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Adenosine strongly potentiates pressor responses to nicotine in rats

(caffeine/blood pressure/sympathetic nervous system)

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ABSTRACT **Intravenous infusion of subhypotensive doses of adenosine strongly potentiates the pressor response of anesthetized rats to nicotine. A dose of nicotine (40 μg/kg, i.v.), which, given alone, elicits a peak increase in diastolic pressure of ≈15 mm Hg, increases pressure by ≈70 mm Hg when arterial plasma adenosine levels have been increased to 2 μM from a basal concentration of ≈1 μM. The pressor response to cigarette smoke applied to the lungs is also strongly potentiated during infusion of adenosine. Slightly higher adenosine concentrations (≈4 μM) attenuate pressor responses to electrical stimulation of preganglionic sympathetic nerves, or to injections of the α-adrenergic agonist phenylephrine, but continue to potentiate pressor responses to nicotine. Low doses (0.25–5 μg/kg) of the synthetic adenosine receptor agonists 5′-*N*-cyclopropylcarboxamidoadenosine, 2-chloroadenosine, and N^6-L-phenylisopropyladenosine also potentiate pressor responses to nicotine. Caffeine and theophylline (10 mg/kg) block the potentiating effect of adenosine, and also decrease basal responses to nicotine, suggesting that endogenous adenosine might normally potentiate some nicotine responses. The synergism between nicotine and adenosine appears to take place within sympathetic ganglia.**

In addition to serving as a constituent of biologically important molecules such as adenosine 3′,5′-cyclic monophosphate, adenosine triphosphate, *S*-adenosylmethionine, and coenzyme A, the purine nucleoside adenosine can also modify neurotransmission and affect other physiological processes via interaction with specific adenosine receptors on the outer surface of various excitable cells (1). The methylxanthines caffeine and theophylline are potent antagonists at these receptors (2).

Administration of adenosine to animals can elicit many responses, including sedation, hypotension, bradycardia, protection against experimentally induced seizures, suppression of the evoked release of several neurotransmitters, and suppression of lipolysis (3–5). Adenosine can influence physiological processes by modifying the release of neurotransmitters or hormones; the responses of tissues to neurotransmitters, drugs, or hormones; or the rates of cellular processes operating independently of particular neurotransmitters or hormones. In assessing the response of a physiological system to adenosine, it is important to differentiate between these three modes of action, because the net direction (inhibitory versus facilitatory) of the influence of adenosine on neurotransmission can be different, even within a single population of synapses or neuroeffector junctions, at presynaptic versus postsynaptic sites. For example, in the isolated rabbit kidney, adenosine acts both to inhibit the evoked release of norepinephrine from vascular sympathetic terminals and postsynaptically to enhance vascular responsiveness to norepinephrine; the net effect is to enhance vasoconstrictor responses to stimulation of the renal nerve, even though norepinephrine output during nerve stimulation is decreased (6). Adenosine can be produced ubiquitously and is present in plasma and cerebrospinal fluid (7, 8); the nucleoside can therefore potentially act at a number of different loci, both central and peripheral, within the complex neural circuitry involved in the regulation of a single physiological function, such as maintenance of blood pressure or heart rate. Neither normal plasma adenosine levels nor the relative and absolute sensitivities of neural and cellular processes to adenosine have been well characterized in intact animals. The studies described below explore the effects of controlled measured alterations in arterial plasma adenosine concentrations on the responses of blood pressure to several pharmacological and physiological treatments that modify sympathetic neurotransmission.

METHODS

Male Sprague–Dawley rats (Charles River Breeding Laboratories) weighing 250–350 g were used in all experiments.

In animals anesthetized with Nembutal (50–60 mg/kg, i.p.), a silastic catheter (Dow–Corning 602–135) was introduced into the aorta via the left carotid artery for blood pressure measurement, periodic withdrawal of blood samples for assay of adenosine content, and, in some experiments, for intra-arterial drug administration. For intravenous administration of adenosine and other compounds, a multiple catheter, consisting of three lengths of PE-10 polyethylene tubing encased in a sheath of silastic tubing (Dow–Corning 602–155), was implanted in the right atrium via the right external jugular vein; bolus injections of drugs could thereby be given without interrupting a concurrent steady intravenous infusion of adenosine.

