Review

Pacemaker activity in the upper urinary tract

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Abstract

Ureteral peristaltic activity begins with the origin of electrical activity at pacemaker sites. These sites are located in the proximal portion of the urinary collecting system. The 'atypical' smooth muscle cells at these sites fire 'pacemaker' potentials at a frequency higher than the 'driven' action potentials recorded from typical smooth muscle cells. In contrast to typical smooth muscle cells, these atypical pacemaker cells have less than 40% of their cellular area occupied by contractile filaments and demonstrate a sparse immunoreactivity for alpha-smooth muscle actin. Expression of c-Kit, a tyrosine kinase receptor, correlates with the onset of organized ureteral peristalsis in the embryo. Capsaicin-sensitive sensory afferents and the endogenous release of tachykinins and prostaglandins are involved in the maintenance of normal ureteral peristalsis.

Key words: upper urinary tract, pacemaker, ureter, renal pelvis

Under normal conditions, peristalsis in the upper urinary tract begins with the origin of electrical activity at pacemaker sites located in the proximal portion of the urinary collecting system. This electrical activity propagates distally giving rise to the mechanical event of peristalsis, renal pelvic and ureteral contractions, which propel urine from the kidney to the bladder (Bozler, 1942; Weiss *et al.*, 1967; Constantinou, 1974; Gosling and Dixon, 1974; Tsuchida and Yamaguchi, 1977; Morita *et al.*, 1981). The propagating contraction wave moves the urine in front of it in a distal direction. Under normal flows, the urine between two contractions waves takes the form of a bolus which is propelled distally until it passes through the ureterovesical junction to enter the bladder. An efficient contraction wave completely coapts the ureteral wall (Woodburne and Lapides, 1972).

The electromyogram of ureteral peristalsis resembles that of the heart (Orbelli and von Brucke, 1910) (Fig. 1) and if one places two electrodes on the ureter, each wave would be detected first by the proximal and then by the distal electrode. The electrical activity propagates distally from cell to cell across low resistance areas of close cell-to-cell contact referred to as

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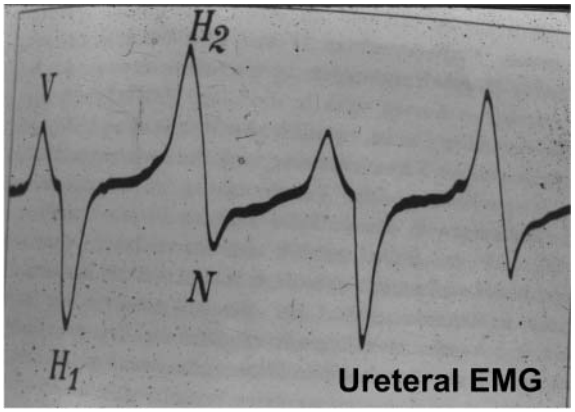


Fig. 1. Ureteral Electromyogram (EMG) showing resemblance to cardiac EMG. From Orbelli and von Brücke (1910).

intermediate junctions (Uehara and Burnstock, 1970; Libertino and Weiss, 1972). Conduction velocity in the ureter is relatively slow ranging from 2 to 6 cm/sec (Kobayashi, 1964; Kuriyama *et al.*, 1967). Conduction velocity in cardiac Purkinje fibers ranges from 1.5 to 2 m/sec (Rosen *et al.*, 1981) and conduction velocity in the dorsal and ventral roots of the spinal cord range from 10–100 m/sec (Biscoe *et al.*, 1977).

