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Differential effects of selective adenosine A_1 and A_{2A} receptor agonists on dopamine receptor agonist-induced behavioural responses in rats

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Abstract

The effects of the systemic (i.p.) administration of the selective adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA) and the selective adenosine A_{2A} receptor agonist sodium 2-*p*-carboxyethyl)phenylamino-5′-*N*-carboxamidoadenosine (CGS 21680) on different dopamine receptor agonist-induced behaviours were studied in the male rat. CGS 21680 (1 μmol/kg), but not CPA, was found to counteract the stereotypies induced by the non-selective dopamine receptor agonist apomorphine (0.25 mg/kg s.c.). Low doses of CGS 21680 (0.1 μmol/kg) and high doses of CPA (3 μmol/kg) counteracted yawning induced by the dopamine D_2 selective agonist quinpirole (0.05 mg/kg). On the other hand, low doses of CPA (0.3 μmol/kg) antagonized grooming induced by the selective dopamine D_1 receptor-selective agonist SKF 38393 (10 mg/kg i.p.), while CGS 21680 was ineffective. These results are consistent with the proposed existence of a selective antagonistic modulation of dopamine D_1 and D_2 receptors by adenosine A_1 and A_{2A} receptors, respectively. The ability of CGS 21680 to counteract apomorphine-induced stereotypies is weaker compared to its previously reported antagonistic effect of amphetamine-induced motor activity. This supports the hypothesis that adenosine A_{2A} receptor agonists may be potential antipsychotic drugs with a low potential for extrapyramidal side effects. © 1998 Elsevier Science B.V.

Keywords: Dopamine D_1 receptor; Dopamine D_2 receptor; Adenosine A_1 receptor; Adenosine A_{2A} receptor; Stereotypy; Yawning; Grooming

1. Introduction

Many experimental data indicate the existence of a strong adenosine-mediated inhibitory modulation of central dopaminergic neurotransmission (reviewed in Ferré et al., 1992, 1997). An important part of this adenosine–dopamine interaction seems to be due to the existence of specific antagonistic interactions between subtypes of adenosine and dopamine receptors in the striatum, mainly between adenosine A_1 and dopamine D_1 and between adenosine A_{2A} and dopamine D_2 receptors. (Ferré et al., 1992, 1997). These antagonistic receptor–receptor interactions seem to be segregated in the two subtypes of striatal γ-aminobutyric acidergic (GABAergic) efferent neurons. The GABAergic striatopallidal neurons are regulated by interacting adenosine A_{2A} and dopamine D_2 receptors. On the other hand, the GABAergic striatonigral–striatoentopeduncular neurons seem to be regulated by interacting adenosine A_1 and dopamine D_1 receptors (Ferré et al., 1997). In fact, striatal adenosine A_{2A} and dopamine D_2 receptors are mainly localized in the striatopallidal neurons, while the striatonigral–striatoentopeduncular neurons are the preferential localization of dopamine D_1 receptors. Although adenosine A_1 receptors are widely distributed, they are colocalized with dopamine D_1 receptors in the striatonigral–striatoentopeduncular neurons (Ferré et al., 1997).

At the behavioural level, it has been shown in reserpinized mice that adenosine A_1 and A_{2A} receptor agonists at low doses selectively counteract the motor activating effects induced by dopamine D_1 and D_2 receptor agonists, respectively (Ferré et al., 1994). Also in reserpinized mice and in rats with a 6-OH-dopamine-induced unilateral lesion of the nigrostriatal pathway, adenosine A_1 receptor antagonists selectively enhance dopamine D_1 receptor agonist-induced motor activation, while adenosine A_{2A} receptor antagonists enhance both dopamine D_1 and dopamine D_2 receptor agonist-induced motor effects (Pinna et al., 1996; Popoli et al., 1996). These behavioural results fit very well with the hypothesis of segregated adenosine A_{2A}

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receptor-dopamine D_2 receptor and adenosine A_1 receptor–dopamine D_1 receptor interactions in the two main different subtypes of striatal GABAergic efferent neurons. Although adenosine A_{2A} and dopamine D_1 receptors are not located on the same striatal efferent neurons, the adenosine A_{2A} receptor antagonist-induced potentiation of D_1 receptor-mediated motor activation could be explained by an interaction at the network level, similar to the synergistic effect of dopamine D_1 and D_2 receptor agonists (Robertson and Robertson, 1986; Paul et al., 1992). On the other hand, the failure of adenosine A_1 receptor antagonists to modify the motor effects of dopamine D_2 receptor agonists (Popoli et al., 1996) could be explained by the more widespread distribution of adenosine A_1 receptors.