For electrical stimulation of preganglionic sympathetic nerves, the arterial and venous catheters were implanted in ether-anesthetized animals. The rat was then pithed by inserting a stainless steel tube (13 gauge) through the orbit and the foramen magnum, into the spinal column to the level of the sixth cervical vertebra; this destroys the brainstem and effectively severs the spinal cord from the brain altogether (9). Through this trocar, a steel rod (1-mm diameter) was inserted down the length of the spinal column, terminating in the sacral vertebrae. The portion of the rod that remained inside the trocar was insulated with a silastic sheath. The animal was respired artificially with room air (1 ml per 100 g of body weight, 50 strokes per min) via a tracheal cannula for the duration of the experiment. Skeletal muscle was paralyzed with pancuronium bromide (0.02 mg/kg, i.v.) and an indifferent electrode was inserted under the skin of the right hindlimb. Monophasic pulses (0.1 msec duration, 0.1–20 pulses per sec, 10–80 V) were applied with a Grass S11 stimulator.

In the isolated hindlimb preparation, both carotid arteries were cannulated, and blood from the right carotid artery was

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Abbreviations: L-PIA, N^6-(L-phenylisopropyl)adenosine; D-PIA, N^6-(D-phenylisopropyl)adenosine; CPCA, *N*-cyclopropylcarboxamidoadenosine; 2-ClA, 2-chloroadenosine.

perfused directly into the cannulated right femoral artery via a constant-flow infusion pump. The flow rate was adjusted to maintain basal hindlimb perfusion pressure, recorded distally to the pump, at 100 mm Hg. The 2- to 3-min circulation time delay through the pump and tubing of the perfusion circuit allowed us to discriminate between drug effects at the neuroeffector junction (vascular smooth muscle and sympathetic nerve terminals) and effects mediated through modification of the firing rate of postganglionic sympathetic nerves, which remain intact and functional in this system. Systemic drug injections could be given into the descending aorta via the left carotid artery catheter (through which blood pressure was continuously monitored); drugs could also be injected directly into the hindlimb perfusion circuit proximal to the pump.

Arterial blood pressure and hindlimb perfusion pressure were monitored with Statham (Hato Rey, PR) 23PD pressure transducers interfaced with a Grass 7C polygraph.

Blood samples (0.3 ml) were rapidly withdrawn via the arterial catheter into syringes previously loaded with 0.3 ml of ice-cold heparinized (200 units/ml) saline containing 0.5 mM dipyridamole (Boehringer Ingelheim, Ridgefield, CT), which inhibits the uptake of adenosine into cells. Each sample was immediately centrifuged and 0.45 ml of the supernatant was deproteinized by mixing with 0.15 ml of 15% trichloroacetic acid followed by centrifugation. The final supernatant was neutralized with excess calcium carbonate.

Adenosine in plasma extracts was assayed by high-pressure liquid chromatography, using a Waters μBondapak C-18 reversed-phase column with isocratic elution (10% methanol in 10 mM potassium phosphate, pH 6.0) at a flow rate of 1.7 ml/min at 30°C (10). Adenosine was detected by UV absorbance at 254 nm.

Adenosine (5 mg/ml in 0.9% saline) was administered as an intravenous infusion at constant flow rates ranging from 10 to 100 μl/min with a Harvard (South Natick, MA) syringe pump.

Nicotine, phenylephrine, and the adenosine derivatives N^6-(L-phenylisopropyl)adenosine (L-PIA), N^6-(D-phenylisopropyl)adenosine (D-PIA), *N*-cyclopropylcarboxamidoadenosine (CPCA) (all three generously provided by John W. Daly), and 2-chloroadenosine (2-ClA) (Sigma) were administered as intravascular bolus injections in a volume of 0.1 ml of physiological saline. A recovery time of at least 10 min was allowed between successive injections of nicotine or the adenosine derivatives to ensure reproducibility of responses to these drugs.

For administration of cigarette smoke, anesthetized rats were artificially ventilated as described above, and air was drawn into the respiration pump through a lit cigarette for 15 pump strokes (≈20 sec). Other drugs (hexamethonium bromide, phentolamine, atropine, reserpine, caffeine, and theophylline) were administered intravenously (except for reserpine, which was injected intraperitoneally) in a volume of 1 ml of 0.9% saline per kg of body weight.

