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Selective adenosine A_{2A} receptor/dopamine D_2 receptor interactions in animal models of schizophrenia

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Abstract

In the apomorphine-induced climbing mouse assay, the potencies of the selective adenosine A_1 receptor agonist, N^6-cyclohexyladenosine (CHA), and the selective A_{2A} adenosine receptor agonist, 2-*p*-(2-carboxyethyl) phenethylamino 5′-*N*-ethylcarboxamidoadenosine (CGS 21680), and various dopamine receptor antagonists were as follows: SCH 23390 = haloperidol > raclopride > CHA = CGS 21680. While in catalepsy, their potencies were SCH 23390 > haloperidol > raclopride > CGS 21680. CHA failed to induce catalepsy due to significant sedation/ataxia. The combined administration of the ED_{15} dose of CHA failed to potentiate the ED_{50} value of SCH 23390, raclopride, or haloperidol in the apomorphine-induced climbing mouse assay. However, the combined administration of the ED_{15} dose of CGS 21680 significantly decreased the ED_{50} of raclopride by 8.0-fold and haloperidol by 35-fold. The adenosine A_{2A} receptor antagonist, 1,3,7-trimethyl-8-(3-chlorostyryl)xanthine (CSC), significantly decreased catalepsy induced by raclopride and haloperidol, while the adenosine A_1 receptor antagonist, 1,3-dimethyl-8-phenylxanthine (8-PT), was ineffective. The present results show that in behavioral assays predictive for antipsychotic activity, adenosine receptor agonists block behaviors in a similar manner to dopamine receptor antagonists.

Keywords: Adenosine receptor agonist; Dopamine receptor antagonist; Behavioral interaction; Catalepsy; Schizophrenia

1. Introduction

The purinergic compound adenosine has been described as a neuromodulator and adenosine receptor analogues can inhibit neuronal firing (Fredholm et al., 1993), inhibit neurotransmitter release (Fredholm and Dunwiddie, 1988) and decrease locomotor activity (Durcan and Morgan, 1989; Barraco et al., 1993). In contrast, adenosine receptor antagonists such as the methylxanthine caffeine, exhibit a variety of stimulant effects on the central nervous system (Snyder, 1985). Two subtypes of purinoceptors, the P_1 and the P_2 purinoceptor, have been identified by pharmacological studies. Several P_1 purinoceptor subtypes designated adenosine A_1, A_{2A}, A_{2B} and A_3 receptors have been identified by molecular cloning techniques (Mahan et al., 1991; Fink et al., 1992; Maenhaut et al., 1990; Zhou et al., 1992). These receptors are coupled to adenylyl cyclase; the adenosine A_1 receptor and the adenosine A_3 receptor are coupled negatively, while the adenosine A_{2A} receptor is coupled positively to adenylyl cyclase (Zhou et al., 1992; Schwabe et al., 1993). The adenosine A_1 and A_{2A} receptor subtypes are differentially distributed in the central nervous system (CNS). While the adenosine A_1 receptor subtype has widespread distribution throughout the cortex, hippocampus and cerebellum, the adenosine A_{2A} receptor subtype is only distributed to dopamine-innervated areas such as the caudate putamen, nucleus accumbens and olfactory tubercles, areas implicated in schizophrenia (Schiffmann et al., 1993).

In behavioral assays that are predictive for efficacy in schizophrenia, adenosine receptor agonists have been shown to block behavior in a similar manner to dopamine receptor antagonists. Adenosine receptor agonists have been shown to antagonize apomorphine-induced climbing behavior in mice with similar potencies as the antipsychotic agents, haloperidol and chlorpromazine. In addition, these agents decreased amphetamine-induced locomotion in rats (Heffner et al.,

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1989). While these studies used adenosine receptor agonists with affinity for both the adenosine A_1 and A_{2A} receptor subtypes, the behavioral antipsychotic effects were best correlated with the adenosine A_{2A} receptor subtype (Durcan and Morgan, 1989).

