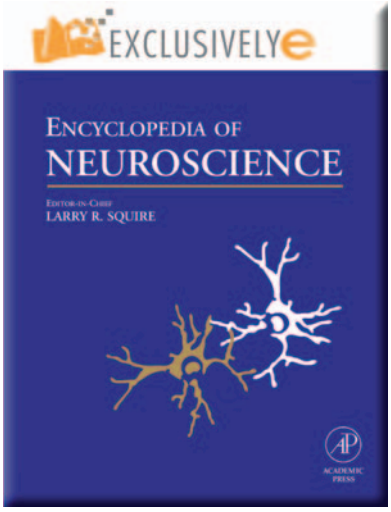

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Autonomic Neuroeffector Junction

G Burnstock, Royal Free and University College Medical School, London, UK

Introduction

Within the past 30 years, new discoveries have changed our understanding of the organization of the autonomic nervous system (ANS), including the structure of the autonomic neuroeffector junction and the multiplicity of neurotransmitters which take part in the process of autonomic neuroeffector transmission, as well as cotransmission, neuromodulation, receptor expression, and long-term (trophic) signaling. An outstanding feature of autonomic neurotransmission is the inherent plasticity afforded by its structural and neurochemical organization and the interaction between neural mediators and environmental factors. In this way, autonomic neurotransmission is matched to ongoing changes in demands and can sometimes be compensatory in pathophysiological situations.

Structure of the Autonomic Neuromuscular Junction

The autonomic neuromuscular junction differs in several important respects from the better known skeletal neuromuscular junction; it is not a synapse with the well-defined prejunctional and postjunctional specializations established for the skeletal neuromuscular synapse or ganglionic synapses. A model of the autonomic neuroeffector junction has been proposed on the basis of combined electrophysiologic, histochemical, and electron-microscopical studies. The essential features of this model are that the terminal portions of autonomic nerve fibers are varicose, transmitters being released *en passage* from varicosities during conduction of an impulse, although excitatory and inhibitory junction potentials are probably elicited only at close junctions. Furthermore, the effectors are muscle bundles rather than single smooth muscle cells and are connected by low-resistance pathways (gap junctions) that allow electrotonic spread of activity within the effector bundle. In blood vessels, the nerves are confined to the adventitial side of the media muscle coat, and this geometry appears to facilitate dual control of vascular smooth muscle by perivascular nerves and by endothelial relaxing and contracting factors. Neuroeffector junctions do not have a permanent geometry with postjunctional specializations, but rather the varicosities are continuously moving, and their special relation with muscle cell membranes changes with time, including dispersal and reformation of receptor clusters. For example, varicosity movement is likely to occur in cerebral blood arteries, where there is a continuously increasing density of sympathetic innervation during development and aging and in hypertensive vessels or those that have been stimulated chronically *in vivo*, where there can be an increase in innervation density of up to threefold.

Varicose Terminal Axons

In the vicinity of the effector tissue, axons become varicose, varicosities occurring at 5–10 μm intervals (Figure 1(a)), and branches intermingle with other axons to form the autonomic ground plexus, first described by Hillarp in 1946. The extent of the branching and the area of effector tissue affected by individual neurons vary with the tissue. Autonomic axons combined in bundles are enveloped by Schwann cells. Within the effector tissue, they partially lose their Schwann cell envelope, usually leaving the last few varicosities naked.

The density of innervation, in terms of the number of axon profiles per 100 muscle cells in cross-section, also varies considerably in different organs. For example, it is very high in the vas deferens (Figure 2(a)), iris, nictitating membrane, and sphincteric parts of the gastrointestinal tract but low in the ureter, uterus, and longitudinal muscle coat of the gastrointestinal tract. In most blood vessels, the varicose nerve plexus is placed at the adventitial border, and fibers rarely penetrate into the medial muscle coat (Figure 2(b)).

Junctional Cleft

The width of the junctional cleft varies considerably in different organs. In the vas deferens, nictitating membrane, sphincter pupillae, rat parotid gland, and atrioventricular and sinoatrial nodes in the heart, the smallest neuromuscular distances range from 10–30 nm. The minimum neuromuscular distance varies considerably in different blood vessels. Generally, the greater the vessel diameter, the greater the separation of nerve and muscle. Thus, minimal neuromuscular distances in arterioles and in small arteries and veins are about 50–100 nm, in medium to large arteries the separation is 200–500 nm, whereas in large elastic arteries where the innervation is sparser, the minimum neuromuscular distances are as wide as 1000–2000 nm. Serial sectioning has shown that at close junctions in both visceral and vascular organs, there is fusion of prejunctional and postjunctional