RESULTS

Effect of Adenosine on the Pressor Response to Nicotine. Intravascular administration of nicotine (40 μg/kg) to anesthetized rats resulted in a transient pressor response; the peak increase in diastolic pressure (15.8 ± 2.2 mm Hg) was observed 4–6 sec after its injection into the descending aorta. The basal concentration of adenosine in arterial plasma in anesthetized rats was 1.0 ± 0.2 μM. When plasma adenosine levels were elevated to, and maintained at, 2.0 ± 0.2 μM by an intravenous infusion of adenosine (0.15 mg/kg per min, i.v.), the pressor response to nicotine was increased more than 4-fold, to 70.0 ± 6.4 mm Hg ($P < 0.005$). This potentiation was gradually diminished as arterial adenosine concentrations were increased beyond 2 μM (Figs. 1 and 2).

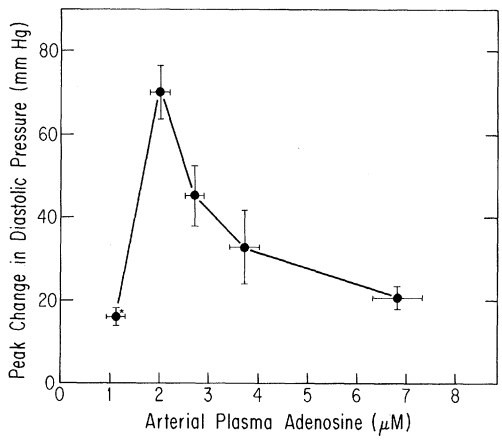

FIG. 1. Relationship between arterial plasma adenosine concentration and pressor response to nicotine in rats. Nicotine (40 μg/kg, i.v.) was administered to anesthetized rats before (●*) and during (●) intravenous infusion of adenosine at controlled rates ranging from 0.15 to 0.9 mg/kg per min. Arterial blood samples were withdrawn (for assay of adenosine) immediately before nicotine injection. Each animal ($n = 5$) provided data for each plasma adenosine concentration; data represent mean ± SEM for both peak pressure increase and arterial adenosine concentration.

Pressor responses to nicotine, both before and during potentiation by adenosine, were almost completely abolished by pretreatment with hexamethonium bromide (10 mg/kg), reserpine (3 mg/kg given 24 and 48 hr before testing), and phentolamine (1 mg/kg) (Table 1). Application of cigarette smoke to the lungs of anesthetized rats through a respiration pump resulted in either slight hypotension or no change in blood pressure; however, during infusion of adenosine, cigarette smoke elicited a strong pressor response (Fig. 3).

Effect of Adenosine on Pressor Responses to Phenylephrine or to Electrical Stimulation of Preganglionic Sympathetic Nerves. The pressor response to a bolus injection of the adrenergic agonist phenylephrine (1 μg/kg, i.v.) was attenuated during intravenous infusion of adenosine, as was the pressor response to electrical stimulation of preganglionic sympathetic nerves (2 pulses per sec, 0.1 msec pulse duration, 30 V, 20-sec train duration) (Figs. 2 and 4). Responses to electrical stimulation at frequencies ranging from 0.1 to 20 pulses per sec, and at voltages between 10 and 80 V, were also attenuated by adenosine; enhancement of the pressor response

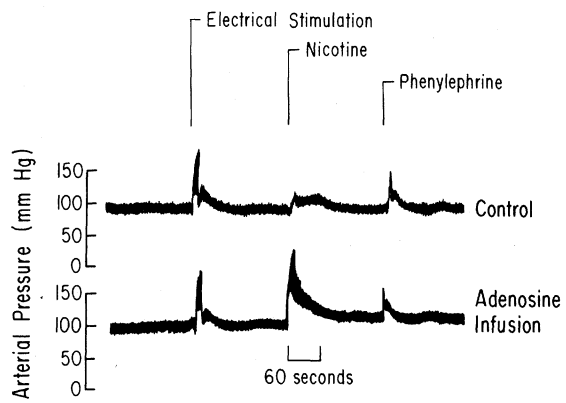

FIG. 2. Effect of adenosine infusion on pressor responses to electrical stimulation, nicotine, or phenylephrine in pithed rats. Pressor responses to electrical stimulation (2 pulses per sec, 0.1-msec pulse duration, 10-sec train duration, 50 V), nicotine (40 μg/kg, i.v.), or phenylephrine (1 μg/kg, i.v.) were monitored before (upper trace) and during (lower trace) infusion of adenosine (0.15 μg/kg per min).

