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A ROLE FOR NITRIC OXIDE (NO) IN THE CONTROL OF THE NORMAL FUNCTION OF THE HUMAN PROSTATE: AN IMMUNOHISTOCHEMICAL AND FUNCTIONAL STUDY

Hypothesis / aims of study
Investigative work implicated a role for nitric oxide (NO) in the control of the normal function of the human prostate. It has been speculated that drugs interfering with the NO - cyclic GMP pathway, such as selective inhibitors of the cyclic GMP phosphodiesterase (PDE) 5 or nitric oxide donor drugs, may represent potential new strategies for the treatment of lower urinary tract symptomatology (LUTS) and benign prostatic hyperplasia (BPH). Nevertheless, to date, knowledge on the occurence of the nitric oxide synthase (NOS) isoforms endothelial NOS (eNOS) and neuronal NOS (nNOS) in the human prostate is still sparse. While nNOS was only shown in nerve fibers branching within the transition zone, the localization of eNOS has been controversely discussed: Some authors reported the presence of eNOS in small vessels interspersing the prostate tissue, whereas others showed eNOS immunoreaction in glandular and subglandular structures. The aim of our study was to re-evaluate the distribution of eNOS and nNOS in the transition zone of the human prostate by means of light and electron microscopy (LM, EM) and examine the functional effects of nitric oxide donors on isolated human prostate tissue.

Study design, materials and methods
In accordance with the regulations of the local ethical committee, macroscopically normal human prostate tissue from the transition zone was obtained from 15 male patients (aged 54 - 76 years) who had undergone surgery for localized carcinoma of the prostate or urinary bladder. Using the organ bath technique, the effects of sodium nitroprusside (SNP), S-nitrosoglutathione (GSNO), S-nitrosocysteine (SNC) and linsidomine (SIN-1), as well as CNP (1 nM - 1.0/10 µM), known as an endogenous ligand of the membrane-bound guanylyl cyclase (GC-B), on the tension induced by norepinephrine (NE) of prostate tissue strips were investigated. The tissue was also exposed to three different concentrations of the drugs and the production of cGMP and cAMP was determined. The occurrence of eNOS and nNOS in cryosections of prostate tissue was examined by means of advanced fixation and staining procedures, the Tyramide Signal Amplification (TSA) technique.

Results
The tension induced by 40 µM NE of isolated prostate tissue was dose-dependly reversed by the drugs. The rank order of efficacy was: SNP > GSNO > SIN-1 > SNC = CNP (1 µM). The reversion of tension induced by the highest drug concentrations (R_{max}) ranged from 50 % relaxation (SNP) to 42 % relaxation (CNP). Relaxing effects of the drugs were paralleled by a 2-fold to 40-fold and 2-fold to 45-fold increase in tissue levels of cAMP and cGMP, respectively. Immunohistochemistry revealed that nNOS immunosignals were not only present in small nerve fibers interspersing stromal parts of the transition zone but also in glandular structures. EM images showed that nNOS immunoreaction was limited to the cytoplasm of the glandular epithelial cells. eNOS immunostaining was significantly present in endothelial cells of small vessels supplying glandular structures. This labeling was irregularly distributed throughout the cells. In contrast, no eNOS reaction was observed in epithelial layers of prostatic glandules.

Interpretation of results
Our results underline the significance of NO-pathway in the control of the human prostate and give rise to the speculation that nNOS is involved in the control of stromal and glandular tissue function, whereas eNOS might be related to the regulation of glandular perfusion and, thus, secretory activity. The findings from the immunohistochemical studies counteract the hypothesis of eNOS in glandular structures as a source of NO production.

Concluding message
The findings provides a rationale for the future use of compounds enhancing the production of cyclic GMP in the management of in the so-called benign prostatic symptom (BPS). Such drugs may effectively interfere with physiological mechanisms regulating stromal smooth muscle tone and tissue proliferation. However, it remains to be established as to whether the favorable in vitro effects of drugs interfering with cGMP-pathway, such as GSNO and SIN-1, can be translated into a reasonable clinical profile with an acceptable therapeutic benefit to side-effect ratio.

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