Selective ligands have now been identified for both the adenosine A_1 and A_{2A} receptor subtypes. N^6-Cyclohexyladenosine (CHA) and 2-*p*-(2-carboxyethyl) phenethylamino 5′-*N*-ethylcarboxamidoadenosine (CGS 21680) are selective agonists for the adenosine A_1 and A_{2A} receptor subtypes, respectively. CGS 21680 has greater than 100-fold selectivity for the adenosine A_{2A} receptor as compared to the adenosine A_1 receptor, while CHA is 392-fold more selective for the adenosine A_1 receptor than the adenosine A_{2A} receptor (Bruns et al., 1986; Abbracchio et al., 1993). 1,3-Dimethyl-8-phenylxanthine (8-PT) and 1,3,7-trimethyl-8-(3-chlorostyryl)xanthine (CSC) are selective antagonists at the adenosine A_1 and A_{2A} receptor subtypes, respectively (Bruns et al., 1986; Jacobson et al., 1993b). CSC has been found to be 520-fold more selective for the adenosine A_{2A} receptor than the adenosine A_1 receptor, while 8-PT is 10-fold more selective for the adenosine A_1 receptor than the adenosine A_{2A} receptor (Jacobson et al., 1993a; Bruns et al., 1986). The purpose of the present investigation was to access the efficacy of the adenosine receptor agonists in two assays predictive for schizophrenia, and in addition, to determine selective synergistic interactions between these adenosine ligands and selective dopamine ligands.

2. Materials and methods

2.1. Subjects

Male Wistar rats (300–450 g) and CD-1 mice (18–26 g) (Charles River) were housed under standard laboratory conditions as outlined in the 'NIH Guide for the Care and Use of Laboratory Animals' (National Institute of Health Publications, No. 85-23, revised 1983) with a 12 h light/12 h dark cycle and allowed free access to food and water.

2.2. Drugs

Apomorphine (Sigma, St. Louis, MO, USA), 2-*p*-(2-carboxyethyl) phenethylamino 5′-*N*-ethylcarboxamidoadenosine (CGS 21680), 1,3,7-trimethyl-8-(3-chlorostyryl)xanthine (CSC), N^6-cyclohexyladenosine (CHA), 1,3-dimethyl-8-phenylxanthine (8-PT), SCH 23390 (Research Biochemicals, Natick, MA, USA), haloperidol (McNeil Pharmaceuticals, Spring House, PA, USA) raclopride (Astra, Worcester, MA, USA), were administered with appropriate pretreatment times in this study. All compounds were suspended or dissolved in distilled water with a drop of Tween 80 and administered in an injection volume of 1 ml/kg for rats and 1.0 ml/100 g for mice. The final volume was prepared to account for salt content and the dosage was expressed as 100% base.

2.3. Apomorphine-induced climbing mouse assay

In the apomorphine-induced climbing mouse assay (Costall et al., 1978), mice were randomly assigned to groups of eight and individually placed in wire stick cages ($10 \times 10 \times 25$ cm) where they were allowed to acclimate for 60 min. Compounds were administered intraperitonealy (i.p.) with appropriate pretreatment times prior to subcutaneous (s.c.) administration of apomorphine at 1.5 mg/kg. Climbing behavior was assessed at 10, 20, and 30 min after apomorphine administration according to the following scoring scale: four paws on the bottom of the cage, no climbing = 0; two paws on the wall, rearing = 1; four paws on the wall, full climbing = 2. Each group's climbing scores were totaled, and compared to the control response to determine the antagonism of climbing induced by apomorphine. The ED_{50} values with 95% confidence limits were calculated for antagonism of apomorphine-induced climbing by means of the Litchfield and Wilcoxon (1949) method.