Although these behavioural results are consistent with the specific interactions between striatal adenosine and dopamine receptors found in biochemical studies, they have been obtained in animals with striatal dopamine depletion, known to result into changes of the pharmacological properties of both striatal adenosine and dopamine receptors (reviewed in Ferré et al., 1997). Therefore, in the present study, the ability of the adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA) and the selective adenosine A_{2A} receptor agonist sodium 2-*p*-carboxyethyl)phenylamino-5′-*N*-carboxamidoadenosine (CGS 21680) to influence different dopamine receptor agonists-induced behaviours were studied in naive rats, without striatal dopamine denervation.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (A-Lab, Sollentuna, Sweden), weighing 350–450 g at the time of the experiments, 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) and light conditions with a 12-h light/dark cycle (lights on at 0700 h). All the experiments were performed between 0800 and 1500 h.

2.2. Compounds

The following compounds were used: sodium 2-*p*-carboxyethyl)phenylamino-5′-*N*-carboxamidoadenosine (CGS 21680) (a gift from Ciba-Geigy, Summit, NJ); N^6-cyclopentyladenosine (CPA) (RBI, Natick, USA); apomorphine hydrochloride (apomorphine, RBI); (±)-SKF-38393 hydrochloride (SKF 38393, RBI); (−)-quinpirole hydrochloride (quinpirole, RBI). All drugs were dissolved in saline. CGS 21680, CPA and SKF 38393 were administered i.p., in a volume of injection of 5 ml/kg. Apomorphine and quinpirole were administered s.c. into the neck in a volume of 2 ml/kg.

2.3. Behavioural analysis

After habituation for 1 h to the sound-proofed and dimly illuminated experimental room, the animals were placed in single Macrolon cages (dimensions: $20 \times 38 \times 16$ height) and allowed to explore the experimental cage for 1 h before the administration of either saline, CGS 21680 or CPA. Behavioural measurements were performed 15 min later, immediately after the administration of either apomorphine (0.25 mg/kg), SKF 38393 (10 mg/kg) or quinpirole (0.05 mg/kg). The experimenter was always blind to the treatment conditions. A pilot study determined that the 0.25 mg/kg dose of apomorphine induced a wide range of oral stereotypies (licking, biting and bobbing head) with a low interindividual variability. The doses of quinpirole and SKF38393 used were 0.05 mg/kg and 10 mg/kg, respectively, which have been previously reported

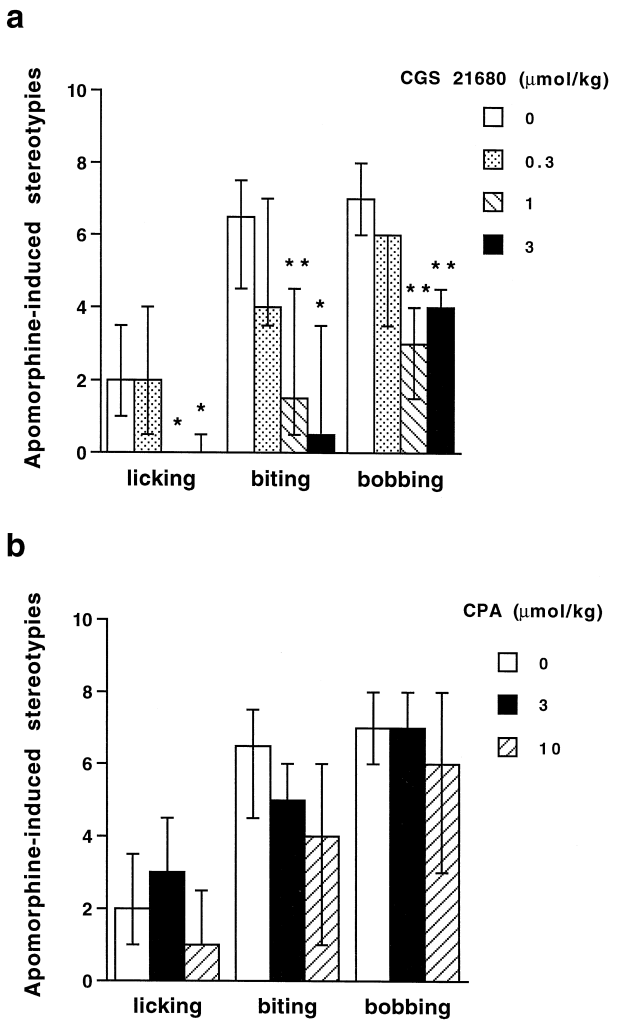

Fig. 1. Effect of the adenosine A_{2A} receptor agonist CGS 21680 (a) and the adenosine A_1 receptor agonist CPA (b) on licking, biting and bobbing head behaviours induced by apomorphine (0.25 mg/kg s.c.). Results are expressed in medians and interquartile ranges ($n = 8$–12 per group). * and **: $P < 0.05$ and $P < 0.01$, compared to the group treated with saline (0 μmol/kg).

