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Adenosine A_{2A} Agonists: A Potential New Type of Atypical Antipsychotic

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The systemic intraperitoneal (i.p.) administration of the adenosine A_{2A} agonist CGS 21680 was found to dose-dependently antagonize spontaneous and amphetamine-induced (1 mg/kg i.p.) motor activity with similar ED50 values (about 0.2 mg/kg). The ratios between the ED50 values for induction of catalepsy and for antagonizing amphetamine-induced motor activity for CGS 21680, haloperidol, and clozapine were 12, 2, and > 30, respectively. Furthermore, CGS 21680 was comparably much stronger than haloperidol or clozapine at antagonizing the motor activity induced by phencyclidine (2 mg/kg subcutaneously) than motor activity induced by amphetamine (1 mg/kg i.p.). In conclusion, the present results show a clear "atypical" antipsychotic profile of the adenosine A_{2A} agonist CGS 21680 in animal models.
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KEY WORDS: *Adenosine receptors; Amphetamine; Phencyclidine; Catalepsy; Antipsychotics; Schizophrenia*

The systemic administration of adenosine agonists in rodents has been shown to induce a pronounced dose-dependent depression of spontaneous motor activity (Vapaatalo et al. 1975; Snyder et al. 1981; Durcan and Morgan 1989; Heffner et al. 1989; Nikodijevic et al. 1991; Jacobson et al. 1993; Ferré et al. 1994a). This behavioral effect is most probably mediated at the central level, since it is also induced after their intraventricular or intracerebral administration (Barraco et al. 1983, 1993). Furthermore, the administration of an adenosine antagonist which poorly penetrates the blood-brain barrier could not counteract an adenosine agonist-induced motor depression (Durcan and Morgan 1989b; Nikodijevic et al. 1991).

Four different subtypes of adenosine receptors are found in the brain: A_1, A_{2A}, A_{2B} and A_3 (for a recent review, see Fredholm 1995). Adenosine A_1 and A_{2B} receptors have an ubiquitous distribution, being present in neurons and glial cells, and adenosine A_3 receptor distribution is still poorly documented. On the other hand, adenosine A_{2A} receptors are mostly localized in the striatum (Jarvis et al. 1989) and, particularly, in the GABAergic striopallidal neurons, which connect the striatum with the pallidal complex (globus pallidus and ventral pallidum) (Schiffmann et al. 1991; Fink et al. 1992). By using different agonists with different selectivities for the different adenosine receptor subtypes, it has been shown that motor depression can be induced after the stimulation of adenosine A_1, A_{2A} and A_3 receptors (Vapaatalo et al. 1975; Snyder et al. 1981; Durcan and Morgan 1989, Heffner et al. 1989; Nikodijevic et al. 1991; Jacobson et al. 1993; Ferré et al. 1994a). The motor depression induced by adenosine A_1 and A_{2A} receptor stimulation has been well characterized while little is known about the adenosine A_3-induced motor depression (Jacobson et al. 1993). Adenosine A_1 agonists induce motor depression and motor incoordination (ataxia) at similar doses and the animal shows a "flat body" posture (Snyder et al. 1981; Heffner et al. 1989; Ferré et al. 1994a). Adenosine A_{2A} agonists show a clear separation between the doses inducing motor depression and ataxia (Heffner et al. 1989). Furthermore, adenosine A_{2A} agonists have been described to induce cata-

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lepsy after their central or systemic administration (Ferré et al. 1991a; Zarrindast et al. 1993; Kanda et al. 1994; Hauber and Münkle 1995; Kafka and Corbett 1996). Finally, adenosine A_{2A} agonists, as well as A_1 agonists, have been reported to reduce conditioned avoidance responding (Martin et al. 1993). Therefore, adenosine A_{2A} agonists have similar behavioral effects in the experimental animal as those induced by neuroleptics, and it has been suggested that they could be used as antipsychotics (Heffner et al. 1989; Ferré et al. 1991a; Martin et al. 1993).

Many experimental results suggest that the motor depressant effects of adenosine agonists are mediated by a counteraction of central dopaminergic neurotransmission (reviewed in Ferré et al. 1992). Stimulation of striatal adenosine A_1 receptors *in vivo* and *in vitro* preparations have been shown to decrease dopamine release (for recent reports, see Jin et al. 1993; Ballarin et al. 1995). However, this presynaptic mechanism cannot explain the effects of adenosine A_{2A} agonists. We have found evidence for the existence of a specific antagonistic interaction between adenosine A_{2A} and dopamine D_2 receptors in the striatum (Ferré et al. 1991a,b,c, 1992, 1993a,b, 1994a,b,c), which seems to be the major mechanism of action responsible for the adenosine A_{2A} agonist-induced counteraction of dopaminergic neurotransmission. CGS 21680 is a very selective agonist for adenosine A_{2A} receptors, with about 100 times more affinity for A_{2A} than A_1 or A_3 receptors and with an even lower affinity for A_{2B} receptors (Fredholm et al. 1994). CGS 21680 decreases the affinity of dopamine D_2 receptors for dopamine agonists and it impairs D_2 signal-transduction in the rat striatum (Ferré et al. 1991c, 1993b, 1994b). Furthermore, CGS 21680 counteracts some behavioral and neurochemical striatal D_2 receptor-mediated effects: it inhibits the motor activation induced by dopamine D_2 agonists (Ferré et al. 1991a, 1994a; Morelli et al. 1994), and it antagonizes the D_2-mediated modulation of GABA release in the striopallidal neurons (Ferré et al. 1993b, 1994b; Mayfield et al. 1996) and the D_2 agonist-induced decrease in striatal acetylcholine release (Jin et al. 1993).

