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Lack of adenosine A_1 and dopamine D2 receptor-mediated modulation of the cardiovascular effects of the adenosine A_{2A} receptor agonist CGS 21680

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Abstract

Some behavioral and biochemical effects of the systemically administered adenosine A_{2A} receptor agonist 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamidoadenosine (CGS 21680) in rats are potentiated by adenosine A_1 receptor agonists and counteracted by dopamine D2 receptor agonists. In the present study we compared potentiating and antagonistic interactions between CGS 21680 and adenosine A_1 and dopamine D2 receptor agonists on motor activity and on cardiovascular responses (arterial blood pressure and heart rate). The motor-depressant effects produced by CGS 21680 (0.5 mg/kg, i.p.) were potentiated by the adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA, 0.3 mg/kg, i.p.) and counteracted by the dopamine D2 receptor agonist quinpirole (0.5 mg/kg, i.p.). In contrast, neither CPA nor quinpirole significantly modified the decrease in arterial pressure or the increase in heart rate induced by CGS 21680. However, the adenosine A_{2A} receptor antagonist 3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-7-methyl-1-propargylxanthine phosphate disodium salt (MSX-3, 3 mg/kg, i.p.) counteracted both the motor-depressant and cardiovascular effects of CGS 21680. Therefore, the effects of the systemically administered adenosine A_{2A} receptor agonist CGS 21680 on cardiovascular function, in contrast to its effects on motor behavior, appear to be independent of the effects of adenosine A_1 and dopamine D2 receptor activity.

Keywords: Adenosine A_{2A} receptor; Adenosine A_1 receptor; Dopamine D2 receptor; Cardiovascular; Motor activity

1. Introduction

Adenosine is a potent modulator of cardiovascular function. Its effects are mostly depressant and involve both central and peripheral mechanisms as well as different adenosine receptor subtypes, mostly adenosine A_1, A_{2A} and A_{2B} receptors (Shryock and Belardinelli, 1997; Spyer and Thomas, 2000; Tabrizchi and Bedi, 2001; Scislo et al., 2001). Adenosine A_1 and A_{2A} receptors are found in blood vessels and in cardiac tissue (Shryock and Belardinelli, 1997), as well as in the nucleus tractus solitarius, the major relay nucleus for the central processing of cardiovascular control (Castillo-Meléndez et al., 1994; St. Lambert et al., 1996; Rosin et al., 1998). Systemic administration of adenosine A_1 or adenosine A_{2A} receptor agonists produces hypotension and it is currently believed that these effects are mostly due to a direct cardiac depressant effect of adenosine A_1 receptor agonists and to a direct peripheral vasodilatation induced by adenosine A_{2A} receptor agonists (Evoniuk et al., 1987; Appel et al., 1995; Mathot et al., 1995a). Local administration of adenosine A_{2A} receptor agonists in the nucleus tractus solitarius produces a pronounced decrease in blood pressure and heart rate, while adenosine A_1 receptor agonists produce the opposite effects (Barraco et al., 1991). Therefore, central adenosine A_{2A} receptors appear also to play some role in the hypotensive effects induced by the systemic administration of adenosine A_{2A} receptor agonists.

Adenosine A_{2A} receptors located centrally in the striatum seem to be mainly responsible for some behavioral and biochemical effects of peripherally administered adenosine

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A_{2A} receptor agonists, which include depression of motor activity and expression of immediately early genes (Nikodijevic et al., 1990, 1991; Karcz-Kubicha et al., 2003a, 2003b). These centrally mediated effects of adenosine A_{2A} receptor agonists can be potentiated by co-administration of adenosine A_1 receptor agonists and counteracted by dopamine D2 receptor agonists (Nikodijevic et al., 1990, 1991; Ferré et al., 1991; Karcz-Kubicha et al., 2003a,b). In the present study, we compared the effects of the adenosine A_1 receptor agonist N^6-cyclopentyladenosine (CPA) and the dopamine D2 receptor agonist quinpirole on adenosine A_{2A} receptor-mediated cardiovascular and motor activity effects induced by systemic administration of 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamidoadenosine (CGS 21680). In contrast to the effects on motor activity (Nikodijevic et al., 1990, 1991) and striatal immediate-early gene expression (Karcz-Kubicha et al., 2003b), the effects of the adenosine A_{2A} receptor agonist CGS 21680 on cardiovascular function were found to be independent of the effects of adenosine A_1 receptor and dopamine D2 receptor agonists.

