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Major Autonomic Neuroregulatory Pathways Underlying Short- and Long-Term Control of Cardiovascular Function

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Abstract Short-term and long-term blood pressure (BP) regulation and its maintenance at levels adequate to perfuse tissue organs involve an integrated action of multiple neural, cardiovascular, renal, endocrine and local tissue control systems. In the recent year, there has been a growing interest in the understanding of neural pathways key to BP control. For instance, through major advances in studies using both anesthetized and conscious animals, our knowledge of the essential neural mechanisms that subserve the baroreceptor, cardiopulmonary and chemoreceptor reflexes, and those evoked by the activation of stress pathways has dramatically increased. While the importance of these neural pathways in the maintenance of cardiovascular homeostasis is well established, the recognition of the central processing nuclei that integrate various afferent inputs to produce synchronous adjustments of autonomic outflows is still progressively expanding. Based on the literature provided thus far, the present review provides an overview in relation to the important neural determinants of BP control and later offers a concise description of major neuronal pathways that control autonomic outflows to the cardiovascular system in the short and long term.

Keywords Blood pressure · Sympathetic nerve activity · Baroreflex · Cardiopulmonary reflex · Chemoreflex · Stress pathways

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Introduction

The autonomic nervous system (ANS), which comprises a set of highly differentiated and closely regulated pathways, is a collection of afferent and efferent neurons that link the central nervous system (CNS) with the effector organs and is responsible for involuntary control of various visceral structures including the heart and vasculature [1–4]. Blood pressure is a function of cardiac output and systemic vascular resistance, two variables that are controled by the ANS. Cardiac output is dependent upon three regulated variables: end-diastolic volume, cardiac contractility and heart rate (HR). End-diastolic volume, the volume of blood in the ventricular chamber before contraction, is determined by venous pressure. Venous pressure is related to blood volume and venous smooth muscle tone; both of which are regulated by the sympathetic nervous system (SNS). Cardiac contractility and HR, in turn, are under control of both the sympathetic and parasympathetic divisions of the ANS, whereas systemic vascular resistance is modulated by the SNS [5, 6].

Autonomic neuroregulation (tonic and reflex) of BP is accomplished in the short term through a series of differentiated neural pathways that integrate mechanical and chemical inputs (e.g. baroreceptor, cardiopulmonary and chemoreceptor reflex pathways) to modify efferent sympathetic and parasympathetic activities to different target organs. Humoral factors such as circulating hormones, norepinephrine (NE), epinephrine, angiotensin II (Ang II), endothelin, histamine, bradykinin and nitric oxide (NO) can modulate these neuronal pathways and impact long-term BP regulation. In view of the present literature, this review therefore aims to provide an overview of key concepts in relation to neural determinants and modulators of BP, and later presents a concise description of major neuronal pathways controling autonomic outflows to the cardiovascular system in the short and long term.

Neural Control of the Heart

The heart receives dual innervation from the parasympathetic (vagal postganglionic neurons) and sympathetic (sympathetic postganglionic neurons) divisions of the ANS [7–9]. These components exert a powerful antagonistic influence on the heart by modulating cardiac rate (chronotropy), conduction velocity (dromotropy), contraction (inotropy) and relaxation (lusitropy) [2, 10•, 11, 12]. Cardiac vagal preganglionic neurons (CVPN) project onto cardiac vagal postganglionic neurons located within the intracardiac ganglia, sinoatrial (SA), atrioventricular (AV) and cranioventricular ganglia [13, 14]. Sympathetic postganglionic neurons similarly project through the intracardiac ganglia or directly innervate atrial and ventricular myocardium [15–17]. The chronotropic and dromotropic effects are mediated by both cardiac vagal and sympathetic postganglionic neurons innervating the SA and AV nodes [7, 18–21], whereas the inotropic and lusitropic effects are primarily mediated by sympathetic and parasympathetic nerve fibres innervating atrial and ventricular myocytes [8, 10•]. Efferent vagus nerve activity also has tonic and basal effects that inhibit sympathetic activation and NE release at a presynaptic site of action. This facilitation of cardiac vagal input explains why cardiac vagal activity dominates over those of cardiac sympathetic postganglionic neurons at rest, a response known as "accentuated antagonism" [22, 23]. In a static or dynamic state, elevated cardiac sympathetic drive can be overridden by intense vagus nerve discharge [24]. Given the ability to modulate both HR and stroke volume, the autonomic innervation of the heart provides an important remote mechanism to rapidly adjust cardiac output to meet short-term changes in the body needs: e.g. responding to changes in BP, volume, or composition [pH, oxygen partial pressure (PaO_2), carbon dioxide partial pressure ($PaCO_2$), endogenous mediators or toxins], or reacting to environmental challenges such as exercise or stress [2].

Sympathetic Neural Control of the Blood Vessels

Blood vessels receive sympathetic inputs but mostly lack parasympathetic innervation. Postganglionic sympathetic nerve fibres are confined to the adventitial–medial junction of most arteries, arterioles and veins supplying muscle, viscera and skin [25, 26]. The arterioles are the major contributors to total peripheral resistance, which makes sympathetic control of those vascular beds critical to the regulation of systemic BP [4, 27]. In contrast to arteries, veins contain less smooth muscle and receive limited sympathetic innervation, yet they can still contract in response to sympathetic activation [6, 26]. They serve primarily as capacitance vessels as they are more distensible and able to accommodate large volumes of blood. Venules and capillaries, however, lack smooth muscle and are not directly innervated by sympathetic nerves [2, 4].

In addition to NE, which binds α_1- and α_2-adrenergic receptors located on vascular smooth muscle cells and develops muscle tension [28–30], vascular sympathetic nerve endings may also release substances such as neuropeptide Y (NPY) or adenine triphosphate (ATP) as cotransmitters. These are capable of producing vasoconstriction by activating vascular NPY Y1 receptors or purinergic P2X receptors, respectively, and increasing intracellular calcium concentration [31]. Neuropeptide Y may also potentiate the vasoconstrictor-effecting properties of NE and ATP [31].

Cardiovascular sympathetic efferent nerves are classified into three populations: thermosensitive, glucosensitive and barosensitive [5]. The thermosensitive group consists primarily of vasoconstrictor neurons supplying the tail artery in the rat [32], analogous to those supplying cutaneous vascular beds in humans, recruited to cope with changes in body temperature, but can also be activated by emotional stimuli or hyperventilation [33]. The glucosensitive group of sympathetic neurons control epinephrine release from the adrenal gland in response to hypoglycaemia or exercise activity [34, 35]. These two groups of neurons are weakly, if at all, coupled to the cardiac cycle or inhibited by the baroreceptor reflex, thus suggesting a less important role in the control of BP [5, 33, 35]. The last and by far largest class of cardiovascular sympathetic efferents is the barosensitive group. These neurons, which innervate the blood vessels supplying the heart, kidneys, muscle and other visceral organs, show ongoing activity at rest (sympathetic tone) and are subject to numerous reflex regulatory pathways that operate in feedback or feedforward manner, and their activity is strongly coupled to the cardiac cycle and respiration, which consequently suggests a primary role for these nerves in short- and/or long-term BP stability [5, 33, 36–38]. Increasing sympathetic outflow beyond this tonic level causes more vasoconstriction, whereas withdrawing sympathetic tone causes vasodilation.