Conduction in the ureter is similar to that in cardiac tissue, even to the extent that the Wenckebach phenomenon, a partial conduction block, has been demonstrated in the ureter as it has been in specialized cardiac fibers (Weiss *et al.*, 1968) (Fig. 2). When the *in vivo* ureter is stimulated electrically at a rate slower than the spontaneous ureteral peristaltic rate, the ability to initiate a ureteral response with each stimulus is inconsistent. This is because some of the electrical stimuli are being applied during the refractory period created by the spontaneous ureteral peristaltic activity. As the rate of electrical stimulation is increased, a rate is reached at which there is a 1:1 correspondence between the stimulus and the response to the stimulus. This rate of electrical stimulation is relatively slow, but greater than the spontaneous peristaltic rate of the ureter. With further increases in the rate of stimulation various forms of conduction block are noted because stimuli are applied during the refractory period created by the previous electrically induced contraction. At a critical rate, Wenkebach periods were observed, and with further increases in stimulation rate, 2:1 and higher degrees of block between stimulus and response ensue. Wenkebach periods are characterized by a progressive increase in the interval between the stimulus and the response to the stimulus until finally a stimulus does not yield a response. Since the magnitude of increase in the stimulus to response interval decreases with each stimulus until a response is missed, there is an apparent acceleration of the electrogram response before each pause. The interval of the pause is less than twice the interval between the previous two responses. At times spontaneous Wenckebach periods are observed in the ureteral electrograms of unstimulated ureters, that is, the interval between recorded electrical impulses decreases with an apparent increase in the frequency of electrical activity until a pause

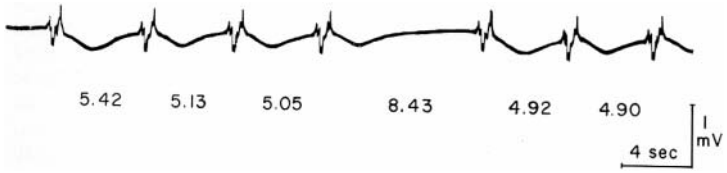


Fig. 2. Ureteral EMG from dog showing spontaneous Wenckebach cycles. Numbers indicate interval between successive ureteral electrogram complexes in seconds. From Weiss *et al.* (1968).

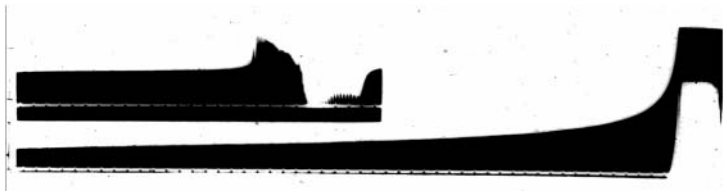


Fig. 3. Spontaneous slow rise in negativity recorded from pacemaker region in the guinea pig. From Bozler (1942).

occurs and the process repeats itself.

In 1942, Bozler was the first to demonstrate pacemaker activity at the extreme renal end of the upper urinary tract (Bozler, 1942) (Fig. 3). He studied isolated ureters from the dog, cat and guinea pig which were dissected up to the renal pelvis. He localized the pacemaker to the extreme renal ends of the ureter by placing two external electrodes close together on the ureter and observing which of the leads became negative first. The procedure was repeated, shifting the leads in the direction from which the impulses were arising. At the renal end of the collecting system the biphasic surface electrogram became inverted, indicating the localization of the site of impulse initiation. Using small surface electrodes, Bozler also demonstrated the presence of spontaneous subthreshold changes in transmembrane potential preceding the action potential in the region of the pacemaker. These potentials occurred in two forms: 1) a gradual depolarization, similar to spontaneous diastolic depolarization in the heart, which upon reaching the threshold potential gave rise to a conducted action potential; and 2) oscillations in the transmembrane potential, which gradually increased in magnitude until an action potential occurred. Irisawa and Kobayashi in 1962 using intracellular microelectrodes demonstrated a gradual depolarization of the cell membrane preceding the action potential of the isolated guinea pig ureter (Irisawa and Kobayashi, 1962).

