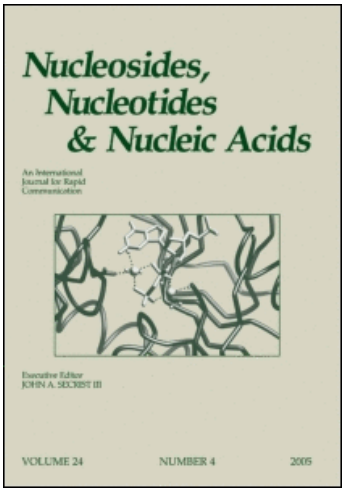

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Effects of Adenosine Agonists on Camp Accumulation in Adult and Newborn Rat Aortic Smooth Muscle Cell Cultures

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EFFECTS OF ADENOSINE AGONISTS ON cAMP ACCUMULATION IN ADULT AND NEWBORN RAT AORTIC SMOOTH MUSCLE CELL CULTURES

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Abstract: In aortic smooth muscle cell cultures of adult and newborn rats, the NECA-induced cAMP accumulation was enhanced in adults. The inhibitory effect of the A_1-receptor is unlikely to be the main factor responsible for this large difference.

Adenosine A_1- and A_2-receptors have been associated with a decrease or an incrase in cAMP levels respectively. These changes parallled an opposit change in DNA synthesis (Jonzon et al., 1985). Since PDGF-stimulated proliferation of arterial SMC is considered as a key event in the formation of the atherosclerotic lesion, adenosine could be a modulator of the development of artherosclerosis. We have therefore evaluated the effects of two adenosine analogs on cAMPC levels in aortic SMC from adult and newborn rats.

MATERIALS AND METHODS

Cell culture: Aortae of 5-day old or 8-month old rats were used for preparing the cells. Before the experiments all cultures were made quiescent by transfer to serum-free medium for 24 hours. The cell number was determined by an electronic cell counter.

Determination of cAMP: cAMP concentrations were measured using a modification of the protein binding method of Brown et al (1971).

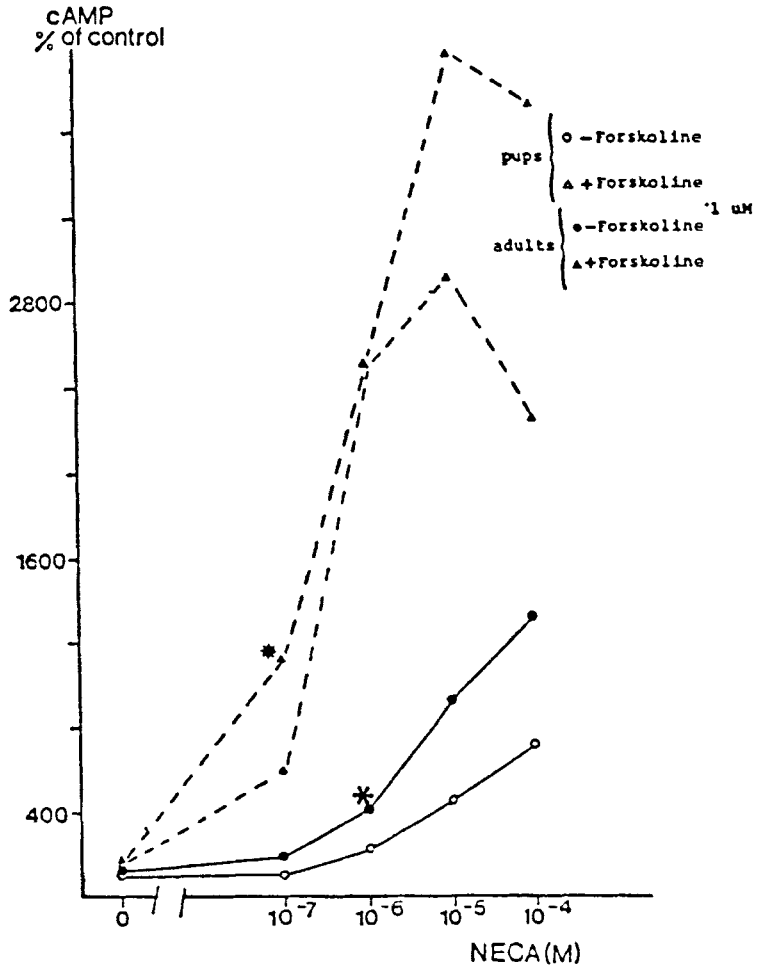

FIG. 1 Effect of NECA. Each point is the mean of one triplicate culture. The first significative increase vs pups is shown with an asterisk. *, *: $p < 0.05$, Student's t-test.