2. Materials and methods

2.1. Subjects and drugs

Male Sprague–Dawley rats, weighing 300–350 g, were used in all experiments. Animals were maintained in accordance with guidelines of the Institutional Animal Care and Use Committee of the Intramural Research Program, National Institute on Drug Abuse, NIH. The adenosine A_1 receptor agonist CPA, the adenosine A_{2A} receptor agonist CGS 21680 and the dopamine D2 receptor agonist quinpirole hydrochloride (quinpirole) were purchased from Sigma (St. Louis, MO). The adenosine A_{2A} receptor antagonist 3-(3-hydroxypropyl)-8-(*m*-methoxystyryl)-7-methyl-1-propargylxanthine phosphate disodium salt (MSX-3) was synthesized at the Pharmaceutical Institute, University of Bonn, Germany (Sauer et al., 2000).

All drugs were dissolved in sterile saline (with a few drops of 0.1 N NaOH for MSX-3; final pH: 7.4) and administered intraperitoneally (i.p.) in a volume of 2 ml/kg of body weight (3 ml/kg for MSX-3). The combination of CGS 21680 and CPA was administered as a single injection. MSX-3 and quinpirole were administered 10 min before CGS 21680, CPA or the combination. The doses of CGS 21680 (0.5 mg/kg, i.p.), CPA (0.3 mg/kg, i.p.), MSX-3 (3 mg/kg, i.p.) and quinpirole (0.5 mg/kg, i.p.) were the same as those recently used in experiments showing centrally mediated adenosine A_{2A} receptor-adenosine A_1 receptor and dopamine D2 receptor-adenosine A_{2A} receptor interactions by analyzing the striatal expression of the immediate-early gene c-*fos* (Karcz-Kubicha et al., 2003b). Furthermore, in previous experiments 0.5 mg/kg (i.p.) of CGS 21680 and 0.3 mg/kg (i.p.) of CPA were found to be minimal doses with maximal motor-depressant effects and a dose of 3 mg/kg (i.p.) of the adenosine A_{2A} receptor antagonist MSX-3 (Sauer et al., 2000) was found to be a minimal dose with a maximal motor-activating effect (Karcz-Kubicha et al., 2003a).

2.2. Locomotor activity recording

Motor activity was monitored with a MED associates' activity monitor (MED Associates St. Albans, VT), which consisted of Plexiglas cages ($43.2 \times 43.2 \times 30.5$ cm) equipped with a 16×16 array of photocells spaced every 2.5 cm near the base of the cage (horizontal beams). Any movement that interrupted a photo beam was recorded as a motor count and this event provided no feedback to the rat. A predefined "box" size of 2×2 photo beams had to be broken before a movement was considered ambulatory. Starting at time 0, the box was centered on the animal; when the animal moved from inside to outside the box, it was considered ambulatory and the box re-centered on the animal. The animal was considered to remain in ambulatory movement status until it did not leave the last re-centered box in less than a resting delay of 500 ms. Locomotor activity or ambulatory counts were the number of motor counts while in ambulatory movement status. General motor activity was defined as the number of horizontal beams that were interrupted by the subject during a particular interval.

Motor activity was measured for 30 min in animals non-habituated to the activity cages, immediately after they were introduced into the cages. This is the period of maximal exploratory activity when rats are exposed to a new environment. After 30 min, the animals habituate and they show a very low degree of motor activity and the effect of motor-depressant agents becomes difficult to evaluate. Statistical comparisons among differently treated groups were made with one-way analysis of variance (ANOVA), followed by Fisher's protected least significant difference (PLSD) post hoc tests.

