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Adenosine A_2 receptors modulate haloperidol-induced catalepsy in rats

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Abstract

The effect of adenosine A_1 and A_2 receptor agonists and antagonists was investigated on haloperidol-induced catalepsy in rats. Pretreatment (i.p.) with the non-selective adenosine receptor antagonist, theophylline, or the selective adenosine A_2 receptor antagonist, 3,7-dimethyl-1-propargylxanthine (DMPX), significantly reversed haloperidol-induced catalepsy, whereas the selective adenosine A_1 receptor antagonists, 8-phenyltheophylline and 8-cyclopentyl-1,3-dipropylxanthine produced no effect. Similar administration of the adenosine A_2 receptor agonists, 5′-(*N*-cyclopropyl)-carboxamidoadenosine and 5′-*N*-ethylcarboxamidoadenosine (NECA), and the mixed agonists with predominantly A_1 site of action, N^6-(2-phenylisopropyl) adenosine or 2-chloroadenosine, potentiated haloperidol-induced catalepsy. Higher doses of the adenosine agonists produced catalepsy when given alone. However, N^6-cyclopentyladenosine, a highly selective adenosine A_1 receptor agonist, was ineffective in these respects. The per se cataleptic effect of adenosine agonists was blocked by DMPX and the centrally acting anticholinergic agent, scopolamine. Scopolamine also attenuated the potentiation of haloperidol-induced catalepsy by adenosine agonists. Further, i.c.v. administration of NECA and DMPX produced a similar effect as that produced after their systemic administration. These findings demonstrate the differential influence of adenosine A_1 and A_2 receptors on haloperidol-induced catalepsy and support the hypothesis that the functional interaction between adenosine and dopamine mechanisms might occur through adenosine A_2 receptors at the level of cholinergic neurons. The results suggest that adenosine A_2, but not A_1, receptor antagonists may be of potential use in the treatment of Parkinson's disease.

Keywords: Haloperidol; Catalepsy; Theophylline; Adenosine receptor agonist; Adenosine receptor antagonist

1. Introduction

Adenosine is known to mediate its effects through four major receptor subtypes, termed A_1, A_{2A}, A_{2B} and A_3 (Palmer and Stiles, 1995). An interesting feature of adenosine A_{2A} receptors is their co-expression and ability to interact with dopamine D_2 receptor sites in the brain. While adenosine A_1 receptors are widely expressed in different areas of the central nervous system (CNS) (Mahan et al., 1991; Reppert et al., 1991), adenosine A_{2A} receptors are almost exclusively localized in dopamine-innervated areas of the CNS such as striatum, nucleus accumbens and olfactory tubercle (Fink et al., 1992; Schiffmann et al., 1991). Activation of adenosine A_{2A} receptors reduces the affinity of ligands for dopamine D_2 receptor agonist binding sites in striatal membranes (Ferre et al., 1991c). In behavioural studies, several lines of evidence have revealed that adenosine A_{2A} receptors can modulate striatal processes involved in the control of locomotor activity (Barraco and Bryant, 1987; Barraco et al., 1993; Durcan and Morgan, 1989) and stereotypy (Barraco, 1991). Moreover, stimulation of central adenosine A_{2A} receptors by intracerebroventricular (Ferre et al., 1991b) or systemic (Zarrindast et al., 1993) administration of adenosine agonists is reported to induce catalepsy in laboratory animals. Furthermore, the non-selective adenosine receptor antagonist, theophylline, and the selective adenosine A_{2A} receptor antagonist, KF17837, have been shown to antagonize haloperidol-induced catalepsy (Casas et al., 1988; Kanda et al., 1994), an animal model for Parkinson's disease (Hornykiewicz, 1973). Recently, theophylline has been shown to improve motor scores and mental well-being of parkinsonian patients (Mally and Stone, 1994).

The region-specific distribution of adenosine A_1 and A_{2A} receptors and their differential physiological functions (Brown et al., 1990; Jin et al., 1993) appear to confer selectivity in the regulation of behaviour by these receptors (Jain et al., 1995; Normile and Barraco, 1991). However, the functional role of these subtypes of receptors in the extrapyramidal system has not been documented. There-

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fore, the present investigations were designed to examine the effect of adenosine A_1 and A_2 receptor agonist and antagonists on catalepsy induced by haloperidol, an antipsychotic agent with dopamine receptor-blocking activity. In view of the regulation of striatal cholinergic transmission by adenosine A_{2A} receptors (Kurokawa et al., 1996), the study was extended to explore the possibility of an interaction between adenosine and dopamine through the cholinergic system.

2. Materials and methods

2.1. Animals

Male Wistar rats weighing 150–200 g maintained on a 12/12 h light/dark cycle were used. Food and water were continuously available in the home cages. All the experiments were carried out between 08:00 and 14:00 h.

2.2. Measurement of catalepsy

Catalepsy of an individual rat was measured in a stepwise manner by a scoring method as described below (Kulkarni et al., 1980). The method assessed the ability of an animal to respond to an externally imposed posture. *Step I* – The rat was taken out of the home cage and placed on a table. If the rat failed to move when touched gently on the back or pushed, a score of 0.5 was assigned. *Step II* – The front paws of the rat were placed alternately on a 3-cm high block. If the rat failed to correct the posture within 15 s, a score of 0.5 for each paw was added to the score of step I. *Step III* – The front paws of the rat were placed alternately on a 9-cm high block. If the rat failed to correct the posture within 15 s, a score of 1 for each paw was added to the scores of step I and II. Thus, for an animal, the highest score was 3.5 (cut-off score) and reflects total catalepsy.

