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PRESENCE OF BETA3 ADRENERGIC RECEPTORS (B3-ARS) IN THE RAT SPINAL CORD AND THEIR FUNCTIONAL RELEVANCE IN MICTURITION UNDER NORMAL CONDITIONS AND IN A MODEL OF PARTIAL URETHRAL OBSTRUCTION

Hypothesis / aims of study
Currently the use of β3-AR selective agonists as a new treatment option for patients with OAB/LUTS is being evaluated. The human bladder detrusor muscle contains β3-ARs, and at present, it is believed that β3-AR selective agonists exert their effects on voiding function via a peripheral site of action. However, β3-ARs, which were first discovered in adipose tissue, have recently been found in human and rat brain tissue.
The aim of this study was to assess whether β3-ARs are present in the rat spinal cord, and whether there exists differences in β3-AR expression between normal and obstructed animals. In addition, the study aimed to evaluate the functional relevance of spinal β3-ARs on micturition. Therefore, the urodynamic effects of an intrathecally administered β3-AR selective agonist, BRL 37344, was evaluated in rats with or without partial urethral obstruction (PUO).
Study design, materials and methods
Thirty-eight male Sprague-Dawley rats underwent either PUO (n = 23) or sham-operation (n = 15). The mortality rate of PUO was 10.5%. Two weeks after operation, nineteen of the total animals were used for immunostaining (PUO n = 5; sham n = 4) and Western blot analysis (PUO n = 5: sham n = 5). A polyclonal anti-β3-AR-antibody (sc-1473, Santa Cruz) was used to evaluate the presence of β3-ARs in sacral and thoracolumbar rat spinal cord segments.
Fifteen of the 38 animals were used for functional experiments, whereas a β3-AR selective agonist, BRL-37344 (Sigma-Aldrich), was given intrathecally (100 nmol) to obstructed (n = 10) and non-obstructed (n = 5) rats. Bladder function was assessed by ongoing cystometry in non-anesthetized animals without any restraint before and after drug administration.
Results
Beta3-ARs were present in a scattered distribution in all areas of the grey matter (ventral horn, intermediolateral regions, and dorsal horn) in sacral as well as thoracolumbar rat spinal cord segments. There was no difference in β3-AR distribution between sacral and thoracolumbar segments. Beta-3-ARs were evenly distributed in all grey matter layers (lamina I – X), excluding an accumulation of β3-AR-positive cells in the sacral ventral horn, most likely corresponding to the Onuf's nucleus. There was a trend of increased β3-AR expression in obstructed rats, however, this was not statistically significant.
In the functional experiments, obstructed rats showed (two weeks after PUO) an increased bladder weight (174 ± 12 mg vs. 284 ± 35 mg; mean ± SEM, $p < 0.05$), reduced bladder capacity and micturition volume, increased micturition frequency, decreased compliance, and increased basal, threshold, and maximum pressure, as well as spontaneous activity (all $p < 0.05$) when compared to age-matched non-obstructed controls. Intrathecally administered BRL 37344 showed no effect in non-obstructed rats. In obstructed rats intrathecal BRL 37344 significantly reduced bladder pressures and spontaneous activity and decreased micturition frequency (all $p < 0.05$).
Interpretation of results
In the rat, β3-ARs are present in all spinal cord centres of neuronal micturition control (sympathetic, parasympathetic, and somatic), with a trend of increased β3-AR expression in obstructed animals. In obstructed animals, a centrally acting β3-AR selective agonist normalized deranged urodynamic parameters towards values seen in non-obstructed animals; the drug had no effect in non-obstructed animals. This suggests that β3-ARs within central pathways are of functional relevance under PUO conditions.
Concluding message
Besides their well established peripheral site of action in the treatment of voiding dysfunction, β3-AR selective agonists might exert relevant effects at a central nervous site of action.

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What were the subjects in the study?	**ANIMAL**
Were guidelines for care and use of laboratory animals followed or ethical committee approval obtained?	**Yes**
Name of ethics committee	**Animal Care and Use Committee (ACUC) of Wake Forest University**