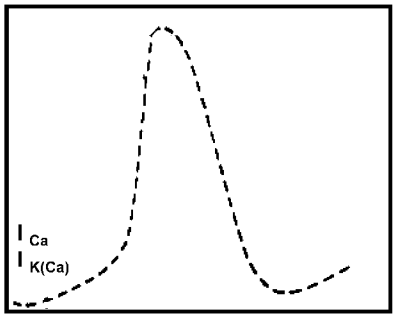
Weiss and associates using techniques classically used to define the sinus node origin of the cardiac impulse (Eyster and Meek, 1913) localized a pacemaker in the proximal portion of the *in situ* canine upper urinary tract (Weiss *et al.*, 1967). Unipolar surface electrodes were used since the unipolar electrogram provides information with respect to the position of an electrode relative to the point of origin of electrical activity (Hoffman and Cranefield, 1960). If an

electrode is placed at a site where a wave of electrical activity terminates, that is at a site where all activity is approaching the electrode and none passing away, the electrogram consists only of a positive deflection. If the electrode is placed at a site along the course of an electrical wave, the electrogram is biphasic with a positive deflection as the wave is approaching the electrode followed by a negative deflection as the wave is proceeding away from the electrode. At the site of origin of electrical activity, the unipolar electrogram shows an initial rapid negative deflection without a previous positive deflection, indicating that all the electrical activity is passing away from the electrode and none is approaching the electrode. As the unipolar electrode was moved toward the proximal portion of the *in vivo* canine upper urinary tract, a tracing of initial negativity was recorded, indicating an underlying pacemaker site.

The electric properties of excitable tissues depend on the distribution of ions across the cell membrane and on the relative permeability of the cell membrane to these ions. The resting membrane potential (RMP) of a ureteral muscle cell in a non-excited or resting state is determined primarily by the distribution of potassium ions (K^+) across the cell membrane and by the relative selective permeability of the membrane to K^+ (Hendrickx *et al.*, 1975). The RMP in the ureter and in other smooth muscles is considerably less than the K^+ equilibrium potential, with values of –33 to –70 mV (Kuriyama *et al.*, 1967). The resting membrane potential is primarily dependent on tetraethylammonium (TEA) and charbydotoxin sensitive Ca^{2+}-dependent K^+ current ($I_{K(Ca)}$). The RMP of a non-pacemaker cell is stable and the cell becomes activated when it is excited by an external stimulus whether it be electrical, mechanical or chemical or by propagation of electrical activity from an adjacent activated cell.

When the ureteral cell is excited, its membrane loses its preferential permeability to K^+ and becomes more permeable to Ca^{2+} ions that move inward across the cell membrane primarily through fast L-type Ca^{2+} channels and give rise to the upstroke of the action potential (Kobayashi, 1965; Sui and Kao, 1997a, 1997b). Sodium (Na^+) ions also may play a role in the upstroke of the ureteral action potential (Kobayashi, 1964, 1965). The rate of rise of the upstroke of the ureteral action potential is relatively slow, 1.2 ± 0.06 V/sec in the cat, which accounts for the slow conduction velocity in the ureter (Kobayashi, 1969). After reaching the peak of its action potential, the membrane maintains a depolarized state for a period of time (plateau of the action potential) before the transmembrane potential returns to its resting level (repolarization). The plateau phase depends on the persistence of an inward Ca^{2+} current, Na^+ influx through a voltage-dependent Na^+ channel, an inward calcium dependent chloride current ($I_{Cl(Ca)}$), in the rat but not in the guinea pig ureter, and the weakness of an outward voltage-gated and Ca^{2+}-activated K^+ current (Kuriyama and Tomita, 1970; Imaizumi *et al.*, 1989; Smith *et al.*, 2002). In the guinea pig there are oscillations on the plateau of the action potential which appear to depend on the repetitive activation of an inward Ca^{2+} current and of an outward Ca^{2+}-dependent K^+ current (Kuriyama and Tomita, 1970; Imaizumi *et al.*, 1989). Repolarization is due to activation of an outward Ca^{2+}-dependent K^+ current ($I_{K(Ca)}$) which is sensitive to inhibition by tetraethylammonium (TEA) and charbydotoxin and of a voltage dependent Ca^{2+}-insensitive outward K^+ current (I_{TO}) that is TEA insensitive and 4-aminopyridine (4-AP) sensitive (Imaizumi *et al.*, 1989, 1990; Lang, 1989; Sui and Kao, 1997c).

