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Review article

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Multimodal, device-based therapeutic targeting of the cardiovascular autonomic nervous system

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Abstract

The miniaturization of implantable sensors and actuators, combined with advances in interactive modelling and high-resolution imaging, is propelling the use of medical devices for counteracting impaired neural control of the cardiovascular system. In this Review, we discuss the current effectiveness of this technology for modulating autonomic activity in numerous cardiovascular conditions, including high blood pressure, heart failure and cardiac arrhythmias. We advocate for smarter closed-loop bionic devices fitted with feedback from multiple sensors to allow adaptive, state-dependent control, and discuss how the adoption of artificial intelligence technology would facilitate auto-personalization to meet the needs of patients. We also describe how transcriptomics of autonomic circuits can guide device-based approaches. Finally, the use of stem cell therapies to target sympathetic circuits more precisely will help to optimize the therapeutic effects of autonomic modulation for the treatment of arrhythmia. For bioelectronic medicine to achieve clinical utility in neurocardiology, these innovations must demonstrate improved efficacy beyond that offered by contemporary interventions.

Sections

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Key points

- Emerging evidence suggests that bioelectronic strategies that involve the site-specific targeting of the autonomic circuit could be used to treat cardiovascular diseases, including arrhythmia, heart failure and neurogenic hypertension.
- Advances in implantable sensor technology and device miniaturization, together with the design of closed-loop bioelectronics linked to multi-feedback sensors, should contribute to the development of therapies to modulate autonomic nervous system activity.
- Combining artificial intelligence and machine learning technologies with novel neuroceutical devices could result in optimized and personalized parameter set points that respond to physiological feedback within a closed-loop system, thereby enabling dynamic state-dependent adjustment.
- Advances in Bluetooth technology might facilitate real-time device readout, effectiveness and feedback dosing of neuroceutical devices.
- The use of transcriptomics to understand whether visceral reflex pathways are associated with distinct phenotypes might enable highly selective functional neuromodulation in device-based medicine.
- The autografting of novel biomaterials into the autonomic nervous system or to the end organ, such as the heart, to alter excitability with closed-loop bioelectronics is promising for the treatment of arrhythmias.

Introduction

The past five years have seen an explosion in research to understand and test the clinical efficacy of modulating the autonomic nervous system to treat cardiovascular disease (CVD)[1–10]. This effort has been reinforced by focused funding from the National Institutes of Health in the USA for the SPARC[11] and REVEAL[12] programmes as well as from the Leducq Foundation[13], which together seek to understand how organ systems are interconnected, and whether end organ function can be therapeutically modulated via the autonomic nervous system. These research efforts bridge the specialties of neurology and cardiology (to form the subspecialty of 'neurocardiology') and provide a pathway for novel therapeutic targeting[14,15]. In this Review, we describe the emerging potential of the field of 'neuroceuticals', which is based on site-specific targeting of autonomic circuits to develop a bioelectronic strategy to treat CVDs, including arrhythmia, heart failure (HF) and neurogenic hypertension. To fully appreciate the intricacies of applying neuroceuticals to the autonomic nervous system, we discuss pertinent clinical trials assessing surgical interventions and devices to treat CVDs, which have thus far yielded inconsistent findings. We also reflect on current bioelectronic modalities, their limitations and how best to achieve greater efficiency in the future. Specifically, a deeper understanding of the anatomical features of the autonomic nervous system[16] (a major goal of the SPARC programme, including determining sex-specific and developmental differences[17]) and greater insights into the closed-loop connectivity that permits interorgan crosstalk might result in more successful, better personalized devices. The use of closed-loop connectivity would mimic physiological feedback, such that the variable being controlled would operate around a predetermined set point. Insights into the genetic and molecular characteristics of cardiovascular circuits gained over the past five years[18–32] may now enable neuroceuticals to be integrated more selectively with these pathways to further improve interventional specificity and clinical outcomes[33,34]. Finally, looking beyond neuroceuticals, we explore the potential of using cocultures of neurons and cardiomyocytes derived from human induced pluripotent stem cells (hiPSCs) generated from people with congenital or inherited CVD to identify potential therapeutic targets to restore autonomic balance[14,35,36]. We also highlight the latest advances in biomaterials, including the generation of three-dimensional (3D) brain–heart organoids, which, when combined with single-cell RNA sequencing datasets, might facilitate target discovery to refine neuromodulation therapy.

The good and bad of autonomic control

The autonomic nervous system is a crucial part of the peripheral nervous system that controls involuntary physiological functioning of the cardiovascular, digestive, immune, metabolic, renal, respiratory and thermoregulatory systems (Fig. 1). In the circulatory system, the autonomic nervous system is crucial for maintaining homeostasis by relaying information via the basal ganglia, spinal and brainstem circuits that trigger appropriate patterns of motor response via multilevel reflex loops[37–40] (Fig. 1). These loops coordinate sympathetic and parasympathetic motor activity that regulates, for example, heart rate, cardiac contractility, conduction speed, the rate of ventricular relaxation, the vessel tone of arterioles and venules, hormone release and metabolism. Aberrant activity in peripheral receptors (including baroreceptors, mechanoreceptors and chemoreceptors) and afferent fibres, as seen in HF, cardiomyopathies or arterial hypertension, is often the initiating step in the dysregulation of autonomic balance[41–43]. In addition, altered processing of this information in the cardiovascular centres in the brain also contributes to increased sympathetic activity[44,45]. However, autonomic nervous system dysregulation is prognostic for both the development and progression of CVD[4,46,47] (Fig. 2). Indeed, the rationale for targeting the autonomic nervous system is underpinned by the observation that its dysfunction precedes overt clinical signs of HF and hypertension[7,48,49], much of which is attributable to 'dysautonomia', reflecting excessive sympathetic activity and recessive parasympathetic activity. This imbalance leads to hyperactivity of the adrenergic drive, arteriole and venule constriction, hypertension and the promotion of pro-inflammatory and proarrhythmic states; this proarrhythmic state is a cause of sudden cardiac death[49–51] (Fig. 2). Sympathetically mediated structural remodelling of the myocardium and vascular smooth muscles also results in muscle stiffening and organ failure. The sensitization of sensory afferents leads to aberrant activity and reflex sympathoexcitation that derails homeostatic regulation. Therefore, CVD is, in part, a disease of the autonomic nervous system and, as such, offers opportunities for multimodality modulation via device implantation or gene- or cell-based therapies (Fig. 3). To date, neuroceutical devices have been used to treat numerous diseases, including neuropathic pain[52–55], movement disorders related to Parkinson disease[56,57], sleep apnoea[58], gastrointestinal motility disturbances[59], HF[60,61] and hypertension[62,63].

The need for neuroceuticals to treat CVD

Hypertension

Hypertension (defined globally as a persistent blood pressure of >140/90 mmHg) is the leading modifiable risk factor for CVD[64–71] and affects 26% of the global adult population (~1.2 billion individuals), with prevalence doubling between 1990 to 2019 (ref. 72). Epidemiological findings indicate that people with well managed hypertension