2.3. Drugs and solutions

Drugs used in the present study were haloperidol (Searle India), theophylline, 3,7-dimethyl-1-propargylxanthine (DMPX), 8-phenyltheophylline, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), 5′-(*N*-cyclopropyl)-carboxamidoadenosine (CPCA), 5′-*N*-ethylcarboxamidoadenosine (NECA), N^6-(2-phenylisopropyl)adenosine (R-PIA), 2-chloroadenosine, N^6-cyclopentyladenosine (CPA) (all from Research Biochemicals International, Natick, MA, USA) and scopolamine HBr (Sigma, St. Louis, MO, USA).

Haloperidol was obtained in an injectable form. 8-Phenyltheophylline and DPCPX were dispensed in a 1% carboxymethylcellulose suspension. CPCA was dissolved in slightly acidified saline. All other drugs were dissolved in normal saline.

2.4. Drug treatment

All drugs were injected i.p., unless mentioned otherwise. Catalepsy was induced by haloperidol and measured every 30 min up to 3 h following its administration. In some experiments, adenosine receptor agonists/antagonists were given 30 min prior to haloperidol or vehicle, in order to test the effect of these agents on catalepsy. In similarly designed other experiments, the anticholinergic agent, scopolamine, was given alone or simultaneously with adenosine agonists, 30 min before haloperidol or the vehicle treatment.

NECA and DMPX were also infused i.c.v. in some experiments to eliminate their systemic effects. For stereotaxic surgery rats were anaesthetized with sodium pentobarbital (50 mg/kg, i.p.) and mounted in a stereotaxic frame (Inco, Ambala, India). A stainless steel canula (outer diameter 0.75 mm) was implanted into the right lateral ventricle of each rat at coordinates 0.8 mm posterior to bregma, 1.8 mm lateral from midline and 3.3 mm ventral from the surface of the skull according to the atlas of Paxinos and Watson (1985). The canula was fixed to the skull with dental cement. After surgery the animals were kept in separate cages and a recovery period of 5–6 days was allowed before the start of experiments. In one group of these animals, catalepsy was induced by i.c.v. infusion of NECA (2.5 and 3.5 μg/rat). In other groups, DMPX (50 μg/rat), NECA (0.02 μg/rat) or saline was infused i.c.v. at 90 min after intraperitoneal haloperidol (0.5 mg/kg) treatment and the peak catalepsy was assessed 60 min thereafter. The per se effect of these doses of NECA and DMPX at 60 min was also examined in a different group of animals. The injection volume of 4 μl was maintained for the i.c.v. infusion.

At the end of i.c.v. experiments, injection sites were verified by injecting the equivalent volume of 1% methylene blue and eventually examining the brain sections for the presence of dye in the ventricle. The present study used the data only from those animals in which canula placement occurred at the target coordinates.

2.5. Statistical analysis

The data were analysed using Kruskal-Wallis one-way ANOVA with differences between rank means being assessed using the non-parametric Mann-Whitney *U*-test. A value of $P < 0.05$ was considered to be statistically significant (Siegel, 1956).

3. Results

3.1. Cataleptic effect of haloperidol and its reversal by adenosine antagonists

Haloperidol at 0.5 and 1 mg/kg doses produced significant catalepsy in rats. The onset of the response was

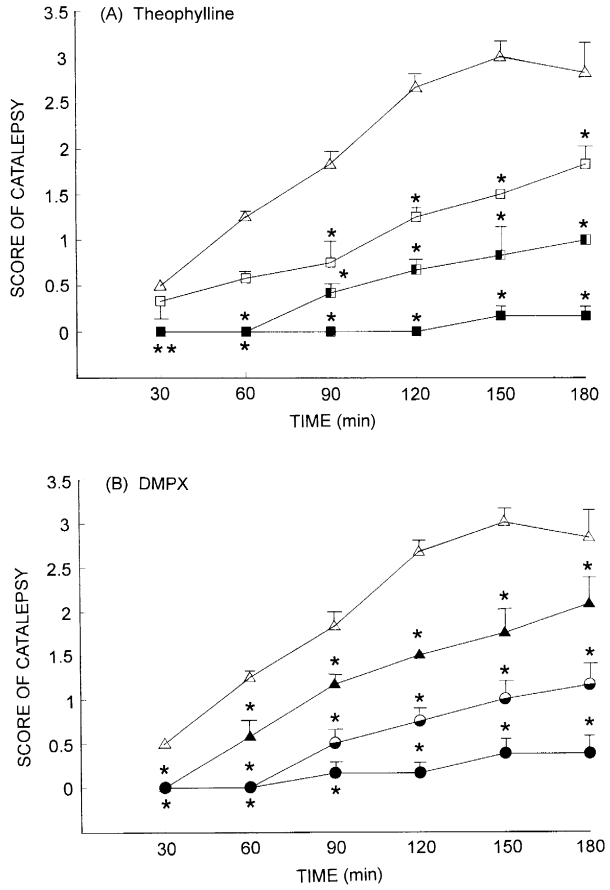

Fig. 1. Effects of theophylline or DMPX on haloperidol-induced catalepsy in rats. Theophylline, DMPX, or saline in the control group, was i.p. injected 30 min prior to haloperidol (1 mg/kg, i.p.) and catalepsy was recorded at 30, 60, 90, 120, 150 and 180 min after haloperidol treatment. Groups are: (A) control (△), theophylline 4 (□), 8 (◧) and 12 mg/kg (■); (B) control (△), DMPX 1 (▲), 1.5 (◒) and 2 mg/kg (●). Each point represents mean ± S.E.M. for 6 rats per group. * $P < 0.05$, Mann-Whitney *U*-test.

