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Methylxanthines Reverse the Adipsic and Aphagic Syndrome Induced by Bilateral 6-Hydroxydopamine Lesions of the Nigrostriatal Pathway in Rats

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CASAS, M., G. PRAT, P. ROBLEDO, M. BARBANOJ, J. KULISEVSKY AND F. JANÉ. *Methylxanthines reverse the adipsic and aphagic syndrome induced by bilateral 6-hydroxydopamine lesions of the nigrostriatal pathway in rats.* PHARMACOL BIOCHEM BEHAV **66**(2) 257–263, 2000.—This study investigated whether methylxanthines (caffeine and theophylline) would restore food and water intake in rats made aphagic and adipsic by bilateral 6-hydroxydopamine lesions of the nigrostriatal bundle, and these results were compared with the effects of *d*-amphetamine, the dopamine D_1 agonist SKF 38393, and the $D_{2/3}$ agonist quinpirole. In a separate experiment, we investigated whether the selective D_1 antagonist, SCH 23390, or the selective D_2 antagonist, sulpiride, would prevent the caffeine-induced restoration of food and water intake in bilaterally 6-hydroxydopamine denervated rats. The results showed that caffeine, theophylline, and quinpirole significantly reversed the aphagia and adipsia observed in lesioned animals. SKF 38393 had no significant effects on water intake, while it significantly restored food intake at the highest dose used. In contrast, *d*-amphetamine had no significant effects on food or water intake. Results from the second experiment showed that sulpiride attenuated the caffeine-induced restoration of food and water intake in lesioned rats to a greater extent than did SCH 23390. These data suggest that methylxanthines may mediate their effects on food and water intake in bilateral 6-hydroxydopamine-lesioned rats through an action at the dopaminergic system. © 2000 Elsevier Science Inc.

Caffeine Theophylline Dopamine agonists Dopamine Antagonists Food and water intake
SKF 38393 Quinpirole Sulpiride SCH23390

BILATERAL 6-hydroxydopamine (6-OHDA) lesions of the nigrostriatal bundle (NSB) produce a behavioral syndrome characterized by aphagia, adipsia and akinesia (41). Low doses of nonspecific dopamine receptor agonists such as apomorphine (28,31), L-DOPA or ET-495 (28) have been shown to restore eating and drinking in this model.

Methylxanthines (MTX), including caffeine and theophylline, show a similar behavioral profile to psychostimulant drugs such as amphetamine and cocaine in animals and humans (16). In humans, MTX increase vigilance (27) and delays sleep (24). In animals, MTX increase locomotor activity (33), and depending on the physiological state of the animal, they can either produce anorexia or have no effects [see (1)]. Although several mechanisms of action for MTX have been described [for review, see (16)], one of the most accepted is an antagonistic effect on adenosine receptors (8,14,38). However, recent evidence supports previous studies showing that MTX may produce their psychostimulant effects through a dopaminergic mechanism (2,3,4,42). For instance, caffeine-induced locomotor activity is blocked by both dopamine D_1 and D_2 receptors antagonists (17), and rats that are tolerant to caffeine show crosstolerance to dopamine D_1 and D_2 receptor agonists (18). In addition, caffeine potentiates the locomotor stimulant effect of dopaminergic agonists (23).

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Although evidence suggests that MTX possess dopaminergic-like properties, effects of MTX on regulatory behaviors in bilateral 6-OHDA nigrostriatal lesioned rats have not been demonstrated. Therefore, the present study was designed to investigate whether caffeine and theophylline would reverse the aphagia and the adipsia induced by bilateral 6-OHDA lesions of the NSB. Additionally, we investigated the effects of the indirect dopamine agonist *d*-amphetamine, the selective D_1 dopamine receptor agonist, SKF 38393, and the $D_{2/3}$ dopamine receptor agonist, quinpirole, on the aphasic and adipsic syndrome induced by these lesions. In a second experiment, we investigated the effects of selective D_1 and D_2 dopamine antagonists on caffeine's effects on food and water intake in 6-OHDA–lesioned rats.

