Functional Neuroanatomy of the Peripheral Autonomic Nervous System

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Introduction

John Newport Langley, a Cambridge (England) physiologist, coined the term "autonomic nervous system (ANS)" in 1898, a term that included the thoracolumbar sympathetic and craniosacral (later termed parasympathetic) outflows as well as the local nervous system of the gut (came to be known later as the enteric nervous system (ENS) [1–5]). It is notable that he also introduced the terms "pre-and postganglionic" fibers in 1895. Following the demonstration by W. H. Gaskell of the craniosacral and thoracolumbar outflows toward the end of the nineteenth century [6], Langley proposed the term parasympathetic for the craniosacral outflow in 1905 and sympathetic for the thoracolumbar outflow [1, 2]. For some incomprehensible reason, the ENS was only recognized decades later in 1970 [3] (see below). Despite this early recognition of the ANS, which permeates throughout entire body systems and organs subserving vital functions for living beings, this important component of the nervous system has been a long neglected topic in the field until Shy and Drager [7] in 1960 directed our attention to a relentlessly progressive neurodegenerative disease initially involving the central autonomic neurons and later somatic nervous system (cerebellar-parkinsonian or parkinsonian-cerebellar syndrome). Since then there has been a surge of interest, particularly among academic neurologists. (Many physicians, however, remain uncertain even now about how to deal with disorders of the ANS).

The ANS basically controls the body's internal environment, maintaining the internal homeostasis (steady state) without conscious perception (involuntary) of almost all organs and systems in the body (e.g., cardiovascular, respiratory, gastrointestinal, and genitourinary systems, and endocrine functions as well as the Harvard physiologist Walter B. Cannon's "fight-or-flight" response under stressful situations (1915)) [8]. In contrast, the somatic (voluntary) nervous system is responsive to the external environment with conscious perception [8]. These two systems work in unison to control the body's homeostasis, constantly adapting to in order to keep the vital functions stable. It is astonishing to think how the ANS has been neglected by clinicians for nearly a century after the introduction of the topic by Langley.

Traditionally, the ANS has been divided into two divisions (the third division was reintroduced later): sympathetic and parasympathetic, and each division has central and peripheral components [9–15]. These are predominantly efferent fibers, but autonomic afferent fibers also exist, participating in vital reflex and other functions (see below). The internal homeostasis is maintained by three divisions of the ANS (sympathetic nervous system [SNS], the parasympathetic nervous system [PNS], and the enteric nervous system; see below), which are closely integrated and influenced by the central autonomic network [3, 15–17]) (see also Chap. 2). For a detailed description, readers are referred to some excellent texts [4, 5, 15]. Figures 3.1, 3.2, and 3.3 schematically outline the traditional two extrinsic divisions of the ANS and their connections.

The Sympathetic Efferent Organization

Anatomically the SNS is located at a central (spinal) level from C8-T1 to L1–L2 segments of the spinal cord and a peripheral level. The intermediolateral neurons in the

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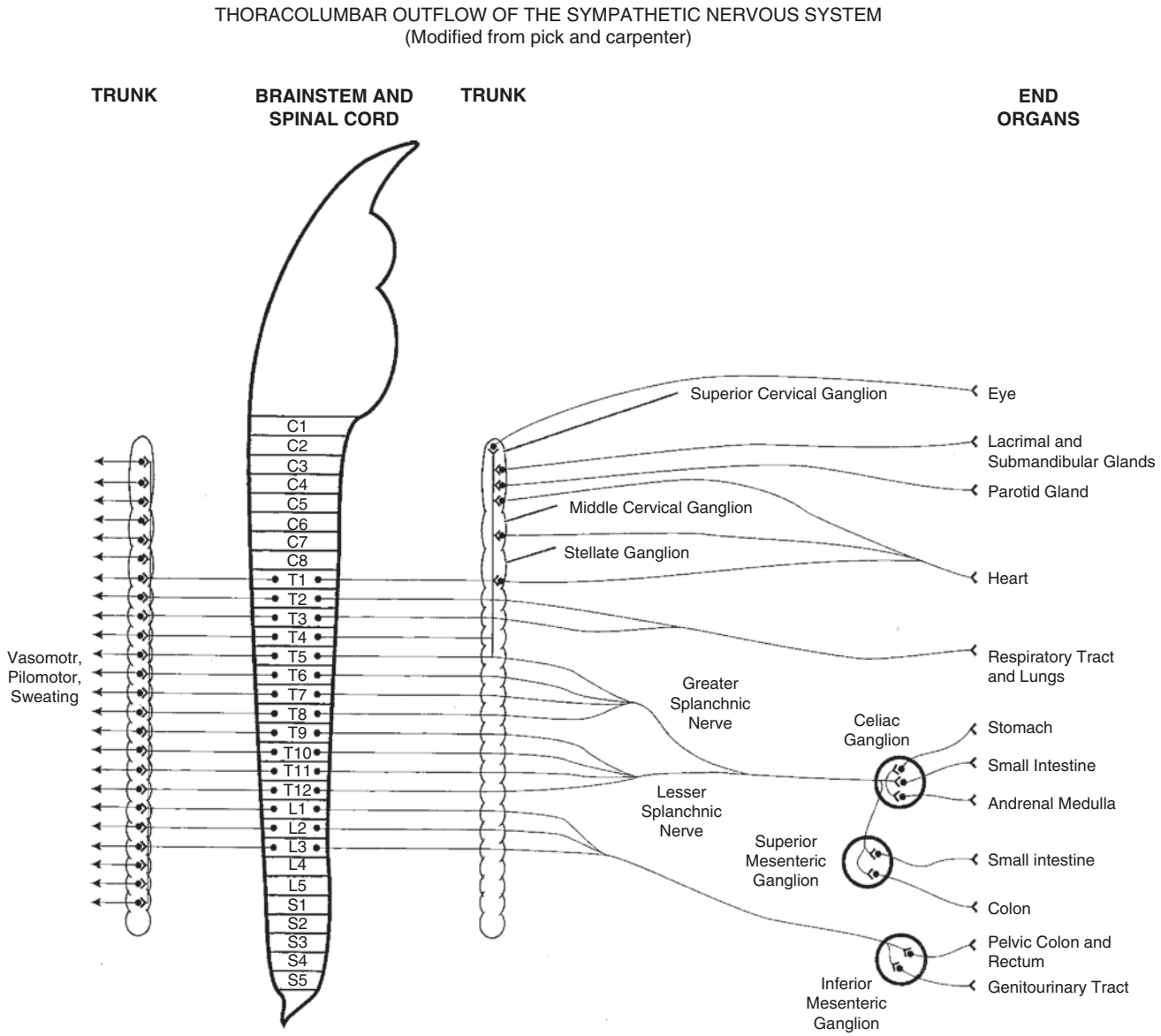

