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Effects of adenosine A_{2A} receptor agonist, CGS 21680, on blood pressure, cardiac index and arterial conductance in anaesthetized rats

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Abstract

The effects of 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamidoadenosine (CGS 21680) on blood pressure, total peripheral resistance, cardiac index, heart rate and arterial conductance in different vascular beds in the presence and absence of hexamethonium (ganglionic blocker) and phenylephrine (α_1-adrenoceptor agonist) were investigated in pentobarbitone-anaesthetized rats using a radioactive microsphere technique. CGS 21680 (0.1, 0.3 and 1.0 μg/kg/min) significantly decreased blood pressure and total peripheral resistance, and increased heart rate and cardiac index. In addition, after infusion with CGS 21680 (0.1, 0.3 and 1.0 μg/kg/min) arterial conductance in coronary bed significantly increased. However, while CGS 21680 (0.3 and 1.0 μg/kg/min) significantly increased conductance in skeletal muscle, it significantly decreased splenic arterial conductance. Moreover, CGS 21680 (1.0 μg/kg/min) significantly increased conductance in cerebral arterial bed. Infusion with hexamethonium (200 μg/kg/min) resulted in significant reduction in blood pressure, heart rate and cardiac index whereas stroke volume and total peripheral resistance remained unchanged. In animals that were pretreated with hexamethonium (200 μg/kg/min), further administration of CGS 21680 (0.3 μg/kg/min), compared to CGS 21680 alone, significantly reduced blood pressure, heart rate and cardiac index but did not affect total peripheral resistance or conductance in any vascular bed. Administration of phenylephrine (7 μg/kg/min) resulted in a significant increase in blood pressure and total peripheral resistance, and a significant reduction in cardiac index and heart rate. In animals infused with phenylephrine and CGS 21680 combined, in comparison to those animals that received CGS 21680 alone, no significant differences in blood pressure, heart rate, total peripheral resistance, cardiac index or conductance in any vascular beds were found. Our present findings suggest that CGS 21680 decreased blood pressure by decreasing total peripheral resistance, and increased cardiac index possibly through a reflex-mediated increase in heart rate. Moreover the coronary arterial bed is the most sensitive and cerebral arterial bed is the least sensitive to the effects of CGS 21680. In addition, the autonomic nervous system did not appear to play a major role in the actions of CGS 21680 on arterial conductance, and there was no difference in the action of this compound in the states of normal and raised vascular tone.

Keywords: CGS 21680; Adenosine A_{2A} receptor; Vascular conductance; Radioactive microsphere technique

1. Introduction

The existence of two subtypes of adenosine receptor (A_1 and A_2) in the cardiovascular system is very well established (for review see Pelleg and Porter, 1990). However, additional evidence has been presented which indicates the presence of other subtypes of adenosine receptors, A_3 (Carruthers and Fozard, 1993; Fozard and Hannon, 1994) and A_4 (White and Angus, 1987; Daut et al., 1990; Belloni and Hintze, 1991; Von Beckerath et al., 1991) in the vasculature. Moreover, there is also evidence in the literature which supports the view that different subtypes of A_2 receptor contribute to the vasodilator actions of adenosine (Nees et al., 1987; Hargreaves et al., 1991; Tabrizchi and Lupichuk, 1995).

Stimulation of A_2 receptors produces vasorelaxation in vitro (Makujina et al., 1992; Lewis et al., 1994; Balwierczak et al., 1991; Gurden et al., 1993) and vasodilatation and thus hypotension in vivo (Hutchison et al., 1989; Webb et al., 1991, 1993; Casati et al., 1993). The presence of A_2 receptors in blood vessels have been demonstrated in aorta of rat (Lewis et al., 1994; Moritoki et al., 1990; Rose'Meyer and Hope, 1990) and coronary artery of many species namely guinea pig (Vials and Burnstock, 1993),

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dog (Kusachi et al., 1983; Gurden et al., 1993), bovine (Cushing et al., 1991), porcine (Abebe et al., 1994) and human (Ramagopal et al., 1988; Makujina et al., 1992). In addition, the existence of A_2 receptors was also demonstrated in human internal mammary artery and saphenous vein (Makujina et al., 1992).