METHOD

Animals

Male Sprague–Dawley rats were housed individually in cages provided with wire mesh floors to prevent the rats from eating their feces. Rats were maintained in a temperature (21 ± 2°C) and humidity (40–60%) controlled environment with a 12 L:12 D cycle (lights on at 0800 h). This experiment was carried out in compliance with the European Communities Council Directive of November 24, 1986 (86/609/EEC) for care and use of laboratory animals.

Drugs

The 6-OHDA HCl (Sigma, Spain) was dissolved in 0.9% physiological saline containing 0.02% ascorbic acid. The 6-OHDA was prepared fresh daily. Apomorphine-HCl, caffeine anhydrous, theophylline anhydrous (Sigma, Spain), SKF 38393, and SCH 23390 (RBI, Spain) were dissolved in warm physiological saline. Quinpirole (RBI, Spain) and *d*-amphetamine (Sigma, Spain) were dissolved in physiological saline. Sulpiride (Sigma, Spain) was dissolved in sterile water containing 5% glucose and a drop of acetic acid. All doses were calculated as free base, and were injected subcutaneously (SC) in a volume of 1 ml/kg of body weight. Sulpiride and SCH 23390 were given just prior to the administration of caffeine.

Surgical Procedure

Rats weighing 200 ± 10 g were anaesthetized with sodium pentobarbital (40 mg/kg body weight IP) and placed in a David Kopf stereotaxic frame with the incisor bar set at 2.4 mm (22). They were injected bilaterally in the NSB (A −4.4, L ±1.2, V −7.8 mm, calculated from bregma and dura) with 8 μg in 4 μl (per side) of 6-OHDA HCl (calculated as free base), using a Hamilton syringe at a rate of 1 μl/min. This lesion has been shown to extensively and bilaterally deplete forebrain dopamine (41).

Postoperative Period

For 3 days following surgery, food pellets and water were available at all times. In addition, moist palatable food and water in dishes were also offered for 15 min every day. Food and water intake, as well as body weight was recorded every 24 h during the postoperative period. Animals were considered aphagic and adipsic when they did not eat dry food or drink tap water, when they pushed food and drink away, and lost 20 to 35% of their initial body weight. Rats which drank water, ate food, and did not lose any weight were excluded from the study. Animals were considered akinetic when they showed rigidity and lack of locomotion (34).

Experimental Groups

For Experiment I, 152 rats were randomly allocated into 20 groups and injected with either caffeine: 5 mg/kg (n = 8), 15 mg/kg (n = 9), 30 mg/kg (n = 8), and 60 mg/kg (n = 8), theophylline: 5 mg/kg (n = 8), 15 mg/kg (n = 8), 30 mg/kg (n = 8), and 60 mg/kg (n = 8), *d*-amphetamine: 0.5 mg/kg (n = 9), 1 mg/kg (n = 8), 2 mg/kg (n = 8), the dopamine D_1 agonist, SKF 38393: 2 mg/kg (n = 8), 4 mg/kg (n = 7), 8 mg/kg (n = 8), and 16 mg/kg (n = 9), the dopamine D_2 agonist, quinpirole: 0.05 mg/kg (n = 8), 0.1 mg/kg (n = 8), 0.5 mg/kg (n = 6), and 2.5 mg/kg (n = 8), or saline 1 ml/kg (n = 8). For Experiment II, 42 rats (n = 6 per group) were randomly allocated into seven groups and injected with either caffeine (30 mg/kg) plus vehicle, caffeine (30 mg/kg) plus the dopamine D_1 antagonist, SCH 23390 (0.1, 0.3, and 1.0 mg/kg), or caffeine (30 mg/kg) plus the D_2 antagonist, sulpiride (5, 15, and 30 mg/kg).

Testing Procedure

Animals were tested on the fourth day after surgery. Although in this study we did not measure directly the degree of dopaminergic depletion, previous studies have shown that similar bilateral lesions (i.e., 8 μg of 6-OHDA in 4 μl of vehicle, injected bilaterally into the NSB), produce a complete disappearance of dopaminergic nerve terminals in the striatum 2–3 days after the lesion (28).

