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Publisher *Taylor & Francis*

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## Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

### R-N<sup>6</sup>-Phenylisopropyladenosine Produces Tracheal Contraction Through A<sub>1</sub> Adenosine Receptor and Challenges Prostanoid Mechanisms

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**To cite this Article** Froldi, G. , De Biasi, M. , Fassina, G. and Puglisi, L.(1991) 'R-N<sup>6</sup>-Phenylisopropyladenosine Produces Tracheal Contraction Through A<sub>1</sub> Adenosine Receptor and Challenges Prostanoid Mechanisms', *Nucleosides, Nucleotides and Nucleic Acids*, 10: 5, 1151 – 1153

**To link to this Article:** DOI: 10.1080/07328319108047259

**URL:** <http://dx.doi.org/10.1080/07328319108047259>

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R-N<sup>6</sup>-PHENYLISOPROPYLADENOSINE PRODUCES TRACHEAL CONTRACTION THROUGH A<sub>1</sub> ADENOSINE RECEPTOR AND CHALLENGES PROSTANOID MECHANISMS

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Abstract - The type of purinergic receptor involved in tracheal contraction by R-N<sup>6</sup>-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<sup>6</sup>-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<sub>1</sub> and A<sub>2</sub> 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<sub>1</sub> 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<sub>2</sub>, antagonized the contractile effect of PIA without affecting the relaxant component. Indomethacin, a cyclo-oxygenase 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

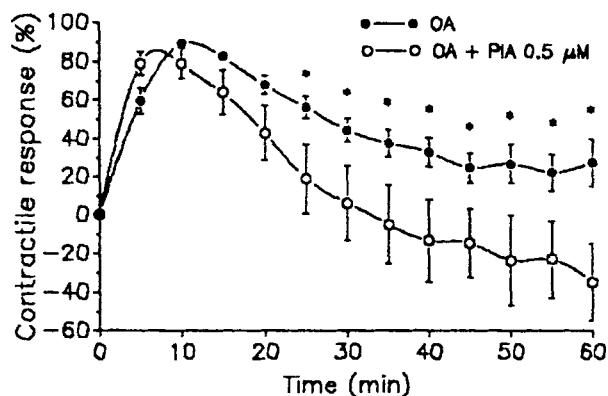


FIG. 1 Comparison between contractile response of ovalbumin (OA 10  $\mu\text{g/ml}$ ) alone (●) and in the presence of PIA 0.5  $\mu\text{M}$  (○), added prior to ovalbumin challenge, in sensitized guinea pig tracheae. Responses were expressed as % of maximal OA induced contraction.  
\*:  $P < 0.05$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

by radioimmunoassay (RIA). PIA produces a two-fold increase of  $\text{PGF}_{2\alpha}$  and  $\text{PGE}_2$  (that show contractile and relaxant activity, respectively) but did not affect the level of 6-keto $\text{PGF}_{1\alpha}$ ,  $\text{PGD}_2$  and  $\text{TXB}_2$ .

In actively sensitized tracheal rings ovalbumin (10  $\mu\text{g/ml}$ ) induced a contractile response that recovered to basal tone within more than 60 min. In the presence of PIA 0.5  $\mu\text{M}$ , the recovery phase was significantly shortened (FIG. 1).

In the medium of sensitized tracheae, before antigen challenge, the ratio  $\text{PGE}_2/\text{PGF}_{2\alpha}$  was about 4 times higher than in not sensitized tracheal chains. Antigen challenge produced a remarkable reduction of  $\text{PGE}_2$  and an increase of  $\text{PGF}_{2\alpha}$  in the medium of sensitized tissue. In these experimental conditions, PIA 0.5  $\mu\text{M}$ , added 20 min before ovalbumin challenge, increased production of  $\text{PGE}_2$  without affecting the release of  $\text{PGF}_{2\alpha}$ .

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<sub>2</sub> and PGF<sub>2</sub> $\alpha$  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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