evident 30 min after drug administration and reached a maximum at 150 min. Prior administration of the non-selective adenosine receptor antagonist, theophylline (4, 8 and 12 mg/kg), or the selective adenosine A_2 receptor

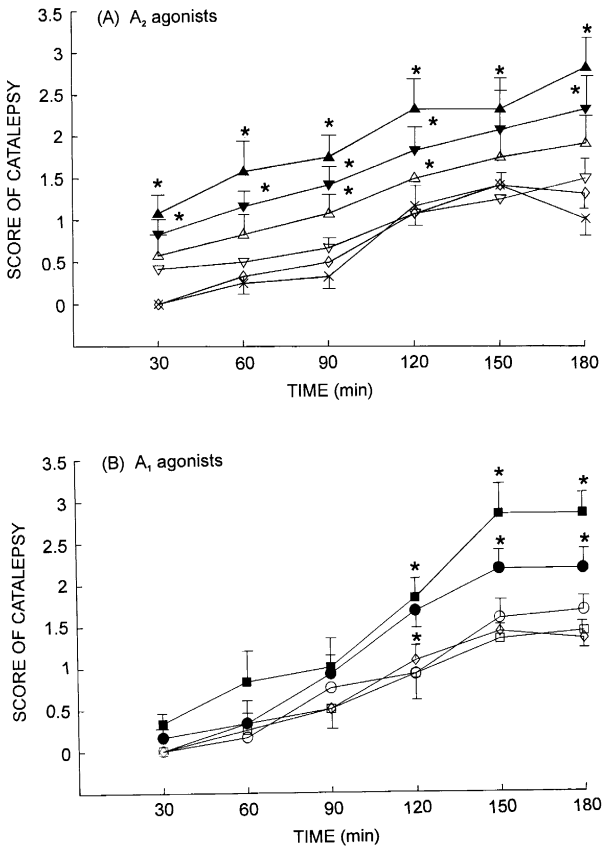

Fig. 2. Effects of subthreshold doses of the A_2 agonists, NECA and CPCA, or the predominantly A_1 agonists, R-PIA and 2-chloroadenosine, and a combination of each of these drugs with scopolamine on haloperidol-induced catalepsy in rats. Adenosine agonists, or saline in the control group, were i.p. administered 30 min prior to haloperidol (0.5 mg/kg, i.p.). Scopolamine (0.10 mg/kg, i.p.) was given simultaneously when combined with the adenosine agonists. Catalepsy was recorded at 30, 60, 90, 120, 150 and 180 min after haloperidol treatment. Groups are: (A) control (◇), control + scopolamine (×), NECA 0.05 mg/kg (▲), scopolamine + NECA 0.05 mg/kg (△), CPCA 0.07 mg/kg (▼), scopolamine + CPCA 0.07 mg/kg (▽); (B) control (◇), R-PIA 0.25 mg/kg (●), scopolamine + R-PIA 0.25 mg/kg (○), 2-chloroadenosine 0.20 mg/kg (■), scopolamine + 2-chloroadenosine 0.20 mg/kg (□). Each point represents mean ± S.E.M. for 6 rats per group. * $P < 0.05$, Mann-Whitney *U*-test.

Table 1
The effect of adenosine A_1 receptor antagonists, 8-phenyltheophylline and DPCPX on haloperidol (0.5 mg/kg, i.p.)-induced catalepsy in rats

Treatment	Dose (mg/kg)	Catalepsy score at different time intervals (min) after haloperidol treatment					
		30	60	90	120	150	180
Saline + haloperidol	0.5	0.00 ± 0.00	0.42 ± 0.09	0.58 ± 0.09	1.17 ± 0.12	1.50 ± 0.00	1.33 ± 0.12
8-Phenyltheophylline + haloperidol	0.5 + 0.5	0.00 ± 0.00	0.58 ± 0.17	0.67 ± 0.18	1.17 ± 0.18	1.42 ± 0.09	1.25 ± 0.12
	2.5 + 0.5	0.17 ± 0.12	0.67 ± 0.23	0.83 ± 0.12	1.33 ± 0.12	1.50 ± 0.00	1.33 ± 0.12
	10.0 + 0.5	0.00 ± 0.00	0.67 ± 0.23	0.83 ± 0.18	1.25 ± 0.34	1.58 ± 0.22	1.25 ± 0.19
DPCPX + haloperidol	0.5 + 0.5	0.00 ± 0.00	0.33 ± 0.12	0.50 ± 0.14	1.08 ± 0.17	1.42 ± 0.09	1.17 ± 0.12
	2.5 + 0.5	0.00 ± 0.00	0.25 ± 0.12	0.33 ± 0.12	1.00 ± 0.00	1.33 ± 0.12	1.17 ± 0.12
	10.0 + 0.5	0.00 ± 0.00	0.50 ± 0.20	0.67 ± 0.12	1.08 ± 0.09	1.67 ± 0.18	1.25 ± 0.14

8-Phenyltheophylline, DPCPX, or saline in the control group, was i.p. injected 30 min prior to haloperidol treatment. Each value represents mean ± S.E.M. for 6 rats per group. Comparisons between different groups at their respective time intervals found no significant difference, $P < 0.05$, Mann-Whitney *U*-test.

