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The adenosine A_{2A} antagonist MSX-3 reverses the effort-related effects of dopamine blockade: differential interaction with D1 and D2 family antagonists

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Abstract

Rationale—Brain dopamine (DA) participates in the modulation of instrumental behavior, including aspects of behavioral activation and effort-related choice behavior. Rats with impaired DA transmission reallocate their behavior away from food-seeking behaviors that have high response requirements, and instead select less effortful alternatives. Although accumbens DA is considered a critical component of the brain circuitry regulating effort-related choice behavior, emerging evidence demonstrates a role for adenosine A_{2A} receptors.

Objective—Adenosine A_{2A} receptor antagonism has been shown to reverse the effects of DA antagonism. The present experiments were conducted to determine if this effect was dependent upon the subtype of DA receptor that was antagonized to produce the changes in effort-related choice.

Materials and methods—The adenosine A_{2A} receptor antagonist MSX-3 (0.5–2.0 mg/kg IP) was assessed for its ability to reverse the effects of the D1 family antagonist SCH39166 (ecopipam; 0.2 mg/kg IP) and the D2 family antagonist eticlopride (0.08 mg/kg IP), using a concurrent lever pressing/chow feeding procedure.

Results—MSX-3 produced a substantial dose-related reversal of the effects of eticlopride on lever pressing and chow intake. At the highest dose of MSX-3, there was a complete reversal of the effects of eticlopride on lever pressing. In contrast, MSX-3 produced only a minimal attenuation of the effects of SCH39166, as measured by regression and effect size analyses.

Conclusions—The greater ability of MSX-3 to reverse the effects of D2 vs. D1 blockade may be related to the colocalization of D2 and adenosine A_{2A} receptors on the same population of striatal neurons.

Keywords

Operant; Reinforcement; Motivation; Behavioral economics; Reward; Decision making; Activation

Introduction

Activational aspects of motivated behavior (i.e., vigor, persistence, work output) are highly adaptive because they enable organisms to overcome obstacles or work-related response costs that are necessary for obtaining significant stimuli (Salamone 1991, 1992; Salamone et al. 1997, 2003, 2007; Salamone and Correa 2002; Van den Bos et al. 2006). In humans, symptoms such as anergia, psychomotor slowing, and fatigue, which reflect pathologies in behavioral activation, are fundamental aspects of depression and other psychiatric and neurological disorders (Tylee et al. 1999; Stahl 2002; Demyttenaere et al. 2005; Salamone et al. 2006, 2007; Yurgelun-Todd et al. 2007; Capuron et al. 2007; Majer et al. 2008). Nucleus accumbens dopamine (DA) has been shown to be a critical component of the brain circuitry controlling behavioral activation and effort-related behavioral processes. Rats with nucleus accumbens DA depletions are very sensitive to ratio requirements in operant schedules (Sokolowski and Salamone 1998; Aberman and Salamone 1999; Correa et al. 2002; Mingote et al. 2005) and show alterations in response allocation in tasks that measure effort-related choice behavior (Salamone et al. 1991, 1997, 2003, 2005, 2006, 2007). Several studies in this area have employed maze tasks to assess effort-related choice (Salamone et al. 1994; Cousins et al. 1996; Floresco et al. 2008), while others have used a concurrent fixed ratio 5 (FR5)/chow feeding procedure (Salamone et al. 1991, 2002, 2003, 2007). In the FR5/chow feeding task, rats can choose between responding on a FR5 lever-pressing schedule for a highly preferred food (i.e., high carbohydrate operant pellets) or approaching and consuming freely available food (i.e., less preferred standard rodent chow). Typically, untreated rats that are trained with this procedure spend most of their time pressing the lever for the preferred food and eat very little of the concurrently available chow. Relatively low doses of DA antagonists that act on either D1 or D2 family receptors, including haloperidol, *cis*-flupenthixol, SCH 23390, SCH39166, raclopride, and eticlopride, all suppress lever pressing for food, but actually increase chow intake (Salamone et al. 1991, 2002; Cousins et al. 1994; Koch et al. 2000; Sink et al. 2008). The DA terminal region most closely associated with these effects of impaired DA transmission is the nucleus accumbens (Salamone et al. 1991; Cousins et al. 1993; Cousins and Salamone 1994; Sokolowski and Salamone, 1998; Koch et al. 2000; Nowend et al. 2001). The effects of DA antagonists or accumbens DA depletions differ substantially from the effects produced by pre-feeding to reduce food motivation (Salamone et al. 1991) and also differ from the actions of appetite-suppressant drugs with different pharmacological profiles, including amphetamine (Cousins et al. 1994), fenfluramine (Salamone et al. 2002), and cannabinoid CB1 antagonists and inverse agonists (Sink et al. 2008). These appetite-related manipulations all fail to increase chow intake at doses that also suppress lever pressing.

