(2-furyl)[1,2,4]triazolol[1,5-*c*]quinazolin-5-amine (CGS 15943), like caffeine, is an antagonist at adenosine A_1 and A_{2A} receptors and a behavioral stimulant in animals. The two drugs have overlapping discriminative effects. Enhancement of dopamine-mediated neurotransmission appears to contribute to the behavioral effects of caffeine. This study was conducted to determine if there is a dopamine component to the discriminative effects of CGS 15943. Squirrel monkeys discriminating between i.m. injections of 1.0 mg/kg CGS 15943 and vehicle generalized dose-dependently and completely to eight dopamine receptor agonists that encompass a variety of mechanisms and sites of action, both pre- and postsynaptic. The discriminative effects of the training dose of CGS 15943 were blocked dose-dependently and completely by the dopamine receptor antagonists *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390; D_1) and eticlopride (D_2). Thus, the discriminative effects of CGS 15943 have a dopamine component that appears to be mediated by both the D_1 and D_2 families of dopamine receptors. The monkeys also generalized to selective inhibitors of the neuronal transporters of norepinephrine (nisoxetine) and serotonin (fluoxetine), indicating that monoamines other than dopamine also contribute to the discriminative effects of CGS 15943.

Keywords: Drug discrimination; (Nonhuman primate); Monoamine; Dopamine receptor

1. Introduction

At least some of the behavioral stimulant effects of caffeine in laboratory animals appear to be due to competitive blockade of adenosine A_1 and/or A_{2A} receptors. These include increasing the locomotor activity of rodents (Snyder et al., 1981) and the rate of lever pressing of monkeys (Spealman, 1988). In addition to blocking adenosine receptors, caffeine has actions on intracellular systems; for example, it inhibits the activity of cyclic nucleotide phosphodiesterases. These actions appear to contribute to the behavioral depressant effects of high doses of caffeine and might limit the behavioral stimulant effects of lower doses (Daly, 1993).

9-Chloro-2-(2-furyl)[1,2,4]triazolol[1,5-*c*]quinazolin-5-amine (CGS 15943), a triazoloquinazoline derivative, is a potent antagonist at adenosine receptors, with some selectivity (i.e., 5- to 10-fold) for the adenosine A_{2A} receptor over the adenosine A_1 receptor (Williams et al., 1987; Jarvis et al., 1989). Like caffeine, CGS 15943 is a behavioral stimulant in animals. It dose-dependently increases the locomotor activity of rats (Holtzman, 1991) and the rate at which squirrel monkeys press a lever to avoid an aversive stimulus (Howell and Byrd, 1993), and is 10–30 times more potent than caffeine in doing so. Unlike caffeine, CGS 15943 does not inhibit the activity of cyclic nucleotide phosphodiesterases (Williams et al., 1987), increasing the likelihood that effects that the two drugs have in common are mediated by the blockade of adenosine receptors.

Adenosine A_{2A} receptors in the brain are localized to postsynaptic neurons of the basal ganglia, often co-expressed with dopamine D_2 receptors (Martiniz-Mir et al., 1991; Ferré et al., 1992). Data from neurochemical as well as from behavioral studies suggest that activation of these receptors reduces neurotransmission mediated by dopamine D_2-like receptors (Ferré et al., 1991a,b). Similar types of experimental evidence indicates that activation of adenosine A_1 receptors reduces neurotransmission mediated by dopamine D_1-like receptors (Ferré et al., 1996). These observations have led to the hypothesis that behavioral

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stimulant effects of caffeine reflect, in part, the enhancement of dopamine-mediated neurotransmission that occurs when the negative modulatory influence of adenosine is blocked (Ferré et al., 1992; Ferré, 1997). Consistent with this hypothesis, caffeine-induced stimulation of the locomotor activity of rats is blocked by *R*(+)-7-chloro-8-hyroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH 23390) and eticlopride (Garrett and Holtzman, 1994), antagonists selective for the dopamine D_1 and D_2 families of receptors, respectively. In addition, rats discriminating a low dose of caffeine (i.e., 10 mg/kg) generalize completely to nonxanthine psychomotor stimulants, such as cocaine and amphetamine (Mumford and Holtzman, 1991), drugs whose discriminative effects have a prominent and well-documented dopamine component (Goudie, 1991; Woolverton, 1991). These rats also generalize completely to CGS 15943. Conversely, monkeys discriminating CGS 15943 generalize completely to caffeine (Holtzman, 1996).

The present study was conducted in order to evaluate the role of dopamine in the discriminative stimulus effects of CGS 15943 in squirrel monkeys. Monkeys with a stable history of CGS 15943 discrimination were tested for stimulus generalization to dopamine receptor agonists that encompass a variety of mechanisms and sites of action. Some of those drugs, notably cocaine and amphetamine, interact with brain monoamine systems in addition to dopamine. Therefore, the monkeys also were tested for stimulus generalization to selective inhibitors of the neuronal uptake of norepinephrine and serotonin. The ability of monoamine-receptor antagonists to block the discriminative effects of the training dose of CGS 15943 also was determined. Morphine and phencyclidine, discriminable drugs whose primary actions are on nonmonoamine neuronal systems, served as controls for pharmacological selectivity.

