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Endogenous adenosine and hemorrhagic shock: Effects of caffeine administration or caffeine withdrawal
(blood pressure/hypotension/sympathetic nerve function/methylxanthines)

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ABSTRACT Plasma adenosine concentrations doubled when rats were subjected to 90 min of profound hemorrhagic shock. Administration of caffeine (20 mg per kg of body weight), an adenosine-receptor antagonist, attenuated the hemorrhage-induced decrease in blood pressure. In contrast, chronic caffeine consumption (0.1% in drinking water), followed by a brief period of caffeine withdrawal, amplified the hypotensive response to hemorrhage. These data suggest that endogenous adenosine participates in the hypotensive response to hemorrhage and that caffeine may protect against, and caffeine withdrawal may exacerbate, this response.

Adenosine, a product of ATP hydrolysis, is released from some hypoxic tissues (1–3) and can produce a number of physiological effects including hypotension, bradycardia, sedation, and hypothermia (4–6). Adenosine has been shown to inhibit norepinephrine release from sympathetic nerve terminals (7–10); to attenuate contractile responses of vascular smooth muscle to electrical stimulation or norepinephrine; and to cause vasodilation, even in the absence of sympathetic innervation (11, 12). However, the nucleoside also potentiates the pressor response to nicotine within sympathetic ganglia (13); and in the kidney, it potentiates the effects of sympathetic nerve stimulation by increasing the vasoconstrictor response to catecholamine release (14, 15). Most of the actions of adenosine appear to be mediated by specific adenosine receptors, which can be blocked by methylxanthines such as caffeine (16–18). Thus, caffeine administration blocks adenosine-induced hypotension in rats at concentrations that correspond to those needed in vitro to displace adenosine-receptor ligands from neural tissue (19).

Since adenosine may be released from hypoxic tissues during hemorrhagic shock, we have examined its possible involvement in the hypotension produced by subjecting rats to hemorrhage. Our findings indicate that plasma adenosine concentrations are increased in such animals and that treatments that influence adenosine receptors (i.e., acute caffeine administration or chronic caffeine administration followed by caffeine withdrawal) can cause parallel changes in the magnitude of the resulting hypotension.

METHODS

Male Sprague-Dawley rats, retired breeders weighing ≈600 g (Charles River Laboratories), were anesthetized with chloralose (50 mg per kg of body weight) and urethane (500 mg per kg of body weight) administered by i.p. injection, and the left carotid artery was cannulated with PE-50 tubing for blood pressure measurement and for blood removal. Arterial blood pressure was measured with a Grass polygraph (model 7C) and Statham transducers. Blood pressure was recorded continuously; data were derived from the measurements obtained at the end of each 15-min period.

We examined the effects of hypotension on plasma adenosine in animals subjected to hemorrhagic shock. Anesthetized rats were bled in 1-ml increments every 5 min until blood pressure (systolic) reached ≈50 mmHg; anesthetized and operated control animals remained normotensive throughout the experiment.

Blood (0.5 ml) for adenosine assay was collected concomitantly in both groups into chilled syringes (containing ice-cold heparinized [200 units/ml] saline and 0.5 mM dipyridamole) immediately after and 30, 60, and 90 min after systolic blood pressure had fallen to 50 mmHg in the animals subjected to hemorrhagic shock. Samples were centrifuged and the supernatant fluids were deproteinized with trichloroacetic acid and then reconstituted (20, 30). The final supernatant fluid was purified on a boronate affinity gel, and it was then applied to disposable columns containing 1 ml of Affi-Gel 601 (Bio-Rad), washed with 0.25 M ammonium acetate (pH 8.8), and eluted with 0.1 M formic acid. The eluate was evaporated to dryness and reconstituted with 0.2 ml of deionized water immediately before assay. Adenosine in plasma extracts was assayed by high-pressure liquid chromatography with a Waters μBondapak C18 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; it was detected by UV absorbance at 259 nm with a sensitivity of 0.1 μM.

We next determined whether administering caffeine (in schedules likely to increase or decrease the sensitivity of adenosine receptors) caused parallel alterations in the hypotensive response to hemorrhage (20). Animals prepared as described above were pretreated with caffeine (20 mg per kg of body weight, administered through the arterial cannula) or saline. Twenty minutes later, the animals were bled every 15 min in increments representing 5% of their total blood volume (estimated from body weight).

In another series of experiments, caffeine-withdrawn animals were produced by adding the methylxanthine (0.1%) to drinking water for 14 days and then replacing it with tap water for 14 hr prior to the experiment; control animals consumed tap water throughout this time period (20). Anesthetized and cannulated animals were then bled in increments representing 5% of their blood volume, as described.

Data were expressed as means ± SEM and analyzed by two-way analysis of variance followed by a Tukey test. Mortality data were analyzed by Fisher's exact test because of small sample sizes.

RESULTS

Ninety minutes of hemorrhagic hypotension was associated with a doubling of the plasma adenosine concentration (Fig. 1), from 2.0 ± 0.6 to 3.9 ± 0.6 μM (P < 0.02 for the effect of hemorrhage; P > 0.1 for the effect of time; no interaction between the main effects).
**DISCUSSION**

Our data show that circulating adenosine and adenosine receptors participate in blood pressure control and, particu-
The methylxanthines are known to block adenosine receptors in humans as well as in animals (28), and our findings suggest that acute methylxanthine administration may also be useful in treating some types of hypotension. These compounds may have the added advantage of attenuating the renal vasoconstriction and potentially preventing the renal failure that can accompany circulatory shock (14, 15, 29). Moreover, the precipitous withdrawal of caffeine may be hazardous to patients about to undergo blood loss. Indeed, we have used caffeine for our studies because it is widely consumed and thus might actually be involved in hemodynamic changes occurring with human hemorrhage.