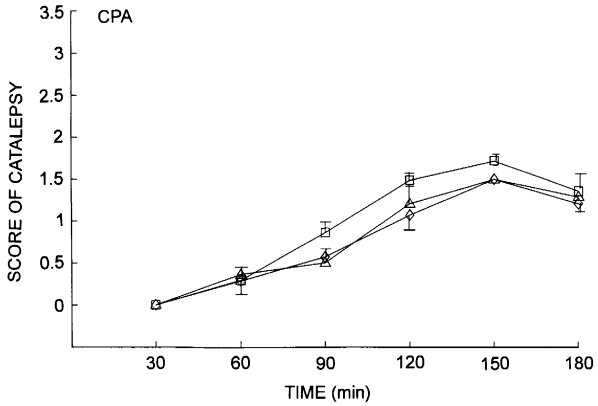

Fig. 3. Effect of CPA on haloperidol-induced catalepsy in rats. CPA, or saline in the control group, was i.p. injected 30 min prior to haloperidol (0.5 mg/kg, i.p.) and catalepsy was recorded at 30, 60, 90, 120, 150 and 180 min after haloperidol treatment. Groups are: control (◇), CPA 0.25 (△) and 1.0 mg/kg (□). Each point represents mean ± S.E.M. for 6 rats per group.

antagonist, DMPX (1, 1.5 and 2 mg/kg), reversed haloperidol (1 mg/kg)-induced catalepsy in a dose-dependent manner (Fig. 1). In contrast to this, the selective adenosine A_1 receptor antagonists, 8-phenyltheophylline (0.5, 2.5 and 10 mg/kg) and DPCPX (0.5, 2.5 and 10 mg/kg), produced no effect on haloperidol (0.5 mg/kg)-induced catalepsy (Table 1). None of the adenosine antagonists alone had any effect.

3.2. Potentiation of haloperidol-induced catalepsy by adenosine agonists and its reversal by scopolamine

Pretreatment with subthreshold doses of the selective adenosine A_2 receptor agonists, CPCA (0.07 mg/kg) and NECA (0.05 mg/kg), or the mixed agonists with predominantly adenosine A_1 receptor activity, R-PIA (0.25 mg/kg) and 2-chloroadenosine (0.2 mg/kg), potentiated the catalepsy induced by haloperidol (0.5 mg/kg) (Fig. 2). However, the selective adenosine A_1 receptor agonist, CPA, at 0.25 and 1.0 mg/kg doses had no significant effect on haloperidol (0.5 mg/kg)-induced catalepsy (Fig. 3). At these doses none of the adenosine agonists showed any cataleptic effect per se.

Scopolamine (0.1 mg/kg) significantly reversed the potentiating effect of adenosine agonists on haloperidol