2. Methods

2.1. Subjects

The subjects were four adult male squirrel monkeys (*Saimiri sciureus*), designated S85, S88, S90 and S92. They had been trained previously to discriminate between i.m. injections of CGS 15943 and its vehicle and had undergone generalization testing with a series of methylxanthine derivatives (Holtzman, 1996). Between experimental sessions, the monkeys were housed two per cage in a vivarium where they had continuous access to food and water. The lights in the vivarium were illuminated from 0700 to 1900 h. The care and use of the monkeys conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and experiments were performed according to a protocol that had been approved by the Institutional Animal Care and Use Committee of Emory University.

2.2. Procedure

The monkeys were trained and tested in a discrete-trial avoidance/escape procedure, as described previously (Holtzman, 1996). During experiments, they were seated in a testing chamber and secured by a Plexiglas waist plate. The chamber was inside of ventilated enclosure that was sound-attenuating. The monkey sat facing two levers that were mounted 10 cm apart. A Plexiglas barrier separated the monkey from the levers. The barrier had 2.5×4.0 cm openings on each end; a monkey could press a lever by extending its arm through the opening on the same side as that lever, but could not reach both levers at the same time. The start of a trial was signaled by illumination of the house light in the testing chamber. Beginning 5.0 s later, an electric current of constant intensity (3.0–5.0 mA) was passed through a pair of brass electrodes that rested lightly on a shaved portion of the monkey's tail. The current was applied for 1.0 s every 3.0 s. In training sessions, a response on the correct choice lever at any time during a trial ended the trial, extinguished the houselight, and initiated a 50-s intertrial interval. In test sessions, a response on either choice lever ended the trial. During intertrial intervals a yellow stimulus light located at eye level between the two lever was illuminated and each response resulted in the delivery of a 30-ms electrical stimulus to the tail of the monkey. This latter contingency helped to restrict responding to the period when a trial was in progress. A response on the incorrect choice lever in a training session did not end the trial and that trial was recorded as incorrect. In the absence of a response, a trial ended after the delivery of three electrical stimuli and was recorded as an incomplete trial. Two monkeys had been trained to press the right choice lever in sessions that had been preceded with an injection of 1.0 mg/kg CGS 15943 and to press the left choice lever in sessions that had been preceded with an injection of drug-free vehicle. The other two monkeys had the opposite lever assignments. Training and test sessions consisted of 25 trials.

Test sessions with both choice lever activated usually were conducted twice weekly, 3 to 4 days apart, in order to assess stimulus generalization to novel drug conditions. Training sessions with only the correct choice lever activated were conducted at least three times each week to maintain stable discrimination performance. CGS 15943, 1.0 mg/kg, suspended in 1% methylcellulose or the 1% methylcellulose vehicle was injected i.m. 30 min before a training session; drug and vehicle were administered on an alternating basis. If a monkey failed to complete correctly at least 22 of the 25 trials of a training session, the next scheduled test session was postponed until correct responding in 22 of 25 trials occurred in four consecutive training sessions.

Drugs were tested for stimulus generalization in an unsystematic order that was different for each monkey; the pretreatment interval was 30 min. Tests of potential anta-

gonists of the discriminative effects of CGS 15943 were conducted at the end of the study. The potential antagonists were administered 15 min before the training dose of CGS 15943, 45 min before the test session. Doses of each drug initially were assigned for testing in a random sequence that also included the vehicle of the drug being tested. However, because of prominent interanimal differences in sensitivity to many of the drugs, dose ranges often were readjusted during the course of testing a particular drug in a particular monkey.

2.3. Drugs

The following drugs were purchased from RBI (Natick, MA): CGS 15943, apomorphine hydrochloride, (±)-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol HCl (SKF 38393), *R*(−)-propylnorapomorphine hydrochloride (NPA), (−)-quinpirole hydrochloride, (±)-*N*-allyl-1-phenyl-2,3,4,5-tetrahydro-(1*H*)-3-benzazepine-7,8-diol HBr ((±)-SKF 77434), 1-[2-[bis(4-fluorophenyl) methoxy]ethyl]-4-[3-phenylpropyl]piperazine diHCl (GBR 12909), *R*(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine HCl (*R*(+)-SCH 23390), *S*(−)-eticlopride hydrochloride and ketanserin tartrate. *d*-Amphetamine sulfate and phentolamine methanesulfonate were purchased from Sigma (St. Louis, MO), morphine sulfate was obtained from Penick (Newark, NJ), cocaine hydrochloride and phencyclidine hydrochloride (PCP) were provided by the National Institute on Drug Abuse (Rockville, MD), and nisoxetine hydrochloride and fluoxetine hydrochloride were provided by Eli Lilly and Company (Indianapolis, IN).

