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Pacemakers in the Upper Urinary Tract

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1. Introduction

In the upper urinary tract, the mechanisms by which urine is transported from the kidney to the bladder remain little understood. For the last 35 years, it has been thought that pyeloureteric autorhythmicity arises in specialized electrically active atypical smooth muscle cells (SMC) that have many of the morphological and electrical features of cardiac sino-atrial cells and are predominantly located in the proximal regions of the ureteropelvic junction (UPJ). However, increasing evidence indicates that ICC-like cells (ICC-LC), displaying many of the morphological features of intestinal ICC and immuno-reactivity to antibodies raised against the c-*Kit* proto-oncogene, are present in the UPJ of a number of mammals. These cells are c-Kit-positive in upper urinary tract (UUT) of mouse and Human, c-kit-negative in guinea pig (Lang JR et al 2006.) c-*Kit* immuno-reactivity also appears developmentally at the same time of coordinated unidirectional peristaltic contractions in mouse embryonic ureters in organ culture. Moreover, the development of the ureteric structure and peristaltic contractions in organ colture can be prevented upon exposure to the c-Kit antibody, ACK45 (David SG et al 2005), suggesting that ICC-LC play a crucial role in promoting pyeloureteric peristalsis.

ICCs were first described by Ramon Y Cajal in 1893 as primitive neurons in the gastrointestinal system (GIS) (Lang JR et al 2006; Cajal SR 1893). Infact, ICCs were firstly found in relation to the Auerbach plexus, but also in the submucosal plexus and between the muscle layers. Moreover, mice with spontaneous mutations of the c-kit genes, and that are deficient in ICCs, lack spontaneous slow waves in the intestine and display uncoordinated peristalsis (Streuker et al 2003). Further investigations revealed that ICCs play a role as pacemaker cells, between neurons and smooth muscle cells, are originally derived from the mesenchymal tissue, and are responsible for conduction of the slow wave electrical potential for peristaltic movements (Sanders KM 1996). Local decreases in or a lack of c-kit immunoreactivity on ICCs in the gut have been detected in Hirschsprungs's disease, infantile hypertrophic pyloric stenosis, and slow transmission constipation. Recently, mucosal ICC were reported at the human ureteropelvic junction (UPJ), the submucosal and muscolar layers of the rat vase deferents, between the stroma of smooth muscle layers and glandular layers of guinea pig prostate, between the smooth muscle fibers and neurons of guinea pig bladder and in the rabbit urethra (Solari V et al 2003). Also in the UUT, ICCs

have shown to be responsible for initiating, coordinating and producing ureteropelvic peristaltic movements at the intercaliceal area, providing the passage of urine from the caliceal system through the ureter to the bladder (Sergeant et al 2000).
Several studies have been performed in uni-calyceal mammals as mouse, dog, rat, guinea pig and rabbit as well in multi-calyceal species such as human and pig. In multi-calyceal mammals minor calyces combine to form several major calyces, which fuse together to form the renal pelvis. In the isolated pig renal pelvis, small amplitude contractile and electrical activity originates at the border of the major and minor calyces. Upon injection of saline into the upper calyx, these peristaltic waves propagate through the lower calyces to the renal pelvis and the UPJ. During periods of low urine production only a few of the muscle contractions in the renal pelvis travel through to the ureter (Morita T et al 1981). With higher rates of diuresis, transmission improves until there is a one-to-one propagation of all contractions to the ureter (Constantinou CE et al 1974, 1976). The ureter in human and pig displays spontaneous contractions *in vitro*. In contrast the ureter in dog, rabbit, pig and rat contracts spontaneously *in vitro* only in the presence of excitatory agonists (Morita T et al 1986; Patacchini R et al 1998) or if the renal pelvis is left attached (Golenhofen K et al 1973; Gosling JA et al 1971; Lang RJ et al 2001). In both uni-calyceal and multi-calyceal mammals, circumferentially cut strips of muscle wall dissected from the same region contract at the same frequency. However contraction frequency decreases with distance from the renal fornix as strips are dissected from the middle and lower calyces, renal pelvis and UPJ (Gosling JA et al 1971; Hannapel J et al 1978; Zhang Y & Lang RJ 1994). Thus researchers have located the primary pacemaker in the most proximal calyceal regions of the renal pelvis.

