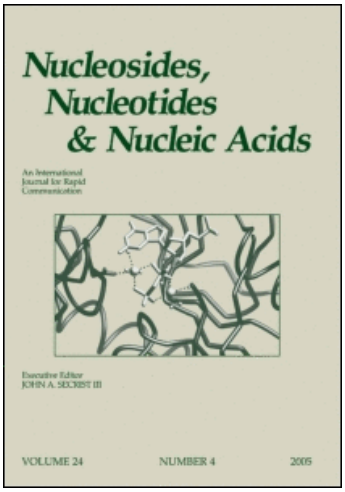

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A_1 and A_2 Adenosine Receptors Involvement in Controlling Purine and Acetylcholine Release From Rat Hippocampal Slices

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A_1 AND A_2 ADENOSINE RECEPTORS INVOLVEMENT IN CONTROLLING PURINE AND ACETYLCHOLINE RELEASE FROM RAT HIPPOCAMPAL SLICES.

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Abstract: The different role of presynaptic A_1 and A_2 adenosine receptor subtypes on a possible autoregulation of endogenous purine outflow as well as on the ACh release, simultaneously assayed, was evaluated in rat hippocampal slices, at rest and under a field electrical stimulation.

The biochemical and physiological mechanisms that control purine secretion are not sufficiently known, even if the existence of an autoregulation of purine release, as well as it was widely described for other neurotransmitter systems, was more than once suggested.

In this study, the possible autoregulation of endogenous purine release and their influence on ACh one were investigated in slices of rat hippocampus, at rest and under field electrical stimulation (30 mA/cm^2, 5 msec for 5 min at 5 Hz). Fractional release of labelled purines and ACh, derived, at the same time, from slices incubated for 30 min with ^3H-adenosine and ^{14}C-choline chloride and cosidered as tracers of their released total amounts, were simultaneously assayed.

The involvement of A_1 sites in the regulation of ^3H-purine and ^{14}C-ACh releases was evaluated by using 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) (from 1 to 200nM), a selective A_1 receptor antagonist. The drug did not affect basal releases of both ^3H-purine and ^{14}C-ACh, thus suggesting that they did not seem to be subjected to an inhibiting A_1-mediated regulation. On the contrary, DPCPX progressively increased the electrically evoked ^3H-purine outflow, beginnning from the dose of 10nM. The simultaneous evoked ^{14}C-ACh release, instead, was differently

affected: at 10nM it was reduced, while it was dose-dependently increased at higher doses. These results confirmed the well known inhibitory control that adenosine exerted on transmitter release, via A_1 receptor sites, and they supported the hypothesis of an A_1-mediated inhibitory autoregulation of purine release.

Considering the observed effect of DPCPX on its whole, it seemed reasonable to suppose that the possible A_1-mediated control on ACh and purine releases became to be effective only when remarkable amounts of purine were released, as well as it occurred under electrical stimulation. Furthermore, since different concentrations of DPCPX needed to counteract the adenosine control on purine and ACh releases respectively, it was possible to hypothesize that the inhibitory purinergic autoreceptor and the adenosine receptor controlling the evoked release of ACh could belong to different subclasses of A_1 receptor with a different sensitivity to endogenous adenosine.

PD115,199 (0.5-1μM), an antagonist with a high potency on A_2 receptor[1], significantly reduced basal ^{3}H-purine outflow more than that observed for the evoked one. Only the highest dose parallely affected the ^{14}C-ACh release too. These findings were suggestive for an A_2-mediated positive "tonic" control on the basal releases of transmitters as ACh and cotransmitters as purines. The involvement of A_2 receptor in an autoregulatory mechanism of purine release was confirmed by the effect of NECA (50-100nM), a mixed A_1/A_2 agonist, administered alone or in combination with DPCPX. 50nM NECA produced only an inhibitory threshold effect, whereas 100nM NECA significantly inhibited both ^{3}H-purine and ^{14}C-ACh outflows. These effects were consistent with a prevalent activation of A_1 receptor. Conversely, the stimulating effect on purine and ACh releases, due to the simultaneous administration of NECA and DPCPX aimed at obtaininig a selective activation of A_2 receptors sites, confirmed that they were positively involved in the adenosine-mediated control of purine and transmitter releases, as it was more than once suggested[2,3].

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