CGS 15943 was suspended in 1% methylcellulose and was sonicated before injection. Amphetamine, cocaine, NPA, quinpirole, eticlopride, SCH 23390, morphine and phencyclidine were dissolved in 0.9% saline solution. SKF 38393, SKF 77434, nisoxetine, fluoxetine, phentolamine and ketanserin were dissolved in distilled water. Apomor-

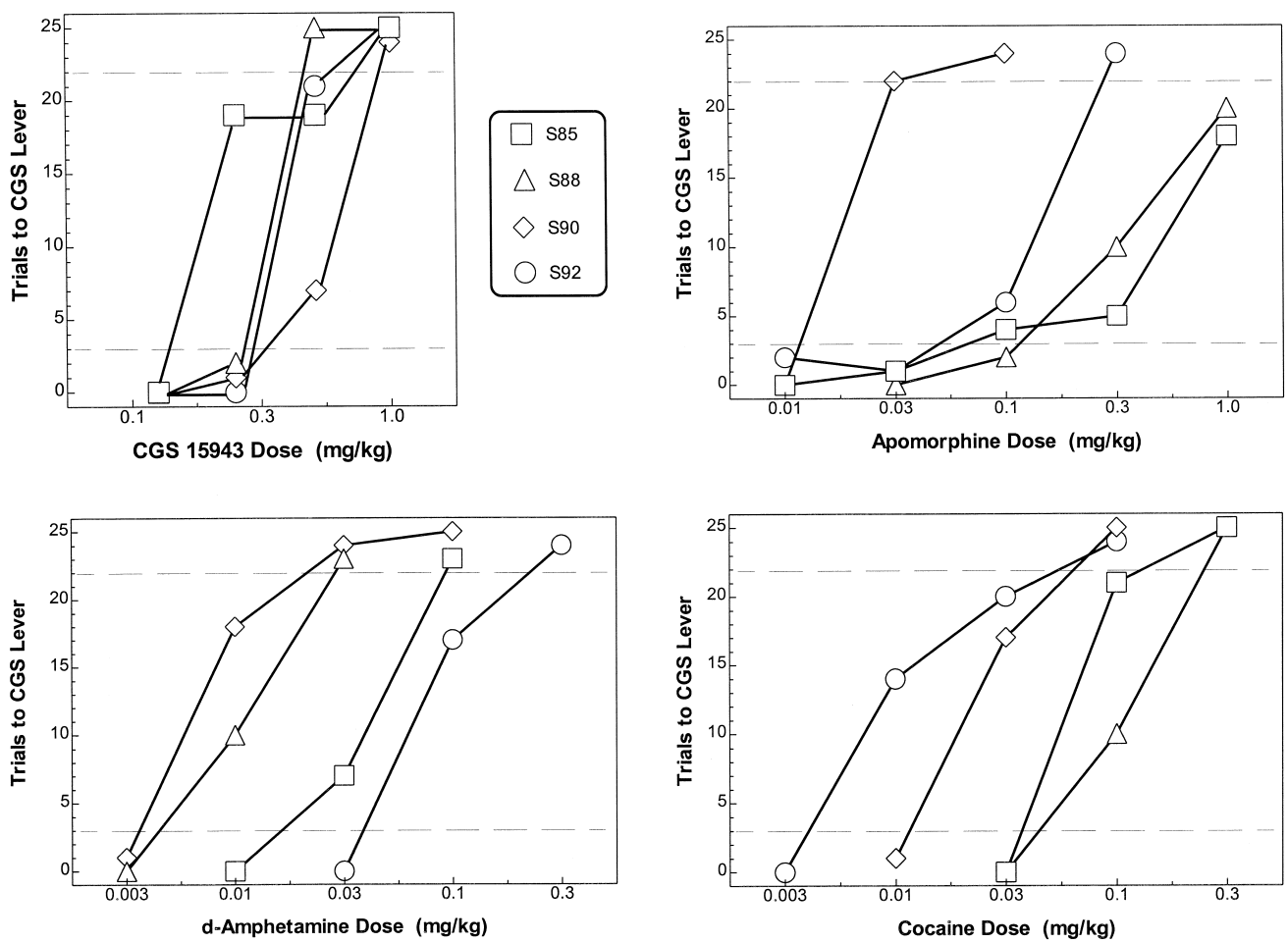

Fig. 1. Stimulus generalization curves for CGS 15943, apomorphine, amphetamine and cocaine for each of four squirrel monkeys trained to discriminate between 1.0 mg/kg CGS 15943 and its vehicle. The ordinate is the number of trials completed on the choice lever appropriate for CGS 15943 in a 25-trial session; the remaining trials of the session were completed on the choice lever appropriate for vehicle. A negligible number of trials were completed on the CGS 15943-appropriate choice lever in test sessions that followed injection of the vehicles for these or other drugs; therefore, the results from vehicle test sessions are not shown in any of the figures. The upper and lower dashed lines indicate the minimum levels at which the discrimination performance of the monkeys was maintained in training sessions with 1.0 mg/kg CGS 15943 and vehicle, respectively.

phine was dissolved in distilled water containing 0.2% ascorbic acid and GBR 12909 was dissolved in one part dimethylsulfoxide and three parts distilled water. Drugs and vehicles were injected into a thigh muscle in a volume of 0.5–1.0 ml per kg of body. All drug doses refer to the free base.

2.4. Data analysis

Discrimination data are presented as the number of trials completed on the CGS 15943-appropriate choice lever; the remaining trials of a session were completed on the lever appropriate for the methylcellulose vehicle. The ED_{50} was defined as the drug dose that would have resulted in selection of the CGS 15943-appropriate lever in 12.5 trials of a test session. It was estimated for each animal by linear regression of the ascending part of the stimulus-generalization curve when at least three points were available and by simple interpolation when there were only two points to use; doses were transformed to logarithm_{10}. The AD_{50} was defined as the dose of drug that when administered before 1.0 mg/kg CGS 15943 reduced selection of the CGS 15943-appropriate choice lever to 12.5 trials per session. It was calculated in the same manner as the ED_{50} was. ED_{50}s and AD_{50}s were converted from mg/kg to μmol/kg for potency comparisons among drugs. They were evaluated by analysis of variance for repeated measures, followed by the Student–Newman–Keuls test for multiple comparisons among all means.