2. Ultrastructure of the upper urinary tract (UUT)

A compact layer of epithelial cells (mucous membrane) lines the lumen on the full length of the UUT stand, on a lamina propria of varying thickness containing collagen fibrils, myofibroblasts, as well as numerous small blood vessels and unmyelinated axon bundles. A layer of smooth muscle cells (SMC) surrounds the lamina propria. In the most proximal inter-renal regions of attachment of the UUT to the renal fornix, the pelvi-calyceal junction, cells are arranged in an open network, with large areas of intervening connective tissue. In the renal pelvis, SMC are arranged in small randomly oriented bundles, which create a plexiform layer of interconnecting bundles, separated by areas of connective tissue. In contrast the muscle wall of the ureter is arranged into an inner circular and an outer longitudinal layer of closely pace SMC. Surrounding these layers the adventitia is made up of connective tissue and fibroblasts and containing blood vessels, nerve bundles and lymphatic vessels (Notley RG 1978).

3. Atypical, typical smooth muscle and ICC-like cells in the UUT

Two types of smooth muscle cells within the muscle wall of the UUT have been identified under the light and electron microscope: 'atypical' and 'typical' SMC (Gosling JA & Dixon JS 1972,1974). A third population of electrically-active cells has been described in the UUT in human and many mammals (Lang RJ et al 2001; Gosling JA & Dixon JS 1974) which may well play a fundamental role in pyeloureteric autorythmicity.
Atypical SMCs have an irregular morphology and a non-specific cholinesterase. They have been described as long thin cells, having a small nucleus and being irregularly-shaped due to

the presence of many long branching processes. Their contractile myofilaments are arranged in bundles which are separated by large areas of cytoplasm containing Golgi cisternae, granular endoplasmic reticulum and small mitochondria occupying 3% of cell sectional area (Klemm MF et al 1999; Gosling JA & Dixon JS 1972) . They form areas of close apposition with each other and with typical SMC, these appositions being separated by long portions of naked membrane. In uni-calyceal kidneys, atypical SMC were firstly described as forming a discrete layer which begins at the pelvi-calyceal junction and continues the length of the renal pelvis to the UPJ (Dixon JS & Gosling JA 1970; Gosling JA & Dixon JS 1970,1971). In the rat and guinea pig, atypical SMC represent 22% and 80%, respectively, of the SMC present in the pelvi-calyceal junction. (Lang RJ et al 2001; Gosling JA & Dixon JS 1974)

In multi-calyceal kidneys, 'atypical' SMC alone form the muscle coat of each minor calyx. A thin sheet of loosely-arranged atypical SMC extends between the minor calyces creating an open network near the point of attachment to the kidney (Gosling JA & Dixon JS 1972,1974; Dixon JS & Gosling JA 1973,1982), the space between cells being filled with collagen-rich connective tissue and axon bundles (Lang RJ et al 2001; Klemm MF et al 1999; Dixon JS & Gosling JA 1970). A gradual thickening of the wall of the UUT of all mammals with distance from the pelvi-calyceal junction indicates the increasing presence of 'typical' SMC.

'Typical' SMC are described as long spindle-shaped cell, filled by contractile filament and surrounded by a continuous basal lamina and containing a large round/oval shaped nucleus and generally grouped into bundles. In the pig 'typical' SMC are evident in the major calyx, renal pelvis and ureter (Gosling JA & Dixon JS 1974 ; Dixon JS & Gosling JA 1970) . In the guinea pig and rat, typical SMC represent 78–83% and >98% of the SMC in the proximal renal pelvis and UPJ, respectively. The relative proportion of contractile-filament rich typical SMC and atypical SMC has been shown by immuno-staining sections of the pelvi-calyceal junction (P-CJ), renal pelvis (RP) and ureter for α smooth muscle actin, and it has been reported that the intensity of immuno-reactivity for α smooth muscle actin increases along the length of the UUT (Lang RJ et al 2001; Gosling JA & Dixon JS 1974).

ICC-like cells (ICC-LC) are the recently described population of electrically- active cells in the UUT (Lang RJ et al 2001; Gosling JA & Dixon JS 1974) and they seem to play a fundamental role in pyeloureteric autorythmicity. Under the electron microscope, these cells are stellate in appearance, the cytoplasmic area containing an oval-shaped nuclear region, numerous mitochondria (4% of cell sectional area), well-developed Golgi apparatus, but no contractile filaments or immuno-reactivity to α smooth muscle actin. The plasma membrane of these cells also displays a discontinuous basal lamina and numerous calveolae. These interstitial cells form close appositions both 20nm and adherens junctions, with themselves (80% of cells) and SMC. Thus these cells display many of the morphological features used to distinguish ICC, from fibroblasts within the wall of the intestinal tract (Huizinga JD et al 1997; Huizinga JD 2005). In the guinea-pig UUT, ICC-LC lay within in the lamina propria of the pelvi-calyceal region and the renal pelvis and do not form close associations (<30nm) with nerve bundles, nor they were identified in the ureter (Gosling JA & Dixon JS 1974). These cells are also immunoreactive to antibodies raised against c-kit proto oncogene, a member of the receptor-tyrosine kinase family. Several studies described ICC-LC in UUT. Solari *et al.* described that *c-kit* positive cells in human UPJ had a fusiform cell body with 2 distinct dendrites (Solari et al 2003), Pezzone *et al.* described *c-kit* positive cells in the mouse UUT as being stellate in appearance (Pezzone MA et al 2003). Networks of these *c-kit* positive cells were located adjacent to the inner longitudinal muscle layer and between the inner and outer SMC layers (Solari et al 2003, Pezzone MA et al 2003).