Two standard pellets weighing between 10 and 14 g, as well as 50 ml of water in calibrated drinking bottles were available for each animal during the test session. Rats were observed in their individual cages for 4 h by two independent investigators blind to the treatment each rat received. Following drug administrations, two separate quantitative measures were made: 1) the percentage of animals capable of eating and drinking. Animals were considered capable of eating food when they approached, handled, and chewed on the food. Animals were considered capable of drinking water when they licked on the water dispenser. 2) The amount of food and water consumed. At the end of the test session, the observers weighed the pieces of food that fell beneath the cage, and the uneaten pellets inside the cage. Then, these were subtracted from the total weight given before drug administrations. Water intake was quantified by measuring the amount of water left in the bottle and subtracting it from the initial quantity.

Statistical Analysis

Differences between the total amount of food (g in 4 h) and water (ml in 4 h) intake for the different groups were analyzed using one-way ANOVAs, followed by the Duncan post hoc test for individual comparisons.

RESULTS

Seventy-five percent of the lesioned animals lost between 25–30% of their initial body weight, revealing deficits in drinking and eating behavior. No significant differences were observed in body weight between the different groups ($p >$ 0.05). These animals also showed a hunched posture, were hyporesponsive to handling, and had difficulties walking.

Experiment I

Food intake. The effects of caffeine, theophylline, SKF 38393, and quinpirole on food intake and the percentage of animals eating food are shown in Fig. 1. The data for the control group injected with saline is not shown on the graph. In

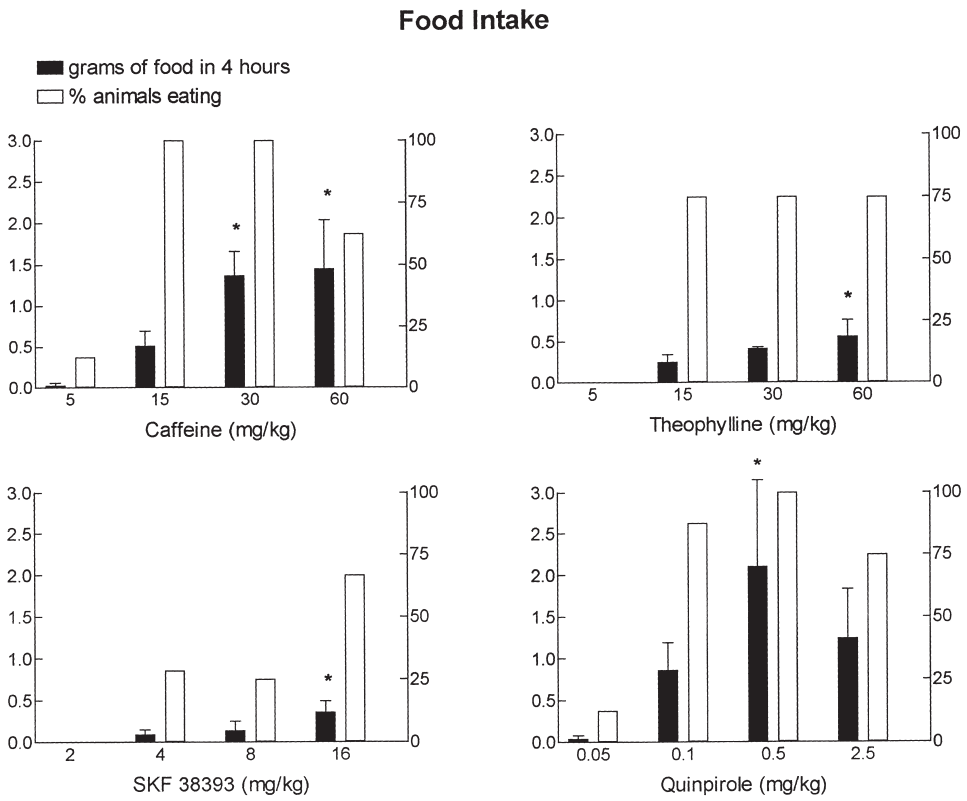

FIG. 1. Effects of caffeine (5, 15, 30, and 60 mg/kg; n = 8–9), theophylline (5, 15, 30, and 60 mg/kg; n = 8), SKF 38393 (2, 4, 8, and 16 mg/kg; n = 7–9), and quinpirole (0.05, 0.1, 0.5, and 2.5 mg/kg; n = 6–8) on food intake. Mean grams of food + SEM consumed in 4 h (black bars) are plotted on the left axis, and the percentage of animals consuming food (open bars) are plotted on the right axis. *$p < 0.05$ (Duncan test) significant differences as compared to saline injection.