Although most vascular beds are innervated by sympathetic nerve fibres, their responsiveness to sympathetic neural input can either be selective depending on the type of stimulus, or vary in intensity according to the vessel anatomical location [5]. Regardless of the type of vascular sympathetic efferent, arterioles of the skin, muscle, renal and splanchnic circulations appear to show robust constriction in response to factors triggering sympathetic activation such as anxiety [39], exercise [40], heat stress [41, 42], low salt intake [43] and hypoxia [44], whereas cerebral and coronary arterioles seem to be less responsive [2]. Target specific differences in the level of sympathetic activity suggest that efferent sympathetic activity to various vascular beds is differentially regulated, as shown in numerous studies [15, 35, 45••, 46, 47]. For instance, Yoshimoto and colleagues (2010) showed that an infusion of Ang II in rats kept on high salt diet decreased renal

sympathetic nerve activity (SNA) by 40 % during the first 7 days and then returned towards control levels by day 10 of Ang II. Lumbar SNA, by contrast, remained at control levels throughout the Ang II period. Such differential responsiveness, which is an area of active investigation [46, 48–51], is important to redistribute cardiac output mainly through constricting non-essential vascular beds, while preserving flow to vital organs in the setting of global SNS activation [2].

Sympathetic Neurohumoral Control

The SNS also exerts more prolonged, indirect cardiovascular effects via activation of several powerful hormonal systems which mainly include the following:

1. *The sympathoadrenal system*: Chromaffin cells of the adrenal medulla receive sympathetic preganglionic neurons (SPNs) that promote the synthesis and release of mainly epinephrine along with NE into the bloodstream [35, 52]. These circulating catecholamines play a major role in cardiovascular regulation through modulating cardiac and vascular adrenergic receptor responses [28].
2. *The renin-angiotensin-aldosterone system (RAAS)*: The RAAS exerts powerful effects on determining long-term level of SNA. Postganglionic sympathetic nerves synapse onto renin-producing juxtaglomerular cells in the walls of the renal afferent arterioles. Increased renal SNA triggers the commonly known cascade of the RAAS pathway, which ultimately results in Ang II formation. Ang II, via an angiotensin type 1 (AT_1) receptor mediated action, modulates cardiovascular function through either directly promoting systemic vasoconstriction action which increases peripheral resistance and BP, or stimulating adrenocortical secretion of aldosterone, a hormone which increases renal tubular sodium and water reabsorption, thereby increasing blood volume and BP [53–56]. A crosstalk relationship between the activity of SNS and RAAS has also been identified, whereby Ang II acts to evoke NE release through a presynaptic site of action on postganglionic sympathetic nerve terminals, enhance synaptic transmission through sympathetic ganglia [52, 57], or influence central neural processing via the circumventricular organs, particularly the subfornical organ and the area postrema [36, 52], hence evoking activation of central sympathetic outflow and increasing BP. The relative contribution of the peripheral versus central effects of Ang II to autonomic control of cardiovascular function is not thoroughly characterized and is perhaps hampered by our limited knowledge of the key autonomic nuclei within the brain modulated by Ang II.

Reflex Control of Blood Pressure

Maintenance of BP and cardiovascular homeostasis at levels adequate to perfuse body tissues and organs is an essential requirement for the constancy of the internal environment and survival. Regulation of BP is accomplished via a series of differentiated arterial and non-arterial reflex pathways that integrate a variety of sensory afferent inputs (pressure, volume, chemical, etc.) to tightly maintain autonomic balance and correct changes in BP. Here, major autonomic reflexes responsible for BP control are reviewed.

The Arterial Baroreceptor Reflex

The baroreceptor reflex buffers moment-to-moment changes in BP by altering parasympathetic and sympathetic outflow, thereby producing reflex changes in HR and total peripheral resistance. Baroreceptors, stretch receptors located within the aortic arch and carotid sinus, detect changes in vascular distensibility and send sensory afferent impulses to the cardiovascular regulatory center in the brain stem [5, 36]. Specifically, these receptors represent a complex arrangement of sensory terminals located mostly in the inner adventitia of the arterial wall (Fig. 1), where strain develops most effectively and deforms nerve endings responsible for generation of the sensory signals [58]. In the rat, the sensory terminal region of aortic baroreceptors is located between two elastic laminae which are arranged in concentric layers within the arterial wall. The nerve cell membrane of the sensory terminal is attached to a basal lamina which connects vascular smooth muscle cells in the media and the elastic lamina in the adventitia (Krauhs, 1979). The precise molecular mechanism for impulse generation at the sensory nerve terminal is not completely known; however, various cellular elements are thought to play a role including voltage-gated ion (Na^+, K^+ or Ca^{2+}) channels [59], transient receptor potential vanilloid 1 (TRPV1) [60], or P_2 purinoceptors [61].

The baroreceptor afferent signal, which directly correlates with the stretch of the vessel wall in which those receptors are located [62], is conveyed via specialised nerve fibres—low-pressure-threshold myelinated A-fibres and high-pressure-threshold unmyelinated C-fibres [63–65]—within the vagus nerve and carotid sinus nerve in humans [2, 36], or the aortic depressor nerve (ADN) and carotid sinus nerve in rodents and rabbits [66–69]. Cell bodies of aortic baroreceptor and carotid sinus baroreceptor neurons are located in the nodose ganglion and the petrosal ganglion, respectively [65].

Baroreceptor afferents terminate within the nucleus tractus solitarius (NTS) and directly excite, via a glutamatergic synapse, second-order neurons (Fig. 1) [70–72], located within the intermediate and caudal NTS [73]. The NTS represents a principal integrative center for circulatory control. For example, it receives direct inputs from higher brain centers (e.g.