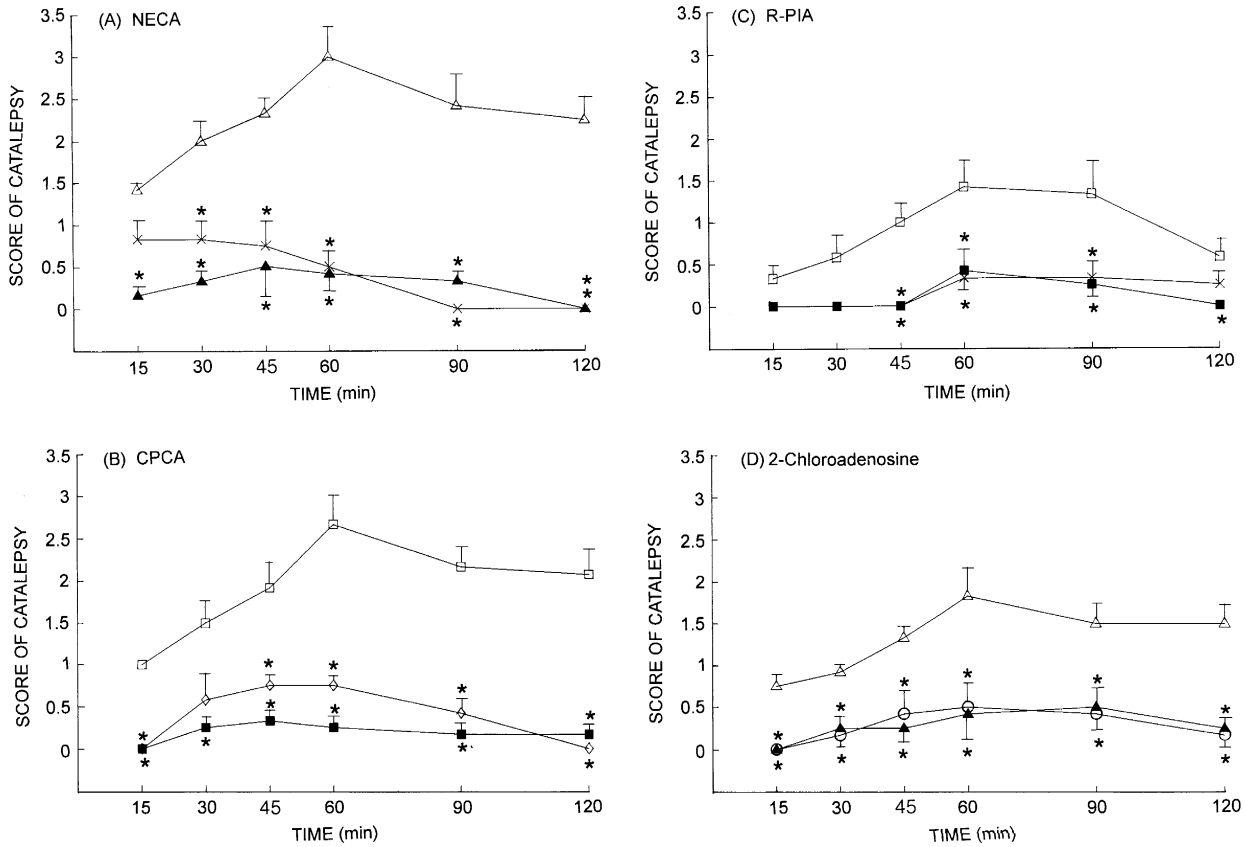

Fig. 4. Effects of DMPX and scopolamine on catalepsy induced by the A_2 agonists, NECA (0.5 mg/kg) and CPCA (0.7 mg/kg), or the A_1 agonists, R-PIA (2.5 mg/kg) and 2-chloroadenosine (2.0 mg/kg), in rats. DMPX (1.5 mg/kg), scopolamine (0.25 mg/kg), or saline in the control group, was i.p. injected 30 min prior to adenosine agonists. Catalepsy was recorded at 15, 30, 45, 60, 90 and 120 min after i.p. treatment with these adenosine agonists. Groups are: (A) saline + NECA (△), DMPX + NECA (▲), scopolamine + NECA (×); (B) saline + CPCA (□), DMPX + CPCA (■), scopolamine + CPCA (◇); (C) saline + R-PIA (□), DMPX + R-PIA (×), scopolamine + R-PIA (■); (D) saline + 2-chloroadenosine (△), DMPX + 2-chloroadenosine (▲), scopolamine + 2-chloroadenosine (○). Each point represents mean ± S.E.M. for 6 rats per group. * $P < 0.05$, Mann-Whitney *U*-test.

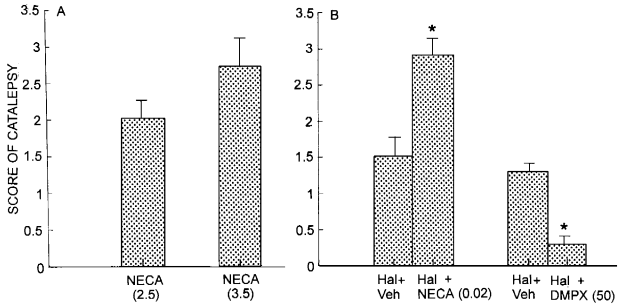

Fig. 5. Mean catalepsy scores after (A) intracerebroventricular administration of NECA (2.5 and 3.5 μg, 60 min before test) or (B) a combination of a subthreshold dose of NECA (0.02 μg, i.c.v.) or DMPX (50 μg, i.c.v.) with haloperidol (Hal) (0.5 mg/kg, i.p.). In combination studies, NECA, DMPX or vehicle was administered 90 min after haloperidol treatment and the catalepsy was tested 60 min thereafter (i.e. after 150 min of haloperidol treatment). Each bar represents mean ± S.E.M. for 5–6 rats per group. * $P < 0.05$ versus haloperidol + vehicle (Veh), Mann-Whitney *U*-test.

(0.5 mg/kg)-induced catalepsy (Fig. 2). At this dose, scopolamine produced no change in the cataleptic effect of haloperidol.

3.3. Cataleptic effect of adenosine agonists and its reversal by DMPX and scopolamine

At relatively high doses, animals treated with CPCA (0.7 mg/kg), NECA (0.5 mg/kg), R-PIA (2.5 mg/kg) or 2-chloroadenosine (2 mg/kg) showed a significant cataleptic response 15 min after drug administration which reached a maximum at 60 min. In contrast, animals treated with CPA (up to 1.5 mg/kg) did not show any sign of catalepsy or locomotor depression. The prior administration of either DMPX (1.5 mg/kg) or scopolamine (0.25 mg/kg) counteracted the cataleptic effect of adenosine agonists significantly (Fig. 4).

3.4. Effect of i.c.v. administration of NECA and DMPX on haloperidol-induced catalepsy

I.c.v. infusion of a 2.5 and 3.5 μg dose of NECA produced significant catalepsy. The mean catalepsy scores at 60 min are presented in Fig. 5.