In addition to nucleus accumbens DA, other brain areas and transmitters are involved in effort-related processes, including prefrontal cortex, amygdala, and ventral pallidum (Walton et al. 2002, 2003, 2006; Denk et al. 2005; Schweimer et al. 2005; Schweimer and Hauber 2006; Floresco and Ghods-Sharifi 2007; Floresco et al. 2008; Farrar et al. 2008). Recent research also has implicated the purine nucleoside adenosine in this type of function (Farrar et al. 2007; Font et al. 2008; Mingote et al. 2008). Adenosine A_{2A} receptors are primarily localized in striatal areas, including both neostriatum and nucleus accumbens (Jarvis and Williams 1989; Schiffmann et al. 1991; DeMet and Chiciz-DeMet 2002; Ferré et al. 2004), and there is a functional interaction between DA D2 and adenosine A_{2A} receptors (Fink et al. 1992; Ferré 1997; Hillion et al. 2002; Fuxe et al. 2003). This interaction has typically been investigated in connection with neostriatal motor functions that are potentially related to parkinsonism (Ferré et al. 1997, 2001; Hauber and Munkel 1997; Svenningsson et al. 1999; Hauber et al. 2001; Wardas et al. 2001; Morelli and Pinna 2002; Jenner 2003, ²⁰⁰⁵; Correa et al. 2004; Pinna et al. 2005; Ishiwari et al. 2007; Salamone et al. 2008a, b). More recently, researchers have begun to identify additional functions of adenosine A_{2A} receptors related to cognition (Takahashi et al. 2008) and motivation (O'Neill and Brown 2006; Farrar et al. 2007; Mingote et al. 2008; Font et al. 2008). Font et al. (2008) recently demonstrated that injections of the adenosine A_{2A} agonist CGS 21680 into the nucleus accumbens produced effects that resembled those of accumbens DA depletions or antagonism, i.e., they decreased lever pressing and increased chow intake in rats responding on the concurrent choice procedure. Farrar et al. (2007) described the involvement of adenosine A_{2A} receptors in modulating the effects of DA blockade on behavioral performance using the concurrent FR5/feeding procedure. In this study, a low systemic dose of the DA antagonist haloperidol induced the typical shift from lever pressing to approaching and feeding upon the freely available rodent chow, and injections of the adenosine A_{2A} antagonist MSX-3 increased lever pressing and decreased chow intake in haloperidol-treated rats, reversing the haloperidol-induced shift in behavior (Farrar et al. 2007).

The current work was undertaken to examine the role of DA/adenosine A_{2A} receptor interactions in effort-related choice behavior, using the concurrent lever pressing/chow feeding procedure. More specifically, the present experiments were conducted to determine if the ability of an adenosine A_{2A} receptor antagonist to reverse the effect of a DA antagonist is dependent upon the particular subtype of DA receptor that was being blocked. Previous work in this area has mostly focused upon the ability of adenosine A_{2A} receptor antagonists to reverse the effects of D2 family antagonism (e.g., Correa et al. 2004; Ishiwari et al. 2007; Farrar et al. 2007; Salamone et al. 2008a, b), and much less is known about the interaction between adenosine A_{2A} receptors and the actions of D1 family antagonists (see Hauber et al. 2001). The adenosine A_{2A} receptor antagonist MSX-3 (0.5–2.0 mg/kg IP) was assessed for its ability to reverse the effects of the D1 family antagonist SCH39166 (ecopipam; 0.2 mg/kg IP) and the D2 family antagonist eticlopride (0.08 mg/kg IP), using the concurrent lever pressing/chow feeding procedure. It was hypothesized that, due to the colocalization of DA D2 receptors and adenosine A_{2A} receptors in striatum and nucleus accumbens, and the well-documented interactions between these receptors, MSX-3 would be more effective at reversing the effects of a D2 antagonist than a D1 antagonist on the concurrent lever pressing/chow feeding procedure.

Materials and methods

Animals

Twenty-two drug-naïve, adult male Sprague–Dawley rats (Harlan Sprague Dawley, Indianapolis, IN, USA) were used in these experiments. The rats weighed 295–352 g at the start of the experiment and were initially deprived to 85% of their free-feeding body weight,

but then were allowed modest growth (i.e., an additional 5–10%) throughout the experiment. The rats were housed in a climate-controlled animal colony maintained at 23°C, with 12 h light–dark cycle (lights on 07:00 h), and had access to water ad libitum in their home cages. Animal protocols were approved by the University of Connecticut Institutional Animal Care and Use Committee, and the studies were conducted according to NIH guidelines for animal care and use.