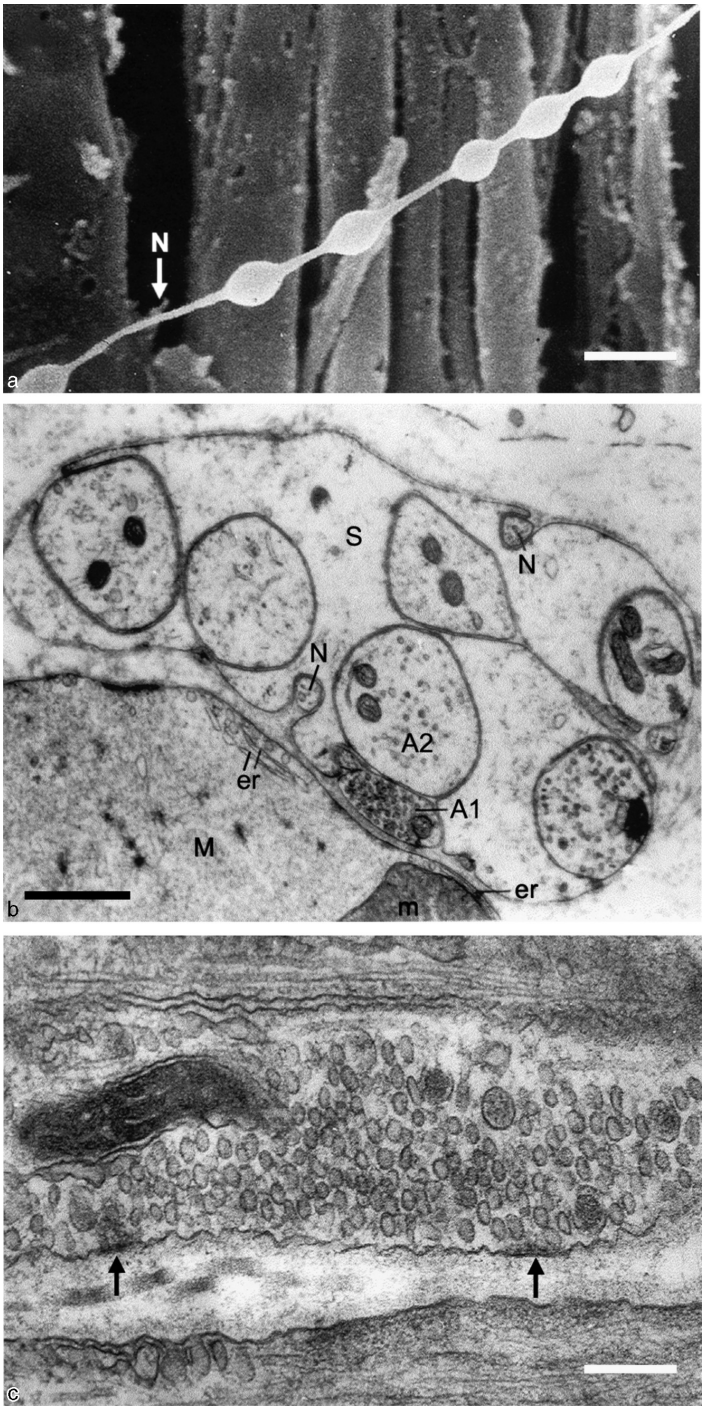

Figure 1 (a) Scanning electron micrograph of a single terminal varicose nerve fiber(N) lying over smooth muscle of small intestine of rat. Intestine was pretreated to remove connective tissue components by digestion with trypsin and hydrolysis with HCl. (b) A medium-size intramuscular bundle of axons within a single Schwann cell (S). There is no perineurial sheath. Some axons, free of Schwann cell processes, contain synaptic vesicles (e.g., A1 and A2). For nerve profile A1, there is close proximity (about 80 nm) to smooth muscle (M) with fusion of nerve and muscle basement membranes. Most of the axons in bundles of this size have few vesicles in the plane of section, but they resemble the vesicle-containing axons of the larger trunks in that they have few large neurofilaments. The small profiles (N), less than 0.25 μm in diameter, are probably intervaricosity regions of terminal axons. m, mitochondria; er, edoplasmic reticulum. (c) Autonomic varicosities with dense prejunctional thickenings and bunching of vesicles, probably representing transmitter release sites (arrows), but there is no postjunctional specialization. Scale bar = 3 μm (a), 1 μm (b), and 0.25 μm (c). (a) Reproduced from *The Airways: Neural Control in Health and Disease*, 1988, 1–22, Autonomic neural control mechanisms: With special reference to the airways, Burnstock G, figure 1, copyright Marcel and Dekker. With kind permission of Springer Science and Buisness Media. (b) Reproduced from *The Journal of Cell Biology*, 1963, vol. 19, pp. 529–550, by copyright permission of The Rockfeller University Press. (c) Courtesy of Phillip R Gordon-Weeks.

