Research Paper

Journal of Vascular Research

J Vasc Res 2008;45:323–332
DOI: 10.1159/000119095

Received: July 13, 2007
Accepted after revision: November 24, 2007
Published online: March 3, 2008

# Sympathetic Innervation of Human Mesenteric Artery and Vein

David J. Birch[a, b] Mark Turmaine[c] Paul B. Boulos[b] Geoffrey Burnstock[a]

[a]Autonomic Neuroscience Centre, and [b]Department of Surgery, Royal Free and University College Medical School, and [c]Department of Anatomy, University College London, London, UK

**Key Words**
Human mesenteric artery · Sympathetic innervation

**Abstract**
***Background:*** Innervation of blood vessels shows inter-species variability. There are few studies on the innervation of human vessels; thus, healthy mesenteric vessels were studied to identify the expression of immunomarkers and the morphology of sympathetic innervation as the basis for a study of mesenteric vessels in inflammatory bowel disease. ***Methods and Results:*** Electron microscopy studies examined the relationships of nerves to smooth muscle cells. In veins, nerves were distributed throughout the medial smooth muscle coat, often in close apposition (50 nm) to smooth muscle cells. In arteries, nerves were located at the adventitial-medial border, few closer than 2,000 nm to smooth muscle cells, often with interposing connective tissue and Schwann cell processes. There was a significantly greater nerve density in veins than in arteries (227 vs. 41 $mm^2$; $p = 0.03$). Immunohistochemical studies revealed the presence of sympathetic and sensory-motor nerves in arteries and veins. ***Conclusions:*** It is suggested that in humans with an upright stance, the mesenteric venous system plays a particularly important role in controlling mesenteric capacitance, which is reflected by their dense innervation. It is speculated that transmitters released from perivascular nerves supplying the human mesenteric arteries may play a long-term (trophic) role in addition to short-term signalling roles.



## Introduction

Perivascular nerves supply the smooth muscle of human mesenteric blood vessels, working with the endothelium as part of the 'dual control' mechanism to control blood flow to the organs [1]. The nerves are primarily sympathetic, containing noradrenaline (NA), adenosine 5′-triphosphate (ATP) and neuropeptide Y (NPY) as co-transmitters [2, 3]. Sensory-motor nerves [4] and projections of nerve fibres from the enteric nervous system may also be present [5, 6].

Studies of vessels from the guinea pig have shown a wide variability in the response to nerve stimulation in vitro [3, 7–10], perhaps related to the non-synaptic nature of vascular neuromuscular junctions with variations in the width of the junctional cleft [11]. At the extreme, guinea pig mesenteric arteries were responsive, whereas the renal arteries were not [12]. Ultrastructural differences were identified between these vessels, which may account for the difference in response, including a wide neuromuscular gap and the presence of interposed connective tissue in the non-functional group. Inferior mesenteric neurons projecting to mesenteric arteries are distinct from neurons projecting to mesenteric veins [13].There are surprisingly few published morphological studies on the innervation of human vessels. However, light microscope immunohistochemical descriptions of the innervation of human mesenteric artery are available [14], and a functional study showed that the magnitude of the vasomotor response induced by perivascular

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com


1018–1172/08/0454–0323$24.50/0

Accessible online at:
www.karger.com/jvr

Prof. Geoffrey Burnstock
Autonomic Neuroscience Centre, Royal Free and University College Medical School
Rowland Hill Street
London NW3 2PF (UK)
Tel. +44 20 7830 2948, Fax +44 20 7830 2949, E-Mail g.burnstock@ucl.ac.uk

nerve stimulation was larger in the vein than in the artery [15]. The purpose of this study was to investigate differences in the ultrastructural relationships of the nerves and smooth muscle in human mesenteric arteries and veins and the expression of immunomarkers for neurotransmitters commonly found in perivascular nerves that may relate to their responsiveness and to provide control information for studies of the innervation of human mesenteric vessels in inflammatory bowel disease.

## Materials and Methods

Human mesenteric specimens (n = 6 for artery and vein) were obtained at the time of surgery in patients operated on for non-inflammatory conditions, the majority for left-sided cancer of the colon and rectum. Informed consent for the procedures was obtained using a standard consent form.

The mesenteric specimens (approximately 3–5 mm in diameter) were immediately placed in ice-cold Hanks' solution and transported to the laboratory. Mesenteric segments were taken from parts furthest from the lesion being excised, close to the bowel wall, to avoid interference with the lymph nodes in the specimen that are examined by the pathologists to obtain prognostic information and to ensure that these specimens represented healthy tissue.

Segments of artery and vein were carefully dissected from the specimen using a dissecting microscope. These segments were dealt with in 2 ways: segments (5 mm long) were placed in cold Krebs' solution for immunohistochemical analysis, and other small sections were fixed in a freshly made solution of 2% glutaraldehyde and 2% paraformaldehyde in 0.1 M cacodylate buffer, prior to processing for electron microscopy (n = 3). Corresponding sections of artery and vein were kept together, to allow comparison of vessels from the same part of the mesentery.

*Immunohistochemical Staining*

Segments of mesentery were removed in the operating theatre and immediately placed in cold Hanks' balanced salt solution. The marginal vessels or vasa rectae of 1–3 mm diameter were then dissected free of excess fat and connective tissue and slit longitudinally. Segments were fixed for at least 2 h in 4% paraformaldehyde. When fixed, the stretched dimensions were retained. Specimens were then washed in phosphate-buffered saline and stored at 4°C until processed.

Whole-mount segments of mesenteric artery and vein were stained using a standard indirect immunofluorescence technique. Briefly, background staining was reduced by incubation in normal donkey serum (1:10) for 2 h at room temperature. Rabbit-derived polyclonal antibodies to tyrosine hydroxylase (TH), NPY, vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP), nitric oxide synthase, choline acetyltransferase (for acetylcholine), 5-hydroxytryptamine or protein gene product 9.5 (PGP9.5) were applied for 36 h in a humid chamber at room temperature, using concentrations as shown in table 1. After washing 3 times in 0.1% Triton in phosphate-buffered saline, biotinylated donkey anti-rabbit antibody was applied for 2 h. After further washing, streptavidin-fluorescein was applied for 1 h. Specimens were again washed prior to counterstaining in Pontamine sky blue. This has been shown to reduce background fluorescence [16]. Sections were then mounted on glass slides in Citifluor, an anti-fading compound (Citifluor Ltd., London, UK).