this group, none of the animals (n = 8) consumed any food. Statistical analysis revealed a significant main effect of caffeine on food intake, $F(4, 34) = 4.56$, $p < 0.005$. Post hoc comparisons showed that caffeine at the dose of 30 and 60 mg/kg significantly increased food intake with respect to saline ($p < 0.05$). Similarly, theophylline injections had a significant effect on food consumption, $F(4, 34) = 3.33$, $p < 0.03$. Post hoc analysis revealed that only the dose of 60 mg/kg significantly increased food intake with respect to saline ($p < 0.05$). Although the amount of food consumed by animals treated with caffeine was greater than the amount consumed by animals treated with theophylline at the same doses, no statistically significant differences were found between the two groups.

In contrast to caffeine and theophylline, *d*-amphetamine (data not shown) induced very little food intake at the dose of 0.5 mg/kg (0.11 ± 0.05 g/4 h), and no food was consumed at the doses of 1 or 2 mg/kg. The D_1 receptor agonist SKF 38393 produced a small, but significant main effect on food intake, $F(4, 34) = 2.77$, $p < 0.04$, which was significantly higher than saline at the dose of 16 mg/kg ($p < 0.05$). Quinpirole induced greater amounts of food intake than SKF 38393 [significant main effect: $F(4, 31) = 2.67$, $p < 0.05$], which were significantly higher than saline at the dose of 0.5 mg/kg ($p < 0.05$).

Water intake. The effects of caffeine, theophylline, SKF 38393, and quinpirole on water intake and the percentage of animals drinking water are shown are shown in Fig. 2. The data for the control group injected with saline are not shown on the graph. In this group, none of the animals (n = 8) drank any water. A significant main effect, $F(4, 34) = 10.0$, $p < 0.0001$, on water intake was observed after caffeine administration (15, 30, and 60 mg/kg), which was significantly greater than that observed after a saline injection ($p < 0.05$). Theophylline had a significant main effect on water intake, $F(4, 34) = 11.26$, $p < 0.0001$, which was significantly higher than saline at the doses of 30 and 60 mg/kg ($p < 0.05$). The amount of water intake observed in the rats injected with theophylline at a dose of 60 mg/kg was significantly greater than the one observed with caffeine at the same dose, $F(1, 15) = 6.71$, $p < 0.02$. Amphetamine (data not shown) induced nonsignificant amounts of water intake at the dose of 0.5 mg/kg (0.01 ± 0.01 ml/4 h), and at the dose of 2 mg/kg (0.1 ± 0.05 ml/4 h). SKF 38393, induced very little water intake that was not statistically significant, $F(4, 33) = 1.26$, $p < 0.30$. In contrast, animals injected with quinpirole showed high amounts of water intake [significant main effect: $F(4, 31) = 4.81$, $p < 0.04$]. Significant increases with respect to saline were observed with the doses of 0.1, 0.5, and 2.5 mg/kg ($p < 0.05$).