2.3. Cardiovascular experiments

Following arrival in the laboratory, rats were given 1 week to adapt. Surgery was then performed to implant telemetry transmitters (Data Sciences International, St. Paul, MN) for the measurement systemic blood pressure. Details of the surgery are given elsewhere (Tella et al., 1999). Briefly, under isoflurane anesthesia, a 4- to 5-cm-long incision was made on the midline of abdomen. The descending aorta was exposed below the bifurcation of the renal arteries. A vascular clamp was placed immediately posterior to the renal artery and a curved 21-gauge needle was used to puncture the vessel anterior to the bifurcation. The catheter of the transmitter was inserted about 2 cm into the aorta, the area was dried and a drop of adhesive (Vet Bond) was applied to the catheter entry point. The trans-

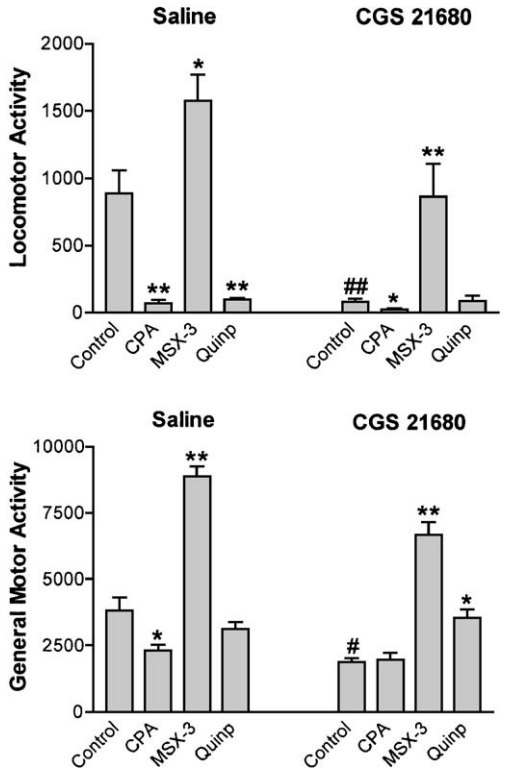

Fig. 1. Locomotor activity (top graph) and general motor activity (bottom graph) in non-habituated rats during the first 30 min after the systemic administration of saline or the adenosine A_{2A} receptor agonist CGS 21680 (0.5 mg/kg, i.p.) with the concomitant administration of the adenosine A_1 receptor agonist CPA (0.3 mg/kg, i.p.) or the previous administration (10 min before) of saline (control), the adenosine A_{2A} receptor antagonist MSX-3 (3 mg/kg, i.p.) or the dopamine D2 receptor agonist quinpirole (Quinp; 0.5 mg/kg). The results are expressed as means ± S.E.M. ($n = 6$/group) of the total locomotor or motor counts. ANOVA followed by Fisher's PLSD post hoc comparisons were used for statistical comparisons. * and **: $P < 0.05$ and $P < 0.01$ versus the respective control group; # and ##: $P < 0.05$ and $P < 0.01$ versus the saline-control group.

mitter was then sutured to the abdominal musculature and the abdominal incision and the skin were closed. An i.p. injection of 50,000 U/kg dual penicillin was given to safeguard against infections.

One to 2 weeks following surgery, experimental procedures began. During the experimental session, the animal's entire home cage (with food and water removed) was placed on top of the telemetry receiver. Mean arterial blood pressure and heart rate were then monitored for up to 2 h. Testing continued daily (Monday–Friday) until the cardiovascular parameters were stable from session to session. Animals were then given an i.p. injection of saline just prior to placement of the cage on the telemetry receiver, at least two times per week until cardiovascular parameters following saline injection remained stable. Testing with the adenosine drugs was then started, with test drugs given i.p. no more frequently than two times per week, usually on Tuesdays and Fridays, with control saline injections given on Thursdays.