To our knowledge the effects of A_2 receptor stimulation on arterial conductance in vivo has never been investigated. Conductance is believed to be a better index of changes in vascular tone in situations, like in vivo, where blood flow changes to a much greater extent than the pressure (Lautt, 1989). In the present study we have examined the effects of the selective A_{2A} receptor agonist 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamidoadenosine (CGS 21680) (Hutchison et al., 1989) on blood pressure, total peripheral resistance, cardiac index, heart rate as well as vascular conductance in intact anaesthetized rats. In addition, the influence of CGS 21680 on haemodynamics and vascular conductance were examined following treatment with hexamethonium (ganglionic blocker) or phenylephrine (α_1-adrenoceptor agonist), two different conditions where cardiac index was significantly impaired.

2. Materials and methods

2.1. Surgical preparation

Male Sprague-Dawley rats (350–450 g) were anaesthetized by intraperitoneal injections of sodium pentobarbitone (65 mg/kg). Catheters (polyethylene tubing, i.d. 0.58 mm, o.d. 0.965 mm) were inserted into both femoral arteries and veins. In addition, a catheter was inserted into left jugular vein and another was advanced via the right carotid artery into the left ventricle. The catheters were filled with heparinized saline (25 IU/ml). Body temperature was maintained at 37°C via a rectal thermometer and a heating pad connected to a thermistemp temperature controller (Model 71; Yellow Spring Instrument Co., OH, USA). Following completion of surgery and before commencement of experiments baseline values of arterial blood pressure, heart rate and left ventricular pressure were continuously monitored for 20–30 min. Pressures were recorded with a pressure transducer (PD23B Gould Statham, CA, USA) connected to a Grass polygraph (Model PRS7C8B). Heart rate was electronically derived from the upstroke of the arterial pulse pressure by a tachograph (Grass, Model 7P4G). Cardiac output and regional flow distribution were measured using microsphere technique.

2.2. Microsphere technique

This technique has been described in detail elsewhere (Pang, 1983). Briefly, suspensions of microspheres (15 μM diameter, New England Nuclear, MA, USA) labeled with either ^{57}Co or ^{113}Sn (25000–30000 microspheres in 150 μl) were injected into the left ventricle over a period of 10 s. Blood was withdrawn for 1 min at the rate of 0.35 ml/min starting 15 s before microsphere injection using an infusion/withdrawal pump (Harvard pump Model 940, MA, USA) from a femoral artery. Microspheres were injected before and after infusion of saline/drug. The order of injections of microsphere was reversed in half of the experiments so that half of the rats received ^{57}Co and half received ^{113}Sn first. After the second microsphere injection animals were killed by a bolus injection of KCl. Blood samples, tissue samples, syringes used for injections and collections of blood and test tubes used for holding microsphere samples were counted for radioactivity using a Searl 1185 dual channel automatic gamma counter (Nuclear-Chicago, IL, USA). The ^{57}Co counts were corrected for ^{113}Sn spillover (30%). Only 40 g each of muscle or skin were taken for counting. The samples of skin were obtained from dorsal and ventral areas and the muscle samples were taken from chest, abdomen, limbs and back.

2.3. Experimental protocol

The selectivity of CGS 21680 was examined in two groups of rats ($n = 5$ in each group). Animals were infused continuously with 8-cyclopentyl-1,3-dipropylxanthine, a selective A_1 receptor antagonist (1 μg/kg/min) or vehicle (dimethyl sulfoxide, 9.0 μl/kg/min) for 30 min. Fifteen minutes after the start of infusion with A_1 receptor antagonist or vehicle, animals were infused with CGS 21680 (1.0 μg/kg/min) for 15 min.