Fig. 3.1 Thoracolumbar outflow of the sympathetic nervous system shown schematically. (Modified from Pick [4] and Carpenter [11])

thoracolumbar spinal segments provide preganglionic nerve fibers, which are thinly myelinated fibers (white rami communicantes) measuring 2–3 μm in diameter and leave the intermediolateral column neurons along the ventral roots from C8 or T1 to L2 segments of the spinal cord (see Fig. 3.3). These preganglionic fibers then leave the ventral roots and pass to the nearest paravertebral sympathetic chain (trunk) located bilaterally on two sides of the vertebral column consisting of a series of ganglia connected with intervening nerves (see Figs. 3.1 and 3.2). The sympathetic chain extends from the base of the skull to the coccyx where the two trunks join in front of the coccyx to form a terminal ganglion called coccygeal or ganglion impar. There are three cervical ganglia (superior, middle, and inferior or stellate ganglia), 10–12 thoracic, four lumbar and four sacral ganglia, for a total of 22–23 ganglia (see Fig. 3.1). The preganglionic sympathetic fibers passing to the sympathetic chain may pursue one or more of the following three routes [16]: 1. Immediately synapse at the same level with a ganglion to leave the trunk as postganglionic fibers; 2. Ascend or descend in the sympathetic chain and leave the chain (trunk) as postganglionic fibers after synapsing with the paravertebral ganglia; 3. Leave the thoracic paravertebral trunk as splanchnic nerves (the greater, lesser, and least splanchnic nerves) to synapse with the nearby prevertebral ganglia (e.g., celiac, aorticorenal, superior, and inferior mesenteric ganglia, including previsceral and terminal ganglia). The postganglionic nerve fibers emerge to innervate the abdominal and pelvic viscera [4, 5, 15]. Some preganglionic fibers will pass through the chain to directly innervate the adrenal medulla. The preganglionic sympathetic fibers destined to innervate pupils of the eye and skin of the head and neck pass through the stellate and middle cervical ganglia without synapsing to the superior cervical ganglia where fibers synapse and postganglionic unmyelinated fibers (Gray