Behavioral procedures

Test sessions were conducted in operant conditioning chambers (28×23×23 cm; Med Associates). Initially, rats were trained to lever press for 4 days on a continuous reinforcement schedule (30-min sessions; 45-mg pellets, Bioserve, Frenchtown, NJ, USA, were used for all operant behavior tests) and subsequently were changed to an FR5 schedule (30-min sessions, 5 days/week) and trained for several additional weeks. Rats were then shifted to the concurrent FR5/chow feeding procedure following the initial FR5 training. For this procedure, weighed amounts of lab chow (Lab Diet, 5P00 Prolab RMH 3000, Purina Mills, St. Louis, MO, USA; typically 15–20 g, three large pieces) were concurrently available on the floor of the chamber during the FR5 sessions. At the end of the session, rats were immediately removed from the chamber, and food intake was determined by weighing the remaining food, including spillage. Rats were trained until they attained stable baseline levels of chow intake and lever pressing (i.e., consistent responding over 1,200 lever presses per 30 min) before drug testing began. For most baseline days, rats did not receive supplemental feeding; however, over weekends and after drug tests, rats typically received supplemental chow in the home cage. Rats typically consumed all operant pellets that were delivered during each session, including both baseline and drug treatment days.

Pharmacological agents

SCH39166 (ecopipam; (6*aS-trans*)-11-chloro-6,6*a*,7,8,9,13*b*-hexahydro-7-methyl-5*H*-benzo [*d*] naphtha[2,1-*b*]azepin-12-ol hydrobromide) was obtained from Tocris Bioscience (Ellisville, MO, USA) and was dissolved in a 0.3% tartaric acid solution (pH=4.0), which was also used as the vehicle control condition for experiment 1. SCH39166 binds to D1 receptors with high affinity, but unlike SCH23390 binds to 5HT_{2A} and 5HT_{2C} receptors with a very low affinity (Alburges et al. 1992). Eticlopride (S(–)-3-chloro-5-ethyl-*N*-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-methoxybenzamide hydrochloride) was obtained from Sigma Chemical (St. Louis, MO, USA) and was dissolved in a 0.9% saline solution, which also was used as the vehicle control condition for experiment 2. SCH39166 and eticlopride doses and pretreatment times were selected based upon pilot studies and also upon a recent publication (Sink et al. 2008). Based upon the dose/response curves in the Sink et al. (2008) paper, the present doses of SCH39166 and eticlopride (0.2 and 0.08 mg/kg, respectively) were selected because they were relatively low doses that reliably decreased lever pressing and increased chow intake to roughly the same extent. The adenosine A_{2A} antagonist used was MSX-3 ((*E*)-phosphoric acid mono-[3-[8-[2-(3-methoxyphenyl)vinyl]-7-methyl-2,6-dioxo-1-prop-2-ynyl-1,2,6,7-tetrahydropurin-3-yl] propyl] ester disodium salt), which was synthesized at the laboratory of Dr. Christa Müller at the Pharmazeutisches Institut, Universität Bonn, in Bonn, Germany. Preparation of the drug solution consisted of dissolving MSX-3 (free acid) in 0.9% saline and adjusting the pH by titrating with microliter quantities of 1.0 N NaOH until the solid drug was in solution. The final pH was typically 7.5±0.2, although never exceeding 7.8. MSX-3 is a pro-drug that is cleaved in vivo to the pharmacologically active compound MSX-2 (Hockemeyer et al. 2004). Doses of MSX-3 were chosen based upon the results of Farrar et al. (2007). In both experiments, combined drug treatments were administered IP (see descriptions of individual experiments for drug administration schedule).

Experimental procedures

The rats were thoroughly trained on the concurrent FR5/chow feeding procedure (see above) before drug testing began, and different groups of rats were used for each experiment. All experiments used a within-groups design, with each rat receiving all combined IP drug treatments in their particular experiment in a randomly varied order (one treatment per week; no treatment sequences were repeated across different animals in the same experiment). Baseline training (i.e., non-drug) sessions were conducted four additional days per week. The specific treatments and testing times are listed below.

Experiment 1: ability of MSX-3 to reverse effort-related effects of SCH39166—

On the test day, subjects ($n=11$) were injected with either tartaric acid vehicle (20 min before testing) plus saline vehicle IP (20 min before testing), 0.2 mg/kg SCH39166 IP (20 min before testing) plus saline vehicle IP (20 min before testing), or 0.2 mg/kg SCH39166 IP (20 min before testing) plus various doses of MSX-3 injected IP (0.5, 1.0, and 2.0 mg/kg; 20 min before testing). The lead time for both drugs was 20 min; thus, each rat received two consecutive injections, with MSX-3 or vehicle being first. The order of the combined drug treatments was assigned randomly and each subject received each condition of MSX-3/SCH39166 (Veh/Veh, Veh/0.2, 0.5/0.2, 1.0/0.2, 2.0/0.2 mg/kg IP) over 5 weeks.