Blockade of dopamine D_2 receptors in the ventral striatum (ventromedial caudate-putamen, nucleus accumbens and olfactory tubercle) seems to mediate the antipsychotic action of neuroleptics or, at least, their therapeutical effect on the positive symptoms of schizophrenia. On the other hand, dopamine D_2 receptor blockade in the dorsal striatum (dorsolateral caudate-putamen) seems to mediate their extrapyramidal side effects (Fuxe et al. 1977; Borison et al. 1983; Altar et al. 1986; Ögren et al. 1986; Robertson and Fibiger 1992). Atypical antipsychotics, like clozapine, have a low incidence of these side effects. Some studies suggest that a preferential blockade of dopamine D_2 receptors in the ventral striatum may be one of the main factors responsible for the atypical profile of an antipsychotic drug (Borison et al. 1983; Altar et al. 1986; Ögren et al. 1986; Robertson and Fibiger 1992). We have recently proposed that adenosine A_{2A} agonists, such as CGS 21680, could have an atypical antipsychotic profile (Ferré et al. 1994b) since: (1) CGS 21680 exerts a more powerful motor depression when infused in the ventral than in the dorsal striatum (Barraco et al. 1993); (2) a stronger antagonistic A_{2A}–D_2 interaction is also observed in the ventral striatum (Ferré et al. 1994b). In the present work we present evidence for a clear atypical antipsychotic profile of CGS 21680, by studying the effects of the systemic administration of CGS 21680 on spontaneous as well as amphetamine- and phencyclidine (PCP)-induced motor activity, and CGS 21680-induced catalepsy in rats.

METHODS

Animals

Male Sprague-Dawley rats (A-Lab, Sollentuna, Sweden) weighing 300–350 g were housed in groups of four in type IV Macrolon cages, with free access to pellets and water. They were kept under standardized laboratory conditions (temperature 22 ± 2 °C, 60% humidity) with a 12-hour light/dark cycle (lights on at 07.00 hours). All the experiments were performed between 08.00 and 15.00 hours.

Compounds

The following compounds were used: sodium 2-*p*-carboxyethyl-phenylamino-5′-*N*-carboxamidoadenosine (CGS 21680) (a gift from Ciba-Geigy Corporation, Summit, NJ); D-amphetamine sulfate (amphetamine) (SIGMA, St. Louis, MO); phencyclidine hydrochloride (PCP) (SIGMA); haloperidol (SIGMA); clozapine (SIGMA). Haloperidol and clozapine were dissolved in a drop of acetic acid which was made up to volume with saline, and adjusted to pH 6 by adding NaOH. The other drugs were simply dissolved in saline. CGS 21680 (0.03–10 mg/kg) and amphetamine (1 mg/kg) were administered i.p., in a volume of injection of 5 ml/kg. Haloperidol (0.01–1 mg/kg), clozapine (0.03–30 mg/kg), and PCP (2 mg/kg) were administered s.c. into the neck in a volume of 2 mg/kg.

Motor Activity Measurement

Horizontal activity (motility), vertical activity (rearings), and locomotion were simultaneously recorded in twelve animals (in individual cages) by means of a multicage infrared-sensitive motion detection system (Motor-products, Sweden) (Ögren et al. 1979). The dimensions of the activity cages were 20 × 38 × 16 (height). Horizontal movements were detected by 40 photosen-

sors placed in the floor of the motility meters. The sensors were mounted in 4 × 4 cm squares covering the entire measurement area. Rearings were measured by five photosensors placed in rows separated by 5 cm and covering the entire measurement area. The vertical detectors were mounted 13 cm above the floor of the measurement box. Each photoconductive cell operated independently of each other. The pulses were fed to electromechanical printing counters. Locomotion was defined as the movement between two rows of photosensors located at opposite ends of the cage floor. Motility was defined as any movement covering each photosensor, i.e., a distance of 4 cm. The rats were first accustomed to the experimental room for 40 min prior to the beginning of motor activity recording. For the spontaneous motor activity experiments, CGS 21680 or saline were administered 10 min before the animals were placed in the motor cages without any habituation period. For the amphetamine- and PCP-induced motor activity experiments, the animals were placed in the motor cages 40 min before the administration of amphetamine or PCP (habituation period). CGS 21680, haloperidol, clozapine or saline were administered 15 minutes before amphetamine or PCP. Dose-response experiments were performed to know which doses of amphetamine and PCP induced a similar increase in motor activity. The doses of amphetamine (1 mg/kg) and PCP (2 mg/kg) used were chosen according to their ability to induce a similar peak effect on motility, since it was already known that PCP reduces rearing activity (Ögren and Goldstein, 1994). ED50 values for the motor depressant effects of CGS 21680, haloperidol and clozapine were determined by non-linear regression analysis (Graph-Pad InPlot software). The average of counts for motility, rearings and locomotion obtained during different 5-minute periods was used for statistical comparisons. For the statistical analysis one-way ANOVA with Fisher's PLSD posthoc comparisons was used.