3. Results

The sensitivity of the monkeys to the training drug in the present study [ED_{50} (95% confidence limits): 0.38 (0.22–0.64) mg/kg] was similar to their sensitivity in the preceding study (Holtzman, 1996) in which they were tested with a series of methylxanthine derivatives [ED_{50} (95% confidence limits): 0.43 (0.27–0.67) mg/kg]. Fig. 1 contains the stimulus generalization curves for CGS 15943 for each of the four monkeys. Neither the vehicle for CGS 15943 nor the vehicles for the other drugs examined resulted in an average of more than one trial per session

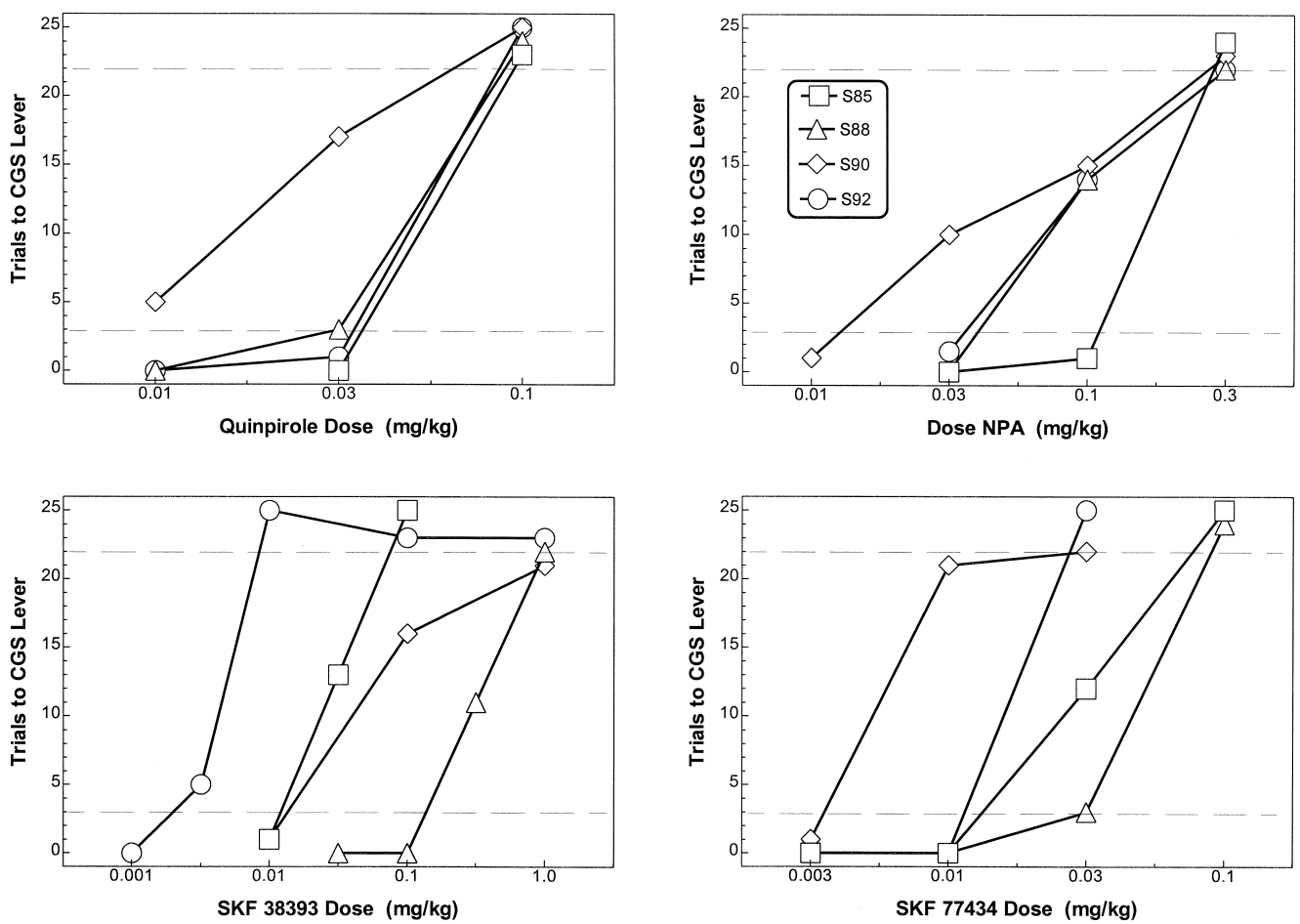

Fig. 2. Stimulus generalization curves for agonists selective for the dopamine D_1 (SKF 38393, SKF 77434) or the dopamine D_2 (quinpirole, NPA) family of receptors in each of four squirrel monkeys trained to discriminate between 1.0 mg/kg CGS 15943 and its vehicle. Other details are the same as in Fig. 1.