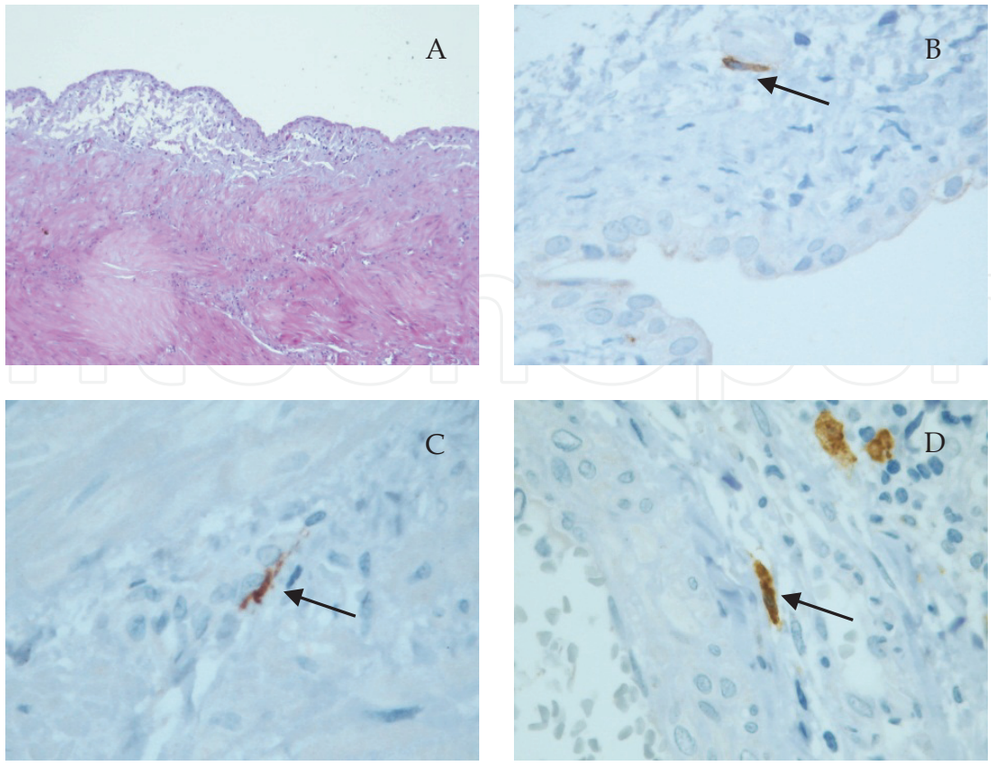

Fig. 1. Ureteral wall showing both the urothelium layer and a portion of smooth muscle layer (A) (H&H, Original magnification 125x) CD117 immunostaining displaying a cytoplasmic immunopositive Cajal cells in subepithelial (B), smooth muscle layer (C) and adventitial (D) sites (arrows), together with some mast-cells (Original magnification 250x)

There is general agreement that the number of these *c-kit* positive cells was greatest in the proximal renal pelvis and decreased with distance from the UPJ (Thompson CB 1995, Metzger R et al 2004, Pezzone MA et al 2003). Differences in technologies and antibodies used when fixing and staining preparations have been evoked to explain the variation of *c-kit* staining observed between species by different laboratories (Sleator W 1955, Pezzone MA et al 2003). Double labelling experiments have discounted the possibility that these c-kit-positive cells are mast cells, fibroblasts or macrophages (Metzger R et al 2004).