Catalepsy Measurement

The rats were first placed in individual cages and accustomed to the experimental room for 60 minutes prior to the beginning of catalepsy measurement. Catalepsy was measured 20, 40, 60, 90, 120, and 240 minutes after the administration of CGS 21680, haloperidol, or clozapine. Every testing time catalepsy was first measured with the vertical grid test followed by the bar test (Ögren and Goldstein, 1994). For the grid test a wire mesh grid box (23 × 33 × 16) was used. The animals were placed on the grid with their heads up and the four legs abducted and extended. The period spent on the grid without moving was measured (descent latency). Catalepsy was considered to be interrupted when the animal moved any of its four paws. The test was limited by a cut off time of 120 seconds. For the bar test, a test cage box with a horizontal plastic bar (1.5 cm) placed 7 cm above the cage floor was used. The forepaws of the animal were gently placed on the bar and the animal was timed from that time until both forepaws were removed from the bar or until the cut off time (120 seconds) was reached. The animals were left in their individual cages between each test time. Catalepsy was defined as present when the mean of the three highest values was at least 15 seconds. The proportion of animals that were cataleptic according to this criterion was calculated for each dose level of the drugs and the ED50 values were determined by nonlinear regression analysis. The ED50 value was defined as the dose at which 50% of the animals were cataleptic (Ögren and Goldstein 1994).

RESULTS

Spontaneous Motor Activity

The animals showed a strong exploratory activity during the first 20 minutes of observation, which consisted of an increase in motility, rearings, and locomotion (Figures 1 and 2). CGS 21680 dose-dependently inhibited all aspects of spontaneous motor activity with similar ED50 values (around 0.2 mg/kg).

Amphetamine- and PCP-Induced Motor Activity

In dose-response experiments (data not shown) amphetamine 1 mg/kg i.p. and PCP 2 mg/kg s.c. were

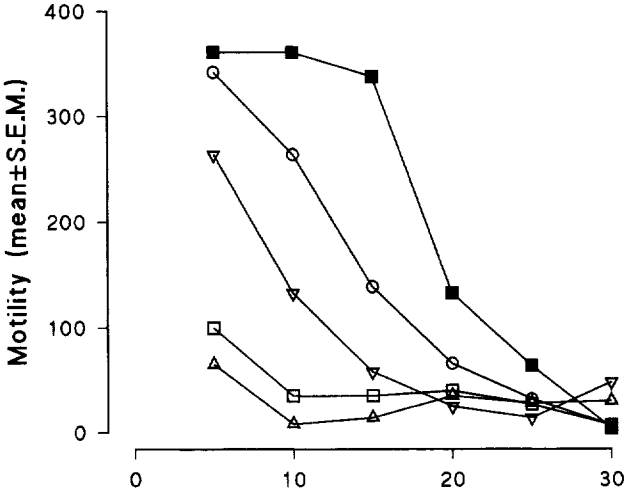

Figure 1. Time-course of the spontaneous motor activity (motility) in rats after the systemic administration of saline (filled squares) or CGS 21680 0.1 mg/kg (open circles), 0.3 mg/kg (open inverse triangles), 1 mg/kg (open squares), or 2 mg/kg (open triangles). Results are expressed as mean counts/5 minutes; $n = 6$/group.