**Table 1.** Details of antisera

| Antigen | Source | Dilution |
|---|---|---|
| TH | Affiniti (UK) | 1:500 |
| NPY | Biogenesis (UK) | 1:2,000 |
| VIP | Incstar (USA) | 1:2,000 |
| SP | Genosys (UK) | 1:1,000 |
| CGRP | Affiniti (UK) | 1:1,000 |
| 5-HT | Incstar (USA) | 1:250 |
| PGP9.5 | Ultraclone (UK) | 1:2,000 |
| ChAT | Biogenesis (UK) | 1:250 |
| NOS | Eurodiagnostica (Sweden) | 1:250 |

SP = Substance P; 5-HT = 5-hydroxytryptamine; ChAT = choline acetyltransferase; NOS = nitric oxide synthase.

The slides were viewed on a Leica TCS 4D confocal microscope (Leica, Heerbrugg, Switzerland) using an objective magnification of ×25 (unless the nerves were too fine to be seen at the initial magnification, when ×40 objective was used). Three representative fields were then recorded, having set the depth of tissue scanned ('z-series') to include all visible nerves in each field. The z-series and the projected image were then stored digitally on optical disk.

The digital images were analysed for the total fluorescent area, which is proportional to the total number of nerves within bundles, using Scion image analysis software (NIH, USA). Images were converted to negative black-and-white format. The greyscale level that demarcated the boundary between the background and the nerves was chosen individually for each image and converted to a binary image, which was subjected to the process of 'closing', which has the effect of removing small background speckles up to a predefined size. The total fluorescent area of nerves in the visual field was measured for each of the immunomarkers and expressed as a percentage of that for PGP9.5 (taken as the total nerve population).

*Electron Microscopy*

Corresponding segments of mesenteric artery and vein were obtained from the vessels directly entering the bowel wall (the vasa recta). Specimens were transferred to a solution of 1% osmium tetroxide in 0.1 M cacodylate buffer for secondary fixation, after which they were stained en bloc with 2% uranyl acetate in distilled water and embedded in Araldite resin. Ultrathin sections were then cut. Secondary staining was performed with 4% uranyl acetate and lead citrate. The sections were viewed on a JOEL 1010 transmission electron microscope (JOEL Instruments, Akishima, Japan). The location of perivascular nerves was determined using both low and high power to discover the relationship of the nerves to the vascular smooth muscle and other components of the vessel