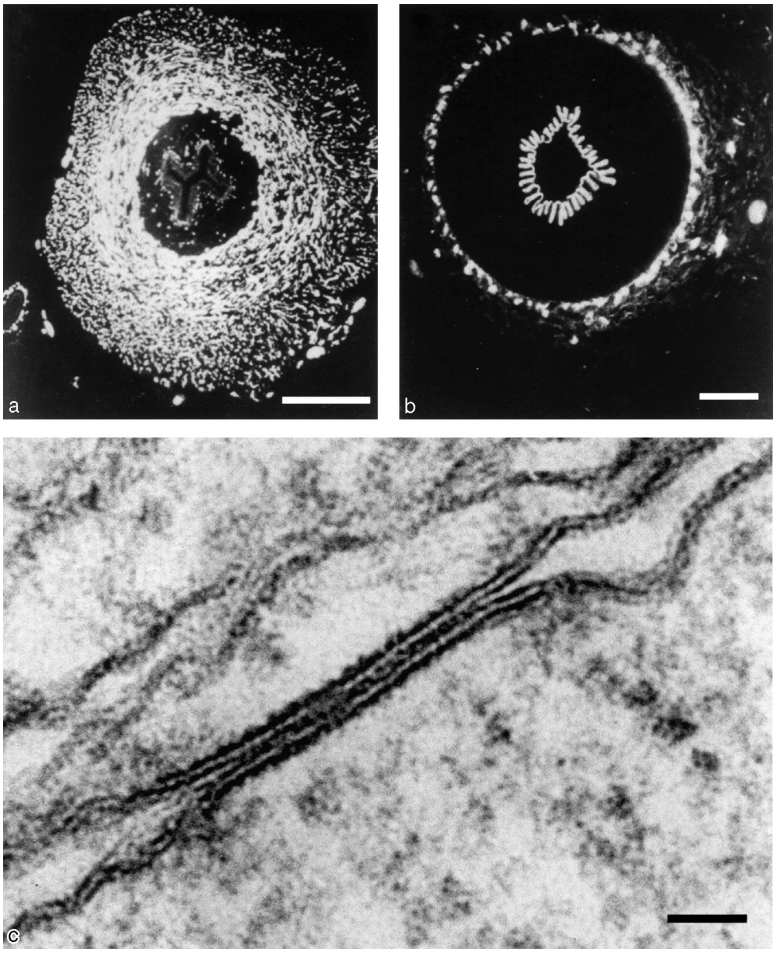

Figure 2 Comparison between the adrenergic innervation of the densely innervated vas deferens of the guinea pig (a) and the rabbit ear artery (b), in which the adrenergic fibers are confined to the adventitial-medial border. The inner elastic membrane shows a nonspecific fluorescence (autofluorescence). (c) A gap junction between two smooth muscle cells grown in tissue culture. Scale bar = 500 μm (a), 50 μm (b), and 50 nm (c). (a, b) Reproduced from *Adrenergic Neurones: Their Organisation, Function and Development in the Peripheral Nervous System*, 1975, Burnstock G and Costa M, plate 9, copyright Chapman and Hall. With kind permission of Springer Science and Buisness Media. (c) Reproduced from *The Journal of Cell Biology*, 1971, Vol. 49, pp. 21–34, by copyright permission of The Rockfeller University Press.

basal lamina (see Figure 1(b)). In the longitudinal muscle coat of the gastrointestinal tract, autonomic nerves and smooth muscle are rarely separated by less than 100 nm. However, in the circular muscle coat, close (20 nm) junctions are common, sometimes several axon profiles being closely apposed with single muscle cells.

Prejunctional and Postjunctional Specialization

Although there are many examples of prejunctional thickenings of nerve membranes in varicosities associated with accumulations of small synaptic vesicles, representing sites of transmitter release (see Figure 1(c)), there are no convincing demonstrations of postjunctional specializations, such as membrane thickening or folding or indeed absence of micropinocytic vesicles; this is in keeping with the view that even close junctions might be temporary liaisons.

Muscle Effector Bundles and Gap Junctions

The smooth muscle effector is a muscle bundle rather than a single muscle cell – that is, individual muscle cells are connected by low-resistance pathways that allow electrotonic spread of activity within the effector bundle. Sites of electrotonic coupling are represented morphologically by areas of close apposition between the plasma membranes of adjacent muscle cells. High-resolution electron micrographs have shown that the membranes at these sites consist of gap junctions (see Figure 2(c)). Gap junctions (or nexuses) vary in size between punctate junctions,

which are not easily recognized except in freeze-fracture preparations, and junctional areas more than 1 μm in diameter. The number and arrangement of gap junctions in muscle effector bundles of different sizes in different organs and their relation to density of autonomic innervation have not been fully analyzed. It is interesting that partial denervation has been shown to result in an increase in gap junctions.