Rats were divided randomly into eight groups ($n = 6$ in each). Time-control group (I) received continuous infusion of saline (0.0193 ml/min) for 25 min as well as a further infusion of saline (0.037 ml/kg/min) for the last 15 min of the experiment. Groups II, III and IV received continuous infusion of saline (0.0193 ml/min) for 25 min and an infusion of CGS 21680 at doses of 0.1, 0.3 or 1.0 μg/kg/min for the last 15 min, respectively. Groups V and VI received continuous infusion of hexamethonium (200 μg/kg/min) for 25 min and further infusions of either saline (0.037 ml/kg/min) or CGS 21680 (0.3 μg/kg/min) for the last 15 min, respectively. The dose of hexamethonium (200 μg/kg/min) used in the present study was one that blunted responses to sympathetic nerve activation. Groups VII and VIII received continuous infusion of phenylephrine (7 μg/kg/min) for 25 min and further infusions of saline (0.037 ml/min) or CGS 21680 (0.3 μg/kg/min) for the last 15 min. The dose of phenylephrine that was chosen was based on preliminary studies which showed this dose to produce sustained increase in blood pressure (+25%). All measurements were performed twice, once when arterial pressure and heart rate were stabilized after surgery and once 25 min following infusion with saline/drug.

2.4. Chemicals

Phenylephrine, hexamethonium and CGS 21680 were dissolved in normal saline (0.9%) solution. 8-Cyclopentyl-1,3-dipropylxanthine (108 μg/ml) was dissolved in dimethyl sulfoxide. CGS 21680 and 8-cyclopentyl-1,3-dipropylxanthine were purchased from Research Biochemicals International (Natick, MA, USA), and phenylephrine and hexamethonium from Sigma Chemical Company (St. Louis, MO, USA).

2.5. Data and statistical analysis

Blood pressure is reported as diastolic arterial pressure plus one third of the difference between systolic and diastolic arterial pressures, cardiac index is cardiac output divided by body weight, total peripheral resistance is cardiac index divided by blood pressure, stroke volume is cardiac index divided by heart rate and arterial conductance is flow divided by blood pressure.

Paired Student's t-test was used to analyze the effects of drugs within the same groups between control and treatment. The effects of CGS 21680 in the presence and absence of either hexamethonium or phenylephrine were compared using analysis of variance followed by Duncan multiple range test. A difference at $P < 0.05$ was considered to be significant.

3. Results

3.1. Selectivity of CGS 21680

Infusion with vehicle (dimethyl sulfoxide) or 8-cyclopentyl-1,3-dipropylxanthine did not have any significant effect on blood pressure or heart rate. Baseline value for blood pressure and heart rate in groups that received vehicle or 8-cyclopentyl-1,3-dipropylxanthine were 111 ± 3.0 mm Hg and 110 ± 6.0 mm Hg, and 390 ± 15 beats/min and 376 ± 8 beats/min, respectively. Hypotensive effects of CGS 21680 were not affected by treatment of animals with either 8-cyclopentyl-1,3-dipropylxanthine or vehicle. CGS 21680 was able to reduce blood pressure in animals treated with 8-cyclopentyl-1,3-dipropylxanthine and vehicle to 65.0 ± 5.0 and 69.8 ± 8 mm Hg, respectively. Infusion with CGS 21680 increased heart rate in 8-cyclopentyl-1,3-dipropylxanthine and vehicle-treated animals to 435 ± 17 beats/min and 420 ± 16 beats/min, respectively.

3.2. Effects of CGS 21680 in intact animals

Baseline values of blood pressure, heart rate, total peripheral resistance, cardiac index, stroke volume and arterial conductance were not statistically different among eight groups of rats. Further, in the time-control group, no significant differences were found between the baseline and final haemodynamic measurements.