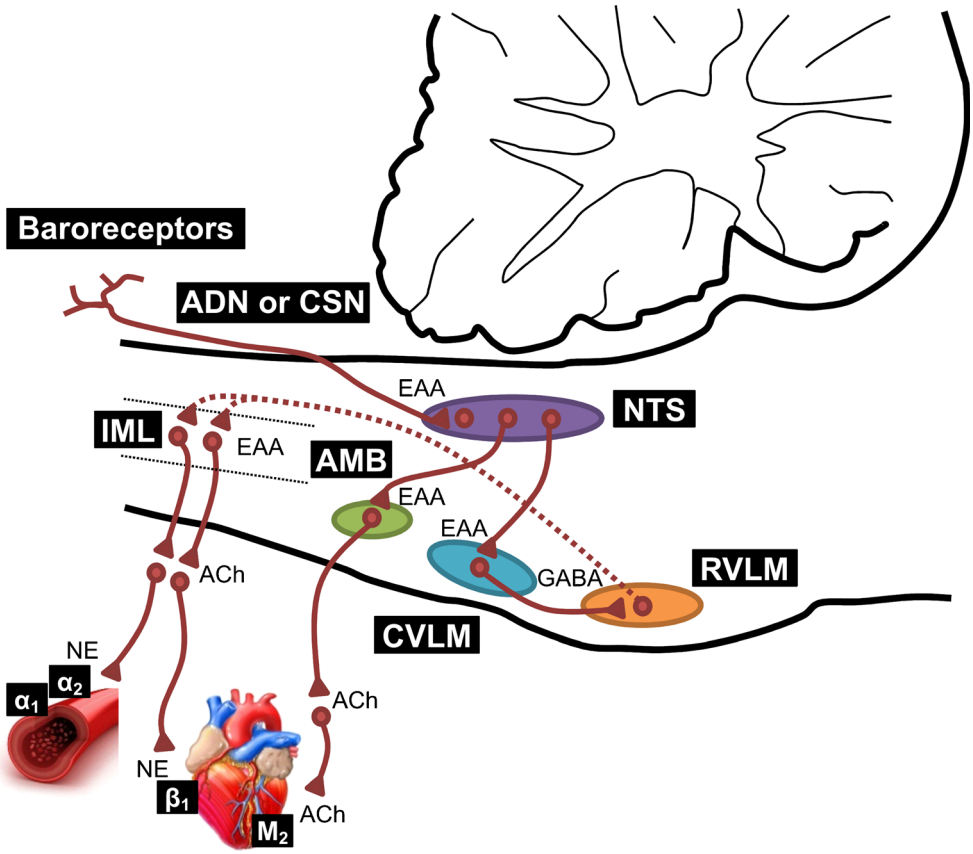

Fig. 1 Baroreceptor reflex pathway within the lower brainstem region. *ADN*, aortic depressor nerve; *CSN*, carotid sinus nerve; *NTS*, nucleus tractus solitarius; *CVLM*, caudal ventrolateral medulla; *RVLM*, rostral ventrolateral medulla; *AMB*, nucleus ambiguus; *IML*, intermediolateral cell column in the spinal cord; *EAA*, an excitatory amino acid; *GABA*, γ-aminobutyric acid; *ACh*, acetylcholine; and *NE*, norepinephrine . Pathway description taken from [36]

inhibitory inputs from the paraventricular nucleus, PVN) [74] which may play a role in modulating the baroreflex arc or controling BP in the long term, and it is the region where sensory afferent fibres innervate the large systemic arteries and cardiopulmonary region, and polysynaptic inputs from many sympathetic and somatic afferents terminate [75–78]. The NTS is essential for the transmission of baroreceptor information, since lesions of the NTS completely abolish the baroreflex in rats [79] and humans [80]. Similarly, bilateral blockade of excitatory amino acid receptors, N-methyl-D-aspartate (NMDA), in the NTS by microinjection of kynurenate, a glutamate receptor antagonist, abolishes the baroreflex [81]. In contrast, microinjection of glutamate or Ang II into the NTS simulates baroreceptor activation, with a fall in arterial BP and HR [82, 83].

Sympathetic outflow to the heart and vasculature is modulated through a relay circuit involving the NTS, caudal ventrolateral medulla (CVLM) and rostral ventrolateral medulla (RVLM; Fig. 1). The NTS neurons conveying baroreceptor signals send glutamatergic projections to the CVLM [84], whereby activation of the NTS evokes only monosynaptic excitatory responses to CVLM-projecting NTS neurons [85]. Neurons within the CVLM use an inhibitory GABAergic synapse which exerts a continuous and powerful restraining influence on the discharge properties of sympathoexcitatory neurons within the RVLM [5, 36, 72, 86]. Evidence supporting a sympathoinhibitory effect for the CVLM brain stem region was deduced based on numerous studies showing that lesions of the CVLM [87] and inhibition with the $GABA_A$ receptor agonist muscimol [88] or with the glutamate receptor antagonist kynurenate [89] produce long-lasting pressor and sympathoexcitatory responses, whereas stimulation of the CVLM results in depressor and sympathoinhibitory responses [90]. Interestingly, neurons within the CVLM have been shown to exhibit a tonic activity that is independent of baroreceptor drive [87, 91] and may serve a potential role in long-term regulation of BP [86].

Barosensitive inhibitory neurons of the CVLM project monosynaptically to bulbospinal sympathoexcitatory neurons in the RVLM bilaterally [92]. The RVLM neurons synapse on the SPNs in the intermediolateral (IML) cell column of the spinal cord [71, 72]. Due to their direct projection to cardiac and vasomotor SPNs in the thoracic and lumbar spinal cord, sympathoexcitatory neurons in the RVLM are also called presympathetic neurons [36]. The RVLM presympathetic neurons are inhibited by baroreceptor activation during ADN electrical stimulation or BP elevations when recorded intracellularly [93] or extracellularly [94, 95]. Microinjection of bicuculline, a $GABA_A$ receptor antagonist, in the RVLM blocks the baroreceptor-mediated inhibition of RVLM sympathoexcitatory neurons [96]. Activity of the RVLM presympathetic neurons is believed to be a major factor in

driving tonic activity in the SPNs [97]. It has been hypothesized that RVLM barosensitive neurons preferentially regulate SNA to the skeletal muscle arteries, splanchnic arteries, heart and kidneys [98–100]. However, anatomical studies have yet to provide convincing evidence in support of this hypothesis [5, 101]. Importantly, the RVLM is also the region where inputs from other brain regions converge (e.g. sympathoexcitatory inputs from the PVN which is driven by AT_1 receptors in the RVLM) and may therefore contribute to long-term BP regulation [5, 36, 102].

Vagal efferent outflow to the heart (Fig. 1) is modulated through a neuronal circuit involving the NTS and CVPNs principally located within the nucleus ambiguus, the intermediary zone and the dorsal motor nucleus of the vagus (DMNV) [103–105]. Bilateral blockade of the NMDA receptors in the NTS by microinjection of kynurenate abolishes baroreflex-mediated bradycardia [81]. Stimulation of the pathway from the NTS activates excitatory NMDA and non-NMDA-receptor-mediated postsynaptic currents in vagal cardiac neurons in the nucleus ambiguus [106]. There is also a tonically active GABAergic input to the CVPN that plays an important role in tonic and reflex control of HR [107]. Blockade of $GABA_A$ receptors by microinjection of bicuculline into the nucleus ambiguus produces a dose-dependent bradycardia, which can be reversed by the $GABA_A$ receptor agonist, muscimol [108]. $GABA_A$ agonists microinjected in the nucleus ambiguus prevent the reflex slowing of the heart in response to BP increases evoked with phenylephrine [108].

