Tachycardia Caused by $A_{2A}$ Adenosine Receptor Agonists Is Mediated by Direct Sympathoexcitation in Awake Rats

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ABSTRACT

Adenosine-induced tachycardia is suggested to be mediated via $A_{2A}$ receptors; however, the exact mechanism for this effect remains to be understood. The present study was carried out using regadenoson, a selective $A_{2A}$ adenosine receptor agonist, to determine the role of the $A_{2A}$ receptor subtype in adenosine-induced tachycardia. Regadenoson (0.3–50 μg/kg) given as a rapid i.v. bolus to awake rats caused a dose-dependent increase in heart rate (HR). Mean arterial pressure (MAP) increased at lower doses, whereas at higher doses, there was a decrease in MAP. The increase in HR was evident at the lowest dose (0.3 μg/kg) of regadenoson at which there was no appreciable decrease in MAP. Pretreatment with 30 μg/kg ZM 241385 [4-(2-[7-amino-2-(2-furyl)-[1,2,4]-triazolo-[2,3-a]-[1,3,5]-triazin-5-ylamino]ethyl)phenol], an $A_{2A}$ receptor antagonist, attenuated the decrease in MAP and the increase in HR caused by regadenoson. Pretreatment with metoprolol (1 mg/kg), a β-blocker, attenuated the increase in HR but had no effect on the hypotension caused by regadenoson. In the presence of hexamethonium (10 mg/kg), a ganglionic blocker, the tachycardia was completely prevented even though MAP was further reduced. Regadenoson treatment (10 μg/kg) significantly ($p < 0.05$) increased plasma norepinephrine levels almost 2-fold above baseline. The dissociation of HR and MAP effects by dose, time, and pharmacological interventions provides evidence that tachycardia caused by regadenoson is independent of the decrease in MAP and may not entirely be baroreflex-mediated, suggesting that regadenoson may cause a direct stimulation of the sympathetic nervous system via activation of $A_{2A}$ adenosine receptors.

Adenosine elicits a wide variety of cardiovascular effects that are mediated by four distinct subtypes ($A_1$, $A_{2A}$, $A_{2B}$, and $A_3$) of G-protein-coupled receptors (Belardinelli et al., 1989; Fredholm et al., 2001; Dhalla et al., 2003). Coronary vasodilation caused by adenosine, which is primarily mediated by the $A_{2A}$ receptor subtype, led to the use of this nucleoside in myocardial perfusion imaging studies with radionuclide agents (Verani, 1991; Iskandrian et al., 1994). Myocardial perfusion imaging using adenosine or $A_{2A}$ receptor agonists as coronary vasodilators is accompanied by a significant sinus tachycardia (Johnston et al., 1995; Udelson et al., 2004; Hendel et al., 2005). The adenosine receptor subtype responsible for the tachycardia has been proposed to be the $A_{2A}$ receptor (Koos et al., 1993; Alberti et al., 1997); however, this remains to be conclusively established, as well as the mechanism of the acceleration of the heart rate.

$A_{2A}$ adenosine receptor agonists cause vasodilation in most vascular beds by a direct action on $A_{2A}$ receptors on endothelial and vascular smooth muscle cells (Belardinelli et al., 1998; Hein et al., 1999). The peripheral vasodilation causes a decrease in arterial pressure, which in turn elicits a baroreflex-mediated activation of the sympathetic nervous system (SNS) and thereby an increase in heart rate. This has been proposed to be the mechanism underlying the increase in heart rate (HR) caused by adenosine and $A_{2A}$ receptor agonists (Nekoeiean and Tabrizchi, 1996; Alberti et al., 1997). However, it has been shown that adenosine elicits a direct positive chronotropic effect (Koos et al., 1993) and that activation of $A_{2A}$ receptors leads to direct stimulation of the autonomic nervous system (Koos and Chau, 1998). In this regard, adenosine has also been shown to cause stimulation of carotid body chemoreceptors (McQueen and Ribeiro, 1981; Biaggioni et al., 1987). The adenosine receptor subtype responsible for chemoreceptor activation by adenosine and stable analogs has been proposed to be the $A_2$ receptor (McQueen and Ribeiro, 1986).