DMPX (50 μg) or NECA (0.02 μg) infused i.c.v. in haloperidol (0.5 mg/kg)-treated animals reversed or potentiated respectively the peak cataleptic effect of haloperidol while producing no effect per se (Fig. 5).

4. Discussion

Neuroleptics such as haloperidol induce catalepsy in rodents by blockade of striatal dopamine receptors (Ossowska et al., 1990). The results of the present study show that this catalepsy can be influenced by activation or blockade of adenosine receptor subtypes. Systemic administration of the non-specific antagonist with greater affinity for adenosine A_2 receptors, theophylline (Ferre et al., 1991a), and the selective adenosine A_2 receptor antagonist, DMPX (Ukena et al., 1986), reversed, whereas the adenosine A_2 receptor agonists, CPCA and NECA (Jacobson et al., 1992), exacerbated haloperidol-induced catalepsy. Moreover, NECA or DMPX when injected i.c.v. had a similar effect as that seen after their systemic administration, showing that their effects on catalepsy were independent of their systemic actions. The results of i.c.v. administration also ruled out the possibility of the involvement of a pharmacokinetic component that is present after haloperidol treatment. Reversal of haloperidol-induced catalepsy by theophylline has also been reported earlier (Casas et al., 1988; Dijk et al., 1991). Conversely, the adenosine A_{2A} receptor agonist, CGS 21680, is known to induce catalepsy and may possess therapeutic potential as an antipsychotic agent (Ferre et al., 1991b). Thus, it seems that adenosine A_2 receptors regulate central dopamine D_2 transmission. The colocalization of adenosine A_2 receptors and dopamine D_2 receptors in the striatum (Fink et al., 1992) indicates that this might be the site where such regulation could take place. Indeed, the functional interaction between adenosine A_2 and dopamine D_2 receptors is known to occur in the striatopallidal neurons (Pollack and Fink, 1995). Furthermore, adenosine agonists are known to reduce locomotor activity (Barraco et al., 1993) and apomorphine-induced contralateral rotations in 6-hydroxydopamine hydrobromide-lesioned rats (Vellucci et al., 1993), by an action at adenosine A_2 receptors, whereas adenosine antagonists, methylxanthines, can induce hyperactivity (Snyder et al., 1981) and potentiate the locomotion and rotational behaviour induced by dopamine agonists (Ferre et al., 1991a; Fuxe and Ungerstedt, 1974). These reports seem to indicate a type of interaction between adenosine A_2 and dopamine D_2 transmission that is consistent with our results.

Unlike adenosine A_{2A} receptors, which are confined to striatum, adenosine A_1 receptors are ubiquitous to several brain areas such as cortex, cerebellum, hippocampus and thalamus (Reppert et al., 1991). Activation of adenosine A_1 receptors by the highly selective agonist CPA (Jacobson et al., 1992) had no effect with regard to catalepsy. However, the predominantly adenosine A_1 receptor agonists, R-PIA and 2-chloroadenosine (Daly, 1982), potentiated haloperidol catalepsy and also induced catalepsy per se at the higher doses. R-PIA and 2-chloroadenosine have been shown to have some affinity for adenosine A_2 receptors also (Daly et al., 1986; Williams, 1987). In this study the per se cataleptic effect of these agents was blocked by pretreatment with DMPX, a selective adenosine A_2 receptor blocker, suggesting an A_2 site of action. Thus, the contribution of adenosine A_1 receptor activation to the effects of R-PIA and 2-chloroadenosine seems unlikely. This is supported by previous studies indicating that the adenosine A_1 receptor antagonist, 8-phenyltheophylline

(Jacobson et al., 1985), does not reverse adenosine agonist-induced catalepsy (Zarrindast et al., 1993). Unlike adenosine A_2 receptor antagonists, 8-phenyltheophylline, and the highly selective adenosine A_1 receptor antagonist, DPCPX (Bruns et al., 1987), failed to affect haloperidol-induced catalepsy even at a wider dose range. These results further contribute to support a selective interaction between adenosine A_2 and dopamine D_2 receptors to modulate cataleptic response.

The functional interplay between dopamine and acetylcholine in the brain is well established (Bowers and Roth, 1972; Ahtee and Kaariainen, 1974; Sethy and Van Woert, 1974). A disinhibition of cholinergic neurons in the striatum has been reported after treatment with neuroleptic drugs (Hertting et al., 1989); enhanced cholinergic activity in the striatum causes dyskinesia and tremors. Furthermore, adenosine is known to regulate cholinergic transmission in the CNS (Forloni et al., 1986). While activation of adenosine A_1 receptors causes inhibition of acetylcholine release, activation of adenosine A_2 receptors, which are on cholinergic nerve terminals, causes stimulation of acetylcholine release (Brown et al., 1990), or counteracts the D_2 receptor-mediated inhibition of acetylcholine release (Jin et al., 1993). Moreover, the binding sites for the adenosine A_{2A} receptor agonist, CGS 21680, were found to co-purify with cholinergic synaptosomes in the rat striatum in one study (James and Richardson, 1993). In view of these reports, we examined the possibility of cholinergic involvement in the actions of adenosine analogues. The centrally acting anticholinergic agent, scopolamine, blocked the per se cataleptic effect of adenosine agonists as well as their influence on haloperidol-induced catalepsy. This indicates that the interaction between dopamine and adenosine might occur at the level of cholinergic neurons. Such a possibility seems likely in the light of the evidence that the effect of adenosine A_2 receptor activation on acetylcholine is greater in the absence of dopaminergic innervation (Kurokawa et al., 1996). The exact mechanism of the cholinergic contribution, however, is ambiguous and awaits further clarification.