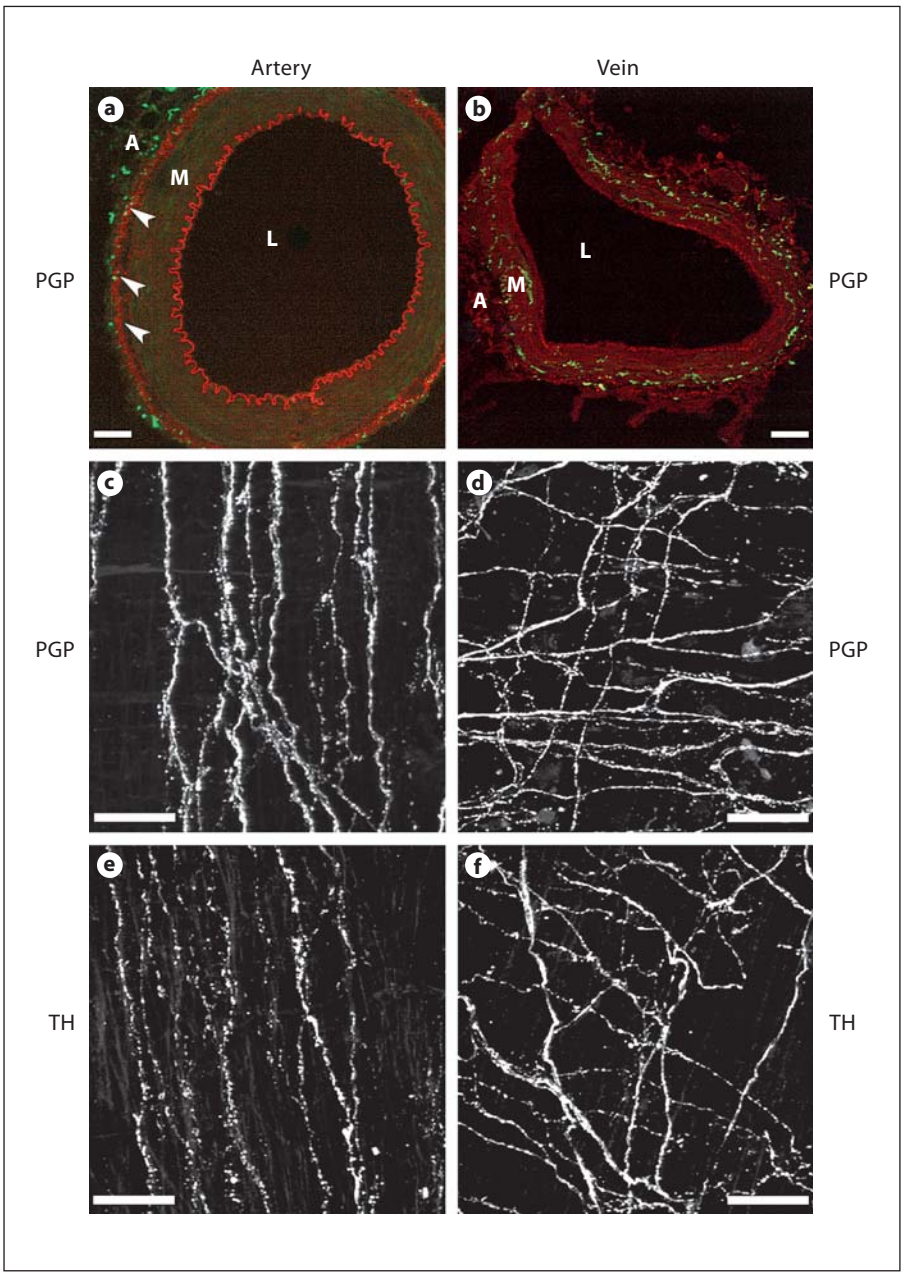


**Fig. 1. a**, **b** Confocal images of transverse sections of human mesenteric arteries and veins. Perivascular nerves stained for PGP9.5 (green) can be seen. In the artery, nerves are located at the adventitial (A)/medial (M) border (arrowheads). Note the well-defined external elastic lamina. In the vein, nerves are distributed throughout the media. L = Lumen. **c–f** Confocal images of whole-mount preparations of human mesenteric arteries and veins. The longitudinal axis of the vessels is from top to bottom and the nerve bundles are orientated longitudinally. Immunostaining for PGP9.5 (**c**, **d**) and TH (**e**, **f**). Scale bars = 100 μm (**a**, **b**), 50 μm (**c–f**).

wall. To quantify the nerve densities of the vessels, each image was examined and the number of nerves counted. The total area of the adventitia and the media was then determined (in $mm^2$), and the number of nerves per millimetre was calculated.

## Results

*Immunohistochemical Analysis*

The general neuronal marker PGP9.5 was used to visualize nerves within arteries and veins. In the arteries, nerves were distributed at the junction of the adventitia and the media, close to the external elastic lamina (fig. 1a). In the veins, nerves were distributed throughout the muscular layer of the media (fig. 1b).

The nerve densities of the 2 vessel types differed significantly. In the arteries, the mean nerve density was $41/mm^2$, whereas in the veins, the density was $227/mm^2$ ($p = 0.03$, paired t test).

Nerves immunoreactive to PGP9.5, TH and NPY were identified in arteries and veins (fig. 1a–f, fig. 2a, b), orien-

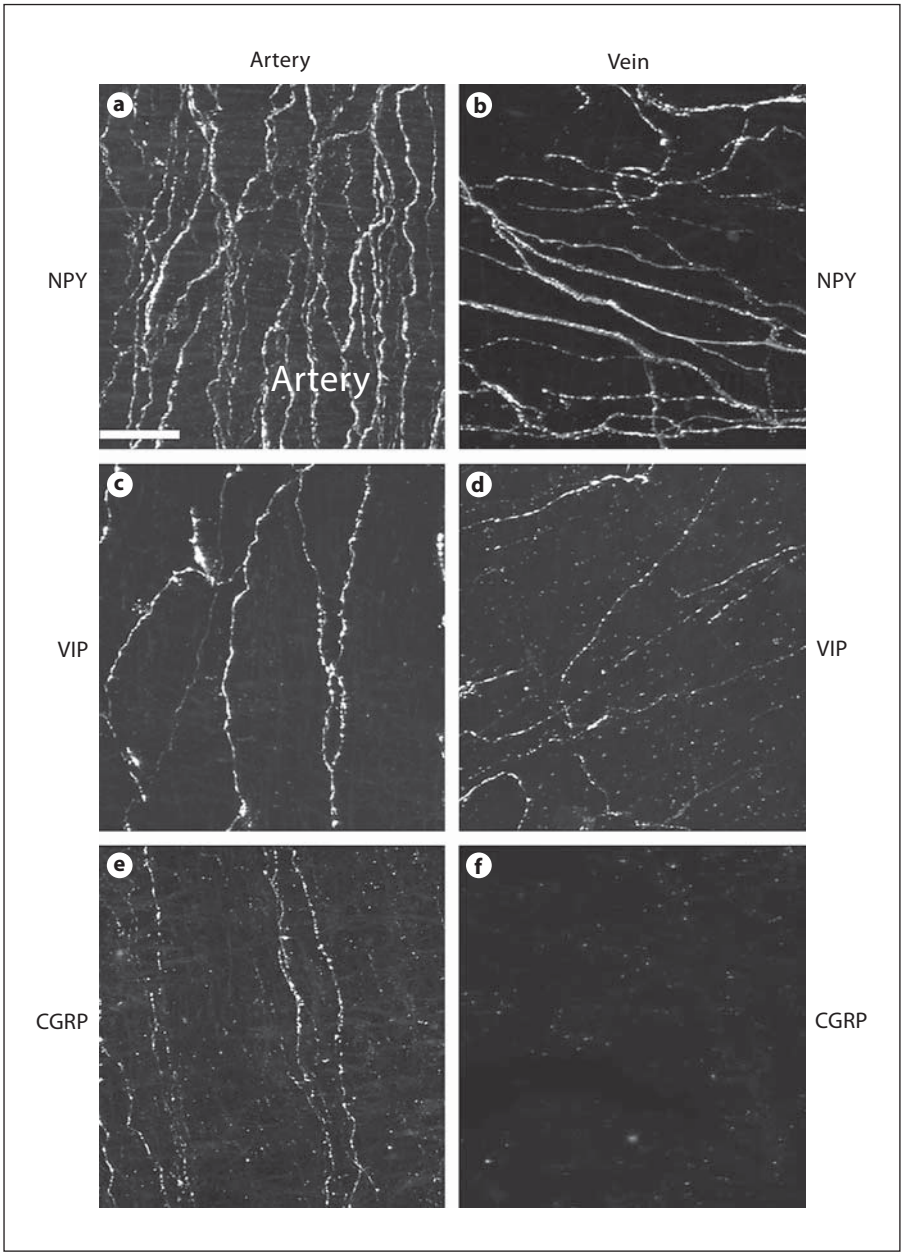


**Fig. 2.** Confocal images of whole-mount preparations of human mesenteric arteries and veins. Immunostaining for NPY (**a**, **b**), VIP (**c**, **d**) and CGRP (**e**, **f**). Scale bar = 50 μm.

tated longitudinally in arteries (fig. 1a, c, e, 2a), whereas in the corresponding veins, nerves formed a reticular pattern (fig. 1b, d, f, 2b). Nerves immunoreactive to VIP were identified in both arteries and veins (fig. 2c, d), although at a lower density than with staining for TH and NPY. Sparse substance P immunoreactivity was also identified in most control arteries and all veins, the nerves being very fine with well-defined varicosities. Nerves immunoreactive to CGRP were seen in most arteries (fig. 2e) but in none of the veins (fig. 2f). Immunoreactivity to 5-hydroxytryptamine was occasionally seen in arteries and more often in veins of a low intensity. No nerves immunoreactive to nitric oxide synthase or choline acetyltransferase were identified in either arteries or veins. The percentage of nerves immunoreactive for the various immunomarkers, as a percentage of PGP9.5, are shown in table 2.

