

## **INHIBITORY EFFECTS OF PROPIVERINE AND ITS METABOLITES ON AN OVERACTIVE BLADDER DEPEND ON THE SUPPRESSION OF C-FIBER BLADDER AFFERENT ACTIVITY IN RATS**

### Hypothesis / aims of study

The efficacy of systemic administration of antimuscarinic drugs for decreasing the symptoms of the overactive bladder is well documented and thought to be mainly due to their pronounced effects on the muscarinic receptors of the detrusor muscle. However, antimuscarinic drugs act mainly during the storage phase, allowing an increase of the bladder capacity and decreasing urgency; therefore, they may exert an inhibitory effect on bladder afferent nerves. This study was done to determine whether the effects of antimuscarinics depend on the suppression of the C-fiber bladder afferent nerves. We administered propiverine (PRO) and its active metabolites intravenously.

### Study design, materials and methods

To induce desensitization of C-fiber bladder afferent nerves, resiniferatoxin (RTX; 0.3 mg/kg) was injected subcutaneously in female Sprague-Dawley rats 2 days prior to left middle cerebral artery occlusion (MCAO). As controls we used rats treated with vehicle (ethanol and saline). Insertion of a polyethylene catheter through the bladder dome and MCAO were performed under halothane anesthesia. The effects of intravenous (0.2 – 2000 M/kg) administration of PRO (acts as antimuscarinic and calcium channel blocking agents), and its metabolite M-1 (PRO (N->O)); acts as a calcium channel blocking agent) and M-2 (DPr-PRO (N->O)); acts as an antimuscarinic agent), on cystometrography were investigated in conscious rats with cerebral infarct (CI).

### Results

Bladder capacity (BC) was markedly reduced after MCAO in both RTX-treated and vehicle-treated rats (RTX-CI and VEH-CI rats, respectively). Low doses (0.2, 2 nM/kg) of PRO, M-1 and M-2 significantly increased BC in VEH-CI rats without decrease in the bladder contraction pressure (BCP) or increase in the residual volume (RV), but had no effects on BC in RTX-CI rats. At the higher doses (200, 2000 nM/kg) PRO, M-1 and M-2 increased BC in both RTX-CI and VEH-CI rats. Percentage increases in BC of RTX-CI rats were significantly lower than those of VEH-CI rats. The highest dose (2000 nM/kg) of PRO and M-2 produced a slight but significant increase in RV in VEH-CI rats, but had no influence in RTX-CI rats.

### Interpretation of results

Intravenous propiverine and its metabolites at low doses enlarged the bladder in C-fiber-intact CI rats. In contrast, propiverine and its metabolites did not enlarge the bladder in C-fiber-desensitized CI rats, supporting the hypothesis that this drug improves the overactive bladder by inhibition of the C-fiber bladder afferent.

### Concluding message

C-fiber bladder afferents are believed to make a more than minor contribution to the micturition reflex in pathological conditions. Therefore, antimuscarinic drugs might be more effective in diseases in which C-fiber bladder afferents are predominantly involved.