Receptor Localization on Smooth Muscle Cells

The distribution of P2X purinoceptors on smooth muscle cells in relation to autonomic nerve varicosities in urinary bladder, vas deferens, and blood vessels has been examined recently by using immunofluorescence and confocal microscopy. Antibodies against the $P2X_1$ receptor, the dominant receptor subtypes found in smooth muscle, and an antibody against the synaptic vesicle proteoglycan SV2 showed clusters of receptors (about $0.9 \times 0.2\,\mu m$ in size) located beneath varicosities. Many more small clusters (about $0.4 \times 0.04\,\mu m$) were present on the whole surface of smooth muscle cells unrelated to varicosities; they may represent pools of receptors that can migrate toward varicosities to form large clusters. In blood vessels, small clusters of P2X receptors are present on cells throughout the medial muscle coat, whereas large clusters are restricted to the muscle cells at the adventitial surface. α_2-Adrenoceptors appear to be located only in extrajunctional regions, so the possibility that noradrenaline (NA) is released from more distant varicosities has been raised. There are hints from studies of receptor-coupled green fluorescent protein chimeras that the receptor clusters are labile, dispersing when a varicosity moves to a new site where clusters reform, perhaps within a 20–30 min timescale.

Model of Autonomic Neuroeffector Junction

A model of the autonomic neuromuscular junction has been proposed on the basis of combined electrophysiologic, histochemical, and electron-microscopical studies described earlier (**Figures 3(a) and 3(b)**). The essential features of this model are that the terminal portions of autonomic nerve fibers are varicose, transmitter being released *en passage* from varicosities during conduction of an impulse, although excitatory junction potentials (EJPs) and inhibitory junction potentials are probably elicited only at close junctions. Furthermore, the effectors are muscle bundles rather than single smooth muscle cells, which are connected by low-resistance pathways (gap junctions) that allow electrotonic spread of activity within the effector bundle. In blood vessels, the nerves are confined to the adventitial side of the media muscle coat, and this geometry appears to facilitate dual control of vascular smooth muscle by endothelial relaxing and contracting factors and perivascular nerves.

Neuroeffector junctions do not have a permanent geometry with postjunctional specializations, but rather the varicosities are continuously moving, and their special relation with muscle cell membranes changes with time. For example, varicosity movement is likely to occur in cerebral blood arteries, where there is a continuously increasing density of sympathetic innervation during development until old age, and in vessels that have been stimulated chronically *in vivo*, where there can be an increase in innervation density of up to threefold, including an increase in the number of varicosities per unit length of nerve from 10–20 per 100 μm to 30 per 100 mm.

Autonomic effector junctions appear to be suitable not only for neurotransmission but also for neuromodulation. A neuromodulator is defined as any substance that modifies the process of neurotransmission. It may achieve this either by prejunctional action that increases or decreases transmitter release or by postjunctional action that alters the time course or extent of action of the transmitter or by both (**Figure 3(c)**).

Finally, it should be emphasized that if this model of the autonomic effector junction is true, then the earlier emphasis on looking for images of specialized nerve-cell close apposition may not be appropriate. If a varicosity has a passing close relation with a cell and releases transmitter to act on receptors expressed on that cell (e.g., most cells, epithelial cells, or even immune cells), then, in effect, that cell is innervated.

Autonomic Neurotransmission

The Multiplicity of Neurotransmitters in the Autonomic Nervous System

A neurotransmitter is a chemical substance released from nerves on electrical stimulation and which acts on specific receptors on adjacent effector cells to bring about a response, thus acting as a chemical messenger of neural activation. In early studies, acceptance of a substance as a neurotransmitter required satisfaction of the following criteria: (1) the presynaptic neuron synthesizes and stores the transmitter; (2) the transmitter is released in a calcium-dependent manner; (3) there should be a mechanism for terminating the activity of the transmitter, either by enzymatic degradation or by cellular uptake; (4) local exogenous application of the substance should mimic its effects following release due to electrical nerve stimulation; and (5) agents that block or