It is becoming clear that ICC and ICC-like cells in various urogenital and intestinal tissues can also be divided into a number of subpopulations on the basis of their immuno-reactivity or -negativity to c-kit, vimentin, actin filaments, ion channel populations (Lang RJ et al 2001; Gosling JA & Dixon JS 1974), receptors (Van der AaF et al 2004) and gap junction subunits. In human and less frequently pig, another population of 'vertically-orientated' *c-kit* positive spindle shape cells was present between the basal cells of the transitional epithelium (Metzger R 2004). The number of these radially arranged *c-kit* positive cells was greatest in the intermediate ureter and lowest in the renal pelvis. The role of these *c-kit* positive cells remains little unknown but it is interesting that these cells are present in an area that is richly innervated by sensory nerves suggesting that these ICC may be acting as an intermediate between the afferent innervation and the urothelium and maybe they are responsible even for initiating, coordinating and producing ureteropelvic peristaltic movements at the intercaliceal area, providing the passage of urine from the caliceal system through the ureter to the bladder.

4. Pacemaking in the UUT and electrical recordings

Pressure recordings and intracellular and extracellular electrophysiological investigations have established that every peristaltic contraction of the renal pelvis and ureter is preceded by a complex 'ureteric' or 'driven' action potential. Driven action potentials have a time course consisting of an initial slow membrane depolarization followed by a single or multiple rapidly-rising spike(s), which partially repolarize to a plateau phase (100ms to > 1s in duration) followed by a second repolarization to an afterhyperpolarization which decays back to the resting membrane potential (Sleator W et al 1955, Shuba MF 1977).

It has been also established that the probability of recording ureteric or 'driven' action potentials increased with distance from the renal fornix, from 75% of cells in the proximal renal pelvis to 89% in the distal renal pelvis and 100% of cells in the ureter. This gradient of recording action potentials with distance is due to an increasingly more negative membrane potential and a decreasing frequency of action potential discharge with distance from the renal fornix.

Atipical SMC and ICC-LC are described as pacemakers cells, essential for the induction and propagation of contractile electrical pulse.

Atypical SMC seems to be essential pacemaker cells of pelviureteric peristalsis. Investigators have envisaged that autorhythmicity within the upper urinary tract involves a 'chain of coupled linear oscillators' with the most proximal oscillator firing at the highest frequency, The decreasing presence of 'atypical' SMC with distance from the papillate base has been correlated with the decreasing frequency of contraction.

Atypical SMC have higher frequency (8-15 min-1) transient potentials of a simple waveform, those potentials are frequently (83% of cells) recorded in short "atypical" SMC (90–230μm in length) in the pelvi-calyceal junction of the guinea pig renal pelvis (Patacchini R et al 1998; Klemm MF et al 1999; Seki N et al 1990, Tsuchida S et al 1992). These transient potentials were recorded less frequently in the proximal renal pelvis (10% of recordings) and never in the ureter (Lang RJ et al 2001; Gosling JA & Dixon JS 1974). High frequency transient potentials and driven action potentials in the renal pelvis and ureter have been demonstrated by research groups, to be abolished by nifedipine, suggesting that Ca2+ entry through voltage gated L-type Ca2+ channels is essential in the initiation, maintenance or propagation of these electrical events. This model implies that the intrinsic frequency of pacemaking atypical SMC decreases with distance from the papilla base which would require morphologically similar cells having different expression profiles of voltage- and Ca2+-activated ion channels and pacemaking apparatus as their location increases with distance from the papilla.

Diuresis also has an important role in ureter peristalsis. It has been suggested that diuresis to distend the muscle wall which increases, in an unknown manner, the 'coupling' of the pacemaker regions in the longitudinal direction until the highest frequency oscillator in the proximal regions entrains the oscillators in the distal regions of the renal pelvis.

Furthermore simultaneous extracellular recordings from numerous sites on the sheep renal pelvis have revealed that only one pacemaker region on the pelvi-calyceal border is active at any one time and that the pathway of conduction might meander throughout the renal pelvis. The site of the pacemaker signal on the pelvi-calyceal border can shift spontaneously, conduction delays or block of the wave of excitation can occur at any point or time (Lammers WJ et al 1996). These observations do not support the concept of summation of subthreshold pacemaker activity. Rather it suggests that one pacemaker region in the proximal portion of the UUT dominates to drive neighbouring regions and that conduction