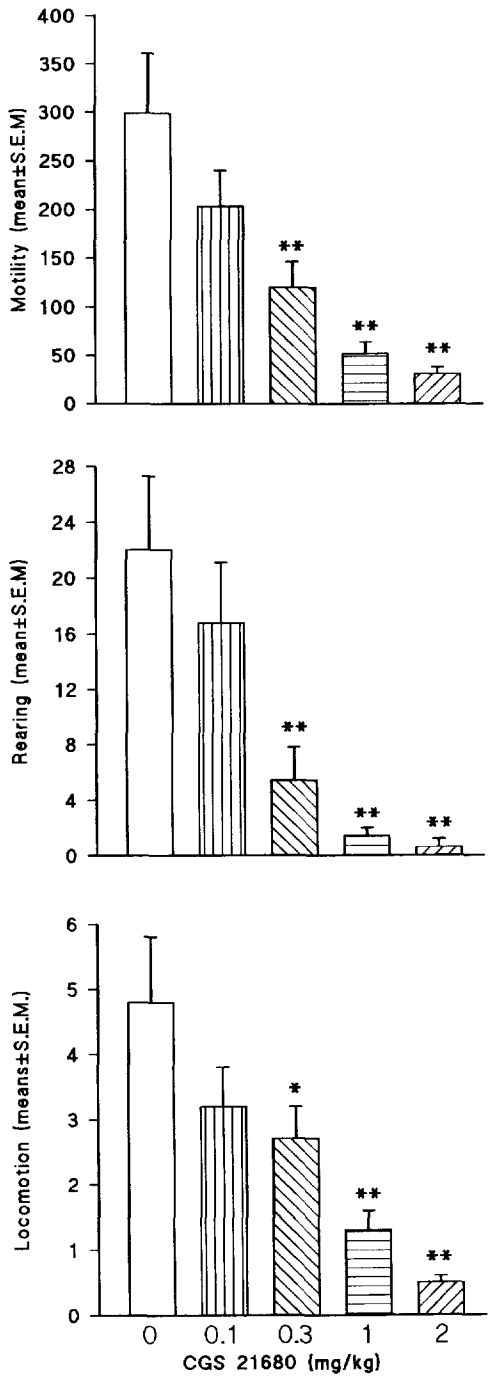

Figure 2. Spontaneous motor activity (motility, rearings, and locomotion) in rats after the systemic administration of saline (CGS 21680 0 mg/kg) or CGS 21680 0.1, 0.3, 1 or 2 mg/kg. Results are expressed as mean ± S.E.M. counts/5 minutes obtained during the first 20 minutes of observation. The ED50 values of CGS 21680-induced motor depression for motility, rearing, and locomotion were 0.2, 0.2, and 0.3, respectively. * and **: significantly different (ANOVA, $p < 0.05$ and $p < 0.01$, respectively) compared to the saline-treated group; $n = 6$/group.

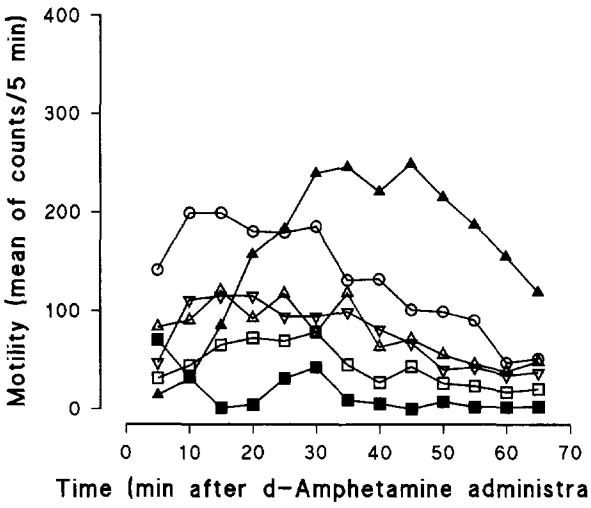

Figure 3. Time-course of the amphetamine (1 mg/kg)-induced motor activity (motility) in habituated rats after the systemic administration of saline (filled triangles) or CGS 21680 0.1 mg/kg (open circles), 0.3 mg/kg (open inverse triangles), 1 mg/kg (open squares), or 2 mg/kg (open triangles). The curve with closed squares shows the motor activity in control animals without amphetamine treatment. Results are expressed as mean counts/5 minutes; $n = 8$–10/group.

found to induce a similar peak effect on motility (peak effect of about 250 counts/5 minutes) (Figures 3 and 5). With these doses PCP induced a higher increase in locomotion than amphetamine and, as previously described, PCP decreased rearing activity (Ögren and Goldstein 1994) (Figures 4 and 6).

CGS 21680 dose-dependently inhibited the motor activating effects of amphetamine and PCP. However, quantitative and qualitative differences were found. CGS 21680 antagonized by about 75% both amphetamine- and PCP-induced increases in motility, although lower doses of CGS 21680 could be used to antagonize the effects of PCP (Figures 4 and 6). In fact, the ED50 value of the depressant effect of CGS 21680 on PCP-induced motility was lower than the ED50 value for the depressant effect of CGS 21680 on spontaneous motor activity (Figures 2 and 6). CGS 21680 was also found to shift to the left the time course of amphetamine- but not of PCP-induced increase in motility (Figures 3 and 5). The increase in locomotion induced by PCP was counteracted by 70% using low doses of CGS 21680. On the other hand, even high cataleptogenic doses of this compound (see below) did not counteract the amphetamine-induced increase in locomotion (Figures 4 and 6). Finally, the rearing activity induced by amphetamine was completely counteracted by CGS 21680 with a similar ED50 value to that obtained for the CGS 21680-mediated antagonism of amphetamine-induced

