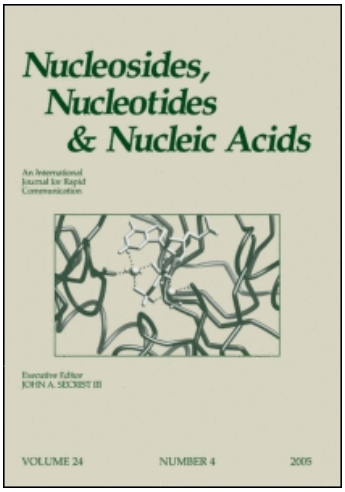

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cAMP Phosphodiesterase Activity Evaluation in Human Carcinoma of Salivary Glands

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cAMP PHOSPHODIESTERASE ACTIVITY EVALUATION IN HUMAN CARCINOMA OF SALIVARY GLANDS

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□ *The aim of this study was to evaluate differences of cAMP-PDE activity in human salivary glands, between a control group and some different benign tumours groups and, where present, with 2 malignant tumors groups. The value of the enzymatic activity in the groups analysed was 50% lower than control samples. The differences between the control group (82 ± 7.9 nmols/mg of protein) and the 3 pathologic groups (Benign A: 44 ± 6.2; Malignant A: 40 ± 16; Benign B: 40 ± 14.2; Malign A: 9.1; Benign C: 22 nmols/mg of protein) are statistically significant.*

Keywords cAMP; Carcinoma; Cyclic nucleotides; Phosphodiesterase; Salivary glands

INTRODUCTION

Cyclic adenosine monophosphate (cAMP) is an essential second messenger for cellular signal transduction generated by G protein-linked receptors. Its identification as a distinct intracellular second messenger was followed closely by an intensive search for effector proteins in various organisms. cAMP is not only able to mediate the action of a number hormones and neurotransmitters, but also is an activator of different protein kinases. Phosphodiesterases (PDEs) are a super family of enzymes that degrade the intracellular second messengers, cyclic AMP, and cyclic GMP. The existence of multiple PDE families, isoenzymes, and splice variants presents an opportunity for complex regulation of cyclic nucleotide levels.

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Moreover, current studies have shown PDE activities are regulated by multiple inputs from other signalling systems and that they may be key factor in the cellular differentiation and apoptosis.[1,2] The existence of numerous intracellular cAMP receptors, as well as the restricted tissue distribution of cAMP kinase and the lack of well characterized physiological substrates, has hindered a clear understanding of the physiological roles of cAMP kinase, and consequently of cAMP.

Recently, additional families of cAMP receptors have been described that include phosphodiesterases and ion channels. Cyclic nucleotide phosphodiesterase activity has been measured in muscle biopsies taken from healthy controls and from cancer patients.[3,4]

The process of carcinogenesis involve not only the increase of cell proliferation, but also the decrease of programmed cell death (apoptosis), which is known to be regulated by cAMP.[5]

MATERIALS AND METHODS

Samples

Thirty-seven human glandular resection samples were used in this study. Group A (n = 13) included 11 benign tumors, Lymphadenoma and Warthin's Tumors, 2 malignant cancers, carcinoma of the parotid gland and pleomorphic adenocarcinoma. Group B (n = 7) included 6 benign tumours, pleomorphic adenoma, and one malignant cancer, lymphoma of the parotid gland. Group C included only a single sample of basal cell adenoma. Sixteen samples from healthy individuals served as controls.

Methods

Different methodologies were used as described: partial purification of phosphodiesterases,[1] cAMP PDE assay,[6,7] and analysis of cAMP phosphodiesterase activity by reverse-phase HPLC.[7,8]

Protein Content

Protein content was determined using a bicinchoninic acid protein determination kit from Sigma with bovine serum albumin as a standard.

Data Processing

Fisher's PLSD, Scheffe, Bonferroni/Dunn were used to evaluate the presence of statistically significant differences.