*Electron Microscopy*

Nerves were identified by electron microscopy. In both the arteries and the veins, they appeared as unmy-

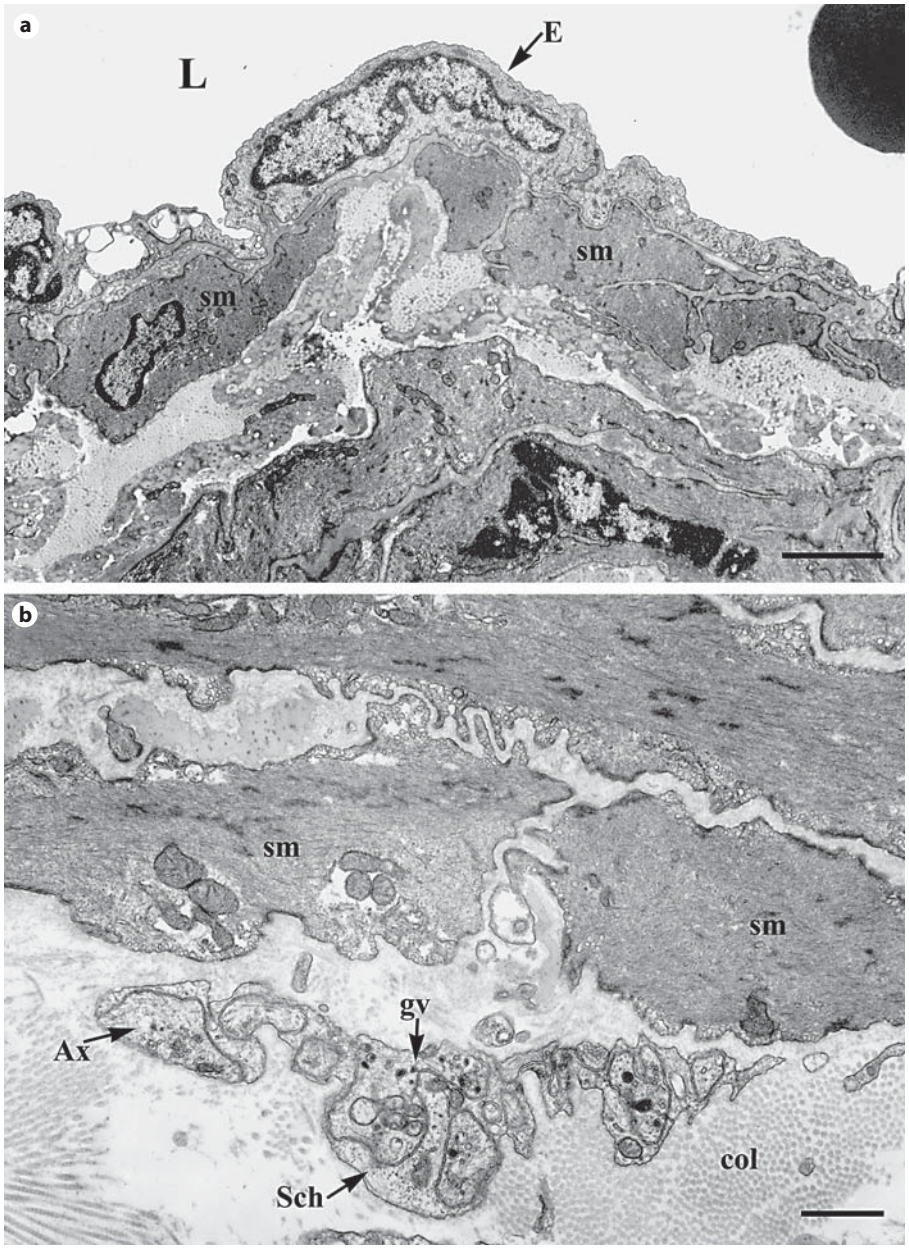


**Fig. 3. a** High power view of an endothelial cell (E) in a human mesenteric vein in close association with underlying smooth muscle cells (sm) in the intima. A dense connective tissue matrix is present. L = Lumen. **b** Medial-adventitial border of a vein showing the lack of an external elastic lamina and the close apposition of nerves, some containing granular vesicles (gv), within the adventitia to the medial smooth muscle without collagen (col) interposed. Sch = Schwann cell process; Ax = axon. Scale bars = 2 μm (**a**), 1 μm (**b**).

elinated fibres, with a number of nerve profiles enveloped within a single Schwann cell sheath. Vesicles could be seen in many of the nerve profiles (fig. 3b).

The nerves in the veins were situated throughout the muscular media as well as at the adventitial-medial border. In many of the images, the nerve fibres approach the muscle cells and are seen to be in close apposition (fig. 3b, 4b, c). In some of the veins, capillaries of the vasa vasorum were present. These sometimes appeared to be related to nerve bundles (fig. 4a). The intima was thickened, with sub-intimal connective tissue and smooth muscle cells (fig. 3a).

