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Institutionen för Molekylär Medicin och Kirurgi

ON THE ROLE OF NITRIC OXIDE IN LOWER URINARY TRACT DISEASE

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ABSTRACT

Nitric oxide (NO) is an important biological molecule with a variety of functions. Among other, it is a signalling molecule capable of inducing smooth muscle relaxation and vasodilatation, it regulates proliferation, can induce apoptosis and act as an effector molecule in host defence reactions and in immune regulatory processes. High levels of NO are also seen in inflammatory diseases and NO is thought to play a role in tumour biology. The present thesis mainly focuses on the role of NO in the pathogenesis of bladder pain syndrome/interstitial cystitis (BPS/IC), the role for NO in bladder tumour biology and its potentially cytotoxic effects following *Bacillus Calmette Guérin* (BCG) treatment.

In bladder biopsies from patients with classic BPS/IC we found an increased inducible nitric oxide synthase (iNOS) expression at both transcriptional and protein levels compared to controls. These findings were correlated with high levels of endogenously formed NO in the same patients. iNOS expression was localized to the urothelium and macrophages both in the urothelial layer and in the submucosa.

Local NO formation in patients with bladder tumours of different stage and grade was increased in patients with a carcinoma in situ (CIS) lesion alone or concomitant with a papillary tumour as compared to healthy controls and patients with papillary bladder tumours without concomitant CIS. The same relationship was observed for iNOS with higher levels of mRNA and protein expression in patients with CIS. After BCG treatment for bladder cancer, iNOS was up regulated in the urothelium but was also seen in immune competent cells in the submucosa. Luminal NO was significantly elevated, as was iNOS mRNA expression, in BCG treated patients compared to controls. Furthermore, iNOS protein expression was found in the BCG treated patients when biopsies were examined using Western blot technique. In patients with high-risk non-muscle invasive bladder cancer (NMIBC) polymorphisms in the iNOS and endothelial nitric oxide synthase (eNOS) genes influenced treatment response following BCG instillations.

In conclusion, our results demonstrate an elevation of NO levels in the bladder in patients with classic BPS/IC that in all probability originate from an increased expression of iNOS in urothelial and immune competent cells in the bladder wall. In addition, NO levels are higher in patients with CIS lesions than in patients with papillary bladder tumours and this increase is also likely due to an elevated expression of iNOS. Furthermore, NO levels are higher in the bladder after BCG treatment and are likely to reflect an increased expression of iNOS in bladder urothelial cells and immune competent cells in the submucosa. These findings are in line with previous results implicating that BCG may act through NO/NOS pathways, which is further supported by our observations that polymorphisms in the iNOS and eNOS genes may influence treatment outcome for BCG.