Continuous infusion with CGS 21680 dose dependently reduced blood pressure and total peripheral resistance and increased heart rate and cardiac index without changing stroke volume (Table 1). CGS 21680 was able to significantly ($n = 6$; $P < 0.05$) lower blood pressure and total peripheral resistance while significantly ($n = 6$; $P < 0.05$) increasing heart rate and cardiac index in comparison to initial baseline value at all three doses tested (Table 1). At the lowest dose, CGS 21680 (0.1 μg/kg/min) significantly ($n = 6$; $P < 0.05$) increased conductance in the heart without significantly ($n = 6$; $P < 0.05$) altering conductance in any other vascular bed (Fig. 1A). The second highest dose of CGS 21680 (0.3 μg/kg/min) significantly ($n = 6$; $P < 0.05$) increased conductance in heart and muscle while decreasing conductance in spleen (Fig. 1B). There were no significant changes in conductance in any other bed during infusion of CGS 21680 at 0.3 μg/kg/min (Fig. 1B). The highest dose of CGS 21680 (1.0 μg/kg/min) significantly ($n = 6$; $P < 0.05$) increased arterial conductance in heart, muscle and brain while it reduced conductance in spleen (Fig. 1C). There were no significant changes in conductance in any other arterial bed following administration of CGS 21680 at 1.0 μg/kg/min (Fig. 1C).

3.3. Effects of CGS 21680 in hexamethonium-treated animals

Infusion with hexamethonium (200 μg/kg/min) resulted in significant ($n = 6$; $P < 0.05$) reduction in blood

Table 1
Effects of CGS 21680 (0.1, 0.3 and 1.0 μg/kg/min) on blood pressure (BP) (mm Hg), heart rate (HR) (bpm), cardiac index (CI) (ml/min/kg), total peripheral resistance (TPR) (mm Hg/ml/min/kg) and stroke volume (SV) (ml/kg/beat) in sodium pentobarbitone-anaesthetized rats. Means ± S.E. $n = 6$.

	Control	0.1	Control	0.3	Control	1.0
BP	108 ± 3.3	96 ± 5 [a]	111 ± 2	76 ± 6 [a]	111 ± 3	63 ± 5 [a]
HR	407 ± 14	427 ± 14 [a]	400 ± 11	432 ± 14 [a]	389 ± 14	438 ± 14 [a]
CI	221 ± 10	257 ± 14 [a]	242 ± 9	279 ± 11 [a]	205 ± 4	262 ± 11 [a]
TPR	3.26 ± 0.2	2.29 ± 0.1 [a]	3.04 ± 0.1	1.88 ± 0.2 [a]	3.20 ± 0.1	1.40 ± 0.1 [a]
SV	0.55 ± 0.03	0.60 ± 0.03	0.59 ± 0.02	0.63 ± 0.02	0.53 ± 0.02	0.52 ± 0.03

[a] Significantly different from control $P < 0.05$.