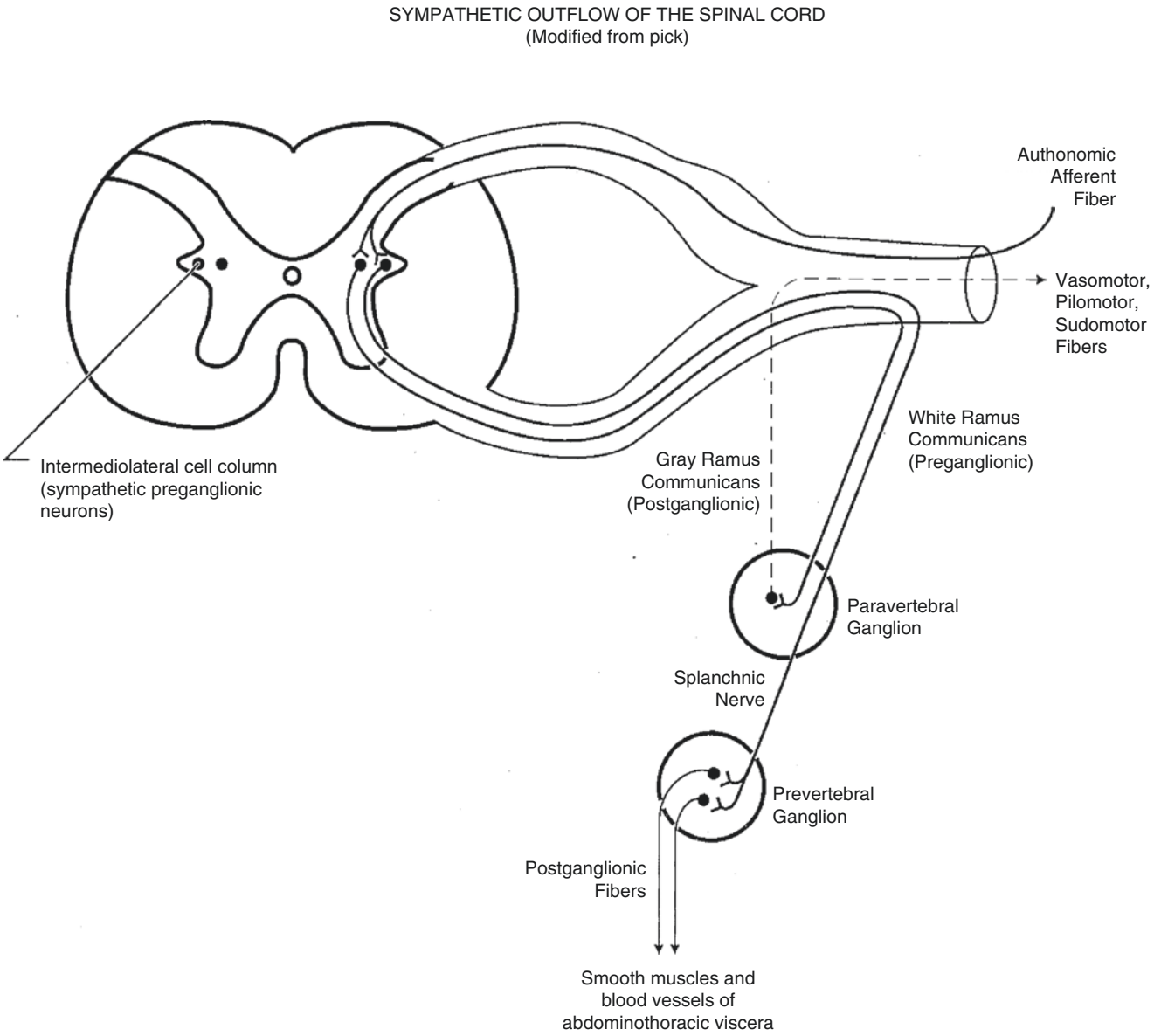

Fig. 3.2 Schematic diagram to show sympathetic outflow of the spinal cord

rami communicantes) innervate pupils and other structures in the head and neck. Prevertebral ganglia are located in the midline, anterior to the vertebral column. Previsceral or terminal ganglia are located close to the peripheral target structures. In the SNS, the preganglionic fibers are short but the postganglionic fibers are long. This lengthwise arrangement is reversed in the PNS, that is, the preganglionic fibers are long, whereas the postganglionic fibers are short. The postganglionic sympathetic fibers, which are unmyelinated, travel as gray rami communicantes along the spinal and peripheral nerves to the blood vessels to control limb circulation (vasomotor), sweat glands (sudomotor), and arrectores pilorum muscles of the skin (pilomotor), as well as the blood vessels of the voluntary muscles and the bones of all four limbs.

The sympathetic fibers from T1-T4 spinal segments and the cervical ganglia form the cardiac plexus to control the rhythm and contraction of the heart. The respiratory system is innervated by T2-T7 segments through stellate ganglion and upper five thoracic ganglia forming the pulmonary plexus. The esophageal plexus is formed by the postganglionic fibers from T2-T7 spinal cord segments with synapses at stellate and T2-T4 thoracic ganglia. Stomach, duodenum, and pancreas are controlled by T6-T10 segments through celiac ganglia. Celiac, aorticorenal, superior, and inferior mesenteric ganglia receiving innervation from T6-L2 segments control the rest of the small intestine and colon, including the rectum and anus. The genitourinary system is controlled by the hypogastric plexus receiving innervation from T10-L2 spinal cord segments. L1 and L2 spinal cord segments (through hypogastric plexus) control ejaculation in men. The T4-T9 segments control the upper trunk, whereas T10-L2 segments control the lower trunk below the umbili-