In the mesenteric artery, there is a well-developed fenestrated external elastic lamina separating the medial smooth muscle cells from the adventitial connective tissue (fig. 5a). Perivascular nerves in the arteries were often outside the external elastic lamina (fig. 5b). Nerve profiles were rarely seen closer than 2 μm to the smooth muscle. Many nerve bundles in the adventitia were surrounded by collagen (fig. 5c). The smooth muscle cells of

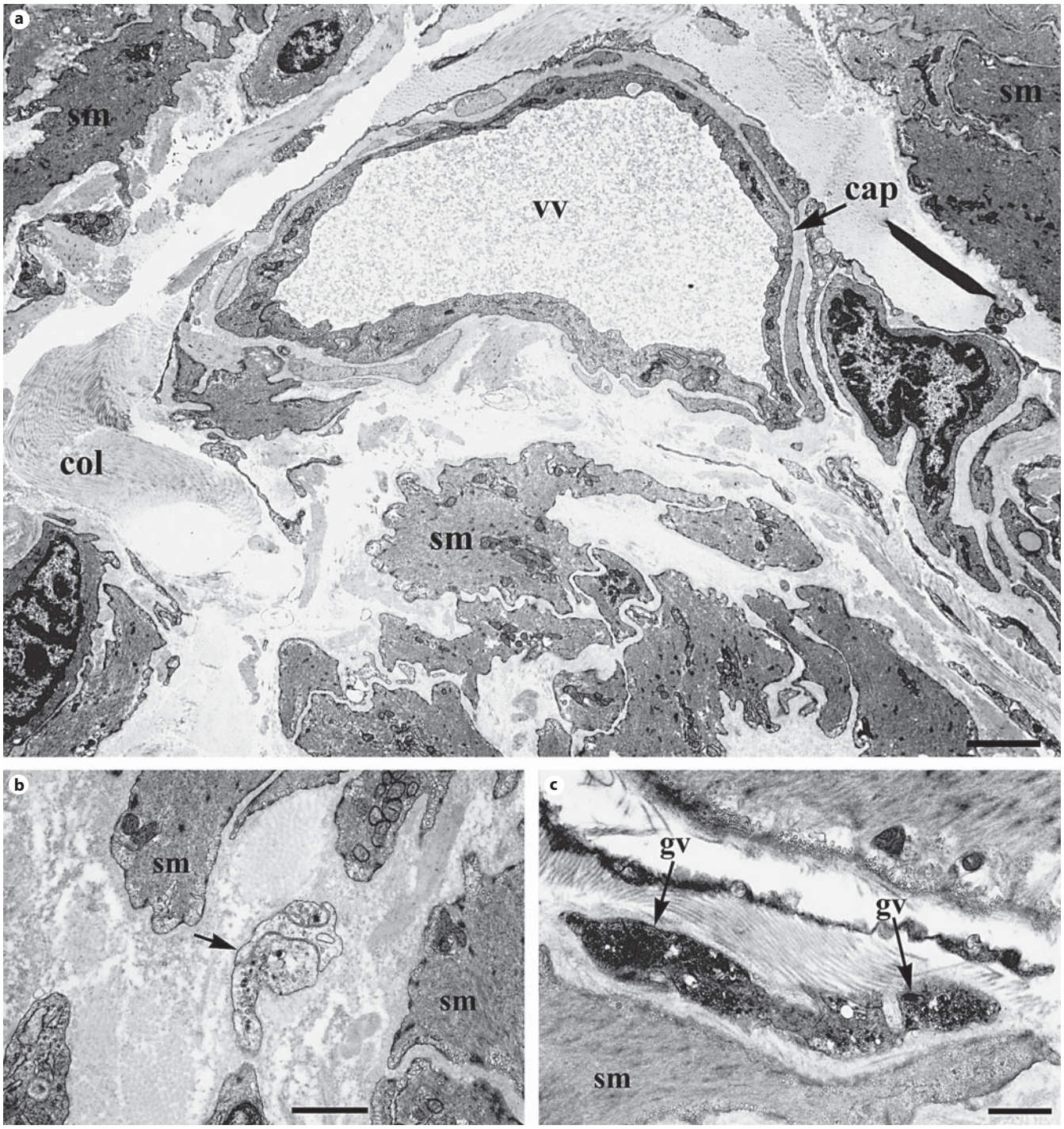


**Fig. 4.** Electron micrograph of the media of human mesenteric vein. **a** The wall of the vein appears to have a less organized orientation of the smooth muscle (sm) compared with the artery, though this may relate to the state of contraction at the time of fixation or because of the presence of the vasa vasorum (vv); within the blocks of smooth muscle cells, there is less collagen (col) and elastic material than between smooth muscle cells in the artery. Capillaries (cap) of the vasa vasorum are often found in the inner media, which is sometimes associated with small nerve bundles and Schwann cells (see higher magnification micrograph in **c** ). **b** A section through the media showing substantial collagen between the blocks of smooth muscle cells. A nerve bundle (arrow) is present. **c** High magnification of nerve fibres containing granular vesicles (gv) in close apposition to smooth muscle cells with no Schwann cell processes interposed. Scale bars = 2 μm (**a**), 3 μm (**b**), 1 μm (**c**).