Experiment II

Food intake. The effects of SCH 23390 (0.0, 0.1, 0.3, 1.0 mg/kg) on caffeine-induced restoration of food intake and the percentage of animals eating food are shown in Fig. 3a. A significant main effect of dose on food intake was observed, $F(3,$

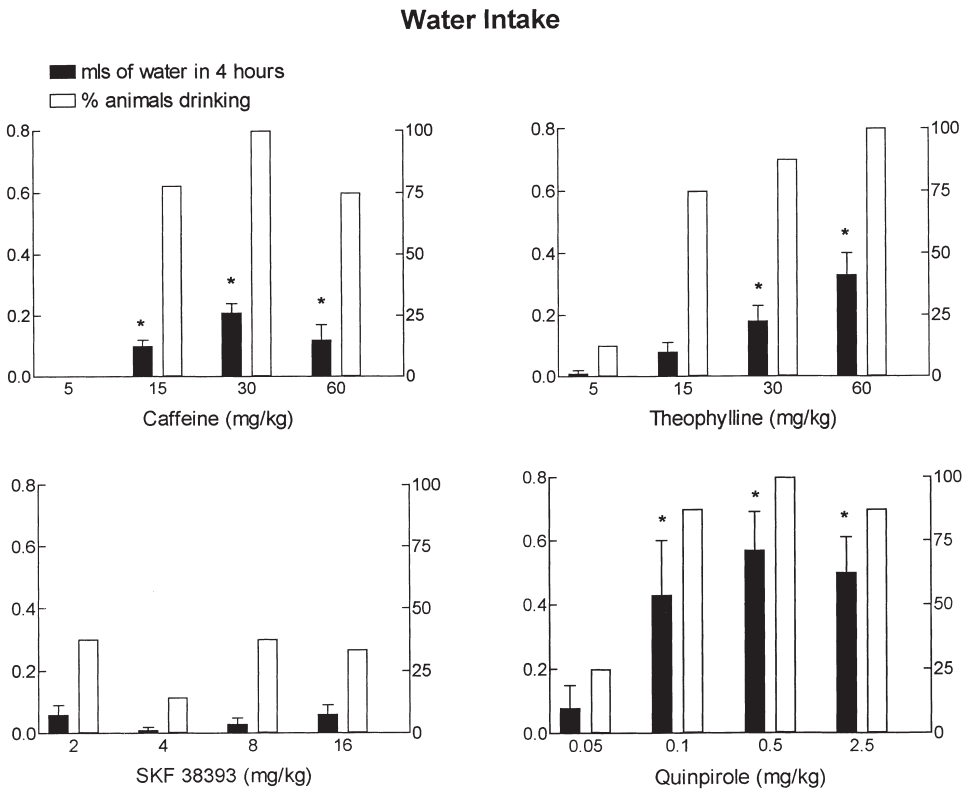

FIG. 2. Effects of caffeine (5, 15, 30, and 60 mg/kg; n = 8–9), theophylline (5, 15, 30, and 60 mg/kg; n = 8), SKF 38393 (2, 4, 8, and 16 mg/kg; n = 7–9) and quinpirole (0.05, 0.1, 0.5, and 2.5 mg/kg; n = 6–8) on water intake: mean ml of water + SEM consumed in 4 h (black bars) are plotted on the left axis, and the percentage of animals drinking water (open bars) are plotted on the right axis. *$p < 0.05$ (Duncan test) significant differences as compared to saline injection.

22) = 3.94, $p < 0.03$. Even though rats injected with the different doses of SCH 23390 plus caffeine (30 mg/kg) consumed significantly less food with respect to the group injected with caffeine plus vehicle ($p < 0.05$), most of the rats still consumed food in these groups (83.3–100%).

The effects of sulpiride (0, 5, 15, and 30 mg/kg) on caffeine-induced restoration of food intake and the percentage of animals eating food are shown in Fig. 3b. Statistical analysis showed a significant main effect of dose on food intake, $F(3, 28) = 4.79$, $p < 0.009$. Post hoc comparisons revealed that in the groups injected with caffeine (30 mg/kg) plus sulpiride at the dose of 15 or 30 mg/kg, rats consumed significantly less food compared to the group injected with caffeine plus vehicle ($p < 0.05$).

Water intake. The effects of SCH 23390 (0.0, 0.1, 0.3, and 1.0 mg/kg) on caffeine-induced restoration of water intake and the percentage of animals drinking water are shown in Fig. 4a. Statistical analysis showed a significant main effect of dose on water intake, $F(3, 22) = 6.88$. $p < 0.002$. However, while the rats injected with the different doses of SCH 23390 (0.1, 0.3, and 1.0 mg/kg) plus caffeine (30 mg/kg) drank significantly less water compared to the group injected with caffeine plus vehicle, ($p < 0.05$), most of the rats in these groups still drank water (100, 66.7, and 83.3%, respectively).