Pacemaker cells are cells in which electric activity arises spontaneously. Pacemaker fibers



•Opening and Slow Closure of Voltage-Activated L-Type Ca^{++} Channels
•Prostanoids Amplify

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•Opening and Closure of Voltage and Ca^{++} Dependent K^+ Channels
•Increased Inward Movement on Na^+
•Decreased in Pump Extrusion of Na^+ From Cell

Fig. 4. Ionic conduction underlying pacemaker activity in upper urinary tract.

differ from non-pacemaker fibers in that their resting potential is lower (less negative) and does not remain constant but rather undergoes a slow spontaneous depolarization (Lang and Zhang, 1996). When the membrane potential reaches the threshold potential, the upstroke of an action potential occurs. Changes in the frequency of action potential development in pacemaker cells may result from a change in the level of the resting potential, a change in the level of the threshold potential, or a change in the rate of slow spontaneous depolarization. The spontaneous depolarization characteristic of pacemaker activity in the upper urinary tract is due to the opening and slow closure of voltage-activated L-type Ca^{2+} channels which are amplified by prostanoids (Santicioli *et al.*, 1995). This activity is opposed by the opening and closure of voltage and Ca^{2+} dependent K^+ channels (Lang and Zhang, 1996) (Fig. 4). Increased inward movement of Na^+ and decreased pump extrusion of Na^+ also are factors in the spontaneous depolarization of the membrane which is characteristic of pacemaker activity. It has been suggested that prostaglandins and excitatory tachykinins, released from sensory nerves help maintain autorhythmicity in the upper urinary tract and that autonomic neurotransmitters have little role in maintaining pyelo-ureteral motility (Lang *et al.*, 2001; 2002).

Gosling and Dixon provided morphologic evidence of specialized pacemaker tissue in the proximal portion of the urinary collecting system. Atypical muscle cells were identified in the wall of the renal calix and pelvis (Gosling, 1970). These cells are smaller than typical smooth muscle cells observed in the upper urinary tract, have a cytoplasm that stains less well with Masson trichrome, and have smaller nuclei than other smooth muscle cells. Furthermore, they lack staining for non-specific cholinesterase (Dixon and Gosling, 1982). Species differences exist in the location of these atypical pacemaker smooth muscle cells. In species possessing a relatively simple uni-calyceal collecting system such as the dog, cat, rabbit, rat and guinea pig, atypical pacemaker cells extend in a continuous layer from the region of the renal pelvis

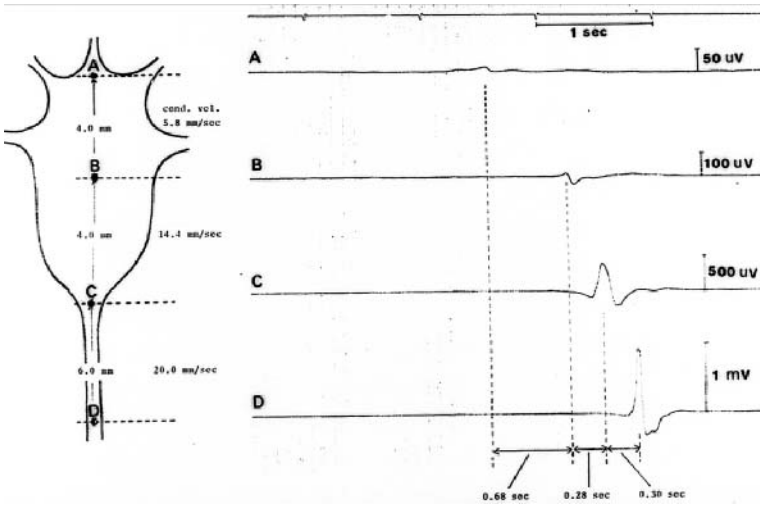

Fig. 5. Tracing of EMGs in dog ureter with impulses starting at a pacemaker region and propagating distally. With permission of Takashi Morita.

attachment to the parenchyma to the region of the uretero-pelvic junction (Gosling and Dixon, 1974). In contrast, in species with a more complex multi-calyceal system such as the pig, sheep and human the atypical pacemaker cells are confined to the area of the major and minor calyces.