Experiment 2: ability of MSX-3 to reverse effort-related effects of eticlopride—

After baseline training on the concurrent lever pressing/chow feeding procedure, a separate group of rats ($n=11$) was treated with either saline vehicle (30 min before testing) plus saline vehicle IP (20 min before testing), 0.08 mg/kg eticlopride IP (30 min before testing) plus saline vehicle IP (20 min before testing), or 0.1 mg/kg eticlopride IP (30 min before testing) plus various doses of MSX-3 injected IP (0.5, 1.0, and 2.0 mg/kg; 20 min before testing). The order of the combined drug treatments was assigned randomly and each subject received each condition of MSX-3/eticlopride (Veh/Veh, Veh/0.08, 0.5/0.08, 1.0/0.08, 2.0/0.08 mg/kg IP) over 5 weeks.

Statistical analyses

Total number of lever presses and gram quantity of chow intake were analyzed with repeated measures analysis of variance (ANOVA). When the overall ANOVA was significant, non-orthogonal planned comparisons using the overall error term were used to compare each treatment with the DA antagonist plus vehicle control condition. The alpha level for each comparison was kept at 0.05 because the number of comparisons was restricted to the number of treatments minus one (Keppel 1991; pp 110–139). With this analysis, each condition that combined DA antagonist plus MSX-3 was compared with its respective DA antagonist plus vehicle condition using the planned comparisons. In addition, the Tukey test was used to assess all possible paired comparisons of different means within each experiment. Orthogonal analysis of trend and effect size analyses also were used to compare the results of the different experiment. Trend analysis (Keppel 1991) assesses the presence of mathematical functions (e.g., linear, quadratic, cubic) in ANOVA data. The present analyses used Systat 7.0, and the factorial ANOVA with trend analysis also tested for interactions across the linear, quadratic, and cubic trends. Effect size calculations (R^2 values; Keppel 1991) were performed to assess the magnitude of the treatment effect (i.e., the size of the treatment effect expressed as the proportion of total variance accounted for by treatment variance; for example $R^2=0.3$ reflects 30% of the variance explained) across experiments and measures.

Results

Experiment 1: MSX-3 reversal of effect of D1 antagonist SCH39166

MSX-3 partially attenuated the effects of SCH39166 on the concurrent lever pressing/chow feeding task. The overall treatment effect for lever pressing was statistically significant (Fig. 1; [$F(4,40)=32.4, p<0.001$]). Planned comparisons revealed that SCH39166 decreased lever pressing compared to injection of Veh/Veh ($p<0.01$). MSX-3 produced a very modest reversal of the suppression of lever pressing induced by SCH39166, with all three doses being significantly different from SCH39166 plus vehicle ($p<0.05$). Nevertheless, all doses of MSX-3 plus SCH39166 also were significantly different from Veh/Veh (Tukey test, $p<0.05$). The overall treatment effect for chow intake also was statistically significant (Fig. 2; [$F(4,40)=15.3, p<0.05$]). Planned comparisons revealed that SCH39166 increased chow intake compared to injections of Veh/Veh. However, no doses of MSX-3 attenuated the effect of SCH39166; there were no significant differences found between the chow consumption in the SCH39166 alone condition vs. SCH39166 in combination with any dose of MSX-3. Furthermore, all doses of MSX-3 plus SCH39166 were significantly different from Veh/Veh (Tukey test, $p<0.05$).

Experiment 2: MSX-3 reversal of effect of D2 antagonist eticlopride

The effects of DA blockade induced by the D₂ antagonist eticlopride were substantially attenuated by co-administration of the adenosine A_{2A} antagonist MSX-3 (Fig. 3 and Fig. 4). In terms of lever pressing, the overall treatment effect was statistically significant (Fig. 3; [$F(4,40)=7.14, p<0.01$]). Compared to Veh/Veh, injection of 0.08 mg/kg eticlopride significantly reduced lever pressing as shown by planned comparisons ($p<0.01$). Planned comparisons also revealed that all three doses of MSX-3 co-administered with eticlopride significantly increased lever pressing compared to eticlopride administered alone ($p<0.01$). In addition, none of the doses of MSX-3 plus eticlopride significantly differed from Veh/Veh (Tukey test) at the $\alpha=0.05$ level. The overall treatment effect for chow intake also was statistically significant (Fig. 4; [$F(4,40)=6.75, p<0.01$]). Chow intake was significantly increased by eticlopride relative to treatment with Veh/Veh ($p<0.01$). Chow consumption was significantly reduced at all three doses of MSX-3 plus eticlopride compared to eticlopride alone ($p<0.05$ at the 0.5 mg/kg dose of MSX-3, $p<0.01$ at the 1.0 and 2.0 mg/kg doses of MSX-3). The effect was dose dependent, but appeared to be most robust at the 2.0 mg/kg dose of MSX-3. The two highest doses of MSX-3 (1.0 and 2.0 mg/kg) plus eticlopride did not significantly differ from Veh/Veh (Tukey test).