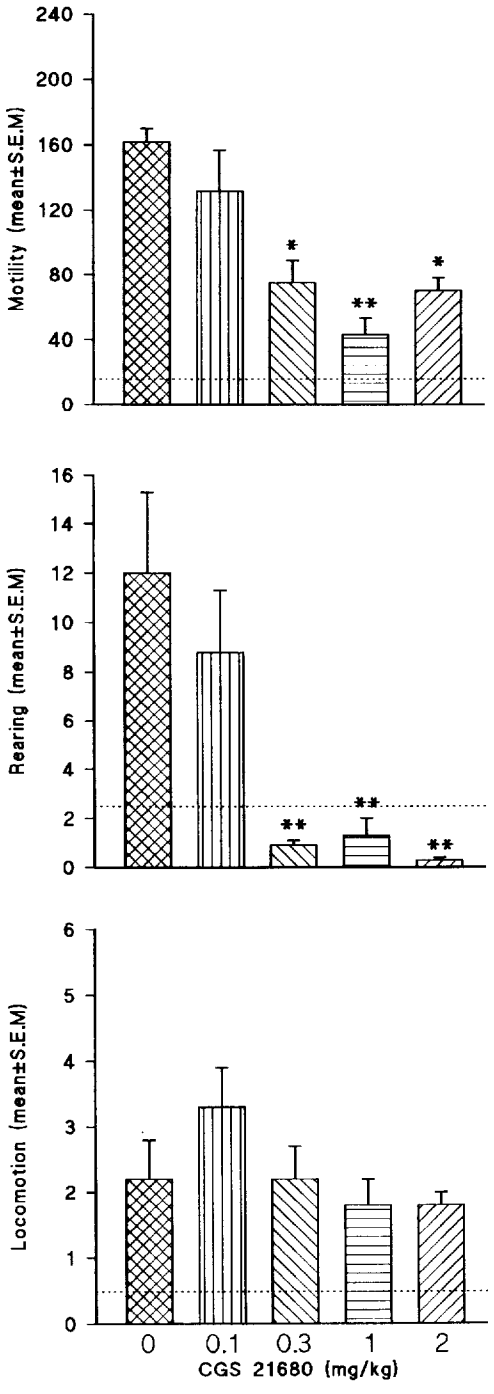

Figure 4. Amphetamine (1 mg/kg)-induced motor activity (motility, rearing, and locomotion) in habituated rats after the systemic administration of saline (CGS 21680 0 mg/kg) or CGS 21680 0.1, 0.3, 1, or 2 mg/kg. Results are expressed as mean ± S.E.M. counts/5 minutes obtained during the first 65 minutes of observation. The ED50 values of CGS 21680-mediated counteraction of amphetamine-induced motility and rearing were 0.17 and 0.17, respectively. The horizontal dotted line shows the motor activity in control animals, without amphetamine treatment. * and **: significantly different (ANOVA, $p < 0.05$ and $p < 0.01$, respectively) compared to the saline-treated group; $n = 8$–10/group.

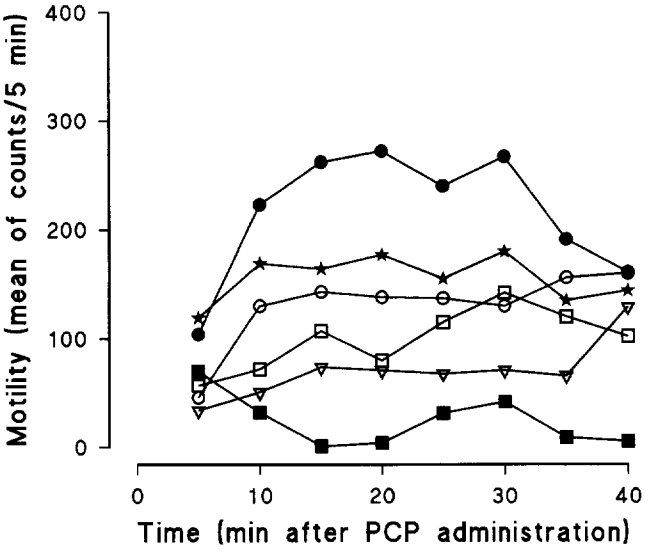

Figure 5. Time-course of the PCP (2 mg/kg)-induced motor activity (motility) in habituated rats after the systemic administration of saline (filled circles) or CGS 21680 0.03 mg/kg (closed stars), 0.1 mg/kg (open circles), 0.3 mg/kg (open inverse triangle), or 1 mg/kg (open squares). The curve with closed squares shows the motor activity in control animals without PCP treatment. Results are expressed as mean counts/5 minutes; $n = 8$/group.

increases in motility (Figure 4). In fact, lower values than those found in animals treated with saline were obtained (Figure 4). High doses of CGS 21680 also decreased the already low level of rearing activity associated with PCP treatment (Fig. 6).

Haloperidol and clozapine also dose-dependently decreased amphetamine- and PCP-induced motor activity (data not shown). The ED50 values of haloperidol-mediated counteraction of amphetamine- and PCP-induced motility were 0.04 and 0.3 mg/kg, respectively (Table 1). The ED50 values of clozapine-mediated counteraction of amphetamine- and PCP-induced motility were 0.9 and 1.6 mg/kg, respectively (Table 1).

