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EFFECT OF A SELECTIVE PROSTACYCLIN RECEPTOR (IP) ANTAGONIST ON THRESHOLD VOLUME IN THE REFILL MODEL

Hypothesis / aims of study

Recently, mechanosensitive c-fibers have been proposed to play a functional role in bladder overactivity and hypersensitivity. These normally silent afferents can be recruited during inflammation and other pathological conditions to lower volume thresholds and induce bladder overactivity. It has also long been known that prostanoids are released from the urothelium during distension and changes in pH and osmolarity [1]. The IP receptor ligand, prostacyclin (PGI_2) is the most common of the prostanoids released in the human bladder [2]. IP receptors are located on c-fibers and thus could play a functional role in sensing bladder filling. In this study, we examined the effects of a selective IP receptor antagonist, RO3244019, on bladder threshold volume (TV), threshold pressure (TP) and contraction amplitude (AMP) in the anesthetized rat and dog Refill Models. Conducting these studies under anesthesia unmasks a greater role for c-fiber reflexes [3].

Study design, materials and methods

Female Sprague Dawley rats were anesthetized with urethane. The femoral vein and urinary bladder dome were cannulated for the administration of drug and measurement of bladder pressure, respectively. Both ureters were ligated and transected proximal to the ligation. The external urethral orifice was ligated to maintain controlled bladder volumes. Following surgery, the bladder was infused at 100 μl/min until a volume-induced bladder contraction (VIBC) occurred at which time the TV was measured. After 5 minutes the bladder was drained and allowed to rest for 30 minutes. Filling and draining occurred until two consecutive TVs were within 10%. Once two stable baselines were recorded the rats were dosed with either vehicle (n = 6) or RO3244019 (3 mg/kg, i.v., n = 9) 3 minutes prior to the next bladder filling cycle.

Female Beagle Dogs were surgerized under isoflurane anesthesia. Both femoral veins and urinary bladder dome were cannulated for the administration of drug and measurement of bladder pressure, respectively. Both ureters were ligated and cannulated proximal to the ligation. The urethra was occluded using a foley catheter. Following surgery the dogs were maintained under anesthesia with pentobarbital i.v. The urinary bladder was filled via the foley catheter at a rate of 10% of the TV per minute (first time infusion rate was 5 ml/min). Once a bladder contraction was obtained, the bladder was manually drained via the bladder dome cannula and allowed to rest for 10 minutes. Following 3 straight baselines, where TVs were within 10% of each other, two consecutive doses of RO3244019 (1.0 and 3.0 mg/kg, i.v., n = 4) or vehicle (n = 4) were dosed for the next two filling cycles. Data for both dog and rat are presented as percent change from baseline.

Results

Table 1: Rat Refill

	TV (% change)	**TP (% change)**	**AMP (% change)**
RO3244019 (3 mg/kg, i.v.)	**86.9 ± 19.1	23.6 ± 17.1	*-15.5 ± 2.59
VEHICLE	-1.52 ± 6.73	5.98 ± 7.85	11.8 ± 9.55

Table 2: Dog Refill

RO3244019 (mg/kg, i.v.)	**TV (% change)**	**TP (% change)**	**AMP (% change)**
1.0	*24.4 ± 4.58	9.67 ± 2.91	-5.37 ± 4.20
VEHICLE (1.0)	4.83 ± 4.73	0.75 ± 5.48	3.21 ± 4.15
3.0	**33.1 ± 4.25	16.7 ± 7.87	-18.3 ± 5.70
VEHICLE (3.0)	6.96 ± 5.43	-0.94 ± 5.02	-2.36 ± 8.26

Statistical comparisons to vehicle are performed using a two sample t-test with equal or unequal variance assumption; *$0.01 \leq p < 0.05$, **$p < 0.01$

Interpretation of results

The IP antagonist RO3244019 significantly increased TV compared to the vehicle controls in the rat (86.9%, 3.0 mg/kg) and dog (24.4% at 1.0 mg/kg and 33.1% at 3.0 mg/kg) Refill models. In the rat, AMP was slightly and significantly decreased (-15.5%) at 3.0 mg/kg and in the dog there was a similar but insignificant decrease of -18.3%. Also, TP was increased in both the rat and dog (23.6% and 16.7%, respectively) however the change was not significant. The increase in TV demonstrates a selective IP antagonist may reduce c-fiber sensitivity, thus raising the volume needed to trigger the micturition reflex.

Concluding message

These data confirm a role for prostacyclin in sensing bladder fullness in the rat and dog. One might speculate that local suppression of prostacyclin function, for example using an IP antagonist, may be beneficial in treating irritative urinary storage symptoms.

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3. Effect of urethane anesthesia on the micturition reflex in capsaicin-treated rats. *J. of the Auton. Nerv. Sys.* 1990. **30**, 247-252.