Comparisons across experiments 1–2: trend analyses and effect sizes

Across experiments 1 and 2, 0.2 mg/kg SCH39166 and 0.08 mg/kg eticlopride produced comparable effects on lever pressing and chow intake in the absence of MSX-3. Mean ($\pm$ SEM) number of lever presses in the groups that received SCH39166 or eticlopride plus vehicle was as follows: SCH39166 plus vehicle, 284.4 ($\pm$ 54.1); eticlopride plus vehicle, 338.9 ($\pm$ 121.1). These values did not differ from each other ($t=0.68, df=20, n.s.$). Mean ($\pm$ SEM) amount of chow intake (in grams) in the groups that received SCH39166 or eticlopride plus vehicle was as follows: SCH39166 plus vehicle, 5.05 ($\pm$ 0.39); eticlopride plus vehicle, 5.29 ($\pm$ 0.67). These values also did not differ from each other ($t=0.30, df=20, n.s.$).

In order to make comparisons between the effects of MSX-3 in the two experiments, data from the Veh/Veh condition were excluded, and two-way factorial ANOVAs (dose of MSX-3 vs. DA antagonist) with orthogonal analysis of trend were performed on the lever pressing and chow data. With the lever pressing data, there was a significant interaction between the dose of MSX-3 and the particular DA antagonist used [$F(3,60)=2.77, p<0.05$], and there also was a significant interaction of the linear trends [$F(1,20)=9.1, p<0.01$]. For the chow intake data,

factorial ANOVA also showed a significant interaction between the dose of MSX-3 and the DA antagonist used [$F(3,60)=3.3, p<0.05$] and a significant interaction of the linear trends [$F(1,20)=9.1, p<0.01$]. These analyses demonstrate that the dose/response functions for the effect of MSX-3 in the presence of eticlopride differed significantly from the functions observed when MSX-3 was co-administered with SCH39166. Effect size analyses also were performed on these data, based upon separate ANOVAs performed on each drug experiment and each measure, again excluding the Veh/Veh data. There were marked differences in effect sizes between the two experiments. For the lever pressing data, the effect size in the eticlopride experiment (i.e., the R^2 value of the ANOVA with the Veh/Veh data excluded) was 0.331, while in the SCH39166 experiment it was substantially lower ($R^2=0.117$). Similarly, the chow intake data also revealed a moderate effect size for the effect of MSX-3 in animals treated with eticlopride ($R^2=0.249$), but a very low one in animals treated with MSX-3 and SCH39166 ($R^2=0.016$). Finally, responding in rats that received MSX-3 plus a DA antagonist was compared with the condition in which they received Veh/Veh injections. Rats that received SCH39166 plus 1.0 mg/kg MSX-3 (i.e., the MSX-3 condition with the highest mean) pressed the lever at a rate that was only 35.5% of that seen after Veh/Veh injection, while rats that received 1.0 or 2.0 mg/kg MSX-3 with eticlopride responded at much higher levels (65.0% and 85.3%, respectively) compared to the combined vehicle control condition.