The effects of sulpiride (0, 5, 15, and 30 mg/kg) on caffeine-induced restoration of water intake and the percentage of animals drinking water are shown in Fig. 4b. Statistical analysis showed a significant main effect of dose on water intake, $F(3, 28) = 10.66$, $p < 0.001$. Post hoc comparisons revealed that in the groups injected with caffeine (30 mg/kg) plus sulpiride at the dose of 15 or 30 mg/kg, rats drank significantly lower amounts of water compared to the group injected with caffeine plus vehicle ($p < 0.05$).

DISCUSSION

In agreement with previous studies (28,31,36,41), we found that rats with bilateral 6-OHDA lesions of the NSB showed profound dysfunctions including, aphagia, adipsia, and body weight loss, suggesting extensive dopamine depletions in the nigrostriatal dopaminergic system. It is unlikely that any residual striatal dopamine remained, because we found that *d*-amphetamine injections failed to significantly restore food or water intake in these rats.

Caffeine and theophylline increased food and water intake in lesioned animals revealing a reversal of the aphagia and adipsia produced by bilateral 6-OHDA lesions of the dopaminergic nigrostriatal pathway. These results can be contrasted with those observed in normosensitive rats. Caffeine has been shown to produce either anorexia (35), or no effect (7). On the other hand, theophylline does not alter the amount of food consumed, but disturbs the circadian rhythm of food intake (37). With respect to water intake, it has been shown that caffeine reduces water intake in water-deprived rats (6), whereas low

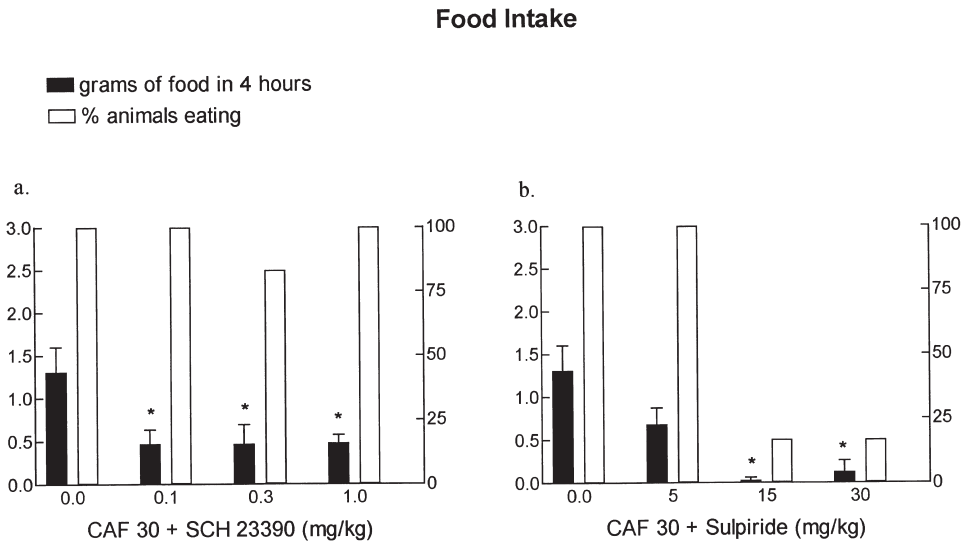

FIG. 3. Effects of sulpiride (5, 15, and 30 mg/kg) (left) and SCH 23390 (0.1, 0.3 and 1.0 mg/kg) (right) on caffeine-induced restoration of food intake. Black bars are mean grams of food + SEM consumed in 4 h (plotted on the left axis), and white bars are percnet of animals that consumed food (plotted on the right axis). *$p < 0.05$ (Duncan test) significant differences as compared to caffeine (30 mg/kg) plus saline injection.

doses of caffeine increase schedule-induced drinking in animals with free access to food, but not in food deprived rats (43).