Work Organization

The samples were divided into 4 groups: Group A included the lymphadenoma, Whartin's tumors (benign), and Adenocarcinoma (malignant); Group B included pleomorphic adenoma (benign) and lymphomas of the parotid gland (malignant); and Group C included the basal cell adenomas (benign). The alphabetical order indicates the severity of the benign pathologies in increasing order. The control group was represented by healthy patients. We also quantified intracellular concentrations of cAMP, the second messenger toward which the catalytic action of some PDE families is directed.

RESULTS AND DISCUSSION

The value of the cAMP-phosphodiesterase activity for the sixteen control samples was 82 ± 8 nmols/mg protein. The 11 samples in Group A with benign pathologies (Warthin-Lymphadenoma) showed a medium activity of 44 ± 6 nmols/mg protein against 40 ± 16 nmols/mg of proteins of the malign in the same group. In Group B, the mean cAMP-phosphodiesterase activity was 40 ± 14 nmols/mg proteins in the benign pathologies, 6 pleomorphic adenomas, against the malignant in the same group, parotid lymphoma, that was 9 nmols/mg proteins. The last group, C (n = 1), had a activity of 22 nmols/mg protein (Figure 1).

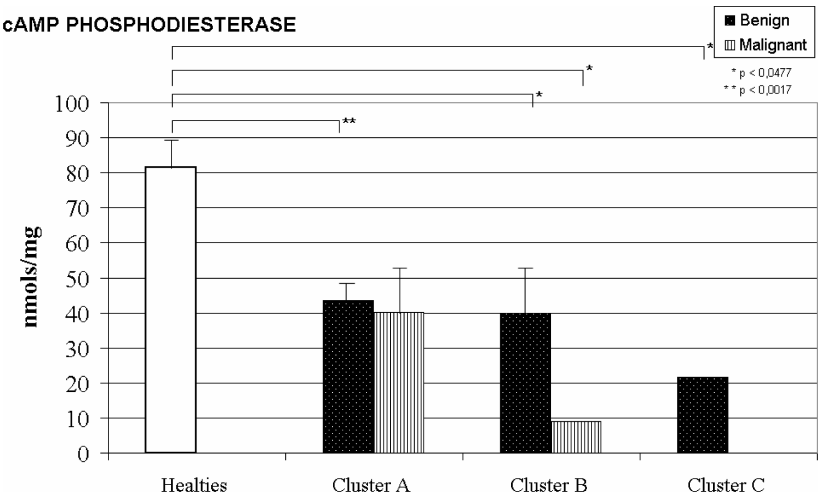

FIGURE 1 cAMP phosphodiesterase activity in human carcinoma of salivary glands.

GROUP A

cAMP-phosphodiesterase activities in this Group were 50% lower than controls, with similar reductions in benign and malignant tumor samples.

GROUP B

In this Group B, the enzyme activity was on average 50% lower than controls in the benign tumor samples, but the one sample taken from a malignant tumor was 9-fold lower than controls.

GROUP C

The single sample in this group was taken from a benign tumor (basaloid adenoma) and showed a 60% lower activity than controls.

We observed a large decrease of PDE activity expression in the analyzed salivary gland resections when compared to control tissues.

It is very important to underline the clearly decreasing activity of PDE in benign and malign pathologies in comparison with control samples.

CONCLUSION

The results of this study show decreased phosphodiesterase activity in benign tumors (Warthin's tumor, pleomorphic adenoma, and myoepithelioma). This could indicate that, while the tumor remains in the benign phase, the decrease of PDE activity is counterbalanced by a parallel decrease of adenylate cyclase activity, which would reestablish the base values of cyclic nucleotides. We hypothesize that lower phosphodiesterase acitivites contribute to intracellular changes that characterize these pathologies. A further decrease in PDE activity is observed in malignnant tumors (adenocarcinoma and parotid lymphoma), confirming previous reports.

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