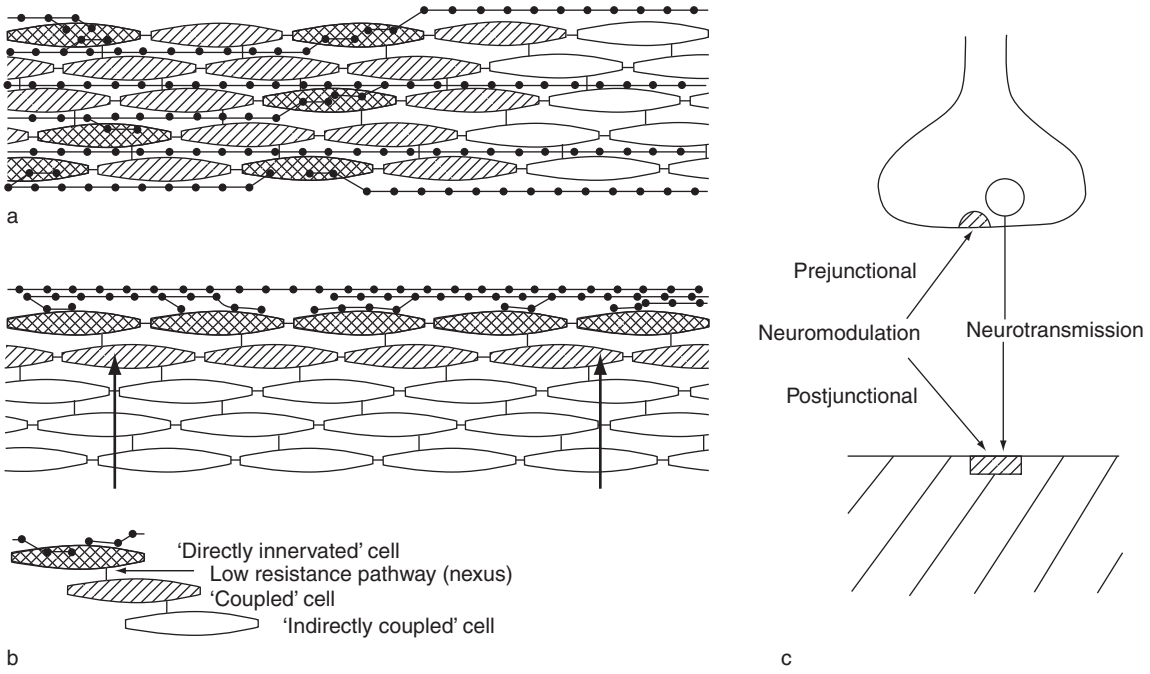

Figure 3 (a) Schematic representation of control of visceral smooth muscle. Directly innervated cells (cross-hatched) are those that are directly activated by neurotransmitter; coupled cells (hatched) are those where junction potentials spread from directly innervated cells, when a sufficient area of the muscle effector bundle is depolarized, a propagated action potential will activate the indirectly coupled cells (white). (b) Schematic representation of control of vascular smooth muscle by nerves (-●-●-) and endothelial factors (arrows). (c) Schematic representation of prejunctional and postjunctional neuromodulation. (a, b) Reproduced from *Adrenergic Neurones: Their Organisation, Function and Development in the peripheral Nervous System*, 1975, Burnstock G and Costa M, figure 18 (a) and (b), copyright Chapman and Hall. With kind permission of Springer Science and Buisness Media. (c) Reproduced from: Royal College of Physicians. *Advanced Medicine 18*. Sanner M (ed). London: Pitman Medical, 1982. Copyright © 1982 Royal College of Physicians. Reproduced by permission.

potentiate the endogenous activity of the transmitter should also affect local exogenous application in the same way.

The classical view of autonomic nervous control as antagonistic actions of NA and acetylcholine (ACh) causing either constriction or relaxation, depending on the tissue, was changed in the early 1960s when clear evidence of a nonadrenergic, noncholinergic (NANC) system was presented. About a decade later, studies of autonomic neurotransmission revealed a multiplicity of neurotransmitters in the ANS. Neurally released substances, including monoamines, amino acids, neuropeptides, adenosine 5′-triphosphate (ATP), and nitric oxide (NO) were identified (see Table 1). Since NO does not conform to the constraints of the criteria outlined earlier, although it certainly acts as a rapid chemical messenger in the ANS, a reappraisal of the criteria for defining a neurotransmitter was proposed by Hoyle and Burnstock in 1996, taking into account evidence for nonvesicular, Ca^{2+}-independent release of some classical neurotransmitters and the intracellular site of action of NO. The rapid expansion of the number of proposed autonomic neurotransmitters in recent years, including endothelin, secretoneurin, pituitary adenylate cyclase-activating peptide (PACAP), which is similar in structure to vasoactive intestinal polypeptide (VIP), glutamate, and carbon monoxide, makes it likely that the list is still incomplete.

