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EXPRESSION OF CYCLIC AMP AND CYCLIC GMP PHOSPHODIESTERASE (PDE) ISOENZMYMES IN THE HUMAN PROSTATE: AN IMMUNOHISTOCHEMICAL STUDY

Hypothesis / aims of study

Experimental studies have demonstrated a fundamental significance of the cyclic nucleoside monophosphates cyclic AMP and cyclic GMP in the control of human urogenital tract tissues including the prostate. Cyclic nucleotides are synthesized by the activity of adenylyl- and guanylyl cyclases and degraded by cyclic nucleotide phosphodiesterases (PDE), a heterogenous group of hydrolytic enzymes. With the introduction of sildenafil citrate (VIAGRA™), the concept of phosphodiesterase (PDE) inhibition has gained tremendous interest in the field of urology. In order to elucidate further the significance of cyclic nucleotide mediated pathways in the control of the normal function of the human prostate we evaluated by means of immunohistochemistry the expression and distribution of cAMP- and cGMP-PDE isoenzymes in the transition zone.

Study design, materials and methods

In accordance with the regulations of the local ethical committee, human prostate tissue was obtained from six (6) male patients (aged 54 - 67 years) who had undergone surgery for localized carcinoma of the prostate or urinary bladder. Non-tumorous tissue was excised from the transition zone and immediately placed in an ice-cold solution of 4% formaldehyde in phosphate buffered saline (PBS, pH 7.4). Freeze sections (10 µM) were thaw-mounted onto glass slides and exposed to primary antibodies directed against the PDE isoenzymes 3 (cGMP-inhibited PDE), 4 (cAMP-PDE), 5 (cGMP-PDE), and 11 (Dual substrate PDE). Then, sections were incubated with either fluorescein isothiocyanate- (FITC) or Texas Red- (TR) labeled secondary antibodies. Visualization was commenced by means of conventional laser fluorescence microscopy.

Results

TR immunofluorescence revealed that PDE4 was abundantly present in the fibromuscular stroma as well as in glandular structures of the transition zone. Small arteries interspersing the stroma presented staining in the adventitia to a certain degree only. In contrast to the distribution of PDE4, immunostaining indicating PDE5 and the dual substrate PDE11 was mainly observed in glandular regions. While PDE5 staining was found to be most prominent in the entire glandular structure, dot-like immunofluorescence related to the expression of PDE11 was mainly present in epithelial layers. While significant immunosignals related to PDE5 were also detected in stromal parts of the sections, staining indicating the distribution of PDE11 in the fibromuscular stroma was inferior when compared to the activity registered in the glandules. No immunoreactivity specific for PDE3 could be detected.

Interpretation of results

Our results, for the first time, demonstrate the presence of immunoreactive protein related to cAMP and/or cGMP PDE isoenzymes in the transition zone of the human prostate and present evidence that these isoenzymes are not evenly distributed in the tissue, thus indicating that different PDEs may have different functions in the prostate.

Concluding message

The findings are in support of the hypothesis that there might be a rationale for the use of PDE inhibitors, which are able to elevate intracellular levels of cyclic nucleotides cAMP and cGMP, in the pharmacotherapy of the so-called benign prostatic symptom (BPS). Such drugs may effectively interfere with physiological mechanisms regulating stromal smooth muscle tone and tissue proliferation.

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