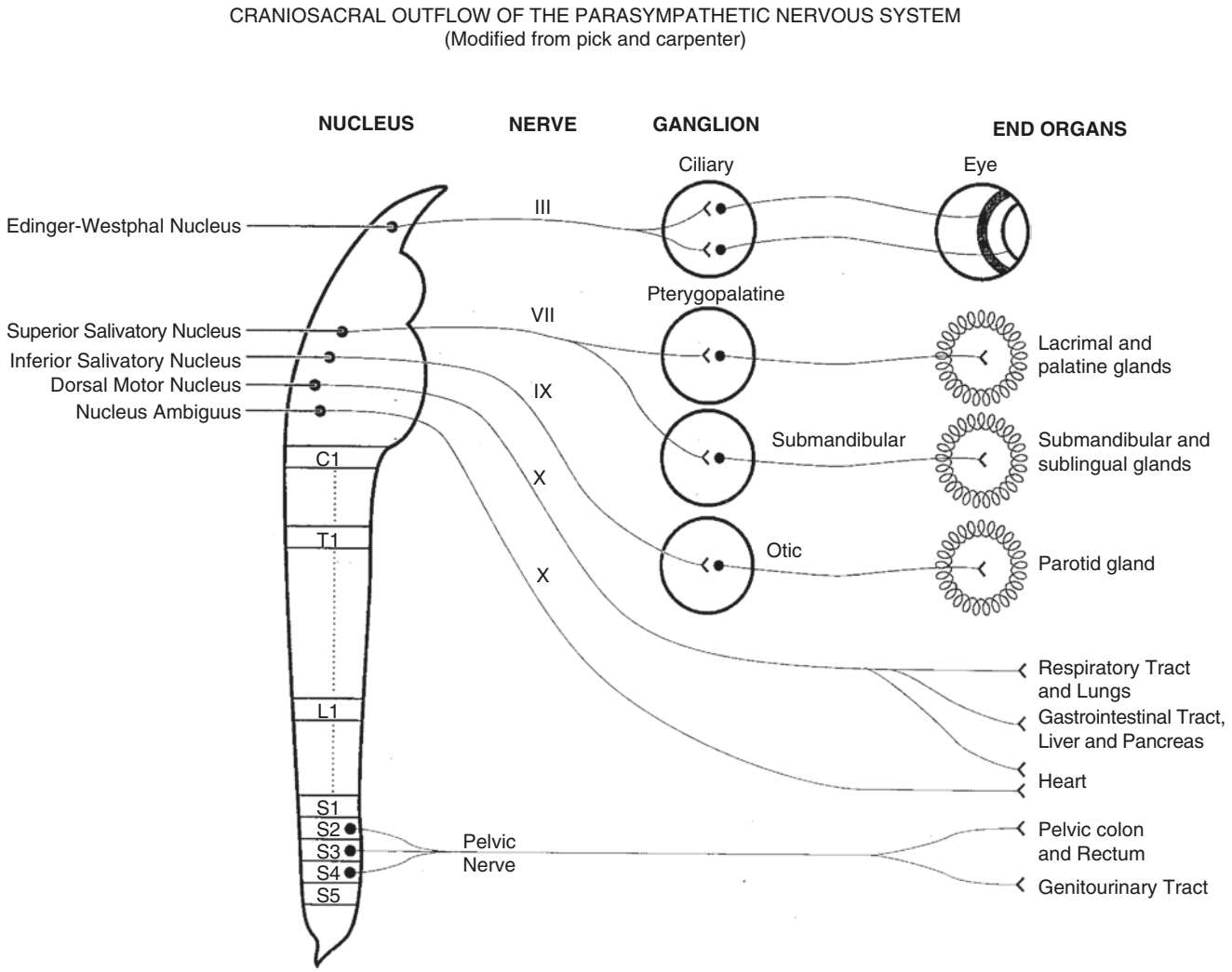

Fig. 3.3 Craniosacral outflow of the parasympathetic nervous system shown schematically. (Modified from Pick [4] and Carpenter [11])

cus. The rostral four thoracic segments innervate the upper limbs, while T12-L2 segments innervate the lower limbs. The ciliospinal center (of Budge) for pupillary dilatation is located in the C8-T1 segments. The splanchnic neurons from T4-L2 segments send impulses to the abdominal viscera.

The Parasympathetic Efferent Organization

The efferent parasympathetic nervous system (PNS) consists of the cranial and sacral subdivisions. The parasympathetic preganglionic neurons are located within the nuclei of the third, seventh, ninth, and tenth cranial nerves. The tectal outflow arises from the Edinger–Westphal nucleus in the midbrain, which sends preganglionic fibers to the ciliary ganglion from which the postganglionic fibers innervate the ciliary muscle of accommodation and sphincter pupillae muscle for pupilloconstriction.

The salivatory nuclei are located in the reticular formation at the pontomedullary junction. The superior salivatory nucleus sends efferent secretomotor and vasodilator fibers through the chorda tympani branch of the seventh nerve to innervate the lacrimal, sublingual, submandibular, and mucosal glands in the nasal cavity and palate.

The inferior salivatory nucleus sends efferent preganglionic fibers through the ninth cranial nerve to the otic ganglion, and via the auriculotemporal nerve, a branch of the mandibular division of the trigeminal nerve, innervates the parotid gland.

The preganglionic fibers from the dorsal motor nucleus of the vagus and the nucleus ambiguus in the medulla travel to innervate the heart and the smooth muscles of the thoracoabdominal viscera.

The preganglionic neurons of the sacral division of the parasympathetic system are located in the gray matter lateral to the central canal of the second, third and fourth sacral divisions of the spinal cord, and travel in the ventral spinal roots. These fibers form the nervi erigentes or the pelvic nerves and terminate in the postganglionic cell bodies located in the pelvic plexus. The postganglionic fibers originating from the pelvic plexus terminate at the distal segment of the sigmoid colon, the rectum, the urinary bladder, and the reproductive system.

The urinary bladder, including the lower urinary tract, is controlled by three groups of neurons (the pelvic, hypogastric, and pudendal nerves):

- The sacral parasympathetic (S2-S4 segments) forming the pelvic nerves
- The thoracolumbar SNS (T10-L2 segments of the spinal cord) fibers forming the hypogastric nerves
- The sacral somatic segments (S2-S4) forming the pudendal nerve