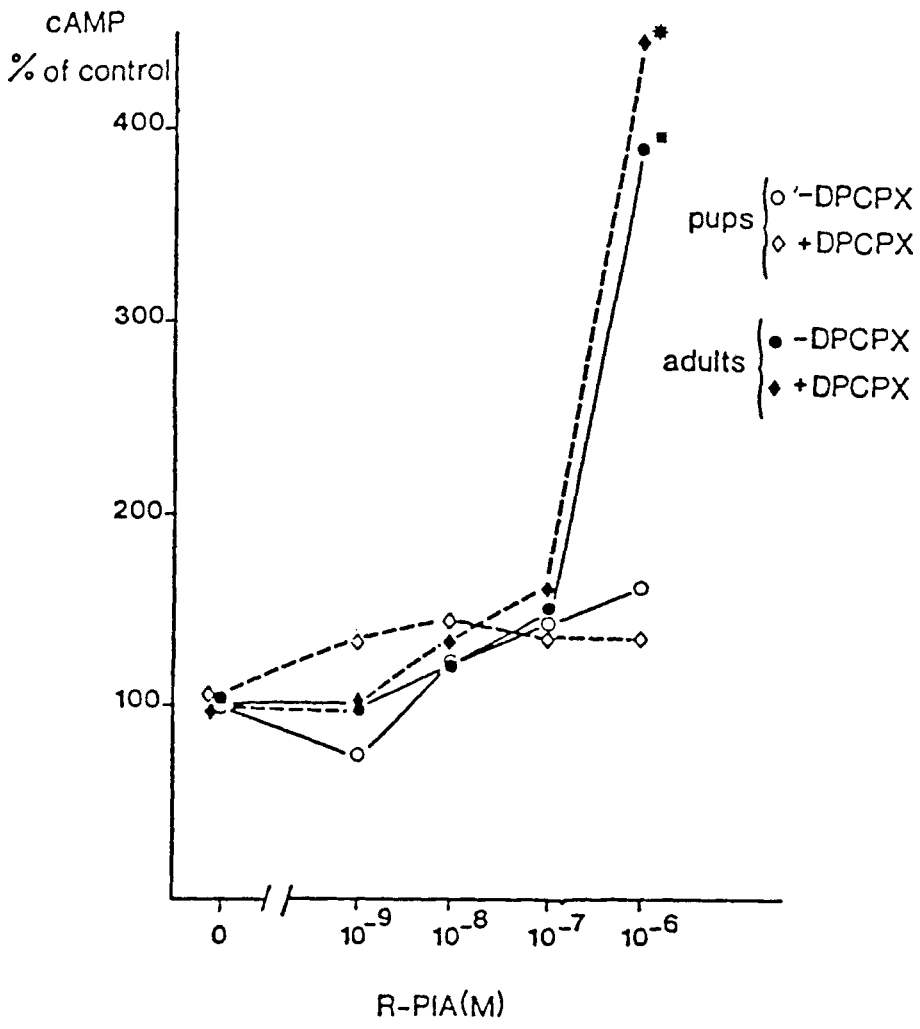

FIG. 2 Effect of R-PIA, in presence of 10 μM forskoline. Each point represents the mean of 3 determinations. The S.D. was less than 20 %. *,■ $p < 0.05$ vs pups. Student's t-test

RESULTS

The basal cAMP levels were 20.7 ± 2.0 nM/10^5 cells and 25.9 ± 9.5 nM/10^5 cells for pups and adults respectively (mean ± SD of six determinations).

The addition of NECA (0.1-100 μM) enhanced the level of cAMP in cells of both origine, in a dose-dependent manner. There was a significant increase from 0.1 μM and 1 μM NECA for adults and pups respectively. The accumulation of cAMP obtained in adult SMC is significantly higher, for all NECA concentrations tested in the range 10^{-7}-10^{-4}M, than in cells from young animals. Forskolin 1 μM potentiated the effect of NECA and the difference between pups and adults remained (FIG. 1).

The A_1-receptor agonist R-PIA enhanced cAMP accumulation at micromolar concentration (FIG. 2). At nanomolar concentration, R-PIA tended to counteract the increase in cAMP evoked by 10 μM forskolin in the pup cells whereas no inhibition could be seen in parallel experiments in adult cells. Furthermore, in the presence of 10^{-8}M DPCPX, an A_1-receptor selective antagonist, this decrease was abolished.

DISCUSSION

Dissimilarities between SMC from adults and pups have been observed. These two types of cells present the same phenotype, i.e. not contractile and capable of DNA synthesis but the adult SMC have been dedifferenciated after few days of culture and they are considered as a model of the proliferative atherosclerotic lesion. They are also more sensitive than pups to mitogenes like EGF or PDGF even if the binding characteristics are similar.

Our study shows that SMC from adult rats respond better to NECA and to R-PIA, at concentrations that affect A_2-receptor, than pups SMC. This discrepancy can not be explained by a difference in the A_1-response considering that the decrease in cAMP accumulation seen with nanomolar

R-PIA concentrations in presence of forskolin (10 μM) was very small and that it remained after blockade of A_1-receptors with DPCPX.

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