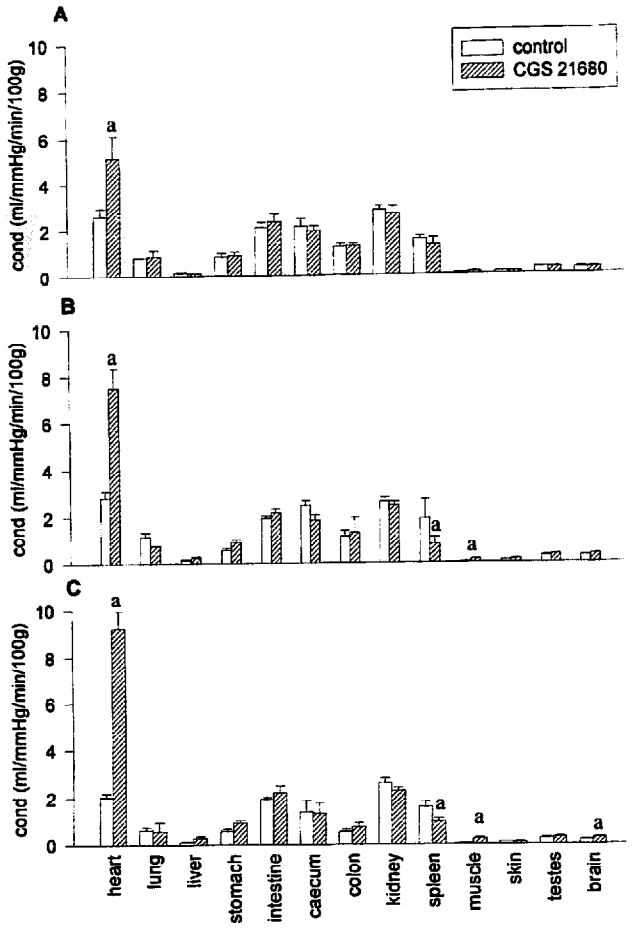

Fig. 1. Effects of CGS 21680 (A) 0.1 μg/kg/min, (B) 0.3 μg/kg/min, and (C) 1.0 μg/kg/min on arterial conductance (ml/mm Hg/min/kg) in sodium pentobarbitone-anaesthetized rats. [a] Significant difference from before treatment $P < 0.05$. Means ± S.E. $n = 6$.

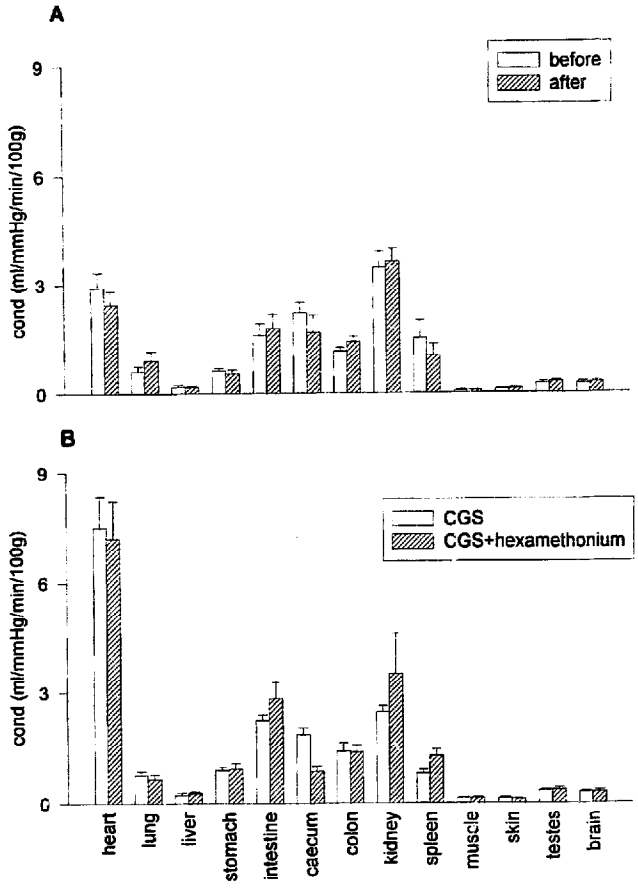

Fig. 2. Effects of (A) hexamethonium (200 μg/kg/min) or (B) hexamethonium (200 μg/kg/min) and CGS 21680 (0.3 μg/kg/min) combined on arterial conductance (ml/mm Hg/min/kg) in the sodium pentobarbitone-anaesthetized rats. Means ± S.E. $n = 6$.

pressure, heart rate and cardiac index whereas stroke volume and total peripheral resistance remained unchanged (Table 2). Furthermore, hexamethonium did not significantly affect vascular conductance in any arterial bed (Fig. 2A). In animals that were pretreated with hexamethonium further administration of CGS 21680 (0.3 μg/kg/min), compared to CGS 21680 alone, significantly ($n = 6$; $P < 0.05$) reduced blood pressure, heart rate, cardiac index but did not affect stroke volume, total peripheral resistance or conductance in any arterial bed (Table 3; Fig. 2B).

3.4. Effects of CGS 21680 in phenylephrine-treated animals

Administration of phenylephrine (7 μg/kg/min) resulted in a significant ($n = 6$; $P < 0.05$) increase in blood pressure and total peripheral resistance, and a significant

Table 2
Effects of hexamethonium (HEXA) (200 μg/kg/min) and phenylephrine (PE) (7 μg/kg/min) on blood pressure (BP) (mm Hg), heart rate (HR) (bpm), cardiac index (CI) (ml/min/kg), total peripheral resistance (TPR) (mm Hg/ml/min/kg) and stroke volume (SV) (ml/kg/beat) in sodium pentobarbitone-anaesthetized rats. Means ± S.E. $n = 6$.