Table 1. Effect of pharmacological and surgical treatments on pressor response to nicotine before and during adenosine infusion

Treatment	Peak pressor response to nicotine (40 μg/kg, i.v.), mm Hg	
	Basal	Adenosine (0.15 mg/kg per min)
None	15.8 ± 2.2	70.0 ± 6.4
Caffeine (10 mg/kg)	4.6 ± 1.0*	10.5 ± 2.1†
Theophylline (10 mg/kg)	4.4 ± 1.8*	18.8 ± 5.6†
Hexamethonium (10 mg/kg)	0.0 ± 0.0†	6.8 ± 3.3†
Phentolamine (1 mg/kg)	5.2 ± 2.3*	18.8 ± 5.6†
Reserpine (3 mg/kg)	8.8 ± 4.3*	21.2 ± 4.8†
Atropine (1 mg/kg)	16.6 ± 4.5	64.4 ± 10.2
Adrenalectomy	12.3 ± 4.1	64.0 ± 5.6
Pithing	23.7 ± 4.4	85.2 ± 8.3

After pharmacological or surgical treatments, pressor responses (peak change in diastolic pressure) to nicotine (40 μg/kg, i.v.) were determined before (middle column) and during (right column) an infusion of adenosine (0.15 mg/kg per min). Values represent mean ± SEM for 6–8 rats per treatment group.
*Difference from no-treatment group, $P < 0.05$.
†Difference from no-treatment group, $P < 0.01$.

to electrical stimulation was never observed in this system (data not shown).

Effect of Synthetic Adenosine Derivatives on the Pressor Response to Nicotine. Administration of low doses (0.1–10 μg/kg) of the synthetic adenosine-receptor agonists 2-ClA, L-PIA, D-PIA, and CPCA resulted in dose-related potentiations of the pressor responses to nicotine that were qualitatively similar to the potentiation observed during infusion of adenosine (Fig. 5).

After administration of 2-ClA (5 μg/kg, i.v.), the peak pressure increase in response to nicotine (40 μg/kg) was enhanced from a basal value of 14.3 ± 3.9 mm Hg to 67.5 ± 2.9 mm Hg ($P < 0.01$); higher or lower doses of 2-ClA produced less marked potentiation, and the threshold dose for eliciting a significant potentiation was 1 μg/kg ($P < 0.05$). CPCA caused significant potentiation at a dose of 0.25 μg/kg ($P < 0.05$); however, the maximum pressor response to 40 μg of nicotine per kg that could be elicited after administration of any dose of this compound was 32.5 ± 6.6 mm Hg; the maximum potentiation was thus less than half that elicited by 2-ClA. The largest potentiation of the response to nicotine that could be produced by L-PIA, to 31.3 ± 6.6 mm Hg (observed at a dose of 5 μg/kg), was also much lower than the maximal

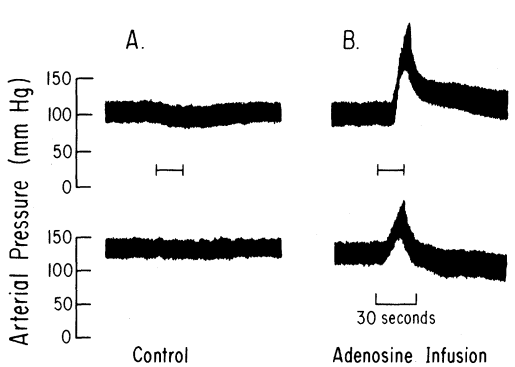

FIG. 3. Effect of adenosine on response of blood pressure to cigarette smoke. Blood pressure tracings of two of six anesthetized rats are shown. Cigarette smoke was applied to the lungs through a respirator pump during the period represented by the horizontal bars. (*A*) Basal responses to cigarette smoke (15 pump strokes). (*B*) Responses to cigarette smoke during infusion of adenosine (0.15 mg/kg per min, i.v.).

