Published in final edited form as:
Neuroscience. 2010 September 29; 170(1): 268–280. doi:10.1016/j.neuroscience.2010.05.068.

DIFFERENTIAL EFFECTS OF SELECTIVE ADENOSINE ANTAGONISTS ON THE EFFORT-RELATED IMPAIRMENTS INDUCED BY DOPAMINE D1 AND D2 ANTAGONISM

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Abstract

Mesolimbic dopamine (DA) is a critical component of the brain circuitry regulating behavioral activation and effort-related processes. Rats with impaired DA transmission reallocate their instrumental behavior away from food-reinforced tasks with high response requirements, and instead select less effortful food-seeking behaviors. Previous work showed that adenosine A_{2A} antagonists can reverse the effects of DA D_2 antagonists on effort-related choice. However, less is known about the effects of adenosine A_1 antagonists. Despite anatomical data showing that A_1 and D_1 receptors are co-localized on the same striatal neurons, it is uncertain if A_1 antagonists can reverse the effects DA D_1 antagonists. The present work systematically compared the ability of adenosine A_1 and A_{2A} receptor antagonists to reverse the effects of DA D_1 and D_2 antagonists on a concurrent lever pressing/feeding choice task. With this procedure, rats can choose between responding on a fixed ratio 5 lever-pressing schedule for a highly preferred food (i.e., high carbohydrate pellets) vs. approaching and consuming a less preferred rodent chow. The D_1 antagonist ecopipam (0.2 mg/kg IP) and the D_2 antagonist eticlopride (0.08 mg/kg IP) altered choice behavior, reducing lever pressing and increasing lab chow intake. Co-administration of the adenosine A_1 receptor antagonists DPCPX (0.375, 0.75, and 1.5 mg/kg IP), and CPT (3.0, 6.0, 12.0 mg/kg IP) failed to reverse the effects of either the D_1 or D_2 antagonist. In contrast, the adenosine A_{2A} antagonist KW-6002 (0.125, 0.25 and 0.5 mg/kg IP) was able to produce a robust reversal of the effects of eticlopride, as well as a mild partial reversal of the effects of ecopipam. Adenosine A_{2A} and DA D_2 receptors interact to regulate effort-related choice behavior, which may have implications for the treatment of psychiatric symptoms such as psychomotor slowing, fatigue or anergia that can be observed in depression and other disorders.

Keywords

operant; reinforcement; motivation; behavioral economics; behavioral activation; reward; decision making

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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 separate them from significant stimuli (Salamone 1991, 1992; Salamone et al. 1997, 2003, 2007; Salamone and Correa 2002; van de Bos et al. 2006). Several lines of evidence implicate dopamine (DA), particularly in nucleus accumbens, as a critical component of the brain circuitry regulating behavioral activation and effort-related processes (Salamone et al., 1991, 2003, 2005, 2007; Vezina et al., 2002; Zhang et al., 2003; Wakabayashi et al., 2004; Barbano and Cador, 2006, 2007; Cagniard et al., 2006; Phillips et al., 2007; Floresco et al., 2008; Salamone, 2010). The increased activity induced by periodic food presentation is accompanied by increases in accumbens DA release, and is reduced by DA antagonism and accumbens DA depletions (Salamone 1986, 1988; McCullough and Salamone 1992). Rats with accumbens DA depletions are very sensitive to ratio requirements in operant schedules (Sokolowski and Salamone 1998; Aberman and Salamone 1999; Correa et al. 2002; Ishiwari et al. 2004; Mingote et al. 2005), including progressive ratio schedules (Aberman et al. 1998; Hamill et al. 1999). Moreover, rats with impaired DA transmission show alterations in response allocation on tasks that measure effort-related choice behavior (Salamone et al. 1991, 1997, 2003, 2005, 2006, 2007). Studies of effort-related choice behavior typically offer animals alternative paths to obtain reinforcement, which involve cost/benefit trade-offs related to the work requirements for obtaining the reinforcer. Some investigations of effort-related choice have employed a T-maze barrier task (Salamone et al. 1994; Cousins et al. 1996; Walton et al. 2002, 2003; Denk et al. 2005; Floresco and Ghods-Sharifi 2007; Bardgett et al. 2009; Correa et al. 2009), and others have used effort discounting procedures (Floresco et al. 2008; Bardgett et al. 2009). Additional studies have employed a concurrent fixed ratio 5 (FR5)/chow feeding procedure (Salamone et al. 1991, 2002, 2003, 2007). With this task, rats can choose between responding on a FR5 lever-pressing schedule for a highly preferred food (i.e., high carbohydrate precision pellets) vs. approaching and consuming a freely available but less preferred food (rodent chow). Trained rats spend most of their time lever pressing for the preferred food, and eat very little of the concurrently available lab chow. Rats treated with relativity low doses of D_1 or D_2 family antagonists, or with intra-accumbens injections of D_1 or D_2 antagonists, show a suppression of food-reinforced lever pressing, but increased levels of chow intake (Salamone et al. 1991, 1996; 2002; Cousins et al. 1994; Koch et al. 2000; Nowend et al. 2001; Sink et al. 2008; Farrar et al. 2010). This task has been extensively studied, and considerable evidence indicates that the shift from lever pressing to chow intake that is induced by DA antagonism or accumbens DA depletions is not due to effects on appetite or food preference, and is not related to the kinds of forepaw motor control deficits that are seen after ventrolateral neostriatal DA depletions (Salamone et al. 1991, 1993, 2002, 2007, 2009; Cousins et al. 1993; Nowend et al. 2001; Sink et al. 2008).

Although mesolimbic DA is a critical component of the brain circuitry regulating work output and effort-related choice behavior (Salamone and Correa 2002; Salamone et al. 2003, 2005, 2006), other brain areas and transmitters also are involved (Walton et al. 2002, 2003; Floresco and Ghods-Sharifi 2007; Salamone et al. 2007; Farrar et al. 2008; Hauber and Sommer, 2009). Recent studies have implicated the purine nucleoside adenosine in this type of function (Salamone and Correa 2009). Striatal areas, including neostriatum as well as nucleus accumbens, have a high concentration of adenosine A_{2A} receptors (Jarvis and Williams 1989; Schiffmann et al. 1991; DeMet and Chicz-DeMet 2002; Ferre et al. 2004). There is a functional interaction between DA D_2 and adenosine A_{2A} receptors, which are co-localized on enkephalin-containing medium spiny neurons (Fink et al. 1992; Ferré 1997; Ferré et al., 1997, 2008b; Hillion et al. 2002; Fuxe et al. 2003). Frequently, this interaction has been investigated in connection with neostriatal motor functions that are 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 identified additional functions of the A_{2A} receptor related to cognition (Takahashi et al. 2008) and motivation (O'Neill and Brown 2006; Mingote et al. 2008; Font et al. 2008). It has been demonstrated that the adenosine A_{2A} agonist CGS 21680, when microinjected into the nucleus accumbens, produced effects on instrumental behavior and effort-related choice that resembled those produced by accumbens DA depletions or antagonism (Font et al. 2008; Mingote et al. 2008).

Several studies have shown that adenosine A_{2A} antagonists such as MSX-3 and KW-6002 are capable of reversing the effects of the DA D_2 antagonists haloperidol and eticlopride, including experiments that used the concurrent FR5/feeding choice procedure (Farrar et al. 2007; Worden et al. 2009; Salamone et al. 2009), and the T-maze barrier choice task (Mott et al. 2009; Correa et al. 2009). These observations are consistent with anatomical data showing that adenosine A_{2A} and DA D_2 family receptors are co-localized in the same medium spiny neurons (Fink et al. 1992; Ferré 1997; Hillion et al. 2002; Fuxe et al. 2003). Yet despite the growing body of evidence demonstrating that the effort-related effects of D_2 antagonists can be reversed by adenosine A_{2A} antagonists (Salamone and Correa 2009), less is known about the general pattern of the interaction between antagonists that act upon specific subtypes of DA and adenosine receptors, and how this interaction regulates effort-related choice behavior. A few studies have shown that the adenosine A_1 antagonist DPCPX could not reverse the effects of haloperidol on the concurrent FR5/feeding task (Salamone et al. 2009) or the T-maze barrier choice procedure (Mott et al. 2009). Nevertheless, the ability of adenosine antagonists with different patterns of receptor selectivity to reverse the effort-related effects of DA D_1 and D_2 family antagonists remains uncertain. Furthermore, in view of the fact that adenosine A_1 and DA D_1 receptors tend to be co-localized on the same striatal neurons (Ferré 1997, 2008; Ferré et al. 1997, 2005), it is particularly important to determine if A_1 antagonists are capable of reversing the effects of DA D_1 antagonists.