	Control	HEXA	Control	PE
BP	113 ± 4.0	88 ± 5 [a]	110 ± 4	137 ± 4 [a]
HR	396 ± 9	363 ± 10 [a]	398 ± 9	381 ± 9 [a]
CI	244 ± 7	197 ± 9 [a]	232 ± 9	193 ± 10 [a]
TPR	2.90 ± 0.24	2.63 ± 0.27	2.90 ± 0.10	4.8 ± 0.8 [a]
SV	0.60 ± 0.01	0.54 ± 0.02	0.58 ± 0.02	0.50 ± 0.05

[a] Significantly different from control $P < 0.05$.

Table 3
Effects of CGS 21680 (0.3 μg/kg/min) on blood pressure (BP) (mm Hg), heart rate (HR) (bpm), cardiac index (CI) (ml/min/kg), total peripheral resistance (TPR) (mm Hg/ml/min/kg) and stroke volume (SV) (ml/kg/beat) in the presence and absence of hexamethonium (HEXA) (200 μg/kg/min) or phenylephrine (PE) (7 μg/kg/min) in pentobarbitone-anaesthetized rats. Means ± S.E. $n = 6$.

	CGS 21680	HEXA + CGS 21680	PE + CGS 21680
BP	76 ± 6.0	53 ± 6.0 [a]	109 ± 5 [a]
HR	432 ± 14	380 ± 16 [a]	428 ± 10
CI	279 ± 9	208 ± 9 [a]	268 ± 8
TPR	1.88 ± 0.13	1.47 ± 0.14	2.68 ± 0.13
SV	0.63 ± 0.02	0.55 ± 0.04	0.63 ± 0.01

[a] Significantly different from CGS 21680 alone $P < 0.05$.

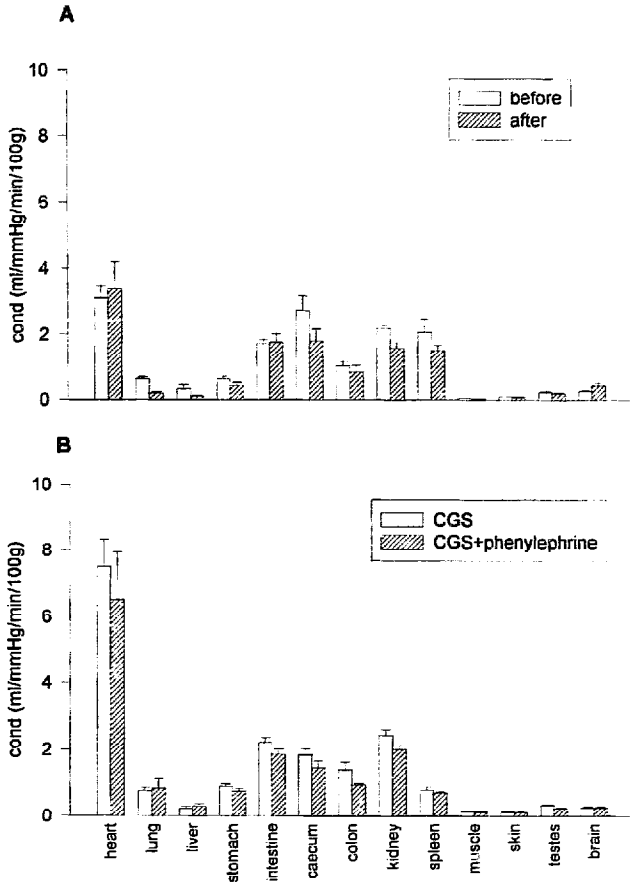

Fig. 3. Effects of (A) phenylephrine (7 μg/kg/min) and (B) phenylephrine (7 μg/kg/min) and CGS 21680 (0.3 μg/kg/min) combined on arterial conductance (ml/mm Hg/min/kg) in pentobarbitone-anaesthetized rats. Means ± S.E. $n = 6$.