In conclusion, the present study indicates that cholinergic transmission has an important role in the modulatory action of adenosine receptor agonists and antagonists on haloperidol-induced catalepsy. The results also support the previous suggestion (Kanda et al., 1994) that adenosine A_2 receptor antagonists can be exploited for their therapeutic potential as antiparkinsonian drugs.

References

Ahtee, L., Kaariainen, I., 1974. The role of dopamine in pilocarpine-induced catalepsy. Naunyn-Schmiedeberg's Arch. Exp. Pathol. Pharmacol. 284, 25.

Barraco, R.A., 1991. Behavioral actions of adenosine and related substances. In: Phillis, J.W. (Ed.), Adenosine and Adenine Nucleotides as Regulators of Cellular Function. CRC Press, Boca Raton, p. 339.

Barraco, R.A., Bryant, S.D., 1987. Depression of locomotor activity following bilateral injections of adenosine analogs into the striatum of mice. Med. Sci. Res. 15, 421.

Barraco, R.A., Martens, K.A., Parizon, M., Normile, H.J., 1993. Adenosine A_{2A} receptors in the nucleus accumbens mediate locomotor depression. Brain Res. Bull. 31, 397.

Bowers, M.B., Roth, R.H., 1972. Interaction of atropine-like drugs with dopamine-containing neurons in rat brain. Br. J. Pharmacol. 44, 301.

Brown, S.J., James, S., Reddington, M., Richardson, P.J., 1990. Both A_1 and A_{2A} purine receptors regulate striatal acetylcholine release. J. Neurochem. 55, 31.

Bruns, R.F., Fergus, J.S., Badger, E.W., Bristol, J.A., Santay, L.A., Hartman, J.D., Hays, S.J., Huang, C.C., 1987. Binding of the A_1 selective antagonist 8-cyclopentyl-1,3-dipropylxanthine to rat brain membranes. Naunyn-Schmiedeberg's Arch. Pharmacol. 335, 59.

Casas, M., Ferre, S., Guix, T., Jane, F., 1988. Theophylline reverses haloperidol-induced catalepsy in the rat: possible relevance to the pharmacological treatment of psychosis. Biol. Psychiatry 24, 642.

Daly, J.W., 1982. Adenosine receptors: targets for future drugs. J. Med. Chem. 25, 197.

Daly, J.W., Padgett, W., Thompson, R.D., Kusachi, S., Bugni, W.J., Olsson, R.A., 1986. Structure-activity relationship for N^6-substituted adenosine at a brain A_1 adenosine receptor with comparison to an A_2 adenosine receptor regulating coronary blood flow. Biochem. Pharmacol. 35, 2467.

Dijk, S., Krugers, H.J., Korf, J., 1991. The effect of theophylline and immobilization stress on haloperidol-induced catalepsy and on metabolism in the striatum and hippocampus, studied with lactography. Neuropharmacology 30, 469.

Durcan, M.J., Morgan, P.F., 1989. Evidence for adenosine A_2 receptor involvement in the hypomobility effects of adenosine analogues in mice. Eur. J. Pharmacol. 168, 285.

Ferre, S., Herrera-Marschitz, M., Grabowska-Anden, M., Casas, M., Ungerstedt, U., Anden, N.E., 1991a. Postsynaptic dopamine/adenosine interaction
II. Postsynaptic dopamine agonism and adenosine antagonism of methylxanthines in short-term reserpinized mice. Eur. J. Pharmacol. 192, 31.

Ferre, S., Rubio, A., Fuxe, K., 1991b. Stimulation of adenosine A_2 receptors induces catalepsy. Neurosci. Lett. 130, 162.

Ferre, S., Von Euler, G., Johansson, B., Fredholm, B.B., Fuxe, K., 1991c. Stimulation of adenosine high affinity A_2 receptors decreases the affinity of dopamine D_2 receptors in rat striatal membranes. Proc. Natl. Acad. Sci. USA 88, 7238.

Fink, J.S., Weaver, D.R., Rivkees, S.A., Peterfreund, R.A., Pollack, A.E., Adler, E.M., Reppert, S.M., 1992. Molecular cloning of the rat A_2 adenosine receptor: selective co-expression with D_2 dopamine receptors in rat striatum. Mol. Brain Res. 14, 186.

Forloni, G., Fisone, G., Consolo, S., Ladinsky, H., 1986. Qualitative differences in the effects of adenosine analogs on the cholinergic systems of rat striatum and hippocampus. Naunyn-Schmiedeberg's Arch. Pharmacol. 334, 85.

Fuxe, K., Ungerstedt, U., 1974. Action of caffeine and theophylline on supersensitive dopamine receptors: considerable enhancement of receptor response to treatment with dopa and dopamine receptor agonist. Med. Biol. 52, 48.

Hertting, G., Zumstein, A., Jackisch, R., Hoffman, I., Starke, K., 1989. Modulation by endogenous dopamine of release of acetylcholine in the caudate nucleus of the rabbit. Naunyn-Schmiedeberg's Arch. Pharmacol. 315, 111.