Discussion

In the present studies, a concurrent lever pressing/chow feeding task was used to investigate the interaction between an adenosine A_{2A} antagonist, MSX-3, and the selective DA D1 and D2 family antagonists SCH39166 (ecopipam) and eticlopride. These studies were undertaken to determine if the ability of an adenosine A_{2A} receptor antagonist to reverse the effect of a DA antagonist was dependent upon the subtype of DA receptor that was being blocked. Administered in the absence of MSX-3, the DA D1 antagonist SCH39166 and the D2 antagonist eticlopride both showed similar effects, i.e., there was a shift from lever pressing to chow intake, such that drug-induced decreases in lever pressing were accompanied by increases in chow intake. These effects of SCH39166 and eticlopride are consistent with those reported in a recent paper (Sink et al. 2008). Previous research has demonstrated that systemic injections of DA antagonists with varying selectivity profiles, including non-selective as well as D1 and D2 family selective drugs, all decreased lever pressing for food but substantially increased consumption of the concurrently available chow (Salamone et al. 1991, 1996, 2002; Cousins et al. 1994; Koch et al. 2000). Despite the fact that D1 and D2 family antagonists have been reported to have different effects on several behaviors, such as temporal patterning of food intake (Clifton et al. 1991; Clifton 1995), these drugs have consistently been shown to produce similar effects on response allocation as measured by the concurrent lever pressing/feeding task. However, this type of effect is not produced by all drug classes or conditions; the shift from lever pressing to chow intake was not seen in rats treated with the cannabinoid CB1 antagonists AM251 or AM4113 (Sink et al. 2008), which are putative appetite suppressants, or in animals treated with the appetite suppressants fenfluramine (Salamone et al. 2002), or amphetamine (Cousins et al. 1994). Moreover, these effects were not produced by pre-feeding to reduce food motivation (Salamone et al. 1991). This pattern of findings, together with other bodies of evidence, has been interpreted to mean that low-to-moderate doses of DA antagonists are not acting as appetite suppressants that generally blunt primary food motivation, but instead are acting on other processes (e.g., behavioral activation, instrumental response output, response allocation, effort-related processes; Salamone et al. 1991, 1997, 2002, 2003, 2005, 2007; Kelley et al. 2005; Baldo and Kelley 2007; Barbano and Cador 2007; Niv et al. 2007; Phillips et al. 2007; Floresco et al. 2008; Sink et al. 2008).

The adenosine A_{2A} antagonist MSX-3 was able to produce a substantial attenuation of the behavioral effects of the D2 antagonist eticlopride. Co-administration of MSX-3 with

eticlopride led to a very large increase in lever pressing compared to eticlopride alone. The reversal was virtually complete, as marked by the observations that rats that received the two highest doses of MSX-3 (i.e., 1.0 and 2.0 mg/kg) along with eticlopride showed significant increases in responding compared eticlopride alone, they failed to differ significantly from the Veh/Veh condition, and their mean number of responses increased to levels that were 65.0–85.3% of control levels. The chow intake data showed essentially the mirror image of this pattern. The effect of eticlopride was to produce a compensatory increase in chow intake in rats with suppressed lever pressing, and MSX-3 also was able to attenuate this effect. Rats that received the two highest doses of MSX-3 (i.e., 1.0 and 2.0 mg/kg) together with eticlopride showed significant decreases in chow intake compared to eticlopride alone, and their level of chow intake also failed to differ significantly from that shown under the Veh/Veh condition. Taken together, these data indicate that MSX-3 was able to produce a marked reduction in the behavioral effects of eticlopride in animals responding on this task. The present data are consistent with a recent study indicating that MSX-3 was able to reverse the effects of the DA antagonist haloperidol, which is somewhat D2 selective, in rats responding on the concurrent lever pressing/chow intake task (Farrar et al. 2007).

In contrast to the ability of MSX-3 to produce a robust reversal of the effects of the D2 antagonist eticlopride, MSX-3 only produced a partial effect on the actions of the D1 antagonist SCH39166. Although MSX-3 produced a modest increase in lever pressing in rats treated with SCH39166, none of the doses of MSX-3 were effective at reducing chow intake in SCH39166-treated rats. Also, several lines of evidence indicate that the effects of MSX-3 on lever pressing in rats treated with SCH39166 were much smaller than those produced in the eticlopride experiment. Trend analyses indicated that the linear component of the dose/response function for the effect of MSX-3 in the presence of eticlopride differed significantly from the function observed when MSX-3 was co-administered with SCH39166. In addition, the effect size for the ability of MSX-3 to increase lever pressing in eticlopride-treated rats was moderately large ($R^2=0.331$), while the effect size in the SCH39166 experiment was considerably lower ($R^2=0.117$). Finally, rats that received SCH39166 plus 1.0 mg/kg MSX-3 (i.e., the MSX-3 dose that produced the highest mean number of responses) pressed the lever at a rate that was only 35.5% of that seen after Veh/Veh injection, a level that significantly differed from Veh/Veh, while rats that received 1.0 or 2.0 mg/kg MSX-3 with eticlopride responded at much higher levels and did not differ from Veh/Veh. Taken together, the results of these experiments suggest that the adenosine A_{2A} antagonist MSX-3 was more effective at reversing the effect of a D2 antagonist than a D1 antagonist.