reduction in cardiac index and heart rate (Table 2). However, phenylephrine did not significantly alter stroke volume or conductance in any arterial bed (Table 2; Fig. 3A). Administration of CGS 21680 (0.3 μg/kg/min) during infusion with phenylephrine resulted in a reduction in blood pressure. However, blood pressure still remained significantly ($n = 6$; $P < 0.05$) higher when compared to blood pressure in animals that had received CGS 21680 (0.3 μg/kg/min) alone (Table 3). There were no significant differences in heart rate, total peripheral resistance, cardiac index, stroke volume or conductance in any arterial beds in animals that were infused with phenylephrine and CGS 21680 combined and animals that received CGS 21680 alone (Table 3; Fig. 3B).

4. Discussion

In the present study we tested the selectivity of CGS 21680 for A_2 receptors on blood pressure and heart rate in animals treated with 8-cyclopentyl-1,3-dipropylxanthine, a selective A_1 receptor antagonist (Moos et al., 1985). In a previous study it was reported that 8-cyclopentyl-1,3-dipropylxanthine at dose that we used (1 μg/kg/min) completely blocked the bradycardic effects of selective A_1 receptor agonist, N^6-cyclopentyladenosine (Kuan et al., 1992). We found that 8-cyclopentyl-1,3-dipropylxanthine did not have any effects on either hypotensive or tachycardic responses that were produced by the highest dose of CGS 21680 (1.0 μg/kg/min) that was used in our study. Thus indicating that CGS 21680-mediated effects were not due to stimulation of A_1 receptors. The selectivity of CGS 21680 for A_2 versus A_1 receptors had previously been reported to be > 170-fold (Jarvis et al., 1989).

The results of this study show that the effects of selective A_{2A} receptor agonist, CGS 21680 (Hutchison et al., 1989), on arterial conductance is dose-dependent. It is unlikely that the autonomic nervous system is involved in the actions of CGS 21680 (0.3 μg/kg/min) on arterial conductance. Moreover, the vascular actions of this agonist remain unperturbed in a state of increased vascular tone following exogenous infusion with phenylephrine.

CGS 21680 at all three doses decreased blood pressure due to reduction in total peripheral resistance while it increased both heart rate and cardiac index. Since, CGS 21680 at the doses tested did not significantly alter stroke volume, then it is most likely that the increase in cardiac index was a result of an increase in heart rate. The increase in heart rate could be either due to the direct effects of CGS 21680 on the myocardium or alternatively as a result of reflex activation of the sympathetic nervous system following a reduction in vascular resistance. This study per se can not confirm or reject any direct effect of CGS 21680 on the myocardium. However, in animals treated with the ganglionic blocker, hexamethonium, the increase in heart rate to CGS 21680 was prevented. This most likely would suggest that the increase in heart rate in intact animals by CGS 21680 was perhaps due to reflex activation of the sympathetic nervous system. A similar effect on the heart has been previously reported (Webb et al., 1991, 1993; Hutchison et al., 1989). Furthermore, our conclusion that the increase in heart rate may be a reflex-mediated effect is in agreement with the reports that tachycardia induced by CGS 21680 was attenuated in the presence of metoprolol, a selective β_1-adrenoceptor antagonist (Webb et al., 1991), and lack of tachycardic response to CGS 21680 in the pithed rats (Fozard and Carruthers, 1993a,b). Moreover, the lack of direct positive chronotropic effect of CGS 21680 in isolated heart (Hutchison et al., 1989), and its lack of direct effect on heart automaticity in the rat isolated right ventricle (Hernandez et al., 1994) provides further support for the idea that the actions of CGS 21680 on the heart rate were indirect.