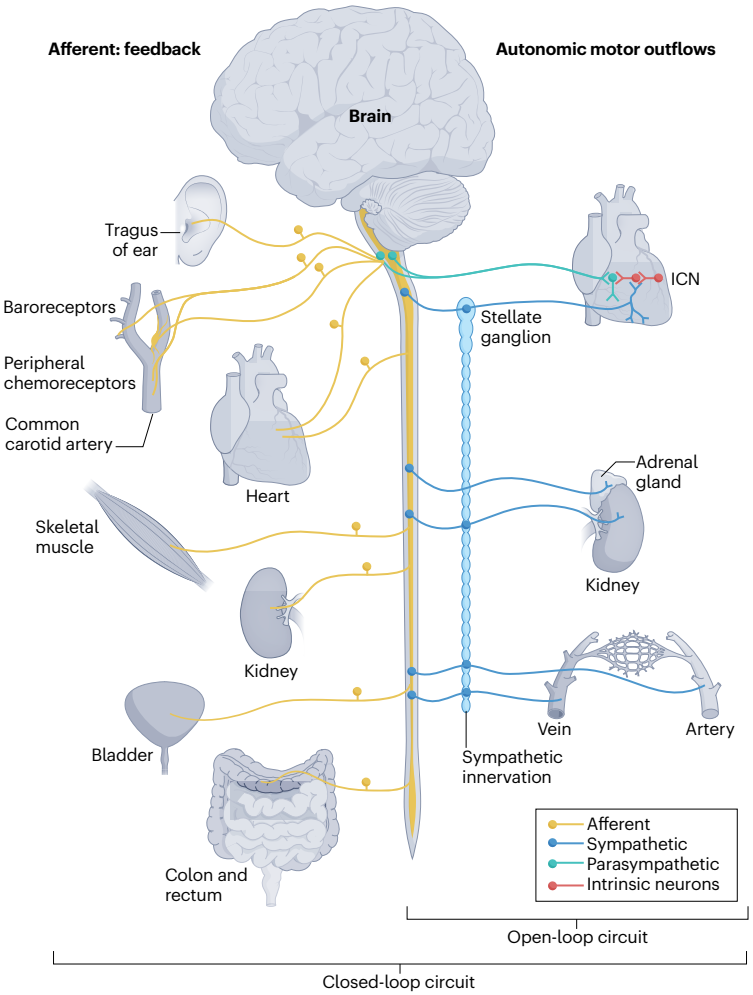


Fig. 1 | Integrative sensory neural control of the blood circulation mediated by the autonomic nervous system. Interoception provides homeostatic feedback control of numerous physiological parameters, including blood pressure (baroreceptors), blood acidity and oxygen levels (peripheral chemoreceptors), exercise (mechanoreceptors and metaboreceptors), renal function, distension of the bladder, colon and rectum, and nociception. Through the integration of sensory traffic via spinal or brainstem autonomic circuits, command signals are generated relative to a central set point to cardiovascular target organs. The pathway from sensory neurons (afferent) to motor neurons (efferent) constitutes a closed-loop reflex pathway that equates afferent feedback to the magnitude of motor command. In disease settings, increases in set point, reflex sensitivity and afferent (aberrant) tonicity can occur. An open-loop system is the modus operandi of many currently available devices, but such a system can cause the short-circuiting of afferent sensory feedback, resulting in an inability to regulate target organs relative to their physiological set point and abnormal physiological responses. Next-generation devices should be designed to couple with a sensor or sensors to provide physiological control and allow operation around a predetermined set point or incorporate a diurnal cycle if present, for example. ICN, intrinsic cardiac neuron.

(blood pressure <140/90 mmHg) remain at an increased cardiovascular risk[73–75]. One possible explanation is that elevated or variable levels of sympathetic activity are not being well controlled[76,77]. Certain frontline medications for hypertension (for example, calcium channel antagonists and some diuretics) either do not affect or increase sympathetic nerve activity, caused in part by arterial baroreceptor unloading when blood pressure falls[77–79]. β-Blockers decrease sympathetic activity, mostly at the level of presynaptic β_1 and β_2 adrenergic receptors[80]. However, this effect is heterogeneous and is dependent on the specific medication and its selectivity, rather than on drug class[77,81]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II type 1 receptor blockers (ARBs) lower sympathetic activity at the peripheral and central levels[77,82,83], but not to baseline levels despite normalization of blood pressure, which contributes to the residual cardiovascular risk in treated patients[77,84]. Notably, administration of a calcium channel antagonist and/or a diuretic together with an ACE inhibitor or ARB has been shown to nullify the anti-sympathetic activity response of the angiotensin-targeting drugs[77]. A recent study in 219 patients showed that anti-hypertensive treatment does not normalize muscle sympathetic nerve activity regardless of drug classes and whether given singly or in combination, even when blood pressure reaches values lower than 130/80 mmHg[85].

Importantly, given that these findings are based on sympathetic activity measured at rest, we question whether stress-induced surges in sympathetic activity (that trigger hypertension crises) can be controlled by medication or device therapy. Blood pressure surges, which occur during physical stress (including during exercise) and emotional stress (anxiety), contribute to severe adverse events such as myocardial ischaemia, stroke, renal injury, retinal damage, aneurysm rupture and aortic dissection[86–89], probably mediated by excessive adrenergic activity. Blood pressure surges also occur in people treated with ACE inhibitors and ARBs[90], suggesting that although these drugs might control sympathetic activity at baseline[77], they do not prevent sympathoactivation during stress. Furthermore, exercise triggers exaggerated pressor responses in both untreated people with hypertension and in drug-treated patients with controlled blood pressure at rest[91]. One approach to prevent these surges in blood pressure is the use of adrenergic receptor blockers or centrally acting sympatholytics that suppress sympathetic activity (such as clonidine), but these drugs are associated with adverse effects such as drowsiness, dry mouth, orthostatic hypotension and dizziness[92,93]. Therefore, device therapy might be an advantageous alternative to pharmacotherapy to prevent blood pressure variability by tempering but not abolishing sympathetic activity (discussed in more detail below).

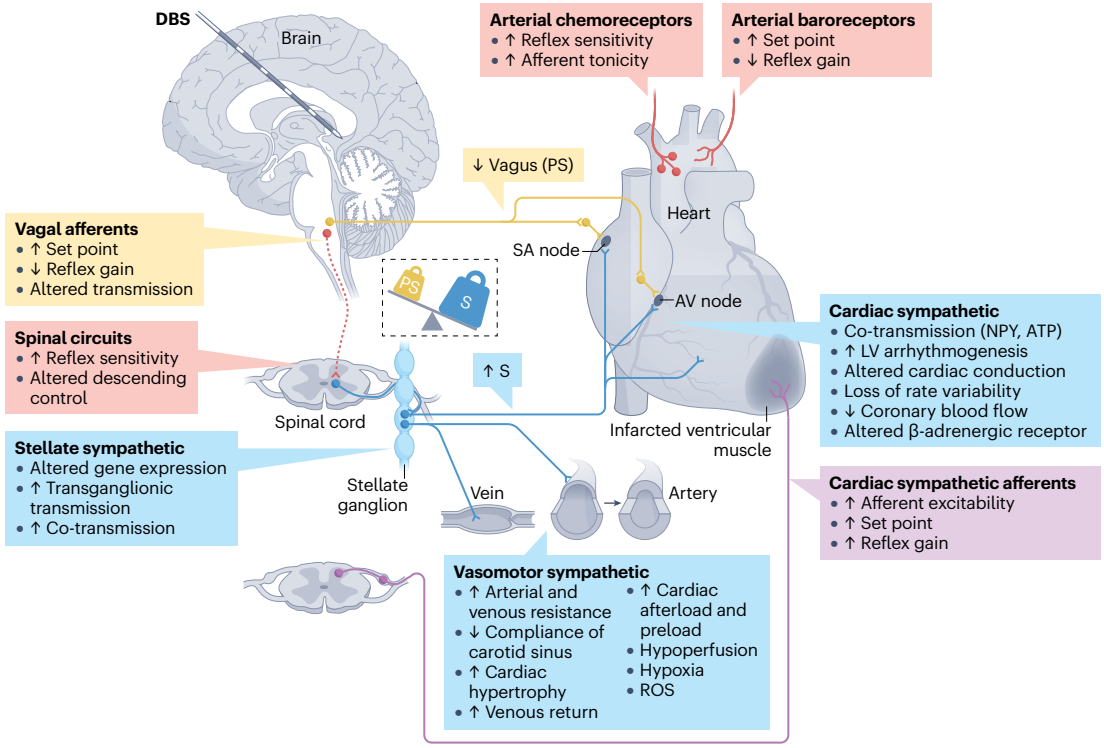


Fig. 2 | Autonomic dysregulation and pathological phenotypes in heart failure. The major changes occurring in heart failure development after myocardial infarction are highlighted. Typical of many other cardiovascular diseases, myocardial infarction causes an autonomic imbalance, with increases in sympathetic activity to the heart and vasculature, and reduced cardiac vagal transmission. These changes are associated with altered homeostatic reflexes, including depression of the baroreceptor reflexes and an increase in the chemoreceptor and metaboreceptor reflexes, as well as an elevated reflex gain set point and altered descending control. Excessive sympathetic activity triggers the release of co-transmitters – such as ATP and neuropeptide Y (NPY) – and results in cardiac inflammation, increased preload or afterload, hypoperfusion, hypoxia and oxidative stress, all of which promote the development of atherosclerosis and arrhythmia[103]. Some of the experimental and clinical interventions and methods targeting autonomic dysfunction to treat heart failure include ablation of nerves, repurposed drugs and pacemakers, and neuroceuticals, such as deep brain stimulation. AV, atrioventricular; DBS, deep brain stimulation; LV, left ventricular; PS, parasympathetic; ROS, reactive oxygen species; S, sympathetic; SA, sinoatrial.