ABBREVIATIONS: regadenoson/CVT-3146, adenosine, 2-[4-(methylamino)carbonyl]-1H-pyrazol-1-yl]; ZM 241385, 4-(2-[7-amino-2-(2-furyl)-[1,2,4]-triazolo-[2,3-a]-[1,3,5]-triazin-5-ylamino]ethyl)phenol; CGS 21680, 2-p-(2-carboxyethyl)phenethylamino-5′-N-ethylcarboxamidoadenosine; NECa, 5′-N-ethylcarboxamido-adenosine; SNS, sympathetic nervous system; SNP, sodium nitroprusside; MAP, mean arterial pressure; MET, metoprolol; HEX, hexamethonium; ANOVA, analysis of variance; NE, norepinephrine.
To further establish the role of A2A receptors and the mechanism of the tachycardia caused by adenosine and A2A receptor agonists, we used regadenoson (also known as CVT-3146), a novel A2A adenosine receptor agonist (Gao et al., 2001). Regadenoson has been shown to be selective for the A2A adenosine receptors versus the A1, A2B, and A3 receptor subtypes in radioligand binding and functional studies (Gao et al., 2001). This A2A receptor agonist is currently being developed as a pharmacological “stress” agent (coronary vasodilator) for myocardial perfusion imaging using radionuclides (Hendel et al., 2005). Clinical data show that rapid i.v. injections of regadenoson cause a transient (2–5 min) near-maximal increase in coronary blood flow velocity, which is accompanied by a sinus tachycardia of approximately 20 ± 2 beats per minute (bpm) (Kerenisky et al., 2002). A pharmacokinetic study of regadenoson in healthy volunteers revealed that regadenoson causes a dose (concentration)-dependent sinus tachycardia with minimal or no changes in systolic and diastolic arterial blood pressure (Cannon et al., 2003). This finding is similar to the observations reported in laboratory animals with adenosine (Koos et al., 1993) and more recently in humans using another selective A2A receptor agonist, binodenoson (Barrett et al., 2005). Altogether, these observations suggest that the A2A adenosine receptor-mediated sinus tachycardia may not entirely be due to a baroreceptor reflex triggered by a decrease in arterial pressure. Thus, the present study was undertaken to determine whether regadenoson-induced tachycardia is solely baroreflex-mediated or also due to a direct activation of the SNS.

Materials and Methods

Chemicals. Regadenoson (adenosine, 2-[4-(methylamino)carbonyl]-1H-pyrazol-1-yl) was synthesized by the Department of Bio-Organic Chemistry (CV Therapeutics) and was dissolved in saline. Metoprolol, hexamethonium, and sodium nitroprusside were purchased from Sigma (St. Louis, MO) and were dissolved in saline. ZM 241385 (4-(2-[7-amino-2-(2-furyl)-1,2,4-triazolo-[2,3-a]-1,3,5-triazin-5-ylamino)ethyl)phenol) was purchased from Tocris Cookson Inc. (Ellisville, MO) and was dissolved in 5% dimethyl sulfoxide in deionized water.

Animals. Male Sprague-Dawley rats weighing 300 ± 50 gm with two indwelling canulas (carotid artery and jugular vein) were purchased from Charles River Laboratories, Inc. (Wilmington, MA). Animals were maintained on a 12-h light and dark cycle and received standard laboratory rat chow and water ad libitum. All experimental procedures were performed under the protocol approved by the Institutional Animal Care and Use Committee (CV Therapeutics, Inc.) and in accordance with the recommendations set forth in the Guide for the Care and Use of Laboratory Animals published by the National Research Council.

Experimental Protocol. All experiments were carried out in unrestrained awake rats. On the day of the experiment (at least 1 week after the intravascular cannulation), the animal was weighed and placed in a small cage to acclimatize to the environment for at least 1 h prior to the commencement of the experiment. Food was withheld during the experiment, but water was given ad libitum. Baseline measurements were recorded for at least 30 min before starting treatment. Rats were given intravenous injections of regadenoson up to 2 doses each of 0.3, 1.0, 3, 10, and 30 μg/kg at 30-min intervals or longer (at the higher doses) to ensure that the parameters being measured returned to baseline levels before the next dose was given. Sodium nitroprusside (SNP) was given as an i.v. bolus at 0.1-, 3-, and 10-μg/kg doses. In experiments with ZM 241385 (A2A adenosine receptor antagonist), metoprolol (β1-adrenoceptor antagonist), or hexamethonium (ganglionic blocker), these agents were given as an i.v. bolus to the rats 10 min prior to regadenoson. The doses used for these agents were derived from the literature (Poucher et al., 1996) and/or were tested by giving repeated injections of the blocking agents to determine the dose that ensured complete blockade of the response consistent with the action of each agent (data not shown). All test compounds were injected via the jugular vein catheter.

