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Urological Research

Mast Cells and Histamine Responses of the Ureter, Ultrastructural Features of Cell-to-Cell Associations and Functional Implications*

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Summary. In this study of normal adult human and ovine ureters, a characteristic distribution of a large population of typical mast cells was described by light and electron microscopy. Pharmacological studies were used to ascribe a functional role for these cells in normal and pathological states. In the structural investigations typical mast cells with their cytoplasm packed with characteristic electron dense granules were found in close vincinity to smooth muscle cells. A close association between mast cells and a fibroblast like La-cell and non myelinated nerve fibers was noted. The prevalence of mast cells was higher in human ureters. Human and sheep ureteral ring preparations exhibited spontaneous rhythmical contractions in vitro. Addition of histamine (10^{-6}–10^{-5} M) induced an increase in the frequency of contractions and enhanced the basal tone particularly in human samples. It is likely that histamine under pathological conditions such as renal colic and inflammatory reactions is released from mast cells within the ureter and induces a state of forceful contractions and pain fibre stimulation.

Key words: Mast cells – Ureter – Histamine – Ureteral peristalsis – Renal colic

Introduction

Mast cells, with their specific membrane receptors, are usually found at sites where potentially noxious substances are likely to enter the body. They are located in the bronchial and gastrointestinal muscosa, in the skin and in connective tissue around venules. The induction of inflammation by mast cells is caused by the release of a variety of preformed potent biological mediators and by their inherent capacity to generate de novo, active biological material from the local environment [21]. Mast cells, however, have also been described in other locations where there is no apparent entry of harmful agents as in normal arterial blood vessels [15].

Our recent ultrastructural work on the sheep ureters [2] was extended to human specimens where we have found a large number of mast cells. The presence of these cells, in the ureter has never been reported. The objective of the present investigation was to study the distribution of these structures in apparently normal ureters and to carry out in-vitro experiments concerning their possible functional role. A preliminary report has been given at the American Association of Anatomists meeting in Washington [20].

Materials and Methods

Seven human ureters were used for this study. These were classified as clinically normal and were obtained from patients undergoing nephrectomy due to kidney tumors (2) nonfunctioning kidney with hypertension (2) kidney stones (2) and also from a donated kidney (1) intended for transplantation. Ureteral preparations were also obtained freshly from 6 male Australian Merino sheep weighing 22–35 kg. The animals were killed by exsanguination and specimens of the proximal part of the ureter were obtained for studies of ultrastructure and in vitro motility.

Electron Microscopy

Samples were cut into 1 mm thick rings which were immediately immersed in 3% glutaraldehyde phosphate buffer pH 7.3 at 4 °C for 3–4 h. The tissues were then post-fixed in 1% osmium tetroxide dehydrated in graded ethanol and embedded in Araldite. Orientation of the block was achieved by examining 1 μm sections stained with toluidine blue which were also used for light microscopy. Ultrathin sections were cut using a LKB Nova Ultratome, mounted on G200 grids, stained with alcoholic uranyl acetate and lead citrate and viewed in Joel 1200CX electron microscope.

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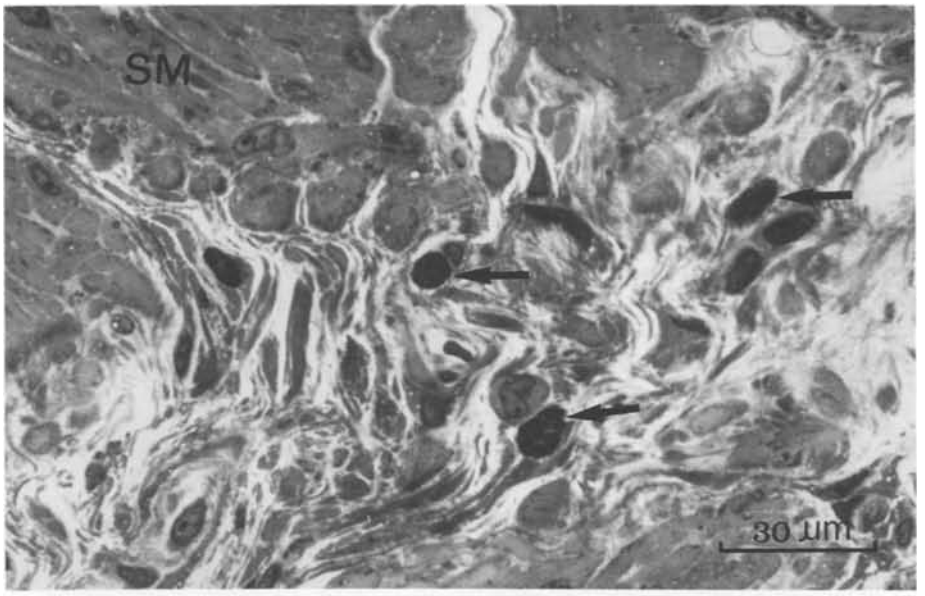