Catalepsy

CGS 21680 dose-dependently induced catalepsy with the bar test (ED50 = 2 mg/kg) but not with the grid test (data not shown). With 10 mg/kg of CGS 21680 the animals were alert but clearly hypotonic ("flat body posture") and they had signs of pronounced peripheral side effects (tachycardia and diarrhea). Haloperidol induced catalepsy with both the grid test (ED50 = 0.15; data not shown) and, with the bar test (ED50 = 0.09) (Table 1, Figure 7). Clozapine only induced some catalepsy with the bar test at 30 mg/kg (Table 1, Figure 7).

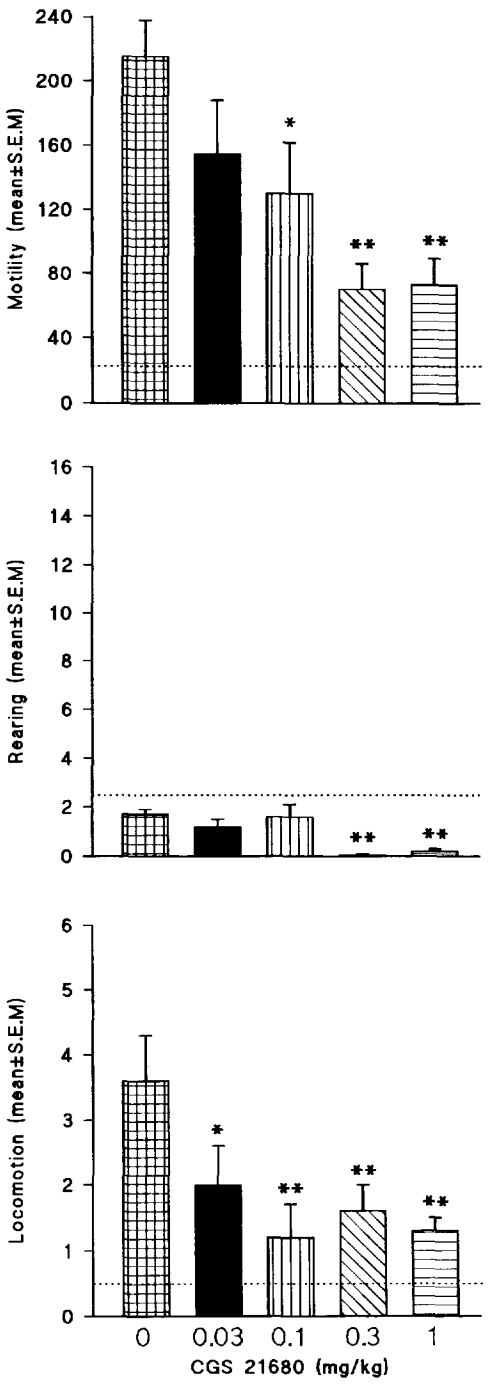

Figure 6. PCP (2 mg/kg)-induced motor activity (motility, rearings, and locomotion) in habituated rats after the systemic administration of saline (CGS 21680 0 mg/kg) or CGS 21680 at 0.03, 0.1, 0.3, or 1 mg/kg. Results are expressed as mean ± S.E.M. counts/5 minutes obtained during the first 65 minutes of observation. The ED50 values of CGS 21680-mediated counteraction of PCP-induced motility and locomotion were 0.05 and 0.01, respectively. The horizontal dotted line shows the motor activity in control animals, without PCP treatment. * and **: significantly different (ANOVA, $p < 0.05$ and $p < 0.01$, respectively) compared to the saline-treated group; $n = 8$/group.

DISCUSSION

Experimental evidence has been found for a stronger antagonistic interaction between adenosine A_{2A} and dopamine D_2 receptors in the ventral compared to the dorsal striatum (Ferré et al. 1993a, 1994b). It was therefore postulated that adenosine A_{2A} agonists could have antipsychotic properties with an atypical profile (Ferré et al. 1994b), since the antipsychotic and extrapyramidal side effects of neuroleptics seem to be mediated, at least partially, by the blockade of dopamine D_2 receptors in the ventral and dorsal striatum, respectively (Fuxe et al. 1977; Borison et al. 1983; Altar et al. 1986; Ögren et al. 1986; Robertson and Fibiger 1992). Furthermore, the adenosine A_{2A} agonist CGS 21680 has been found to selectively potentiate the effects of dopamine D_2 antagonists (Ferré et al. 1994b; Kafka and Corbett 1996). Therefore, it was also proposed that adenosine A_{2A} agonists could be used in combination with dopamine D_2 antagonists, to reduce the incidence of extrapyramidal side effects (Ferré et al. 1994b). Finally, prolonged treatment with the typical antipsychotic haloperidol, but not with the atypical antipsychotic clozapine, was associated with an increased antagonistic A_{2A}–D_2 interaction and with an upregulation of both dopamine D_2 and adenosine A_{2A} receptors in the rat striatum (Ferré et al. 1994c; Parsons et al. 1995). It was suggested that the increased A_{2A} receptor function could be an endogenous protective mechanism which could avoid the development of extrapyramidal side effects (Ferré et al. 1994c), which have been proposed to correlate with the upregulation of striatal dopamine D_2 receptors (Klawans and Rubovits 1972). Therefore, it was postulated that A_{2A} receptor agonists could also be useful for the treatment of the neuroleptic-induced extrapyramidal side effects (Ferré et al. 1994c).

