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Review

Autonomic and sensory nerve modulation of peristalsis in the upper urinary tract

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ABSTRACT

The primary function of the upper urinary tract is to propel urine and various water-soluble toxic compounds from the kidneys to the bladder for storage and evacuation to maintain body ionic balance and contribute to the regulation of blood volume and pressure. The mechanism by which the upper urinary tract propels urine has long been considered to be myogenic in origin as peristaltic contractions in vivo and in vitro (pyeloureteric peristalsis) propagate in a manner little affected by drugs that block nerve conduction or the sympathetic and parasympathetic transmission. However, it is now well established that the release of intrinsic prostaglandins and neuropeptides from primary sensory nerves (PSNs) helps to maintain pyeloureteric peristalsis. Electrical field stimulation of PSNs evokes species-specific positive inotropic and chronotropic effects that have been attributed to release of excitatory tachykinins superimposed on negative inotropic and chronotropic effects associated with the release of calcitonin gene related peptide (CGRP), a rise in cellular cyclic-adenosine monophosphate (cAMP) and a protein kinase A-dependent activation of glibenclamide-sensitive ATP-dependent K^+ (K_{ATP}) channels. This review summarises the existing evidence of the nervous control of the upper urinary tract and recent evidence suggesting that the autonomic innervation may indirectly modulate pyeloureteric peristalsis via the activation of PSN nicotinic receptors and via the modulation of K_V7 channels located on interstitial cells within the renal pelvis wall.

Contents

Abbreviations: Ach, acetylcholine (Ach); Ad, adrenaline; AKAP, A kinase anchoring protein; Ano1, anoctamin-1 Ca^{2+}-activated Cl^- channel encoded by the ANO1 gene; α-SMA, α-smooth muscle actin; ASMCs, atypical smooth muscle cells; eYFP, enhanced-yellow fluorescent protein; BEC, basal epithelial cells; $[Ca^{2+}]_i$, intracellular concentration of Ca^{2+}; $Ca_V3.2$, 'T-type' Ca^{2+} channel; cAMP, cyclic-adenosine monophosphate; CGRP, calcitonin gene related peptide; CIRC, Ca^{2+}-induced release of Ca^{2+}; COX-2, cyclooxygenase-2; DAPI, 4′,6-diamidino-2-phenylindole, dihydrochloride; DAG, diacylglycerol; FIC, fibroblast-like interstitial cell; FIB SEM, focused ion bean scanning electron microscopy; GFP, green fluorescent protein; GPCR, G protein coupled receptor; hCGRP, human calcitonin gene related peptide (CGRP); IBMX, 3-isobutyl-1-methylxanthine; ICC, interstitial cells of Cajal; K_{ATP}, glibenclamide-sensitive ATP-dependent K^+ channels; $K_V71–5$, K^+ channel subunits encoded by KCNQ1–5 genes; M, mast cell; MASSIVE, Multi-modal Australian Sciences Imaging and Environment; NB, nerve bundle; P, papilla; PIP_2, phosphatidylinositol 4,5-bisphosphate; PGP9.5, protein gene product 9.5; PKJ, pelvis-kidney junction; PKC, protein kinase C; PLC, phospholipase C; PSN, primary sensory nerve; Psym, parasympathetic nerve; RA, renal artery; RV, renal vein; SIC, sub-urothelial interstitial cell; STD, spontaneous transient depolarisation; STIC, spontaneous transient inward current; STOC, spontaneous transient outward current; TK, tachykinins; TRPV1, transient receptor potential vanilloid 1; TSMCs, typical smooth muscle cells; TTX, tetrodotoxin; U, urothelium.

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1. Introduction

Even though there is ample evidence of a parasympathetic, nitrergic and sympathetic innervation within the upper urinary tract and that activation of the receptors for their neurotransmitters can modulate pyeloureteric peristalsis there is little evidence that these autonomic nerve networks play any direct role in maintaining pyeloureteric autorhythmicity. Any positive and negative inotropic and chronotropic effects evoked upon stimulation of intrinsic nerves have been mostly attributed to the stimulation of PSNs. In this review we summarise the existing evidence of the nervous control of the upper urinary tract and propose that the autonomic innervation may indirectly affect pyeloureteric peristalsis via the activation of PSN nicotinic receptors and the release of CGRP or via G-protein coupled receptor (GPCR)-mediated depletion of membrane-bound phosphatidylinositol 4,5-bisphosphate (PIP_2) and the closure of K_V7 channels located on non-muscle cells within the renal pelvis wall.