Cotransmission

The concept of cotransmission was first formulated by Burnstock in 1976, incorporating hints in the earlier literature from both vertebrate and invertebrate systems. It is now well established. Immunohistochemical evidence of coexistence of more than one neurotransmitter should not necessarily be interpreted as evidence of cotransmission, since in order for substances to be termed cotransmitters, it is essential that postjunctional actions to each substance be shown to occur via their own specific receptors. For example, many neuropeptides have slow trophic actions on surrounding tissues, and this may be their primary role, or they may act as neuromodulators. The relative contribution of each transmitter to neurogenic responses is dependent on the parameters of

Table 1 Established and putative neurotransmitters/neuromodulators in the autonomic nervous system

Noradrenaline (NA)
Acetylcholine (ACh)
Adenosine 5′-triphosphate (ATP) and other nucleotides
Nitric oxide (NO)
Carbon monoxide (CO)
5-Hydroxytryptamine (5-HT)
Dopamine (DA)
γ-Aminobutyric acid (GABA)
Glutamate (GLU)
Neuropeptides
Neuropeptide Y (NPY)/pancreatic polypeptide (PP)
Enkephalin (ENK)/endorphin (END)/dynorphin (DYN)
Vasoactive intestinal polypeptide (VIP) and related peptides PHI and PHM
Pituitary adenylate cyclase-activating peptide (PACAP)
Substance P (SP)/neurokinin A (NKA)/neurokinin B (NKB)
Calcitonin gene-related peptide (CGRP)
Somatostatin (SOM)
Galanin (GAL)
Gastrin releasing peptide (GRP)/bombesin (BOM)
Neurotensin (NT)
Cholecystokinin (CCK)/gastrin (GAS)
Angiotensin II (AII)
Adrenocorticotrophic hormone (ACTH)
Secretoneurin
Endothelin (ET)

Reproduced from Burnstock G (2007) Structural and chemical organization of the autonomic nervous system with special reference to nonadrenergic, noncholinergic transmission. In Mathias CJ and Bannister R (eds.) *Autonomic failure. A textbook of clinical disorders of the autonomic nervous system.* Oxford: Oxford University Press, by permission of Oxford University Press.

stimulation. For example, short bursts (1 s) of electrical stimulation of sympathetic nerves at low frequency (2–5 Hz) favor ATP release whereas longer periods of nerve stimulation (30 s or more) favor NA release.

Peptides, purine nucleotides, and NO (identified by localization of nitric oxide synthase (NOS)) are often found together with the classic neurotransmitters, NA and ACh. In fact, the majority of nerve fibers in the ANS, if not all, contain a mixture of different neurotransmitter substances that vary in proportion in different tissues and species and during development and disease. The widespread use of double and triple immunohistochemical labeling techniques has been critical to the demonstration of co-localization of potential cotransmitters within the same nerve fiber and has been invaluable when combined with electron microscopy. Different neurotransmitters within the same varicosity may be localized in the same or separate vesicular populations using post-embedding colloidal gold techniques. In the gastrointestinal tract, many neurons contain multiple transmitters. ATP is a cotransmitter with calcitonin gene-related peptide (CGRP) and substance P (SP) in many sensory–motor nerves and with NO and VIP in enteric NANC inhibitory nerves. Transmitters with seemingly diverse and opposing effector action are sometimes co-localized in the same neuron, but generally they act in the same way and usually synergistically.

The precise combinations of neurotransmitters (and neuromodulators) contained in individual neurons and their projections and central connections, termed their 'chemical coding' by Furness and Costa in 1997, has been defined in studies of the enteric nervous system and peripheral autonomic and sensory ganglia.

Neurotransmission at the sympathetic neuroeffector junctions: Evidence for co-release and roles of NA, ATP, and neuropeptide Y It is now recognized that the main neurotransmitters/neuromodulators in postganglionic sympathetic nerves are NA, ATP, and neuropeptide Y (NPY). These substances are co-released in varying proportions, depending on the tissue and species, and also on the parameters of stimulation. Short bursts at low frequency particularly favor the purinergic component whereas longer periods of nerve stimulation favor the adrenergic component, and NPY release is optimal with high-frequency intermittent bursts of stimulation. A considerable variability in the contribution of a purinergic component to sympathetic neurotransmission has been demonstrated in different blood vessels; for example, rabbit saphenous and mesenteric arteries have a substantial purinergic component, whereas in the rabbit ear artery, the purinergic component is relatively small. In intestinal submucosal arteries, the responses to sympathetic nerve stimulation are mediated solely by ATP, with NA acting as a prejunctional modulator via α_2-adrenoceptors. The initial electrophysiological postjunctional response to sympathetic nerve stimulation is a rapid, transient EJP, which is mediated by ATP. In some vessels, the EJP is followed by a slow depolarization, which is mediated by NA. Postjunctionally, the effects of ATP and NA released as sympathetic cotransmitters are generally synergistic. NA and ATP can depress sympathetic neurotransmission by prejunctional modulation, via α_2-adrenoceptors or predominantly via P1 receptors following extracellular breakdown to adenosine, but also via P2 receptors in some vessels. Prejunctional P2 receptor-mediated increase in NA release has also been reported.

