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CHARACTERIZATION OF DP AND EP PROSTANOID RECEPTORS ON THE MICTURITION REFLEX

Hypothesis / aims of study

Prostanoids have been shown to regulate urinary bladder function and are likely to act as neuromodulators of afferent transmission by Aδ fibres and capsaicin-sensitive C fibres [1]. Conversely, cyclooxygenase (COX) inhibitors have not been shown to be efficacious in treating overactive bladder (OAB). This may be due to opposing elements of the arachidonic acid pathway where some prostanoids are promoting continence while others are stimulating micturition. Multiple prostanoid receptor mRNAs that include those for EP_1, EP_3 and EP_4 were found to be present in dorsal root ganglion cells (DRG) and a majority of the neurons are C-fibres [2]. DP and EP_2 receptors are found on postsynaptic neurons of the dorsal and ventral horn. The aim of this study was to examine the role of the EP and DP receptors in mediating the micturition reflex. AH6809, a DP/EP_1/EP_2/EP_3 receptors antagonist, SC19220, an EP_1 receptor antagonist, butaprost free acid, an EP_2 receptor agonist, and sulprostone, an EP_3 receptor agonist, and BWA 868c, a DP receptor antagonist were administered in the anaesthetized rat refill model to measure their effects in bladder threshold volume (TV) and contraction amplitude (AMP).

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 or drugs (i.v.) 3 minutes prior to the next bladder filling cycle. Data are presented as percent change from the baseline.

Results

Table 1: Effects of DP and EP Agonists and Antagonists on Refill Model Parameters

Drug	**Dose (mg/kg, iv)**	**TV (% Change)**		**AMP (% Change)**	
		Vehicle	Drug	Vehicle	Drug
AH6809	10	-7.19 ± 8.11	-43.50 ± 7.24**	8.74 ± 9.83	36.26 ± 20.17
Sulprostone	0.3	7.50 ± 9.36	98.92 ± 31.13*	4.18 ± 3.83	-21.51 ± 8.16*
SC19220	3	7.67 ± 6.56	10.77 ± 10.59	-8.35 ± 5.79	-5.76 ± 5.62
Butaprost (free acid)	0.3	5.61 ± 8.60	-11.64 ± 11.34	-16.87 ± 5.21	-3.50 ± 6.00
BWA 868c	3	7.67 ± 6.56	-12.47 ± 6.76	-8.35 ± 5.79	-1.68 ± 5.07

Statistical comparisons to vehicle are performed using a two sample t-test with equal or unequal variance assumption; n = 4-9; *$0.01 \leq p < 0.05$, **$p < 0.01$

Interpretation of results

AH6809, a mixed DP/EP_1/EP_2/EP_3 antagonist, significantly decreased the TV (-43.50%), an effect likely attributed to one or more of these four prostanoid receptors. Further studies with individual prostanoid receptor compounds revealed that only sulprostone, an EP_3 agonist, caused significant changes in TV (+98.92%) and AMP (-21.51%). SC19220, butaprost (free acid), and BWA 868c did not demonstrate any significant effects in bladder TV and AMP. Therefore, the effect of sulprostone led us to believe that the results of AH6809 were due to the blocking of EP_3 receptors. EP_3 receptors play an inhibitory role in bladder contractions by increasing the TV to initiate the micturition reflex. Immunohistochemical studies have confirmed the presence of EP_3 receptors in the rat dorsal root ganglion (DRG) and dorsal

horn of the spinal cord, suggesting their presence on the terminals of primary afferents [3]. The present data demonstrate that EP_3 receptors may play a role in mediating micturition, possibly via actions on the C-fibres in the DRG.

Concluding message

The results suggest that EP_3 receptors are important in mediating the micturition reflex by increasing the bladder TV. EP_3 agonists may potentially be beneficial in treating OAB symptoms.

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