Evidence For 5-HT\textsubscript{7} 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-HT\textsubscript{7} 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-HT\textsubscript{7} 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, NaHCO\textsubscript{3} 25, KCl 4.7, KH\textsubscript{2}PO\textsubscript{4} 1.2, CaCl\textsubscript{2} 2.5, MgSO\textsubscript{4} 1.2, glucose 11.6] at 37°C and gassed with 95%O\textsubscript{2}/5%CO\textsubscript{2}. Cumulative concentration-response curves were constructed for 5-carboxamidotryptamine (5-CT, 10 nM-1\textmu M), a 5-HT\textsubscript{1}/5-HT\textsubscript{7} receptor agonist, and AS-19 (10 nM-1\textmu M), a selective 5-HT\textsubscript{7} receptor agonist, in the absence and presence of increasing concentrations of the selective 5-HT\textsubscript{7} receptor antagonist SB269970 (1nM-1\textmu M) or atropine (5 \textmu M). 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 pD\textsubscript{2} 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 E\textsubscript{max} was reduced to 63 ± 7% of control (n=6). Higher concentrations of SB269970 (up to 10 \textmu M) did not completely obliterate the response to 5-CT suggesting that 5-CT, which is a non-selective 5-HT\textsubscript{1}/5-HT\textsubscript{7} agonist, may be activating additional 5-HT receptors, such as the 5-HT\textsubscript{1A} receptor. The muscarinic receptor antagonist atropine (5 \textmu M) completely blocked the contractile responses elicited by both AS-19 (n=4) and 5-CT (n=9). The amplitude of neurogenic contractions elicited by electrical field stimulation was significantly increased by 53 ±11% in the presence of 50nM AS-19 (n=5).

Taken together these data indicate that 5-HT\textsubscript{7} 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-HT\textsubscript{7} receptors may therefore represent a viable therapeutic strategy for treating overactive bladder and urinary incontinence.

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