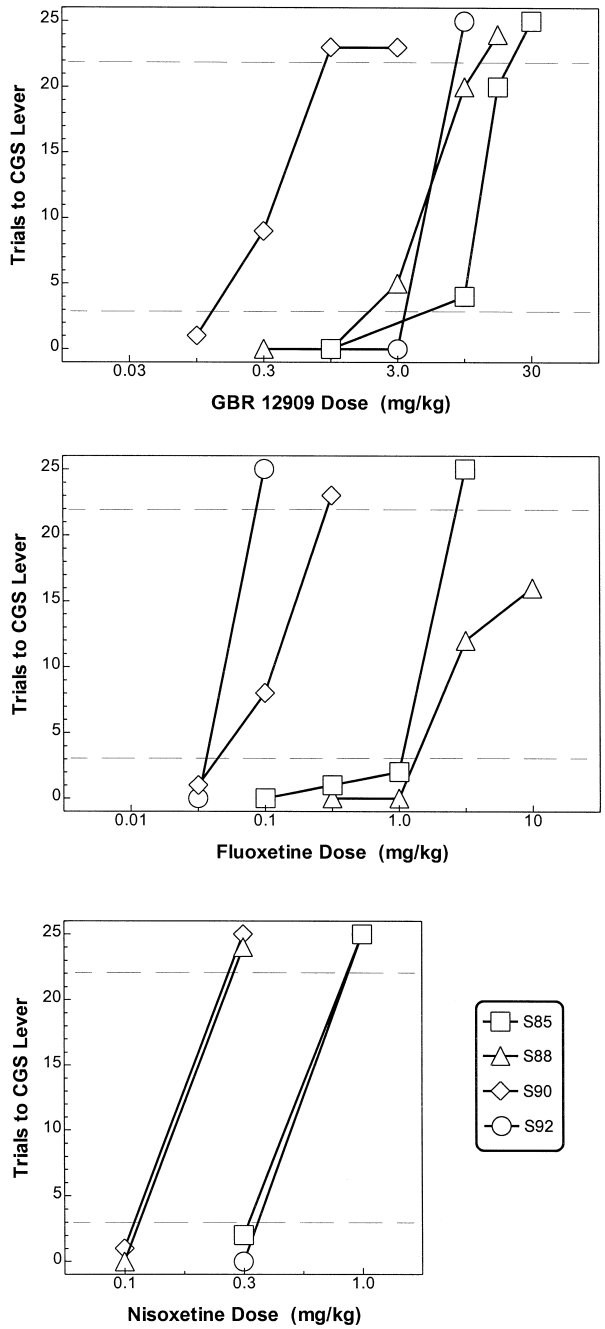

Fig. 3. Stimulus generalization curves for selective inhibitors of the neuronal uptake of dopamine (GBR 12909), serotonin (fluoxetine), and norepinephrine (nisoxetine) in each of four squirrel monkeys trained to discriminate between 1.0 mg/kg CGS 15943 and its vehicle. Other details are the same as in Fig. 1.

being completed on the CGS 15943-appropriate choice lever; for the sake of simplicity, data for drug vehicles are not shown in the figures.

All of the monkeys generalized completely or almost completely to the eight dopamine receptor agonists that were tested: apomorphine, amphetamine and cocaine (Fig. 1), SKF 38303, SKF 77434, quinpirole and NPA (Fig. 2), and GBR 12909 (Fig. 3). Of these, the dopamine D_1 receptor agonist SKF 77434 was the most potent (Fig. 2) and the dopamine uptake inhibitor GBR 12909 was the least potent (Fig. 3). On a molar basis, SKF 77434 was 19 times more potent than CGS 15943 whereas GBR 12909 was one-fifth as potent (Table 1). As is evident in the figures, interanimal variability in sensitivity to the dopamine receptor agonists was considerable. S90 was the most sensitive monkey in tests of stimulus generalization to six of the eight dopamine receptor agonists and monkey S92 displayed the greatest sensitivity to the other two, cocaine (Fig. 1) and SKF 38393 (Fig. 2). As a consequence of this interanimal variability, differences in potencies among apomorphine, agonists selective for dopamine D_1 or D_2 receptors, amphetamine and cocaine were not statistically reliable (Table 1). However, all of these drugs were significantly more potent than GBR 12909, and SKF 77434 and amphetamine were significantly more potent than CGS 15943 (Table 1).

The monkeys also generalized completely or almost completely to two drugs that act on monoamine neurotransmitter systems other than dopamine: fluoxetine, a selective inhibitor of the serotonin neuronal transporter, and nisoxetine, a selective inhibitor of the norepinephrine neuronal transporter (Fig. 3). Nisoxetine was significantly more potent than GBR 12909 in occasioning selection of the CGS 15943-appropriate choice lever, whereas the potency of fluoxetine was not different from that of either nisoxetine or GBR 12909 (Table 1). In contrast, neither morphine (1.0–5.6 mg/kg) nor phencyclidine (0.03–0.3 mg/kg) occasioned substantial CGS 15943-appropriate responding (Fig. 4), even though each drug was tested up to a dose that caused slumping body postures indicative of motor impairment in all of the monkeys.