Measurement of Cardiovascular Responses. All measurements were done in unrestrained awake animals. Heart rate and arterial pressure were monitored continuously throughout the experiment. The arterial catheter was connected to a pressure transducer (MLT0698; ADInstruments, Inc., Colorado Springs, CO) and transducer signal conditioner (model 13-6615-50; Gould Instrument Systems, Inc., Valley View, OH) to monitor arterial pressure. Arterial pressure (diastolic and systolic) and HR were recorded using a Gould PONEMAH system (Gould Instrument Systems, Inc.). Mean arterial pressure (MAP) was calculated (in mm Hg) 2/3 diastolic + 1/3 systolic blood pressure.

Measurement of Norepinephrine Levels. A separate group of animals was used for measurement of norepinephrine levels. Animals were weighed and placed in metabolic cages with both the arterial and venous catheters attached to infusion sets (needles 21-gauge, volume 0.17 ml; Terumo Medical Corp., Somerset, NJ). Regadenoson was injected into the venous site, and blood samples were drawn from the arterial site. Blood was withdrawn using a 1-ml syringe with 25-gauge needle and placed in a plasma separator tube (on ice) containing EDTA (Microtainer brand). The samples were centrifuged at 8000 rpm (4°C) for 5 min, and plasma were stored in a microtube (on ice) containing a 10-μl aliquot of EDTA-glutathione (Sigma) preservative. Plasma samples were then transferred to −80°C until analyzed. Plasma norepinephrine concentrations were determined by HPLC using the electrochemical detection method as described in detail elsewhere (Boudreau et al., 1993).

Data Analysis. Data are presented as percent change ± S.E.M. from baseline. Baseline values are presented under Results and/or figure legends. Statistical comparisons among various treatment groups were carried out using two-way repeated measures ANOVA followed by Bonferroni’s post hoc test. Differences between two groups were determined by Student’s t test. Differences among mean values were considered significant when the p value was less than 0.05.

Results

Effect of Regadenoson on Heart Rate and Mean Arterial Pressure. In awake rats, the mean baseline value for HR was 345 ± 26 bpm. As illustrated in Fig. 1A, regadenoson given as an i.v. bolus (1, 3, 10, 30, and 50 μg/kg) caused a dose- and time-dependent increase in HR. The increase in HR caused by regadenoson was clearly detectable at 1 min, although small (−10%, p < 0.001), at a dose as low as 1 μg/kg. At higher doses, the increases in HR were in the range of 15 to 30% above basal (p < 0.001). As to the time course of the changes in HR caused by regadenoson, the increases in HR, independent of the doses, were evident at as early as 1 min after the i.v. bolus. At lower doses (1 μg/kg) of regadenoson, the HR returned to baseline within 2.5 min, whereas at higher doses, not only did the tachycardia last longer (15–30 min) but the magnitude of the effect was also greater (Fig. 1A).

In awake rats, the mean baseline value for mean arterial pressure (MAP) was 106 ± 4 mm Hg. Regadenoson caused dose- and time-dependent changes in MAP (Fig. 1B). Regadenoson caused a small but not significant increase in MAP at a dose of 0.3 (Fig. 2A) and 1 μg/kg (Fig. 1B), whereas at
higher doses, there was a significant (p < 0.001) decrease in MAP (~20% decrease at 50 μg/kg), which was noted as early as 1 min after the injection. MAP returned to baseline within 5 min at lower doses (<10 μg/kg) of regadenoson, whereas at higher doses (30 and 50 μg/kg), MAP remained slightly below baseline up to 30 min postinjection. A similar pattern was observed in the effect of regadenoson on systolic and diastolic pressure (data not shown).

Summarized in Fig. 1C are the maximal changes (% control) in MAP and HR caused by various doses of regadenoson. There was no significant change in MAP at lower doses (0.3–3 μg/kg). A significant decrease in MAP was observed only at 10 μg/kg and at higher doses. However, increases in HR were observed at doses of 1 and 3 μg/kg when there were no appreciable decreases in MAP. The maximal increase in HR was achieved at the 3-μg/kg dose of regadenoson, whereas the maximal decrease in MAP was observed at the highest regadenoson dose studied (50 μg/kg). It is important to note that the maximal increase in HR was observed at the 3-μg/kg dose of regadenoson, at which there was very small decrease in MAP. Thereafter, no further increase in HR was observed with increasing doses of regadenoson, even though the peak response in MAP continued to grow.

