Role of hyperpolarization-activated cyclic nucleotide gated cation channels in pyeloureteric peristalsis

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It has long been recognised that the movement of fluid and solutes from the kidney to the bladder is achieved by the means of spontaneous propagating contractions (pyeloureteric peristalsis) that are triggered by pacemaker cells situated in the most proximal regions of the renal pelvis. In the renal pelvis of the guinea pig, rat and mouse, we have previously reported that atypical smooth muscle cells (SMCs), which form a bundle of thin, often-branching cells near the base of the papilla are the mostly likely candidates to act as these pacemaker cells. However, several populations of interstitial cells (ICs) identified by their selective immuno-staining for voltage-operated K^+ (Kv7.5) channels, tyrosine receptor kinase, Kit, or hyperpolarisation-activated cation channels, HCN3, have also been proposed to play a fundamental role in pyeloureteric peristalsis.

Recently, Cain *et al.* (2011) demonstrated that the transgenic manipulation of various components (Smo or GLI3) of the Sonic Hedgehog signalling pathway within the urothelium of the developing embryonic ureter induces nonobstructive hydronephrosis, unco-ordinated pyleoureteric contractions and a complete loss of immuno-staining for Kit and HCN3 in cells within the renal pelvis adventitia. Moreover, blockade of HCN channels with ZD7288 (15-30 μM) disrupts the coordinated proximal-to-distal propagation of contractions and membrane depolarisation in the mouse upper urinary tract (Hurtado *et al.*, 2010). We have confirmed that ZD7288 (10-20 μM) reduced the frequency and velocity of propagating contractions, as well as the frequency of their underlying Ca^{2+}-entry dependent action potentials. ZD7288 had no effect on the sustained contractions evoked upon exposure to 30 mM K^+ saline or phenylepherine (10 μM). The effects of ZD7288 on pelviureteric peristalsis were mimicked by indomethacin (10 and 20 μM), the blocker of prostaglandin synthesis. Unlike ZD7288, however, the inhibitory effects of indomethacin could readily be restored upon exposure to dinoprost (10 nM), the stable analog of PGF_{2a}.

Electrophysiological recordings with 2 intracellular microelectrodes failed to reveal the tell-tale ‘delayed sag and rebound excitation’ in the time course of electrotonic potentials evoked by a constant hyperpolarizing current injection which would indicate the presence of an HCN current in the SMCs of the renal pelvis wall. Moreover, we never recorded the characteristic slowly-developing, little-inactivating inward current evoked during long-duration hyperpolarizing steps to potentials negative of −50 mV in single typical or atypical SMCs or in suburothelial ICs, freshly isolated from the renal pelvis, even though we could readily recorded an HCN current in cultured dorsal root ganglia.

We conclude that while present evidence suggests that atypical SMCs are likely to be the fundamental pacemakers in the renal pelvis, suburothelial and adventitial ICs are intimately involved in the initial development of the ureter and the maintenance of functional pyeloureteric peristalsis. It has yet to be established whether they are involved in the remodelling of the upper urinary tract during congenital obstructive or nonobstructive hydronephrosis and hydorureter.

Cain JE, Islam E, Haxh F, Blake J & Rosenblum ND (2011) *Journal of Clinical Investigation* **12:** 1199-206.
Hurtado R, Bub G & Herzlinger D. (2010) *Kidney International* **77:** 500-50.