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Role of Presynaptic Purinoceptors and Cyclic AMP on the Noradrenaline Release in Cat Cerebral Arteries

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Abstract—Field electrical stimulation (ES), K^+ (50 mM) or ionophore X-537A (0·01 mM) induced tritium release from cat cerebral arteries preincubated with [^{3}H]noradrenaline (NA). Adenosine and AMP (0·5 mM) did not modify tritium release caused by ionophore X-537A, but these agents and ATP (0·5 mM) significantly reduced that elicited by ES and K^+; this reduction was antagonized by 1-methyl-3-isobutylxanthine (MIX; 0·05 mM). Inosine (0·5 mM) and the agonist of purinergic A_2-receptors, 5′ *N*-ethylcarboxamide adenosine (NECA; 0·5 mM) had no effect, but the agonist of purinergic A_1-receptors L-N6-phenylisopropyl adenosine (L-PIA; 0·1 mM) diminished tritium efflux caused by ES and K^+. The adenosine inhibition of ES-induced radioactivity release was not affected by indomethacin (0·05 mM). MIX (0·05 mM) increased tritum release evoked by ES and K^+. Agents that increase intracellular cyclic (c)AMP levels, such as dibutyryl cAMP (0·5 mM), the phosphodiesterase inhibitor Ro 20-1724 (0·1 mM), and the activators of adenylate cyclase, forskolin (0·005 mM) and NaF (2 mM) reduced tritium secretion elicited by ES and K^+. However, the intracellular increase of cyclic GMP (cGMP) caused by 8-Br-cGMP did not affect this secretion. Dipyridamole (0·05 mM) and the adenosine deaminase inhibitor erythro-9-2-hydroxy-3 nonyl adenosine (EHNA; 0·1 mM) also produced inhibition of tritium secretion elicited by ES and K^+. Dipyridamole reduced both the uptake of [^{3}H]NA and [^{3}H]adenosine. These results indicate that in these vessels: (1) presynaptic inhibition of exocytotic NA release induced by adenosine, ATP, and AMP is mainly mediated by purinoceptors of the A_1-subtype, without participation of prostaglandins; (2) the non-exocytotic release is not presynaptically modulated; (3) intracellular increases of cAMP, but not of cGMP, reduced NA release; and (4) the effects of dipyridamole and EHNA appear to be mediated by augmentation of intracellular levels of adenosine by preventing its neuronal uptake and its adenosine deaminase inactivation, respectively.

Cerebral blood vessels of different animal species receive a dense adrenergic innervation originating in the superior cervical ganglia (Owman et al 1974; Edvinsson & MacKenzie 1977; Marín & Rivilla 1982). The stimulation of the adrenergic nerve endings present in cerebral and peripheral vessels produces the co-release of noradrenaline (NA) and ATP (Su 1978; Muramatsu et al 1981; Burnstock 1988). ATP released is successively dephosphorylated to ADP, AMP, and adenosine (Su 1978; Enero 1981; Snyder 1985); adenosine is taken up into the adrenergic nerve endings and reconverted to ATP and related nucleotides (Su 1978, 1983) or to inosine by the enzyme adenosine deaminase (Bruns 1980; Snyder 1985).

Adenosine acts on adenosine receptors or purinoceptors (P_1, which are of the subtypes A_1 and A_2) present on the surface of the cell membrane, that can be blocked by methylxanthines (Van Calker et al 1979; Londos et al 1980; Schwabe et al 1985). Each subtype of the purinoceptor can be discriminated with selective adenosine analogues; thus, 5′ *N*-ethylcarboxamide adenosine (NECA) is a more potent agonist of A_2-receptors than L-N6-phenylisopropyl adenosine (L-PIA), while the reverse potency order is observed in A_1-receptors (Londos et al 1980; Snyder 1985).