block is a dynamic process and modulated by a number of factors such as wall stress or the hormonal/neurotransmitter/prostaglandin milieu. These mechanisms may explain the conduction block between the renal pelvis and the ureter evident *in vivo* under conditions of low urine production which is relieved during periods of increased diuresis.
ICC-LC have been described as a population of active cells which may well be responsible for additional autorythmicity. A number of investigators have demonstrated that ICC-LC form close appositions with themselves and with neighboring typical and atypical SMC, suggesting electrical connectivity and conduction.
Intracellular microelectrode impalements have been made from the serosal surface of the pelvi-calyceal junction and renal pelvis of the guinea pig and it has been that 11–17% of cells fired spontaneous action potentials with a distinctive time course consisting of a single spike followed by a quiescent plateau and a rapid repolarization. (Klemm MF et al 1999).
In the guinea pig UUT contractions occur regularly from a stable baseline at a frequency (4–7 min) essentially similar to the frequency of driven action potential discharge and lower than the frequency of discharge of transient potentials (Zhang Y et al 1994; Lang RJ et al 2002). Spontaneous transient potentials arise in atypical SMC and propagate to neighbouring typical SMC and ICC-like cells, triggering driven and intermediate action potentials, respectively.
The mechanisms involved in the generation and propagation of pacemaker potentials in SMC display considerable variation between tissues and species.
In conclusion, except for the very proximal regions of the UTT and distal ureteric regions, it looks that two populations of pacemaker cells, atypical SMC and ICC-LC, are present in any portion of UUT and that the drive of each pacemaker system on any typical SMC bundle varies with distance from the papilla base. Importantly, to the best of our knowledge, there aren't any pharmacological agents at present that selectively identify, block or activate the drive of either pacemaker system. Although c-kit antibody binding to unfixed tissues allows for the identification and selective recording from c-kit-positive ICC-LC, there are no vital stains selective for atypical SMC or c-kit-negative ICC-LC to allow a similar targeted examination of their influence on muscle wall contractility. Anyway, a complete electrophysiological and pharmacological profile of c-kit- positive/negative ICC-LC and atypical SMC at the single cell level and the establishment of any species differences or changes in properties might be crucial before the development of a complete model of UPJ autorhythmicity.
The renal pelvis and ureter represent a functional system with myogenic excitation, generation and conduction. The coordination between renal pelvis and ureteral peristalsis is an important part of the hydrodynamics of the upper urinary tract. Contraction waves arising from the upper and urinary tract, and propagation may require the direct involvement of ICCs, which are the pacemaker cells in SMC. As in gastrointestinal motility, ICCs may have a significant role in the propagation, coordination and modulation of UUT peristalsis. As in the gastrointestinal tract damage, several studies have been done to identify a possible pathogenetic factor of altered ICC in genitourinary disease as primary vesicoureteral reflux, congenital ureteropelvic junction obstruction and primary obstructive megaureter.

5. Congenital ureteropelvic junction obstruction

Congenital ureteropelvic junction (UPJ) obstruction is the most common cause of neonatal hydronephrosis with a frequency of 1/1,000 to 2,000 newborns. Previous and recent studies

showed abnormal innervation patterns and abnormalities of smooth muscle or collagen in UPJ cases, including absent or deficient muscle and muscular malorientation, suggesting a basis for disordered function and obstruction (Solari V et al 2003).

The renal pelvis and ureter represent a functional system with myogenic excitation, generation and conduction. The coordination between renal pelvis and ureteral peristalsis is an important part of the hydrodynamics of the upper urinary tract. Contraction waves arising from the upper urinary tract, and propagation may require the direct involvement of ICCs, which are the pacemaker cells in smooth muscle. As described, ICCs may have a significant role in the propagation, coordination and modulation of ureteropelvic peristalsis. Decreased expression of c-kit positive ICCs in UPJ obstruction may cause the failure of transmission of peristaltic waves across the UPJ, resulting in the failure of urine to be propelled from the renal pelvis into the ureter in UPJ obstruction. Solari et al (Solari V et al 2003) examined the status of UPJ innervation using immunohistochemistry with antiperipherin antibody (type III intermediate filament, a specific marker for peripheral neurons, and nerve fibers). Peripherin immunoreactive nerve fibers were markedly decreased in obstructed UPJ samples. So in patients with UPJ obstruction there is not only defective intramuscular innervation of UPJ, but also altered distribution of ICCs, which are coordinators of peristaltic activity. The lack or deficient expression of ICCs in the UPJ may lead to defective generation of pacemaker activity, thus, causing peristaltic activity dysfunction.

The lack or absence of c-kit positive ICCs in obstructed UPJ specimens suggests that this might be responsible for motility disturbance of the upper ureter. The possible link between absent ICCs and other features reported in obstructed UPJ cases, such as neuronal depletion in the muscle layers, justify additional studies. Further investigations of ICCs are still necessary to understand better the pacemaker mechanism in the human upper urinary tract and the unknown etiology of the failure of spontaneous contractions to propel urine from the renal pelvis through the ureter in patients with UPJ obstruction.