**Temporal Relationship between Changes in Heart Rate and Mean Arterial Pressure.** Figure 2 shows the
time course of changes in HR and MAP caused by three different doses (0.3, 3, and 50 µg/kg) of regadenoson. At the 0.3 µg/kg dose (Fig. 2A), there was a small but significant (p < 0.05) increase (11 ± 2%) in HR at 1 min, whereas there was no significant change in MAP. HR returned to baseline values within 10 min of the regadenoson injection. At 3 µg/kg dose (Fig. 2B), there was greater than 20% increase in HR above baseline (p < 0.01), whereas there was no appreciable decrease in MAP. At this dose, HR returned to baseline values within 15 min after regadenoson injection. At the 50 µg/kg dose (Fig. 2C), there was a significant decrease (18 ± 2%, p < 0.01) in MAP; however, the maximal HR response was not very different from the 3-µg/kg dose. At the 50-µg/kg dose of regadenoson, HR remained elevated for 30 min, even though the MAP returned to near normal levels within 5 min.

Pharmacological Interventions. To determine whether the A2A receptor subtype was responsible for mediating the tachycardia and hypotension caused by regadenoson, the animals were pretreated 10 min prior to administration of regadenoson with ZM 241385 (Fig. 3, ZM), an A2A receptor antagonist. ZM itself had no significant effect on HR or MAP. Regadenoson (3 µg/kg) caused a 16 ± 1% (p < 0.01) increase in HR and a 5 ± 3% decrease in MAP. Pretreatment with ZM completely prevented the decrease in MAP and significantly (p < 0.01) attenuated the increase in HR (to 6 ± 1% above baseline) caused by regadenoson.

To investigate the role of the SNS in the tachycardia induced by regadenoson, animals were pretreated with the β-blocker metoprolol (MET) at a dose of 1 mg/kg (Fig. 4). Treatment with MET caused a small decrease (5% below baseline) in HR but had no effect on MAP. Regadenoson (3 µg/kg) caused a 16 ± 1% (p < 0.01) increase in HR, which was significantly blunted after pretreatment with MET (−1 ± 3%) (Fig. 4). MET treatment had no effect on the hypotension caused by regadenoson (Fig. 4B).

The ganglionic blocker hexamethonium was used to further establish the role of the SNS in the tachycardia induced by regadenoson (Fig. 5). Treatment with hexamethonium (HEX) alone caused a significant reduction (40%) in MAP, which recovered somewhat within 5 min. HEX had no significant effect on HR. Regadenoson (10 µg/kg) caused a significant (p < 0.01) increase (27 ± 3%) in HR, which was completely prevented by HEX (Fig. 5A). Regadenoson caused a significant (p < 0.01) decrease (11 ± 2%) in MAP. Pretreatment with HEX resulted in a greater decrease (49%) in MAP by regadenoson (Fig. 5B).

Comparison with Sodium Nitroprusside. The effects of regadenoson on HR and MAP were compared with those of the vasodilator SNP. SNP is a nonselective vasodilator that causes hypotension mediated by nitric oxide that results in baroreflex-mediated increases in HR. SNP caused a dose-dependent decrease in MAP, which was accompanied by a
A proportional increase in HR (Fig. 6A). Similar to SNP, regadenoson decreased MAP in a dose-dependent manner, but unlike SNP, the associated increase in HR was not proportional to the magnitude of decrease in MAP (Fig. 6B). This is further illustrated in Fig. 6C, which shows the relationship between changes in HR and MAP by SNP and regadenoson.