As shown above, two separate pathways are responsible for regulating vagal and sympathetic outflow, both of which are recruited to alter HR and SNA, and counteract changes in BP. Increases in arterial BP stimulate afferent baroreceptor discharge, triggering reflex inhibition of efferent sympathetic outflow to the heart and vasculature, and activation of parasympathetic outflow to the heart. The resultant decreases in vascular resistance, stroke volume and HR then reduce arterial BP back to baseline levels. Decreases in arterial BP have the opposite effect, evoking reflex increases in peripheral vascular resistance, stroke volume and HR to restore arterial BP. Given the high sensitivity of baroreceptors to altered vascular stretch, the firing pattern of arterial baroreceptors increases rapidly during early systole and decreases during late systole/early diastole. These phasic responses become more apparent at lower pressures, a time when baroreceptor discharge frequency is reduced, and less apparent at higher pressures, when the baroreceptor discharge frequency is increased [2, 109–111]. An inability for the baroreflex to adequately buffer changes in BP may be due to various factors, such as an inability of the baroreceptor afferents to sense changes in BP, the central relay nuclei to produce changes in vagal or sympathetic outflow, or the heart or vasculature to respond to autonomic inputs.

Function and strength of the arterial baroreflex are often represented by a sigmoid logistic function, with a direct relationship existing between afferent baroreceptor discharge and arterial pressure, and an inverse relationship existing between BP and either efferent SNA or HR [112, 113, 114••]. An important property of the arterial baroreceptor reflex is the ability to operate around a new baseline BP, a phenomenon known as "baroreceptor resetting" (Fig. 2). Any component (e.g. afferent, central or efferent) of the baroreceptor reflex is able to reset and influence reflex control of BP [62, 115–119]. In other words, the afferent signal may become modified in the face of sustained elevations or reductions in BP, the CNS may "re-wire" its connections that regulate sympathetic and parasympathetic outflows, and/or the amount of SNA to different vascular beds may reset to varying degrees. The degree to which target organs, especially the kidney, respond to reset reflex control of SNA may also help determine the long-term level of BP and development of hypertension.

A resetting of arterial baroreflex can be acute or chronic. Acute resetting is a reversible process where receptors reset only partially, demonstrated within ≤20 min after arterial pressure has been elevated [120, 121] and often occurs during conditions such as nociception, emotional stimuli, or increased physical activity during exercise [40, 122–124]. Here, the efferent baroreflex function curve shifts to the right and upwards, in the absence of an evident reduction in sensitivity (the slope of the steepest portion of the baroreflex relationship). This adaptive response allows BP, efferent SNA and HR to stay at higher levels and then fall back to baseline levels

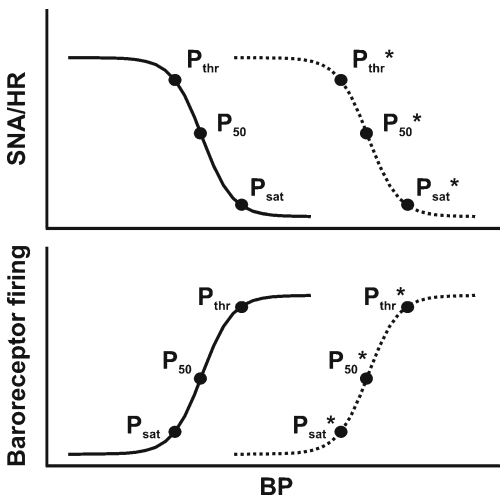

Fig. 2 Baroreflex function curves of efferent sympathetic nerve activity (SNA)/heart rate (HR) (*upper panel*) and afferent activity (*bottom panel*) illustrating resetting of the baroreflex relationship in response to increased blood pressure (BP). Note the rightwards shift resetting in all the pressure parameters of the baroreflex function to higher BP. Pressure threshold (P_{thr}), pressure at midpoint of the curve (P_{50}), pressure saturation (P_{sat}), reset pressure threshold (P_{thr}*), reset pressure at midpoint of the curve (P_{50}*) and reset pressure saturation (P_{sat}*).

when the stimulus is ceased. The transient nature of baroreflex resetting in these settings indicates that alterations in the central components of the baroreflex arc are not related to neuroanatomic changes in the acute settings.

Chronic resetting, on the other hand, results from a sustained elevation in arterial pressure that lasts for longer than a few weeks and is often associated with the development of hypertension [115, 125–129]. Under such conditions, the baroreflex function curve gradually shifts to the right to operate around the new prevailing BP set point (Fig. 2). Over time, as elevated BP persists, the curve may shift upwards to higher resting HR/SNA and the sensitivity and range of the baroreflex mechanism may become impaired, rendering it less capable of buffering acute BP fluctuations. Baroreflex resetting is thought to be governed by neurohumoral mechanisms [5], with a reduction in baroreceptor feedback due to a biasing of the transmission between baroreceptor afferents and second-order neurons in the NTS being a proposed mechanism [70]. In the latter, GABAergic transmission within the NTS driven by inputs from higher brain regions (e.g. hypothalamus and other forebrain regions) or factors such as circulating/brain Ang II can presynaptically or postsynaptically dampen baroreceptor afferent-mediated glutamatergic excitation of the NTS second-order neurons [70, 76, 130].

Under pathological conditions, baroreceptor resetting is thought to be driven by thickening of the arterial wall, a reduction of its distensibility and diminished sensitivity of baroreceptors, leading to impaired afferent traffic [62, 128]. However, chronic resetting that develops in a few weeks as observed during the early stages of hypertension in spontaneously hypertensive rats (SHRs) is not accompanied by vascular hypertrophy and reduced distensibility of the arterial wall [131]. It is therefore possible that, at this stage, resetting is attributed to changes in the baroreceptors themselves and/or other neural elements within the reflex arc as described above. At this point, when vascular remodeling is not established in the SHR, Sapru and Krieger (1979) were able to show that antihypertensive therapy is fully capable of reversing baroreceptor resetting, suggesting that early interventional strategies that lower BP can preserve baroreflex sensitivity (BRS) [132].