In a multi-calyceal kidney, Morita and associates (1981), using extracellular electrodes, recorded low-voltage potentials that appeared to be pacemaker potentials from the border of the pig minor calyces and the major calyx with the contraction rhythm varying between each calyx. They observed the onset of ripple-like contractions arising spontaneously at the border between the upper, middle, and lower major calyces and their minor calyces (Morita *et al.*, 1981; Tsuchida *et al.*, 1981). Electromyograms (EMGs), with a constant discharge interval, were recorded from the same regions suggesting that these may be pacemaker potentials. The waves originating from the upper, middle and lower calyces propagated at different times toward the ureter. In the unicalyceal dog kidney similar contractions were initiated at the pelvi-calyceal border and propagated distally toward the ureter (Morita, 1978). The EMGs recorded at the pelvi-calyceal region of the canine upper urinary tract *in vivo* were characterized by a two phasic slow-rising positive waveform, with no initial negative deflection, whereas EMGs more distally had a higher amplitude and a three phasic wave form with an initial negative deflection (Morita *et al.*, 1984) (Fig. 5). At normal states of hydration the interval between discharges is less in the pelvi-calyceal region than at more distal regions and the discharge intervals at these more distal regions are approximately integral multiples of the discharge intervals of pacemaker potentials measured in the pelvi-calyceal region (Morita *et al.*, 1984; Kondo *et al.*, 1985). The discharge interval increases the more distally one records the electromyograms. This is indicative of a conduction block as the electomyographic wave moves more distally. With diuresis, the discharge interval at the pelvi-calyceal or pacemaker region remains constant whereas the discharge intervals of the EMGs more distally shorten until there is a 1:1 correspondence

between all recorded EMGs indicating that a conduction block is not apparent at high flows. Thus, diuresis does not affect the frequency of pacemaker discharge, but decreases conduction block in the propagation of pelviureteral electrical activity. Norepinephrine decreased the interval between discharges along the ureter but had no affect on the frequency of pacemaker potentials. Isoproterenol also had no affect on the interval of pacemaker discharge, but increased the interval between discharges along the ureter (Morita and Suzuki, 1984; Kondo *et al.*, 1985). Tetrodotoxin and blockers of the autonomic nervous system, both parasympathetic and sympathetic, have little effect on peristalsis suggesting that autonomic neurotransmitters have little role in maintaining pyeloureteral motility (Morita and Tsuchida, 1983; Lang *et al.*, 2001; 2002).

Capsaicin-sensitive sensory afferents and the endogenous release of tachykinins and prostaglandins are involved in the maintenance of normal ureteral peristalsis (Lang *et al.*, 2002). Prostaglandins are synthesized from the fatty acid, arachidonic acid, by enzymatic reactions involving two cyclooxygenase (COX) isoforms, COX-1 and COX-2 (Vane, 1998). COX-1 is constitutively expressed and is involved in the regulation of normal physiologic processes, whereas COX-2 is induced by processes such as inflammation and mitogenesis (Mitchell and Warner, 1999). COX inhibitors have been shown to affect pacemaker potentials and to inhibit spontaneous activity of pyeloureteral smooth muscles suggesting that prostanoid generation is mandatory for the maintenance of ureteral peristalsis (Kimoto and Constantinou, 1991; Santicioli *et al.*, 1995; Davidson and Lang, 2000). It is postulated that prostaglandins and tachykinins maintain autorhythmicity in the upper urinary tract through the maintenance of calcium mobilization. COX-1 and COX-2 immunostaining is most prominent in the urothelial layer of the rat and guinea pig renal pelvis and ureter, although there is some light immunostaining within the muscle layer of these structures (Lang *et al.*, 2002).