The aim of the present work was to analyse in cat cerebral arteries: (1) the subtype of purinoceptors involved in the modulation of exocytotic NA release induced by electrical stimulation (ES) or K^+, and whether the non-exocytotic release caused by the ionophore X-537A is also modulated by these receptors; (2) the activity of processes to incorporate and to degrade (by adenosine deaminase) adenosine; (3) the existence of generating systems of cyclic (c) AMP in the adrenergic terminals and the role of cAMP on the modulation of NA release (this point was investigated because cAMP can play an important role in the neurotransmitter release (Schoffelmeer & Mulder 1983)) and (4) whether cyclic (c) GMP modulates NA secretion, using the membrane permeable compound 8-Br-cGMP.

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Materials and Methods

Noradrenaline release

Cats of either sex, 1·5–3 kg, were anaesthetized with sodium pentobarbitone (35 mg kg^{-1}, i.p.) and killed by bleeding. The brain was carefully removed and placed in Krebs-Henseleit solution (KHS) at 4°C. In this medium, the arteries of the circle of Willis, with its branches, were isolated and cleaned of blood traces and adhering tissues. Then, they were set up in a nylon net and immersed for 30 min in 4 mL KHS at 37°C continuously bubbled with 95% O_2–5% CO_2 (stabilization period). Thereafter, the arteries were incubated for 60 min in 4 mL oxygenated KHS at 37°C containing (±) [^{3}H]NA (0·2 μM, specific activity 12·8 Ci mmol^{-1}). For field ES (80 V, 0·5 ms, 8 Hz, for 1 min), the arteries were transferred into a superfusion chamber with two parallel platinum electrodes, 0·5 cm apart, connected to a stimulator (Cibertec model CS9). The vessels were superfused at a rate of 0·5 mL min^{-1} with oxygenated KHS at 37°C for 100 min. During this period the basal tritium efflux reached a steady state level. At this moment, the superfusate was collected in vials at 3 min intervals (1·5 min, when electrical stimulus was applied).

Stimulation with K^+ or ionophore X-537A was performed in a similar way, except that after 100 min superfusion, the arteries were immersed successively in five vials at 3 min intervals; the third vial contained 50 mM K^+ or 0·01 mM ionophore X-537A, the rest of the vials only KHS. Samples (0·5 mL) of the superfusate or vial solution were added to tubes containing 2 mL of Ready-Solv HP (Beckman) and the radioactivity measured in a scintillation counter (Beckman LS 2800). Two ES periods or exposures to K^+ or X-537A (S_1 and S_2) were applied to the arteries separated by a 30 min interval. The drugs used to modify tritum release were administered 15 min before S_2. Finally, the arteries were blotted, weighed and digested in vials containing 1 mL of H_2O_2 (30% w/v) at 100°C for 5 h and the radioactivity retained was measured as described for the superfusate.

The net stimulation-induced tritium efflux was calculated by the subtraction of tritium release evoked by the stimulus from the basal efflux and was expressed as a fraction of the radioactivity present in the arteries at the beginning of the stimulation period. The ratios of the tritium efflux S_2/S_1 were calculated. To test the effects of the drugs in the basal release (B), the ratio between tritium secretion before S_2 (B_2) and S_1 (B_1) was also determined.

Effect of dipyridamole on [^{3}H]NA and [^{3}H]adenosine uptake

The influence of dipyridamole on [^{3}H]NA or [^{3}H]adenosine uptake was also studied. For this purpose the arteries were treated as above except that dipyridamole (0·05 mM) was administered 10 min before and during the incubation period (60 min) with [^{3}H]NA or [^{3}H]adenosine (0·1 μM, specific activity 30 Ci $mmol^{-1}$). After the washout period (100 min) the arteries were blotted, weighed and digested and the radioactivity retained measured as above.

Solutions, drugs and statistical methods

The composition of KHS (mM) was: NaCl, 115; $CaCl_2$, 2·5; KCl, 4·6; KH_2PO_4, 1·2; $MgSO_4 \cdot 7H_2O$, 1·2; $NaHCO_3$, 25; glucose, 11·1; Na_2 EDTA, 0·03 (to prevent the oxidation of catecholamines). In 50 mM K^+ solution, the NaCl concentration was appropriately reduced to maintain osmolarity.

