Characterization of the of the electrical activity underlying spontaneous contractions in the mouse ureteropelvic junction

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The unique role of the upper urinary tract is to propel urine from the kidneys to the bladder for storage until micturition. The decreasing presence of 'atypical' smooth muscle cells (SMC) with distance from the renal fornix has long been correlated with a decreasing gradient in contraction frequency to suggest that these atypical SMC are the primary pacemaker cells underlying pyeloureteric motility. However, we have previously described the properties of a population of electrically active cells, with many of the morphological features of interstitial cells of Cajal (ICC) the pacemaker cells of the intestine, in the spontaneously active renal pelvis of the guinea pig which was absent in the electrically-quiescent ureter (Klemm *et al.*, 1999). These ICC-like cells were not immuno-reactive to c-Kit, but c-Kit positive cells have recently been described in the upper urinary tract of mouse, pig and human (Metzger *et al.*, 2005).

We have investigated the possible function of c-Kit positive cells in the urinary tract in portions of the mid renal pelvis from humanely killed mice using intracellular microelectrodes containing Lucifer Yellow and in single cells freshly dispersed from the ureteropelvic junction and proximal ureter, using conventional whole cell and single channel patch clamp techniques.

In approximately 60% of microelectrode recordings (at 33°C), muscle contractions (3.2±0.6 min^{-1}, n=9) were directly correlated in time with the discharge of an action potential which consisted of an initial spike followed by a prolonged plateau (1.2±0.3 s, n=9). These action potentials were blocked by nifedipine (1 µM) and the cells identified, *via* Lucifer Yellow filling, as spindle-shaped smooth muscle cells when viewed under a fluorescent microscope. The remaining recordings consisted of higher frequency (33±8 min^{-1}, n=9) electrical discharges which were not directly coupled to muscle contraction. These electrical discharges were recorded in both spindle-shaped smooth muscle cells as well as stellate-shaped cells as revealed by Lucifer Yellow. These high frequency electrical events were reduced only in amplitude and duration by nifedipine (1 µM).

Membrane depolarizing steps to potentials positive to -40 mV applied to single 'spindle-shaped' myocytes under voltage clamp (at 22°C) evoked a Ca^{2+} current upon which was superimposed a transient outward current (I_{Kto}), and a slowly developing outward current which inactivated little over 200 ms. I_{Kto} was 50% inactivated at a holding potential of -84.3 ±2.9 (n=3) mV and selectively blocked by 4-aminopyridine (1-3 mM). The little-inactivating outward current was blocked by tetraethylammonium (TEA 3 mM) or iberiotoxin (100 nM) suggesting that this current arose from the activation of large conductance Ca^{2+}-activated K^+ (BK_{Ca}) channels, which were readily recorded and characterized in excised membrane patches. In contrast, depolarization of stellate- or 'staghorn'-shaped cells to potentials positive to -40 mV evoked only a slowly-developing/decaying outward current that was partially blocked by TEA (2-20 mM). Some of these cells also displayed spontaneous transient inward currents which reversed near -10 mV.

We postulate that contractions of the mouse ureteropelvic junction arise from nifedipine-sensitive action potential discharge in smooth muscle cell bundles. In addition these action potentials could well be driven by pacemaker potentials generated in neighbouring c-Kit positive ICC-like cells observed under the fluorescent microscope.

Klemm, M.F., Exintaris, B. & Lang, R.J. (1999) *Journal of Physiology* **519**, 867-884

Metzger, R., Schuster, T., Till, H., Franke, F.-E. & Dietz, H.G. (2005) *Pediatric Surgery International* **21**, 169-174.