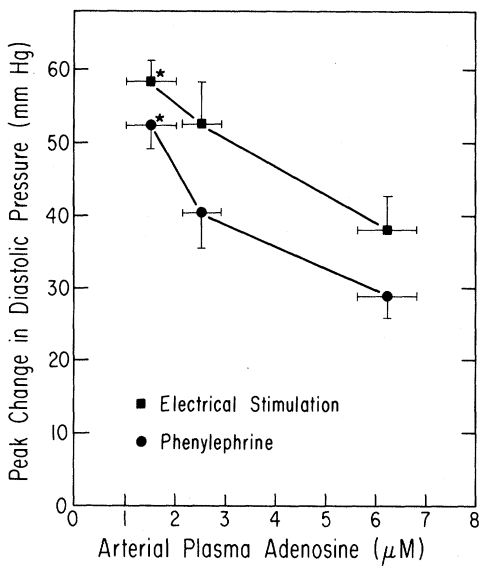

FIG. 4. Relationship between arterial adenosine concentration and pressor responses to electrical stimulation and phenylephrine. Pressor responses to electrical stimulation (2 pulses per sec, 0.1-msec pulse duration, 10-sec train duration, 50 V) and phenylephrine injections (1 μg/kg, i.v.) were monitored before (■*, ●*) and during (■, ●) infusion of adenosine at controlled rates. Points represent data (mean ± SEM) from six rats.

potentiation produced by 2-ClA ($P < 0.05$). D-PIA was the least effective of the analogs tested; significant potentiation of the pressor response to nicotine was not observed at doses <20 μg/kg ($P < 0.05$), and the maximum potentiation that this compound elicited (an increase of 31.2 ± 7.2 mm Hg) was at a dose of 40 μg/kg.

These compounds also caused transient (<10 min for the doses tested) dose-dependent decreases in blood pressure (Fig. 6); their rank order of potency for eliciting hypotension (CPCA > 2-ClA > L-PIA > D-PIA) was the same as for potentiating pressor responses to nicotine.

Effect of Theophylline and Caffeine on Pressor Responses to Nicotine. A basal pressor response to nicotine (40 μg/kg, i.v.) of 14.4 ± 0.9 mm Hg was decreased to 4.6 ± 1.0 mm Hg 10 min after intravenous administration of caffeine at 10 mg/kg ($P < 0.02$). Similarly, theophylline (10 mg/kg, i.v.)

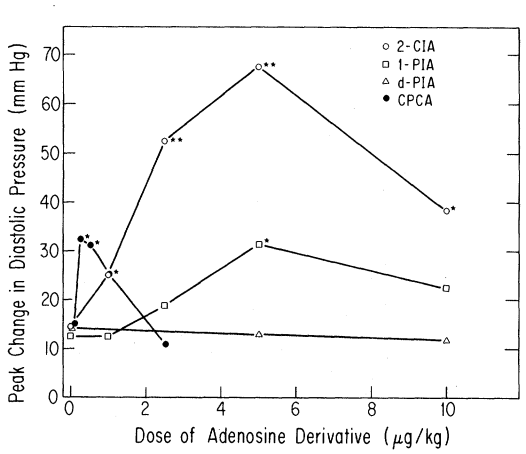

FIG. 5. Relationship between dose of adenosine receptor agonists and pressor response to nicotine. The adenosine derivatives 2-ClA, L-PIA, D-PIA, and CPCA were administered, in doses indicated on the abscissa, 1 min before injection of nicotine (40 μg/kg, i.v.). Points represent mean responses of four rats. *, Differs from control response, $P < 0.05$; **, differs from control response, $P < 0.01$.

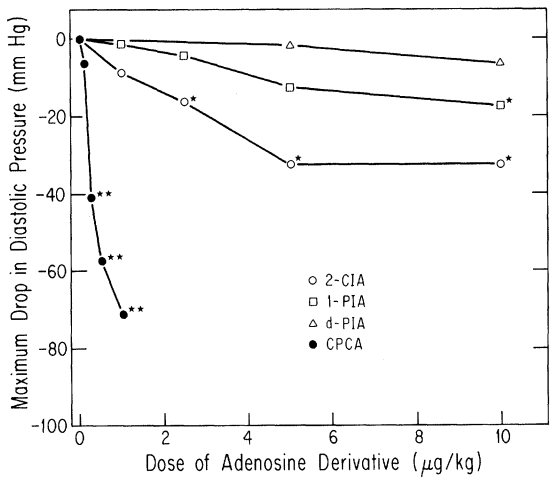

FIG. 6. Hypotensive effects of adenosine receptor agonists as a function of dose. Adenosine derivatives were given intravenously in doses indicated on the abscissa. Points represent mean maximum falls in diastolic pressure for four rats. *, Differs from basal pressure, $P < 0.05$; **, differs from basal pressure, $P < 0.01$.

decreased the pressor response to nicotine to 4.4 ± 1.8 mm Hg from a basal response of 17.7 ± 1.2 mm Hg ($P < 0.02$). This dose of either methylxanthine also blocked the potentiation of the pressor response to nicotine normally observed when adenosine is infused at a rate of 0.15 mg/kg per min (Table 1). Potentiation of the pressor response to nicotine after treatment with theophylline or caffeine (to 43.8 ± 6.9 and 40.5 ± 5.5 mm Hg, respectively) was observed, however, when the rate of adenosine infusion was increased to 0.45 mg/kg per min.