Drugs used were: indomethacin, NaF and KCl (Merck); adenosine hemisulphate, ATP, AMP, inosine, forskolin, tetrodotoxin, NECA, cAMP, dibutyryl-cAMP (db-cAMP), and 8-Br-cGMP (all from Sigma); L-PIA (Boehringer Mannheim); dipyridamole (Boehringer Ingelheim); ionophore X-537A and Ro 20-1724 (4-(3-butoxy-4-methoxybenzyl)-2-imidazolidinone Roche); methyl-3-isobutylxanthine (MIX) (Serva); erythro-9-2-hydroxy-3-nonyl adenosine (EHNA) (Wellcome); [^{3}H]NA and [^{3}H]adenosine (New England Nuclear).

Results are given as mean ± s.e.m. Statistical analysis was by means of Student's *t*-test for paired or unpaired experiments; a probability value of less than 5% was considered significant.

Results

The basal levels of tritium release were increased by dipyridamol from 4·4 ± 0·8% (B_1) to 5·6 ± 0·7% (B_2), but not modified by any of the other compounds used. ES (S_1, 13·8 ± 2·9%, results expressed in % of total uptake) or 50 mM K^+ (S_1, 15·4 ± 3·8%) produced a similar tritium release over basal level, which was higher than that evoked by 0·01 mM ionophore X-537A (S_1, 8·5 ± 0·5%). The presence of cocaine (0·01 mM) and corticosterone (0·01 mM), to block the neuronal or extraneuronal uptake; did not significantly alter the tritium release (results not shown). Tetrodotoxin (1 μM) markedly reduced tritium release evoked by ES (S_2/S_1: control, 0·61 ± 0·03, n = 16; tetrodotoxin, 0·15 ± 0·05, n = 6, $P < 0·01$).

Adenosine, ATP and AMP at 0·5 mM (but not at 0·1 or 0·05 mM), and L-PIA (0·1 mM) reduced tritium secretion elicited by ES or 50 mM K^+ (Figs 1, 2). Indomethacin (0·5 mM) did not modify the effect of adenosine on the electrically-induced radioactivity secretion (Fig. 1). The administration of inosine (0·5 mM or less), NECA (0·5 mM or less), or adenosine plus MIX (0·05 mM) did not alter the tritium release evoked both by ES and K^+. By contrast, MIX (in at least 0·05 mM) markedly increased the tritium overflow induced by the two kinds of stimuli (Figs 1, 2).

cAMP (0·5 mM), db-cAMP (0·5 mM), Ro 20-1724 (0·1 mM), forskolin (0·005 mM) and NaF (2 mM) reduced tritium release induced by ES and K^+ (Fig. 3). Lower concentrations of these drugs did not affect the radioactivity secretion. The permeable compound 8-Br-cGMP (0·5 mM) did not modify the stimulated tritium release (Fig. 3).

The administration of dipyridamole (0·05 mM), or EHNA (0·1 mM), reduced the tritium release elicited by ES and K^+ (Fig. 4). Lower concentrations of these agents did not produce significant effects. On the other hand, adenosine and AMP (both at 0·1 mM) did not significantly modify the

