Evidence for 5-HT7 receptor mediated contraction of the isolated rat detrusor muscle

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5-Hydroxytryptamine (5-HT) plays a role in the control of micturition via actions at central and peripheral sites (Ramage, 2006). Identifying the precise contribution of individual 5-HT receptors is crucial for the development of potential treatments for overactive bladder and urinary incontinence. 5-HT induces contraction of the detrusor muscle via 5-HT receptors located on the smooth muscle but also by receptors at prejunctional sites. 5-HT7 receptors have been suggested to facilitate acetylcholine release in parasympathetic nerve terminals of the human and rat bladder and to relax the pig urinary bladder neck (Palea et al., 2004; D’Agostino et al., 2006; Recio et al., 2009). Here, we provide evidence to support a role for prejunctional 5-HT7 receptors in mediating contraction of the isolated rat detrusor muscle.

The bladder was isolated from adult male Wistar rats (250-350g). Detrusor muscle strips (≈ 8mm x 2mm) were suspended between platinum ring electrodes in an organ bath and connected to an isometric force transducer under 1g of resting tension. Tissues were maintained in modified Krebs-Henseleit buffer [in mM: NaCl 118.1, NaHCO3 25, KCl 4.7, KH2PO4 1.2, CaCl2 2.5, MgSO4 1.2, glucose 11.6] at 37°C and gassed with 95%O2/5%CO2. Cumulative concentration-response curves were constructed for 5-carboxamidotryptamine (5-CT, 10 nM-1μM), a 5-HT1/5-HT7 receptor agonist, and AS-19 (10 nM-1μM), a selective 5-HT7 receptor agonist, in the absence and presence of increasing concentrations of the selective 5-HT7 receptor antagonist SB269970 (1nM-1μM) or atropine (5μM). Electrical field stimulation (trains of 5s every 30s at 5Hz, 50V, 0.5ms pulse duration) was used to investigate the effects of AS-19 on neurogenic contractions of the detrusor muscle.

Both 5-CT and AS-19 elicited a weak contraction of the isolated rat detrusor muscle with pD2 values of 6.7 ± 0.1 (n=33) and 6.9 ± 0.1 (n=23), respectively. Application of the antagonist SB269970 (10nM) completely obliterated the response to AS-19 (n=6), whereas for 5-CT Emax was reduced to 75 ± 8% of control (n=6). Higher concentrations of SB269970 (up to 10μM) did not completely obliterate the response to 5-CT suggesting that 5-CT, which is a non-selective 5-HT1/5-HT7 agonist, may be activating additional 5-HT receptors, such as the 5-HT1A receptor. The muscarinic receptor antagonist atropine (5 μM) completely blocked the contractile responses elicited by both AS-19 (n=9) and 5-CT (n=5). The amplitude of neurogenic contractions elicited by electrical field stimulation was increased by 15.1 ± 10.4% in the presence of 50nM AS-19 (n=5).

Taken together these data indicate that 5-HT7 receptors are located prejunctionally in the rat detrusor muscle and their activation facilitates acetylcholine release to elicit a contraction of the smooth muscle. Targetting these 5-HT7 receptors may therefore represent a viable therapeutic strategy for treating overactive bladder and urinary incontinence.

Palea, S. et al. (2004). BJU Int. 94, 1125-1131

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