Localization of the Site of Interaction of Nicotine and Adenosine. While the transient hypertension that follows nicotine administration is ultimately mediated through the sympathoadrenal system, the cellular locus of action of the alkaloid could be sympathetic nerve terminals, the adrenal medulla, sympathetic ganglia, chemoreceptors in the carotid artery and aortic arch, or sites within the central nervous system. The net response of the cardiovascular system to nicotine thus most likely represents the summation of responses originating at several of these nicotine-sensitive sites; the magnitude of the contribution stemming from each locus might be expected to vary with the amount of nicotine given and the proportion reaching that locus.

Pithing the spinal column eliminated spontaneous peripheral efferent neural activity originating in, or mediated through (as in the case of chemoreceptor reflexes), the central nervous system, but did not significantly affect pressor responses to nicotine or potentiation of these responses by adenosine (Table 1; Fig. 2), suggesting that adenosine (as well as nicotine) is acting peripherally, perhaps at sympathetic ganglia, sympathetic terminals, or the adrenal medulla. Acute bilateral adrenalectomy did not block potentiation of the pressor response to nicotine by adenosine (Table 1).

In the isolated hindlimb preparation, intra-aortic nicotine elicited similar and simultaneous increases in systemic arterial pressure and in hindlimb perfusion pressure; both were strongly enhanced by systemic infusion of adenosine (Fig. 7). The increase in hindlimb perfusion pressure reached its peak value within 4–6 sec after an intra-aortic injection of nicotine, both in the absence and in the presence of an adenosine infusion. Because there is a delay of 2 min for substances introduced into the systemic circulation to reach the hindlimb vasculature via the perfusion circuit tubing, the hindlimb pressor response to the systemic nicotine could not be attributed to an interaction of nicotine with sympathetic terminals or vascular smooth muscle; hindlimb perfusion

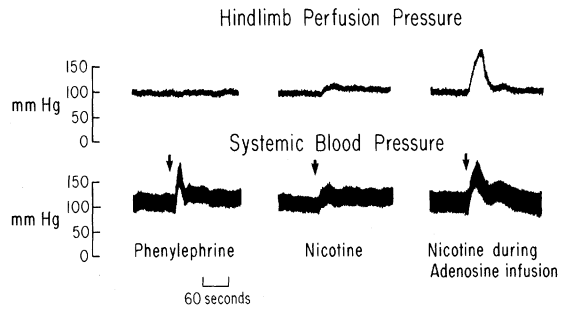

FIG. 7. Effect of intra-aortic phenylephrine or nicotine on systemic arterial pressure and hindlimb perfusion pressure. A rat was prepared with an autoperfused hindlimb as described in *Methods*. (*Left*) Phenylephrine (1 μg/kg, i.a.) elicited a systemic pressor response (lower trace) without modifying hindlimb perfusion pressure (upper trace), confirming separation of systemic and hindlimb circulations. (*Middle*) Nicotine (40 μg/kg, i.a.) elicited a small increase ≈15 mm Hg) in both systemic arterial pressure and in hindlimb perfusion pressure. (*Right*) One minute after beginning the intravenous infusion of adenosine, the pressor response to nicotine was strongly potentiated in both hindlimb and systemic circulation. (At least 2 min are required for substances introduced into systemic circulation to reach hindlimb vasculature via perfusion tubing.)

pressure was in fact decreased by injection of nicotine directly into the perfusion circuit. Adenosine potentiated the hindlimb pressor response to systemic nicotine only when the nucleoside was also infused into the systemic circulation; adenosine infused into the perfusion tubing failed to enhance pressor responses to intra-aortic nicotine injections. Therefore, adenosine apparently intensified nicotine-induced stimulation of postganglionic sympathetic nerve firing. Sympathetic ganglia contain the only synapses in the sympathetic nervous system between the spinal cord and sympathetic terminals. It is therefore most likely that the synergistic interaction between responses to nicotine and adenosine occurs within sympathetic ganglia.