Cardiopulmonary Reflex

Despite the central role of the arterial baroreceptors in the rapid stabilisation of BP, research has shown that reflex control of the cardiovascular functions is dependent not only upon the arterial baroreceptor reflex but also to a great extent on cardiopulmonary reflex function. Nonetheless, our knowledge of this reflex pathway and the central circuit it employs does not appear to be as extensive as the baroreceptor reflex. Cardiopulmonary reflexes, which are major yet diverse cardiovascular reflex pathways, originate in the heart and lungs and play a critical role in the control of sympathetic cardiovascular drive, HR, peripheral vascular resistance, sodium and water excretion, and the release of humoral substances such as vasopressin, renin and atrial natriuretic peptide (ANP) [2, 133–136]. This reflex pathway consists of the following: (1) cardiopulmonary receptors, which are a unique set of chemosensitive and mechanosensitive receptors located within the heart, aorta and lungs [137] and respond either by exposure to chemical irritant (chemosensitisation) or increases in pressure or stress (mechanostimulation) [111, 134, 136, 137]; (2) sensory afferent fibres within the parasympathetic cranial nerve X, including myelinated A-fibres which are activated at lower intensities, and unmyelinated C-fibres which are activated at higher intensities. Both are thought to play a central role in the tonic depression of SNA, HR, vascular tone, and renin secretion, as their severing evokes an increased SNA, HR, renin release and vasoconstrictions of the skeletal muscle, renal and mesenteric vascular beds [135, 137, 138••]; (3) medullary regions regulating visceral function by modulation of efferent sympathetic and parasympathetic innervations; and (4) efferent preganglionic and postganglionic sympathetic and parasympathetic nerve fibres supplying the periphery [137].

The cardiopulmonary reflex, evoked by the unmyelinated C-fibre vagal afferents, and the baroreceptor reflex use common central pathways (Fig. 3) in the brainstem regions to stabilise BP [95, 134, 139]. The vagal afferent fibres terminate in the NTS and act by inducing reflex responses in sympathetic and parasympathetic outflows to the periphery [77, 78, 141]. Sympathetic outflow to the heart and vasculature is then modulated via the CVLM, RVLM and SPNs in the spinal cord [95, 142]. Efferent parasympathetic outflow to the heart is modulated through the nucleus ambiguus and DMNV [141, 143]. Like the baroreceptor reflex, unmyelinated C-fibre vagal afferent stimulation evokes sympathoinhibition, whereas myelinated A-fibre vagal afferent pathways (Fig. 3), like the chemoreceptor reflex (see below), is thought to be sympathoexcitatory, and its responses are modulated through a direct projection from the NTS to the RVLM [139]. As reviewed by Coote (2005), there is also evidence that vagal afferent neurons terminating in the NTS project to the PVN [144, 145], where there is a discrete targeting of spinally projecting oxytocin neurons that innervate cardiac SPNs [146] and a specific pool of GABA inhibitory interneurons [147] that innervate a population of spinally projecting vasopressin neurons that synapse with the renal SPNs [146]. There is also a vasopressin/glutamate projection from the PVN to RVLM spinally projecting vasomotor neurons [148], although the involvement of this projection in the reflex is still unclear.

Several specific, yet sometimes incompletely characterized, cardiopulmonary reflexes have been identified

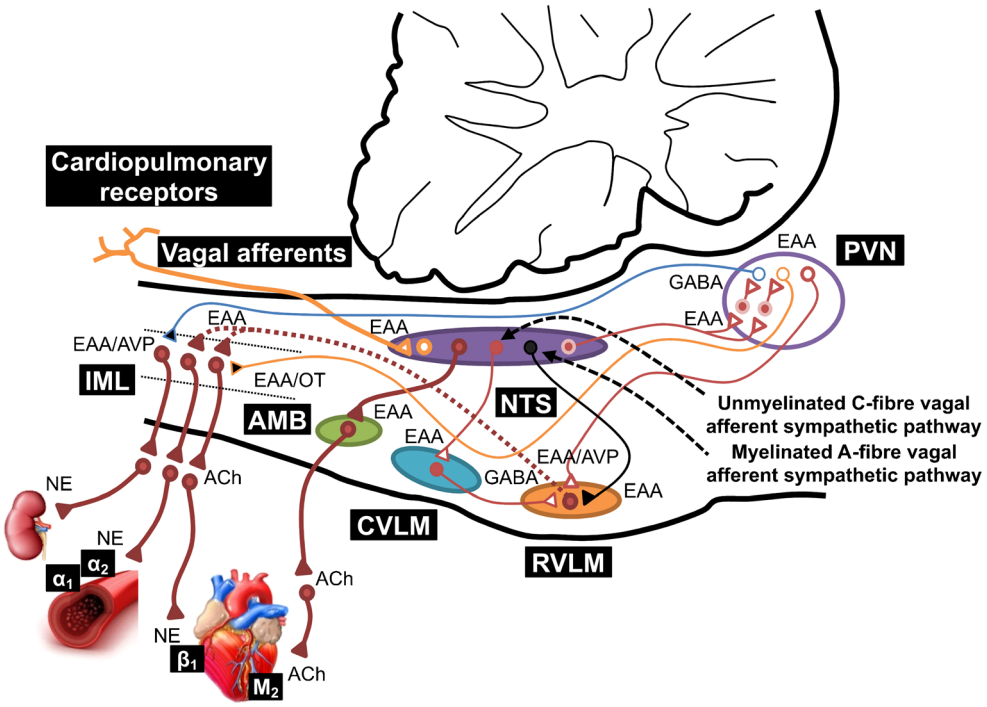

Fig. 3 Cardiopulmonary reflex pathway within the lower brainstem region. *NTS*, nucleus tractus solitarius; *CVLM*, caudal ventrolateral medulla; *RVLM*, rostral ventrolateral medulla; *AMB*, nucleus ambiguus; *IML*, intermediolateral cell column in the spinal cord; *EAA*, an excitatory amino acid; *OT*, oxytocin; *AVP*, arginine vasopressin; *GABA*, γ-aminobutyric acid; *ACh*, acetylcholine; and *NE*, norepinephrine. Pathway description taken from [139, 140]

based on the type of sensory afferent fibre types recruited during activation of the reflex:

1. *Reflexes mediated by myelinated A-fibres of the vagal afferents:*

(a) The best defined cardiopulmonary reflex mediated by the myelinated A-fibre type of the vagal afferent is the Bainbridge reflex. This reflex is initiated by mechanoreceptor activation at the pulmonary vein–atrial junctions in response to increased atrial volume and pressure [149]. Activation of this reflex leads to sympathetically mediated reflex tachycardia [150, 151], with minimal or no apparent effect on cardiac inotropic activity [152]. The reflex differentially affects sympathetic outflow to different target organs, with cardiac SNA reflexively increased, renal SNA decreased, adrenal SNA increased, splanchnic SNA increased or unchanged but lumbar remaining unaffected [151, 153]. Systemic vascular resistance remains unaltered [154]; however, decreases in antidiuretic hormone (vasopressin) [155], cortisol [156] and renin [157] secretions and consequent diuresis are observed [158].
(b) Mechanoreceptors within the pulmonary trunk and the proximal part of the pulmonary arteries (pulmonary baroreceptors) are also endowed with myelinated A-fibre vagal afferents. These pulmonary pathways are activated in response to venous infusions and vena caval occlusions, causing reflex vasoconstriction and an increase in respiratory activity [138••].