For the interaction studies, dose-response curves for antagonizing apomorphine-induced climbing were generated for each agent. Based on the dose-response curve an ED_{15} value was calculated by means of a linear regression analysis (Tallarida and Murray, 1987) for both CHA and CGS 21680. Subsequently, the calculated ED_{15} dose for either CHA or CGS 21680 was administered 60 min prior with various doses of either SCH 23390, raclopride, or haloperidol 30 min prior to the apomorphine challenge. The new ED_{50} values for SCH 23390, raclopride, and haloperidol in the presence of either the ED_{15} dose for CHA or CGS 21680 were then compared to the ED_{50} values for SCH 23390, raclopride, and haloperidol alone, and the potency ratios, regression lines and parallelism were compared for statistical significance at the $P < 0.05$ level of significance (Litchfield and Wilcoxon, 1949; Tallarida and Murray, 1987).

2.4. Catalepsy

Groups of ten male Wistar rats were used in this assay. Catalepsy was scored as previously described (Corbett et al., 1993). For induction of catalepsy, drugs were administered i.p. with a 60 min pretreatment time (except SCH 23390: subcutaneous (s.c.) administration, 30 min pretreatment). For the antagonist studies, 8-PT and CSC were administered 60 min (i.p.) and haloperi-

dol (0.75 mg/kg) and raclopride (1.5 mg/kg) 30 min (i.p.) prior to scoring for catalepsy. The test for catalepsy consisted of placing an individual rat in a white translucent plastic box (26 × 20 × 15 cm) with a wooden dowel mounted horizontally 10 cm from the floor and 4 cm from one end of the box. The floor was covered with approximately 1 cm of bedding material. At the end of a 1 min acclimation period, each rat was gently placed on the bar. The latency (s) for the rat to remove both paws from the bar was recorded for a maximum of 180 s. For every 20 s that the rat maintained the cataleptic posture, it received one point such that maximum catalepsy was represented by a total of nine points. The control group (saline) consistently gave a cataleptic score of 0. The ED_{50} values with 95% confidence limits were calculated for induction of catalepsy by means of the Litchfield and Wilcoxon (1949) method.

2.5. Forced motor activity

In the forced motor activity assay (Dunn et al., 1992), mice were randomly assigned to groups of ten. Compounds were administered i.p. with appropriate pretreatment times prior to testing. During testing, animals were placed on a horizontal wooden rotorod 3.8 cm in diameter and 15 cm long, elevated to a height of 30 cm, which was rotated at a speed of 2 rpm by an adjustable-speed motor. Animals unable to remain on the revolving rotorod for a period of 1 min were considered impaired. The ED_{50} values with 95% confidence limits were calculated for antagonism of forced motor activity by means of the Litchfield and Wilcoxon (1949) method.

3. Results

Fig. 1 summarizes the dose-response effects of the dopamine D_1 receptor antagonist SCH 23390, the dopamine D_2 receptor antagonist raclopride, the antipsychotic agent haloperidol, the adenosine A_1 receptor agonist CHA, and the adenosine A_{2A} receptor agonist CGS 21680, respectively on apomorphine-induced climbing in mice. Each compound dose dependently antagonized climbing behavior with varying potencies. The relative potency for these compounds was: SCH 23390 = haloperidol > raclopride > CHA = CGS 21680. The ability of these compounds to induce catalepsy is shown in Fig. 2. Their relative potency in this assay was: SCH 23390 > haloperidol > raclopride > CGS 21680; catalepsy was not determined for CHA due to significant sedation/ataxia at 2.5 mg/kg. Fig. 3 summarizes the dose-response effects of these compounds in the forced motor activity assay. SCH 23390, raclopride, haloperidol, CHA and CGS 21680 all