Heart failure

HF affects 64 million individuals globally, and the prevalence of HF is increasing, in part due to the ageing global population and the improved survival rates after myocardial infarction[94]. By contrast, the survival rate of people with HF five years after diagnosis is 50%[95]. This poor survival rate indicates that current HF drug therapies can help to manage the disease and slow its progression, but are not curative. Guideline-directed medication therapy for HF with reduced ejection fraction includes β-blockers, mineralocorticoid receptor antagonists and sodium–glucose cotransporter 2 (SGLT2) inhibitors, in addition to an ACE inhibitor, ARB or combined angiotensin receptor–neprilysin inhibitor[96,97]. By contrast, treatment options for people with HF with preserved ejection fraction are much more limited, and include SGLT2 inhibitors[98–100], as well as glucagon-like peptide 1 receptor agonists in people with HF with preserved ejection fraction and obesity[101]. We note that autonomic imbalance is apparent in both people with HF with reduced and preserved ejection fraction[102]. Although β-blockers are used to temper sympathetic drive to the heart and the macula densa in the kidney, their efficacy is reduced in the presence of high sympathetic activity or high concentrations of noradrenaline. In such conditions, neuropeptide Y (NPY) is co-released with noradrenaline and can trigger arrhythmias, including left ventricular (LV) tachycardia and sudden cardiac death, even with β-blocker therapy[103]. However, these arrhythmias can be tempered in humans by performing cardiac sympathetic denervation through cervico–thoracic denervation from the T1 ganglion to the T4 ganglion[104–106], or experimentally in pigs by blocking NPY activity with electrical stimulation[107]. These findings support the need to reduce cardiac sympathetic activity using strategies beyond β-blockade. Bioelectronic block strategies that bridge chemical release kinetics to stimulus intensity have been further optimized through the use of neuromodulator and neuropeptide sensors for precise brain circuit integration in vivo[108]. Adapting this technology to end-organ neural control to provide real-time chemical feedback for closed-loop neuromodulation is now on the horizon.

All told, despite an armoury of old and new medications, an unmet clinical need in the management of hypertension and HF remains. Given that the aetiology of both hypertension and HF involves autonomic dysregulation and that evidence suggests that the use of front-line pharmacological treatment, especially during stress conditions, does not improve autonomic balance, devices designed to rebalance sympathetic and parasympathetic tone might, together with adjunct pharmacological therapy, provide a superior treatment option and help

to overcome drug intolerance and poor drug compliance[109]. In obesity, increased sympathetic activity is needed to stimulate metabolic rate to reduce body weight[110], whereas NPY produced by sympathetic neurons protects against obesity by sustaining thermogenic fat[111]. Therefore, unlike in hypertension and HF, selective activation of sympathetic nerves innervating adipose tissue might prove advantageous in individuals with obesity.

Nerves with afferent and autonomic motor axons

The vagus nerves in the heart exert powerful anti-arrhythmic effects after myocardial infarction[112], and their impairment is a negative prognostic indicator for all-cause death[113] and sudden cardiac death[114]. The vagus nerves have also been considered a promising therapeutic target in HF[115], although the stimulation of these nerves has been regarded as a crude intervention, given their axonal complexity. In this section, we consider sensory and autonomic motor axons together, given that most nerves contain both types of fibre.

Vagus nerves

The vagus nerves have been targeted electrically for the treatment of numerous conditions in humans, including epilepsy, depression and obesity[116]. In the setting of HF (Figs. 2 and 3), electrical stimulation of the cervical vagus nerve via an invasive procedure involving a cuff electrode connected to an implanted power pack was initially validated in an open-label, single-centre study that demonstrated promising results for the safety and tolerability of chronic vagal nerve stimulation (VNS) and an improvement in quality of life and LV function in people with severe systolic HF compared with baseline measures[115,117].

Three multicentre randomized trials were subsequently conducted (ANTHEM-HF[118,119], INOVATE-HF[120] and NECTAR-HF[121]) to assess the safety and feasibility of artificially increasing vagal tone and to ascertain whether treated patients experienced improvements in cardiac remodelling and function. Vagal tone can be artificially increased in a direct manner via the activation of the vagal cardiomotor axons in the cervical vagus nerve, or indirectly via the stimulation of vagal afferent fibres to reflexively stimulate the vagal cardiomotor fibres. In this regard, electrode polarity and stimulation parameter settings were set to drive either efferent motor fibres preferentially (INOVATE-HF[120]) or to not discriminate between afferent and efferent fibres (ANTHEM-HF[118,119] and NECTAR-HF[121]). The studies differed in many respects, such as assessing only right-sided VNS (INNOVATE-HF[120] and NECTAR-HF[121]) or comparing right-sided versus left-sided stimulation parameters (ANTHEM-HF[118,119]), including frequency, duration, amplitude and duty cycle, or comparing electrode polarity and open-loop delivery (NECTAR-HF[121] and ANTHEM-HF[118,119]) versus closed-loop delivery achieved by synchronizing the stimulus to the R-wave of the electrocardiogram (INNOVATE-HF[120]). These differing methodologies and parameters contributed to the inconsistent and disappointing findings from these trials. ANTHEM-HF[118,119] was the most successful of the three studies, and showed that VNS resulted in an increase in LV ejection fraction, a reduction in resting heart rate and increases in heart rate variability, 6-minute walk distance and quality-of-life score compared with baseline measures. The results of the follow-up, randomized, controlled ANTHEM-HFrEF Pivotal trial[122] are awaited, although this study was terminated early for reasons unrelated to futility, patient safety or device function. In the INOVATE-HF trial[120], people treated with VNS