Fig. 1. Light micrograph of semithin section (1 µm) of human ureter, stained with toluidine blue showing a number of mast cells (*arrows*) within the smooth muscle layers (*SM*)

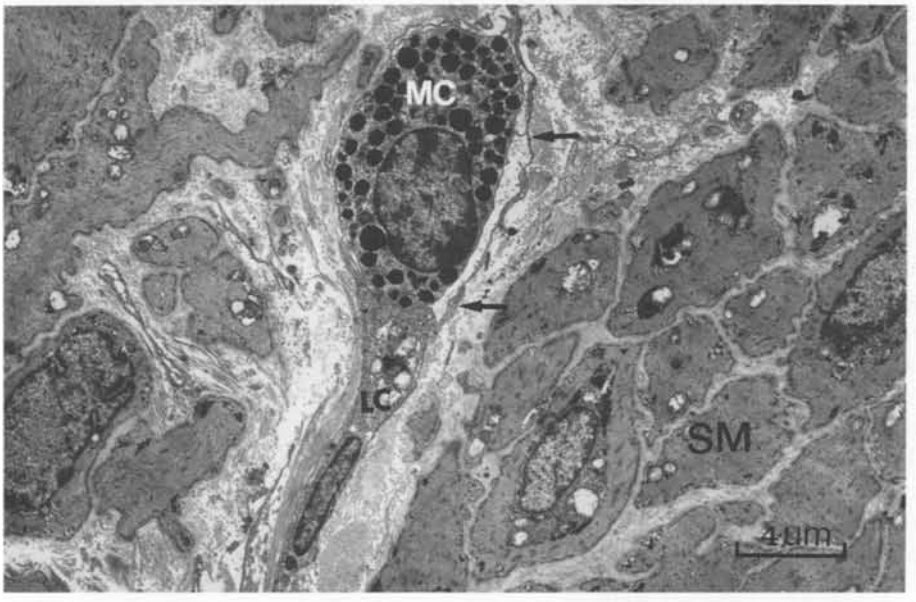


Fig. 2. Low power electron micrograph of a mast cell (*MC*) and an La-cell (*LC*) within the smooth muscle layers (*SM*) of human ureter. The cytoplasmic processes of the La-cell are indicated by arrows