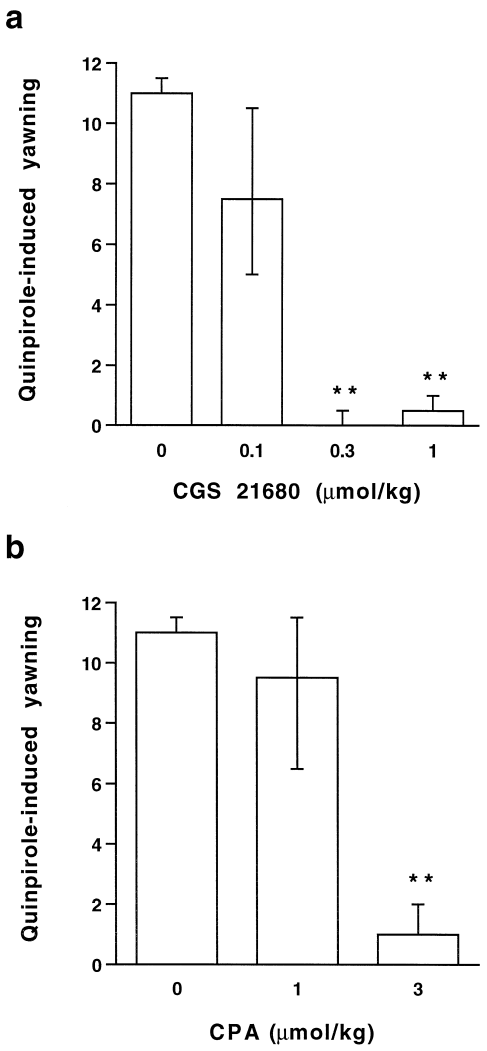

Fig. 2. Effect of the adenosine A_{2A} receptor agonist CGS 21680 (a) and the adenosine A_1 receptor agonist CPA (b) on yawning behaviour induced by the dopamine D_2 receptor agonist quinpirole (0.05 mg/kg s.c.). Results are expressed in medians and interquartile ranges ($n = 6$–8 per group). $**$: $P < 0.01$, compared to the group treated with saline (0 μmol/kg).

to be ED_{max} doses in the same rat strain for the induction of yawning and grooming, respectively (Longoni et al., 1987a; Serra et al., 1987; Wachtel et al., 1992).

Stereotypies were scored according to the following scale: 0 = no stereotypies present; 1 = intermittent or occasional stereotypies; 2 = continuous stereotypies. A stereotypy score (for each stereotypy) was determined every 10 min for a total period of 60 min by direct observation during 1-min periods (per rat) and the final accumulated stereotypy score represents the entire observation period. The scoring system is similar to that previously described by Arnt et al. (1987). Yawning was determined counting of the total number of yawns for a period of 30 min. Grooming was scored according to the following scale (similar to that previously described by Molloy and Waddington, 1984): 0 = no grooming present; 1 = grooming of any form; 2 = intense grooming, a characteristic pattern of grooming of the face with the forepaws followed by vigorous grooming of the hind flank with the snout. Grooming score was determined every 10 min for a total period of 30 min by direct observation during 1-min periods and an accumulated grooming score was obtained. Kruskal–Wallis and Mann–Whitney *U*-tests were used for the statistical analysis.

3. Results

3.1. Apomorphine-induced stereotypies

With apomorphine, three kinds of stereotypies were seen at the 0.25 mg/kg s.c. dose: licking, biting and bobbing head. CGS 21680 significantly inhibited the three