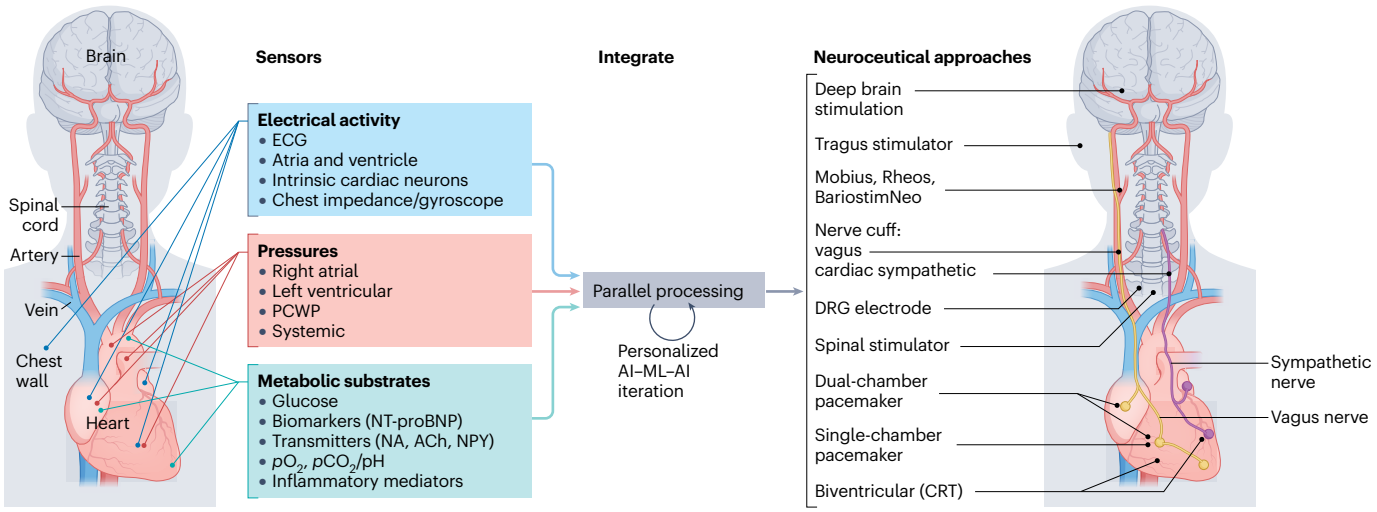


Fig. 3 | Proposed configurations of neuroceutical device actuators with incorporated sensory feedback and AI–ML technologies for treating cardiac diseases. The goal of neuroceutical device therapy is to emulate physiological control of the circulation using sensory feedback. Listed on the right are existing neuroceutical devices that modulate sensory systems (tragus or carotid sinus baroreceptors), peripheral systems (vagus or dorsal root ganglia, DRG), central nervous system structures (spinal cord) and end organs (heart). The activity of these devices depends on incoming electrical, pressure and mechanical inputs controlled by sensors located in the periphery, as shown on the left. Future studies must integrate several sensory modalities within a neuroceutical device to achieve optimal therapeutic outcomes for cardiovascular diseases. Sensory inputs need to be integrated, and with their corresponding evoked organ responses, 'learn' through artificial intelligence (AI) and machine learning (ML) algorithms to optimize the transfer function (or gain) of afferent-to-efferent transmission, thereby automating the personalization of device-mediated treatment. This approach ensures an appropriate response for given inputs and hence more closely emulates physiological processes. Future devices will need to be equipped with sensors permitting the integration of parallel processing with the ability to regulate multiple outputs simultaneously. ACh, acetylcholine; CRT, cardiac resynchronization therapy; ECG, electrocardiogram; NA, noradrenaline; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PCWP, pulmonary capillary wedge pressure; pCO_2, partial pressure of carbon dioxide; pO_2, partial pressure of oxygen.

showed improvements in their New York Heart Association (NYHA) classification of HF and 6-minute walk distance compared with baseline, but showed no changes in haemodynamic parameters[120]. In the NECTAR-HF trial[121], no improvements in cardiac remodelling, LV ejection fraction, peak VO_2 or plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels were observed in treated patients compared with baseline measures, but quality of life substantially improved. In some people, VNS was associated with adverse events, including transient mild dysphonia, cough and oropharyngeal pain, irrespective of whether left-sided or right-sided stimulation was performed. These adverse effects restricted stimulation intensity and might have limited treatment efficacy.

Several reasons might underlie these underwhelming clinical findings. In the vagus nerve, afferent and efferent fibres travel in the same nerve sheath, making selective targeting of sensory versus motor axons challenging unless an anodal block is incorporated into the stimulation paradigm. The human vagus nerve contains >25,000 fibres, of which 74% are visceral sensory fibres (the majority from the gastrointestinal tract) and the remainder are motor nerves containing both parasympathetic (13%) and sympathetic (13%) nerve fibres[123]. In the INOVATE-HF trial[120], stimulation techniques included an anodal block to drive activation of motor fibres. The more encouraging outcomes of the ANTHEM trial[118,119], in which no attempt was made to select for afferent or efferent fibres, suggests that afferent, not motor axon, stimulation might be optimal. Both myelinated (34%) and unmyelinated (66%) fibre types reside within afferent and efferent vagus nerves. Whether unmyelinated fibres, which have a higher stimulation threshold than myelinated fibres, would have been activated and the importance of this distinction between fibre types are unknown. Regarding vagal innervation of the heart[124], the human superior cardiac branches comprise parasympathetic, vagal sensory and sympathetic fibres, with the left cardiac branch containing the bulk of the sympathetic efferents[123]. Given the presence of sympathetic fibres in the cardiac branch, we propose that the strategy of using VNS to restore cardiac autonomic imbalance might be flawed in its current form. Given that the heart is a single midline organ, the left and right vagus nerves in the heart are likely to have substantial functional differences. Indeed, the right vagus nerve innervates the atria and sinoatrial node preferentially, whereas the left vagus nerve also functionally innervates the ventricles[124,125]. The treatment protocol of all three HF clinical trials included stimulation of the right vagus nerve, with ANTHEM-HF including people with either left-sided or right-sided VNS[118–121].

Taken together, these trial data suggest that VNS for the treatment of HF is compounded by several factors, including which side to stimulate (left or right); whether myelinated and/or unmyelinated fibres are activated; whether the stimulus is synchronized to the heartbeat, as in the INOVATE-HF study[120], or is instead coupled to other physiological cues such as blood pressure or breathing rate[126,127] (Fig. 4b); whether the stimulus should be temporally adjusted to dynamically changing physiological cues; the optimal stimulation frequencies to be used (1–20 Hz) and whether these should be phasic or patterned with on/off cycles or even pauses in stimulation[128]; whether afferents and/or efferent fibres should be selected[129]; and, finally, given this complexity, how the protocols for titration and optimization of stimulation should be developed[128]. To address vagal sensory nerve specificity, stimulation of a branch of the vagus nerve innervating parts of the ear has been performed, and a spatially selective VNS strategy using a multielectrode cuff placed around the nerve has been developed[130,131]. We acknowledge the large-scale work needed to identify appropriate stimulation frequencies around the 'neural fulcrum', defined as the balance between afferent fibre-mediated reductions in cardiac vagal outflow counteracted by direct activation of the cardiac vagal inputs, which facilitates bidirectional stimulation without a change in heart rate[132]. This concept has been the basis of the subsequent ongoing ANTHEM HFrEF Pivotal trial[122].

Auricular branch of the vagus nerve. The auricular branch of the vagus nerve (known as Alderman's or Arnold's nerve) innervates the outer ear and might provide a way to selectively activate a subpopulation of vagal sensory fibres (Fig. 3). Arnold's nerve originates from the petrosal and jugular ganglia and traverses through the mastoid canaliculus to the ear, terminating in the skin of the external auditory meatus and adjacent tympanic membrane[133]. The termination of the nerve in the skin of the external auditory meatus permits its activation using non-invasive transcutaneous electrical stimulation, avoiding the costs and complications associated with implanting cuff electrodes and power packs. Successful stimulation sites for vagal modulation in humans and animals have included the inner tragus and cymba concha[133]. Studies in rats have indicated that stimulation of the small myelinated fibres (Aβ), but not the unmyelinated C fibres, is necessary for a therapeutic effect[134], at least in the treatment of seizures. Therefore, low-level transcutaneous stimulation of the auricular branch of the vagus nerve has been employed clinically for the treatment of numerous diseases, including CVD[133].

Numerous small, randomized clinical studies and preclinical investigations that have assessed the efficacy of tragus stimulation to treat CVD have reported favourable outcomes. For example, in dogs, low-level tragus stimulation decreased cardiac sympathetic activity and reduced their susceptibility to arrhythmia after myocardial infarction[135]. In people with ST-segment elevation myocardial infarction, low-level tragus stimulation reduced the incidence of reperfusion-related ventricular arrhythmia and increased LV ejection fraction[136]. Furthermore, tragus stimulation has been shown to suppress paroxysmal atrial fibrillation compared with sham control[137,138] and improve symptoms of postural orthostatic tachycardia syndrome[139] in humans. In healthy individuals, tragus stimulation improved baroreceptor reflex sensitivity[140], and reduced LV contractility, output and workload[141], although these effects were accompanied by increases in blood pressure and total peripheral resistance, possibly as a compensatory reflex response.

Beyond the cardiovascular effects, tragus stimulation has also helped people with treatment-resistant depression[142]; improved glucose tolerance and reduced systolic blood pressure in people with pre-diabetes mellitus[143]; improved associative memory in healthy older individuals[144]; and increased survival after lethal sepsis in mice through its anti-inflammatory effects[145]. The wide-ranging therapeutic effects of tragus stimulation might be related to the divergent pathways that are activated in the brain. For example, based on functional magnetic resonance imaging studies in humans, stimulation of the tragus activates the upper cervical dorsal horn (laminae I–IV), the nucleus tractus solitarius, the cuneate nucleus and the caudal trigeminal nucleus[133].