2. *Reflexes mediated by unmyelinated C-fibres of the vagal afferents:* These include reflexes initiated in the atria, ventricles, coronary arteries and lungs:

(a) Atrial mechanoreceptors respond to increased atrial volume and pressure by causing bradycardia and vasodilation [138••, 159].
(b) Mechanoreceptors in the left ventricle and coronary arteries respond to increased ventricular diastolic pressure and afterload by causing vasodilation [138••].
(c) Ventricular chemoreceptors are stimulated by toxic and irritant chemicals including plant alkaloids (e.g. veratridine, veriloid and protoveratrine, initially described as anithypertensives before the 1960s), nicotine, capsaicin, venoms (e.g. snake, insects and marine animals), and synthetic organic compounds (e.g. ethylacetoacetate, thioureas, halogenated anesthetics and the serotonin 5-HT_3 receptor agonist phenylbiguanide). Endogenously occurring substances stimulating these receptors are potassium chloride, bradykinin, prostaglandins, prostacyclin, histamine, serotonin and reactive oxygen species [111, 137, 160, 161]. Chemostimulation of these receptors evokes what is often referred to as the Bezold–Jarisch (BZJ) reflex, the activation of which is characterized by a powerful reflex sympathoinhibition, bradycardia, widespread vasodilation and hypotension [111, 137, 162]. Clinically, this reflex can be triggered during intracoronary injection of contrast agent or myocardial ischemia, which releases endogenous chemical factors (e.g. bradykinin and prostaglandins) that can contribute to the activation of this reflex, which is therefore thought to have a

cardioprotective action [138••, 160, 162]. There is also evidence that mechanical stimulation of afferents by strong contractions of an under-filled left ventricle can also evoke the BJZ reflex [138••, 160].

(d) Marked lung inflation (e.g. mechanical stimulation, pulmonary edema or congestion) activates juxtapulmonary capillary receptors (J-receptors) in the lungs, leading to respiratory sinus arrhythmia, bradycardia, sympathoinhibition, peripheral vasodilation, and hypotension [163–166].

Chemoreceptor Reflex

The chemoreceptor reflex mechanism is primarily involved in the control of ventilation; however, it can also modulate neural pathways regulating mean arterial BP. Stimulation of this reflex is triggered by hypoxia, hypercapnia and/or acidosis, leading to increases in parasympathetic, sympathetic and phrenic nerve activities [34, 44, 167, 168•]. The peripheral chemoreceptors, which are located in the carotid bodies at the bifurcation of the common carotid arteries and in aortic bodies in the region of the aortic arch, are highly specialised receptors; the activation of which is primarily evoked by a reduction in PaO_2 of the arterial blood [2, 36, 101, 111, 160, 169]. Arterial chemoreceptors are thought to be type 1 glomus cells that contain and release multiple neurotransmitters into the synaptic cleft activating presynaptic (i.e. on the type 1 glomus cells) and postsynaptic (i.e. chemoafferent terminals) receptors, utilising catecholamines (especially dopamine), acetylcholine, met- and leuenkaphalins, substance P, NPY, galanin, calcitonin-gene-related peptide, serotonin and endothelins [170]. Similar to baroreceptor afferent fibres, chemoreceptor afferents are located within the vagus nerve in humans and the carotid sinus nerve in humans and rats [36, 69, 101, 171] and relay sensory signals to the brain that reflexively elicit hyperventilation, bradycardia and sympathetically mediated vasoconstriction in most vascular beds. The increase in ventilation tends to increase oxygen saturation of the blood, while the bradycardia and sympathetic vasoconstriction acts to reduce oxygen consumption by the tissues to thus maintain the oxygen reserve and vital organ perfusion [2, 36, 169, 172, 173]. The initial bradycardic response to arterial chemoreceptor activation is then usually followed by tachycardia at steady state as hyperventilation inhibits efferent vagal outflow to the heart [169]. If BP is within the normal range, the chemoreflex does not exert a powerful cardiovascular response because of the predominant inhibitory effect of the arterial baroreceptor reflex. However, if BP falls below 80 mmHg, activation of the chemoreflex potentiates the baroreflex-mediated vasoconstriction to restore BP to normal levels [2].

Like baroreceptor afferent fibres, chemoreceptor primary afferent fibres terminate in the NTS (Fig. 4); however, in contrast to the baroreflex pathways, chemoreceptor signals are transmitted to the RVLM via a direct excitatory glutamatergic projection [174–176], increasing the activity of the SPNs. Bilateral microinjections of the glutamate receptor antagonist kynurenate into the RVLM abolish the sympathoexcitatory and pressor responses following peripheral chemoreceptor activation [177]. A non-glutamatergic neurotransmission of the sympathoexcitatory component of the chemoreflex at the NTS level has also been suggested [178]. Cardiac vagal efferent activity and chemoreflex-induced bradycardia, which share similar yet separate neurochemical mechanisms in the NTS to those of baroreflex-mediated bradycardia, are regulated via relay circuit which involves the NTS and nucleus ambiguus and/or DMNV; all of which are recruited to increase the activity of CVPN [175, 179]. Evidence supporting a common neuroanatomical pathway for the parasympathetic component of chemoreflex and baroreflex in the NTS came from studies demonstrating that activation of 5-HT_3 serotonin receptors in the NTS abolished the cardiovagal component of both the baroreflex and chemoreflex [180]. However, microinjection of baclofen, a $GABA_B$ agonist, into the NTS affected the bradycardic response to baroreflex [181] but not chemoreflex activation [175], suggesting that the parasympathetic component of baroreflex and chemoreflex are regulated by two different inhibitory mechanisms.

Over the last decade, animal studies and advances in electrophysiological recordings have significantly progressed our understanding of the central network responding to a chemoreflex stimulus. There is evidence that the pontomedullary region may contain multiple sites for central chemoreception, including the NTS, retrotrapezoid nucleus, pre-Bötzinger complex, and raphe [101, 182•, 183–185]. Importantly, the two major chemoreception locales (peripheral and central) that drive breathing are hypothesized to be combined at the retrotrapezoid nucleus [182•]. A rise in CNS $PaCO_2$ has also been shown to evoke marked increases in SNA to the heart and blood vessels in both humans and experimental animals [186, 187]. The effect of hypercapnia is generally linked to series of events, whereby brain extracellular fluid acidification stimulates central chemoreceptors to activate the respiratory pattern generator. This ultimately drives the sympathetic generating network by phasically exciting the RVLM [182•, 188, 189], the sympathoexcitatory neurons of which are known to be intrinsically pH-sensitive and receive excitatory synaptic inputs from the retrotrapezoid nucleus [190]. During central chemoreceptor stimulation, RVLM sympathoexcitatory neurons exhibit patterns of central respiratory-related activity that are similar to those of barosensitive sympathetic ganglionic neurons [191, 192].

