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Autonomic control of the urogenital tract

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ABSTRACT

The urogenital tract houses many of the organs that play a major role in homeostasis, in particular those that control water and salt balance, and reproductive function. This review focuses on the anatomical and functional innervation of the kidneys, urinary ducts and bladders of the urinary system, and the gonads, gonadal ducts, and intromittent organs of the reproductive tract. The literature, especially in recent years, is overwhelmingly skewed toward the situation in mammals. Nevertheless, where specific neurochemical markers have been investigated, common patterns of innervation can be found in representatives from most vertebrate classes. Not surprisingly the vasculature, epithelia and smooth muscle of all urogenital organs receives adrenergic innervation. These nerves may contain non-adrenergic non-cholinergic (NANC) neurotransmitters such as ATP and NPY. Cholinergic nerves increase motility in most urogenital organs with the exception of the kidney. The major NANC nerves found to influence urogenital organs include those containing VIP/PACAP, galanin and neuronal nitric oxide synthase. These can be found associated with both smooth muscle and epithelia. The role these nerves play, and the circumstances where they are activated are for the most part unknown.

1. Introduction

The urogenital tract comprises a developmentally and functionally related collection of tissues of mesodermal origin. These include the kidneys, urinary ducts and bladder of the urinary system and the gonads, gonadal ducts, and intromittent organs of the reproductive tract. Not all urogenital organs are homologous between classes and those which share similar embryological origins have often undergone considerable change over time (Kent and Carr, 2000). Kidneys may be called upon to operate in aquatic, marine and desert environments. Reproductive strategies also vary markedly among vertebrates. Fertilization may be external or internal and, oviparous or viviparous strategies may be adopted (Blackburn, 1998; Pollux et al., 2009). Gestation can also vary from weeks (e.g., *Rattus*) to years (e.g., spiny dogfish *Squalus acanthias* (Woodhead, 1976)).

A large proportion of the nervous and endocrine systems are devoted to regulation of urogenital tissues. Whilst the endocrine and nervous systems interact both centrally and peripherally via neurohypophyseal and gonadal hormones, this review focuses on the autonomic motor control of the urogenital tract with some reference to sensory innervation. Despite the diligence of comparative physiologists over the last century, the literature remains overwhelmingly skewed towards the innervation of mammalian tissues. The sensory and motor pathways to mammalian reproductive and urinary systems have been extensively mapped by immunohistochemical and retrograde labelling, and via nerve lesion studies. As a result the neurochemical code of the mammalian peripheral nervous system associated with the urogenital tract is relatively well defined (Gabella, 2003; Keast, 2006).

More information is available for classical adrenergic and cholinergic mechanisms in non-mammalian vertebrates than for neuropeptide or gaseous neurotransmitters. In fact, the rate at which information on non-adrenergic non-cholinergic (NANC) mechanisms is accumulating has slowed dramatically in the last decade. Nevertheless, when these chemical markers have been used in non-mammalian vertebrates, similar populations of neurons have been described. Where data from functional studies are available, the effects of NANC neurotransmitters are similar across species. Whilst some progress has been made in our understanding of the peripheral nervous control of the urogenital tract in non-mammalian species, the same cannot be said for central autonomic control or reflex activation of urogenital organs. Visceral sensory axons have been described in most vertebrates examined so far, however little information exists concerning the functional properties of these nerves or the reflexes they initiate.

The general structure of peripheral autonomic pathways in vertebrates has been reviewed previously (Gibbins, 1994), and in this issue (Nilsson, 2010). These works outline the spinal outflow and location of the main autonomic ganglia. Readers are also referred to a previous extensive review of the urogenital tract by Uematsu (1994).

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2. Kidney

During embryogenesis three stages of kidney development are recognised: the pronephros, opisthonephros and mesonephros (Kent and Carr, 2000). A kidney derived from the pronephros persists in hagfish and as the head kidney in teleosts. The main kidneys in fish and amphibia are derived from the opisthonephros while the metanephric kidney of reptiles, birds and mammals is derived from the posterior part of the mesonephros (Kent and Carr, 2000). The endocrine control of kidney function by arginine vasopressin from the posterior pituitary, aldosterone from the adrenal gland and atrial natriuretic peptide from the heart is relatively well understood, compared with the nervous control (Pang, 1983; Toop and Donald, 2004; Warne et al., 2002).

2.1. Mammals

Unlike in other vertebrates, the kidney is essentially the only osmoregulatory organ in mammals. The mammalian kidney is a highly structured organ which operates a counter-current arrangement of renal tubules and vessels. The mammalian kidney can produce urine which is very hyperosmotic compared to plasma, a feature that separates them from other vertebrates. The kidney is well supplied by autonomic nerves which control renal perfusion, renin release and tubulular epithelial secretion and absorption (El Asfoury, 1951; Mitchell, 1935; Nilsson, 1965; Rump et al., 2003; Wågermark et al., 1968).

Retrograde labelling from rat kidney, using pseudorabies virus, labelled preganglionic neurons in thoracic and high lumbar spinal cord segments (T5-L1) (Huang et al., 2002; Schramm et al., 1993). The central projections to these preganglionic neurons were found in the rostral ventral medulla, medullary raphe, the A5 cell group and the paraventricular nucleus (Schramm et al., 1993). Postganglionic sympathetic neurons which project to the kidney are found largely in prevertebral (celiac), but also in thoracic and lumbar paravertebral chain ganglia in cats and rats (Chevendra and Weaver, 1991; Meckler and Weaver, 1984).