1.1. Pyeloureteric Peristalsis

In most small mammals, urine formed by the nephron functional units passes through the apex (papilla) of a single pyramid-shaped renal medulla into the renal calyx, which is surrounded by a single funnel-shaped renal pelvis (Fig. 1A). In humans, sheep and pig, their kidneys are multi-papillate so that urine is expressed into a number of minor calyces which fuse into several major calyxes and then a single renal pelvis, which extends to the ureter. In uni-papillate mammals, the renal pelvis consists of a lumen-forming squamous urothelium and a thin layer of stromal cells enveloped by a plexus of 'typical' smooth muscle cells (TSMCs) which form a continuous muscle layer of tightly-bundled cells, originating near the base of the papilla, the pelvi-kidney junction (PKJ) and extending to the ureter (Gosling and Dixon, 1974; Klemm et al., 1999). Spontaneous propagating peristaltic contractions originate in the proximal renal pelvis and travel distally to propel expressed urine into the ureter (Golenhofen and Hannappel, 1973). In the mouse and guinea pig, a single peristaltic wave travels the length of the upper urinary system into the ureter (Fig. 2A, B). In the rat, the single peristaltic wave (Fig. 2C*) originating in the PKJ travels to the mid-renal pelvis and often triggers a number of additional high frequency contractions giving rise to more complex patterns of contraction (Davidson and Lang, 2000; Lang et al., 2001). These additional contractions can travel in both antegrade and retrograde directions and are reduced if the temperature is lowered from 35 to 30 °C (Lang et al., 2001). In all three species, spontaneous contraction can originate in the

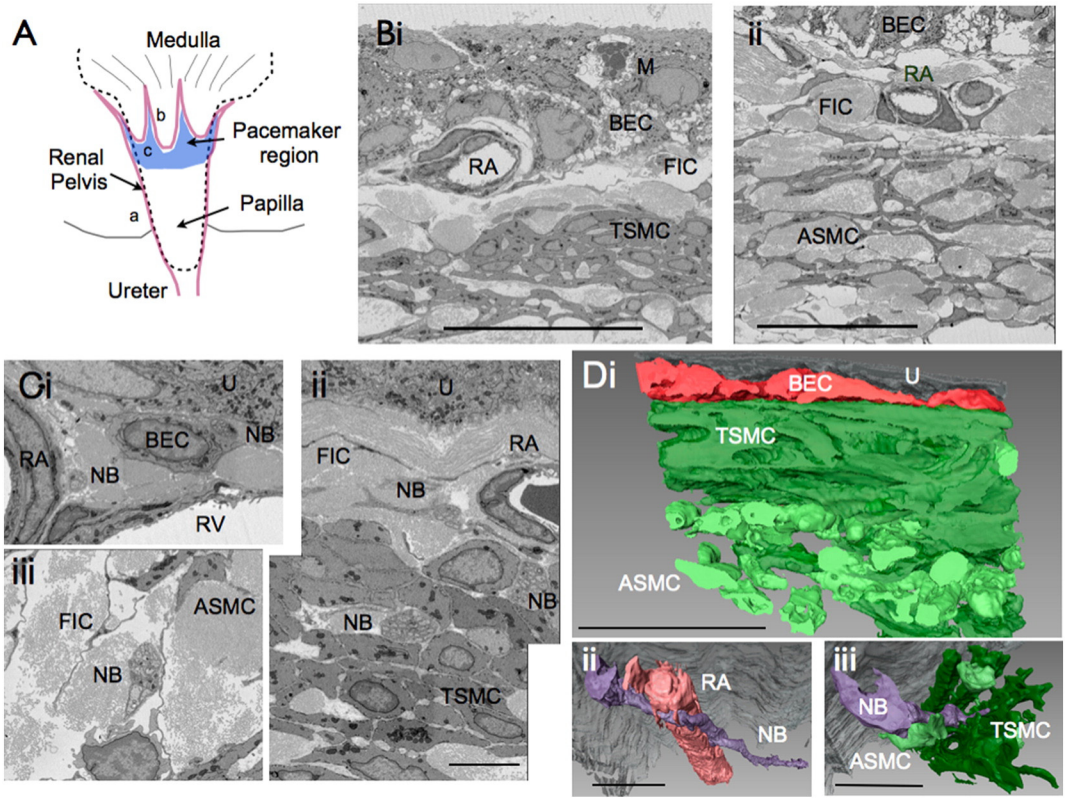

Fig. 1. Ultrastructure of the mid- and proximal renal pelvis. (A) Schematic of the pyeloureteric system of a uni-calyceal kidney as a funnel shaped renal pelvis with a number of 'finger-like' septa attachments to the pelvi-kidney junction. (B) Electron micrograph of the wall of the rat mid- (Aa, Bi) and proximal (Ab, Bii) renal pelvis illustrating the structure of typical and atypical smooth cells (TSMC and ASMC), basal epethelial cells (BECs), renal arteries (RAs) and mast cell (M). (C) Higher magnification micrographs illustrating the nerve bundles (NBs) in close proximity to small renal arteries (RAs), renal veins (RVs), BECs and both TSMCs (Cii) and ASMCs (Ciii). U and FIC indicate the urothelium and fibroblast-like interstitial cells, respectively. (Di) Three-dimensional reconstructions of the cells within the mouse PKJ obtained with a focused ion beam scanning electron microscopy (FIB SEM). Repeated milling (100 nm thick) of a block of proximal PKJ reveals new X–Y surfaces, which are imaged with the SEM to create stacks of 600–900 micrographs. After alignment, individual cells within the stack were identified, volume rendered and displayed in the X–Y dimension. Cells of a similar morphology were colour coded and grouped for easy identification. (Dii–iii) High magnification micrographs of regions in the stack where a nerve bundle makes a close apposition to a small renal artery (Dii), a TSMC bundle and an ASMC (Diii). Calibration bars 30 μm (B), 5 μm (C), $0.5e^5$ nm (Di) and $2e^4$ nm (Dii–iii). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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