**Discussion**

The cardiovascular effects of adenosine have been known for over 60 years. However, only when adenosine was given intravenously to conscious humans, it became evident that this nucleoside could produce sympathetic activation (Biaggioni et al., 1987). Interestingly, most animal studies failed to show sympathoexcitation by systemically administered adenosine. However, studies showed that adenosine could stimulate isolated arterial chemoreceptors (McQueen and Ribeiro, 1981) and studies using selective agonists suggested that this effect was mediated by A2A receptors (McQueen and Ribeiro, 1983, 1986). In animals as well as humans, adenosine and its analogs cause sinus tachycardia and lower systemic blood pressure (Biaggioni et al., 1987; Lappe et al., 1992; Bonizzoni et al., 1995; Alberti et al., 1997; Koos and Chau, 1998; Barrett et al., 2005; Hendel et al., 2005; Schindler et al., 2005). The sinus tachycardia has been attributed to the baroreceptor reflex caused by the decrease in arterial pressure (Webb et al., 1990, 1991; Nekooeian and Tabrizchi, 1996; Alberti et al., 1997). However, there is also evidence that adenosine-mediated tachycardia can occur independent of a decrease in MAP (Lappe et al., 1992; Mathot et al., 1995; Koos and Chau, 1998; Schindler et al., 2005). Thus, the purpose of this study was to establish the role of A2A adenosine receptors and the mechanism underlying the sinus
tachycardia caused by the adenosine analog regadenoson. Regadenoson is highly selective for the A<sub>2A</sub> receptor subtype, has a rapid onset and short duration of action, is readily reversible, and causes sinus tachycardia in humans (Gao et al., 1993; Mathot et al., 1995; Nekooeian and Tabrizchi, 1996; Alberti et al., 2001; Trochu et al., 2003; Hendel et al., 2005). The important and novel finding of the study is that sinus tachycardia mediated by the A<sub>2A</sub> receptor subtype is in great part due to a direct activation of the SNS and not baroreflex-mediated.

A<sub>2A</sub> Receptor-Mediated Responses. The effects of regadenoson on MAP and HR described in the present study are consistent with those reported previously using known selective A<sub>2A</sub> agonists (Webb et al., 1990; Koos et al., 1993; Mathot et al., 1995; Nekooeian and Tabrizchi, 1996; Alberti et al., 1997; Schindler et al., 2005). Hence, the decrease in MAP and tachycardia are commonly observed pharmacological effects of A<sub>2A</sub> agonists. The sinus tachycardia and lowering of MAP caused by regadenoson were completely prevented by pretreatment with a selective A<sub>2A</sub> receptor antagonist ZM 241385, confirming that these effects of regadenoson are mediated by the A<sub>2A</sub> adenosine receptor subtype. Thus, the results of the present study support previous evidence for the role of A<sub>2A</sub> receptors in mediating adenosine-induced hypotension and tachycardia (Webb et al., 1991; Koos et al., 1993; Bonizzoni et al., 1995; Nekooeian and Tabrizchi, 1996; Schindler et al., 2005).

Role of Sympathetic Stimulation in Regadenoson-Induced Tachycardia. Pretreatment with metoprolol completely abolished the HR response without any change in the effect of regadenoson on MAP, indicating that the tachycardia caused by regadenoson is mediated by an increase in sympathetic tone. Likewise, pretreatment with hexamethonium caused a greater fall in MAP by regadenoson, but the increase in HR caused was completely prevented. This finding also suggests that activation of the SNS plays a major role in the tachycardia induced by regadenoson. Furthermore, regadenoson caused almost a 2-fold increase in circulating plasma norepinephrine levels, which is indicative of sympathoexcitation. Previously, it has been shown that NECA, a nonselective agonist of adenosine receptors, caused increase in plasma norepinephrine levels (Laborit et al., 1990). Likewise, adenosine has been shown to increase plasma catecholamine levels in sheep (Koos et al., 1993), an effect that was suggested to be mediated by A<sub>2A</sub> receptors. However, these data do not discriminate between direct and indirect activation of the SNS.