Within the kidney catecholamine containing axons are found in cortex and outer medulla associated with afferent and efferent arterioles, interlobar, arcuate and interlobular arteries, and the vasa recta (McKenna and Angelakos, 1968). Autoradiographic studies have found axons capable of tritiated noradrenaline uptake associated with cortical tubules and the loop of Henle (Barajas et al., 1984, 1985; Barajas and Powers, 1988). Tubule innervation was also demonstrated ultrastructurally (Luff et al., 1991).

Stimulation of renal sympathetic nerves causes a constriction of afferent and efferent arterioles, and reabsorption of sodium and water (DiBona and Kopp, 1997; Johns and Manitius, 1986; Rump et al., 2003). Most of these effects are mediated by α-adrenoceptors although adenosine triphosphate (ATP) and neuropeptide Y (NPY) which are cotransmitters in renal sympathetic nerves contribute to the vascular (Oberhauser et al., 1999; Vonend et al., 2005) and tubular (Ohtomo et al., 1994) effects of nerve stimulation. Sympathetic nerve stimulation also releases renin from juxtaglomerular cells via β-adrenoceptor activation (Rump et al., 2003; Zanchetti et al., 1977).

There is no evidence for a vagal (parasympathetic) innervation of the kidney. Retrograde tracing from renal nerves does not label vagal nuclei (Gattone et al., 1984; Norvell and Anderson, 1983). Intrinsic neurons containing neuronal nitric oxide synthase (nNOS) were observed in the rat kidney (Liu et al., 1996). In addition nNOS is contained in peptidergic sensory nerves (Kopp et al., 2001). There is evidence that nitric oxide contributes to vasodilation and alters proximal tubule absorption (Persson, 2002; Walkowska et al., 2005). Axons immunoreactive for vasoactive intestinal peptide (VIP) have also been demonstrated in the kidney (Barajas et al., 1983). No somata were reported and the origin of these axons is unclear as postganglionic sympathetic renal neurons do not contain VIP (Chevendra and Weaver, 1992).

Axons immunoreactive for substance P (SP) and calcitonin gene related peptide (CGRP) are present throughout the kidney (Kuo et al., 1984b). These are presumably sensory axons and are found throughout the renal pelvis and surrounding the kidney vasculature (Barajas et al., 1991; Knight et al., 1987; Knight et al., 1991). The sensory innervation of the proximal and distal tubules is less dense compared with other structures (Rump et al., 2003). These axons are mechanosensitive (Niijima, 1975) and can participate in spinal reflexes which change renal perfusion (Beacham and Kunze, 1969). They are also likely to be chemosensitive and nociceptive (Rump et al., 2003).

2.2. Fish

2.2.1. Cyclostomes

A role for autonomic nerves has not been demonstrated in cyclostomes. Regulation of kidney perfusion is likely to be via central changes in blood pressure. Noradrenaline has been shown to alter sodium potassium and calcium ions in the renal tubules of the river lamprey *Lampetra fluviatilis* (Goncharevskaia and Monin, 1987).

2.2.2. Elasmobranchs

Direct autonomic motor control of elasmobranch kidney has not been tested functionally or anatomically. Sympathetic ganglia lie adjacent to the kidneys (Gibbins, 1994; Young, 1933) but it is not known if these provide adrenergic innervation. Exogenous adrenaline alters excretion and increases intra-renal blood flow in a number of species (Brown and Green, 1987; Deetjen and Boylan, 1968; Forster et al., 1972; Hentschel, 1988). Whether neuronally released adrenaline activates these receptors should be tested.

In addition to osmoregulation via kidneys (and gills), elasmobranchs have a rectal gland (Kent and Carr, 2000; see also Holgrem and Olsson, this volume). This gland secretes a hypertonic NaCl solution and is thought to be under neural and hormonal control (Acher et al., 1999; Stoff et al., 1988). Nerves immunoreactive to VIP are found within this gland and VIP promotes secretion (Chipkin et al., 1988; Stoff et al., 1979, 1988). In addition to glandular epithelium, the rectal gland contains smooth muscle which contracts in the presence of acetylcholine (ACh). Nitric oxide evokes an initial relaxation followed by contraction (Evans and Piermarini, 2001). The role of this smooth muscle in osmoregulation, or whether this muscle is under nervous control remains to be investigated.

2.2.3. Teleosts

Although typical vertebrate kidney structures such as glomeruli, proximal and distal tubules and collecting ducts are present, the relative abundance of these varies markedly between species. These differences are driven by the different osmoregulatory challenges of marine or freshwater environments (Evans and Claiborne, 2009). Nerves associated with the kidney vessels or parenchyma have been observed in numerous species (Sharma and Kumar, 1982; Shvalev, 1968; Young, 1931). Adrenergic innervation has been demonstrated in several species including Atlantic cod (*Gadus morhua*) (Burnstock, 1969) and rainbow trout (*Oncorhynchus mykiss*) (Elger et al., 1984). The preglomerular arteriole sphincters of rainbow trout, a euryhaline species, have a dense adrenergic plexus and alteration of glomerular blood flow is thought to aid in the transition between freshwater and marine environments (Elger et al., 1984).

The kidney of the rainbow trout also receives an extensive innervation by nNOS-immunoreactive fibres and intrinsic microganglia (Jiménez et al., 2001). The role of these nerves in trout is unclear. However in mammals nitric oxide promotes diuresis and sodium excretion (Mount and Power, 2006).

2.2.4. Dipnoans

There is scant information on the innervation of lungfish kidney. There is evidence that systemic adrenaline causes diuresis, but this