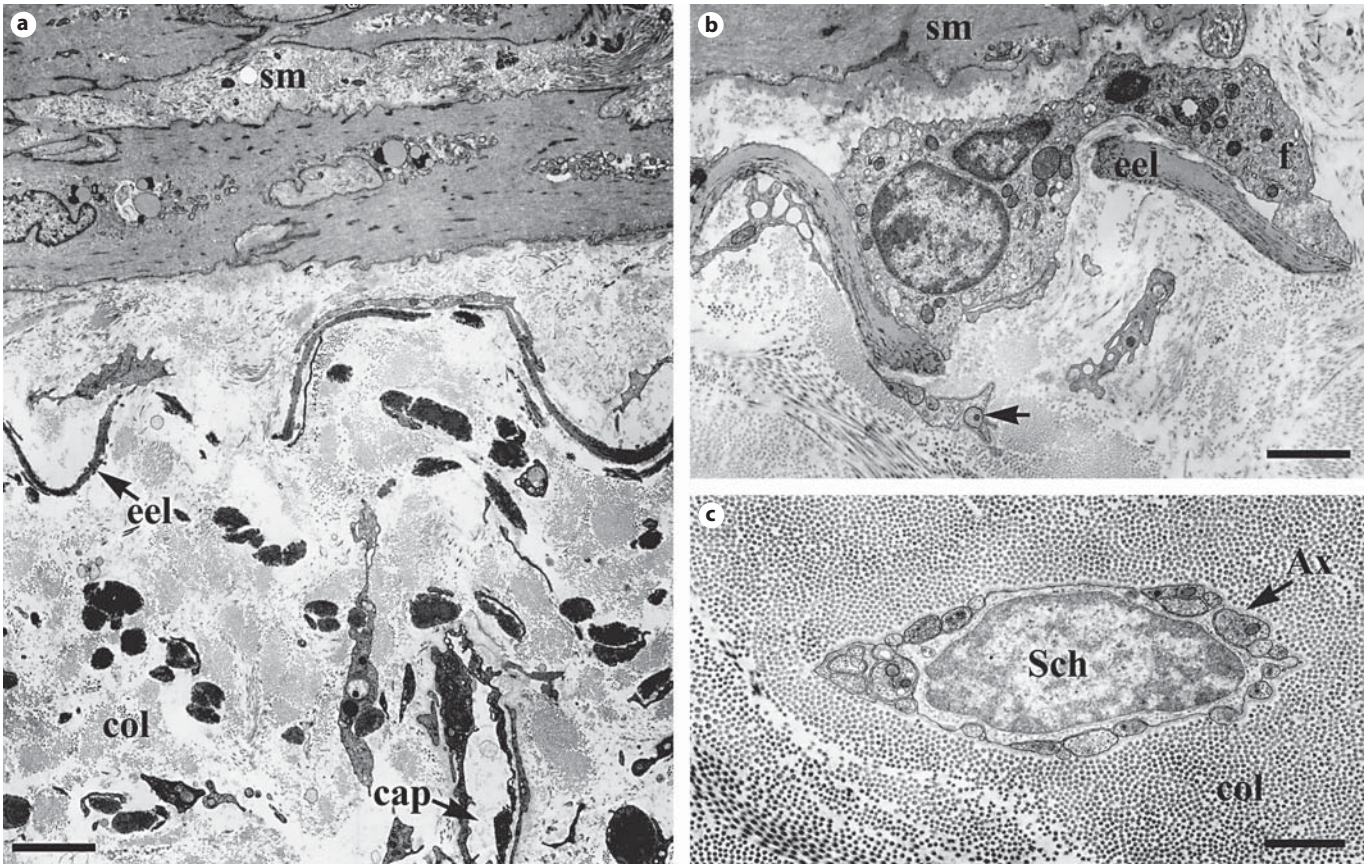


**Fig. 5. a** Electron micrograph showing the adventitial-medial junction in a human mesenteric artery. Smooth muscle fibres (sm) in the media are separated from the fibrous adventitia by a well-defined external elastic lamina (eel). The adventitia contains collagen (col), bundles of longitudinally orientated elastic tissue and capillaries (cap). **b** Electron micrograph showing a nerve fibre (arrow) largely enveloped by a Schwann cell process in the adventitia close to the arterial external elastic lamina. The external elastic lamina is reminiscent of a 'net stocking', but the nerve fibre is not on the medial side. A fibroblast-like cell (f) is interposed between the connective tissue and the medial muscle coat. **c** Axon fibres (Ax) within a nerve bundle in the arterial adventitia with its associated Schwann cell (Sch) are embedded in collagen. Scale bars = 4 μm (**a**), 2 μm (**b**), 1 μm (**c**).

**Table 2.** Percentages of mesenteric perivascular nerves immunoreactive for various immunomarkers as a percentage of those immunoreactive for PGP9.5

| Immunomarker | Artery | Vein |
|---|---|---|
| PGP9.5 | 100 | 100 |
| TH | 70.0 ± 8.2 | 87.9 ± 7.9 |
| NPY | 113.8 ± 12.3 | 130.1 ± 10.4 |
| VIP | 37.7 ± 5.7 | 34.3 ± 6.2 |
| SP | 3.0 ± 0.9 | 4.7 ± 1.5 |
| CGRP | 28.0 ± 8.9 | 0 |
| 5-HT | 1.7 ± 1.1 | 6.07 ± 2.44 |

Data are presented as % ± SEM for 6 specimens. SP = Substance P; 5-HT = 5-hydroxytryptamine.

the arterial media are orientated in a circular fashion, with intercellular connective tissue (fig. 6). The intima in these vessels was thickened, due to subendothelial connective tissue deposition. Within the connective tissue, randomly orientated intimal smooth muscle cells were identified.

## Discussion

Human mesenteric veins were much more densely innervated than the corresponding arteries. This is of interest since, in general, arteries are more heavily innervated than veins [10, 17]. These vessels also had a thick muscu-

