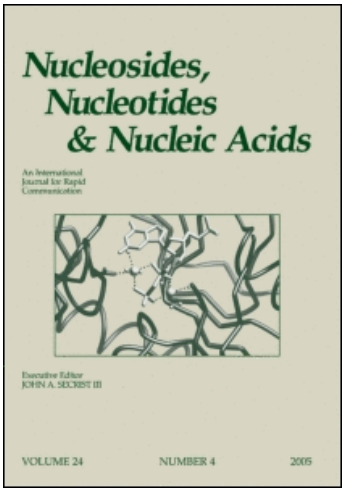

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R-N^6-Phenylisopropyladenosine Produces Tracheal Contraction Through A_1 Adenosine Receptor and Challenges Prostanoid Mechanisms

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R-N^6-PHENYLISOPROPYLADENOSINE PRODUCES TRACHEAL CONTRACTION THROUGH A_1 ADENOSINE RECEPTOR AND CHALLENGES PROSTANOID MECHANISMS

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Abstract - The type of purinergic receptor involved in tracheal contraction by R-N^6-phenylisopropyladenosine (PIA) and the influence of this adenosine analogue on prostaglandin release were studied in normal and in actively sensitized tracheae. Results suggest a balance between adenosine and eicosanoids in the regulation of the airway system.

Adenosine shows both relaxant and contractile effects on the smooth muscle dependently on concentration and on pathophysiological conditions of tracheae (1,2). A possible relation between adenosine and prostanoids in the airway system has been hypothesized (1,3).

In this work, the type of purine receptor involved in the contractile action of adenosine on guinea pig tracheal chains was investigated by using a stable adenosine analogue: R-N^6-phenylisopropyladenosine, (PIA). Further, the influence of PIA on prostanoid release from tracheae of normal and of ovalbumin sensitized guinea pigs was studied.

In tracheal rings, PIA, that is an A_1 and A_2 receptor agonist, showed two opposite effects: contraction, at low concentrations (0.1 μM to 5 μM), and relaxation at higher concentrations. 1,3-Dipropyl-8-cyclopentylxanthine (DPCPX), a highly selective A_1 antagonist, at concentrations 0.01 μM and 0.1 μM abolished only the contractile effect of PIA. Mepacrine (10 μM), an inhibitor of phospholipase A_2, antagonized the contractile effect of PIA without affecting the relaxant component. Indomethacin, a cyclo-oxigenase inhibitor, at low concentrations (0.05 μM and 0.5 μM) antagonized the contractile effect of PIA and potentiated its relaxation.

In order to evaluate the influence of PIA on prostanoid release from guinea pig tracheae, the concentration of prostaglandins in the incubation medium was determined

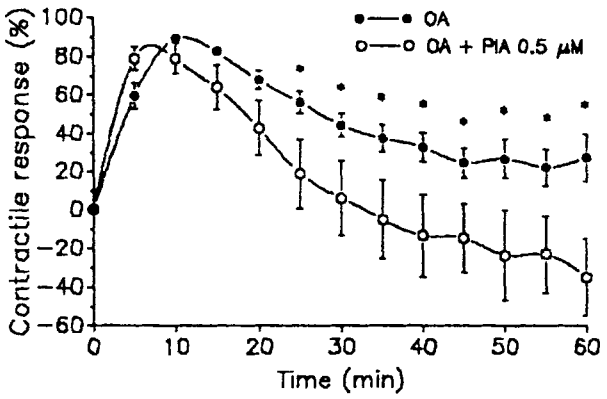

FIG. 1 Comparison between contractile response of ovalbumin (OA 10 μg/ml) alone (●) and in the presence of PIA 0.5 μM (⊙), added prior to ovalbumin challenge, in sensitized guinea pig tracheae. Responses were expressed as % of maximal OA induced contraction.
*: $P<0.05$ compared to values obtained with PIA.

by radioimmunoassy (RIA). PIA produces a two-fold increase of $PGF_{2\alpha}$ and PGE_2 (that show contractile and relaxant activity, respectively) but did not affect the level of 6-keto$PGF_{1\alpha}$, PGD_2 and TXB_2.

In actively sensitized tracheal rings ovalbumin (10 μg/ml) induced a contractile response that recovered to basal tone within more than 60 min. In the presence of PIA 0.5 μM, the recovery phase was significantly shortened (FIG. 1).

In the medium of sensitized tracheae, before antigen challenge, the ratio $PGE_2/PGF_{2\alpha}$ was about 4 times higher than in not sensitized tracheal chains. Antigen challenge produced a remarkable reduction of PGE_2 and an increase of $PGF_{2\alpha}$ in the medium of sensitized tissue. In these experimental conditions, PIA 0.5 μM, added 20 min before ovalbumin challenge, increased production of PGE_2 without affecting the release of $PGF_{2\alpha}$.

These results show that the contractile effect of PIA on tracheal muscle is mediated by the activation of A_1 adenosine receptor and the prostanoid release is involved.

PIA is also able to reduce the recovery time of tracheal tone after antigen challenge. This protection could be related to the influence of PIA on PGE_2 and $PGF_{2\alpha}$ release during ovalbumin challenge. The balance between adenosine and arachidonic acid cascade might be a crucial point in the modulation of the airway tone in pathophysiological conditions.

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