Klemm and associates (1999), using electron and confocal microscopy, identified 'atypical' smooth cells predominately at the pelvi-calyceal junction of the guinea pig upper urinary tract that fired 'pacemaker' potentials at a frequency higher than 'driven' action potentials recorded in 'typical' smooth muscle cells throughout the renal pelvis and ureter. These atypical smooth muscle cells, in contrast to typical smooth muscle cells, have less than 40% of their cellular area occupied by contractile filaments, and demonstrate sparse immunoreactivity for α-smooth muscle actin (Klemm *et al.*, 1999; Lang *et al.*, 2001). These atypical pacemaker cells are spindle shaped, 90–230 μm in length, and their electrical activity consists of simple waveforms with alternating depolarizing and repolarizing phases that occur at a relatively rapid frequency of 8–15/min. Pacemaker potentials have a lower resting membrane potential (RMP), approximately –40 mV, a slower rate of rise, and a lower amplitude than action potentials recorded from non-pacemaker cells. These 'pacemaker' waveforms have a slowly developing prepotential and a smooth transition into the upstroke of the action potential (Lang *et al.*, 1998) (Fig. 6). In the guinea pig these atypical, presumably pacemaker cells comprise >80% of the cells at the pelvi-calyceal junction, about 15% of the cells in the proximal renal pelvis but are not present in the distal renal pelvis nor in the ureter (Klemm *et al.*, 1999). Electrical recordings correlate with histologic findings in that pacemaker potentials were recorded from 83% of cells at the pelvi-calyceal junction, from 15% of cells in the proximal renal pelvis, but not from cells in the distal

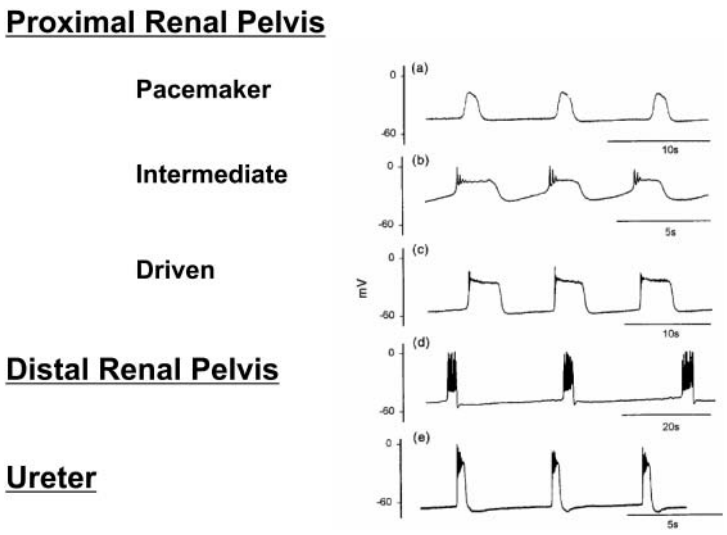

Fig. 6. Action potentials recorded from proximal and distal renal pelvis and ureter of guinea pig. Modified from Lang *et al.* (1998).

renal pelvis or ureter (Klemm *et al.*, 1999).

Most muscle cells of the ureter (100%), distal renal pelvis (97.5%), and proximal renal pelvis (83%) are typical non-pacemaker smooth muscle cells with typical action potentials. These spindle shaped typical smooth muscle cells are longer (150–400 μm) than the atypical pacemaker cells and driven action potentials that are recorded from these cells fire at a lower frequency (3–5/min) than pacemaker potentials. In the guinea pig these action potentials consist of an abrupt, rapidly rising initial spike followed by a period of membrane oscillations and then a plateau phase (Lang *et al.*, 1998). Repolarization of these 'driven' action potentials occurs rapidly and is followed by an after hyperpolarization which reaches a maximum diastolic potential of approximately –60 mV.