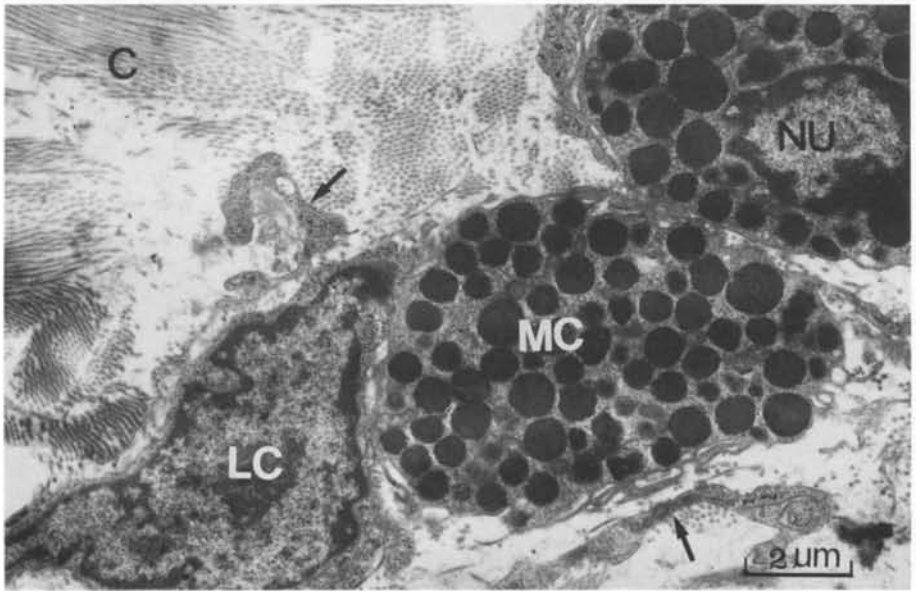


Fig. 3. Two mast cells (*MC*) in lamina propria near the smooth muscle coat of the human ureter. Note presence of La-cell (*LC*) and its cytoplasmic processes (*arrows*). *C* = collagen fibres; *NU* = nucleus of mast cell

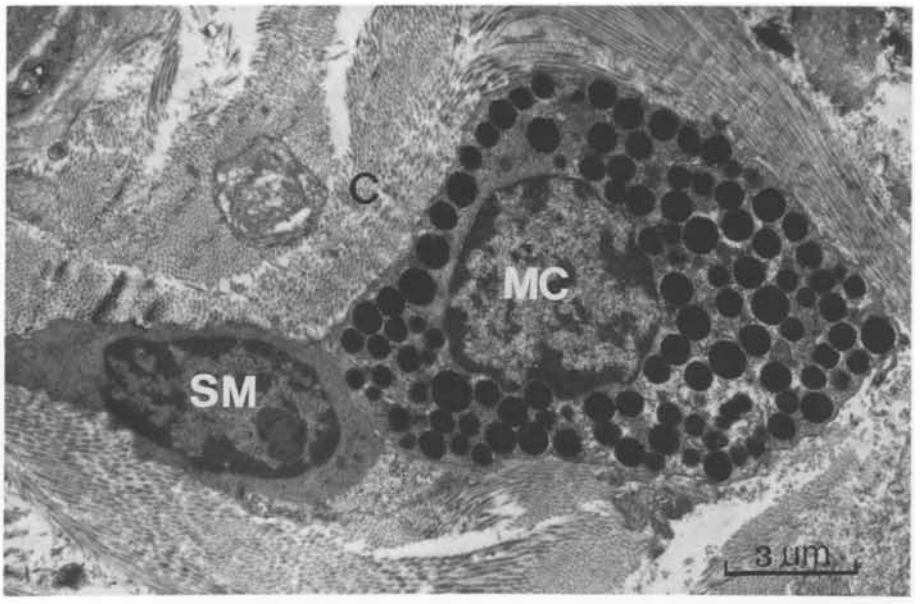


Fig. 4. Mast cell (*MC*) in actual contact with smooth muscle cell (*SM*) in the human ureter. *C* = collagen fibres