Dorsal root ganglion and spinal cord

The targeting of dorsal root ganglia (DRG) for the treatment of arrhythmias was popularized in 1976 when Peter Schwartz and colleagues reported that dorsal root section considerably reduced ectopic beats during coronary occlusion in animal models[146]. This reduction probably resulted from the suppressed activation of the cardiac

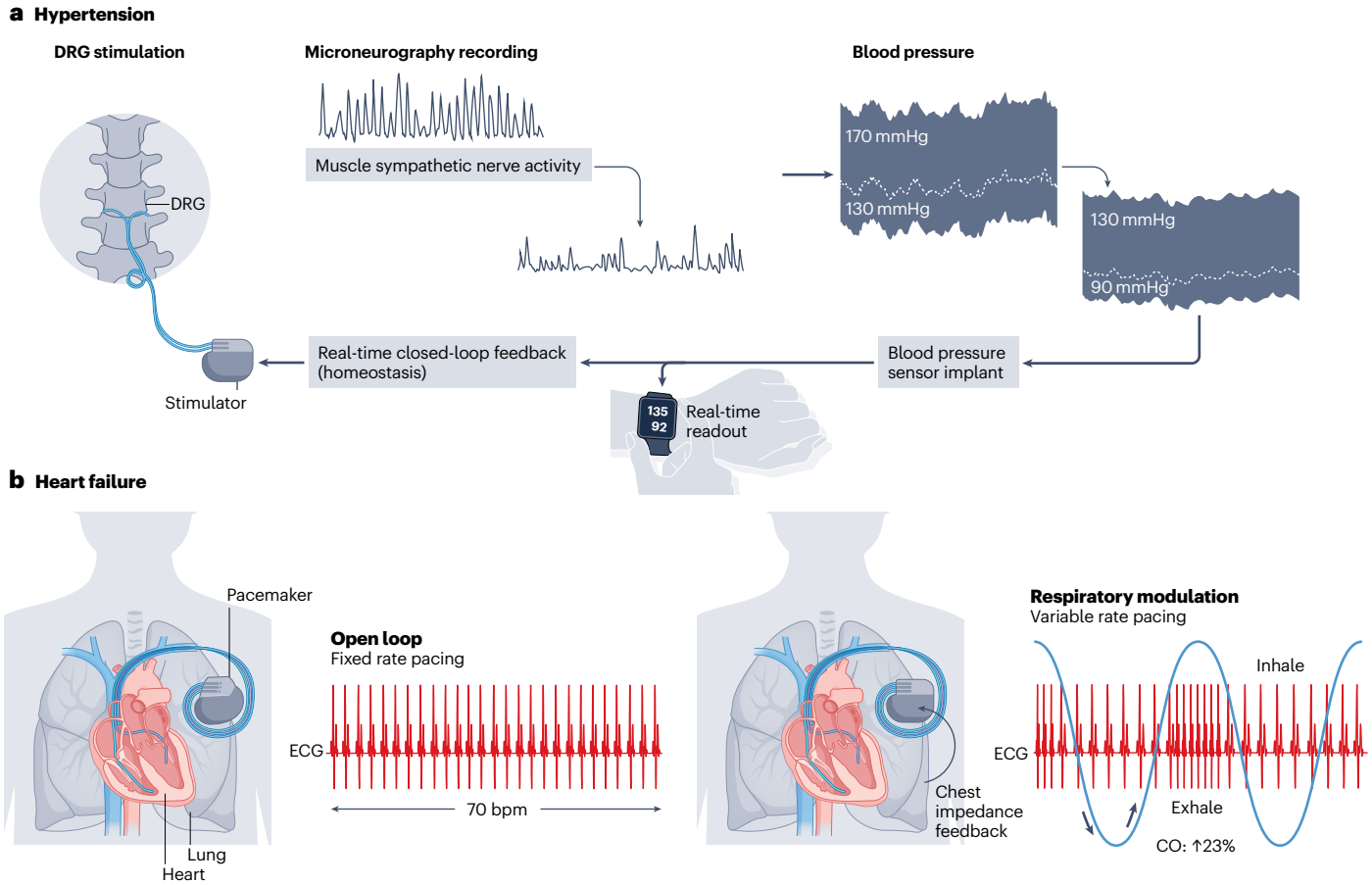


Fig. 4 | Making neuroceuticals more physiological with closed-loop feedback. The development of neuroceuticals that emulate physiological reflex control of the circulation is well underway, with the two examples illustrated indicating both sensing of the variable being modulated and reinstatement of organ-to-organ coupling. **a**, In hypertension, dorsal root ganglion (DRG) stimulation is being investigated for its ability to regulate arterial pressure[149]. Although the current approach does not include feedback control, pressure sensors such as those used to record pulmonary pressure[332] and common carotid artery pressure[333] can be used. In people with an implanted left ventricular assist device, ventricular filling pressure and estimated pulmonary capillary wedge pressure readings can be acquired[334,335]. Suitable integration of the incoming pressure signal to the change in activity of the output device will be needed. Implantable sensors can be monitored in real time on wearables using Bluetooth technology. **b**, In heart failure, at present pacemakers pace the heart metronomically and do not reinstate naturally occurring heart rate variability, which is predominantly driven by breathing and associated with good health and physical fitness. Patients with heart failure have low heart rate variability, but reinstatement of normal heart rate variability has been shown to result in a profound and chronic increase in cardiac output (CO) in animal models of heart failure[218,219]. Incorporation of naturally occurring, physiological modulation such as breathing into future pacemakers might further enhance their efficacy. ECG, electrocardiogram.

sympatho-sympathetic reflex caused by ischaemia, given that afferent fibres of this reflex travel through the dorsal root[146]. Stimulation of the DRG has been used for pain management[147]. This approach is based on the use of electrical stimulation to block incoming nociceptive inputs[148]. The exact mechanisms underlying its efficacy for pain management remain unclear, but might involve alterations of nerve thresholds, activation of inhibitory circuits and segmental, supraspinal circuits, or nerve block, especially when using high-frequency stimulation. This approach might also suppress sympathetic activity, lower blood pressure and prevent the onset of arrhythmia. In people with chronic pain, DRG stimulation reduced blood pressure (Fig. 4a), which was accompanied by reduced muscle sympathetic nerve activity[149]. Similarly, DRG stimulation has been reported to decrease the occurrence of arrhythmia in porcine models of ischaemia[150] and during cardiac pacing with an S1–S2 protocol in pigs[151]. Moreover, spinal cord stimulation protected against transient ischaemia in a rabbit model of myocardial infarction[152], and reduced the risk of ventricular arrhythmia after myocardial infarction in a dog model[153]. Interestingly, in people with spinal cord injury who are prone to hypertension crises caused by afferent sensitization and the loss of descending supraspinal inhibitory control, epidural electrical stimulation stabilized arterial pressure[154]. Stimulation access might provide a means of reprogramming spinal circuitry to reduce spinal hyperreflexia, which might be considered a long-term strategy with the correct stimulation parameter settings, for which artificial intelligence technologies might usefully be harnessed[155,156]. Whether less invasive techniques, such as transcutaneous spinal stimulation of spinal afferents, can be used to control blood pressure is unclear, with some reports indicating

exacerbation of autonomic dysreflexia with augmented hypertensive responses in humans[157].

Surgical denervation of autonomic nerves

Autonomic modulation close to an end organ has the advantage of minimizing off-target effects. In this section, we describe examples of surgical and device-mediated interventions (Figs. 2, 3 and 4).

Cardiac sympathetic denervation

The stellate ganglion and the T2–T4 thoracic ganglia contain postganglionic sympathetic neurons that innervate the heart via the inferior cardiac nerve (Figs. 1, 2 and 3). Despite administration of high doses of β-adrenergic receptor blockers, ventricular arrhythmias and tachycardia can persist and lead to an electrical storm in some people, which can result in sudden cardiac death[7,158]. With high sympathetic activity, co-transmitters such as NPY and ATP can also be released and act on a range of post-junctional receptors that are not being antagonized[159,160].