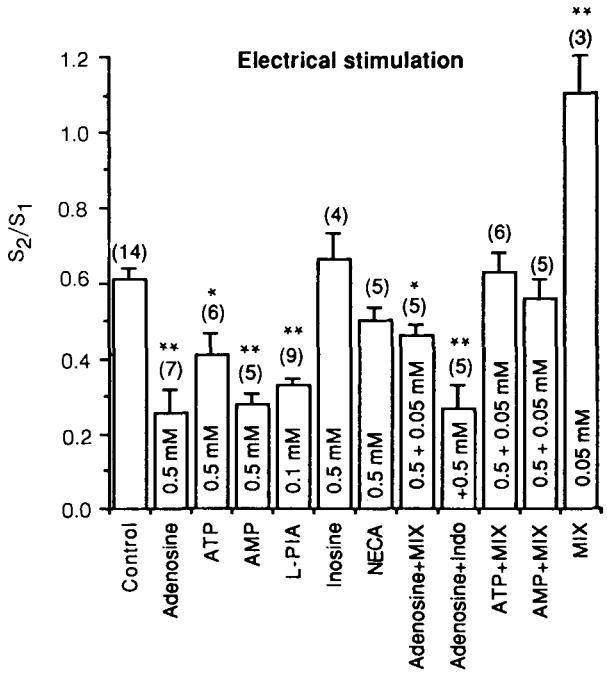

FIG. 1. Effects of adenine compounds on the tritium release elicited by electrical stimulation (80 V, 0·5 ms, 8 Hz, for 1 min) from cat cerebral arteries preincubated with [^{3}H]noradrenaline. Drugs were added 15 min before to S_2. In ordinate, the ratios between net release obtained during two consecutive electrical stimuli (S_1 and S_2) with 30 min interval are shown. Concentrations of drugs and number of experiments are indicated in the columns and in parentheses, respectively. Vertical bars represent s.e.m. * $P < 0·05$, ** $P < 0·001$.

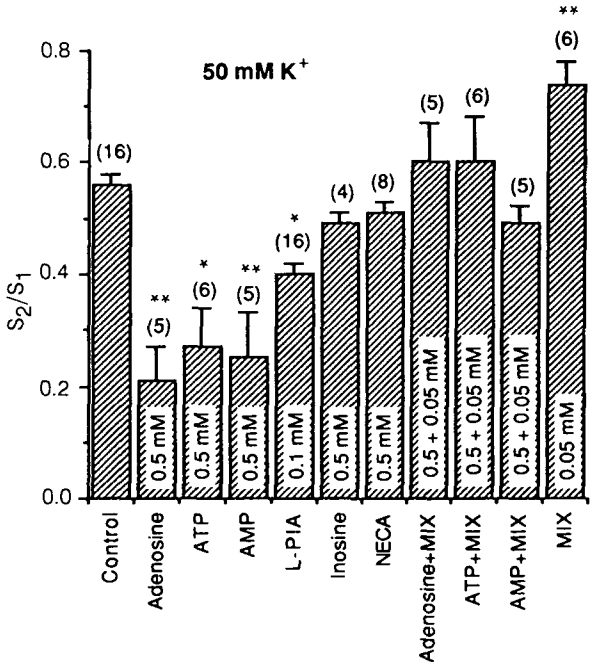

FIG. 2. Effects of adenine compounds on the tritium release induced by 50 mM K^+ from cat cerebral arteries preincubated with [^{3}H] noradrenaline. Details of the experiments and the graph are as in Fig. 1 * $P<0.05$; ** $P<0.001$.

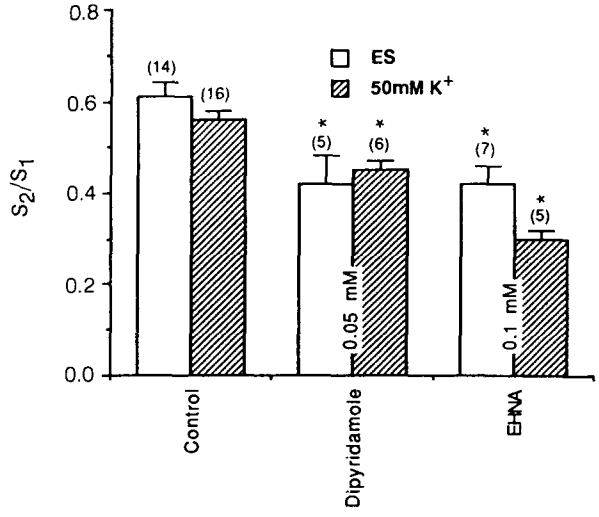

FIG. 4. Effects of dipyridamole and EHNA on tritium release induced by electrical stimulation (ES) and 50 mM K^+ from cat cerebral arteries preincubated with [^{3}H]noradrenaline. Details of the experiments and the graph are as in Fig. 1. * $P<0.05$.

tritium release evoked by the ionophore X-537A (0·1 mM) (S_2/S_1: control, 0.61 ± 0.03, n=6; adenosine, 0.58 ± 0.02, n=6; AMP, 0.62 ± 0.03, n=6).