DISCUSSION

These data reveal two opposing influences of adenosine on the regulation of arterial blood pressure by the sympathetic nervous system: (*i*) potentiation of the pressor response to nicotine and (*ii*) attenuation of pressor responses to injections of the α-adrenergic agonist phenylephrine or to electrical stimulation of sympathetic nerves. The potentiation of pressor responses to nicotine, which is apparently due to an intensification by adenosine of nicotine-induced firing of postganglionic sympathetic nerves, is maximal when arterial plasma adenosine levels are maintained at ≈2 μM. Basal adenosine levels are ≈1 μM, and the threshold concentration for inducing sustained hypotension is 4–6 μM (10).

Phenylephrine elicits a pressor response by interacting directly with α-adrenergic receptors on vascular smooth muscle; therefore, adenosine probably attenuates responses to phenylephrine by decreasing vascular reactivity to catecholamines. The magnitude of this postsynaptic effect is sufficient to account for the degree of attenuation of the pressor response to electrical stimulation of sympathetic nerves observed during adenosine infusion in these studies, although the well-documented ability of adenosine to inhibit catecholamine release (by interacting with receptors on sympathetic terminals) might also be a contributing factor (11).

This dose-dependent attenuation of vascular responsiveness to α-adrenergic stimulation by adenosine might account for the decreased potentiation of the pressor response to nicotine when arterial adenosine levels are increased beyond 2 μM; the pressor response to nicotine is blocked by the α-adrenergic antagonist phentolamine and thus may ultimately

be mediated through α-adrenergic receptors on vascular smooth muscle.

A similar balancing between the opposing effects of concurrent activation of adenosine receptors in ganglia, vascular smooth muscle, and, perhaps, sympathetic terminals by the synthetic adenosine derivatives tested in this study might also explain the differences in the maximum potentiation of the pressor response to nicotine that each of these compounds could elicit. The rank orders of potency that these adenosine derivatives display in potentiating the pressor response to nicotine and in eliciting hypotension (CPCA > 2-ClA > L-PIA > D-PIA) are characteristic of the so-called A2 (or Ra) subtype of adenosine receptor, as defined in brain tissue (12, 13).

The influence of the methylxanthines theophylline and caffeine on sympathetic transmission is generally reported to be facilitatory (14, 15). However, at the low dose (10 mg/kg) used in this study, these drugs, without modifying basal blood pressure, attenuated the pressor response to nicotine and antagonized the potentiating influence of adenosine on the pressor response to nicotine. It is significant that the basal response to nicotine was decreased after treatment with either caffeine or theophylline; this may represent a blockade by methylxanthines of an action of endogenous adenosine in potentiating pressor responses to nicotine.

The molecular or ionic mechanisms underlying the potentiation of the pressor response to nicotine by adenosine are not understood at present. It is striking that adenosine strongly enhances pressor responses to nicotine but attenuates such responses to electrical stimulation of preganglionic sympathetic nerves; the responses to both stimuli are believed to be mediated mainly through nicotinic cholinergic receptors in sympathetic ganglia (16). If the critical site of action of nicotine in eliciting an adenosine-potentiated pressor response is indeed within sympathetic ganglia, then fundamental differences might exist between the electrogenic processes underlying ganglionic responses to nicotine and to acetylcholine. This hypothesis is supported by the finding that the hemicholinium-3 derivative α,α'-bis(dimethylammoniumacetaldehyde diethylacetal)p,p'-diacetylphenyldibromide can block ganglionic responses to nicotine, dimethylphenylpiperazinium or tetramethylammonium at concentrations far below those required to block ganglionic transmission (17). (In preliminary studies, we have found considerable variance in the ability of nicotinic agonists to elicit adenosine-sensitive pressor responses: responses to lobeline and dimethylphenylpiperazinium are strongly potentiated; responses to cytisin and tetramethylammonium are less well potentiated; and responses to acetylcholine and carbamoylcholine are not modified by adenosine.) In this context, it should also be noted that blockade of muscarinic cholinergic receptors with atropine does not alter the capacity of adenosine to potentiate the pressor response to nicotine (Table 1).

Finally, caffeine and nicotine are among the most widely consumed psychoactive agents. Adenosine can alter the response of blood pressure to nicotine applied to the lungs via cigarette smoke. If endogenous adenosine potentiates physiological responses to nicotine in neural populations mediating behavioral or subjective effects of nicotine, then blockade of this potentiation by caffeine might be a relevant aspect of the documented positive correlation between cigarette smoking and coffee consumption (18).

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