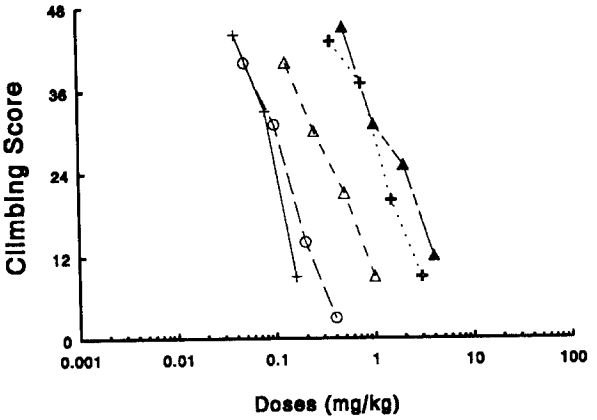

Fig. 1. The effects of various dopamine antagonists and adenosine agonists in the apomorphine-induced climbing mouse assay. SCH 23390 (+ ——— +), raclopride (△ - - - △), haloperidol (○ – – – ○), CHA (+ · · · +), and CGS 21680 (▲ — – — ▲) were administered (mg/kg i.p.), 30 min (CGS 21680 and CHA were administered mg/kg i.p 60 min) prior to the climbing mouse assay. The data are expressed relative to control mice administered saline prior to apomorphine (1.5 mg/kg s.c.) which produced a maximal climbing score of 48. ED_{50} values with 95% confidence limits are shown in Table 1.

dose-dependently induced motor impairment with varying potencies. The relative potency of these compounds was CHA > haloperidol = SCH 23390 > raclopride = CGS 21680.

Table 1 summarizes the ED_{50} values with 95% confidence limits for the dose-response effects of the compounds tested in the apomorphine-induced climbing mouse assay, catalepsy, and the forced motor activity assays. In addition, an ED_{15} value in the apomorphine-induced climbing mouse assay was generated for CHA and CGS 21680. A catalepsy/apomorphine-induced climbing mouse ratio was determined for each agent except CHA as sedation/ataxia prevented the accurate determination of catalepsy. All of the agents tested had a forced motor activity/apomorphine-induced climbing mouse ratio of greater than 3.78, except CHA which had a ratio of 0.39.

Fig. 4A shows that the combined administration of the ED_{15} dose of either CHA or CGS 21680 failed to increase the relative potency of the dopamine D_1 receptor antagonist SCH 23390 in antagonizing apomorphine-induced climbing. Fig. 4B shows that the administration of the ED_{15} dose of CGS 21680 significantly increased the relative potency (8.0-fold) of the dopamine D_2 receptor antagonist raclopride in antagonizing apomorphine-induced climbing. There was no significant interaction between CHA and raclopride in antagonizing apomorphine-induced climbing. A similar profile of activity was observed with the typical antipsychotic agent haloperidol (Fig. 4C). CGS 21680 significantly increased the ED_{50} of haloperidol alone by 35-fold in antagonizing apomorphine-induced climb-

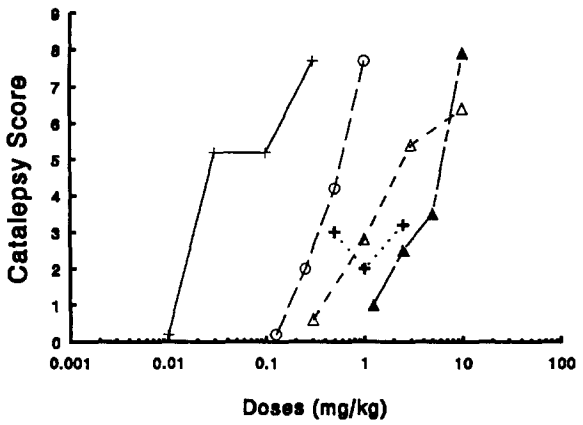

Fig. 2. The induction of catalepsy by various dopamine antagonists and adenosine agonists. SCH 23390 (+ ——— +), raclopride (△---△), haloperidol (○---○), CHA (+ · · · +), and CGS 21680 (▲——▲) were administered (mg/kg i.p.), 60 min (SCH 23390 was administered mg/kg s.c. 30 min) prior to testing for catalepsy. For every 20 s that the rat maintained the cataleptic posture, it received one point such that maximum catalepsy was represented by a total of nine points. The control group (saline) consistently gave a cataleptic score of 0. ED_{50} values with 95% confidence limits are shown in Table 1.

