Spontaneous electrical and Ca^{2+} signals in the mouse renal pelvis that drive pyeloureteric peristalsis

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Pacemakers are ubiquitous throughout the body, setting all sorts of global rhythms, such as diurnal and circadian rhythms, as well as local rhythms that drive the heart and a number of smooth muscle organs. The upper urinary (pyeloureteric) system, consisting of the renal pelvis and ureter, is unique in physiology in that morphological, electrophysiological and Ca^{2+} imaging evidence suggests the presence of two putative pacemaker cell populations: atypical smooth muscle cells (SMCs) situated mostly in the proximal renal pelvis (Lang *et al.,* 2007a,b) and interstitial cells which are distributed throughout the pyeloureteric system and identified by their distinctive spindle- or stellate-shaped morphology and their immuno-reactivity to antibodies raised against the receptor tyrosine kinase, Kit (Pezzone, 2003).

We have recently established in excised strips (Lang *et al.,* 2007a) or single cells (Lang *et al.,* 2007b) of the mouse renal pelvis that:

i. nifedipine-sensitive action potentials and Ca^{2+} waves within the SMC wall are responsible for the peristaltic contractions that propagate the length of the pyeloureteric system.
ii. spindle-shaped atypical SMCs display high frequency spontaneous transient depolarizations (STDs) and Ca^{2+} transients that are reduced but not blocked by nifedipine or ryanodine. Under perforated-patch voltage clamp, a subpopulation of single SMCs displayed spontaneous transient inward currents (STICs) and long-lasting large inward currents (LICs) that could well be responsible for STD generation.
iii. interstitial cells with a morphology and distribution similar to Kit-positive cells display low frequency Ca^{2+} signals that are insensitive to nifedipine but readily blocked by ryanodine. These Ca^{2+} signals have time courses and frequencies similar to the long-lasting nifedipine-insensitive depolarizations recorded with intracellular microelectrodes. After enzymatic dispersal, two distinct populations of interstitial cells display STICS and LICs that are also little affected by 1 mM nifedipine and likely to be cation selective.

We have concluded that reduction but not blockade of STDs in atypical SMCs by nifedipine or ryanodine suggests that Ca^{2+} entry through L type Ca^{2+} channels and Ca^{2+}-induced release of Ca^{2+} (CIRCa) from internal stores is involved in the synchronization and propagation (entrainment) of STDs before they can provide a pacemaker drive to the SMC wall. However, the site of this entrainment that triggers a propagating contraction has yet to be established. Pelviureteric interstitial cells also generate their own non-propagating spontaneous electrical and Ca^{2+} signals albeit at a lower frequency than atypical SMCs. It is not yet clear, however, whether these spontaneously-active cells are indeed Kit-positive interstitial cell of Cajal-like cells and not other interstitial cells such as macrophages or fibroblasts, etc.

Lang RJ, Hashitani H, Tonta MA, Parkington HC, Suzuki H. (2007a) *Journal of Physiology,* **583:** 1049-68.
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Pezzone MA. (2003) *American Journal of Physiology,* **284:** 925-9.