The comparison between the effective doses for antagonizing dopamine-mediated (apomorphine and amphetamine) motor hyperactivity and the doses inducing catalepsy in the rat is likely the most useful experimental approach for evaluating antipsychotic activity and the liability to induce extrapyramidal side effects of a potential antipsychotic drug (see Ögren 1996). Thus a high ratio between the ED50 value for inducing catalepsy and the ED50 value for antagonizing apomorphine- or amphetamine-induced motor activity would indicate an atypical profile (Ögren et al. 1986; Hoffman and Donovan 1995). This is based on the experimental evidence suggesting that: (1) the ventral striatum is a main substrate for the dopamine-mediated motor hyperactivity, while the dorsal striatum is the substrate for catalepsy (Kelly et al. 1975; Ellenbroek et al. 1985; Sharp et al. 1987); (2) blockade of dopamine D_2 receptors in the ventral striatum mediates the antipsychotic action of neuroleptics, while dopamine D_2 receptor blockade in the dorsal striatum mediates their extrapy-

Table 1. ED50 Values (mg/kg) for the Induction of Catalepsy and for the Counteraction of Amphetamine- and PCP-Induced Motility

	Amph-Induced Motility	PCP-Induced Motility	Amph-/PCP-Induced Motility Ratio	Catalepsy	Catalepsy/ Amph-Induced Motility Ratio	Catalepsy/ PCP-Induced Motility Ratio
Haloperidol	0.04	0.3	0.1	0.09	2	0.3
Clozapine	0.9	1.6	0.5	> 30	> 30	> 20
CGS 21680	0.17	0.05	3	2	12	40

ramidal side effects (Ögren et al. 1986; Robertson and Fibiger 1992).

The systemic administration of CGS 21680 was found to dose-dependently antagonize the spontaneous and the amphetamine-induced horizontal activity (motility) and vertical activity (rearings) with similar ED50 values (around 0.2 mg/kg). It has already been described that different typical and atypical antipsychotics have similar ED50 values for their depressant effects on spontaneous and amphetamine-induced motor activity (Jackson et al. 1994), suggesting that the same mechanisms are involved in the elicitation of both types of behavior. However, a clear differential effect of the dopamine D_2 antagonist raclopride, a neuroleptic with an atypical profile in animal models (Ögren et al. 1986; Hoffman and Donovan 1995), has been shown for the spontaneous and amphetamine-induced motor activity when both drugs were infused in the rat nucleus acumbens. Raclopride was found to be much more effective in antagonizing amphetamine-induced than spontaneous motor activity (van den Boss et al. 1988). This is in contrast to some results obtained with systemic administration, showing that raclopride was more effective in antagonizing spontaneous than amphetamine-induced motor activity (Jackson et al. 1994). The same authors found that the atypical antipsychotic clozapine was equally potent in both tests. Altogether these studies show that the comparison between the depressant effects of a potential antipsychotic drug on spontaneous and amphetamine-induced motor activity cannot be used to predict its possible atypical profile.

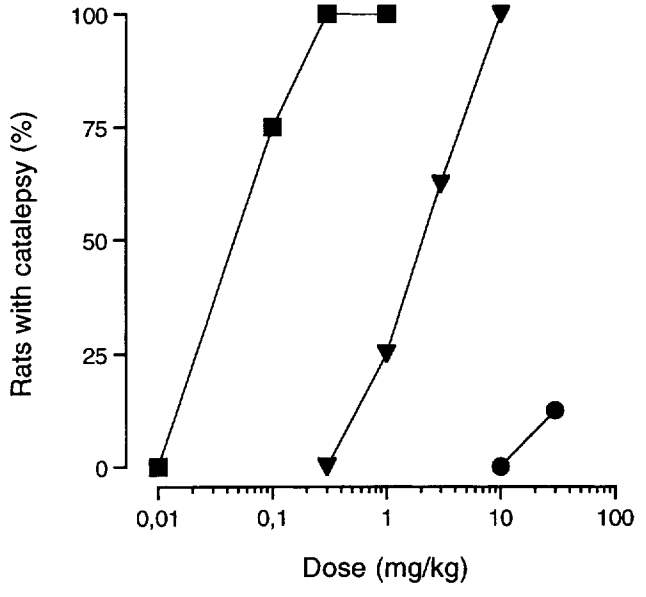

Figure 7. The cataleptic potency of haloperidol (filled squares), CGS 21680 (filled triangles) and clozapine (filled circles) assessed using the bar test. $n = 8$/group. Catalepsy was measured 20, 40, 60, 90, 120, and 240 minutes after the drug administration. Catalepsy was defined as present when the mean of the three highest values was at least 15 seconds. The proportion of animals that were cataleptic according to this criterion was calculated for each dose level of the drugs and the ED50 values were determined by non-linear regression analysis. The ED50 value was defined as the dose at which 50% of the animals were cataleptic.