The Enteric Nervous System

Although Langley in 1898 [2] alluded to the local nervous system of the gut, the enteric nervous system (ENS) has not been known to the medical community until recognized in 1970 [3]. The ENS, derived from the word enteron (gut), also known as the "little brain" of the gut, plays an important role in the functional relationship with the "big brain" (brain–gut axis [17]). The ENS can function to an extent autonomously and semi-independently, but input from the traditional ANS and CNS ("big brain") influences gastro-intestinal (G-I) function through modulation of the ENS [17–22]. The ENS contains three groups of neurons [19–22]: the intrinsic primary afferent neurons, interneurons, and enteric motor neurons (efferent), forming networks to control alimentary behavior. The ENS subserves its functions by using two distinct intestinal plexuses: the myenteric plexus of Auerbach located between outer longitudinal and inner circular smooth muscles (involuntary) of the gut and the submucosal plexus of Meissner. The ENS, using several neuronal circuits, is involved in sensory-motor integration controlling intestinal motility, secretion, local blood flow, absorption, and to an extent these ENS circuits also modulate endocrine and immune functions [17–22]. The intestinal motility (motor pattern) basically consists of two types [20]: the propulsive stereotyped movements of peristalsis and spontaneous cyclical migrating motor complex (MMC). The ENS system involved in these movements consists of the intrinsic afferent neurons, interneurons, and efferent motor neurons forming neural circuits. Both the inner circular and the outer longitudinal smooth muscles of the gut are driven by the enteric neuronal circuits to initiate and propel these movements. The propulsive peristaltic movements are initiated by the sequential contractions of the circular smooth muscles beginning orally and propagating aborally. The enteric neuronal circuits also initiate the spontaneous cyclical MMC, propagating slowly aborally every 90 minutes, which has a circadian rhythm [23] with the lowest velocity during sleep without consistent relationship to the non-rapid eye movement (NREM) / REM sleep cycle [24]. The intrinsic ENS neurons directly control the gut motility and secretion, whereas the extrinsic parasympathetic and sympathetic divisions of the ANS originating from the CNS modulate the ENS neurons at the circuits. The central parasympathetic premotor neurons located in the dorsal motor nucleus (DMN) of the vagus nerve control (excitatory) most of the gut except the distal sigmoid colon and rectum, which are controlled by the parasympathetic outflow of the sacral (S2-S4) segments of the spinal cord. The premotor sympathetic neurons of the thoracolumbar outflow provide inhibitory control of the gut smooth muscles but exert excitatory control over the internal anal and vesical sphincters. In addition to these enteric motor neurons, there are primary enteric afferent neurons responding to both mechanical and chemical stimuli, and these afferent projections from the gut integrate with the central autonomic network for appropriate motor response (see also Chap. 2). These intrinsic primary afferents from the enteric neurons transmit impulses to the CNS via nodose ganglion of the vagus nerve (tenth cranial) and terminate onto the NTS, which provides CNS stimuli for sending efferent message mainly from the DMN of the vagus nerve to the effector organs. These are also somatic afferents projecting to the CNS via dorsal root ganglia. The ENS thus works in concert with the ANS and CNS to maintain the internal homeostasis and stability of the gastrointestinal tract. In addition, the interaction between the "little brain" and "big brain" maintains an awareness of what has been happening in the gut throughout 24 hours (brain–gut axis) [17].

Autonomic Afferent Fibers

In contrast to the general misperception, the ANS contains not only motor or efferent neurons (consisting of two neuron chains: preganglionic and postganglionic motor neurons) but also afferent fibers [3–5, 9, 15, 16, 25] (sensory neurons) transmitting signals to the CAN with its ascending and descending projections to other central ANS structures in the CNS to maintain stability of the internal environment (see also Chap. 2) . The role of the intrinsic primary afferent

originating from neurons of the ENS through brain–gut interaction is to maintain the stability of the internal milieu ("*milieu intérieur*," the term coined by Claude Bernard in 1854) of the alimentary tract (see description above).

An example of an important parasympathetic afferent includes the baroreceptor and chemoreceptor afferents arising from presso- and chemo-receptors located in the carotid sinus and aortic arch [9, 10, 13, 18]. The afferent fibers for these reflexes are mediated by the sinus nerve of Hering, a branch of the glossopharyngeal (ninth cranial) nerve and the aortic nerve of Cyon and Ludwig, a branch of the vagus (tenth cranial) nerve. These fibers send afferent impulses from the mechanoreceptors and chemoreceptors in the walls of the carotid artery, heart, and aorta to the CNS structures controlling circulation and respiration. The baroreceptor afferents terminate on the nucleus tractus solitarius (NTS) [9, 10, 18], an important relay station in the medulla receiving visceral afferents from the cardiovascular, respiratory, and gastrointestinal tracts, as well as taste fibers, and afferents from the baroreceptors and chemoreceptors (see also Chap. 2) (Fig. 3.4). The NTS sends impulses to the medullary reticular formation (ventrolateral medulla), which in turn sends descending bulbospinal projections for vasomotor mediation to the intermediolateral column cells of the spinal cord. The latter through the thoracolumbar sympathetic outflow exerts specific influences on the sympathetic nerves supplying the heart, blood vessels, and adrenal medulla but has no effect on non-cardiorespiratory sympathetic nerves, for example, pupils, sweating, and piloerection. Sympathetic afferent fibers from the viscera traveling with the splanchnic nerves have been described, and other afferents join the somatic nerves on their way to the dorsal root ganglia. The afferents from the respiratory tract and pulmonary receptors terminate also on the NTS via the vagus (tenth cranial) nerve. Finally, general visceral afferents from the gastrointestinal tract also project to the NTS. The efferents arising from the adjacent DMN influence gastrointestinal tract motility and secretion via the vagus nerve and the ENS. The autonomic afferent fibers consist of viscerosensory (e.g., the enteric afferent fibers from cell bodies in the ENS, baroreceptors, and chemoreceptors), somatosensory (e.g., thermoreceptors and noci-