6. Primary vesico-ureteral reflux

Primary vesico-ureteral reflux (VUR) is thought to be caused by a congenital structural deficiency of the trigonal vesico-ureteral junction (VUJ) due to maturational abnormalities. The VUJ represents the boundary line between the low-pressure upper urinary tract and the high variable pressure of the lower urinary tract. It protects the upper tract from reflux using active and passive antireflux mechanisms. The most common explanation of a competent valve mechanism is passive compression of the roof of the intravesical ureter against the underlying detrusor. The length of the intravesical ureter relative to its diameter seems to be the crucial point supporting the 'passive' reflux defence mechanism (Arena S. et al 2007). The 'active' antireflux system is due to the contraction of the longitudinal muscle coat of the VUJ. Active shortening of the longitudinal muscle layer of the transmural and submucosal ureterer areas ejects the bolus of urine into the bladder lumen.

Reductions of the total smooth muscle mass or defective configurations creating insufficient or uncoordinated contractions are accompanied by a decrease in the neuronal supply or aganglionosis. Predominantly in the upper urinary tract, coordinated peristalsis is essential to propel urine from the renal pelvis down to the bladder in a unidirectional way. Those peristaltic waves are generated in the renal pelvis and the proximal ureter by pacemaker cells. Functional and structural alterations of ureteric ends seem to impair the active valve

mechanism of the VUJ, causing VUR (Schwentner C et al 2005). Several studies have shown that the reducing of the total smooth muscle fascicles or a defective configuration creating insufficient or uncoordinated contractions are accompanied by a loss of c-kit-positive ICCs at the VUJ. Manometric findings on refluxing ureteric units (RUs) showed changed manometric patterns. In fact, the pressures recorded in the VUJ in the control and patients with VUR fluctuated rhythmically from a basal pressure to a high pressure during peristalsis (Pmax). While in RUs affected by grade I to III VUR the waves were rhythmic, the manometric profile in grade IV and V VUR was an arrhythmic or 'silent' pattern, with typical bicuspid spikes in the manometric record. Moreover, the basal and maximum pressure were negatively correlated with the grade of VUR (Arena S. et al 2007).

The variable and inconsistent pressures of the peristaltic waves, and the irregular wave rhythm, are likely to result in disturbed urine transport along the distal part of RUs, while the silent ureter might represent an advanced stage of ureteric arrhythmia, suggesting a more damaged ureter resembling a ureteric arrhythmic state.

Histological and histochemical findings showed a varied extent of change in intravesical RU tracts, e.g. muscle disarrangement and atrophy, and increased interstitial fibrosis. It has been reported a significant correlation between the grades of VUR and smooth muscle lesions, in according with Gearhart *et al.* (Gosling JA 1995) who reported a degree of smooth muscle deterioration and more collagen deposition in dilated refluxing ureters than in normal ureters.

Moreover, Oswald *et al.* (Oswald J et al 2004) reported a replacement of muscle bundles by connective tissue, leading to ureteric rigidity. It is patent that a defect of the longitudinal muscle coat implies an impairment of the contraction of the ureteric muscular layer, producing VUR. In fact, both the ostial valve contraction and ureteric peristalsis support an 'active' antireflux mechanism (Oswald J et al 2003). A significant decrease in c kit- positive ICCs, common tissue regulators in assisting peristalsis, has been described. It is not clear why depletion of c-kit-expressing ICCs occurs in RU ends. Interestingly, mammalian ICCs derive from smooth muscle progenitors, whose differentiation is independent of neural crest-derived cell lines (Wu JJ et al 2000). In RU there is a grade-correlated defect of muscle cells, among which c-kit-positive ICCs differentiate inside the ureteric ending, so that the loss of c-kit-positive ICCs might be a consequence of the disruption of muscle cells. Alternatively, as mesenchymal cells, surrounding the mesonephric duct, differentiate into the ureteric inner layer of smooth muscle cells, the delayed elongation of the Wolffian duct endings might be a pathogenetic event for muscular and subsequent ICC defects in VUR. Thus, the late maturation of ureteric ends is coherent with a possible spontaneous resolution of VUR, after postnatal remodelling of the VUJ, as shown for the pathogenesis of primary megaureter (Nicotina PA et al 1997). Loss of c-kit-positive ICCs could be also secondary to ureteric trauma during episodes of VUR, as reported in the proximal segment of obstructed fetal bowel (Khen N et al 2004). Consistently it is acknowledged that that mechanical stress can affect the expression of development genes, providing evidence that molecular signals are not the only forces that are involved in modelling the developing embryo.