Data for statistical comparisons are presented as area-under-the-curve (AUC) for the entire 2-h session. Statistical comparisons among different treatments were made with one-way ANOVA, followed by Fisher's PLSD post hoc tests.

3. Results

Administration of either the adenosine A_1 receptor or the adenosine A_{2A} receptor agonist produced a pronounced depression of locomotor activity and their co-administration produced a significantly stronger depression of locomotor activity than when administered alone (Fig. 1). The depressant effects of both adenosine receptor agonists were less pronounced and a significant potentiating effect was not observed when general motor activity was measured. This might reflect a higher sensitivity of the locomotor activity compared to general motor activity measures. The adenosine A_{2A} receptor antagonist MSX-3 (3 mg/kg, i.p.) produced a significant increase in both locomotor activity and general motor activity and counteracted the effects of CGS

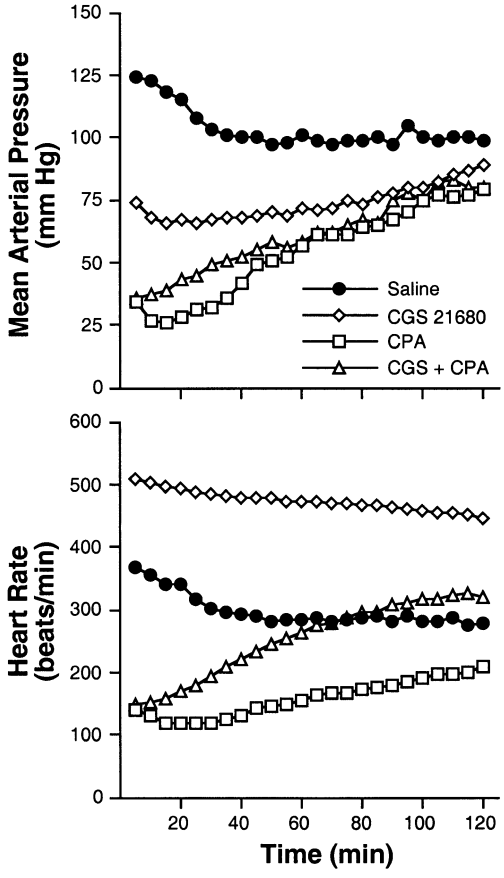

Fig. 2. Time course for mean arterial pressure (top graph) and heart rate (bottom graph) of rats during the first 2 h after systemic administration of saline, the adenosine A_{2A} receptor agonist CGS 21680 (0.5 mg/kg, i.p.), the adenosine A_1 receptor agonist CPA (0.3 mg/kg, i.p.), or the co-administration of CGS 21680 and CPA. Each point is the mean ($n = 3–5$) of consecutive 5-min periods beginning immediately after the i.p. injections.