Dipyridamole (0·05 mM) significantly decreased the uptake of [^{3}H]NA (Fig. 5). We also confirmed the previously described ability of dipyridamole (0·05 mM) to block adenosine uptake (Fig. 5).

Discussion

Effects of adenine compounds on NA release

Tetrodotoxin inhibited tritium release by ES in cat cerebral arteries preincubated with [^{3}H]NA. Since this drug blocks the propagation of nerve impulses (Narahashi et al 1964), this finding indicates that the radioactivity released, which consists largely of NA (Endo et al 1977; Duckles & Rapoport 1979), originates in adrenergic nerve endings.

The secretion of labelled NA elicited by ES or K^+ was reduced to a similar degree by adenosine and nucleotides, AMP and ATP. This effect was antagonized by MIX, suggesting that these adenine compounds act on presynaptic P_1 rather than P_2 purinoceptors (De Mey et al 1979; Schwabe et al 1985; Snyder 1985), either by themselves or more likely by their metabolite adenosine. Similar results and conclusions have been obtained by several authors in different tissues (Su 1978; Moylan & Westfall 1979; Bruns 1980; Khan & Malik 1980; Enero 1981; Muramatsu et al 1981). In addition, the fact that L-PIA reduced and NECA did not affect the exocytotic tritium release evoked both by ES and K^+, indicates that A_1-receptors mediate the actions of these drugs, as occurs in rabbit hippocampus (Jackisch et al 1984,

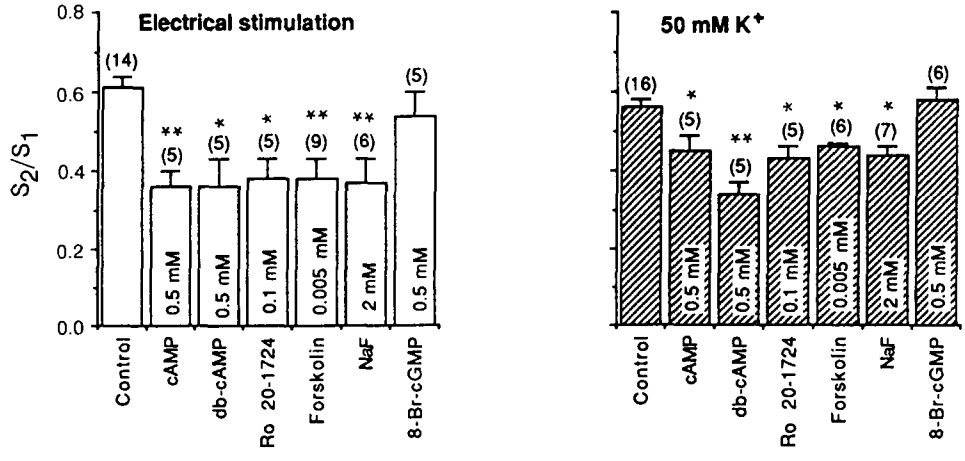

FIG. 3. Effects of cyclic nucleotides and drugs which increase intracellular cAMP or cGMP (8-Br-cGMP) levels on tritium release induced by electrical stimulation and 50 mM K^+ in cat cerebral arteries preincubated with [^{3}H]noradrenaline. Details of the experiments and the graph are as in Fig. 1. * $P<0.05$; ** $P<0.001$.