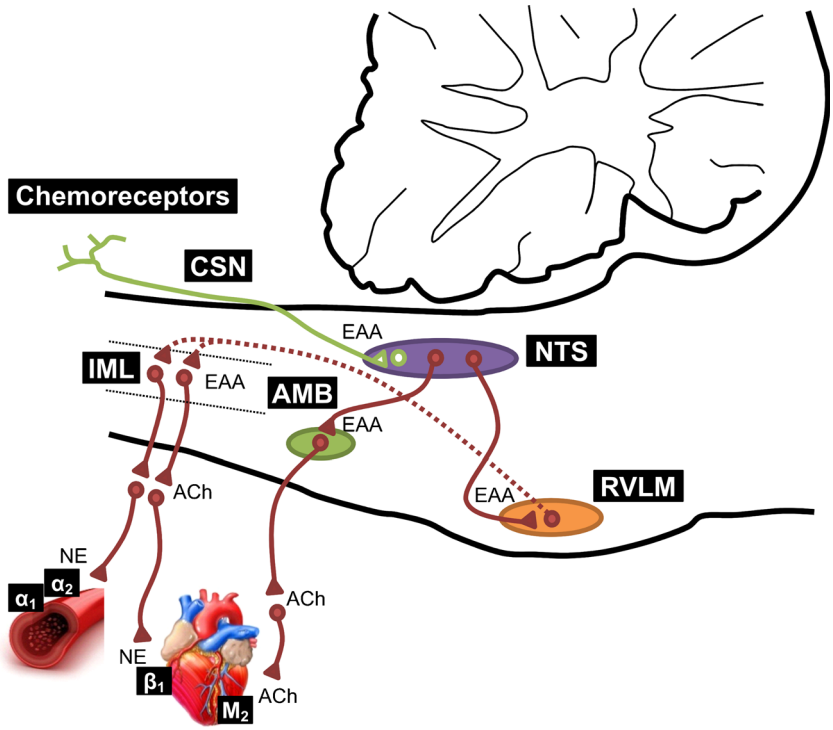

Fig. 4 Peripheral chemoreceptor reflex pathway within the lower brainstem region. *CSN*, carotid sinus nerve; *NTS*, nucleus tractus solitarius; *RVLM*, rostral ventrolateral medulla; *AMB*, nucleus ambiguus; *IML*, intermediolateral cell column in the spinal cord; *EAA*, an excitatory amino acid; *GABA*, γ-aminobutyric acid; *ACh*, acetylcholine; and *NE*, norepinephrine. Pathway description taken from [36]

Short-Term Feedforward Regulation: Activation of Central Stress Pathways

Autonomic cardiovascular responses can also be evoked as part of a more complex behavioral response: for example, exercise or stress [36]. These changes are orchestrated by a complex supramedullary network of neurons in the limbic cortex, amygdala and hypothalamus via synaptic projections to the central autonomic control centers. Among the various behavioral responses, autonomic and cardiovascular responses to stressful stimuli are of particular importance. Indeed, advances in electrophysiological studies over the last two decades have contributed remarkable leaps to our understanding of the central pathways involved during stress exposure. It is well established that acute emotional stress or threatening stimuli evoke marked cardiovascular responses (fight-or-flight response) characterized by increased SNA, HR and BP [36, 193, 194, 195•, 196]. However, similar autonomic outcomes can also be triggered by chronic mental stress related to established diseases including anxiety [197], depression [198] and chronic renal failure [199, 200••].

Activation of limbic system structures including the amygdala, which is involved in the processing of emotions and memory [201], is evoked in response to a stressful stimulus [36, 194, 195•]. Excitatory projections from the amygdala to the dorsomedial hypothalamus (DMH) [202], a nucleus corresponding with the hypothalamic defence area [36, 193] which when disrupted leads to panic like response in rats [203], are thought to be the primary generator for endocrine and autonomic responses to stress (Fig. 5):

1. *The endocrine response:* Central regulation of the hypothalamo-pituitary-adrenocortical (HPA) axis plays a critical role in the processing of the hormonal response to a stressful stimulus [193]. Here, the DMH signals excitation of the PVN [207, 208], whose neurons project down to the median eminence (ME) [209]. Neurons within the ME release corticotrophin-releasing hormone (CRH) [210, 211], which stimulates anterior pituitary production of adrenocorticotrophic hormone (ACTH) [208, 212, 213]. ACTH then acts on the adrenal glands to trigger cortical release of glucocorticoids, which have widespread effects to cope with stress [193, 214].
2. *The autonomic response:* Apart from its primary role in the endocrine response, activation of the PVN neurons was initially thought to play no role in the tachycardic and pressor response to stress [215]. However, Busnardo and co-workers showed that bilateral inhibition of the PVN reduced the pressor response to acute restraints in rats, suggesting that local PVN neurotransmission is involved in the neural pathway that controls autonomic responses to stress [204]. Furthermore, the DMH signals excitation of the RVLM and the raphe pallidus, regions which independently influence the cardiac and vasomotor component of stress reactivity as well as epinephrine release from the adrenal medulla. Synaptic connections between the DMH and RVLM appear to trigger discharge