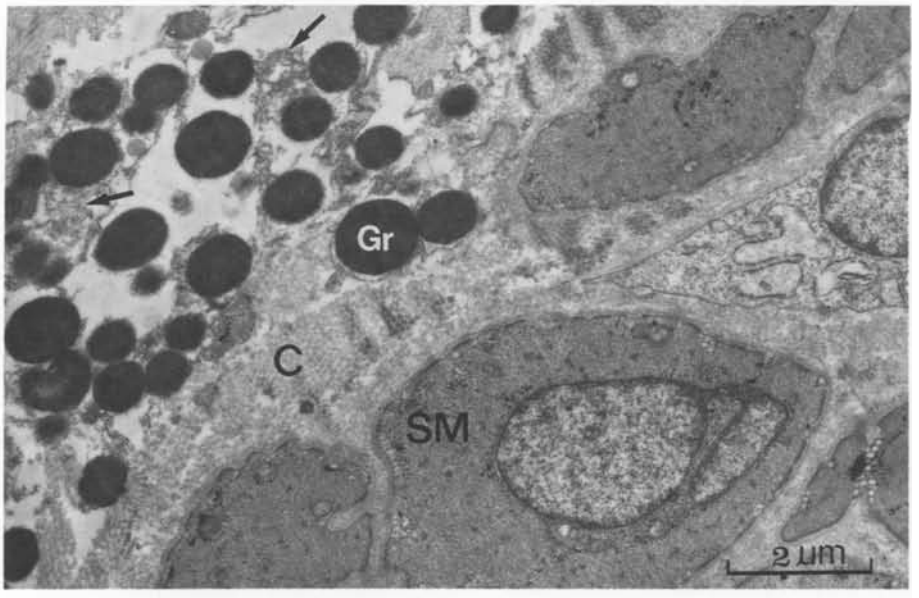


Fig. 5. Free mast cell granules (*Gr*) in close proximity to smooth muscle cells (*SM*) in the human ureter. Cellular remains probably related to mast cells also visibile (*arrows*). *C* = collagen fibres

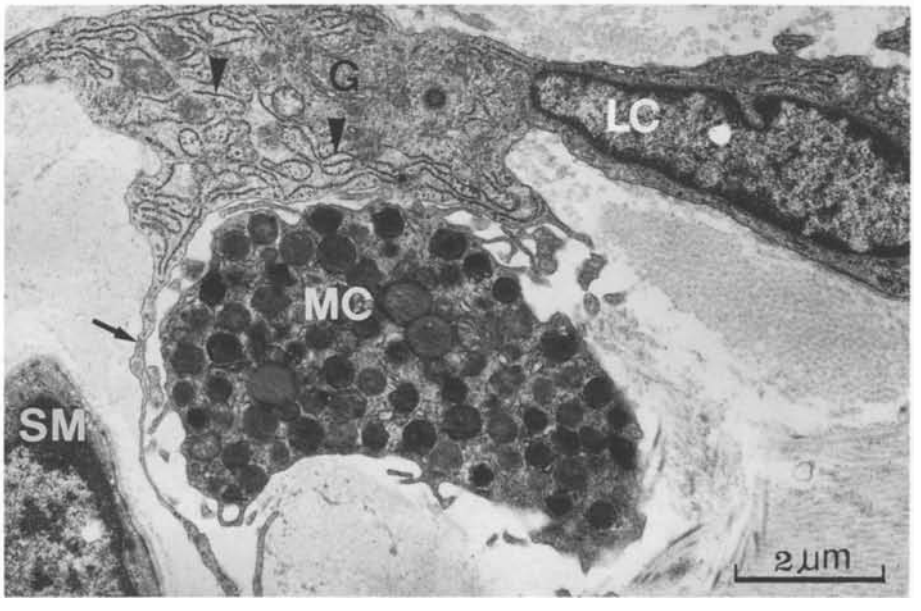


Fig. 6. Mast cell (*MC*) in close contact with an La-cell (*LC*) in the human ureter. Note La-cell cytoplasmic process (*arrow*). *Arrowheads* = rough endoplasmic reticulum; *G* = Golgi apparatus; *SM* = smooth muscle