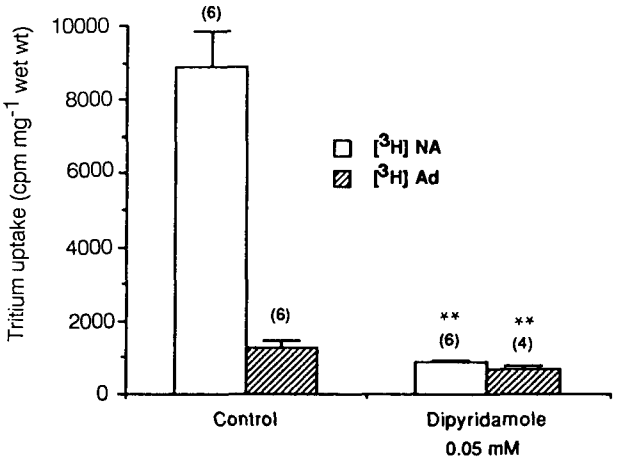

FIG. 5. Effect of dipyridamole on [^{3}H]noradrenaline or [^{3}H]adenosine uptake in cat cerebral arteries. The drug was administered 10 min up to and during the incubation period (60 min). After the washout period (100 min), the tissues were blotted, weighed, digested, and the radioactivity retained measured. Details of the graph are as in Fig. 1. ** $P<0.001$.

1985). Stimulation of these receptors usually effects a reduction of adenylate cyclase activity (Londos et al 1980; Willemot & Paton 1981), which makes it unlikely that the action of adenine compounds involves a cAMP dependent mechanism. Therefore, the inhibition of exocytotic NA release by these agents could be attributed to a reduction in the intracellular Ca^{2+} availability or to an interference with the secretory machinery (Su 1983; Silinsky 1986; Fredholm & Dunwiddie 1988).

Tritium release induced by X-537A was not affected by adenosine or AMP. As this ionophore produces a Ca^{2+}-independent tritium release (Marín & Sánchez 1980), these results indicate that only the exocytotic release can be presynaptically modulated by adenine compounds. Similar results using tyramine have also been reported (Su 1978; Khan & Malik 1980).

Inosine did not affect the release caused by ES or K^+, indicating that this metabolite does not contribute to the inhibitory action of adenosine on adrenergic neurotransmission, as observed in other tissues (Moylan & Westfall 1979; Khan & Malik 1980). On the other hand, the cyclooxygenase blocker indomethacin did not significantly modify the effect of adenosine on tritium release evoked by ES. Such a finding suggests that the inhibitory action of adenosine and related compounds on noradrenergic neurotransmission is not mediated by prostaglandin release. This assumption is in agreement with the results observed in other vessels (Moylan & Westfall 1979; Khan & Malik 1980; Husted & Nedergaard 1981).

MIX was able to increase the tritium secretion caused by ES or K^+. Two possible mechanisms could explain these effects: (1) the blockade of inhibitory presynaptic purinergic receptors occupied by endogenously formed adenosine, or (2) the increase of intracellular cAMP levels by the ability of methylxanthines to inhibit phosphodiesterase (Triner et al 1971; Wells et al 1976). In the tissues in which the latter effect predominates, reductions of NA release by this agent have been reported (Wemer et al 1982), which we also observed in our experiments when the intracellular levels of cAMP were increased (see below). Therefore, in our case, the first assumption is the most likely because Ro 20-1724, another inhibitor of phosphodiesterase without effect on purinoceptors (Chiou & Chang 1988), produced a reduction of tritium secretion. In other blood vessels, theophylline and other xanthines also produce augmentation of [^{3}H]NA release induced by nerve stimulation by mechanisms similar to those suggested above (Moylan & Westfall 1979; Wemer et al 1982) or by transneuronal alteration of Ca^{2+} metabolism by xanthines (Khan & Malik 1980; Markstein et al 1984; Alberts et al 1985).