With respect to the effects of dopaminergic agonists, we found that the pattern of food and water intake restoration was different, depending on the specificity of the dopaminergic agonist used. In fact, the $D_{2/3}$ dopamine receptor agonist, quinpirole, reversed both food and water intake, in a way similar to caffeine, whereas the dopamine D_1 agonist SKF 38393 significantly restored food intake at the highest dose used, but it had no significant effects on water intake. Therefore, it is possible to suggest that in bilaterally denervated rats, postsynaptic dopamine D_2 receptors may be more involved in feeding and drinking behaviors than dopamine D_1 receptors.

In nonlesioned rats, it has been demonstrated that dopamine D_1 receptor agonists consistently reduce food intake when injected systemically (20,32,39,40,44). The lack of clear effects with SKF 38393 in our study with lesioned rats may be, in part, attributed to the fact that this agent can re-

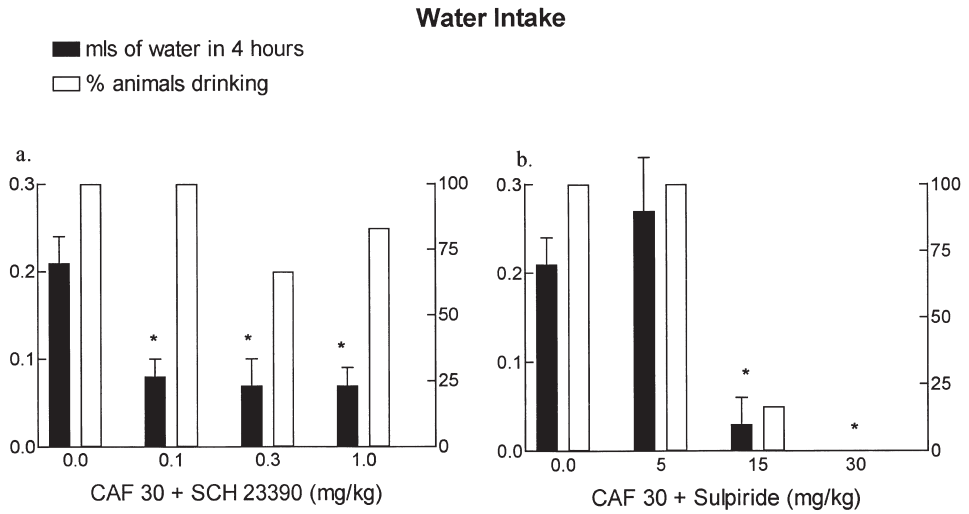

FIG. 4. Effects of sulpiride (5, 15, and 30 mg/kg) (left), and SCH 23390 (0.1, 0.3, and 1.0 mg/kg) (right) on caffeine-induced restoration of water intake. Black bars are mean ml of water + SEM consumed in 4 h (plotted on the left axis), and white bars are percent of animals that consumed water (plotted on the right axis). *$p < 0.05$ (Duncan test) significant differences compared to caffeine (30 mg/kg) plus saline injection.

duce feeding through an action at serotoninergic receptors (44), or to neuroadaptive changes at the D_1 receptor level following dopaminergic depletion. Also, we cannot rule out the possibility that higher doses of SKF 38393 would have been effective in restoring food and water intake in lesioned animals. On the other hand, in nonlesioned rats dopamine D_2 agonists can either reduce (9,10,44), or increase (5,10,32) food and water intake. These contradictory data on the effects of dopamine D_2 receptor agonists on regulatory behaviors in nonlesioned rats may relate to the differential stimulation of pre- and postsynaptic dopamine receptors of these substances. In our study, the doses of quinpirole that restore aphagia and adipsia in denervated rats are anorexic in nonlesioned animals (44), supporting a postsynaptic effect. In addition, this effect appears to be specifically mediated by the neuroadaptive changes induced by the dopaminergic depletion, because pretreatment with reserpine, which produces an acute depletion of catecholamines, potentiates the anorexic effects of quinpirole (44).