In view of these uncertainties about the overall pattern of interaction between selective adenosine and DA antagonists on effort-related choice, the current work was undertaken to examine the role of DA/adenosine receptor interactions using the concurrent lever pressing/chow feeding procedure. More specifically, the present experiments were conducted to determine if the ability of adenosine A_1 or A_{2A} antagonists to reverse the effects of DA antagonists is dependent upon the particular subtype of DA receptor that was being blocked. The adenosine A_1 antagonists DPCPX (0.375–1.5 mg/kg IP) and CPT (3.0–12.0 mg/kg IP) were studied for their ability to reverse the effects of the D_1 antagonist ecopipam (0.2 mg/kg IP) and the D_2 antagonist eticlopride (0.08 mg/kg IP). Both of these adenosine A_1 antagonists were investigated because evidence indicates that they may have different behavioral effects; although DPCPX generally fails to stimulate locomotion when administered on its own, CPT has been shown to induce locomotion in some studies (Martson et al. 1998), and also was reported to reverse some of the behavioral effects of haloperidol (Trevitt et al. 2009). In order to provide a direct and systematic comparison between the effects of adenosine A_1 and A_{2A} antagonism, the A_{2A} selective drug KW-6002 (0.125–0.5mg/kg IP) also was assessed for its ability to reverse the behavioral effects of ecopipam and eticlopride.

EXPERIMENTAL PROCEDURES

Subjects

Adult male, drug- naïve, Sprague- Dawley rats (Harlan Sprague-Dawley, Indianapolis, IN) were housed in a colony maintained at 23°C with 12 hour light/dark cycles (lights on at 0:700 h). Rats (N = 48) weighed 290 – 340 g at the beginning of the study, and were initially food deprived to 85% of their free-feeding body weight for operant training. Rats were fed

supplemental chow to maintain the food restriction throughout the study, with water available *ad libitum* in the home cages. Despite food restriction, rats were allowed modest weight gain throughout the experiment. All animal protocols were approved by the University of Connecticut institutional animal care and use committee, and followed NIH guidelines.

Pharmacological Agents and Selection of Doses

Eticlopride (S(−)-3-chloro-5-ethyl-N-[(1-ethyl-2-pyrrolidinyl)methyl]-6-hydroxy-2-methoxybenzamide hydrochloride) was obtained from Sigma Chemical Co. (St. Louis, MO) and SCH 39166 (ecopipam; (6aS-trans)-11-chloro-6,6a,7,8,9,13b-hexahydro-7-methyl-5H-benzo[d] naphtha[2,1-b]azepin-12-ol hydrobromide, obtained from Tocris, (Ellisville, MO) was dissolved in 0.9% saline. Ecopipam was used because it binds to D_1 receptors with high affinity and selectivity, but has little affinity for $5HT2_A$ and $5HT2_C$ receptors (Alburges et al. 1992). Saline was also used as the vehicle control for the eticlopride and ecopipam injections. SCH 23390 ((R)-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride) also was obtained from Tocris, and dissolved in saline. The adenosine A_{2A} antagonist used was KW-6002, which was generously donated by Lundbeck (Copenhagen, Denmark) and was dissolved in a DMSO/Tween-80/Saline solution. DPCPX (8-cyclopentyl-1,3-dipropylxanthine) was obtained from Tocris, and was dissolved in a 20% ethanol vehicle as in previous studies (Mott et al. 2009; Salamone et al. 2009). CPT (8-cyclopentyltheophylline; Sigma Chemical Co., St. Louis) was dissolved in 0.9% saline, which also was used as the vehicle control for CPT injections. All drug treatments were administered IP (see descriptions of individual experiments for drug injection schedule).

Doses of eticlopride and ecopipam used for the experiments were based upon previous research (Terry and Katz 1994; Clifton et al. 1995; Barrett et al. 2004; Sink et al., 2008; Worden et al., 2009) and on pilot studies. For this type of reversal study, picking a minimally significant dose of the DA antagonist does not ensure a large enough impairment in order to get a full dose/response curve for the reversal effect. The specific doses of each DA antagonist were selected in order to be high enough to produce a robust shift from lever pressing to chow intake (Sink et al. 2008), but low enough not to produce a general disruption of behavior. With eticlopride, the dose chosen (0.08 mg/kg) was slightly higher than the very lowest dose (0.05 mg/kg) that decreased lever pressing and increased chow intake in a previous study (Sink et al. 2008). With ecopipam (SCH 39166), the 0.2 mg/kg dose was also chosen based upon previous data showing that the 0.1 mg/kg dose produced a statistically significant but small decrease in lever pressing and increase in chow intake, but 0.2 mg/kg produced a more robust effect (Sink et al. 2008). Moreover, these doses of eticlopride and ecopipam were previously used in a reversal experiment (Worden et al. 2009). The dose range chosen for DPCPX and CPT was based upon doses listed in published behavioral studies involving IP administration in rats (Prediger et al. 2005; Aubel et al. 2007; Maione et al. 2007; Lobato et al. 2008; Karcz-Kubicha 2003; Marston et al, 1998; Salamone et al. 2009). Because some rats that received the combination of 12.0 mg/kg CPT plus eticlopride showed increased lever pressing compared to eticlopride alone, a second study was conducted to assess the effects of 24.0 mg/kg CPT and eticlopride. An additional study also was conducted to determine if DPCPX could reverse the effects of a D1 antagonist other than ecopipam; SCH 23390 was used for this study.

Behavioral Procedures

Behavioral sessions were conducted in operant conditioning chambers (28 cm × 23 cm × 23 cm; Med Associates). Rats were initially trained to lever press on a continuous reinforcement schedule (30-min sessions; 45-mg pellets, Bioserve, Frenchtown, NJ, were

used for all operant behavior tests) and then were shifted to the FR5 schedule (30-min sessions, 5 days/week) and trained for several additional weeks. Rats were then trained on the concurrent FR5/chow-feeding procedure. With this task weighed amounts of lab chow (Lab Diet, 5P00 Prolab RMH 3000, Purina Mills, St. Louis, MO; 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 levels of baseline lever pressing and chow intake (i.e., consistent responding over 1200 lever presses per 30 min), after which drug testing began. For most baseline days rats did not receive supplemental feeding, however, over weekends and after drug tests, rats usually received supplemental chow in the home cage. On baseline and drug treatment days, rats normally consumed all the operant pellets that were delivered from lever pressing during each session.

Experimental Procedures

Rats were trained on the concurrent FR5/chow-feeding procedure (as described above) before testing began, and each experiment employed different groups of rats. All six 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, with none of the treatment sequences repeated across different animals in the same experiment). Baseline (i.e. non-drug) sessions were conducted four additional days per week. The specific treatments and testing times for each experiment are listed below.