Lang *et al.* (1998) described fibroblast-like cells in the proximal portion of the guinea pig renal pelvis that resemble the interstitial cells of Cajal (ICC), which serve as pacemaker cells in the intestine. These 'ICC-like' cells are irregular shaped with oval nuclei and many branching interconnecting processes and they contain numerous mitochondria, caveolae and a prominent rough endoplasmic reticulum. The 'ICC-like' cells are not immunoreactive for α-smooth muscle actin, which is present in 'typical' smooth muscle cells, or for c-Kit, a tyrosine kinase receptor which is expressed in intestinal ICC pacemaker cells (Klemm *et al.*, 1999). Electrical recordings from these cells demonstrate action potentials with properties intermediate to pacemaker and driven action potentials. In the guinea pig, these intermediate action potentials have a single spike, a plateau without the superimposed spikes seen in driven action potentials and a more slowly developing repolarization phase than that seen in 'typical' smooth muscle cells. Intermediate action potentials are noted in 11–17% of cells at the pelvi-calyceal junction and in both the proximal and distal renal pelvis (Lang *et al.*, 2002). These 'ICC-like' cells in the upper urinary tract do not appear to be pacemaker cells but rather may provide for preferential

conduction'of electrical signals from pacemaker cells to typical smooth muscle cells of the renal pelvis and ureter (Klemm *et al.*, 1999).

Morita *et al.* (1981) in studies of an *in vitro* pig kidney model, observed waves originating at different times from the upper, middle and lower calyces that propagated toward the ureter. The electrograms recorded from the different calyces were not synchronous. These data are in accord with the presence of multiple pacemakers in the multi-calyceal pig kidney (Constantinou *et al.*, 1977; Morita *et al.*, 1981). Pressure changes in the region correlated in a 1:1 ratio with the electrical activity. When infusion was performed into a given calyx, peristalsis only from that calyx propagated toward the pelvis and ureter and the electromyogram discharge interval in the pelvis and ureter were multiples of the discharge frequency of the perfused calyx (Morita *et al.*, 1981). These data suggest that the intracalyceal excretion of urine is an important factor in the propagation of the pacemaker contraction. The multicalyceal porcine kidney is a multi-pacemaker system with pacemakers in the various calyces. Both synchrony and dyssynchrony can occur between the pacemaker activity arising from the individual calyces (Yamaguchi and Constantinou, 1989). Phase locking, phase oscillation, and phase divergence occurs between the contractile activity in the individual calyces. With phase locking, the calyceal contractions of the different calyces are coordinated. Under such conditions pelvic contractions are related to contractions of all of the calyceal regions. With phase oscillation, the region of the calyceal system evidencing the highest frequency is associated with the pelvic contractions. With phase divergence, the calyces contract at different frequencies and pelvic contractions are not correlated with calyceal activity. It has been postulated that multiple pacemakers may fire simultaneously as coupled oscillators and that their summation gives rise to the ureteral action potential and peristaltic activity (Golenhoffen and Hannappel, 1973; Constantinou and Yamaguchi, 1981). In contrast in the sheep kidney, pacemakers appear to fire individually and with time, pacemaker activity shifts from one site to another along the pelvi-calyceal border (Lammers *et al.*, 1996). In the sheep kidney at any one time, it appears that one single pacemaker is responsible for a particular spread of activation, and fusion of activity originating from two or more pacemakers does not take place. In this animal, pacemaker activity is not present in the renal pelvis or at the uretero-pelvic junction (UPJ). The spread of activity from the pacemaker site is slow, heterogeneous and contorted, and multiple areas of partial or total conduction block are seen at all levels of the renal pelvis and at the UPJ.

Although the primary pacemaker for ureteral peristalsis is located in the proximal portion of the collecting system, other areas of the ureter may act as latent pacemakers. Under normal conditions, the latent pacemaker regions are dominated by activity arising from primary pacemaker sites. When a latent pacemaker site is freed of its domination by the primary pacemaker, it, in turn, may act as a functional pacemaker. To demonstrate latent pacemaker sites, Shiratori and Kinoshita (1961) transected *in vivo* dog ureters at various levels. Before transection, peristaltic activity arose from the primary pacemaker located in the proximal portion of the collecting system. When the ureter was transected at the UPJ, antiperistaltic waves of lower frequency than the previous normoperistaltic waves originated from the ureterovesical junction (UVJ). Division of the ureter at the UVJ did not affect the normoperistaltic waves. After division of the midureter, the normoperistaltic waves in the upper segment

