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Review

Sympathetic innervation of the kidney in health and disease: Emphasis on the role of purinergic cotransmission

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ABSTRACT

There is introductory information about non-synaptic transmission at sympathetic neuroeffector junctions and sympathetic nerve cotransmission utilizing noradrenaline and ATP as cotransmitters. Then the organization and location of sympathetic nerves in different sites in the kidney are described, including renal arteries, juxtaglomerular arterioles and renal tubules. Sympathetic nervous control of glomerular filtration rate and of renin secretion are discussed. Evidence, obtained largely from experiments on animals, for sympathetic nerve modulation of the transport of water, sodium and other ions in the collecting duct of the nephron is described. Finally, there is coverage of the roles of sympathetic nerves in renal diseases, including hypertension, diabetes, hypothyroidism and ischaemia.

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1. Introduction

We start with an anecdote concerning the lack of early attention to the roles of sympathetic nerves in the kidney. GB was present at a lecture by a leading kidney physiologist. During the discussion after the

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talk, the speaker was asked why he did not consider the influence of nerves on the various mechanisms he had discussed. 'That is because the nerves in the kidney are not important', he replied, 'because the kidney functions perfectly well after denervation'. Clearly an unacceptable response. Influenced by the beautiful early studies of synaptic transmission in skeletal muscle, ganglia and in the CNS, peopled looked, but did not find, specialised neuroeffector synapses (boutons) on smooth muscle and non-excitable cells in the peripheral system. However, it is clear that non-synaptic transmission is characteristic of neuroeffector transmission in the periphery. Innervation involves release of neurotransmitters from autonomic nerve varicosities making transient contact with effector cells, which possess the receptors to mediate junctional transmission (see Burnstock, 2008). This is described in Section 2.

Another major advance was made when cotransmission involving two or more transmitters was recognised (see Burnstock, 1976). This was in conflict with what was known as Dale's Principle that one nerve only released one transmitter, with the belief that sympathetic nerves release noradrenaline (NA) and parasympathetic nerves acetylcholine. In particular it is now well established that sympathetic nerves release adenosine 5′-triphosphate (ATP) and NA as cotransmitters to both visceral and vascular targets, together with neuropeptide Y (NPY), although this usually acts as a prejunctional modulator after release rather than as a cotransmitter (Burnstock, 2007). The evidence for sympathetic cotransmission will be discussed in Section 3.

Sympathetic nerves in the kidney are involved in a number of physiological processes, including control of renal blood flow, glomerular filtration rate, reabsorption of water, sodium and other ions, release of renin and production of prostanoids. These roles will be explored in the following sections. Finally, the roles of sympathetic nerves in pathophysiological conditions, such as hypertension, diabetes and hypoglycaemia will be discussed. Reviews concerned with purinergic signalling and kidney function are available (Bailey et al., 2012; Leipziger, 2016; Praetorius and Leipziger, 2010).

2. Non-synaptic transmission at sympathetic neuroeffector junctions

Non-synaptic sympathetic nerve transmission to smooth muscle and non-muscular cells has been recognised (see Burnstock, 1986, 2004; Burnstock and Iwayama, 1971; Gabella, 1995). Transmission is 'en passage', where transmitter is released from varicosities that come close to effector cells. Sympathetic nerve fibres become varicose in the vicinity of the effector tissue (Fig. 1; Fig. 2a and b). The width of the junctional cleft is variable; prejunctional thickening on varicosities represent the sites of release of transmitter, but no post-junctional specialisations are present (Fig. 2c). The vascular smooth muscle effector is a muscle bundle rather than a single muscle cell, which are connected by low resistance pathways that allow electrical spreading of activity within the effector bundle (Fig. 3a). Epithelial and immune cells are also transiently innervated when varicosities come close enough to release transmitter to reach the receptors on the cells (Fig. 3b).

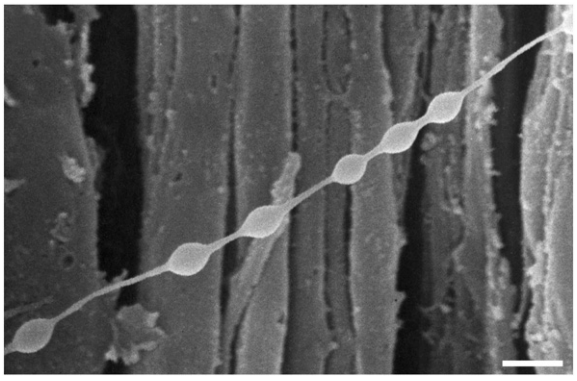

Fig. 1. A scanning electron micrograph of a single terminal varicose nerve fibre lying over smooth muscle of the small intestine of the rat. The intestine was pre-treated to remove connective tissue components by digestion with trypsin and hydrolysis with HCl. Scale bar = 3 μm. (Reproduced from Burnstock (1988) with permission from Marcel Dekker).