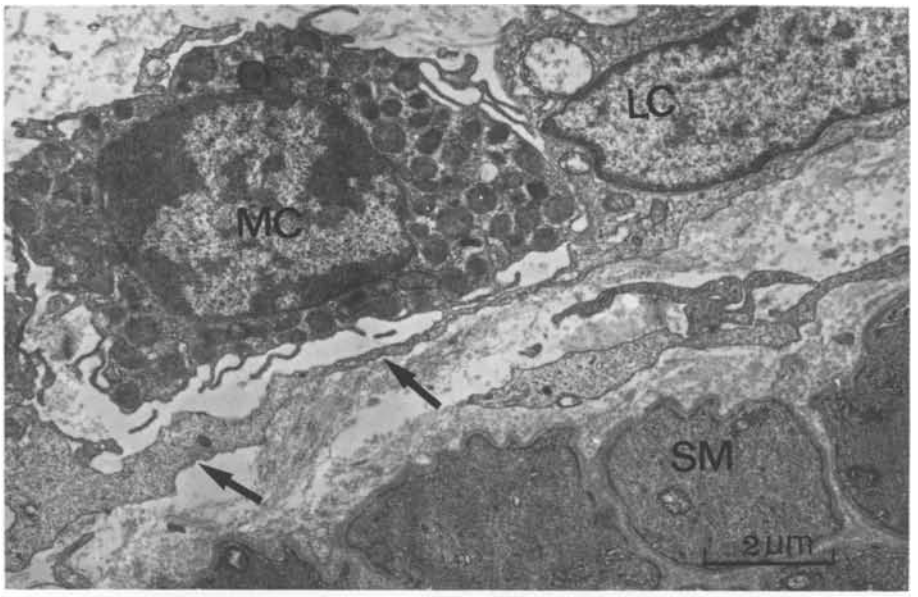


Fig. 7. Mast cell (*MC*) in close contact with an La-cell (*LC*) and its cytoplasmic processes (*arrows*). Both are close to smooth muscle cells (*SM*) in the human ureter

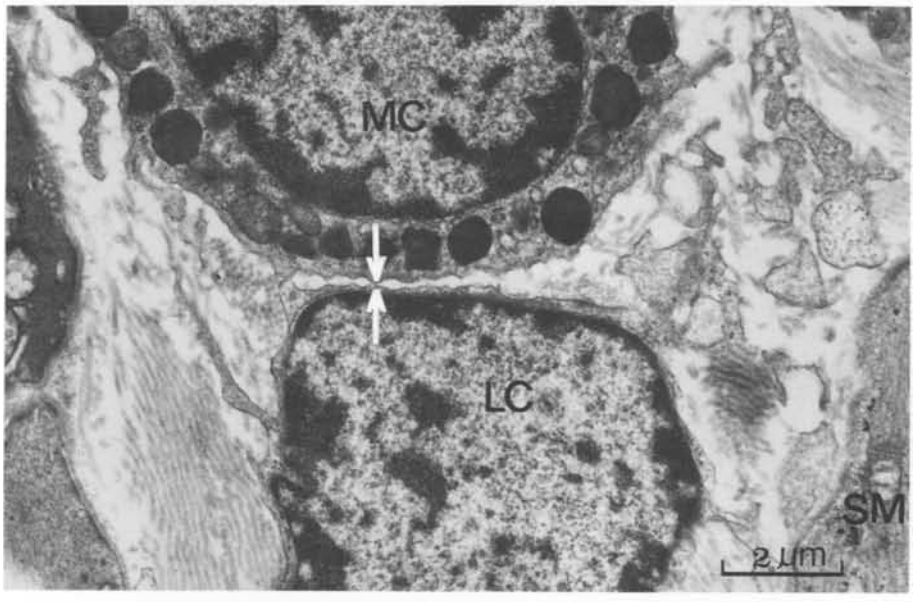


Fig. 8. High power micrograph of human ureter showing a mast cell (*MS*) and an La-cell (*LC*) in close association. Points of contact are formed by ridges of the plasma membranes of the two cells (*arrows*). *SM* = smooth muscle cells