Ability of the A_1 antagonists DPCPX and CPT to reverse the effects of the D_1 antagonist ecopipam (SCH 39166)

On the test day, trained rats (n = 8) received the following treatments: 20 % ethanol vehicle (30 min before testing) plus saline vehicle IP (20 min before testing), 0.2 mg/kg ecopipam IP (20 min before testing) plus 20 % ethanol vehicle IP (30 min before testing), 0.2 mg/kg ecopipam IP (20 min) plus 0.375 mg/kg DPCPX IP (30 min), 0.2 mg/kg ecopipam IP (20 min) plus 0.75 mg/kg DPCPX IP (30 min), 0.2 mg/kg ecopipam IP (20 min) plus 1.5 mg/kg DPCPX IP (30 min). Because DPCPX was unable to reverse the effects of ecopipam, an additional experiment was conducted to determine if the same doses of DPCPX could reverse the effects of a different D_1 antagonist (SCH 23390; 0.1 mg/kg IP; dissolved in saline, injected 60 min before testing). This experiment was conducted to determine if the inability of DPCPX to reverse the effects of ecopipam were unique to the particular D_1 antagonist being used. For the CPT/ecopipam experiment, trained rats (n = 8) received the following treatments: saline vehicle (20 min before testing) plus saline vehicle IP (20 min before testing), 0.2 mg/kg ecopipam IP (20 min before testing) plus saline vehicle IP (20 min), 0.2 mg/kg ecopipam IP (20 min before testing) plus 3.0 mg/kg CPT IP (20 min), 0.2 mg/kg ecopipam IP (20 min) plus 6.0 mg/kg CPT IP (20 min), 0.2 mg/kg ecopipam IP (20 min) plus 12.0 mg/kg CPT IP (20 min).

Ability of the A_1 antagonists DPCPX and CPT to reverse the effects of the D_2 antagonist eticlopride

For the DPCPX/eticlopride experiment, trained rats (n = 8) received the folowing treatments: 20 % ethanol solution vehicle (30 min before testing) plus saline vehicle IP (30 min before testing), 0.08 mg/kg eticlopride IP (30 min before testing) plus 20 % ethanol solution vehicle IP (30 min before testing), 0.08 mg/kg eticlopride IP (30 min before testing) plus 0.375 mg/kg DPCPX IP (30 min before testing), 0.08 mg/kg eticlopride IP (30 min before testing) plus 0.75 mg/kg DPCPX IP (30 min before testing), 0.08 mg/kg eticlopride IP (30 min) plus 1.5 mg/kg DPCPX IP (30 min). For the CPT/eticlopride experiment, trained rats (n = 8) received the following treatments: 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), 0.08 mg/kg eticlopride IP (30 min before testing) plus 3.0 mg/kg CPT IP (20 min before testing), 0.08 mg/kg eticlopride IP (30 min) plus 6.0 mg/kg CPT IP (20 min), 0.08 mg/kg eticlopride IP (30 min) plus 12.0 mg/kg CPT IP (20 min). Because some animals that received the combination of 12.0 mg/kg CPT plus eticlopride showed increased lever pressing compared to eticlopride alone, a second experiment was conducted to assess the effects of a higher dose (24.0 mg/kg CPT) vs. eticlopride. On two successive weeks, rats (n = 8) received each of the following treatments in a randomly varied order: 0.08 mg/kg eticlopride IP (30 min before testing) plus saline vehicle IP (20 min before testing), and 0.08 mg/kg eticlopride IP (30 min) plus 24.0 mg/kg CPT IP (20 min).

Ability of the A_{2A} antagonist KW-6002 to reverse the effects of the D_1 antagonist ecopipam (SCH 39166) and the D_2 antagonist eticlopride

Trained rats (n = 8) received the flowing treatments in the KW-6002/ecopipam experiment: DMSO/Tween-80/Saline vehicle (20 min before testing) plus saline vehicle IP (20 min before testing), 0.2 mg/kg ecopipam (20 min before testing) plus saline vehicle IP (20 min before testing), 0.2 mg/kg ecopipam IP (20 min before testing) plus 0.125 mg/kg KW-6002 IP (20 min before testing), 0.2 mg/kg ecopipam IP (20 min) plus 0.25 mg/kg KW-6002 IP (20 min), 0.2 mg/kg ecopipam IP (20 min) plus 0.5 mg/kg KW-6002 IP (20 min). In the KW-6002/eticlopride study, trained rats (n = 8) received the flowing treatments: DMSO/ Tween-80/Saline vehicle (20 min before testing) plus saline vehicle IP (30 min before testing), 0.08 mg/kg eticlopride IP (30 min before testing) plus saline vehicle IP (20 min before testing), 0.08 mg/kg eticlopride IP (30 min before testing) plus 0.125 mg/kg KW-6002 IP (20 min), 0.08 mg/kg eticlopride IP (30 min) plus 0.25 mg/kg KW-6002 IP (20 min), 0.08 mg/kg eticlopride IP (30 min) plus 0.5 mg/kg KW-6002 IP (20 min).

Statistical Analyses

Total number of lever presses and gram quantity of chow intake from the 30 min sessions were analyzed with repeated measures of 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 eticlopride or ecopipam vehicle control group (Keppel, 1991). For these comparisons, α level was kept at 0.05 because the number of comparisons was restricted to the number of treatments minus one. With this analysis, each condition that combined eticlopride or ecopicpam plus adenosine antagonist was compared with its respective eticlopride or ecopipam vehicle condition using the planned comparisons. Effect size calculations (R^2 values; Keppel, 1991) were performed to assess the magnitude of the reversal effect; these analyses were conducted by removing the vehicle plus vehicle condition, and calculating the R^2 value for the four treatments that included a DA antagonist injection. With this type of calculation, the magnitude of the treatment effect is independent of the number of animals, and is 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

Ability of DPCPX and CPT to reverse the effects of D_1 antagonism

DPCPX failed to attenuate the effects of ecopipam (SCH 39166) on the concurrent lever-pressing/chow feeding task (Fig. 1). There was a overall significant effect of drug treatment on lever pressing [$F(4,28) = 20.539$; $p < 0.001$]. Planned comparisons revealed that ecopipam significantly reduced lever pressing compared to vehicle control ($p< 0.05$), but co-administration of DPCPX with ecopipam did not produce a significant increase in lever

pressing compared to ecopipam plus vehicle at any dose. There also was an overall significant effect of drug treatment on chow intake [F(4,28) =9.088, p < 0.001]. Planned comparisons revealed that ecopipam significantly increased chow increased compared to vehicle control ($p< 0.05$), but co-administration of DPCPX with ecopipam did not significantly decrease chow intake compared to ecopipam plus vehicle. An additional study assessed the ability of DPCPX to reverse the effects of another D1 antagonist, SCH 23390 (Table 1). There was a overall significant effect of drug treatment on lever pressing [F (4,28) = 27.52; $p< .001$]. Planned comparisons revealed that SCH 23390 produced a significant reduction in lever pressing compared to vehicle control ($p< 0.05$), but co-administration of DPCPX with SCH 23390 did not significantly increase lever pressing compared to SCH 23390 plus vehicle (Table 1). There also was a overall significant effect of drug treatment on chow consumption [F (4,28) = 6.99; $p< 0.05$]. SCH 23390 significantly increased chow intake compared to vehicle control ($p< 0.05$), but co-administration of DPCPX with SCH 23390 did not significantly increase lever pressing compared to SCH 23390 plus vehicle. For the CPT/ecopipam experiment (Fig. 2), there was a overall significant effect of drug treatment [F (4,28) = 19.469 $p < .001$]. Planned comparisons revealed that ecopipam significantly reduced lever pressing compared to vehicle control ($p< 0.05$). Co-administration of CPT with ecopipam did not significantly increase lever pressing compared to ecopipam plus vehicle. There also was a significant effect of drug treatment on chow intake [F(4,28) = 8.196, p < .001]. Planned comparisons revealed that ecopipam significantly increased chow intake compared to vehicle control ($p< 0.05$). Co-administration of CPT with ecopipam did not produce a significant decrease in chow consumption compared to ecopipam plus vehicle ($p> 0.05$).