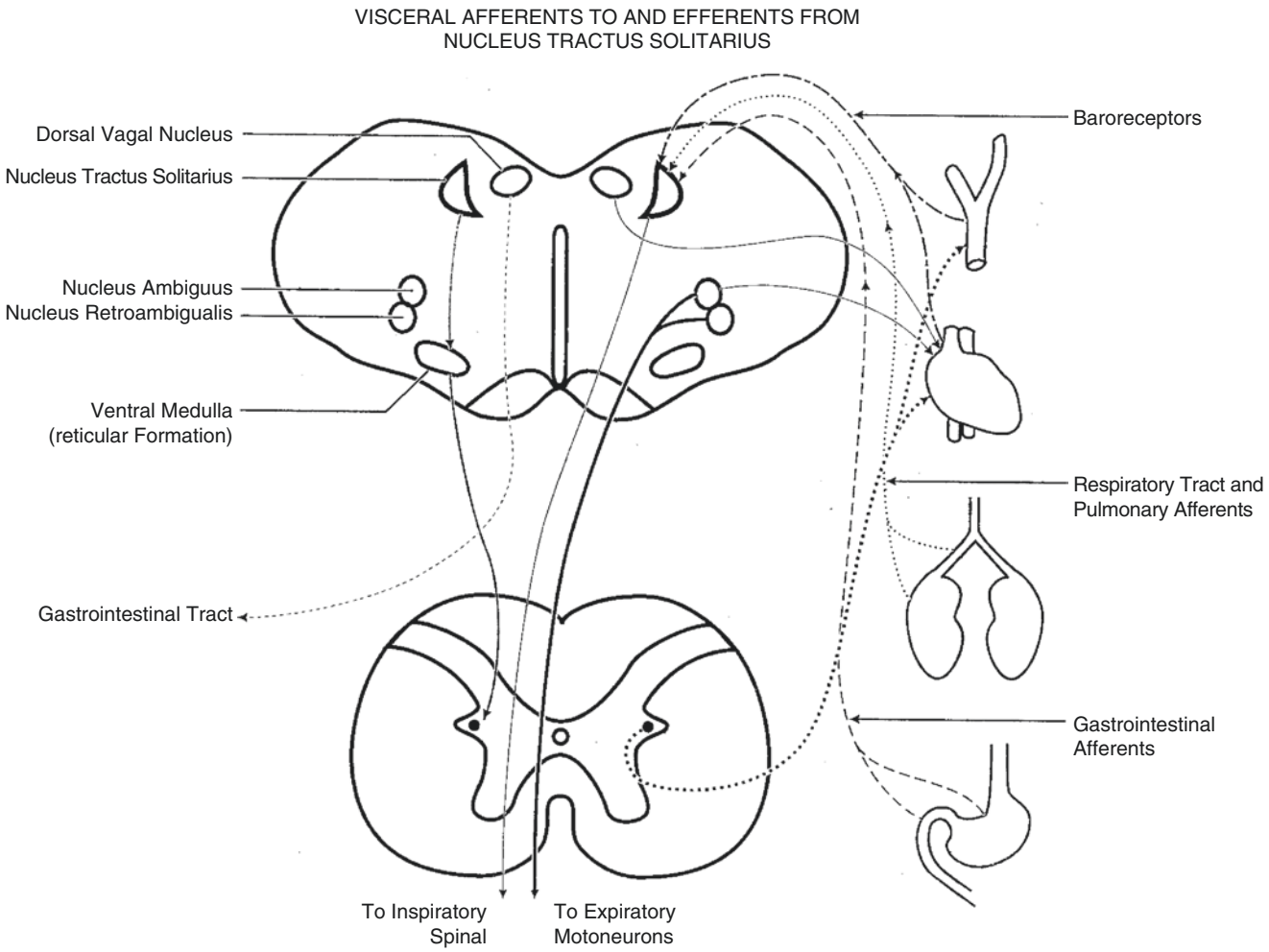

Fig. 3.4 Visceral afferents to and efferents from nucleus tractus solitarius

ceptors), and special sensory fibers (e.g., taste, salivation, and balance receptors in the inner ear) [15, 16, 25]. The afferent ANS fibers most likely participate in visceral sensation and autonomic reflexes, such as respiratory, viscerosomatic, baroreceptor, and vasomotor reflexes.

Pharmacology and Physiology of the ANS (See Also Chap. 5)

Two physiologists, Henry Dale (1914) [26] from London, England, and Otto Loewi (1921) [27] from Frankfurt, Germany, are responsible for discovering acetylcholine as the principal neurotransmitter for the ANS, for which they shared the 1936 Nobel Prize for Medicine [25].

Two chemical transmitters, acetylcholine and norepinephrine, help mediate autonomic functions [14, 25]. Acetylcholine is the neurotransmitter for the preganglionic neurons of both sympathetic and parasympathetic systems, while it is the neurotransmitter for all parasympathetic postganglionic and sympathetic postganglionic fibers innervating sweat glands. For central autonomic regulation, cholinergic neurons play a significant role. There are two receptors for acetylcholine: muscarinic and nicotinic receptors.

Norepinephrine is the neurotransmitter for the sympathetic nervous system. It is released at the postganglionic sympathetic nerve terminals. Two adrenergic receptors, α (alpha) receptors (α1 and α2) and β (beta) receptors (β1 and β2), are responsible for binding of norepinephrine released from the sympathetic nerve endings. The effects of alpha receptors in general are excitatory and those of beta receptors are inhibitory except for the receptors in the heart where they are excitatory. The sympathetic vasodilator fibers to the skeletal muscles and coronary blood vessels may contain cholinergic or beta receptors.

The adrenal medulla, part of the adrenal gland, receives sympathetic preganglionic neurons, but in response to the neurotransmitter acetylcholine it secretes largely adrenaline (epinephrine) with a small amount of noradrenaline (norepinephrine) [22, 25] and a very small amount of dopamine.

The principal neurotransmitter in the ENS, as in other parts of the ANS, is acetylcholine, which is excitatory. There are also inhibiting neurotransmitters like nitric oxide (NO) and vasoactive intestinal polypeptide (VIP). At least 30 neurotransmitters have been identified [17–22] in the ENS, including serotonin, substance P, neuropeptide Y, GABA, and dopamine.

Physiology

The Sherringtonian concept of "*final common motor pathway*" can also be applied (as suggested by Janig in 1986) [25, 28] to the peripheral autonomic nervous system calling it a "*final common autonomic pathway*" as the most important component of the ANS for ultimate control to maintain a stable internal milieu (homeostasis).