Role of cAMP on NA release

To determine the effect of cAMP on NA release from cat cerebral arteries, cAMP or db-cAMP (which is more membrane penetrating than cAMP), the phosphodisterase inhibitor Ro 20-1724 and the adenylate cyclase activators NaF and forskolin (Wemer et al 1982; Seamon & Daly 1983; Fredholm & Dunwiddie 1988) were tested. All these drugs, which produce increases of cellular cAMP levels by different mechanisms, elicit similar reduction of the tritium release evoked by ES and K^+, indicating a negative modulation of NA liberation by cAMP. In other vessels, the elevated cAMP produces an increase (Wemer et al 1982; Schoeffelmeer & Mulder 1983; Markstein et al 1984; Alberts et al 1985), a reduction (Khan & Malik 1980; Wemer et al 1982) or no change (Wemer et al 1982) in the transmitter secretion. The mechanism of this inhibition is complex, but it is probably related to a reduction of intracellular Ca^{2+}, by its uptake in cellular stores or by its extrusion, as well as by phosphorylation of intracellular proteins involved in the stimulus-secretion coupling (Kupfermann 1980; Sulakhe & St. Louis 1980; Wemer et al 1982).

On the other hand, it has been reported that cGMP may (Cubbedu et al 1975; Stjärne et al 1979) or may not (Stjärne 1979; Alberts et al 1985) modulate NA release. The fact that its analogue 8-Br-cGMP, which is able to penetrate the cell membrane, did not modify tritium release evoked by ES or K^+, suggests that cGMP does not modulate NA secretion in these arteries.

Effect of dipyridamole and EHNA

The essential mechanism of action of dipyridamole is the blockade of the rapid transport of adenosine across cell membranes (Nimit et al 1981; Katsuragi & Su 1982). Furthermore, this compound has the ability to block phosphodiesterase (Wemer et al 1982). On the other hand, EHNA as an inhibitor of the adenosine deaminase (Snyder 1985), would prevent intracellular metabolism of adenosine. Therefore both dipyridamole and EHNA may increase the intracellular levels of adenosine by different mechanisms. In cat cerebral arteries, dipyridamole increased the basal tritium release and blocked [^{3}H]NA uptake. This suggests that dipyridamole interferes with NA uptake by adrenergic nerve terminals. This proposed mechanism could explain the reported positive inotropic response induced by dipyridamole in canine papillary muscle, which is largely mediated by NA release by a mechanism different to those of tyramine-like agents (Himori & Taira 1976). Dipyridamole also reduced [^{3}H]adenosine uptake, confirming its reported ability to inhibit the cellular incorporation of adenosine

(Katsuragi & Su 1982). On the other hand, EHNA and dipyridamole decreased to a similar extent the tritium release elicited by ES and K^+, by their capacity to increase the cellular concentrations of adenosine. In the case of dipyridamole, its ability to inhibit phosphodiesterase could also contribute to the total effect. These results indicate the existence of active mechanisms in the adrenergic terminals of cat cerebral arteries for taking up and metabolizing adenosine, and could explain the need to use elevated concentrations of exogenous adenine compounds to inhibit NA release, in order to reach adequate concentrations (around 0·01 mM adenosine) in the synaptic cleft (Su 1978). A low sensitivity of the adrenergic terminals of these arteries to adenine compound is also possible; in this sense, elevated concentrations of these compounds have also been used to inhibit NA release in different vessels, such as rabbit aorta (0·01 to 0·3 mM adenosine, 0·1 mM ADP, and 0·01 mM ATP) (Husted & Nedergaard 1981), and rat portal vein (0·05 to 0·1 mM adenosine) (Moylan & Westfall 1979; Enero 1981).

In conclusion, our results indicate that adenine compounds (nucleotides being metabolized to adenosine) exert modulatory negative effects on the adrenergic neurotransmission, reducing the adrenergic tone of cerebral vessels and facilitating cerebral vasodilation. The purinoceptors involved in these responses appear to be of the subtype A_1. The increase of intracellular concentrations of cAMP, but not of cGMP, also negatively modulates NA release. Finally, in cat cerebral arteries dipyridamole produces a blockade of both adenosine and NA uptake into sympathetic varicosities.

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