Regadenoson-Induced Tachycardia Is Independent of Decrease in MAP. Comparison of the dose-response and time course of the effects of regadenoson on HR and MAP revealed that regadenoson can increase HR independent of decreasing MAP. In support of this conclusion, the 0.3- and 3.0-μg/kg doses of regadenoson significantly increased HR but caused no decrease in MAP. At the higher doses of regadenoson (30 and 50 μg/kg) that cause significant hypotension, MAP returned to baseline, whereas marked tachycardia was still present. The tachycardia outlasted the lowering of MAP by at least 20 to 30 min. These data indicate that a baroreflex-mediated increase in HR may not be the sole mechanism for the tachycardia observed with regadenoson. In fact, this lack of association between changes in HR and MAP has been previously reported for other A<sub>2A</sub> agonists (Lappe et al., 1992; Koos and Chau, 1998; Schindler et al., 2005). In fetal sheep, CGS 21680 caused a significant increase in HR (61%) without an effect on MAP (Koos and Chau, 1998). Lappe et al. (1992) reported that systemic administration of the A<sub>2A</sub> agonist DMPA ((N6-[2-(3,5-dimethoxyphenyl)-2-(2 methylphenyl)ethyl]adenosine) caused sinus tachycardia without a significant change in MAP in awake rats. A recent study shows that peripheral administration of CGS 21680 resulted in both hypotension and tachycardia, whereas central administration (lateral ventricle) caused tachycardia without causing hypotension, suggesting that the hypotensive effect of this A<sub>2A</sub> agonist is mediated by peripheral receptors, whereas the tachycardia is mediated by centrally located A<sub>2A</sub> receptors (Schindler et al., 2005). Altogether, these observations suggest that the tachycardia caused by A<sub>2A</sub> agonists is not solely the result of a reflex response caused by their hypotensive effect. Although the tachycardia and hypotension caused by regadenoson are mediated by the same receptor subtype (A<sub>2A</sub>), differences in receptor reserve (and coupling efficiency) for these two effects could be responsible for the differential sensitivity and duration of the effect. However, this remains to be investigated.

A comparison between cardiovascular responses of regadenoson with that of a pure vasodilator SNP provides additional evidence that tachycardia caused by regadenoson is not simply caused by reflex. SNP is a direct vasodilator that causes relaxation of vascular smooth muscle by nitric oxide and cGMP formation (Ignarro and Kadowitz, 1985). SNP caused a dose-dependent decrease in MAP, which was accompanied by a proportional increase in HR caused by baroreflex-mediated mechanism to keep arterial pressure from falling. However, the decrease in MAP caused by regadenoson was associated with a much greater response in HR and, compared with SNP, seems to be disproportionate to the
magnitude of decrease in MAP. This is more evident in Fig. 6B where changes in HR are plotted against changes in MAP for both agents. A linear relationship was seen between MAP and HR changes caused by SNP but not for regadenoson, indicating a lack of dependence of the increase in HR on MAP changes caused by regadenoson. This analysis provides evidence that the increase in HR caused by regadenoson may not be solely be due to its vasodilatory effects, as is the case for the pure vasodilator SNP.

Mechanism of Sympathetic Stimulation. The mechanism of direct sympathoexcitation caused by A2A agonists remains to be established. Adenosine reportedly activates a variety of afferent nerve terminals (myocardial, renal, and skeletal muscle), leading to sympathetic activation (Katholi et al., 1984; Cox et al., 1989; Costa et al., 2001). In humans, activation of arterial chemoreceptors is particularly prominent during intravenous administration of adenosine, which can lead to increase in ventilation, sympathetic activation with a modest increase in systolic pressure, and increase in HR (Biaggioni et al., 1987, 1991; Engelstein et al., 1994). The receptor subtype that mediates adenosine-mediated activation of arterial chemoreceptors is suggested to be A2A (McQueen and Ribeiro, 1983, 1986; Koos et al., 1993). In contrast, adenosine-induced tachycardia in fetal sheep mediated by A2A receptors was proposed to be attributed to direct activation of the SNS independent of the peripheral arterial chemoreceptors (Koos et al., 1993). Thus, further studies are needed to elucidate the mechanism of A2A receptor-mediated sympathoexcitation.

In conclusion, the results from the present study show that regadenoson causes dose- and time-dependent decreases in MAP and tachycardia in awake rats mediated by A2A adenosine receptors. The dissociation of the effects of regadenoson on HR and MAP by dose, time course, pharmacological interventions, and in comparison with SNP provides evidence that tachycardia observed with regadenoson in this study could not be explained simply by a baroreflex-mediated phenomenon because of the vasodilatory effects of regadenoson. Therefore, we propose that tachycardia was due, in part, to a direct stimulation of arterial chemoreceptors, as suggested by previous studies (McQueen and Ribeiro, 1986; Biaggioni et al., 1987; Engelstein et al., 1994). A limitation of the study is that we have not conclusively proven our hypothesis by directly measuring afferent sympathetic nerve traffic arising from arterial chemoreceptors or studied the effects of regadenoson in chemodenervated animals.

A potential clinical implication of the findings of the present study is that sympathoexcitation caused by A2A agonists should contribute to the diagnostic value of these agents for coronary artery disease in myocardial perfusion imaging studies, because they not only increase coronary vasodilation but also increase heart rate to mimic exercise, a physiological stressor.

References


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