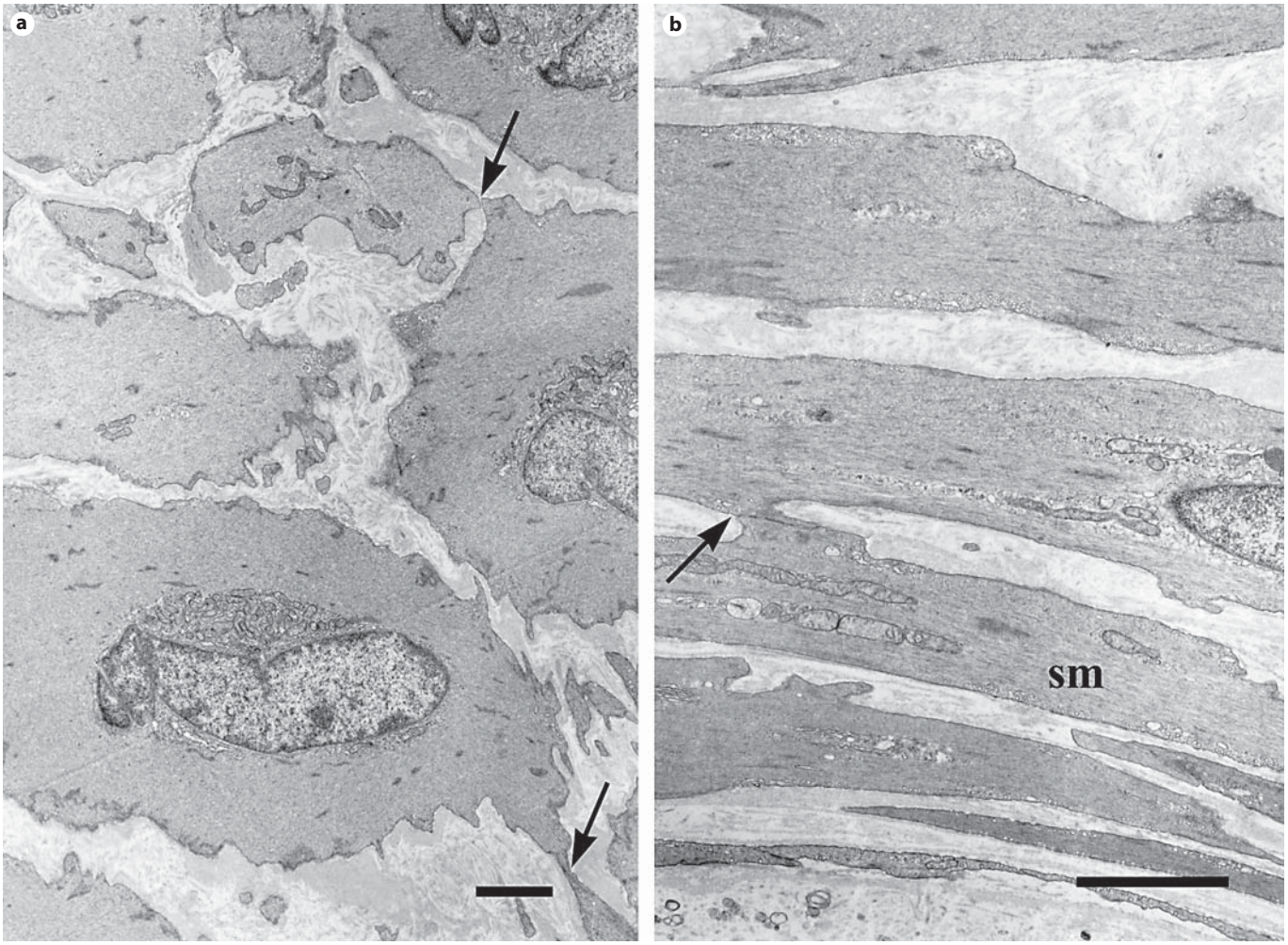


**Fig. 6.** Electron micrograph of smooth muscle from the media of the mesenteric artery orientated in a circular fashion. Cells are separated by collagen except for small areas of close apposition, probably punctate gap junctions (arrows). Sm = Smooth muscle. Scale bars = 2 μm.

lar media. Human mesenteric veins play a particularly important role in controlling mesenteric capacitance in man related to their 2-legged stance compared with 4-legged stance in experimental animals [18, 19]. The high nerve density may reflect the need for fine control of their tone.

In this study, using immunohistochemistry, arteries and veins were shown to have a dense nerve plexus of PGP9.5-immunoreactive nerves. PGP9.5 is a general neuronal marker, although more recently, it has been shown that PGP9.5 might underestimate the total neuron number and there is evidence that the pan-neuronal markers Cuprolinic blue and anti-HuC/D may be more reliable neuronal markers, at least in the gut [20]. This is further supported by the fact that in mesenteric vessels, greater immunoreactivity to NPY was found compared with PGP9.5. Dense plexuses to TH- and NPY-immunoreactive nerves were also found, indicative of sympathetic nerves; the presence of positively stained nerves of CGRP and substance P indicate the presence of sensorymotor nerves, although at a lower density than that of sympathetic nerves.

Vasoconstriction in response to nerve stimulation has been reported for both the human mesenteric artery and vein, although the responses were greater in the vein than in the artery [15]. The constriction was shown to be mediated by sympathetic nerves, involving NA, ATP and NPY as cotransmitters. This is typical of many mamma-

lian vessels [3]. NA and ATP are known to cause constriction of human mesenteric arteries and veins [21], although NPY, while inducing vasoconstriction of human mesenteric veins, failed to constrict arteries. However, it did reduce nerve stimulation-evoked [$^3$H]NA overflow from the mesenteric vein, indicating both a pre- and postjunctional effect [21].

It has been previously noted that some blood vessels, whilst possessing varicose noradrenergic nerve fibres, show difficulties in producing responses to nerve stimulation in vitro, using standard stimulation parameters [12, 22]. The guinea pig renal artery is such a vessel. In these vessels, the nerve varicosities were separated from smooth muscle cells by wide neuromuscular spaces containing cellular and other connective tissue elements. Responsive vessels, such as the guinea pig mesenteric artery, had narrow neuromuscular spaces of as little as 50 nm, with little more than the basement membrane separating the varicosities and muscle cells. Although the walls of the human mesenteric arteries are thick and muscular, typical of resistance arteries, nerves were usually outside the external elastic lamina and there were often large amounts of connective tissue, fibroblasts and processes of other cell types between nerve profiles and the muscle. This is reminiscent of features of guinea pig renal arteries. In the guinea pig, mesenteric arteries have a substantial response to nerve stimulation [12] and are responsible for about one third of the total mesenteric vascular resistance [23].

The anatomical relationships to fibroblasts and smooth muscle cells in the mesenteric arteries studied raise questions about the role of the nerves. In addition to a role in controlling vascular tone, a trophic role has been proposed. Some mature tissues are known to be under trophic control of their nerves. In the heart, the normal development of cardiac muscle is dependent upon an intact sympathetic nerve supply [24]. It appears that ATP and its breakdown product adenosine, rather than NA, may be the agents responsible for this effect [25, 26]. In blood vessels, collagen synthesis increases in blood vessel walls after chemical sympathectomy [27], indicating that nerve activity has an influence on vessel wall structure. There is also evidence that the sensory innervation of blood vessels affects the expression of vasoactive substances by the endothelium [28]. Sensory denervation increases the sympathetic vasoconstriction in rat mesenteric arteries, an effect that is thought to be due to long-term trophic changes in the vessels [29]. Much has yet to be learned about the possible trophic effects of neurotransmitters in addition to their role in vasomotor effects on the innervated smooth muscle.