In the present study, we found that CGS 21680 could increase arterial conductance in the heart at all three doses tested, while only at the two higher doses (0.3 and 1.0 μg/kg/min) it increased arterial conductance in muscle and decreased it in the spleen. Moreover, the highest administered dose of CGS 21680 increased arterial con-

ductance in the brain. It is evident from these findings that the effect of CGS 21680 on arterial conductance was dose-dependent. It may further be argued that there is a differential in sensitivity among different arterial vascular beds to actions of this agonist. Based upon our present findings, it would appear that the coronary arterial bed is the most sensitive while the cerebral arterial bed is the least sensitive to the vasorelaxant effects of CGS 21680. In agreement with our present findings is a study by Toda et al. (1982) in which it was demonstrated that adenosine was more potent in relaxing dog isolated coronary than cerebral arteries. Furthermore, in a recent study on human vasculature, Makujina et al. (1992) also demonstrated that the coronary artery was more sensitive than internal mammary artery or saphenous vein to relaxant actions of CGS 21680. It is possible that the differential sensitivity of various blood vessels to the relaxant effects of CGS 21680 is the result of different distribution of A_{2A} receptors.

We also found that CGS 21680 could increase skeletal muscle arterial conductance but only at the two higher doses that were tested. This observation may be taken to indicate that functional control of blood vessels in the skeletal muscle, in part, is mediated by A_{2A} receptors. The findings of the present study are in agreement with earlier reports that had shown adenosine to have a regulatory role in skeletal muscle blood flow (Belloni et al., 1979; Proctor and Duling, 1982; Ballard et al., 1987). Such evidence may be taken to indicate that adenosine released from skeletal muscle may have a physiological role in the control of muscle blood flow. Infusion of CGS 21680 at the highest dose increased cerebral arterial conductance. Earlier studies using isolated blood vessels had shown that adenosine and adenosine analogues were capable of relaxing cerebral blood vessels (Hardebo and Edvinsson, 1979; Muramatsu et al., 1980; Toda et al., 1982; Edvinsson and Fredholm, 1983). Moreover, based on pharmacological evidence, A_2 receptor subtypes have been reported to be responsible for mediating the actions of adenosine in cerebral arteries (Edvinsson and Fredholm, 1983). The present results with respect to the effects of CGS 21680 on cerebral blood flow may be interpreted as indicating that stimulation of A_{2A} receptors can affect cerebral blood flow in the rat but that this effect will only become apparent if a higher dose of the agonist is employed.

Administration of CGS 21680 was found to decrease arterial conductance in spleen. The significance of this finding is not known nor can it be interpreted by the present knowledge with respect to A_{2A} receptors. However, this finding may indicate a lack of functional role for A_{2A} receptors in the spleen.

It would appear that autonomic nervous system does not play a major role in mediating the effects of CGS 21680 on vascular conductance. Since, there were no significant differences in conductance values in any arterial bed between the animals that received CGS 21680 alone versus those that received hexamethonium and CGS 21680. However, animals treated with CGS 21680 and hexamethonium combined in comparison to animals that were treated with CGS 21680 alone had a significantly lower blood pressure, heart rate and cardiac index. This observation is consistent with the idea that reflex activation of sympathetic nervous system occurred in intact animals following infusion with CGS 21680. It was also apparent that the effects of phenylephrine on cardiac index, heart rate, stroke volume and total peripheral resistance could be reversed by infusion with CGS 21680. Moreover, it is quite clear that exogenous administration of vasoconstrictor does not oppose the vascular actions of CGS 21680 in different beds.

In summary, our study demonstrated that stimulation of A_{2A} receptors by CGS 21680 is associated with an increase in heart, skeletal muscle and cerebral arterial conductance, and a decrease in spleen arterial bed conductance. The heart arterial bed was found to be the most sensitive and the cerebral arterial bed the least sensitive to the effects of CGS 21680. In addition, it was demonstrated that the autonomic nervous system is not involved in the action of CGS 21680 on arterial conductance, and there is no difference in the action of this compound in states of normal and increased vascular tone on arterial conductance.

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