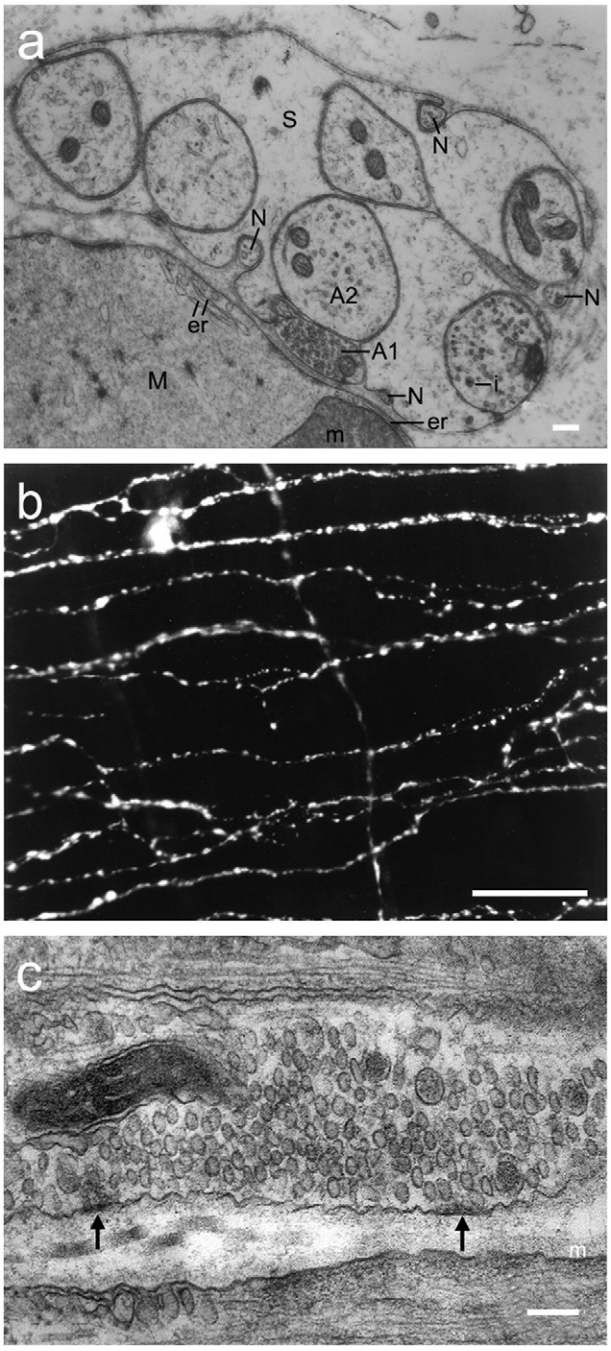

Fig. 2. (a) A medium-sized intramuscular bundle of axons within a single Schwann cell (S) in the guinea pig vas deferens. Varicosity A1 containing many vesicles, perhaps related to the proximity (80 nm) to the muscle cell (M). The small profiles (N), less than 0.25 μ in diameter, are probably sections through intervaricosities and contain neurofilaments. e.r. = endoplasmic reticulum. (Reproduced from Merrillees et al. (1963) with permission from Rockefeller University Press). (b) Whole mount preparation of the sheep mesenteric vein at the level of the inner surface of the adventitia, showing innervation of the medial muscle coat by an autonomic ground plexus consisting of bundles of fine varicose nerves containing noradrenaline. Incubated in formaldehyde vapour for 1 h. Scale bar = 50 μ. (Reproduced from Burnstock (1970) with permission from Edward Arnold). (c) An autonomic varicosity in guinea pig vas deferens showing dense prejunctional thickenings and bunching of vesicles, probably representing transmitter release sites (*arrows*), but there is no postjunctional specialization. (Reproduced from Burnstock (2004) with permission from Elsevier).