Ability of DPCPX and CPT to reverse the effects of D_2 antagonism

In the DPCPX/eticlopride study (Fig. 3), there was a significant overall effect of drug treatment [F (4,28) = 113.248 $p< .001$]. Planned comparisons revealed that eticlopride significantly lowered lever pressing compared to vehicle control ($p< 0.05$), but co-administration of DPCPX with eticlopride did not significantly increase lever pressing compared to eticlopride plus vehicle. There also was a significant effect of drug treatment on chow intake [F(4,28) = 8.449, p < .001]. Eticlopride significantly increased chow intake compared to vehicle control (planned comparisons, $p< 0.05$), but co-administration of DPCPX with eticlopride did not significantly affect chow intake compared to eticlopride plus vehicle. CPT also failed to significantly increase lever pressing and decrease chow intake in eticlopride-treated rats (Fig. 4). With lever pressing, there was a overall significant effect of drug treatment [F (4,28) = 17.349 $p< 0.01$]. Planned comparisons revealed that eticlopride significantly reduced lever pressing compared to vehicle control ($p< 0.05$), but co-administration of CPT with eticlopride did not significantly affect lever pressing compared to eticlopride plus vehicle. There also was an overall significant effect of drug treatment on chow intake [F(4,28) = 10.921 p < .001]. Planned comparisons showed that eticlopride produced a significant increase in chow consumption compared to vehicle control ($p< 0.05$), and co-administration of CPT with eticlopride did not significantly decrease chow consumption compared to eticlopride plus vehicle ($p> 0.05$). However, some of the rats that received 12.0 mg/kg CPT plus eticlopride did show increased lever pressing and decreased chow intake relative to eticlopride plus vehicle. For that reason, a second experiment was performed in which a higher dose of CPT was used. This study revealed that rats that received 24.0 mg/kg CPT plus eticlopride did not differ from eticlopride plus vehicle, either in terms of lever pressing (Mean (± SEM) number of lever presses: eticlopride plus vehicle, 7.0 (±2.62); eticlopride plus 24.0 mg/kg CPT, 69.5 (±36.10); t = −1.69, df = 7, n.s.) or chow intake (Mean (± SEM) amount of chow intake (grams): eticlopride plus vehicle, 4.1 (±0.91); eticlopride plus 24.0 mg/kg CPT, 3.7 (±0.89); t = 0.29, df = 7, n.s.).

Ability of KW-6002 to reverse the effects of D1 or D2 antagonism

KW-6002 produced a partial reversal of the effects of ecopipam (Fig. 5). There was a overall significant effect of drug treatment on lever pressing [F (4,28) = 8.270 $p < 0.01$]. Planned comparisons showed that ecopipam produced a significant reduction in lever pressing compared to vehicle control ($p < 0.05$). Co-administration of KW-6002 with ecopipam significantly increased lever pressing compared to ecopipam plus vehicle, with the highest dose of KW–6002 (0.5mg/kg) increasing lever pressing relative to ecopipam plus vehicle ($p < 0.05$). There also was an overall significant effect of drug treatment on chow intake [$F(4,28) = 5.280$, $p < .001$]. Ecopipam produced a significant increase in chow consumption compared to vehicle control ($p < 0.05$). Administration of KW-6002 with ecopipam did not reverse the increase in chow intake produced by ecopipam plus vehicle. KW-6002 produced a robust and significant reversal of the effects of eticlopride on the concurrent lever pressing/chow-feeding task (Fig. 6). There was on overall effect of drug treatment on lever pressing [$F(4,28) = 11.035$, $p < 0.001$]. Eticlopride produced a significant reduction in lever pressing compared to vehicle control (planned comparison; $p < 0.05$). Co-administration of KW-6002 with eticlopride produced a significant increase in lever pressing at all doses (0.125, 0.25, and 0.5 mg/kg) compared to eticlopride plus vehicle ($p < 0.05$). There also was a significant overall effect of treatment on chow intake [$F(4,28) = 10.029$, $p < 0.001$]. Planned comparisons showed that eticlopride significantly increased chow intake compared to vehicle control ($p < 0.05$). Co-administration of KW-6002 with eticlopride produced a significant decrease in chow consumption at the two highest doses (0.25mg/kg and 0.5mg/kg) compared to eticlopride plus vehicle ($p < 0.05$).

Analysis of Effect Sizes

Table 2 shows the results of the effect size analyses for all the reversal effects in the DPCPX, CPT and KW-6002 experiments with ecopipam and eticlopride. By far, the largest effect size was shown for the ability of KW-6002 to reverse the effects of eticlopride.

DISCUSSION

Motivation is a complex and multifaceted process (Salamone 2010b), and a number of approaches have been used to study the impact of drugs on choice performance under conditions in which animals can select between multiple reinforcers that can be obtained via distinct instrumental behaviors (Routtenberg and Bulloch 1971; Salamone et al. 1994; Floresco et al. 2008; Bardgett et al. 2009). In the present studies, with rats responding on the concurrent FR5/chow feeding choice task, antagonism of either D_1 or D_2 receptors produced a substantial alteration in the relative allocation of behavior, decreasing lever pressing but increasing chow intake. The present results are consistent with previous studies showing that low-to-moderate doses of DA antagonists with varying degrees of selectivity, including cis-flupenthixol, SCH 23390, SCH 83566, haloperidol and raclopride, as well as ecopipam (SCH 39166) and eticlopride, all decrease lever pressing and increase chow intake in rats responding on this task (Salamone et al. 1991, 2002; Cousins et al. 1994; Sink et al. 2008). Because the present study was focused upon the interaction between DA and adenosine antagonists, only a single dose of each DA antagonist was used; nevertheless, the present doses were selected from a previous study that included a wider dose range for both ecopipam and eticlopride (Sink et al. 2008), and are the same doses as those used in a previous study of adenosine/DA interactions (Worden et al. 2009). Research with genetically altered mice also has shown that knockdown of the DA transporter, which elevates extracellular DA levels, can produce the opposite effect in animals tested on this task, i.e., increases in lever pressing and decreases in chow intake (Cagniard et al. 2006).

Several studies have been conducted to assess the validity of the concurrent lever pressing/chow intake choice task for assessing effort-related choice behavior. Attachment of higher ratio requirements (up to FR20) caused animals that were not drug treated to shift from lever pressing to chow intake (Salamone et al. 1997), indicating that this task is sensitive to lever pressing work requirements. Considerable evidence indicates that the shift from lever pressing to chow intake induced by interference with DA transmission is not due to a suppression of appetite for food or a change in food preference. Systemic or intra-accumbens injections of the DA antagonists haloperidol, SCH 23390 and sulpiride at doses that cause the shift from lever pressing to chow intake did not affect intake of either operant pellets or chow, and did not alter preference for the two types of food (Salamone et al. 1991; Koch et al., 2000). Future research should also study the effects of eticlopride and ecopipam on food preference. Additional studies have shown that chow intake is not generally affected by accumbens DA depletions (Koob et al., 1978; Salamone et al., 1993), or by injections of either D_1 or D_2 family antagonists into accumbens core or shell subregions (Baldo et al. 2002). Furthermore, the effects of DA antagonists on the concurrent choice procedure do not resemble those produced by prefeeding to reduce food motivation (Salamone et al. 1991), or appetite suppressant drugs such as amphetamine (Cousins et al. 1994), fenfluramine (Salamone et al. 2002) or CB1 antagonists (Sink et al., 2008); these appetite-related manipulations all fail to increase chow intake at doses that suppress food-reinforced lever pressing. In addition, several studies have demonstrated that the shift from lever pressing to chow intake that is induced by low doses of DA antagonists or accumbens DA depletions is not occurring because of gross impairments in the execution of motor acts that are necessary for lever pressing. DA depletions in ventrolateral neostriatum induce impairments in various markers of forepaw motor control, including grasping, forepaw usage during feeding, feeding rate, and lever press response duration (Salamone et al. 1993; Cousins and Salamone 1996), however, ventrolateral neostriatal DA depletions do not produce the shift from lever pressing to chow intake (Cousins et al. 1993). Instead, rats with ventrolateral striatal DA depletions show a suppression of both lever pressing and chow intake (Cousins et al. 1993). In contrast, conditions that decrease lever pressing and increase chow intake, such as low doses of DA antagonists or accumbens DA depletions, do not impair forepaw usage during feeding, food handling, or feeding rate (Salamone et al. 1990, 1993). Moreover, injections of DA D_1 or D_2 family antagonists into nucleus accumbens core and shell that produced the shift from lever pressing to chow intake did not increase lever press response duration (Nowend et al. 2001). These observations, coupled with results obtained from T-maze barrier choice tasks and discounting procedures, are generally interpreted to mean that low-to-moderate doses of DA antagonists and accumbens DA depletions or antagonism are not acting to suppress appetite or alter food preference, are not producing choice impairments that are dependent upon alterations in delay discounting, and are not producing gross impairments in response capacity, but instead are acting on behavioral arousal, activation, or effort-related processes (Salamone et al., 1991, 1997, 2002, 2003, 2005, 2007, 2009, 2010; Salamone and Correa 2002, 2009; Winstanley et al. 2005; Cagniard et al., 2006; 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; Bardgett et al., 2009; Salamone 2010a,b).