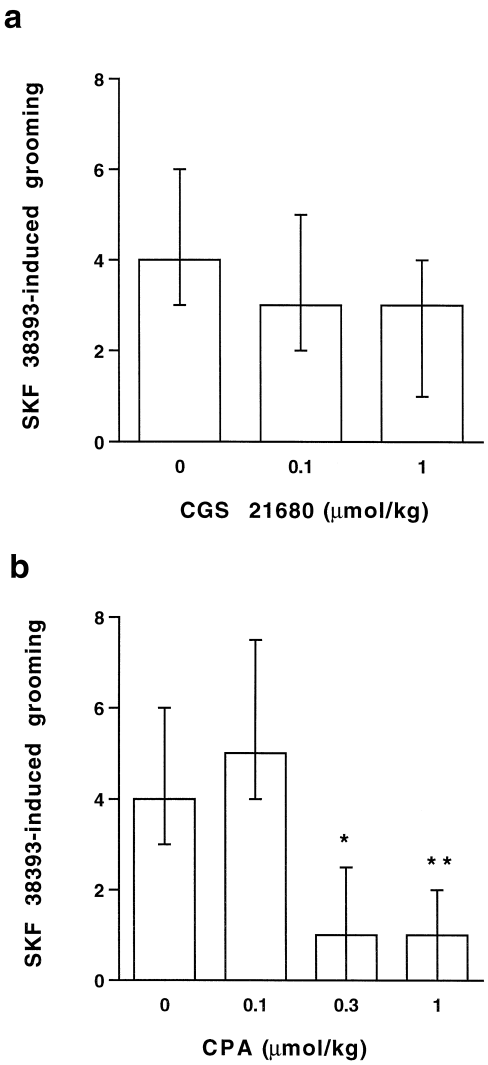

Fig. 3. Effect of the adenosine A_{2A} receptor agonist CGS 21680 (a) and the adenosine A_1 receptor agonist CPA (b) on grooming behaviour induced by the dopamine D_1 receptor agonist SKF 38393 (10 mg/kg i.p.). Results are expressed in medians and interquartile ranges ($n = 6$–8 per group). $*$ and $**$: $P < 0.05$ and $P < 0.01$, compared to the group treated with saline (0 μmol/kg).

kinds of stereotypies with the minimal effective dose (i.e., 1 μmol/kg), while CPA was ineffective (up to 10 μmol/kg)(Fig. 1).

3.2. Quinpirole-induced yawning

Quinpirole 0.05 mg/kg s.c. induced a strong yawning behaviour, which was significantly counteracted by low doses of CGS 21680 (minimal effective dose: 0.1 μmol/kg) and high doses of CPA (minimal effective dose: 3 μmol/kg)(Fig. 2).

3.3. SKF 38393-induced grooming

SKF 38393 10 mg/kg i.p. induced a pronounced grooming behaviour, which was significantly counteracted by CPA (minimal effective dose: 0.3 μmol/kg), but not by CGS 21680 (up to 1 μmol/kg) (Fig. 3).

4. Discussion

The present results agree with the proposed existence of a selective antagonistic modulation of dopamine D_1 and D_2 receptors by adenosine A_1 and A_{2A} receptors, respectively (Ferré et al., 1992, 1997). These interactions predict that adenosine A_1 and A_{2A} receptor agonists would produce similar behavioural effects as dopamine D_1 and D_2 receptor antagonists, respectively (Ferré, 1997). Similar to dopamine D_2 antagonists, the adenosine A_{2A} receptor agonist CGS 21680 counteracted apomorphine-induced stereotypies and yawning induced by the dopamine D_2 receptor agonist quinpirole, but it did not antagonize the grooming behaviour induced by the dopamine D_1 receptor agonist SKF 38393 (Arnt et al., 1987; Longoni et al., 1987a,b; Serra et al., 1987; Wachtel et al., 1992). On the other hand, the adenosine A_1 receptor agonist CPA behaved qualitatively different from dopamine D_1 receptor antagonists, which are known to antagonize these three types of dopamine receptor agonist-mediated behavioural responses at low doses (Arnt et al., 1987; Longoni et al., 1987a,b; Serra et al., 1987; Wachtel et al., 1992). Although low doses of CPA did selectively inhibit grooming induced by SKF 38393, higher doses were required to inhibit quinpirole-induced yawning and they were not even able to antagonize apomorphine-induced stereotypies.

Dopamine D_1 receptors have been shown to exert a permissive role in dopamine D_2 receptor agonist-mediated responses, such as stereotypies and yawning (Arnt et al., 1987; Longoni et al., 1987a,b; Serra et al., 1987; Wachtel et al., 1992). Therefore, the ability of dopamine D_1 receptor antagonists to inhibit apomorphine-induced stereotypies and quinpirole-induced yawning seems to be related to the blockade of a tonic stimulatory effect of endogenous dopamine on dopamine D_1 receptors (Arnt et al., 1987; Longoni et al., 1987a,b; Serra et al., 1987; Wachtel et al., 1992). The present results suggest that adenosine A_1 receptor agonists are less efficacious than dopamine D_1 receptor antagonists at inhibiting dopamine D_1 receptor-mediated effects. Thus, adenosine A_1 receptor stimulation seems to be able to counteract the effects of exogenously administered D_1 receptor agonists, but not the effects of endogenous dopamine on dopamine D_1 receptors. However, it must be pointed out that in the present work, only single doses of the dopamine receptor agonists were used (ED_{max} doses for the yawning induced by quinpirole and for the grooming behaviour induced by SKF 38393). It is therefore still possible that the adenosine A_1 receptor agonist could inhibit the effect of lower doses of the dopamine D_2 receptor agonist. Nevertheless, the present results show a clear differential effect of the adenosine A_{2A} and A_1 receptor agonists on different types of dopamine receptor-mediated behaviours. Thus, low doses of adenosine A_1 and adenosine A_{2A} receptor agonists selectively counteract the dopamine D_1 receptor agonist-induced and the dopamine D_2 receptor agonist-induced behaviours, respectively.