There is a general misconception of a functional universal antagonism between the SNS and the PNS. In fact, the two systems act synergistically to get the best possible autonomic function (e.g., the SNS governs ejaculation, and PNS erection in men to get an effective reproductive function, which does not imply opposite effect), although many appear to have reciprocal and opposing effects [9, 14, 25]. Physiological changes following stimulation of the sympathetic nervous system consist of the following responses: increase in heart rate and blood pressure, piloerection, sweating, pupillary dilation, bronchodilation, vasoconstriction, hyperglycemia, inhibition of the gastrointestinal motility, contraction of the internal anal and urinary bladder sphincters, release of renin and norepinephrine, and secretion of epinephrine (adrenaline) from the adrenal medulla, ejaculation in men, glycogenolysis, and neoglucogenesis.

Parasympathetic responses following activation of the system include the following: bradycardia, vasodilation, pupillary constriction, bronchoconstriction, increased gut motility and peristalsis, increased glandular secretions, contraction of the detrusor muscles in the urinary bladder, and penile erection in men.

There are striking physiological changes in the ANS during sleep (see Chap. 5) [29, 30]. The fundamental changes are two: (1) there is an increased parasympathetic tone during REM sleep and NREM sleep and (2) the sympathetic tone decreases in both stages with intermittent hyperactivation in REM sleep, particularly during phasic eye movements. Because of these sleep-related physiological changes there is pupillary constriction during sleep as well as bradycardia and slight fall of blood pressure (BP); BP fall in sleep is known as "dipping." Respiration is highly vulnerable during sleep because of absence of participation of the voluntary breathing system (only the autonomic or metabolic system remains active), decreased firing rates with reduced participation of the central respiratory neurons in the medulla and pons, as well as impaired hypoxic and hypercapnic ventilatory responses, resulting in mild sleep-related hypoventilation.

Clinico-Anatomical Correlation

From an account of the functional neuroanatomy of the autonomic nervous system as described above, it will now be easy to understand the various clinical manifestations resulting from the autonomic deficits [9].

Pathogenesis of Orthostatic Hypotension An important feature of autonomic failure is orthostatic hypotension in the erect posture manifested clinically by orthostatic intolerance

symptoms (e.g., dizziness, syncope or presyncope, blurring of vision, nausea, and light headedness) resulting from cerebral hypoperfusion. To understand the mechanism of orthostatic hypotension following lesions of the ANS (central or peripheral), it is important to understand the mechanism of maintenance of circulation and BP in the upright posture in a healthy individual [9, 13, 14]. On assuming an upright position there is an intense gravitational stress on the circulation with a shift of blood from the upper to the lower body (about 500–700 mL) and a decrease in central blood volume. This causes diminished venous return to the heart with diminished stroke volume and cardiac output, resulting in a transient postural hypotension with a decrease in blood flow through various organs, including the brain and the splanchnic region. Because of this transient postural fall of BP, immediate compensatory measures are initiated using the neural mechanism through the baroreceptor reflex pathway. This is followed by delayed compensation of humoral and physical (see below) mechanisms.

The baroreceptors in the carotid sinus and aortic arch are immediately stimulated as a result of hypotension as part of body's defense mechanism with transmission of afferent impulses to the nucleus tractus solitarius, an important structure for the baroreflex mechanism in the brainstem. This is followed by sympathetic stimulation from ventral medulla and vagal inhibition. As a result, within 30–45 seconds of assuming the upright position, peripheral resistance, venous return, and cardiac output are all increased, resulting in the restoration of BP to its baseline level in the supine position. The primary baroreceptor mechanism is helped by the humoral mechanism of release of plasma catecholamines, renin and aldosterone, and the physical factors of accumulation of excess tissue fluid in the legs, "muscle pump," and respiratory actions. The neural compensatory mechanism may fail as a result of lesion of the afferent arc, the medullary center, or the efferent arc of the baroreflex mechanism [9, 13, 14]. The lesions in the central nervous system could be in the medulla, the supramedullary regions controlling the nucleus tractus solitaries, or in the pathways from the nucleus tractus solitarius to the ventral medulla, and from there to the intermediolateral neurons of the spinal cord. Hence, diversely located lesions involving the brainstem, hypothalamus, other forebrain and limbic regions, as well as intermediolateral neurons of the spinal cord, sympathetic ganglia, and postganglionic sympathetic fibers, and afferent fibers to NTS may cause orthostatic hypotension.

Extensive lesions of the lumbosacral spinal cord may involve the parasympathetic and sympathetic innervation of the urinary bladder, causing symptoms of urgency, hesitation, and frequency of micturition, dribbling, incontinence, and retention of urine.

Lesions of the sacral parasympathetic neurons in the second, third, and fourth sacral regions may cause erectile dysfunction in men; this is often an early manifestation of autonomic neuropathy. Sympathetic neuropathy affecting the urogenital system may cause retrograde ejaculation of semen into the urinary bladder or failure of ejaculation in men.

The sweat glands are innervated by the postganglionic sympathetic fibers, which receive innervation from the intermediolateral neurons in the spinal cord. Involvement of these sympathetic fibers as well as those in the brainstem or the hypothalamus will cause impairment of sweating in the face, trunk, or the limbs, depending on the site of the lesions.

A perusal of the functional neuroanatomy would make it easily understandable why a lesion of the cervical sympathetic fibers may cause. Horner syndrome or a lesion of the Edinger–Westphal nucleus, or its efferent parasympathetic outflow will cause impairment of pupillary response to light and accommodation. Similarly, lesions of the superior and inferior salivatory nuclei or their efferents will cause diminished lacrimation (dryness of the eyes) and dryness of the mouth.

The heart and circulation are under the control of the sympathetic and parasympathetic nervous systems, and a lesion of the central autonomic network or involvement of its afferent and efferent connections will cause cardiac autonomic denervation, resulting in either persistent tachycardia or other cardiac arrhythmias.