The discriminative effects of the 1.0 mg/kg training dose of CGS 15943 were blocked completely by pretreating the monkeys with either the dopamine D_1 receptor

Table 1
ED_{50} for CGS 15943-appropriate lever selection[a]

Drug	mg/kg	μmol/kg (95% confidence limits)	Relative potency[b]
SKF 77434	0.02	0.07 (0.02–0.25)[c]	19.3
Amphetamine	0.02	0.09 (0.01–0.51)[c,d]	14.8
Cocaine	0.04	0.14 (0.03–0.61)[c,d,e]	9.5
SKF 38393	0.04	0.18 (0.01–3.72)[c,d,e]	7.4
Quinpirole	0.04	0.19 (0.09–0.40)[c,d,e]	7.0
NPA	0.08	0.28 (0.13–0.59)[c,d,e,f]	4.8
Apomorphine	0.16	0.60 (0.06–5.97)[c,d,e,f]	2.2
Nisoxetine	0.22	0.86 (0.33–2.13)[d,e,f]	1.6
CGS 15943	0.38	1.33 (0.77–2.24)[e,f,g]	1.0
Fluoxetine	0.63	2.04 (0.13–34.3)[f,g]	0.7
GBR 12909	3.41	7.53 (0.62–91.6)[g]	0.2

[a] Dose resulting in selection of the CGS 15943-appropriate choice lever in an average of 12.5 trials per session ($n = 4$).
[b] Potency relative to CGS 15943, based upon ED_{50}s (μmol/kg).
[c] ED_{50}s that do not have a superscript in common are significantly different from each other, $P < 0.05$.

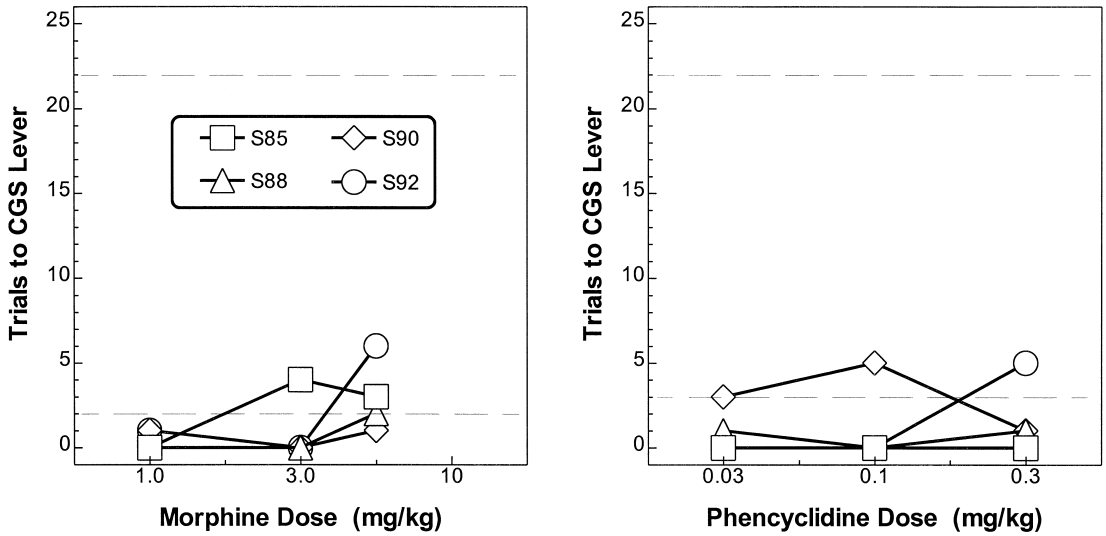

Fig. 4. Monkeys trained to discriminate between 1.0 mg/kg CGS 15943 and its vehicle responded primarily on the choice lever appropriate for the vehicle when they were tested with a range of doses of morphine or phencyclidine. Other details are the same as in Fig. 1.

antagonist SCH 23390, the dopamine D_2 receptor antagonist eticlopride, or the 5-HT_2/5-HT_{1C} receptor antagonist ketanserin (Fig. 5). SCH 23390 was, by far, the most potent antagonist of the three, blocking the discriminative