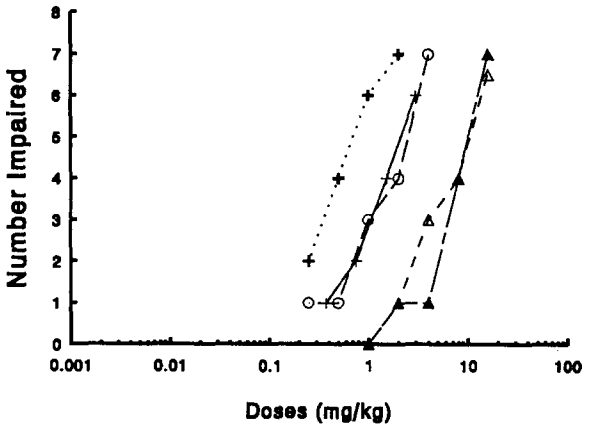

Fig. 3. The effects of various dopamine antagonists and adenosine agonists in the forced motor activity assay. SCH 23390 (+ ——— +), raclopride (△---△), haloperidol (○---○), CHA (+ · · · +), and CGS 21680 (▲——▲) were administered (mg/kg i.p.), 30 min (CGS 21680 and CHA were administered mg/kg i.p 60 min) prior to the forced motor activity assay. Animals unable to remain on the revolving rod for a period of 1 min were considered impaired. ED_{50} values with 95% confidence limits are shown in Table 1.

ing, while there was no significant interaction between CHA and haloperidol in antagonizing apomorphine-induced climbing.

The ability of the adenosine A_1 receptor antagonist 8-PT and the adenosine A_{2A} receptor antagonist CSC to antagonize raclopride- and haloperidol-induced catalepsy is summarized in Table 2. Only the adenosine A_{2A} receptor antagonist CSC significantly reversed both raclopride- and haloperidol-induced catalepsy while the adenosine A_1 receptor antagonist 8-PT was ineffective in this assay.

4. Discussion

The present study shows that the selective adenosine A_{2A} receptor agonist CGS 21680 antagonized apomorphine-induced climbing behavior and induced catalepsy, in a similar fashion as the dopamine D_1 receptor antagonist SCH 23390, the dopamine D_2 receptor antagonist raclopride and the typical antipsychotic agent haloperidol. CGS 21680, raclopride, and haloperidol had catalepsy/apomorphine-induced climbing mouse ED_{50} ratios of 2.26, 7.47, and 3.57, respectively while SCH 23390 had a catalepsy/apomorphine-induced climbing mouse ratio of 0.7. The selective adenosine A_1 receptor agonist CHA only antagonized apomorphine-induced climbing behavior at doses greater than it antagonized forced motor activity indicating sedation/ataxia, and as a result, the induction of catalepsy could not be determined. The present results are in agreement with previous studies. Adenosine receptor agonists have displayed antipsychotic-like effects in animal models predictive for antipsychotic efficacy in rodents, such as the apomorphine-induced climbing behavior, amphetamine-induced locomotion (Durcan and Morgan, 1989;

Table 1
The effects of dopamine antagonists and adenosine agonists in the climbing mouse assay (CMA), forced motor activity (FMA) assays, and catalepsy (CAT)

Compound	ED_{50} values and 95% confidence limits (mg/kg i.p.)					
	CMA		CAT	FMA	CAT/CMA ratio	FMA/CMA ratio
	ED_{50}	ED_{15}	ED_{50}	ED_{50}		
SCH 23390	0.1 (0.09–0.10)	–	0.07 (0.003–1.51)	1.47 (1.23–1.76)	0.70	14.70
Raclopride	0.38 (0.32–0.45)	–	2.84 (0.98–8.29)	6.3 (3.8–10.02)	7.47	16.6
Haloperidol	0.14 (0.13–0.15)	–	0.50 (0.44–0.55)	1.45 (0.81–2.59)	3.57	10.36
CHA	1.32 (1.14–1.53)	0.20	ND	0.51 (0.43–0.61)	ND	0.39
CGS 21680	1.96 (1.05–3.66)	0.35	4.42 (1.76–11.13)	7.4 (4.46–12.31)	2.26	3.78

ED_{50} values with 95% confidence limits were determined from dose-response curves from respective assays. ND = not determined due to ataxia.