Few papers have focused upon the differential interactions between adenosine A_{2A} antagonists and relatively selective D1 or D2 family DA antagonists. Hauber et al. (2001) studied the ability of non-selective and A_{2A} selective adenosine antagonists to reverse the catalepsy induced by the D1 antagonist SCH23390 and the D2 antagonists sulpiride or raclopride. Systemic administration of the non-selective adenosine antagonist theophylline, as well as the A_{2A} selective drug 8-(3-chlorostyryl) caffeine (CSC), was able to reverse the catalepsy induced by systemic administration of either SCH23390 or raclopride. However, the results with intracranial administration were somewhat more mixed. Although intracranial administration of either CSC or MSX-3 was able to reverse the catalepsy induced by intrastratial injections of sulpiride, CSC was less effective than MSX-3 at reversing the cataleptic effects of SCH23390 (Hauber et al. 2001). These previous studies differ from the present work in several ways. The behavioral responses (catalepsy vs. operant behavior) were different, and the striatal subregions most closely associated with these effects are thought to be distinct. Although catalepsy is closely related to neostriatal DA function (e.g., Hauber et al. 2001), the shift in behavior from lever pressing to chow intake that is seen after systemic DA antagonism is not seen after local depletions of DA in anterior or ventrolateral neostriatum (Cousins et al. 1993), but instead has been observed after local DA depletion or antagonism in the nucleus

accumbens (Salamone et al. 1991; Cousins et al. 1993; Cousins and Salamone 1994; Sokolowski and Salamone 1998; Koch et al. 2000; Nowend et al. 2001). Finally, the doses of DA antagonists that are used to induce catalepsy are much higher than those used to produce the shift from lever pressing to chow intake in the concurrent lever pressing/feeding task. For example, Hauber et al. (2001) used 0.75 mg/kg SCH23390 and 1.25 mg/kg raclopride to induce catalepsy. By contrast, previous work has shown that SCH23390 shifts behavior in the concurrent lever pressing/chow feeding tasks at doses as low as 0.05 mg/kg IP (Cousins et al. 1994), and that raclopride is active in doses of 0.05–0.1 mg/kg IP (Salamone et al. 2002). Thus, the present study used low, sub-cataleptic doses of SCH39166 and eticlopride (Hietala et al. 1992; Fowler and Liou 1998), which may account for some of the differences seen between the results of experiments 1 and 2 and those of Hauber et al. (2001).

The differential effects of MSX-3 described above, which depended upon whether it was co-administered with a D1 or D2 family antagonist, could be related to the patterns of cellular distribution that are shown for adenosine and DA receptors in striatal areas such as nucleus accumbens. The present results are consistent with anatomical studies showing that striatal adenosine A_{2A} receptors are more likely to be colocalized in the same neurons with DA D2 family receptors than with D1 family receptors (Fink et al. 1992; Ferré 1997; Svenningsson et al. 1999; Hillion et al. 2002; Fuxe et al. 2003, 2007). Thus, it is possible that MSX-3 was easily able to produce a robust reversal of the effects of eticlopride because adenosine A_{2A} receptors and D2 receptors are localized on the same neurons (i.e., enkephalin positive medium spiny neurons), and these receptors interact directly either because of heterodimerization or convergence on to the same signal transduction pathways (Ferré 1997; Ferre et al. 2008; Svenningsson et al. 1999; Schiffmann et al. 1991). This observation is consistent with studies showing that adenosine A_{2A} receptor antagonists can reverse the expression of Fos-like immunoreactivity in medium spiny neurons that is induced by D2 antagonists (Pinna et al. 1999). In contrast, the relative segregation of D1 and adenosine A_{2A} receptors may make it more difficult for an A_{2A} antagonist to reverse the effects of a D1 antagonist such as SCH39166. Indeed, the nature of this interaction may change when high doses of DA antagonists are administered; as suggested by Hauber et al. (2001), it is possible that an adenosine A_{2A} antagonist is able to reverse the catalepsy produced by a D1 antagonist not because of direct actions on the same neuron, but rather because of interactions involving the overall circuitry of the basal ganglia, including non-striatal regions. Further investigation involving a broader range of behaviors and doses will be needed to provide a more complete characterization of the interactions between various subtypes of adenosine and DA receptors.

In summary, the adenosine A_{2A} antagonist MSX-3 was able to produce a substantial attenuation of the effects of the DA D2 antagonist eticlopride on performance of a concurrent lever pressing/chow feeding procedure. In contrast, MSX-3 was only able to produce a marginal increase in responding in rats treated with the D1 antagonist SCH39166. The modest increase in responding produced by MSX-3 in animals treated with SCH39166 was comparable to that seen in MSX-3 or caffeine-treated animals responding on a schedule that generates a low rate of responding (e.g., fixed interval 240; Randall et al., unpublished data). Overall, the present data are consistent with previous studies showing that adenosine A_{2A} antagonists can reverse the effects of DA D2 antagonists (Correa et al. 2004; Ishiwari et al. 2007; Salamone et al. 2008a), including studies that involve activational aspects of motivation and effort-related processes (Farrar et al. 2007). Furthermore, these studies shed light on the specific nature of the interaction between adenosine A_{2A} and DA D2 receptors, as opposed to D1 receptors. The fact that MSX-3 completely reversed the effects of eticlopride but had only a modest effect on the suppression of lever pressing induced by SCH39166 suggests that, in the presence of a D2 antagonist, adenosine A_{2A} antagonists are not merely stimulating responding in a general or non-specific way, i.e., MSX-3 was not simply producing a stimulant effect in the presence of eticlopride. Rather, the present studies indicate that adenosine A_{2A} antagonism can exert a