In most tissues, including the vas deferens and many blood vessels, NPY does not act as a genuine neurotransmitter, having little direct postjunctional action, but rather acts as a neuromodulator, often by prejunctional attenuation of NA and ATP release

and/or postjunctional potentiation of responses to adrenergic and purinergic components of sympathetic nerve responses. In tissues in which NPY does have a direct vasoconstrictor effect, such as in blood vessels of the spleen and kidney and in coronary and cerebral arteries, the response is characteristically slow in onset and long lasting.

Other substances localized within sympathetic nerves include 5-hydroxytryptamine (5-HT), which is largely taken up by sympathetic nerves and released as a false transmitter. Opioid peptides are also widely distributed in sympathetic neurons where their functional role appears to be related to their prejunctional inhibitory effects on sympathetic neurotransmission.

Neurotransmission at the parasympathetic neuroeffector junctions: The atropine-resistant components of parasympathetic neurotransmission ACh, VIP, ATP, and NO are cotransmitters commonly synthesized in and released from parasympathetic nerves. As with sympathetic cotransmission, the relative functional importance of the cotransmitters in parasympathetic neurotransmission is variable in different tissues and species. For example, NO may be the main mediator of neurogenic vasodilation in cerebral vessels, whereas VIP may be of more importance during neurogenic vasodilation in the pancreas. The coordinated roles of VIP and ACh in parasympathetic neurotransmission were demonstrated in an elegant study of the cat exocrine salivary gland innervation. It showed that VIP and ACh were stored in separate vesicles in the same nerve terminal and were both released on transmural nerve stimulation, but with different stimulation parameters. ACh was released during low-frequency stimulation to increase salivary secretion from acinar cells and to elicit some minor dilatation of blood vessels in the gland. At high stimulation frequencies, VIP was released to produce marked dilatation of the blood vessels in the gland and to act as a neuromodulator postjunctionally on the acinar gland to enhance the actions of ACh and prejunctionally on the nerve varicosities to enhance the release of ACh. ACh was also found to have an inhibitory action on the release of VIP. VIP has since been shown to have a direct vasodilatory action in the submandibular gland in man. PACAP also seems to be present in VIP-containing parasympathetic nerves. NOS is often co-localized with ACh and VIP in parasympathetic nerves innervating blood vessels. Postganglionic nerves from pelvic ganglia containing VIP, ACh, and NOS project to the urethra, colon, and penis. The human bladder body receives a dense parasympathetic innervation comprised predominantly of ACh-containing nerves. In the rodent bladder, ATP is a major cotransmitter in these nerves. However, only a small purinergic component is present in human bladder, except in pathological conditions (discussed later).

Neurotransmission at sensory–motor neuroeffector junctions: The roles of SP, CGRP, and ATP The motor function of sensory nerves, whereby antidromic impulses down collateral fibers result in local release of sensory neurotransmitters, is widespread in autonomic effector systems and forms an important physiological component of autonomic control. To distinguish these nerves from the other subpopulation of afferent fibers that have an entirely sensory role and have terminals containing few vesicles and a predominance of mitochondria, they have been termed 'sensory–motor' nerves.

SP and CGRP are cotransmitters in many unmyelinated, primary afferent nerves. They often coexist in the same large granular vesicles in capsaicin-sensitive nerve terminals. The proportions of coexistence of SP and CGRP vary with species; for example, in the guinea pig, most sensory neurons containing CGRP also contain SP, but in the rat, about 50% of CGRP-containing neurons do not contain SP. In the vasculature, unlike CGRP, SP does not appear to act directly on receptors of the vascular smooth muscle but rather acts via occupation of receptors on endothelial cells lining the lumen to bring about NO release and consequent vasodilation. This action of neurally released SP may be particularly important in the microvasculature, but access of neurally released SP to the endothelium in large vessels is questionable; it is largely released from endothelial cells to act on receptors on endothelial cells to release NO, resulting in vasodilation. ATP is now also established as a cotransmitter with glutamate in small primary sensory nerves mediating mechanical and/or nociceptive signals.