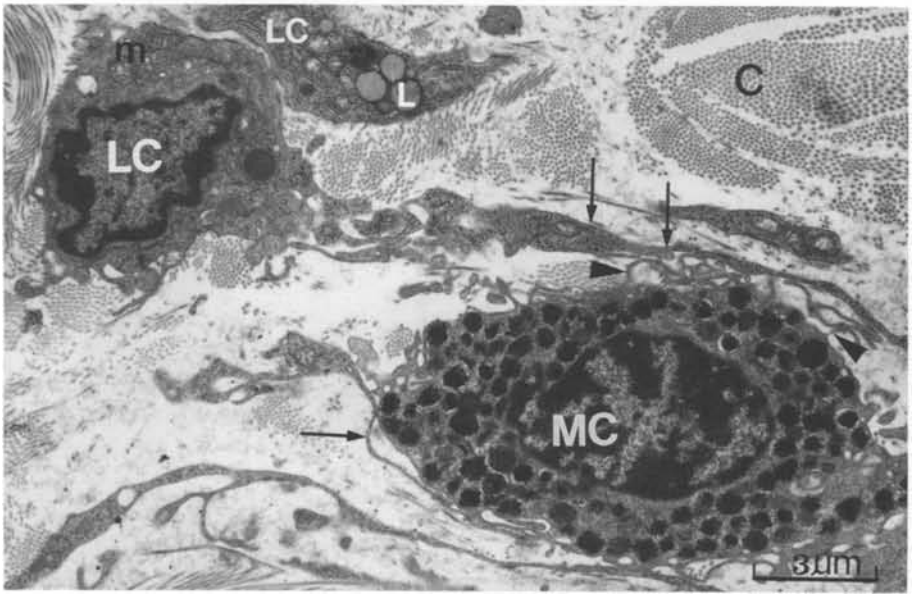


Fig. 9. Two La-cells (*LC*) with their cytoplasmic processes closely associated with mast cell (*MC*) surface infoldings (*arrowheads*), found in the lamina propria near smooth muscle cells in the human ureter. *L* = lipid droplets; *M* = mitochondria; *C* = collagen

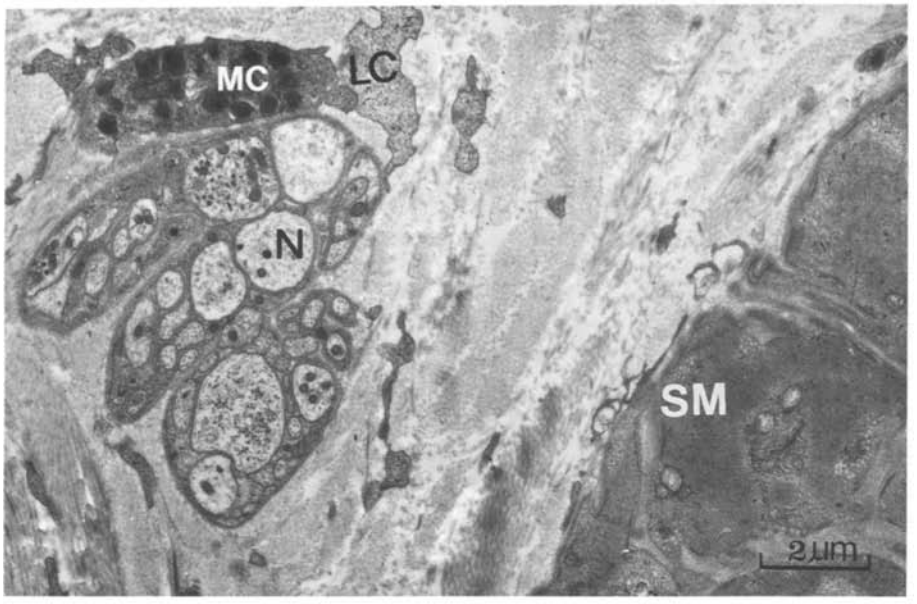


Fig. 10. A bundle of unmyelinated nerve fibres (*N*), a mast cell (*MC*) and part of an La-cell (*LC*) in close contact with each other in the human ureter. *SM* = smooth muscle