relatively specific reversal of a behavioral effect induced by a highly selective D2 antagonist. It is possible that studies of adenosine/DA interactions related to response allocation and effort will add to our understanding of the neurochemical mechanisms that underlie psychiatric symptoms such as psychomotor slowing, anergia, and fatigue in depression and other disorders (Salamone et al. 2006, 2007). Moreover, the results of these studies are consistent with the suggestion that adenosine A_{2A} antagonists may be clinically useful for treating the motor and motivational effects induced by D2 antagonists that are used as antipsychotic drugs in humans (Correa et al. 2004; Ishiwari et al. 2007; Salamone et al. 2008a, b).

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Fig. 1.

Effects of the adenosine A_{2A} antagonist MSX-3 on the lever pressing suppression produced by the DA D_1 receptor antagonist SCH39166. Mean ($\pm$ SEM) number of lever presses after treatment with vehicle or SCH39166 plus various doses of MSX-3 is shown. Veh/Veh (vehicle plus vehicle), SCH/Veh (0.2 mg/kg SCH39166 plus vehicle), SCH/0.5M (0.2 mg/kg SCH39166 plus 0.5 mg/kg MSX-3), SCH/1.0M (0.2 mg/kg SCH39166 plus 1.0 mg/kg MSX-3), and SCH/2.0M (0.2 mg/kg SCH39166 plus 2.0 mg/kg MSX-3). # p <0.01, different from vehicle/vehicle, planned comparison; * p <0.05, different from vehicle plus SCH39166, planned comparison

Fig. 2.

Effects of the adenosine A_{2A} antagonist MSX-3 on the increase in chow intake produced by the DA D1 receptor antagonist SCH39166. Mean ($\pm$ SEM) intake of lab chow (in grams) after treatment with vehicle or SCH39166 plus various doses of MSX-3 is shown. Veh/Veh (vehicle plus vehicle), SCH/Veh (0.2 mg/kg SCH39166 plus vehicle), SCH/0.5M (0.2 mg/kg SCH39166 plus 0.5 mg/kg MSX-3), SCH/1.0M (0.2 mg/kg SCH39166 plus 1.0 mg/kg MSX-3), and SCH/2.0M (0.2 mg/kg SCH39166 plus 2.0 mg/kg MSX-3). $\#p < 0.01$, different from vehicle/vehicle, planned comparison

Fig. 3.

Effects of the adenosine A_{2A} antagonist MSX-3 on the lever pressing suppression produced by the DA D2 receptor antagonist eticlopride (ETI). Mean ($\pm$ SEM) number of lever presses after treatment with vehicle or eticlopride plus various doses of MSX-3 is shown. Veh/Veh (vehicle plus vehicle), ETI/Veh (0.08 mg/kg eticlopride plus vehicle), ETI/0.5M (0.08 mg/kg eticlopride plus 0.5 mg/kg MSX-3), ETI/1.0M (0.08 mg/kg eticlopride plus 1.0 mg/kg MSX-3), and ETI/2.0M (0.08 mg/kg eticlopride plus 2.0 mg/kg MSX-3). # p <0.01, different from vehicle/vehicle, planned comparison; ** p <0.01, different from vehicle plus eticlopride, planned comparison

Fig. 4.

Effects of the adenosine A_{2A} antagonist MSX-3 on the increase in chow intake produced by the DA D2 receptor antagonist eticlopride (ETI). Mean ($\pm$ SEM) intake of lab chow (in grams) after treatment with vehicle or eticlopride plus various doses of MSX-3 is shown. Veh/Veh (vehicle plus vehicle), ETI/Veh (0.08 mg/kg eticlopride plus vehicle), ETI/0.5M (0.08 mg/kg eticlopride plus 0.5 mg/kg MSX-3), ETI/1.0M (0.08 mg/kg eticlopride plus 1.0 mg/kg MSX-3), and ETI/2.0M (0.08 mg/kg eticlopride plus 2.0 mg/kg MSX-3). # p <0.01, different from vehicle/vehicle, planned comparison; * p <0.05, different from vehicle plus eticlopride, planned comparison; ** p <0.01, different from vehicle plus eticlopride, planned comparison