Hornykiewicz, O., 1973. Dopamine in the basal ganglia. Its role and therapeutic implications (including the clinical use of L-DOPA). Br. Med. Bull. 29, 172.

Jacobson, K.A., Kirk, K.L., Daly, J.W., Janzon, B., Li, Y.O., Fredholm, B.B., 1985. A novel 8-phenyl-substituted xanthine derivative is a selective antagonist at A_1 receptor in vivo. Acta Physiol. Scand. 125, 341.

Jacobson, K.A., VanGalen, P.J.M., Williams, M., 1992. Adenosine receptors: pharmacology, structure-activity relationship and therapeutic potential. J. Med. Chem. 35, 407.

Jain, N., Kemp, N., Adeyemo, O., Buchanan, P., Stone, T.W., 1995. Anxiolytic activity of adenosine receptor activation in mice. Br. J. Pharmacol. 116, 2127.

James, S., Richardson, P.J., 1993. The subcellular distribution of [^{3}H]-CGS 21680 binding sites in the rat striatum: copurification with cholinergic nerve terminals. Neurochem. Int. 23, 115.

Jin, S., Johansson, B., Fredholm, B.B., 1993. Effects of adenosine A_1 and A_2 receptor activation on electrically evoked dopamine and acetylcholine release from rat striatal slices. J. Pharmacol. Exp. Ther. 267, 801.

Kanda, T., Shiozaki, S., Shimada, J., Suzuki, F., Nakamura, J., 1994. KF17837: a novel selective adenosine A_{2A} receptor antagonist with anticataleptic activity. Eur. J. Pharmacol. 256, 263.

Kulkarni, S.K., Arzi, A., Kaul, P.N., 1980. Modifications of drug induced catatonia and tremors by quipazine in rats and mice. Jpn. J. Pharmacol. 30, 129.

Kurokawa, M., Koga, K., Kase, H., Nakamura, J., Kuwana, Y., 1996. Adenosine A_{2A} receptor-mediated modulation of striatal acetylcholine release in vivo. J. Neurochem. 66, 1882.

Mahan, L.C., McVittie, L.D., Smyk-Randall, E.M., Nakata, H., Monsma, F.J., Gerfen, C.R., Sibley, D.R., 1991. Cloning and expression of an A_1 adenosine receptor from rat brain. Mol. Pharmacol. 40, 1.

Mally, J., Stone, T.W., 1994. The effect of theophylline on parkinsonian symptoms. J. Pharm. Pharmacol. 46, 515.

Normile, H.J., Barraco, R.A., 1991. N^6-Cyclopentyladenosine impairs passive avoidance retention by selective action at A_1 receptors. Brain Res. Bull. 27, 101.

Ossowska, K., Karcz, M., Wardas, J., Wolfarth, S., 1990. Striatal and nucleus accumbens D_1/D_2 dopamine receptors in neuroleptic catalepsy. Eur. J. Pharmacol. 182, 327.

Palmer, T.M., Stiles, G.L., 1995. Review: Neurotransmitter receptors VII: Adenosine receptors. Neuropharmacology 34, 683.

Paxinos, G., Watson, C., 1985. The Rat Brain in Stereotaxic Coordinates. Academic Press, New York.

Pollack, A.E., Fink, J.S., 1995. Adenosine antagonists potentiate D_2 dopamine-dependent activation of Fos in the striatopallidal pathway. Neuroscience 68, 721.

Reppert, S.M., Weaver, D.R., Stehle, J.H., Rivkees, S.A., 1991. Molecular cloning and characterization of rat A_1-adenosine receptor that is widely expressed in brain and spinal cord. Mol. Endocrinol. 5, 1037.

Schiffmann, S.N., Jacobs, O.P., Vanderhaeghen, J.J., 1991. The striatal restricted adenosine A_2 receptor (RDC8) is expressed by enkephalin but not by substance P neurons. An in situ hybridization histochemistry study. J. Neurochem. 57, 1062.

Sethy, V.H., Van Woert, M.H., 1974. Regulation of striatal acetylcholine concentration by dopamine receptors. Nature 251, 529.

Siegel, S., 1956. Nonparametric Statistics for the Behavioural Sciences. McGraw-Hill Kogakusha, Tokyo.

Snyder, D.H., Katims, J.J., Annau, Z., Bruns, R.F., Daly, J.W., 1981. Adenosine receptors and behavioural actions of methylxanthines. Proc. Natl. Acad. Sci. USA 78, 3260.

Ukena, D., Shamin, M.T., Padgett, W., Daly, J.W., 1986. Analogues of caffeine: antagonists with selectivity for A_2 adenosine receptors. Life Sci. 39, 743.

Vellucci, S.V., Sirinathsinghji, D.J.S., Richardson, P.J., 1993. Adenosine A_2 receptor regulation of apomorphine-induced turning in rats with unilateral striatal dopamine denervation. Psychopharmacology 111, 383.

Williams, M., 1987. Purine receptors in mammalian tissues: pharmacology and functional significance. Annu. Rev. Pharmacol. Toxicol. 27, 315.

Zarrindast, M.R., Modabber, M., Sabetkasai, M., 1993. Influences of different adenosine receptor subtypes on catalepsy in mice. Psychopharmacology 113, 257.