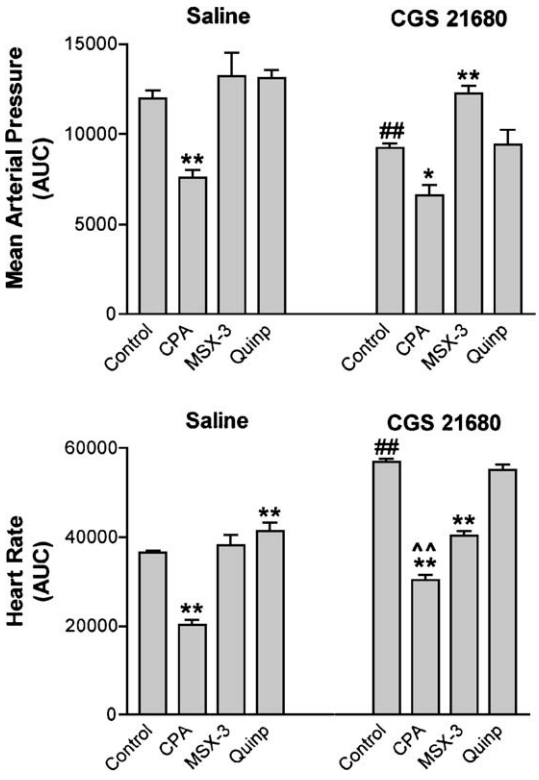

Fig. 3. Mean arterial pressure (top graph) and heart rate (bottom graph) of rats during the first 2 h after the systemic administration of saline or the adenosine A_{2A} receptor agonist CGS 21680 (0.5 mg/kg, i.p.) with the concomitant administration of the adenosine A_1 receptor agonist CPA (0.3 mg/kg, i.p.) or the previous administration (10 min before) of saline (control), the adenosine A_{2A} receptor antagonist MSX-3 (3 mg/kg, i.p.) or the dopamine D2 receptor agonist quinpirole (Quinp; 0.5 mg/kg). The results are expressed as means ± S.E.M. ($n = 3-5$/group) of the area-under-the-curve (AUC). ANOVA followed by Fisher's PLSD post hoc comparisons were used for statistical comparisons. * and **: $P < 0.05$ and $P < 0.01$ versus the respective control group; # and ##: $P < 0.05$ and $P < 0.01$ versus the saline-control group. ^^: $P < 0.01$ versus the saline-CPA group.

21680 (Fig. 1). Quinpirole (0.5 mg/kg, i.p.) produced a significant decrease in locomotor activity but had no significant effect on general motor activity and significantly counteracted the depressant effect of CGS 21680 on general motor activity (Fig. 1).

Fig. 2 shows the time course for mean arterial pressure and heart rate during the first 2 h after systemic administration of saline or the adenosine agonists, alone or in combination. Blood pressure for animals treated with saline was initially around 125 mm Hg, but gradually decreased through the 2-h session to about 100 mm Hg. Heart rate also gradually decreased through the session from about 375 beats/min to just under 300 beats/min. The adenosine A_{2A} receptor agonist CGS 21680 (0.5 mg/kg, i.p.) decreased blood pressure to under 75 mm Hg with concomitant increases in heart rate to over 500 beats/min. Blood pressure recovered to near saline values by the end of the 2-h session, but heart rate remained elevated at the end of the session. The adenosine A_1 receptor agonist CPA (0.3 mg/kg, i.p.) dramatically decreased blood pressure, which recovered to near saline levels by the end of the session. Heart rate for CPA was also reduced dramatically to near 100 beats/min and remained clearly below saline values by the end of the session. When CGS 21680 and CPA were administered together, the blood pressure response (decrease) was similar to that produced by CPA alone. In contrast, while heart rate was initially reduced following co-administration of CGS 21680 and CPA to a level similar to that produced by CPA alone, heart rate recovered much more quickly than it did when CPA was administered alone.

These results were confirmed with statistical analysis of the AUC measure. CGS 21680 produced a significant decrease of blood pressure and a concomitant increase of heart rate. On the other hand, CPA produced a significant decrease of both blood pressure (more evident than with CGS 21680) and heart rate (Fig. 3). After co-administration of CGS 21680 and CPA, blood pressure was not significantly different but heart rate was significantly higher (although still lower compared to controls) than after CPA administration. MSX-3 (3 mg/kg, i.p.) did not produce a significant effect on either blood pressure or heart rate when administered alone and completely counteracted the changes in blood pressure and heart rate produced by CGS 21680. Quinpirole (0.5 mg/kg, i.p.) produced a small but significant increase in heart rate and did not significantly modify the cardiovascular effects of CGS 21680.