In conclusion, this study has revealed the presence of dense sympathetic innervation in human mesenteric arteries and veins, in addition to the presence of sensory motor nerves. The nerve density was significantly greater in the veins than in the arteries. It is suggested that in humans with an upright stance, the mesenteric venous system plays a particularly important role in controlling mesenteric capacitance, reflected by their dense innervation. It is speculated that transmitters released from perivascular nerves supplying the human mesenteric arteries may play a long-term (trophic) role in addition to short-term signalling roles.

## References


1 Burnstock G, Ralevic V: New insights into the local regulation of blood flow by perivascular nerves and endothelium. Br J Plast Surg 1994;47:527–543.
2 Saville VL, Maynard KI, Burnstock G: Neuropeptide Y potentiates purinergic as well as adrenergic responses of the rabbit ear artery. Eur J Pharmacol 1990;176:117–125.
3 Burnstock G: Cotransmission. Curr Opin Pharmacol 2004;4:47–52.
4 Maynard KI, Saville VL, Burnstock G: Sensory-motor neuromodulation of sympathetic vasoconstriction in the rabbit central ear artery. Eur J Pharmacol 1990;187:171–182.
5 Costa M, Furness JB: The origins, pathways and terminations of neurons with VIP-like immunoreactivity in the guinea-pig small intestine. Neuroscience 1983;8:665–676.
6 Ekblad E, Ekman R, Hakanson R, Sundler F: Projections of peptide-containing neurons in rat colon. Neuroscience 1988;27:655–674.
7 Vanhoutte P: Heterogeneity in vascular smooth muscle; in Kaley G, Altura BM (eds): Microcirculation. Baltimore, University Park Press, 1978, vol 2, pp 181–309.
8 Bevan JA, Brayden JE: Nonadrenergic neural vasodilator mechanisms. Circ Res 1987;60:309–326.
9 Morris JL, Gibbins IL: Structure-function relationships of the autonomic nervous system in the thoracic circulations. Proc Aust Physiol Pharmacol Soc 1990;21:29–39.
10 Ralevic V, Burnstock G: Interactions between perivascular nerves and endothelial cells in control of local vascular tone; in Bennett T, Gardiner S (eds): The Autonomic Nervous System. Nervous Control of Blood Vessels. Chur, Harwood Academic Publishers, 1996, vol 8, pp 135–175.
11 Burnstock G: Non-synaptic transmission at autonomic neuroeffector junctions. Neurochem Int 2008;52:14–25.
12 Cowen T: An ultrastructural comparison of neuromuscular relationships in blood vessels with functional and 'non-functional' neuromuscular transmission. J Neurocytol 1984;13:369–392.

13 Browning KN, Zheng Z, Kreulen D L, Travagli RA: Two populations of sympathetic neurons project selectively to mesenteric artery or vein. Am J Physiol 1999;276:H1263–H1272.
14 Buwalda J, Colnot DR, Bleys RL, Groen GJ, Thrasivoulou C, Cowen T: Imaging and analysis of perivascular nerves in human mesenteric and coronary arteries: a comparison between epi-fluorescence and confocal microscopy. J Neurosci Methods 1997;73:129–134.
15 Racchi H, Schliem AJ, Donoso MV, Rahmer A, Zúñiga A, Guzmán S, Rudolf K, Huidobro-Toro JP: Neuropeptide Y $Y_1$ receptors are involved in the vasoconstriction caused by human sympathetic nerve stimulation. Eur J Pharmacol 1997;329:79–83.
16 Cowen T, Haven AJ, Burnstock G: Pontamine sky blue: a counterstain for background autofluorescence in fluorescence and immunofluorescence histochemistry. Histochemistry 1985;82:205–208.
17 Todd ME: Development of adrenergic innervation in rat peripheral vessels: a fluorescence microscopic study. J Anat 1980;131:121–133.
18 Hainsworth R: Vascular capacitance: its control and importance. Rev Physiol Biochem Pharmacol 1986;105:101–173.
19 Hogan QH, Stadnicka A, Kampine JP: Effects of epidural anesthesia on splanchnic capacitance. Adv Pharmacol 1994;31:471–483.
20 Phillips RJ, Hargrave SL, Rhodes BS, Zopf DA, Powley TL: Quantification of neurons in the myenteric plexus: an evaluation of putative pan-neuronal markers. J Neurosci Methods 2004;133:99–107.
21 Pernow J, Svenberg T, Lundberg JM: Actions of calcium antagonists on pre- and postjunctional effects of neuropeptide Y on human peripheral blood vessels in vitro. Eur J Pharmacol 1987;136:207–218.
22 Gallen DD, Cowen T, Griffith SG, Haven AJ, Burnstock G: Functional and non-functional nerve-smooth muscle transmission in the renal arteries of the newborn and adult rabbit and guinea-pig. Blood Vessels 1982;19:237–246.
23 Fenger-Gron J, Mulvany MJ, Christensen KL: Mesenteric blood pressure profile of conscious, freely moving rats. J Physiol (Lond) 1995;488:753–760.
24 Renick SE, Seidler FJ, McCook EC, Slotkin TA: Neuronal control of cardiac and hepatic macromolecule synthesis in the neonatal rat: effects of sympathectomy. Pediatr Res 1997;41:359–363.
25 Osswald W: Mediation by adenosine of the trophic effects exerted by the sympathetic innervation of blood vessels. J Neural Transm Suppl 1991;34:157–162.
26 Burnstock G: Purinergic signalling and vascular cell proliferation and death. Arterioscler Thromb Vasc Biol 2002;22:364–373.
27 Fronek K, Bloor CM, Amiel D, Chvapil M: Effect of long-term sympathectomy on the arterial wall in rabbits and rats. Exp Mol Pathol 1978;28:279–289.
28 Milner P, Burnstock G: Chronic sensory denervation reduces thrombin-stimulated endothelin release from aortic endothelial cells. Experientia 1996;52:242–244.
29 Ralevic V, Karoon P, Burnstock G: Long-term sensory denervation by neonatal capsaicin treatment augments sympathetic neurotransmission in rat mesenteric arteries by increasing levels of norepinephrine and selectively enhancing postjunctional actions. J Pharmacol Exp Ther 1995;274:64–71.