A consideration of the central respiratory mechanism and the close interrelationship among autonomic, respiratory, and hypnogenic neurons makes it plausible to think that lesions in the central brainstem or adjacent structures may cause a variety of respiratory changes in cases of autonomic failure. These changes are particularly notable during sleep in the most well-recognized central degenerative autonomic neuropathy, namely, the Shy–Drager syndrome [3, 14, 31] or multiple system atrophy with progressive autonomic failure. A variety of respiratory changes are noted in this condition [31] (see also Chap. 12).

Lesions of the dorsal vagal motor nucleus of the medulla and its efferent connections will cause difficulty in swallowing and vomiting due to gastroesophageal atony. Other examples of intestinal motility disorders include achalasia, intestinal pseudo-obstruction, irritable bowel syndrome causing constipation or intermittent diarrhea (IBS-C or IBS-D), and urinary or fecal incontinence [22]. These gastrointestinal motility disorders may be caused by an enteric neuropathy due to dysfunction of the myenteric plexus neurons or secondary to an effect on the extrinsic ANS modulating the intrinsic ENS.

The following case example (adapted from Wilson-Pauwels et al., case study 1, [15]) illustrates the role of the

ANS in understanding the concept of "fright-fight-or-flight," the phrase introduced by Cannon [8].

During a short vacation in Maui, an island located in Hawaii, a 20-year-old woman decided to take a swim in the ocean. Suddenly she noticed that the tide was going out and she had difficulty in maintaining her orientation and began to drift farther and farther from the shore. She got frightened and started swimming back to the shore. Her breathing was becoming faster and faster, and she noticed that her heart had begun to pound. She was not particularly a good swimmer but realized that she was having superhuman strength, which enabled her muscles to act vigorously so that she was able to swim against the tide to the shore. On reaching the shore and arriving at the beach she noticed her breathing was rapid, her heart was racing, she was pale, and was having cold sweat in her extremities. She was resting flat, and in course of the next several minutes she began to feel normal; her respiration and heart rate returned to her normal baseline state.

Questions:	1. What is "fright- fight-or-flight" reaction?
	2. How do you explain her vigorous increase of strength?
	3. What are the mechanisms for her respiratory and heart rate changes?
	4. How do you explain her pallor and cold clammy sweaty limbs?

Comments (Based on Clinico-Anatomo-Physiological Correlation)

Answer to Questions 1–3 As discussed previously, the phrase "fright-fight-or-flight" was coined by Cannon [8] to describe a physiologic response to a threat ("fright"), real or perceived, in order to defend from the threat ("fight"), to escape from it ("flight"), or both. These efforts require vigorous energetic action and heavy use of the muscles. The chain of events occurs as follows (steps 1 to 4):

- **Step 1:** In response to a perceived threat the body through the senses (e.g., the eyes [vision] or ears [auditory perception]) sends signals to the amygdala, a part of the limbic system located in the medial temporal lobe bilaterally and responsible for emotional processing. The amygdala immediately sends distressed signals to the hypothalamus, the main ganglion of the autonomic nervous system (ANS), a sort of command center communicating with the rest of the body through the ANS, controlling all the vital organs (e.g., the heart, the lungs, gastrointestinal, genitourinary, and endocrine systems).
- **Step 2:** In this situation of "fright- fight-or-flight" reaction the hypothalamus sends bursts of sympathetic activity (the sympathetic system is predominately located in the posterior hypothalamus). As a result of sympathetic hyperactivity, a cascade of events occur supporting "fight-or-flight" response in the body with a characteristic physiological manifestation as described in step 3.
- **Step 3:** Adrenaline is released from adrenal glands (through activation of hypothalamo–pituitary–adrenal [HPA] axis) [32], and adrenaline is secreted from the adrenal glands. Noradrenaline (norepinephrine) is released from the postganglionic sympathetic nerves, causing vasomotor changes with vasodilatation and increased blood flow to the muscles and coronary arteries, encouraging muscle activation, cardioexcitation, as well as vasoconstriction in the skin and splanchnic regions, and bronchiodilatation with increased oxygen inhalation. In addition, there is increased glycogenolysis (in the liver and muscles), making excess glucose available for extra energy as well as increased cortisol secretion through activation of the HPA axis.
- **Step 4:** The above changes provide excessive energy throughout the body. These physiological changes cause a characteristic clinical presentation that can be summarized as follows: The subject manifests increased BP and heart rate (heart racing with palpitation), hyperventilation, panting, cold, clammy (sweaty) extremities, pallor of the skin of the face and the limbs, piloerection ("goose bumps"), and pupillary dilatation. The sympathetic nervous system uses two types of receptors to bring on the above physiological changes: α receptors (α1 and α2) and β receptors (β1 and β2)—α receptor activation causes vasoconstriction, relaxation of the gut muscles and pupillary dilatation, whereas β receptor activation causes vasodilatation of muscle vessels and coronary arteries, increased heart rate and cardiac contraction (increasing cardiac output), and bronchodilation (allowing increased airflow in and out of the lungs).

Answer to Question 4 How do you explain her cold clammy (sweaty) limbs with pallor of the skin?

Vasoconstriction in the cutaneous vessels caused pallor. Vasoconstriction in the splanchnic region made blood available to muscles and other regions, including the brain, and is responsible for increased peripheral resistance and BP.

Sweating was caused by intense sympathetic stimulation of the sweat glands, which helped dissipate heat generated by intense muscle activation.

It is notable that this description of "fight-or-flight" reaction in the above subject supports the concept of an "autonomic storm" ("autonomic dysreflexia and hyperactivity").

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