4. Discussion

We have recently shown that the systemic administration of the adenosine A_1 receptor agonist CPA potentiates and the dopamine D2 receptor agonist quinpirole counteracts an increase in striatal expression of c-*fos* induced by the systemic administration of the adenosine A_{2A} receptor agonist CGS 21680 (Karcz-Kubicha et al., 2003b). In view of the possible therapeutic implications of these findings (see below), in the present study, we analyzed the cardiovascular effects of the combined systemic administration of centrally active doses of CGS 21680, CPA and quinpirole. Motor activity measures were evaluated in parallel in order to compare with the cardiovascular effects. Furthermore, the effects of combined administration of adenosine A_{2A} and dopamine D2 receptor agonists on motor activity had not been previously reported. In agreement with former studies, the motor-depressant effects produced by the adenosine A_{2A} receptor agonist CGS 21680 were counteracted by a low dose of the selective adenosine A_{2A} receptor antagonist MSX-3 and potentiated by co-administration of the adenosine A_1 receptor agonist CPA (Nikodijevic et al., 1990, 1991; Karcz-Kubicha et al., 2003a).

In line with the existence of antagonistic reciprocal interactions between adenosine A_{2A} and dopamine D2 receptors in the striatum (Ferré et al., 1991, 1997, 2003), the dopamine D2 receptor agonist quinpirole (0.5 mg/kg

i.p.) significantly counteracted the decrease in general motor activity induced by the adenosine A_{2A} receptor agonist. With the experimental conditions used in the present experiments (non-habituated rats), previous studies have shown that the i.p. administration of quinpirole at the same dose used in the present study (0.5 mg/kg) depresses locomotor activity during the initial 30 min of observation, followed by significant increases in locomotor activity (Horvitz et al., 2001). A previously reported qualitative analysis showed that the initial depressant effects of quinpirole on locomotor activity does not reflect a depression of general motor activity, but instead is associated with intense stereotyped behavior, such as sniffing (Horvitz et al., 2001). In the present study, quinpirole also significantly depressed locomotor activity but not general motor activity. The absence of a significant decrease of general motor activity counts with quinpirole indicates a qualitative change in the pattern of general motor activity, with a depression of locomotor activity and a concomitant increase in stereotyped behavior, as found previously. Although CPA and quinpirole produced the same degree of depression of locomotor activity, the adenosine A_1 receptor agonist potentiated while the dopamine D2 receptor agonist did not modify the depression of locomotor activity produced by CGS 21680. In summary, the present results with motor activity parallel our studies on striatal c-*fos* expression, where the same experimental conditions were used (the same animal strain, drugs, doses and route of administration) and potentiating adenosine A_1 receptor-adenosine A_{2A} receptor and antagonistic dopamine D2 receptor-adenosine A_{2A} receptor interactions were demonstrated (Karcz-Kubicha et al., 2003b).