Surgical denervation of the sympathetic nerves was first performed in 1889 to treat epilepsy, and the history of this intervention has been well reviewed[161]. Regarding the treatment of cardiac symptoms, cardiac sympathetic denervation via stellectomy was first performed in humans over a century ago by Jonnesco to treat uncontrollable angina and tachycardia[162]. The procedure was popular in the 1960s[163], but eventually fell out of favour owing to variability in outcomes caused by incomplete surgical resection and the emergence of pharmacological therapies (such as β-blockers) as well as coronary artery bypass surgery and percutaneous coronary interventions. Surgical denervation received research attention again in the 1970s after the seminal work by Schwartz and Malliani[164], who identified the crucial electrophysiological link between the sympathetic nervous system and long-QT syndrome. Since then, cardiac sympathetic denervation via the removal of the lower half of the stellate ganglion (T1 level) and the sympathetic thoracic ganglia (T2–T4 levels), either on the left side to treat channelopathies, including long-QT syndrome and catecholaminergic polymorphic ventricular tachycardia (CPVT), or bilaterally to treat structural heart disease via video-assisted thoracic surgery, has been trialled as a therapy for refractory ventricular arrhythmias and electrical storms[158,165–172]. For those with ventricular tachycardia, administration of local anaesthetic either via thoracic epidural anaesthesia[173] or percutaneous stellate ganglion block[174–176] has also been used with success as an anti-arrhythmic approach to stabilize the patient before ablation or surgical cardiac sympathetic denervation.

In animals, stellectomy has been shown to reduce adverse remodelling caused by myocardial infarction and protect against LV dysfunction, atrial fibrillation and ventricular arrhythmia[165–167,177,178]. The procedure is associated with the usual risks of surgery (such as haemorrhage, infection and pneumothorax), but can also cause eyelid droop, constricted pupil limiting vision in poor light, and facial thermoregulatory dysfunction (symptoms characteristic of Horner's syndrome)[168]. These symptoms arise because only a small proportion of the postganglionic neurons in the stellate ganglion innervate the heart, with the majority projecting to the brachial plexus, subclavian and vertebral arteries, and the brachiocephalic trunk[179–181]. Thus, the targeting of the inferior cardiac nerve via stellectomy occurs at the expense of destroying many other sympathetic nerves and impairing their function. We note that with the use of video-assisted thoracoscopic surgery, the upper part of the stellate ganglion is preserved and the incidence of Horner's syndrome is very low[4,168]. Given that cardiac sympathetic hyperactivity can cause lethal arrhythmias, these adverse effects are considered acceptable, but the binary nature of the therapy is still suboptimal. Decreasing the excitability of the stellate in a site-specific and controllable manner would be the preferred option to maximize cardiac performance.

Renal denervation

The pioneering proof-of-principle work of Henry Krum and colleagues to assess the efficacy and safety of renal denervation in reducing blood pressure involved 45 people with resistant hypertension[182]. Renal denervation resulted in a 27-mmHg reduction in office systolic blood pressure at 12 months, which was associated with a 47% reduction in noradrenaline spillover, indicating a reduction in adrenergic mechanisms. Since then, multiple trials have been performed with mostly encouraging results. Numerous methods of ablation (radiofrequency, ultrasound and chemical) have been vigorously tested using different catheters. Trials on people either taking or not taking anti-hypertensive medications have been performed[183,184]; reductions in ambulatory blood pressure were greater in those who underwent renal denervation (by ~12 mmHg in people who were taking medication at 36 months and ~7 mmHg in those who were off medications after 3 months) compared with those who underwent sham control intervention. The original concept of renal denervation was based on the need to remove renal sympathetic nerves, thereby improving blood flow and glomerular filtration and reducing sodium reabsorption and renin release[185]. However, the renal afferent nerves from the renal pelvis[186] and those originating from the cortical–medullary tissue[187] are also ablated in the procedure. In disease states, these renal afferents are activated and trigger increases in blood pressure and sympathetic tone[188]. In March 2024, a radio-frequency-based catheter and an ultrasound-based catheter were approved by the US Food and Drug Adminstration (FDA) for the treatment of hypertension[189].

However, the Achilles' heel of renal denervation has been the inability to identify those who will best respond to treatment. Interestingly, the importance of renal afferent versus efferent nerves depends on the type of hypertension (for example, salt-sensitive or angiotensin II-sensitive hypertension)[190,191]. Therefore, unsurprisingly, real-world studies of renal denervation have documented non-responders as well as reverse responders, in whom a rise in arterial pressure is observed[192]. Understanding the mechanisms contributing to a fall in blood pressure after renal denervation will provide insights into which tests to perform to select patients for the intervention and the characteristics that best predict positive responders. Future studies will require practical approaches for real-time readout of ablation success during the procedure, given that treatment success depends in part on knowing whether there has been a loss of renal nerves. One approach is to measure renal blood flow (with a flow wire within the renal artery) and vascular conductance responses to handgrip exercises before and after ablation to allow a readout of the success of sympathetic nerve ablation during the procedure[193]. Furthermore, intra-renal artery infusion of stimulants (such as bradykinin and prostaglandins) while measuring reflex-evoked blood pressure responses might reflect the extent of afferent ablation[193].

Pulmonary artery denervation

The walls of the pulmonary artery and its main branches have the greatest densities of autonomic nerve endings within this vascular bed[194]. Intricate and not yet fully understood interactions between afferent signalling from the pulmonary artery and neural control of the blood circulation participate in maintaining cardiovascular

homeostasis[194]. Distension of the pulmonary arterial wall and activation of its baroreceptors increase sympathetic activity to the pulmonary and systemic circulations[194]. In the past decade, pulmonary artery denervation, which involves the lesion of both afferent vagal and efferent sympathetic fibres, has emerged as a potential treatment for pulmonary hypertension[195,196]. Findings from small clinical trials report that pulmonary artery denervation reduced mean pulmonary artery pressure, improved right-sided heart haemodynamics, reduced plasma NT-proBNP levels and improved 6-minute walk distance in people with pulmonary arterial hypertension compared with sham control[195,196]. We note that high pulmonary artery pressure has been associated with marked increases in muscle sympathetic nerve activity in people with pulmonary hypertension[197,198], whereas reduction of pulmonary artery pressure (and thus the unloading of pulmonary baroreceptors) has been shown to lower muscle sympathetic nerve activity in healthy individuals with hypoxic pulmonary vasoconstriction in high-altitude settings[199]. Although pulmonary artery denervation has been performed predominantly in people with pulmonary hypertension, those with post-capillary pulmonary hypertension secondary to LV failure showed improvements in LV function after treatment[200]. Furthermore, the intervention led to favourable results in select patients with end-stage systolic HF and combined precapillary and post-capillary pulmonary hypertension[201]. In a preclinical study, pulmonary artery denervation in dogs with normal pulmonary artery pressures decreased plasma noradrenaline concentrations and increased the threshold for inducing ventricular arrhythmia originating from the right ventricular outflow tract upon left stellate ganglion stimulation[202]. Additional research evaluating the role of pulmonary artery denervation in lowering sympathetic activity to the systemic circulation is needed.

Splanchnic nerve modulation

Mesenteric veins contain ~10% of the body's total blood volume and are densely innervated by sympathetic nerves[203]. Modulation of sympathetic activity to the mesenteric veins to increase their capacitance and unstressed blood volume might provide therapeutic benefits to people with hypertension[203] or HF[204] by reducing venous return. Early results from the REBALANCE-HF trial[205] indicate that in people with HF, ipsilateral ablation of the splanchnic nerve reduced pulmonary capillary wedge pressure during exercise, and an improvement in NYHA category by at least one class was observed in 33% (n = 6) of patients.