Heffner et al., 1989) and catalepsy (Ferré et al., 1991b). While these studies used adenosine receptor agonists with affinity for both the adenosine A_1 and A_{2A} receptor subtypes, the antipsychotic behavioral effects were best correlated with affinity for the adenosine A_{2A} receptor subtype (Heffner et al., 1989).

In the interaction studies, CGS 21680 significantly potentiated the effects of raclopride and haloperidol to antagonize apomorphine-induced climbing behavior, while it failed to potentiate the effects of the dopamine D_1 receptor antagonist SCH 23390 in this assay. In contrast, CHA failed to significantly potentiate either SCH 23390, raclopride, or haloperidol to antagonize apomorphine-induced climbing behavior. These results suggest that there is a selective potentiation of the behavioral effects between the adenosine A_{2A} receptor agonists and the dopamine D_2 receptor antagonists in this animal model predictive for antipsychotic activity (Dunn et al., 1991; Corbett et al., 1993). However, in an animal model of Parkinson's disease, namely unilaterally 6-hydroxydopamine-lesioned rats, Morelli et al. (1994) observed that CGS 21680 completely blocked the contralateral turning induced by the dopamine D_1 receptor agonist SKF 38393 and reduced the turning induced by the dopamine D_2 receptor agonist quinpirole. Unilateral 6-hydroxydopamine-induced lesions of the substantia nigra have been shown to cause a functional supersensitivity of dopamine receptors and second messenger systems (Mileson et al., 1991). Therefore this lesion may alter the interactions between the adenosine and dopamine systems; however, the present study used intact (non-lesioned) animals which may account for these discrepancies. In both the haloperidol- and raclopride-induced catalepsy assays, only the