The adenosine A_{2A} receptor agonist CGS 21680 produced a significant decrease of mean arterial blood pressure and a concomitant increase of heart rate, while the adenosine A_1 receptor agonist CPA produced a significant decrease of both blood pressure (more evident than with CGS 21680) and heart rate, in agreement with previous studies (Evoniuk et al., 1986; Lappe et al., 1992; Jackson et al., 1993; Appel et al., 1995; Mathot et al., 1995a, 1995b; Tabrizchi, 1997; Monopoli et al., 1998). After co-administration of CGS 21680 and CPA, blood pressure was not significantly different and heart rate was significantly higher than after CPA administration. Thus, CGS 21680 partially counteracted CPA-induced bradycardia. These results do not support the commonly suggested mechanism for CGS 21680-induced tachycardia that is thought to result from a baroreceptor-reflex activation of cardiac sympathetic nerves (Tabrizchi, 1997). The results of several previous studies also do not support this interpretation. For example, a methodological pharmacokinetic modeling of the haemodynamic effects of systemically administered CGS 21680 demonstrated that its tachycardic effect remained longer than its hypotensive effect (Mathot et al., 1995a). This was also evident in the current study (Fig. 2). Furthermore, unlike MSX-3 (present results) and (7-(2-phenylethyl)-5-amino-2-(2-furyl)-pyrazolo-[4,3,e]-1,2,4-triazolo[1,5-c]-pyrimidine)) (SCH 58261, Monopoli et al., 1998), other selective adenosine A_{2A} receptor antagonists, such as (*E*)-8-(3-chlorostyryl)caffeine (CSC, Mathot et al., 1995b) or (*E*)-8-(3,4-dimethoxystyryl)-1,3-dipropyl-xanthine) (KF17837, Jackson et al., 1993), counteract the hypotensive, but not the tachycardic effects of CGS 21680. Since a direct tachycardic effect of CGS 21680 in the heart can already be discarded (Hutchison et al., 1989), a central mediation of CGS 21680-induced tachycardia could explain these results. KF17837 crosses the blood–brain barrier to a very low extent (Stone-Elander et al., 1997) and the brain uptake of CSC, although higher than that of KF17837, is rapidly washed out (Ishiwata et al., 2000). On the other hand, preliminary results suggest that 3-(3-hydroxypropyl)-7-methyl-8(*m*-methoxystyryl)-1-propargylxanthine (MSX-2, the active drug to which the pro-drug MSX-3 is converted in vivo; Sauer et al., 2000) has a high degree of brain penetration and is metabolically very stable (see Müller, 2000). However, central mediation of the tachycardic effect of CGS 21680 would imply a site of action different from the nucleus tractus solitarius, since the direct infusion of the adenosine A_{2A} receptor antagonist in this area of the midbrain produces bradycardia rather than tachycardia (see Introduction and Barraco et al., 1991). Finally, CGS 21680 has been reported to bind to two pharmacological types of adenosine A_{2A} receptors, the "typical" and the "atypical" adenosine A_{2A} receptors (Cunha et al., 1994). The tachycardic effect of CGS 21680 could involve the "atypical" adenosine A_{2A} receptor, since it has a higher affinity for SCH 58261 than for other adenosine A_{2A} receptor antagonists (El Yacoubi et al., 2000). However, the affinity of the "atypical" adenosine A_{2A} receptor for MSX-3 and its presence in the periphery need to be determined.

In addition to the well-known striatal adenosine A_{2A} receptor-dopamine D2 receptor interaction and the ability of both receptors to form functional heteromeric receptor complexes (Hillion et al., 2002), a functional antagonistic interaction between adenosine A_{2A} and dopamine D2 receptors has also been described in the rat nodose ganglion (Lawrence et al., 1997), which contains the cell bodies of vagal neurons projecting to the nucleus tractus solitarius. Both adenosine A_{2A} and dopamine D2 receptors are also localized in the nucleus tractus solitarius. However, adenosine A_{2A} receptors appear to be mostly presynaptic, localized not only in the vagal cell bodies in the nodose ganglion, but also in the terminals of vagal afferent neurons in the nucleus tractus solitarius (Castillo-Meléndez et al., 1994), while dopamine D2 receptors are mostly postsynaptic in the nucleus tractus solitarius (Lawrence et al., 1995). This could explain the present finding that systemic administration of the dopamine D2 receptor agonist quinpirole at a behaviorally relevant dose does not modify the changes in cardiovascular function induced by CGS 21680.

The present findings suggest that in contrast to the effects on motor activity and striatal immediate-early gene expression, the effects of the systemically administered adenosine A_{2A} receptor agonist on cardiovascular function are inde-

pendent of the effects of adenosine A_1 receptor and dopamine D2 receptor agonists. These results could have implications for drug therapy. Adenosine A_{2A} receptor agonists, such as CGS 21680, have been suggested to have possible therapeutic applications as both antipsychotic and antihypertensive drugs (Hutchison et al., 1989; Ferré, 1997; Rimondini et al., 1997). Due to the existence of a central, but not peripheral, adenosine A_1–A_{2A} receptor potentiating interaction, the concomitant administration of low doses of adenosine A_1 and A_{2A} receptor agonists could produce antipsychotic effects with less risk of secondary cardiovascular effects. On the other hand, due to the existence of a central, but not peripheral, dopamine D2–adenosine A_{2A} receptor antagonistic interaction, the administration of a dopamine D2 receptor agonist could selectively counteract the unwanted central effects of adenosine A_{2A} receptor agonists when used as antihypertensive drugs.

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