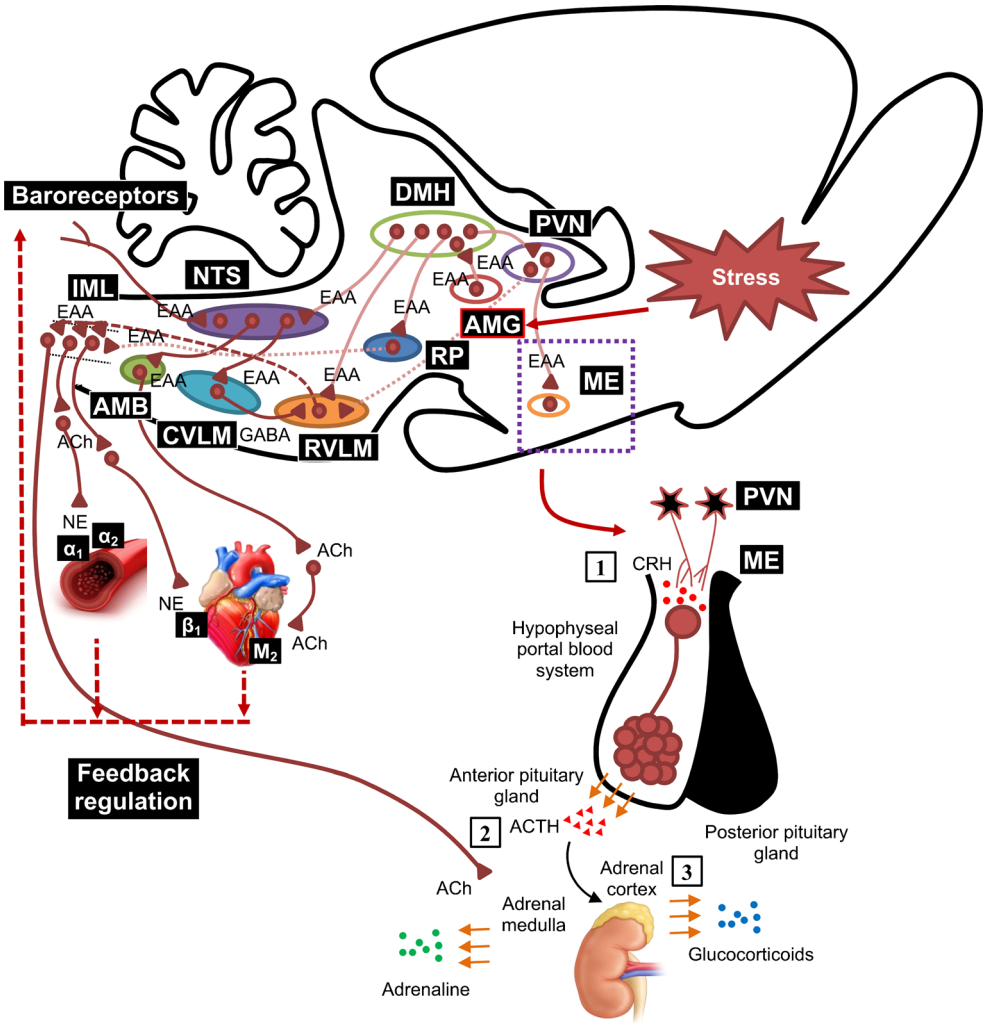

Fig. 5 The neuroendocrine stress pathway. *AMG*, amygdala; *DMH*, dorsomedial hypothalamus; *PVN*, paraventricular nucleus; *ME*, median eminence; *RP*, raphe pallidus; *NTS*, nucleus tractus solitarius; *CVLM*, caudal ventrolateral medulla, *RVLM*; rostral ventrolateral medulla; *AMB*, nucleus ambiguus; *IML*, intermediolateral cell column in the spinal cord; *EAA*, an excitatory amino acid; *GABA*, γ-aminobutyric acid; *CRH*, corticotrophin releasing hormone; *ACTH*, adrenocorticotrophic hormone; *ACh*, acetylcholine; and *NE*, norepinephrine . Pathway description compiled from [36, 194, 195•, 204–206]

from the sympathetic premotor neurons involved in the maintenance of sympathetic vasomotor activity [205] and hence contribute to vasoconstriction and BP elevation. The cardiac sympathoexcitatory component of the stress pathway is evoked by a DMH-mediated excitation of the raphe pallidus [205, 206], whose sympathetic premotor neurons may project directly to the spinal cardiac sympathetic preganglionic neurons [216]. This activation occurs independently of excitation of the sympathetic premotor neurons in the RVLM which normally drives increases in cardiac SNA and contributes to tachycardia. In support of the role of the raphe pallidus in mediating the tachycardic response to stress are studies showing that inhibition of the raphe pallidus abolished the tachycardic response to stress, but not to baroreceptor unloading [217]. Further evidence comes from reports demonstrating a comparable tachycardia in response to activation of the DMH and raphe pallidus neurons [206]. It is important to note, however, that the pattern of sympathetic response preferentially involves the heart, as evidenced by measurements of regional NE spillover during a cognitive challenge [218]. In support of this view is also the finding that the arterial BP response, which is dependent upon the intensity of the stressor, is primarily influenced by the intensity of the tachycardic response—even more so than responses of the vasomotor SNA [219].

Stress-induced stimulation of the DMH neurons can also modulate the baroreceptor reflex through not only descending pathways from the DMH to the RVLM [205] but also via possible direct excitatory projections from the DMH to the NTS neurons [220]. This modulation appears to be critical during defence reactions to stress to ensure that changes in HR and BP can occur simultaneously [194]. The reaction is also associated with resetting of the HR and SNA baroreflex relationship to higher BP, with unaltered HR BRS [122], but increased SNA BRS [123], being reported.

Most recently, Furlong and colleagues have also shown that sympathetic activity during psychological stress is not driven primarily by RVLM sympathetic premotor neurons and that neurons in the PVN, perifornical area, and ventrolateral periaqueductal gray matter may contribute to the resetting

of the baroreceptor-sympathetic reflex that is associated with psychological stress [221•].

Vital to acknowledge is the role of the novel orexinergic system in modifying the autonomic response to psychological stress. Orexin, which originates from a group of neurons located in the dorsal hypothalamus, not only plays a critical role in the control of arousal and expression of motivated behavior but is also thought to be the missing link between psychogenic stress and the resulting cardiovascular response [222••]. Orexin receptors are expressed in the SPNs and RVLM and when activated increases in BP, HR and SNA are observed [222••, 223, 224]. Although this makes orexin a key modulator of the cardiovascular response to stress within the central autonomic network, its mode of action is far from being completely understood.

Summary and Perspectives

The above review clearly demonstrates the fact that cardiovascular neural network is a maze comprising several interconnected signalling pathways that are tightly synchronized and perfectly coordinated to ensure optimal cardiovascular function. The neural pathways involved in the short- and long-term regulation of tonic and reflex autonomic outflows to the heart and vasculature are extremely diverse and can relentlessly respond to a variety of triggering factors including BP, blood volume, blood-borne or exogenous chemicals, hormones, altered PaO_2 or $PaCO_2$ and stressful stimuli. The important question that remains, however, is how these neuronal pathways communicate with one another to execute particular function and maintain cardiovascular homeostasis. Our current knowledge strongly testifies that the CNS is indeed furnished with various, yet sometimes unknown, key integrating nuclei that drive, maintain and protect circulatory functions whenever needed. It goes without saying that our current understanding of this complex neuronal machinery is still limited especially when considering the neuromodulatory influence of higher brain regions such as the paraventricular and the dorsomedial hypothalamic nuclei on medullary regions controling sympathetic and parasympathetic nerve activities to cardiovascular targets. Nonetheless, it is certainly just a matter of time before the literature becomes flooded with some valuable information that pieces this complex puzzle together, which will ultimately progress our understanding of the regulation of this neuronal network as a whole.

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Compliance with Ethical Standards

Conflict of Interest Dr. Salman declares no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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- •• Of major importance

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