In conclusion, RU ends share muscle disarrangement and fibrosis, dysfunction of the ostial valve and impairment of basal VUJ pressure, impairing significantly peristaltic waves. It's shown that the density of c-kit-positive ICCs in VUR negatively correlated with the grade of VUR and positively with Pmax , implying qualitative and quantitative alterations of peristaltic waves in VUR. These observations underline the assumption that VUR is related to an inadequately active mechanism, but further investigations are needed to clarify the origin of architectural lesions and the absence of c-kit- positive ICCs.

7. Congenital primary obstructive megaureter

Congenital megaureter is a term used in many cases of urinary tract dilation detected before and after birth (Shokeir AA et al 2000). In children, the ureteral diameter is usually not >5 mm, and when it is >7 mm, it could be considered a megaureter (Angerri O et al 2007).
The studies by Payabvash et al. (Payabvash S et al 2007) and Kajbafzadeh et al. (Kajbafzadeh AM et al 2006) revealed that the proportion of muscular content in the ureteral wall of an obstructed vesicoureteral junction is significantly lower than that in normal specimens. Lee et al. (Lee BR et al 1992) suggested that active and passive biomechanical wall properties, as well as morphologic parameters, such as decreased smooth muscle and increased collagen content are likely to change in various pathologic situations, including the obstructed megaureter. It has been suggested that abnormal peristalsis might have potentially contributed to the development of both obstructive and the increased collagen of the dilated ureter might be responsible for the abnormal peristalsis.

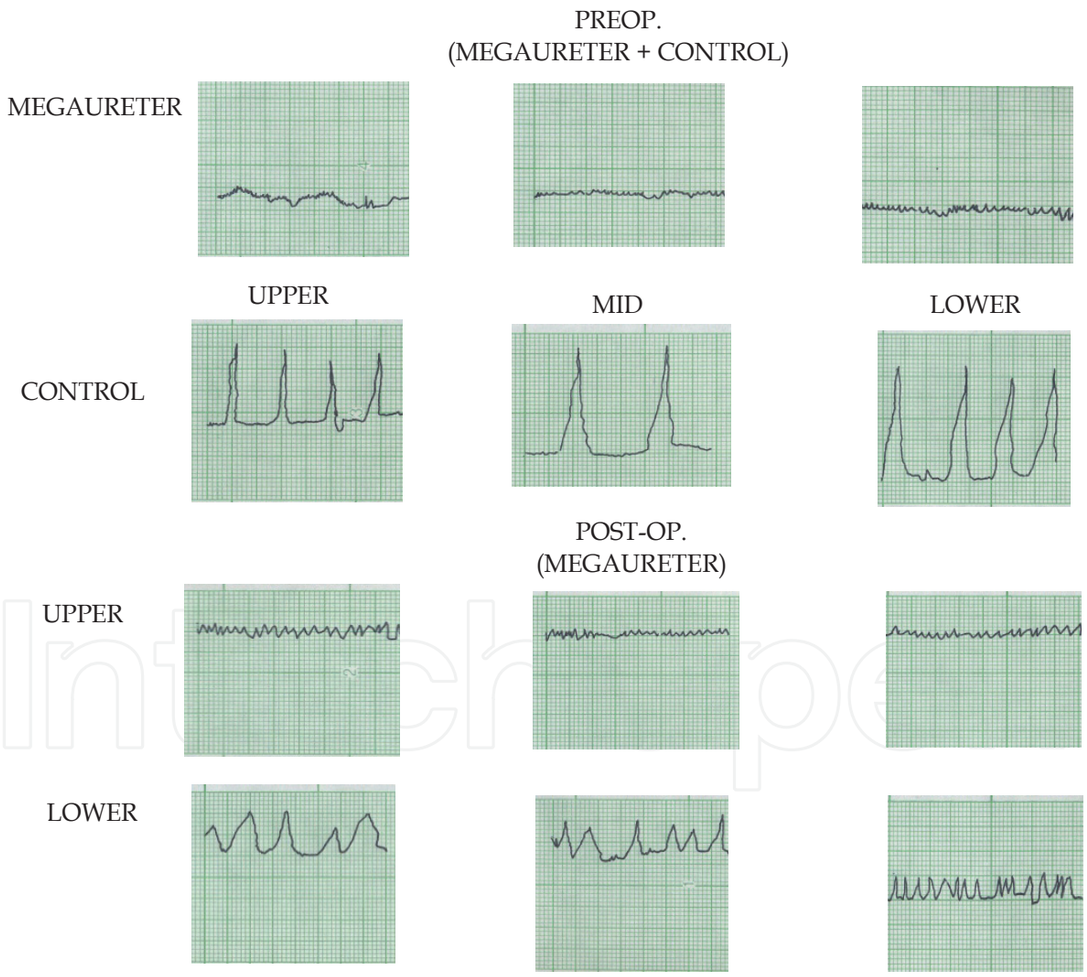

Fig. 2. Electromanometric ureteral findings in unilateral congenital megaureter: the upper track shows an impaired peristalsis in all ureteral parts as compared with contralateral ureter that has normal peristalsis . The post operative findings show only respiratory waves in the dilated upper ureter as compared with the normal peristaltic activity in the lower tract.

