Nicotinic receptors on capsaicin-sensitive sensory afferents modulate peristalsis in the mouse renal pelvis

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Since the earliest examinations of kidney function, it has been recognised that the spontaneous propagating contractions that transport urine from the kidney to the bladder (pelviureteric peristalsis) originate within the most proximal regions of the renal pelvis. The pacemaker signal that triggers the firing of these propagating contractions is thought to originate in atypical smooth muscle cells (ASMCs), which spontaneously fire Ca^{2+} transients that trigger Ca^{2+}-activated spontaneous transient depolarisations (STDs). These STDs sum together to trigger the propagating nifedipine-sensitive action potentials, Ca^{2+} waves and contractions within the typical smooth muscle cells (TSMCs) of the renal pelvis wall. Even though there is evidence of extensive networks of parasympathetic and sympathetic nerves within the renal pelvis it has been difficult to demonstrate that these networks play any efferent role in maintaining or modulating pelviureteric peristalsis, being little affected by tetrodotoxin, guanethidine or atropine.

In this study, we investigated the effects of nicotinic receptor activation on the spontaneous contractions, action potentials and Ca^{2+} transients in TSMCs, as well as the Ca^{2+} transients in ASMCs of the mouse renal pelvis. The effects of nicotinic receptor activation were compared before and after neuropeptide depletion of primary sensory afferents (PSAs) or inhibition of ATP-dependent K^+(KATP) channels.

The kidney and attached ureter were removed from mice killed by cervical dislocation under isoflurane anaesthesia. Contractile activity within the renal pelvis was followed using video microscopy and edge detection software (Diamtrak), while the electrical and Ca^{2+} signals in TSMCs and ASMCs were recorded separately using single intracellular microelectrodes and Fluo-4 Ca^{2+} imaging. Nicotine and carbachol (1-100 μM) transiently reduced the frequency and increased the amplitude of spontaneous phasic contractions in a manner unaffected by L-NAME (200 μM), inhibitor of nitric oxide synthesis or the muscarininc antagonists, 4-DAMP, atropine and pirenzepine (10 nM), but blocked by capsaicin, the depletor of sensory nerve neuropeptides and the nicotinic antagonist, hexamethonium.

These negative chronotropic and delayed positive inotropic effects of carbachol on TSMC contractions, action potentials and Ca^{2+} transients were also inhibited by glibenclamide (1 μM), blocker of KATP channels. Nicotinic receptor-evoked inhibition of the spontaneous Ca^{2+} transients in ASMCs was prevented by capsaicin but not glibenclamide.

We conclude that the negative chronotropic effect of nicotinic receptor activation results from the release of CGRP from intrinsic PSAs, which suppresses Ca^{2+} signalling in ASMCs. PSA-released CGRP also evokes hyperpolarization in TSMCs dependent upon the opening of KATP channels. This hyperpolarization reduces contraction propagation but promotes increased TSMC Ca^{2+} channel opening upon arrival of the next pacemaker signal, this de-inactivation of Ca^{2+} channels underlies the delayed positive inotropic effects of nicotinic receptor activation. Given the relative insensitivity of the upper urinary tract to transmural electrical stimulation, activation of nicotinic receptors on PSAs may well provide a means by which neighbouring parasympathetic nerves modulate pelviureteric peristalsis, analogous to the modulation of PSAs by efferent nerve- and urothelium-derived factors in the bladder.