Similar experiments on the effects of different adenosine analogues on apomorphine-induced stereotypies and yawning in rats have recently been performed (Zarrindast and Sharifzadeh, 1995; Zarrindast et al., 1995). Some results obtained from these studies are not in agreement with the present work, since they suggest that apomorphine-induced yawning is antagonistically modulated by adenosine A_1 but not adenosine A_{2A} receptors (Zarrindast et al., 1995). In those experiments, however, a selective adenosine A_1 and a non-selective adenosine receptor agonist (N^6-cyclohexyladenosine, CHA, and 5′-*N*-ethylcarboxamidoadenosine, NECA, respectively) were used. In agreement with the present work, adenosine A_{2A} receptors were suggested to be mainly responsible for the inhibition of apomorphine-induced licking by adenosine analogues (Zarrindast and Sharifzadeh, 1995). However, it was also suggested that adenosine A_1 receptors played an opposite role to adenosine A_{2A} receptors, since CHA was found to potentiate apomorphine-induced licking. No evidence for such an effect was found in the present experiments, which again may be related to the different adenosine receptor agonists used.

Blockade of dopamine D_2 receptors in the ventral striatum seems to be associated with the antipsychotic effect of neuroleptics while blockade of dopamine D_2 receptors in the dorsal striatum is most probably related to their extrapyramidal side effects (Fuxe et al., 1977; Borison et al., 1983; Altar et al., 1986; Ögren et al., 1986; Robertson and Fibiger, 1992). There exists experimental evidence indicating that the antagonistic A_{2A}–D_2 interaction is stronger in the ventral than in the dorsal striatum, which suggests that adenosine A_{2A} receptor agonists could be used as atypical antipsychotic drugs, i.e., with a low liability to induce extrapyramidal side effects (reviewed in Ferré, 1997).

When considering commonly used tests to evaluate the pharmacological effects of antipsychotics, it is generally accepted that blockade of dopamine receptors in the ventral striatum is associated with the counteracting effects of the motor activation induced by novel stimuli or psychostimulants and for the disruption of active avoidance responses. On the other hand, the counteraction of dopamine agonists-induced stereotypies and the induction of cataleptic immobility are believed to be mainly mediated by blockade of dopamine receptors in the dorsal striatum (reviewed in Ögren, 1996). Therefore, the comparison between the effective doses for antagonizing dopamine receptor-mediated stereotypies or the doses inducing catalepsy with the doses which counteract dopamine receptor-mediated motor activity is considered as a useful experimental approach for evaluating antipsychotic activity and the liability to induce extrapyramidal side effects (Ögren et al., 1986; Hoffman and Donovan, 1995; Ögren, 1996). CGS 21680 has been recently shown to strongly counteract amphetamine- and PCP-induced motor activity (ED50 of 0.3 and 0.1 μmol/kg, respectively, obtained in animals from the same strain and weight as in the present work) (Rimondini et al., 1997). The weaker effect of CGS 21680 for counteracting apomorphine-induced stereotypies (minimal effective dose: 1 μmol/kg) is in agreement with its already reported atypical antipsychotic profile in animal models (Rimondini et al., 1997). These results also agree with the hypothesis of a preferential antagonistic interaction between adenosine A_{2A} and dopamine D_2 receptors in the ventral striatum (Ferré, 1997). The strong counteracting effect of CGS 21680 on yawning induced by quinpirole (minimal effective dose: 0.1 μmol/kg) might be related to the low dose of quinpirole used compared to that of apomorphine, which are necessary to induce yawning and stereotypies, respectively. In fact, lower doses of apomorphine also induce yawning (Longoni et al., 1987a; Serra et al., 1987). On the other hand, it may indicate that quinpirole-induced yawning is a sensitive method to detect antipsychotic activity.

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