Other neuropeptides and transmitters have been localized in sensory–motor nerves. For example, in the human urinary bladder, VIP, cholecystokinin (CCK), and dynorphin (DYN) are present, together with SP and CGRP, in the afferent projections to the lumbosacral spinal cord. In the guinea pig, dorsal root ganglion neurons containing SP, CGRP, CCK, and DYN project to the epidermis and small dermal blood vessels. NOS has been localized in populations of primary sensory neurons of trigeminal and dorsal root ganglia. Endothelin, a potent vasoconstrictor peptide with mitogenic actions, is also localized in neurons of these sensory ganglia, often co-localized with SP.

There are increasing examples in the literature of cross-talk between sensory–motor, sympathetic, and parasympathetic nerves. In the heart, SP has

excitatory effects on cardiac parasympathetic innervation, in contrast to CGRP, which is inhibitory.

Neurotransmission involving intrinsic neurons: Special reference to neurotransmitters localized in nerve cell bodies in the heart, bladder, intestine, and lung

Many intrinsic neurons localized within autonomic neuroeffector tissues are part of the postganglionic parasympathetic system, but there are also intrinsic neurons derived from neural crest tissue that is different from that which forms sympathetic and parasympathetic neurons, such as intrinsic neurons abundant in the gut and possibly subpopulations in the heart and airways.

The most extensive system of intrinsic neurons is in the myenteric and submucous plexuses of the gastrointestinal tract. These enteric neurons contain numerous neuroactive substances, of which the majority are involved in neurotransmission or neuromodulation at the ganglion level and/or have a trophic role; only a small percentage are involved in neuromuscular transmission. The chemical coding of enteric neurons has been examined in detail, particularly in the guinea pig. ATP, NO, and VIP mediate NANC inhibitory neurotransmission in the gut in varying proportions depending on the region. ACh and SP are cotransmitters in enteric excitatory neurons.

There are many intrinsic neurons in the heart, particularly in the right atrium. The neurochemical makeup of the intrinsic cardiac ganglia is heterogeneous and includes a variety of neurochemical markers. For example, subpopulations of atrial intrinsic neurons from newborn guinea pigs immunostain for NPY, 5-HT, heme oxygenase-2, and NOS, and these neurons probably also utilize ACh and ATP.

Most airway intrinsic neurons contain choline acetyltransferase, but NOS and VIP are also found in these neurons in humans. Intrinsic ganglia in the human urinary bladder wall contain a number of neuroactive substances (VIP, NOS, NPY, ATP, galanin, and occasionally tyrosine hydroxylase); in the bladder neck, a few intrinsic neurons contain enkephalin and SP. Intramural ganglia containing NPY and VIP have been identified in human urethra.

Autonomic Neuromodulation

Some substances stored and released from nerves do not have direct actions on effector muscle cells but alter the release and/or the actions of other transmitters; these substances are termed neuromodulators. Many other substances (e.g., circulating neurohormones; locally released agents such as prostanoids, bradykinin, histamine, and endothelin; and neurotransmitters from nearby nerves) are also neuromodulators in that they modify the process of neurotransmission. Many substances that are cotransmitters are also neuromodulators. The wide and variable cleft characteristic of autonomic neuroeffector junctions makes them particularly amenable to the mechanisms of neural control mentioned earlier.

Plasticity of the Autonomic Nervous System

There are some examples of altered expression of neurotransmitters/neuromodulators in autonomic nerves during development and aging; following trauma, surgery, and chronic exposure to drugs; and in disease. Neurons possess the genetic potential to produce many neurotransmitters. The particular combination and quantity that result are partly preprogrammed and partly determined by 'trophic' factors and hormones that trigger the expression or suppression of the appropriate genetic machinery. The plasticity of expression of neural substances cocoordinated to environmental cues allows rapid and precise matching of neurotransmission to altered demands. Several neurotransmitters/neuromodulators are themselves trophic molecules, with mitogenic or growth-promoting/-inhibiting properties.

Conclusions

A combination of the variety of neurotransmitters involved in autonomic neurotransmission and the interactions between sympathetic, parasympathetic, and sensory–motor nerves and those arising from intrinsic ganglia, via mechanisms of cotransmission and pre- and postjunctional neuromodulation, indicate the complexity of peripheral autonomic control and the variety of ways by which autonomic dysfunction can occur. Recent advances in the unraveling of these mechanisms, together with molecular identification of specific receptor subtypes and localization and characterization of their expression, and of the long-term effects of dysfunction, will bring advances toward the design of treatment regimes to combat autonomic failure.

See also: Autonomic Neuroplasticity and Aging; Autonomic Neuroplasticity: Development; Autonomic Neuroplasticity and Regeneration; Autonomic Nervous System; Cotransmission; Gap Junction Abnormalities and Disorders of the Nervous System.

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