URINARY INCONTINENCE

Novel insights into the mechanism of action of mirabegron on human bladder smooth muscle

The β_3 -adrenoceptor agonist mirabegron is a novel agent, which relaxes urinary bladder smooth muscle in patients with overactive bladder syndrome (OAB); however, the exact mechanism of action of this agent remains elusive. Now, findings of research using isolated human urinary bladder smooth muscle (UBSM) strips reveal that mirabegron inhibits parasympathetic neurotransmitter release, in addition to having direct relaxant effects on UBSM.

“The clinical utility of β_3 -adrenoceptor agonists was mainly ascribed to the stimulation of the muscle β_3 -adrenoceptor” explains Anna Maria Condino, a researcher on this project, who also adds “significant improvements in key symptoms in patients with OAB, as well as the reduction of phasic activity during the filling phase suggest a more comprehensive mechanism of action.”

To investigate mirabegron-induced UBSM relaxation, samples from the anterior bladder dome of patients who underwent total cystectomy were mounted under tension in isolated organ baths and attached to force transducers. Bladder strips were perfused with an oxygenated krebs solution and contracted using electrical field stimulation (EFS).

“...mirabegron inhibits parasympathetic neurotransmitter release...”

These EFS-induced contractions were significantly reduced by mirabegron, and were almost completely abolished by tetrodotoxin, implying a neurogenic origin. UBSM strips were loaded with [^3H]-acetylcholine in order to monitor neurotransmitter release. In these UBSM strips, preincubation with mirabegron resulted in dose-dependent inhibition of EFS-evoked acetylcholine release; this effect was confirmed using the selective β_3 -adrenoceptor antagonist L748337.

Interestingly, the non-selective β -adrenoceptor agonist isoprenaline had similar effects upon EFS-evoked acetylcholine release, which were inhibited by β_2 -adrenoceptor antagonists, confirming the importance of other β -adrenoceptors in control of UBSM function.

These findings indicate that the therapeutic effects of mirabegron are mediated in part through activation of pre-synaptic β_3 -adrenoceptors on parasympathetic neurons, which results in inhibition of acetylcholine release, and in turn, a reduction in UBSM contractile force. This effect complements the previously established mechanism of action of this agent on UBSM β_3 -adrenoceptors.

The finding that β_2 -adrenoceptor stimulation can also inhibit neuronal acetylcholine release, whilst not entirely novel, might have important implications both for future drug development processes, and for the substantial population of patients currently using β -blockers.

“The present study demonstrates a reliable method to characterize novel β_3 -adrenoceptor agonists that are potential candidate treatments for overactive bladder, such as solabegron” concludes Condino, who adds that a further investigation is currently ongoing into the effects of β_3 -adrenoceptor agonists upon acetylcholine release from non-neural sources within the urinary bladder.

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Original article D'Agostino, G. *et al.* Involvement of β_3 -adrenoceptors in the inhibitory control of cholinergic activity in human bladder: direct evidence by [^3H]-acetylcholine release experiments in the isolated detrusor. *Eur. J. Pharmacol.* doi:10.1016/j.ejphar.2015.03.074

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