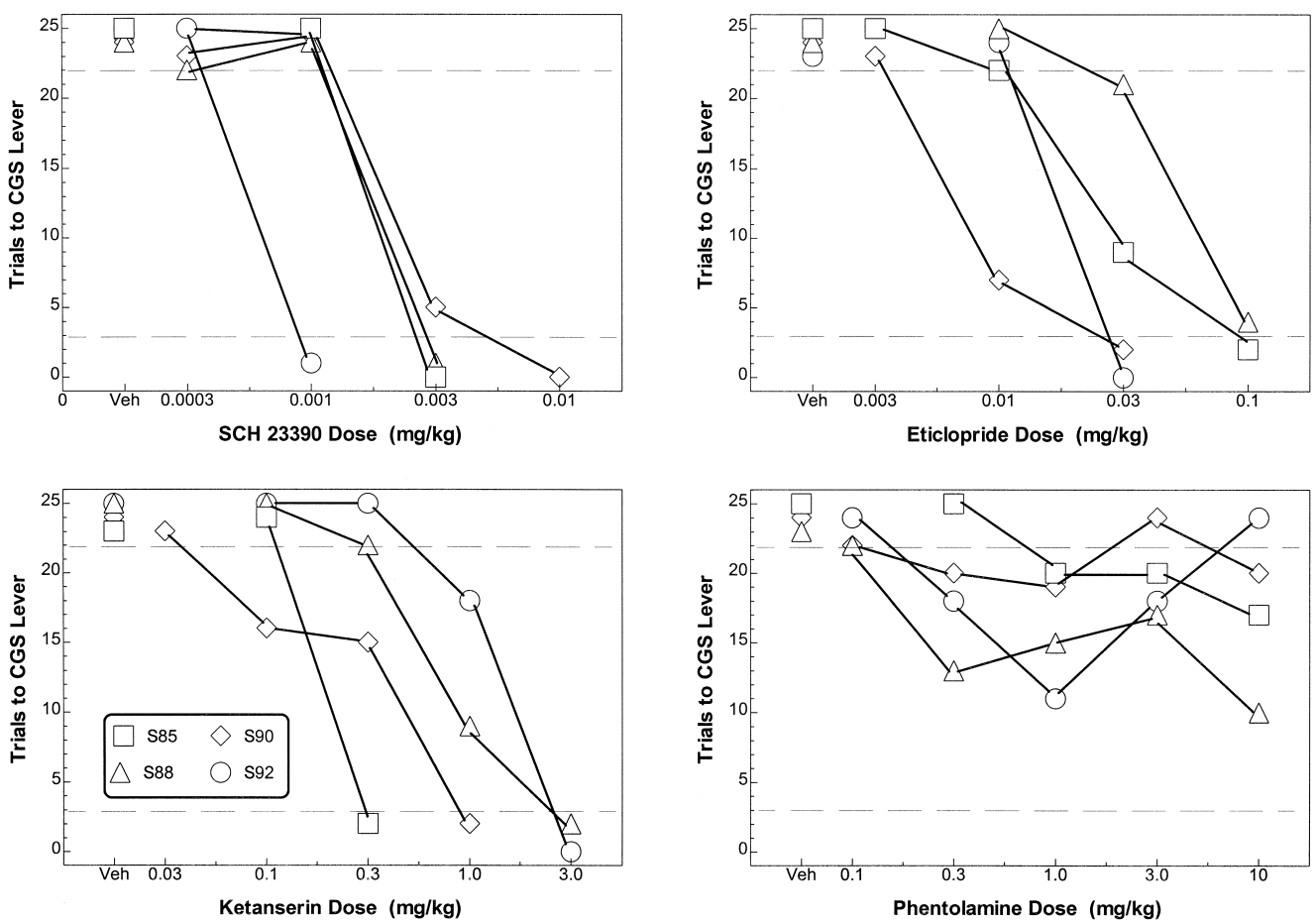

Fig. 5. The discriminative effects of the training dose of CGS 15943 were blocked dose-dependently and completely by antagonists selective for dopamine D_1-like receptors (SCH 23390), dopamine D_2-like receptors (eticlopride), and 5HT_2/5HT_{1C} receptors (ketanserin), but not by the α-adrenoceptor antagonist phentolamine. Points above Veh indicate the results of test sessions that followed the administration of the vehicle for antagonist and the 1.0 mg/kg training dose of CGS 15943. Other details are the same as in Fig. 1.

effects of CGS 15943 completely at doses of only 1.0–10 μg/kg, depending upon the individual monkey. The AD_{50}s (and 95% confidence limits) of the antagonists were 4.97 (1.83–13.5) nmol/kg for SCH 23390, 57.9 (17.5–192) nmol/kg for eticlopride and 1.09 (0.27–4.46) μmol/kg for ketanserin. Thus, on a molar basis, SCH 23390 was 11.6 times more potent than eticlopride and 219 times more potent than ketanserin in antagonizing the discriminative effects of the training dose of CGS 15943. In contrast, pretreatment with the α-adrenoceptor antagonist phentolamine blocked the discriminative effects of CGS 15943 only partially and inconsistently, even at a dose as high as 10 mg (36 μmol)/kg (Fig. 5).

4. Discussion

The results of this study demonstrate that there is a prominent dopamine component to the discriminative stimulus effects of CGS 15943 in squirrel monkeys. CGS 15943 generalized with a variety of directly and indirectly acting dopamine receptor agonists and its discriminative effects were blocked dose-dependently and completely by low doses of dopamine receptor antagonists. These findings are consistent with reports of dopamine involvement in the discriminative effects of a low training dose of caffeine and in the stimulation of locomotor activity by caffeine in rats (Mumford and Holtzman, 1991; Garrett and Holtzman, 1994). They also are consistent with a growing body of literature suggesting there is an inverse relationship between adenosine receptor activation in basal ganglia and dopamine-mediated neurotransmission (see Section 1).

It appears that activation of either the dopamine D_1 or D_2 families of receptors is sufficient to produce CGS 15943-like stimulus control of behavior. The dopamine D_1 receptor agonists SKF 77434 and SKF 38393 and the dopamine D_2 receptor agonists quinpirole and NPA were equipotent in this regard. In addition, the discriminative effects of CGS 15943 were blocked by nanomolar doses of either the dopamine D_1 receptor antagonist SCH 23390 or the dopamine D_2 receptor antagonist eticlopride. These effects of the dopamine receptor antagonists were not a consequence of nonspecific suppression or disruption of the ongoing behavior. The monkeys completed all session trials but shifted their responding in an orderly manner from the CGS 15943-appropriate choice lever to the vehicle-appropriate choice lever. Similar patterns of stimulus generalization and antagonism occur in squirrel monkeys discriminating indirectly acting dopamine receptor agonists, such as cocaine (Spealman et al., 1991), GBR 12909 (Melia and Spealman, 1991) and methamphetamine (Tidey and Bergman, 1998).