It was observed that apoptosis was significantly increased in the primary obstructive megaureter compared with the refluxing one. Kim et al. (Kim HG et al 2006) suggested that cell proliferation and apoptosis might play an important role in the pathogenesis of the obstructive megaureter. In fact, apoptosis of myocytes in the obstructive megaureter might affecr peristalsis. According to Kim et al. (Kim HG et al 2006) peak proliferation is noted during the early stage and apoptosis during the late stage of obstruction in animal models of obstructive ureter. We also hypothesized that the number of ICC-like cells, which are known to play an important role in peristalsis as a pacemaker of smooth muscle contraction, might be altered. As regards, it has been observed a normal distribution of ICCs in both the circular and longitudinal muscle layers of the dilated segments of patients affected by congenital primary megaureter, while a severe muscle hypoplasia and significant less of ICCs occurred in the longitudinal muscle layer of the restricted part of primary obstructive megaureter. Differently, a normal distribution of peripherin positive fibres was present in both the dilated and restricted ureteral segments (Arena F et al 2007).

Because megaureter is also a congenital disease with abnormal peristalsis, it has been hypothesized that the alterations in the number or function of ICC cells might induce discoordination between the signals of the nervous system and smooth muscle, causing abnormal peristalsis and, eventually, resulting in the development of ureteral dilation.

In contrast, a comparison between primary refluxing and obstructive magaureters showed that the number of c-kit-positive cells was clearly different between the obstructive and refluxing megaureters, with the latter having significantly fewer ICC-like cells than the former. Studies of mice with mutations leading to defects in the development of c-kit positive ICC populations have shown that without pacemakers, the coordination of smooth muscle contractions is lost.(Brading AF et al 2005).

Torihashi et al (Torihashi S et al 1999) reported that when c-kit receptors were blocked during development, the ICCs almost entirely disappeared from the small intestine. However, this loss of ICCs was not accounted for using assays for cell death, and closer examination revealed that the remaining ICCs developed ultrastructural features similar to those of smooth muscle cells. According to Burns (Burns AJ 2007) an inherent plasticity between ICCs and smooth muscle cells is regulated by c-kit signaling. c-kit signaling might be necessary for the maintenance and further development of ICC-like cells before and after birth, accounting for the spontaneous improvement of such conditions with time in some cases. According to the study by Mei et al (Mei F et al 2009) the ICC number is reduced after intestinal ischemic injury but makes a dramatic recovery. However, ischemic injury can lead to apoptosis of the ICCs, smooth muscle cells, and enteric neurons. Therefore, the higher c-kit expression in obstructive megaureters as compared to refluxing ureter might have been preceded by a reduction in ICC-like cells after ischemic injury, such as in the intestines, and the remaining increased apoptosis of smooth muscle cells might be the cause of the ureteral dysfunction.

8. Conclusions

ICC-LC are present in the UUT of a number of mammals and they have a crucial role in promoting pyeloureteric peristalsis. Studies showed that ICC-LC are responsible for initiating, coordinating and producing ureteropelvic peristaltic movements at the intercaliceal area, providing the passage of urine from the caliceal system through the ureter to the bladder. In conclusion, as well as in some gastrointestinal diseases (Hirschsprungs's

disease, infantile hypertrophic pyloric stenosis, slow transmission constipation), a local decrease or a lack of c-kit immunoreactivity ICCs-LC may be involved in dysfunctional disease of urinary tract as primary vesicoureteral reflux, congenital ureteropelvic junction obstruction and primary obstructive megaureter.

9. Abbreviations

ACK:	c-kit antibodies
GIS:	gastrointestinal system
ICC:	interstitial cajal cells
ICC-LC:	ICC-like cells
P-CJ:	pelvi-calyceal junction
RP:	renal pelvis
RUs:	refluxing ureteric units
SMC:	smooth muscle cell
UPJ:	ureteropelvic junction
UTT:	upper urinary tract
VUR:	Primary vesico-ureteral reflux
VUJ:	trigonal vesico-ureteral junction

10. References

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