Device therapy for cardiovascular autonomic control

Pros and cons

Device therapy has several advantages over pharmacotherapy (Box 1). In certain diseases, measurement of a variable that can be controlled by a device can be advantageous, given that instant titration or 'dosing' of a device against response will be possible at baseline and at subsequent check-ups. Deep brain stimulation (DBS; Fig. 2) has been used to study cardiorespiratory control[206], and to treat movement disorders[207] and neuropathic pain[208] when conventional pharmacological interventions were ineffective. However, DBS has not been beneficial for targeting aberrant sympathetic activity, given that stimulating peripheral sites might be safer and more tractable (for example, DRG stimulation[149]). Nevertheless, blood pressure and heart rate can readily be measured non-invasively and in real time during the setting up of a device to establish efficacy and stimulation intensity. Measurement of biomarkers, such as NT-proBNP and NPY[103,209–211], or hormones such as catecholamines[212] might offer useful insights, but does not provide the immediacy of feedback obtained with haemodynamic data. The potential for off-target adverse effects with device therapy is lower than that with pharmacotherapy, given that devices can target a specific nerve. Furthermore, the binary property of a device being either powered on or off is advantageous not only for safety, but also for monitoring purposes, given that the efficacy of the device in improving parameters can be measured.

However, there are some major considerations before a patient can consent to receiving cardiovascular device therapy. Although some devices work externally or transcutaneously, most require implantation within the body, a process that is associated with risks of infection and damage to nearby structures, as well as increased healthcare costs. Furthermore, testing of devices during the implantation procedure might not always be informative of their true efficacy, given that sedatives and anaesthetic drugs might depress responses and lead to changes in tissue electrical properties owing to healing and fibrosis after implantation. Once implanted in the body, parameters must be carefully set and checked either remotely or during subsequent clinical visits. If the

Box 1 | Pros and cons of device-mediated modulation in cardiovascular diseases

Pros

- Localized to the organ of interest with a reduction in off-target and systemic effects (for example, with carotid sinus baroreceptor stimulation)
- Compared with drug therapy, device therapy is instantly titratable when adjusted against the desired response (such as blood pressure or heart rate)
- Overcomes problems of drug compliance and drug intolerance
- Solves issues around physical and humanity barriers such as unconscious bias for accessing medical support and medication
- Device treatment can be initiated or ceased at will, as required, which is an important safety consideration and allows checks for treatment efficacy
- For autonomic control, devices can be positioned outside the central nervous system

Cons

- The surgical intervention required to implant the device and replace the battery (unless induction charging is used) is invasive and associated with an increased risk of infection
- Stimulation of whole nerves is likely to activate multiple fasciles or fibre types indiscriminately, which might minimize response efficacy and lead to adverse effects
- Device leads can break, especially in tissues that move (such as the beating heart, cardiac pulsations in arteries, respiratory-related chest movement and locomotion)
- High stimulation intensities (which might be necessary in some treatment protocols) increase the risk of stimulus spread and off-target effects
- High costs compared with cardiovascular drugs
- Removal of a device and its leads can be problematic
- Potential electromagnetic interference with common machines and appliances, such as security scanners and induction cooking hobs

device operates with electrical stimulation, parameter settings must be confined to an intensity that does not affect other nerves or organs so as to avoid any off-target effects. Furthermore, these settings might not produce the desired response or can cause unpleasant sensations (such as paresthaesia, laryngaeal irritation or phonation disturbance with VNS)[121] and is particularly relevant when the effectiveness of a device wanes over time, requiring higher-intensity stimulation.

Finally, devices can fail, leads might break and batteries need replacement, all of which require invasive surgery. Devices that regulate the blood circulation might be implanted near the heart or a pulsating artery, which can accelerate lead breakages caused by motion vibration. Furthermore, removal of devices or leads can be problematic due to their fibrotic encasement[213]. The use of transcutaneous wireless charging (such as via induction) would remove the need for battery replacement[214], and adoption of leadless devices avoids the above-mentioned complications of lead breakages[215–217]. Together, these developments might overcome the existing technical challenges and improve the clinical applicability of device therapy.

Points of intervention and device types

Devices can be implanted outside the central nervous system to modulate the autonomic nerves. Distinct points of intervention around visceral reflex arcs can be targeted. Figures 3 and 4 depict potential points for device intervention that include targeting a sensor, sensory afferent nerves, and preganglionic and postganglionic autonomic nerves. In particular, Fig. 4 depicts a novel bionic device that targets the heart, directly mimicking its autonomically mediated variability based on respiration[127,218,219].

In people with drug-resistant hypertension, renal denervation of sensory and sympathetic nerves has become an approved treatment option on the basis of successful randomized controlled trials[182–184,220]. Other potential interventions for those with drug-resistant hypertension that have been reported but not yet clinically adopted include a baroreceptor amplification stent[221] and neuroceutical therapy (such as baroreceptor activation therapy[222] or DBS[223,224]).

Modulating the sensor. Targeting of sensory sites that modulate the sympathetic nervous system, such as arterial baroreceptors and peripheral chemoreceptors (Figs. 1 and 3), might be beneficial for the treatment of CVDs associated with supraphysiological levels of sympathetic activity[225]. Moreover, in people with hypertension, the persistence of an increased risk of CVD, stroke and all-cause death even when blood pressure is controlled, compared with that in individuals with normotension and similar blood pressure levels, is concerning[73–75] and might reflect that sympathetic activity cannot be modulated by these drugs.

Carotid sinus baroreceptors are the mechanically sensitive nerve endings of petrosal neurons, embedded in a specialized region of the internal carotid artery wall, known as the carotid sinus. The carotid sinus has a larger amount of elastin than other regions of the common carotid artery, making it more compliant and bulbous in appearance. Afferent fibres run along the carotid sinus nerve that joins the glossopharyngeal (IXth cranial) nerve with the termination in the nucleus of the solitary tract in the dorsomedial medulla. A second site for baroreceptors is in the aortic arch, with afferents running along the aortic depressor nerve, a branch of the vagus nerve. Given their stretch-sensitive properties, baroreceptors respond to changes in arterial blood pressure on a beat-by-beat basis. When blood pressure rises, the baroreceptor reflex is triggered and inhibits sympathetic activity and stimulates parasympathetic activity to reduce arteriolar and venule vascular resistance, and cause bradycardia, thereby returning blood pressure to its set point. The opposite pattern of response occurs when blood pressure and the activity of baroreceptors is inhibited. Baroreceptors have pressure thresholds of activation: myelinated afferents respond to lower pressure ranges, whereas higher pressures activate unmyelinated fibres[226]. Such activation (or loading) produces reflex inhibition of sympathetic nerve activity destined for the arterioles, veins and the heart, and activation of the cardiac vagal outflow to trigger bradycardia and reduced cardiac output, which buffers an increase in blood pressure. Unloading of baroreceptors (by reducing arterial pressure, such as during orthostasis) produces a reverse pattern of response that, together with the secretion of renin (to raise angiotensin II levels) and vasopressin, function to raise arterial pressure. A role of baroreceptors in both short-term and long-term regulation of arterial pressure has been proposed[227], and chronic unloading has been shown to cause neurogenic hypertension[228]. However, during the development of hypertension, arterial walls remodel and become stiff, resulting in reduced compliance of the carotid sinus and subsequent baroreceptor desensitization[229,230]. This desensitization contributes to a resetting of arterial pressure over a higher range. Numerous interventions have been developed to activate the arterial baroreceptors (Fig. 3).

Endovascular baroreceptor amplification. The MobiusHD endovascular stent was developed to geometrically expand the stiffened carotid sinus as a way to resensitize the carotid baroreceptor via a procedure known as endovascular baroreceptor amplification[221]. In a prospective, non-randomized, multicentre study that included 47 people with resistant hypertension, declines in office arterial systolic pressure of 25 mmHg and 30 mmHg were observed at 6 months and 36 months after the procedure, respectively[231]. However, a single-centre substudy reported that this decline in blood pressure was not associated with a decrease in muscle sympathetic nerve activity[232]. This unexpected finding might be attributable to the smaller decrease in office systolic blood pressure reported at 3 months (14 mmHg) when autonomic blood pressure control was evaluated. Importantly, the device did not impair baroreceptor reflex sensitivity.