Dopamine is not the only monoamine that appears to be involved in the discriminative effects of CGS 15943. The monkeys in this study generalized completely to nisoxetine, a selective inhibitor of the neuronal norepinephrine transporter. This finding, too, is consistent with the results of a study on the discriminative effects of a low training dose of caffeine in rats, indicating an important noradrenergic component (Holtzman, 1986). Monkeys discriminating amphetamine (Kamien and Woolverton, 1989) and monkeys (Spealman, 1995) and rats (Terry et al., 1994) discriminating a low dose of cocaine (Spealman, 1995) also generalize completely with nisoxetine.

Contrasting with the substitution of nisoxetine for CGS 15943 is the failure of phentolamine, an α-adrenoceptor antagonist, to block the discriminative effects of the training drug. This outcome distinguishes the discriminative effects of CGS 15943 in this study from those of caffeine in rats; phentolamine blocked the discriminative effects of a low caffeine training dose (Holtzman, 1986). However, consistent with the results of the current study, phentolamine did not block the discriminative effects of either amphetamine or cocaine in monkeys, despite the fact that nisoxetine generalized with the training drugs (Kamien and Woolverton, 1989; Spealman, 1995). There are several possible explanations for these apparent discrepancies, species difference, for example. The pharmacokinetics of phentolamine in rats and monkeys might differ, as might the qualitative nature of the discriminative effects that arise from blockade of adenosine receptors and/or the relative contribution to those effects of α- vs. β-adrenoceptor activation. Differences among the training drugs must also be considered. The unique spectrum of activity of caffeine, which includes inhibition of phosphodiesterases, might make a noradrenergic component essential to the stimulus control of behavior by that drug. Enhancement of noradrenergically mediated neurotransmission might be sufficient to mimic the stimulus effects of CGS 15943 (as well as those of amphetamine and cocaine) but not be essential for stimulus control of behavior by CGS 15943.

A third monoamine that appears to have a role in the discriminative effects of CGS 15943 is serotonin. The discriminative effects of CGS 15943 were mimicked (completely, in three of four monkeys) by fluoxetine, a selective inhibitor of serotonin uptake by neurons, and were blocked by ketanserin, a $5\text{-}HT_2$ receptor antagonist. The literature contains abundant evidence of serotonergic modulation of brain dopamine systems. Activation of serotonin receptors can stimulate dopamine release (Parsons and Justice, 1993; Benloucif et al., 1993). Furthermore, serotonergic mechanisms appear to contribute to the discriminative and reinforcing stimulus effects of psychomotor stimulant drugs, such as cocaine (Walsh and Cunningham, 1997). However, in contrast to the effects of fluoxetine in monkeys discriminating CGS 15943, selective serotonin reuptake inhibitors do not substitute for the cocaine cue, even when the training dose of cocaine is relatively low (Terry et al., 1994; Spealman, 1995).

A pattern of broad stimulus generalization to pharmacologically diverse drugs can be the consequence of a func-

tionally low training dose (Holtzman, 1983; Overton, 1984). Several lines of evidence suggest that the training dose of CGS 15943 was, indeed, functionally low. First, the discrimination was acquired slowly, in a median of 174 (range: 82–222) training sessions (Holtzman, 1996). Second, SKF 38393 and SKF 77494, which are low-efficacy agonists at dopamine D_1 receptors (Izenwasser and Katz, 1993; Weed et al., 1997), generalized completely with CGS 15943. In contrast, SKF 38393 occasioned little drug-appropriate responding in squirrel monkeys trained to discriminate SKF 81297, a high-efficacy dopamine D_1 receptor agonist (Rosenzweig-Libson and Bergman, 1993). Third, the ED_{50}s of cocaine, nisoxetine, and GBR 12909 in this study (Table 1) were up to several-fold lower than they were in squirrel monkeys discriminating a ''low'' dose (0.18–0.3 mg/kg) of cocaine (Spealman, 1995). The ED_{50} of a drug varies directly with the magnitude of the discriminative effects of the training drug (Holtzman, 1983). Therefore, these results suggest that the training dose of CGS 15943 engendered a less intense stimulus than did the low training dose of cocaine in the study by Spealman (1995). A discriminative stimulus of relatively low intensity might also account for the variability among animals in their responses to the various test drugs.

Despite the breadth of drugs sharing discriminative effects with CGS 15943, stimulus control of behavior by the training drug did have pharmacological specificity. Morphine, a μ-opioid receptor agonist, and phencyclidine, a noncompetitive antagonist at the *N*-methyl-D-aspartate (NMDA) glutamate–receptor complex, occasioned little CGS 15943-appropriate responding, even though they were tested at doses that are discriminable to squirrel monkeys (Schaefer and Holtzman, 1977; Holtzman, 1982). Rats trained to discriminate magnesium chloride from saline also generalize completely to cocaine and to specific inhibitors of the uptake of dopamine, norepinephrine and serotonin, but generalize only partially to PCP and other NMDA receptor antagonists (Kantak et al., 1997). The relationship, if any, between the discriminative effects of magnesium chloride and those arising from blockade of adenosine receptors is obscure.

In conclusion, squirrel monkeys discriminating an adenosine receptor antagonist that does not inhibit phosphodiesterase activity generalize not only to other drugs that block adenosine receptors (Holtzman, 1996), but also to drugs that enhance neurotransmission mediated by dopamine, norepinephrine, and serotonin. Therefore, this type of drug discrimination procedure might be useful for studying the relationships among brain adenosine and monoamine systems.

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