As described above, anatomical studies have demonstrated that adenosine A_1 receptors are co-localized with DA D_1 receptors in both ventral and dorsal striatal medium spiny neurons (Ferre 1997). Despite this post-synaptic co-localization pattern, the present studies demonstrated that injections of the A_1 antagonists DPCPX and CPT failed to reverse the behavioral effects of the DA D_1 antagonist ecopipam (SCH 39166). These results were not an artifact of using ecopipam as the D_1 antagonist, because similar results were obtained when DPCPX was tested for its effects in rats treated with SCH 23390 (Table 1). In addition, the dose ranges for DPCPX and CPT that were used in the present experiments, though ineffective in terms of reversing the actions of ecopipam and eticlopride, were

nevertheless effective in studies using other behaviors (Prediger et al. 2005; Aubel et al. 2007; Maione et al. 2007; Lobato et al. 2008; Karcz-Kubicha 2003; Marston et al, 1998). Of course, this is not to say that drugs that act on A_1 and D_1 receptors do not interact; there is behavioral evidence of A_1/D_1 receptor interactions from studies involving DA agonists. For example, CPT enhanced the locomotor stimulation produced by the D_1 partial agonist SKF 38393, but not the D_2 agonist quinpirole, in DA depleted animals (Popoli et al., 1996). Nevertheless, the present results indicate that systemic A_1 antagonism does not reverse the effects of systemic D_1 antagonism on operant behavior. There could be several reasons why CPT and DPCPX were unable to reverse the effects of ecopipam. Even though A_1 and D_1 receptors are co-localized postsynaptically on substance-P containing medium spiny neurons, form heteromeric complexes, and converge onto the same signal transduction pathways (Ferré et al. 1997, 2001, 2008b; Fuxe et al., 2007), it also is true that there are a considerable number of pre-synaptic A_1 receptors (Ferre, 2008; Ferré et al. 2008a). Thus, it is possible that some of the presynaptic release-modulating effects of A_1 antagonists work against the postsynaptic effects of A_1 blockade. Furthermore, it should be emphasized that there is a widespread non-striatal distribution of A_1 receptors (Svenningson et al., 1999; Ferré 2008), and that actions on these non-striatal sites could act to cancel out the effects of accumbens A_1 receptor antagonism.

In addition to being ineffective at reversing the actions of the D_1 antagonist ecopipam, DPCPX and CPT also did not significantly affect lever pressing or chow intake in eticlopride-treated rats. The results with DPCPX are consistent with previous reports showing that this drug failed to reverse the effects of haloperidol on effort-related choice behavior (Mott et al., 2009; Salamone et al., 2009). CPT injected in the dose range of 3.0–12.0 mg/kg did not significantly increase lever pressing or decrease chow intake in eticlopride-treated rats in the main study, and an additional experiment showed that 24.0 mg/kg CPT also was ineffective. However, some eticlopride-treated rats that received 12.0 mg/kg CPT did show increased lever pressing. A similar pattern was reported in a recent paper that studied the effects of CPT and DPCPX on the suppression of locomotor activity induced by eticlopride (Collins et al., submitted). This overall pattern suggests that CPT, unlike DPCPX, may have produced a mild partial reversal of the effects of eticlopride. CPT has lower A_1 vs. A_{2A} selectivity than DPCPX (Maemoto et al., 1997), and also can have different behavioral effects (Marston et al., 1998). Nevertheless, the magnitude of the reversal produced by CPT, as measured by the effect size ($R^2 = 0.10$), was still very small.

The only drug that significantly increased lever pressing in rats treated with a DA antagonist was the adenosine A_{2A} antagonist KW-6002. This drug produced a significant but small increase in lever pressing in rats treated with ecopipam, which is consistent with previous results obtained with the adenosine A_{2A} antagonist MSX-3 (Worden et al., 2009). Thus, despite the anatomical data indicating that A_{2A} and D_1 receptors are not generally co-localized on the same medium spiny neurons, it appears that A_{2A} antagonism can consistently produce a mild partial reversal of the effects of D_1 antagonism. Since adenosine A_{2A} receptors and D_1 receptors are relatively segregated on different populations of cells, any interactions between them are likely to involve indirect effects on basal ganglia circuitry, rather than direct actions on the same neuron (Hauber et al., 2001; Pollack and Fink 1996; Worden et al., 2009; Collins et al., in press). The most robust reversal effect observed in the present paper was shown in the experiment with KW-6002 and eticlopride. KW-6002 produced substantial increases in lever pressing and decreases in chow intake in eticlopride-treated rats (Figures 5–6; Table 2). These results are consistent with a growing number of studies demonstrating that adenosine A_{2A} antagonists can reverse the effects of DA D_2 antagonists on effort-related choice behavior in studies using the concurrent choice task (Farrar et al., 2007, 2010; Worden et al., 2009; Salamone et al., 2009), and the T-maze barrier task (Mott et al., 2009; Correa et al. 2009). Furthermore, they are part of a much

larger body of evidence demonstrating that A_{2A} antagonism can generally reverse the effects of D_2 antagonism across a wide range of behavioral contexts, including tasks that involve functions related to ventral and dorsal striatum (Correa et al., 2004; Ishiwari et al., 2007; Salamone et al., 2008a,b; Collins et al. in press). Adenosine A_{2A} receptors are located on enkephalin-positive striatal neurons that also express DA D_2 receptors (Schiffman et al., 1991; Fink et al., 1992; Ferré 1997; Svenningsson et al., 1999; Wang et al., 2000; Hettinger et al., 2001; Chen et al., 2001). A_{2A} and D_2 receptors are capable of forming hetromers, and also converge onto the same cAMP-related signal transduction pathways (Fink et al., 1992; Ferré 1997; Ferré et al., 1997, 2004, 2008b; Svenningsson 1999; Hillion et al., 2002; Fuxe et al., 2003). Recent evidence indicates that doses of adenosine A_{2A} antagonists that reverse the effects of DA D_2 antagonists on tremor and effort-related choice behavior also can reverse the D_2-antagonist-induced enhancement of c-Fos expression in neostriatum (Betz et al., 2009) and nucleus accumbens core (Farrar et al., 2010), respectively. These studies provide a potential neural marker of the direct cellular interaction between D_2 and adenosine A_{2A} receptors.

CONCLUSION

In summary, the present experiments indicate that, despite the co-localization of adenosine A_1 and D_1 receptors in striatal medium spiny neurons, the adenosine A_1 antagonists DPCPX and CPT failed to reverse the effects of the DA D_1 receptor antagonist ecopipam on the concurrent lever pressing/feeding choice task. In general, the effects of the D_1 antagonist ecopipam were harder to reverse with adenosine antagonists than the effects of the D_2 antagonist eticlopride. Furthermore, the adenosine A_{2A} antagonist KW-6002 produced the most robust effects in rats treated with DA antagonists, inducing a partial reversal of the effects of ecopipam and a nearly complete reversal of the effects of eticlopride. These findings can help to explicate the complex nature of the interactions between adenosine and DA receptor antagonists with different patterns of receptor selectivity, and shed light on the neural circuitry involved in behavioral activation and effort-related choice behavior. Future studies should use additional behavioral methods, including discounting tasks and other discrete-trial procedures, to assess the interaction between DA and adenosine (Bardgett et al. 2009; Floresco et al. 2008; Gan et al. 2010). Moreover, these studies also have potential clinical relevance. In humans, symptoms such as anergia, psychomotor slowing, and fatigue reflect pathologies in behavioral activation. These symptoms 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). Thus, the present research may contribute to the development of novel treatments for effort-related disorders in humans, and clearly indicate that adenosine A_{2A} antagonists could be useful for attenuating some of the motivational and other behavioral side effects of D_2 antagonists (Correa et al. 2004; Salamone et al. 2008a,b; Varty et al., 2008).

