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Blyweert W[1], Van der Aa F [1], De Ridder D [1]
1. Department of Urology, UZ Gasthuisberg, Catholic University of Leuven

CANNABINOID THERAPY IN DETRUSOR OVERACTIVITY: LOCAL VERSUS SYSTEMIC EFFECT IN A SPINALISED RAT MODEL

Aims of Study

Systemic administration of cannabinoids has got a beneficial effect in detrusor overactivity, both in human clinical trials and in animal models. Cannabinoids exert their function through the cannabinoid receptors CB1 and CB2.
CB1 receptors are distributed widely throughout the central nervous system including the peri aqueductal grey and the spinal cord. CB1 immunoreactivity has also been demonstrated in human and rodent bladders. There is immunohistochemical evidence for an upregulation of CB1 receptors in neurogenic bladders and in inflammatory disease. CB2 receptors are mainly located on immunological cells.
To our knowledge, the peripheral contribution of cannabinoid therapy never has been studied in detail. We investigated the role of the cannabinoid receptors located on the spinal level and in the bladder in the beneficial effect of cannabinoid administration in detrusor overactivity.
Therefore we compared the urodynamical effect of intraperitoneal vs. intravesical administration of a cannabinoid agonist and antagonist in a spinal cord injured rat model.

Methods

On day 0 we surgically injured the spinal cord of 24 female Whistar rats at level T2-T3 under fluothane anaesthesia. Antibiotics (Ampicilline 0.15 mg/kg) were administered every 2 days and a Crédé manoeuvre was performed twice daily. Rats subsequently developed detrusor overactivity. A polyethylene PE50 catheter was implanted on day 14 in the bladder fundus. On day 21 rats were divided in 2 groups, one for intravesical, the other for intraperitoneal drug administration.
We performed urodynamics before and after administration of vehicle (10% ethanol in saline), WIN-55,212-2 (1µM in 10ml vehicle) or SR 141716A (1µM in 10ml vehicle).
We compared urodynamic parameters (voiding volume, voiding pressure and detrusor pressure) in these 6 groups after drug administration. All parameters were compared using a Kruskall-Wallis Anova, followed by Mann-Whitney U test when significant.

Results

All rats were paraplegic at day 21 and showed signs of detrusor overactivity when urodynamics were performed with saline (NaCl 0.9%).
In the intravesical group, no significant change in urodynamic parameters was observed.
In the intraperitoneal group, a significant change in detrusor pressure was found between all groups ($p < 0.05$ according to Kruskall-Wallis). After intraperitoneal vehicle administration, mean detrusor pressure was 28.92 mmH_2O. After intraperitoneal WIN-55,212-2 administration, mean detrusor pressure was 19.04 mmH_2O. After intraperitoneal SR141716A administration, mean detrusor pressure was 39.41mmH_2O. Mann-Whitney U test for the intraperitoneal group showed $p=0.02$ when comparing vehicle vs. Win-55,212-2; $p=0.02$ when comparing vehicle vs. SR141716A and $p=0.004$ when comparing Win-55,212-2 vs. SR141716A.

Conclusions

Since the spino-bulbo-spinal pathway was interrupted in the spinal cord injured rat model, these observations demonstrate that cannabinoids act not only through central regulatory pathways, but that spinal and bladder CB1 receptors are involved.
Intravesical administration seems ineffective, perhaps due to inefficient tissue penetration of the different drugs.
Systemic administration of cannabinoid agonists significantly decreases detrusor pressure; systemic application of cannabinoid antagonists significantly increases detrusor pressure. These data demonstrate that the beneficial effect of cannabinoid agonists in detrusor overactivity is not mainly due to cannabinoid action in the brain but also due to a peripheral

contribution. Whether this effect is attributed to an activation of cannabinoid receptors on the spinal level, of those located in the bladder or of both is not known.

The effect of the cannabinoid antagonists increasing detrusor pressure suggests a working mechanism opposite to a tonically active endocannabinoid system.