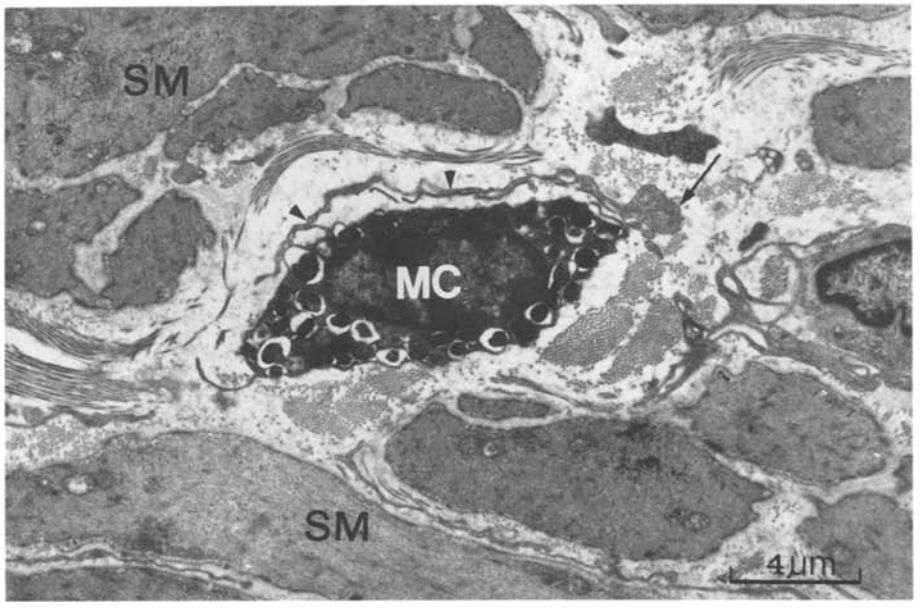
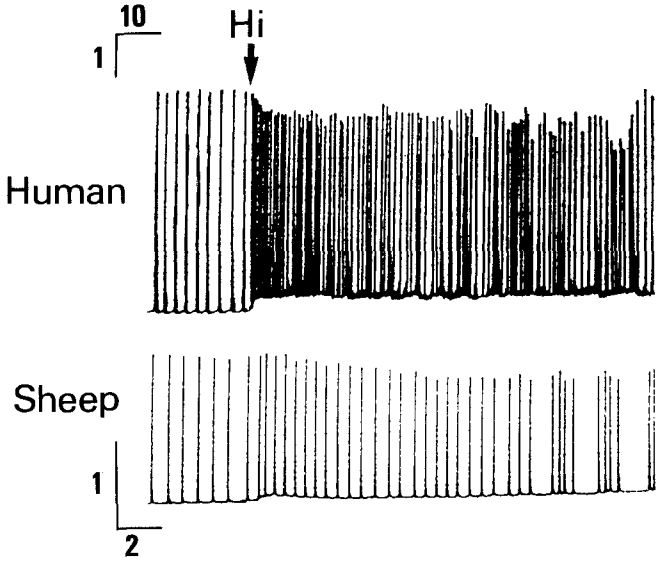


Fig. 11. Mast cell (*MC*) within smooth muscle (*SM*) in the sheep ureter. A small part of an La-cell (*arrow*) and its cytoplasmic processes (*arrowheads*) are present



Functional Studies

Ureteral rings of 4 mm length were used for recording of rhythmic motility, as described previously [17]. The 10 ml organ bath contained Krebs-Henseleit solution at 37 °C and was aerated with a mixture of 95% O_2 and 5% CO_2. The lower end of the preparation was tied to a tissue holder and the upper end connected to a strain gauge force transducer (Dynamometer, UFI) and the tension continously recorded on a Lectromed MX 216 recorder. A pre-tension of 2 g was applied to the preparation which was allowed to equilibrate for 1 h, after which time drugs were administered.

Fig. 12. Ureteral contractions recorded from human and sheep isolated ring preparations. At arrow histamine 10^{-5} M added to organ bath. Note increase in frequency of contractions and rise in baseline tone, particularly in the human preparation. Calibrations: vertical bar, tension in g; horisontal bar, time

Results

Electron Microscopy Human

Examination of semi – thin sections of ureteral rings stained with toluidine blue revealed the presence of a large number of densely granulated cells that exhibited metachromasia, a characteristic feature of mast cells (Fig. 1). Ultrastructurally they appeared irregular in shape with many cytoplasmic processes extending into the surrounding connective tissue. Their nuclei were large and mostly euchromatic and their cytoplasm contained a large number of electron – dense amorphous granules (Fig. 2). These cells were found in both the lamina propria and between smooth muscle cells (Figs. 2 and 3). The large majority, however, were found within or in close proximity to the smooth muscle layers and occasionally even in contact with individual muscle cells (Fig. 4). Moreover, free granules, resembling those of mast cells but slightly less electron dense were observed in the vicinity of smooth muscle cells. These were probably liberated as a result of mast cell degranulation since some cellular remains were also evident (Fig. 5). Closer examination showed an interesting association between mast cells and fibroblast – like cells. These cells were irregular in shape with many long cytoplasmic processes, which interdigitated with mast cell processes (Fig. 6) and the cell bodies of the two cells were often found in close contact. At this point their adjacent plasma membranes formed a series of grooves and ridges (Fig. 8). The cytoplasm of the fibroblast-like cells contained profiles of rough endoplasmic reticulum, mitochondria and few lipid droplets (Fig. 9). This association has not been previously studied in the ureter and we have therefore tentatively designated these cells as La-cells. On occasions, mast cells, La-cells and non-myelinated nerve fibres were found in close contact with each other and near smooth muscle cells (Fig. 10).

