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URODYNAMIC EFFECTS OF A NOVEL PERIPHERAL SELECTIVE CANNABINOID-2-RECEPTOR AGONIST (CANNABINOR) ON BLADDER FUNCTION IN CONSCIOUS RATS

Hypothesis / aims of study

The presence of cannabinoid 1&2 (CB1 & CB2) receptors in in the bladder urothelium has recently been demonstrated [1,2]. In –vitro and in-vivo experiments also showed that CB2 receptors are involved in urothelial afferent signalling mechanisms. However, studies on selective CB2-receptor stimulation are lacking. We therefore aimed to characterize the distribution of CB2 receptors in the rat bladder and to investigate the effects of Cannabinor, a peripherally acting selective CB2 agonist, on isolated rat detrusor and on normal bladder function, as studied by cystometry in conscious, freely moving animals.

Study design, materials and methods

The expression of the CB2 receptor was studied with immunohistochemistry and compared to the distribution of sensory (CGRP) or cholinergic (VAChT) nerves. Effects of Cannabinor, a high affinity agonist with a K_i of 9.7 x 10^{-9} M at the CB2 receptor, were studied on isolated rat detrusor (n=5) or on bladder function in vivo. For cystometric investigations in conscious rats, Cannabinor was given IV at three different dosages (0.3, 1, and 3 mg/kg, n=8). Effects were compared to baseline parameters and vehicle.

Results

CB2 immunoreactivity was expressed in the urothelium, in CGRP-containing nerves and in VAChT-positive nerve fibres of the bladder and in nerve cells of the perivesicular ganglion. In vitro, Cannabinor (0.1µM – 10µM) had no effect on carbachol (0.1µM-0.1mM) contractions. Nerve-induced contractions were reduced by 10 ± 3 % at 1µM of Cannabinor.

Whereas mean micturition interval (MI) was not increased at 0.3 or 1 mg/kg of Cannabinor, 50% of the animals responded with increased MI at these doses (Fig 1). For Cannabinor 3 mg/kg, MI increased from 294 ± 41sec to 423 ± 63 sec (*p<0.02*). Similarly, at 0.3 or 1 mg/kg of Cannabinor, 11 out of 16 rats exhibited increased micturition volume (MV) and bladder capacity (BC). At 3 mg/kg, Cannabinor increased MV from 0.82 ± 0.14 ml to 1.4 ± 0.2 ml *(p<0.001)* and increased BC from 0.83 ± 0.14 to 1.42 ± 0.18 ml *(p<0.001).* At 3mg/kg of Cannabinor, rats exhibited higher values for threshold pressure (p=0.05). At any dose, Cannabinor did not affect basal pressure, flow pressure, maximum pressure or residual volume. Intravenous administration of vehicle did not affect any urodynamic parameters.

Interpretation of results

Considering that CB2-receptors are localized on sensory nerves and in the urothelium, and that Cannabinor had significant effects on “afferent” urodynamic parameters, peripheral CB2-receptor activities may be proposed to be involved in regulation of sensory functions of the micturition reflex. CB2 is also expressed on cholinergic nerves, but effects by Cannabinor on cholinergic nerve activity in the normal isolated bladder appear to be limited.

Concluding message

The present findings form basis to further study CB2-receptor as a target treatment of lower urin tract symptoms.

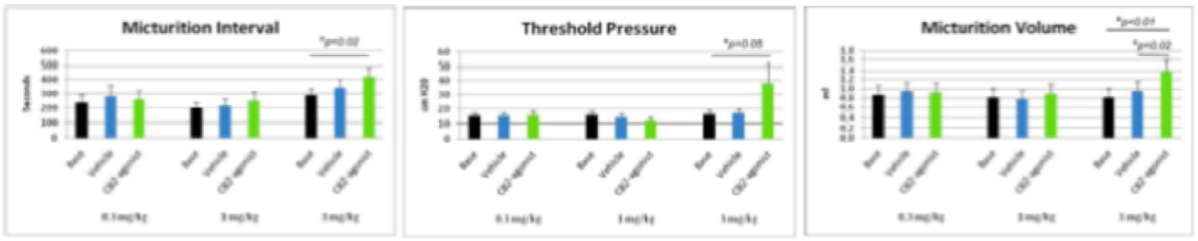

Fig 1 “Acute” Cannabinor 0.1, 0.3, 3 mg/kg IV – micturition interval, threshold pressure and micturition volume

References

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Specify source of funding or grant	**Women’s Health, Procter & Gamble Health Care, Cincinnati, OH, USA, Swedish Medical Research Foundation, the European Urological Scholarship Programme, the Gester’s Foundation, and Holger K Christiansen Foundation.**
Is this a clinical trial?	**No**
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	**Lund University, Sweden**