Acknowledgments

This work was supported by a grant to J.S. from the National Institute of Mental Health (MH078023), and to Merce Correa from Conselleria de Empresa, Universitat i Ciència. Generalitat Valenciana. (BEST/2009/157).

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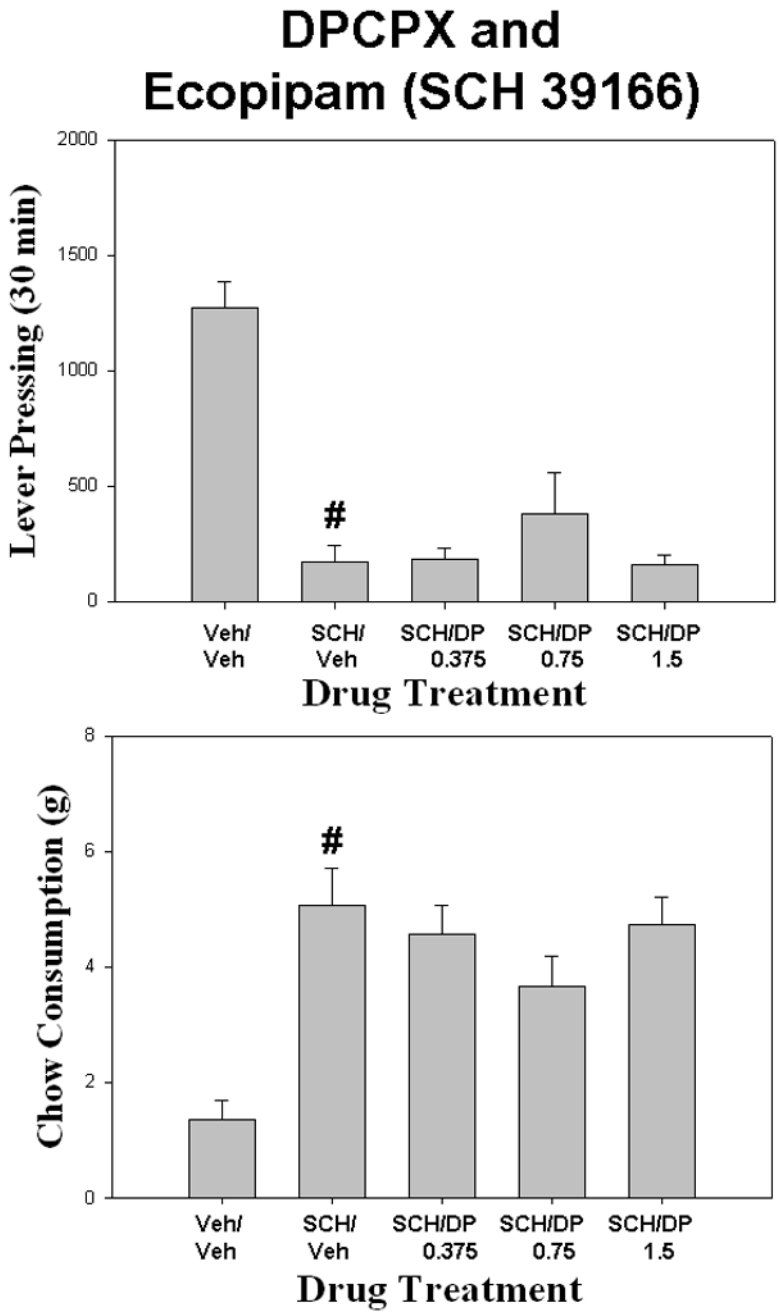

Figure 1.

The effects of the adenosine A_1 antagonist DPCPX on ecopipam-induced changes in performance on the concurrent lever pressing/chow feeding procedure. Rats received IP injections of vehicle plus vehicle (Veh/Veh), 0.2 mg/kg ecopipam (SCH 39166) plus vehicle (SCH/Veh), and ecopipam (SCH 39166) plus 0.375, 0.75, or 1.5, mg/kg doses of DPCPX (SCH/DP). A. Mean (± SEM) number of lever presses (FR5 schedule) during the 30 min session. B. Mean (± SEM) gram quantity of chow intake. Ecopipam significantly decreased lever pressing and increased chow intake relative to vehicle (# $p < 0.05$).

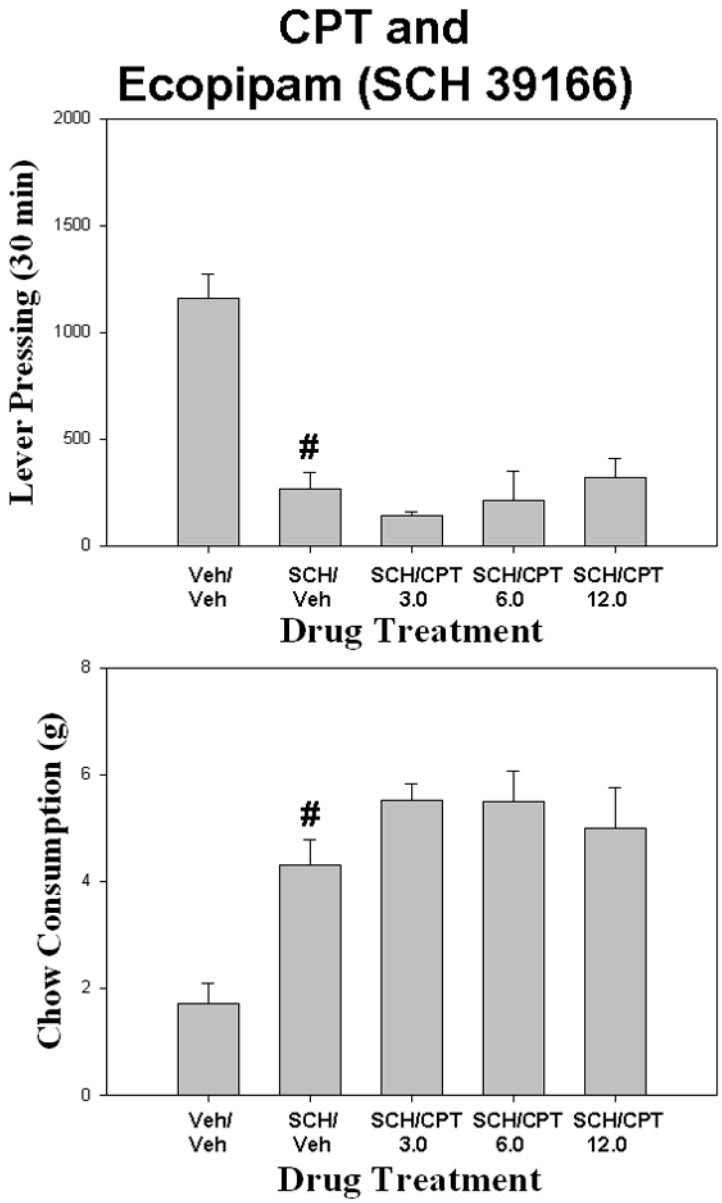

Figure 2.

The effects of the adenosine A_1 antagonist CPT on ecopipam-induced changes in performance on the concurrent lever pressing/chow feeding procedure. Rats received IP injections of vehicle plus vehicle (Veh/Veh), 0.2 mg/kg ecopipam (SCH 39166) plus vehicle (SCH/Veh), and ecopipam plus 3.0, 6.0, or 12.0 mg/kg doses of CPT (SCH/CPT). A. Mean (± SEM) number of lever presses (FR5 schedule) during the 30 min session. B. Mean (± SEM) gram quantity of chow intake. Ecopipam significantly decreased lever pressing and increased chow intake relative to vehicle (# $p < 0.05$).

