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Comorbidity of inflammatory diseases in the lower urinary tract – the link between chronic prostatitis and bladder dysfunction

Akademisk avhandling

Som för avläggande av medicinsk basvetenskap doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal 1737, Ivan Östholm, Medicinaregatan 13B, fredagen den 25 november 2022, klockan 13.00

av Özgü Aydogdu

Fakultetsopponent:

Dr. Betty Exintaris, Senior Lecturer
Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Australia

Avhandlingen baseras på följande delarbeten

I. **Aydogdu, O**., Gocun, P.U., Aronsson, P., Carlsson, T., Winder, M. Prostate-to-bladder cross-sensitization in a model of zymosan-induced chronic pelvic pain syndrome in rats. Prostate 2021 Mar;81(4):252–260. doi: 10.1002/pros.24101

II. **Aydogdu, O**., Gocun, P.U., Aronsson, P., Carlsson, T., Winder, M. Cross-organ sensitization between the prostate and bladder in an experimental rat model of lipopolysaccharide (LPS)-induced chronic pelvic pain syndrome. BMC Urology 2021 Aug 21;21(1):113. doi: 10.1186/s12894-021-00882-9

III. **Aydogdu, O.,** Perez, F., Aronsson, P., Gocun, P.U., Carlsson, T., Sandner, P., Patel, B., Winder, M. Treatment with the soluble guanylate cyclase activator BAY 60-2770 normalizes bladder function in an in vivo rat model of chronic prostatitis. European Journal of Pharmacology 2022 Jul 15;927:175052. doi: 10.1016/j.ejphar.2022.175052.

IV. **Aydogdu, O**., Perez, F., Rataj, J., Nilsson, F., Aronsson, P., Carlsson, T., Sandner, P., Patel, B., Tobin, G., Winder, M. Effects of the soluble guanylate cyclase activator BAY 60-2770 on in vitro bladder contractile responses and receptor expression in a rat model of chronic prostatitis. Submitted manuscript.

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Özgü Aydogdu

Department of Pharmacology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Sweden

Abstract

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a common disease in men that currently lacks satisfactory pharmacological treatment alternatives. The aim of this thesis was to investigate the effects of CP/CPPS on lower urinary tract (LUT) function. Further, we aimed to investigate the effects of treatment with a soluble guanylate cyclase (sGC) activator, BAY 60-2770, on possible alterations in bladder function caused by CP/CPPS.

The effects of CP/CPPS on LUT function were evaluated both *in vivo* (Paper I-III) and *in vitro* (Paper IV). To create a functional animal model for CP/CPPS, rats were intraprostatically injected with either zymosan (Paper I, III, IV) or lipopolysaccharide (LPS, paper II). The effects of BAY 60-2770 on bladder function after induction of chronic prostatitis were examined *in vivo* (Paper III) and *in vitro* (Paper IV). Micturition parameters were investigated in a metabolic cage and alterations in bladder function were assessed with cystometry during *in vivo* rat studies (Paper I, II, and III). The prostate (Paper I-III) and bladder (Paper I-IV) were examined histopathologically. To investigate how the innate bladder contractility and receptor expression were affected by induction of chronic prostatitis, an *in vitro* organ bath set-up was utilized (Paper IV).

The findings in this thesis showed that induction of CP/CPPS led to bladder dysfunction, mainly overactivity. Bladder overactivity was observed regardless of if the prostate inflammation was chemically induced (with zymosan) or induced by LPS (mimicking an infectious focus in the prostate). The data show that the functional changes in the bladder were partly caused by altered afferent signalling. Our findings thus indicated that induction of chronic prostate inflammation could lead to bladder dysfunction via cross-organ sensitization. Cystometry and organ bath experiments showed that induced prostatitis also led to local alterations in the bladder as well as on efferent signalling. Further, our findings showed that treatment with a sGC activator had a dramatic ameliorative effect on functional bladder alterations caused by CP/CPPS.

In conclusion, the findings in this thesis support the hypothesis that cross-organ sensitization between the prostate and bladder can be triggered by chronic inflammation. This complex physiological process may be the reason for the unsuccessful treatment of chronic prostatitis. Targeting the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway, *i.e.*, with sGC activators, could be a promising pharmacological treatment option to alleviate the symptoms of men with CP/CPPS.

Keywords

Chronic pelvic pain syndrome, chronic prostatitis, LUTS, guanylate cyclase activator, BAY 60-2770, NO/cGMP

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