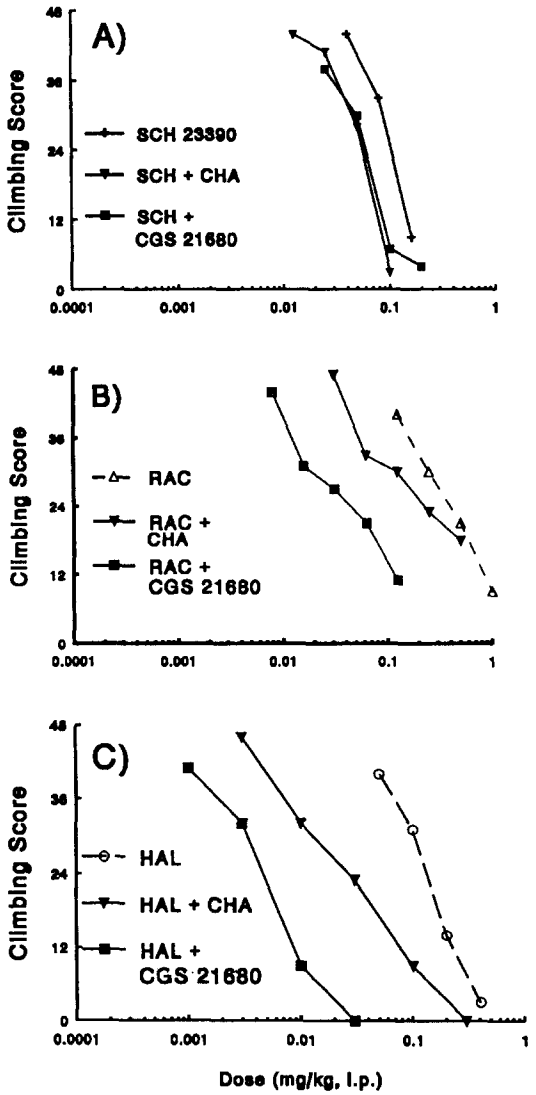

Fig. 4. The combined administration of the ED_{15} dose of either CHA or CGS 21680 failed to potentiate the relative potency of the D_1 antagonist SCH 23390 in antagonizing apomorphine-induced climbing (A). The ED_{15} dose of CGS 21680 significantly ($P < 0.05$) potentiated the ED_{50} dose of raclopride from 0.38 (0.32–0.45) to 0.04 (0.02–0.07) mg/kg i.p. (B), and significantly ($P < 0.05$) potentiated the ED_{50} dose of haloperidol from 0.14 (0.13–0.15) to 0.004 (0.003–0.005) mg/kg i.p. (C). CHA had no significant potentiating effect on the ED_{50} value for raclopride or haloperidol. Statistical significance was determined using linear regression to compare potency ratios, regression lines, and parallelism (Litchfield and Wilcoxon, 1949; Tallarida and Murray, 1987).

Table 2
The effects of the adenosine A_1 antagonist 8-PT and the adenosine A_{2A} antagonist CSC, in antagonizing haloperidol (HAL; 0.75 mg/kg) and raclopride (RAC; 1.5 mg/kg)-induced catalepsy

Compounds	Dose (mg/kg)	Catalepsy score
HAL	0.75	6.6 ± 1.2
8-PT +	5.0	5.6 ± 1.1
HAL	0.75	
8-PT +	10.0	5.3 ± 0.8
HAL	0.75	
HAL	0.75	7.1 ± 0.6
CSC +	5.0	5.7 ± 0.9
HAL	0.75	
CSC +	10.0	4.3 ± 1.1 [a]
HAL	0.75	
RAC	1.5	7.1 ± 1.1
CSC +	10.0	4.4 ± 0.8 [a]
RAC	1.5	
CSC +	5.0	7.6 ± 0.6
RAC	1.5	
RAC	1.5	7.8 ± 0.6
8-PT +	10.0	7.7 ± 0.7
RAC	1.5	
8-PT +	5.0	8.1 ± 0.6
RAC	1.5	

8-PT and CSC were administered 60 min and haloperidol and raclopride 30 min prior to scoring for catalepsy. For every 20 s that the rat maintained the cataleptic posture, it received one point such that maximum catalepsy was represented by a total of nine points. [a] $P < 0.05$, Student's t-test versus HAL group alone. $n = 10$–12 rats per group.

selective adenosine A_{2A} receptor antagonist CSC significantly decreased catalepsy, while the adenosine A_1 receptor antagonist 8-PT failed to significantly reduce the catalepsy in either the haloperidol- or raclopride-induced catalepsy assays. These behavioral results support and extend the previous studies which indicate a selective interaction of the adenosine A_{2A} receptor and the dopamine D_2 receptor at the biochemical level.

The present results show that CGS 21680 has a behavioral profile in two assays predictive for antipsychotic activity similar to the dopamine receptor antagonists, such as SCH 23390, raclopride, and haloperidol. CGS 21680 has a similar ratio of catalepsy/apomorphine-induced climbing mouse as the typical antipsychotic agent haloperidol, indicating a potential for extrapyramidal side effects liability in patients (Morelli and Di Chiara, 1985). This profile of activity of CGS 21680 is in contrast to the low extrapyramidal side effect liability of the atypical antipsychotic agent clozapine, and the putative atypical antipsychotic agents, risperidone and iloperidone, which correlates in vivo to a lack of cataleptic behavior in rodents following acute administration (Kane et al., 1988; Mesotten et al., 1989; Corbett et al., 1993; Meshul et al., 1994; Strupczewski et al., 1995). In addition to extrapyramidal side effect liability, typical antipsychotic agents including haloperidol can induce tardive dyskinesia in patients after prolonged exposure to the drugs. The development of dopamine D_2 receptor supersensitivity after chronic administration of antipsychotic agents has been thought to cause the development of tardive dykinesia. Chronic administration of typical antipsychotic agents to rodents increased the number of dopamine D_2 receptors in rat striatal membranes (Rupniak et al., 1984). Recently, Ferré et al. (1994) have shown that chronic administration of haloperidol to rodents resulted in an increase of dopamine D_2 receptors in the striatum and in addition an increased interaction between the dopamine D_2 receptors and the adenosine A_{2A} receptors as measured by receptor binding. This increased interaction between these two receptors was antagonized by the addition of a low dose of CGS 21680, which was not effective in membrane preparations from neostriatum of non-treated rodents.