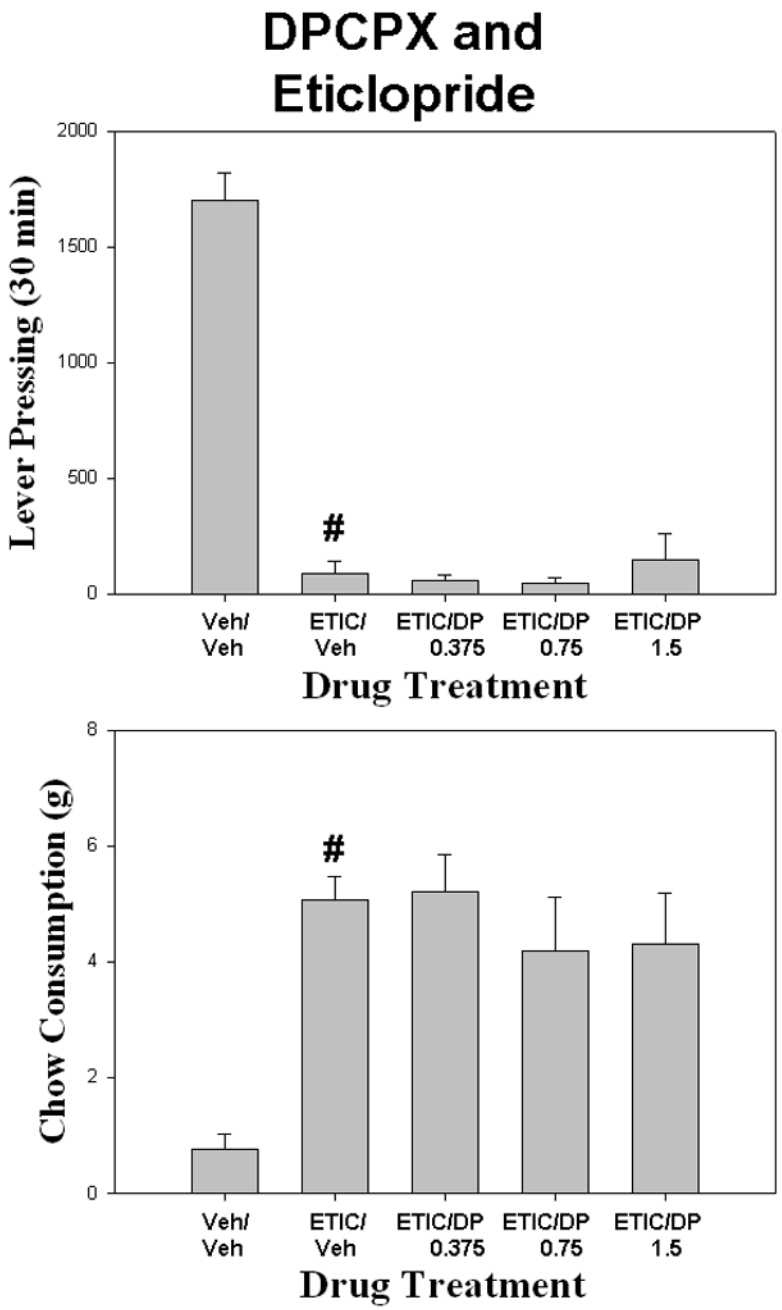

Figure 3.

The effects of the adenosine A_1 antagonist DPCPX on eticlopride-induced changes in performance on the concurrent lever pressing/chow feeding procedure. Rats received IP injections of vehicle plus vehicle (Veh/Veh), 0.08 mg/kg eticlopride plus vehicle (ETIC/Veh), and eticlopride plus 0.375, 0.75, or 1.5, mg/kg doses of DPCPX (ETIC/DP). A. Mean (± SEM) number of lever presses (FR5 schedule) during the 30 min session. B. Mean (± SEM) gram quantity of chow intake. Eticlopride significantly decreased lever pressing and increased chow intake relative to vehicle (# $p < 0.05$).

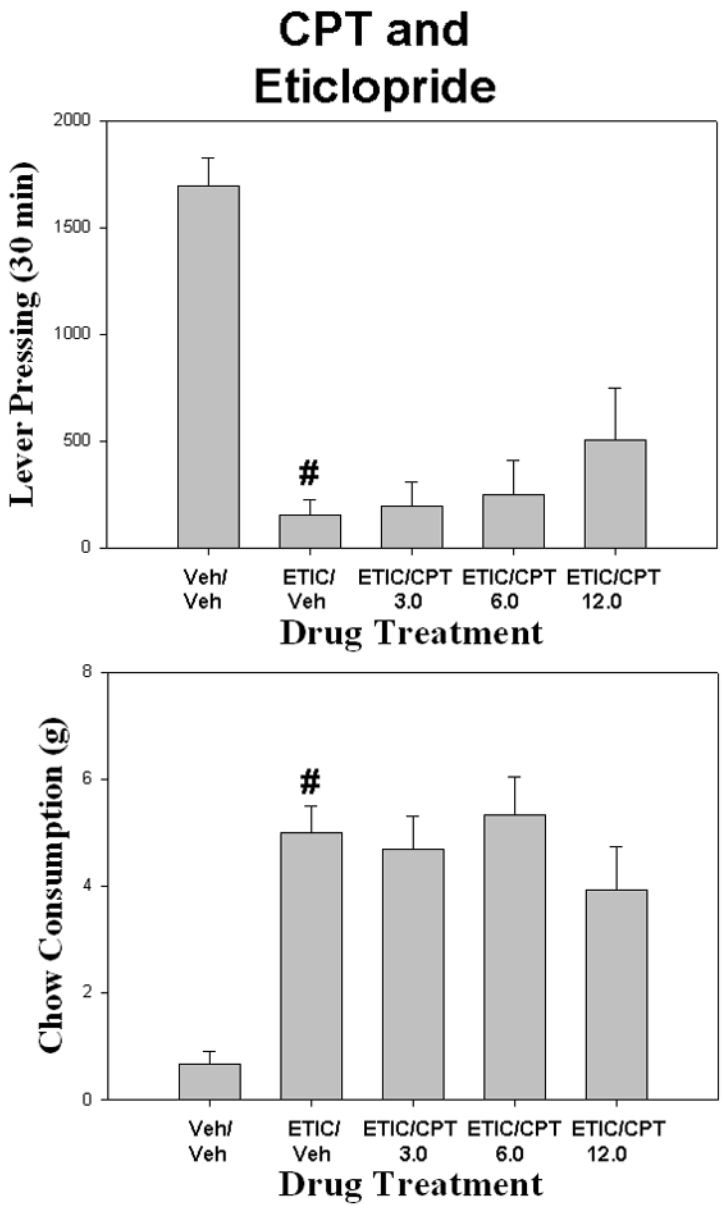

Figure 4.

The effects of the adenosine A_1 antagonist CPT on eticlopride-induced changes in performance on the concurrent lever pressing/chow feeding procedure. Rats received IP injections of vehicle plus vehicle (Veh/Veh), 0.08 mg/kg eticlopride plus vehicle (ETIC/Veh), and eticlopride plus 3.0, 6.0, or 12.0 mg/kg doses of CPT (ETIC/CPT). A. Mean (± SEM) number of lever presses (FR5 schedule) during the 30 min session. B. Mean (± SEM) gram quantity of chow intake. Ecopipam significantly decreased lever pressing and increased chow intake relative to vehicle (# $p < 0.05$).