Several important disparities were observed between the amount of food that animals consumed and the percentage of animals that ate food after the different drug treatments. For instance, while low doses of caffeine slightly increased food intake, they completely restored the percent of lesioned animals eating. In contrast, higher doses of caffeine increased the percent of animals eating to only 62.0%, but greatly increased food intake. In the case of theophylline, while it restored food intake, it never induced eating in 100% of the animals. The dopamine D_1 agonist SKF 38393 restored food intake at the highest dose, but it did not completely restore the percent of animals eating. Similarly, the dopamine D_1 antagonist, SCH 23390, blocked the caffeine-induced restoration of food intake, but it did not significantly affect the percent of animals eating. On the other hand, the dopamine D_2 agonist, quinpirole restored both food intake and the percent of animals eating. Along the same line, the dopamine D_2 antagonist, sulpiride blocked the caffeine-induced restoration of food intake, and it also had an effect on the percent of animals eating.

The two measures used in this study probably reflect different aspects of general motivated behavior. The percentage of animals eating appears to be related to the capacity of the animals to approach the stimulus, whereas the amount of food intake may be more related to the actual consumatory behavior of the animals. As described above, we found that these two measures could be dissociated, depending on the specificity of the drug administered. Thus, dopamine D_1 receptors seem to be more involved in the comsumatory aspects of the behavioral syndrome, whereas dopamine D_2 receptors seem to affect both of these aspects. In this sense, the results observed with MTX appear to be related to activation of both dopamine D_1 and D_2 receptors.

One possible way in which the effects of MTX can be mediated by dopamine D_2 receptors is through the functional postsynaptic antagonistic interaction between A_2/D_2 receptors present in the striatum of denervated rats [(11), and for recent review see (13)]. Thus, MTX potentiate D_2 receptor stimulation through blockade of adenosine A_2 receptors. In line with this hypothesis is our data showing that the dopamine D_2 receptor antagonist, sulpiride at the doses of 15 and 30 mg/kg, significantly attenuated the caffeine-induced restoration of food and water intake. This finding cannot be attributed to an anorexic effect nor to an nonspecific action of sulpiride on motor behavior because it has been shown in nonlesioned rats that at the dose of 25 mg/kg, sulpiride does not significantly reduce food intake (44) or motor activity (29) when given by itself. In addition, sulpiride at similar doses to the ones used here does not attenuate apomorphine-induced increases in locomotor activity in nonlesioned rats (15).

An action of MTX on dopamine D_1 receptors is supported by our results showing that the dopamine D_1 antagonist, SCH 23390, significantly reduced the amount of food and water intake induced by caffeine. Also, it has been shown that paraxanthine, a main metabolite of caffeine (25), binds to D_1 receptors (12). In addition, MTX can influence dopamine D_1 activity through the antagonistic interaction existing between adenosine A_1 and dopamine D_1 receptors in the striatum (13). Nevertheless, further studies with other more specific dopamine D_1 receptor agonists and antagonists are needed to confirm this hypothesis, because both SKF 38393 and SCH 23390 appear to have partial agonistic actions on serotoninergic $5HT_{1C}$ receptors [see (40)].

The mediation of the present effects through a direct antagonistic action of MTX at adenosine receptors is difficult to establish, because a very small amount of data exists on the role of adenosine in regulatory behaviors. One study shows that among several adenosine agonists used, only N6-R-phenylisopropyladenosine (R-PIA) increased food intake in nonlesioned rats, but only after repeated injections, and this effect was not blocked by caffeine (26).

In conclusion, our results in bilateral 6-OHDA denervated rats provide further support for the dopamine-like actions of MTX. Other studies investigating the role of MTX in unilaterally 6-OHDA denervated rats are in line with this hypothesis by showing that caffeine produces long-lasting rotational behavior (4, 19), and potentiates the effects of dopaminergic agonists on this type of behavior (21). Together, these data suggests that MTX may have clinical therapeutic potential in human conditions involving dopaminergic treatments such as Parkinson's disease. In this respect, theophylline has been recently shown to ameliorate the tremor in parkinsonian patients (30).

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