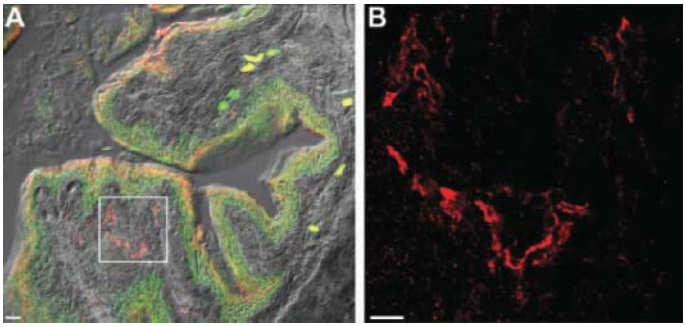

Fig. 7. Confocal image of the network of interstitial cells of Cajal (ICC)-like cells expressing c-kit immunoreactivity (red fluorescence) in mouse ureter (A). B. High-power image offset from Pezzone *et al.* (2003).

remained unchanged, and the lower segment demonstrated antiperistaltic waves, which originated at the UVJ at a frequency less than that of the normoperistaltic waves in the upper segment. Thus, cells at the UVJ of the dog may act as pacemaker cells when freed of control from the primary proximally located pacemaker. Latent pacemaker cells are present in all regions of the ureter (Imaizumi *et al.*, 1989; Meini *et al.*, 1995).

c-Kit is a tyrosine kinase receptor that promotes cell migration and proliferation of melanoblasts, hematopoietic progenitors and primordial germ cells. Mice expressing mutant inactivating c-Kit alleles lack intestinal interstitial cells of Cajal (ICC) and have abnormal intestinal peristalsis. These mice develop bowel obstruction showing that c-Kit is important in the development of pacemaker activity and peristalsis of the gut (Der-Silaphet *et al.*, 1998). Pezzone *et al.* (2003) identified ICC-like c-Kit positive cells in the proximal portion of the mouse ureter (Fig. 7). These investigators suggested that the difference from previous studies in the guinea pig upper urinary tract in which c-Kit positivity was not identified in ICC-like cells (Klemm *et al.*, 1999) may have been due to species differences, the C-kit antibody used, and/or the fixation methods employed. Calcitonin gene-related peptide (CGRP), present in sensory axons of the ureter, may play a role in modulation of ureteral pacemaker cells (Maggi and Giulani, 1991). c-Kit expression was noted to be up-regulated by gestational day 15.5 in the embryonic murine ureter, which is prior to the development of unidirectional ureteral peristaltic contractions (David *et al.*, 2005). Incubation of isolated cultured embryonic murine ureters with antibodies that neutralize c-Kit activity altered ureteral morphology and inhibited unidirectional peristalsis. c-Kit positive cells have been identified in the human ureter (Metzger *et al.*, 2004) and in the human UPJ (Solari *et al.*, 2003). In the presence of obstruction, c-Kit positive ICC-like cells at the UPJ are sparse or absent (Solari *et al.*, 2003).

Thus, pacemaker activity is present in the proximal portion of the upper urinary tract and is influenced by prostaglandins and sensory nerves. The expression of c-Kit correlates with the development of peristaltic activity in the embryonic ureter (Fig. 8).

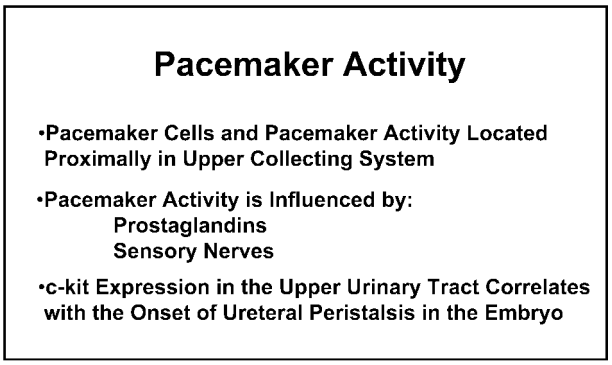

Fig. 8. Pacemaker activity.

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