CGS 21680 has been shown to change the binding properties of the dopamine D_2 receptors but not the dopamine D_1 receptors in rat striatum (Ferré et al., 1991a). In nanomolar concentrations CGS 21680 induced a 30% decrease in affinity for dopamine D_2 receptors for its agonist [^{3}H]NPA in saturation studies. These effects of CGS 21680 were antagonized by the adenosine receptor antagonist 8- phenyltheophylline and were not due to a direct interaction with a dopamine binding site. Neither the affinity of the dopamine D_2 receptor antagonist binding site nor the number of dopamine D_2 receptors was affected by CGS 21680, indicating that it is the agonist binding to the dopamine D_2 receptor that is selectively affected by adenosine. In addition, the stimulation of the adenosine A_1 receptors with R-PIA at a concentration (3 nM) close to its K_d for adenosine A_1 receptors, failed to affect dopamine D_2 agonist binding, indicating a selective adenosine A_{2A} receptor/dopamine D_2 receptor interaction. This adenosine A_{2A} receptor/dopamine D_2 receptor interaction has also been shown to be G protein independent since adenosine A_{2A} receptor agonists unlike GTP do not alter the proportions of high versus low affinity states of the dopamine D_2 receptor (Ferré et al., 1991a; Fuxe et al., 1993). Therefore, these interactions of the adjacent transmembrane regions of the adenosine A_{2A} and dopamine D_2 receptors may induce conformational changes which alter the binding properties and ultimately, cause modulation of the agonist recognition/transduction processes (Agnati et al., 1993). However, Jin et al. (1993) have observed that the electrically evoked release of dopamine and acetylcholine can be inhibited by both adenosine A_1 and A_{2A} receptor agonists, which could be blocked by an adenosine A_1 receptor antagonist. These data suggest that release of dopamine or acetylcholine may be controlled by another unidentified adenosine receptor subtype. However, the large aspiny cholinergic interneurons of the striatum do not contain adenosine A_{2A} receptor mRNA (Schiffmann et al., 1991). Using in situ hybridization techniques, both the adenosine A_{2A} and dopamine D_2 receptors mRNA have been colocalized in γ-aminobutyric acid/enkephalin striatal medium-sized spiny neurons, of the indirect pathway of the basal ganglia-thalamocortical circuits (Schiffmann et al., 1991; Ferré et al., 1993). As a result, the functional antagonism between adenosine A_{2A}/dopamine D_2 receptors in the basal ganglia takes place within these γ-aminobutyric acid/enkephalin striopallidal neurons. Therefore, activation of the adenosine A_{2A} receptors of the indirect pathway in the basal ganglia inhibits dopamine D_2 receptors, as a consequence, administration of adenosine A_{2A} receptor agonists results in a similar behavioral profile of activity as dopamine D_2 receptor antagonists.

In summary, the adenosine A_{2A} receptor agonist CGS 21680 antagonized apomorphine-induced climbing in mice, and induced catalepsy in rats in a similar manner to various dopamine receptor antagonists. CGS 21680 selectively potentiated raclopride in the apomorphine-induced climbing mouse assay indicating an interaction between adenosine A_{2A} and dopamine D_2 receptor subtypes. However, induction of catalepsy in rodents has been associated with extrapyramidal side effect liability in humans suggesting that adenosine A_{2A} receptor agonists may have a similar therapeutic

profile as typical antipsychotic agents in treating schizophrenia.

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