It could be argued that the equipotent effect of CGS 21680 on spontaneous and amphetamine-induced motor activity could be related to an unspecific general depressant effect of the compound due to, for instance, its peripheral side effects, like hypotension (Hutchison et al. 1989; Mathôt et al. 1995). However, the differential effect of CGS 21680 on the different aspects of amphetamine-induced motor activity rules out that possibility. Although CGS 21680 antagonized spontaneous rearings, motility and locomotion with about the same ED50 values, it did not modify amphetamine-induced locomotion. Furthermore, lower doses of CGS 21680 were needed to counteract PCP-induced motor activity than to depress spontaneous motor activity.

High doses of CGS 21680 were needed to induce catalepsy with the bar test (ED50 = 2 mg/kg) and no catalepsy was obtained with the grid test. The animals did not appear sedated, but with the highest dose of CGS 21680 (10 mg/kg) they were clearly hypotonic and had signs of pronounced peripheral side effects (tachycardia and diarrhea). Some of those effects could possibly be related to activation of A_1 receptors, since CGS 21680 is about 100 times more selective for A_{2A} than for A_1 receptors (Hutchison et al. 1989). Although hypotonia could be responsible for the lack of catalepsy in the grid test, the bar test was sensitive enough to show that 100% of the animals were cataleptic with the high hypo-

tonic dose of CGS 21680 (10 mg/kg). A high ratio between the ED50 value for induction of catalepsy and the ED50 value for antagonizing amphetamine-induced motor activity was therefore obtained (12), which clearly establishes an atypical antipsychotic profile of CGS 21680 in these animal models.

It has been suggested that PCP-induced behavioral effects in animals represent an animal model of schizophrenia, since it reproduces both positive and negative symptoms of schizophrenia, while amphetamine only mimics positive symptoms (McKinney 1989; Javitt and Zukin 1991). Conflicting results have recently been obtained which suggest that different types of antipsychotic drugs exert a differential effect on amphetamine- and PCP-induced motor activity. Jackson et al. (1994) found that the atypical antipsychotic clozapine exerts stronger depressant effect on amphetamine- than on PCP-induced motor activation, while Maurel-Remy et al. (1995) found the opposite results. It is difficult to draw any conclusion from both studies, since different doses of amphetamine and PCP were used. Nevertheless, the results obtained by Maurel-Remy et al. (1995) could have been influenced by the high dose of amphetamine used, since clozapine has recently been shown to exert a differential effect on amphetamine-induced motor activity depending on the dose, being much less effective with a high doses of amphetamine (Arnt 1995).

In the present work the differential effect of CGS 21680 on amphetamine- and PCP-induced motor activity was compared with the effect of haloperidol and clozapine. CGS 21680 was comparably much stronger than haloperidol or clozapine at antagonizing the motor activity induced by PCP than the motor activity induced by amphetamine. A possible interpretation of these results is the existence of similar or synergistic effects of N-methyl-D-aspartate (NMDA) and A_{2A} receptors at the cellular level. In this way, A_{2A} receptor stimulation could counteract the effects induced by the PCP-mediated NMDA receptor blockade. For instance, both NMDA and A_{2A} receptor stimulation have been reported to be involved in the haloperidol-induced increase in the expression of the immediate early gene *c-fos* in the rat striatum (Boegman and Vincent 1996). Furthermore, antagonistic effects of adenosine A_{2A} agonists and NMDA antagonists have been described at the behavioral level (Hauber and Münkle 1995). Finally, it must be pointed out that Browne and Welch (1982) described an antagonism of PCP's discriminative properties by adenosine agonists. However, only selective adenosine A_1 agonists were used.

Our results contradict those recently reported by Kafka and Corbett (1996), which suggest that CGS 21680 does not have an atypical antipsychotic profile in animal models. However, in their study the ratio between the ED50 dose for inducing catalepsy in rats (which was very similar to that obtained in the present study) and the ED50 dose for counteracting apomorphine-induced climbing in mice was used as an indicator of atypicality. The ratio was in the same range as the one obtained with the typical antipsychotic haloperidol. The combination of data obtained from different species might well explain the discrepant findings by Kafka and Corbett (1996). On the other hand, the models used in the present work have repeatedly been shown to be a reliable animal model to predict the extrapyramidal side effect liability of antipsychotic drugs in man (Ögren et al. 1984; Ögren et al. 1988; Hoffman and Donovan 1995).

In conclusion the present results show a clear atypical antipsychotic profile of the adenosine A_{2A} agonist CGS 21680 in animal models. However, its peripheral side effects, in particular hypotension (Hutchison et al. 1989; Mathôt et al. 1995), may limit its potential use in schizophrenic patients. Recently, Webb et al. (1993) have demonstrated the development of complete tolerance of the antihypertensive effects of CGS 21680 in conscious spontaneously hypertensive rats following continuous administration. More studies about the prolonged treatment with adenosine A_{2A} agonists in models relevant for schizophrenia are needed to determine if there is also tolerance of the central effects of CGS 21680.

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