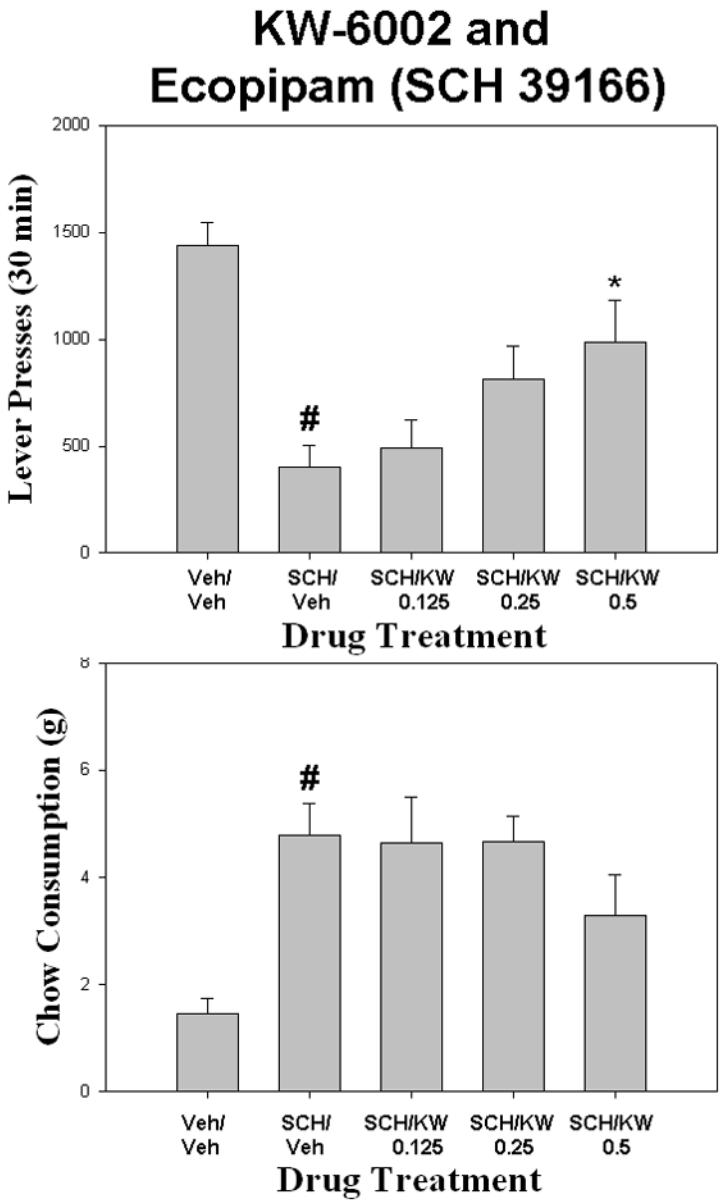

Figure 5.

The effects of the adenosine A_{2A} antagonist KW-6002 on ecopipam-induced changes in performance on the concurrent lever pressing/chow feeding procedure. Rats received IP injections of vehicle plus vehicle (Veh/Veh), 0.2 mg/kg ecopipam (SCH 39166) plus vehicle (SCH/Veh), and ecopipam (SCH 39166) plus 0.125, 0.25, or 0.5, mg/kg doses of KW-6002 (SCH/KW). A. Mean (± SEM) number of lever presses (FR5 schedule) during the 30 min session. B. Mean (± SEM) gram quantity of chow intake. Ecopipam significantly decreased lever pressing and increased chow intake relative to vehicle (# $p < 0.05$). KW-6002 administered to ecopipam-treated rats significantly increased lever pressing at the highest dose relative to treatment with ecopipam alone (* $p < 0.05$).

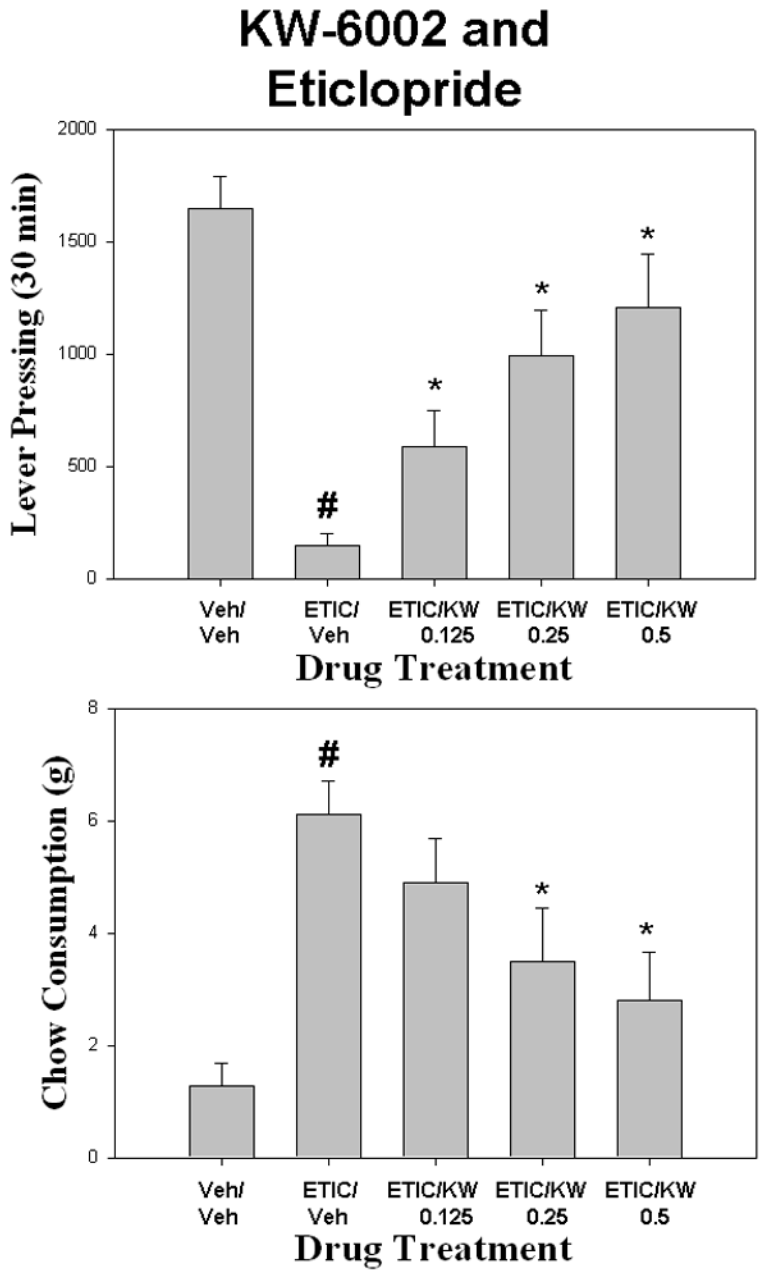

Figure 6.

The effects of the adenosine A_{2A} antagonist KW-6002 on eticlopride-induced changes in performance on the concurrent lever pressing/chow feeding procedure. Rats received IP injections of vehicle plus vehicle (Veh/Veh), 0.08 mg/kg eticlopride plus vehicle (ETIC/Veh), and eticlopride plus 0.125, 0.25, or 0.5, mg/kg doses of KW-6002 (ETIC/KW). A. Mean (± SEM) number of lever presses (FR5 schedule) during the 30 min session. B. Mean (± SEM) gram quantity of chow intake. Eticlopride significantly decreased lever pressing and increased chow intake relative to vehicle (# $p < 0.05$). KW-6002 administered to eticlopride-treated rats significantly increased lever pressing and decreased chow intake relative to treatment with eticlopride alone (* $p < 0.05$).

Table 1

Effect of DPCPX in combination with the D1 antagonist SCH 23390 (0.1 mg/kg). Mean (± SEM) number of lever presses and amount of chow intake (in grams) after injection of vehicle, SCH 23390, and SCH 23390 plus various doses of DPCPX.

Lever Presses	
vehicle plus vehicle	1434.75 (±129.33)
SCH 23390 plus vehicle	339.13 (±85.34)[#]
SCH 23390 plus 0.375 mg/kg DPCPX	290.0 (±52.55)
SCH 23390 plus 0.75 mg/kg DPCPX	404.0 (±160.89)
SCH 23390 plus 1.5 mg/kg DPCPX	451.88 (±115.0)
Chow Intake	
vehicle plus vehicle	1.5 (±0.43)
SCH 23390 plus vehicle	4.75 (±0.65)[#]
SCH 23390 plus 0.375 mg/kg DPCPX	4.19 (±0.45)
SCH 23390 plus 0.75 mg/kg DPCPX	4.11 (±0.75)
SCH 23390 plus 1.5 mg/kg DPCPX	3.53 (±0.61)

[#]different from vehicle plus vehicle, $p < 0.05$

Table 2

Effect size calculations (R^2 values) for the reversal effects.

Experiment	Lever Pressing	Chow Intake
DPCPX vs. ecopipam	0.11	0.12
CPT vs. ecopipam	0.07	0.10
DPCPX vs. eticlopride	0.06	0.05
CPT vs. eticlopride	0.10	0.07
KW6002 vs. ecopipam	0.26	0.10
KW6002 vs. eticlopride	0.43	0.27