Electron Microscopy Sheep

In addition to the lipid droplets previously reported [2] the sheep ureters contained mast cells similar to those of the human ureters (Fig. 11), in both structure and location. Although these were present in great numbers, they were less abundant than in the human.

Functional Studies

Ureteral preparations from human and sheep specimens exhibited spontaneous rhythmic activity as shown in previous studies [3, 17]. Addition of a 10^{-5} M histamine to the organ bath induced an increase in frequency and basal tone as shown in Fig. 12). The effect of histamine was more pronounced in the human preparation with a higher increase in frequency and basal tone than in the sheep.

Discussion

Transmission electron microscopic examination has resulted in the identification of the typical features of mast cells through detailed analysis of their ultrastructure. Typically they are described as variable in shape, appearing round, or elongated with infoldings of the cell membrane with a round nucleus and membrane bound granules [6]. The mast cells found in the present study conform to such criteria. The location within the ureter is somewhat different from the sites reported elsewhere, since they were not limited to the connective tissue space close to blood vessels and lymphatics. The majority were found between smooth muscle cells and some were adjacent to nerve fibres. Whether this has anything to do with their function remains to be elucidated. A close association of mast cells with non-myelinated nerve fibers has been frequently been reported earlier [13] and it has been suggested that this close proximity has to do with pain stimulation [11, 22]. In addition to different sensory and autonomic fibers [7] peptidergic nerves have been reported in the genito – urinary tract [1] and since substace P (SP) and its analogues are potent histamine releasing agents [9, 12] it is likely that the local release of SP will affect ureteral motility, either directly or indirectly through histamine release. Mast cells and their association with fibroblast-like-La-cells in the ureter has not been reported previously although Notley [14] described the presence of fibroblasts in the vicinity of smooth muscle cells. Recently Greenburgh and Burnstock [8] reported a close cell-to-cell interaction between mast cells and fibroblasts in tissue culture.

Much work has been devoted to the anaphylactic degranulation and release process of preformed biogenic amines and newly synthetised prostanoids and leukotrienes, but very little is known about alternative functions other than inflammatory reactions and tissue repair [16]. So far no physiological role has been assigned to mast cells other than in connection with pathological processes and tissue injury. The possiblity of alternative physiological function remains an open question.

The ureter is quite resistant to stimulation with autacoids except prostaglandins [17] which seem to play an important role for the maintenance and transmission of persistalsis [19]. Histamine is another substance which at least in micromolar concentration and above is capable of affecting ureteral peristalsis as shown in this study. Histamine increases frequency of contractions and elevates basal tone through histamine-1 receptor activation [4]. It is likely that histamine under pathological conditions is released within the ureter and induces a state of forceful contractions (= spasm). Moreover histamine if released has powerful algesic properties [10] and could be involved in the genesis of renal colic.

The present study lends support to the theory that histamine release may be involved in painful conditions of the upper urinary tract. An impacted ureteral stone with sharp edges may induce damage to the urothelial barrier

and lead to leakage of acidic and hyperosmolar urine into the lamina propria with its adjacent structures including the most cells. Hyperosmolar fluids are known to trigger histamine release [5] and therefore this could conceivably be a strong algogenic stimulus. Moreover we have recently shown that hyperosmolar fluids induce powerful spastic contractions of the ureteral musculature [18]. This further supports the role of histamine as being a potent candidate for eliciting pain in urinary colic.

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