Electrical stimulation of afferent endings. An alternative method to re-engage carotid sinus baroreceptors is to electrically stimulate their afferent endings. We note that this approach can only work with the assumption that the baroreceptors are reset peripherally and not centrally, and that the endings remain viable despite the remodelling of the arterial wall. The first device with this mechanism of action was the Rheos system (CVRx)[233,234]. This device was implanted bilaterally and induced a prompt decline in systolic blood pressure (~30 mmHg), which was associated with acute reductions in muscle sympathetic nerve activity[233]. At the 2-year follow-up, systolic blood pressure remained 30 mmHg lower than at baseline[234]. In an open-label, non-randomized, long-term follow-up study, 76% (n = 245) of trial participants responded favourably to the Rheos device, and of these responders, 55% achieved the goal blood pressure of <140 mmHg or <130 mmHg in people with diabetes or kidney disease, respectively[235]. These pressure ranges were maintained over a long-term follow-up of 53 months. Despite these promising results, the trial was terminated owing to trial design issues (the Hawthorne effect; changes in anti-hypertensive medications during the trial) and failure to meet the prespecified primary end points for efficacy and safety[236].

A next-generation baroreceptor activation therapy device called the Barostim NEO (CVRx) provided unilateral stimulation and was minimally invasive compared with the Rheos system. In a small feasibility study, people implanted with the Barostim NEO showed a decline in systolic blood pressure of ~16 mmHg, which was associated with inhibition of muscle sympathetic nerve activity[63]. However, the presence of adverse effects at higher stimulation intensities might have limited the efficacy of the device. In a subsequent non-randomized, open-label study, those receiving stable, intensive background medical therapy (unchanged during follow-up) and implanted with the Barostim NEO device showed lower blood pressure levels (~25 mmHg) at the 6-month follow-up[237]. This finding was further confirmed in a prospective observational study that reported reductions in 24-hour ambulatory systolic blood pressure and office systolic blood pressure of 7 mmHg and 22 mm Hg, respectively, at 6 months[238]. Taken together, the trials of these baroreceptor activation devices have all demonstrated that in people with drug-resistant hypertension, the baroreceptor reflex remains functionally viable and capable of chronically reducing arterial pressure, an effect that is in part mediated by suppression of sympathetic tone.

Given the positive outcomes in drug-resistant hypertension, the Barostim NEO device was trialled in people with advanced HF with reduced ejection fraction, given that high sympathetic drive and a depressed baroreflex also exist[239]. People assigned to baroreceptor activation therapy showed improved exercise capacity, quality of life and NYHA classification, and a reduction in the plasma levels of NT-proBNP compared with those in the control group. In December 2023, Barostim NEO received FDA approval for use in people with HF in the USA and received the CE mark for both HF and resistant hypertension in Europe.

Atrioventricular interval modulation. The implantable, rate-responsive Moderato pacemaker uses a novel algorithm of cardiac pacing based on atrioventricular interval modulation (AVIM) and implemented using standard pacing hardware to treat hypertension in people who also require a pacemaker. This device lowered daytime ambulatory systolic blood pressure by ~11 mmHg without the need for arterial baroreflex compensation[240,241]. Shortening of the atrioventricular delay to 20–80 ms reduced the 'atrial kick' effect on ventricular filling, leading to reduced ventricular preload, stroke volume and systolic blood pressure, whereas an opposite haemodynamic effect was obtained with longer atrioventricular delays[242]. To counterbalance the baroreflex-mediated sympathoexcitation (in response to the fall in arterial pressure), the shortening of atrioventricular delay is alternated with cardiac cycles with longer atrioventricular delay[240,242]. The direct effect of AVIM on muscle sympathetic nerve activity is currently being evaluated[243].

Carotid body modulation. Unlike arterial baroreceptor activation, activation of carotid bodies can stimulate sympathetic activity and breathing (Fig. 2). Therefore, any intervention targeting the carotid bodies must attenuate their activity. Studies in animals and humans demonstrated hyperexcitability of carotid bodies in those with CVD, including heightened reflex sensitivity (hyperreflexia) and hypertonicity[43,244–249]. A proof-of-principle study conducted in people with drug-resistant hypertension found that carotid body resection was safe and feasible, and noticeably reduced ambulatory blood pressure and sympathetic activity[250]. In some, anti-hypertensive medications were reduced or withdrawn[250]. Interestingly, those who responded to carotid body resection had greater hypoxic ventilatory responses than those who did not respond. This variable might therefore be used to preselect the people with hypertension who are most likely to benefit from carotid body modulation therapy.

People with HF (class III NYHA) have an exaggerated hypoxic ventilatory response, suggestive of carotid body hyperreflexia[247]. A proof-of-principle study was performed in ten people with HF, who underwent either unilateral or bilateral carotid body resection[251]. Successful carotid body resection was proved histologically, and resulted in decreased muscle sympathetic nerve activity, peripheral chemosensitivity and improved exercise tolerance[251]. In some of those who underwent bilateral carotid body resection, a trend of worsening of oxygen desaturation during sleep was observed, and one person required non-invasive ventilation. Given that bilateral ablation of the carotid body removes oxygen-sensing capacities, a requirement for arousal and rebreathing in the setting of sleep apnoea, this procedure should be avoided in these people.

These surgical studies were followed by the design of an intravascular catheter for radio-frequency ablation of the right carotid body[252]. The catheter was inserted into a jugular vein and equipped with intravascular ultrasound to allow visualization of the bifurcation of the common carotid artery. Unilateral endovascular ablation in people with resistant hypertension resulted in a reduction in ambulatory systolic blood pressure of 10 mmHg at 6 months[253,254]. Furthermore, research from the past three years showed that reversible, acute, chemically mediated suppression of the carotid body in people with HF improved exercise tolerance and systemic vascular conductance[255,256]. These promising device-mediated interventional studies await confirmation in larger-scale trials.

Optimization of device therapy for CVD

The importance of emulating homeostasis. In 1850, the French physiologist Claude Bernard proposed that "the stability of the internal environment is the condition for the free and independent life"[257]. This concept was further developed by Walter B. Cannon, who first introduced the term 'homeostasis' to explain the precise coordinated physiological responses that maintain an internal steady state[258]. This steady state is dependent on a peripheral sensor, or sensors, placed strategically around the circulatory system to detect and monitor the variable being controlled to permit homeostatic control of that variable at a predetermined set point (Fig. 4a). In an analogous way, control theory, which combines engineering and applied mathematics, employs feedback to influence the behaviour of a dynamic system to achieve a desired goal. Using similar principles, the physiological homeostatic regulation of the cardiovascular system involves sensors for pressure (arterial baroreceptors), blood gases (peripheral and central chemoreceptors) and volume (right atrial stretch receptors), sending information via distinct afferent feedback pathways for integration via ganglia, the spinal cord or the brainstem. After integration, motor signals increase or decrease autonomic activity to control, for example, vasomotor tone and cardiac contractility, rate and strength. In stark contrast to physiological reflex control, many contemporary cardiovascular implantable devices operate in an open-loop mode, meaning that they are not regulated by sensory feedback. This design results in an inability to control around a set point, causing lability. Unquestionably, future devices that operate in a closed-loop configuration to mimic homeostatic control around a predetermined set point will be advantageous (Fig. 4).

Establishing the set point of a device. Although incorporation of closed-loop feedback aligns with known physiological processes,

it raises the question of where to set the set point. The following discussion is based on arterial pressure, but is broadly applicable to device-mediated regulation of other systems.

Reflexes regulating arterial pressure operate around a systolic/diastolic pressure of 120/80 mmHg or a mean of ~95 mmHg, which is the universally accepted 'normal' blood pressure set point at rest[259–261]. We proposed that this pressure is optimal for brain perfusion[262] and is remarkably constant across all species except in giraffes[262]. However, blood pressure is extremely variable and resets to different levels between different states of arousal, sleep and exercise. Under conditions of flight or fight, the sympatho-adrenal system is activated, and blood pressure rises to maintain homeostatic control of oxygen and glucose delivery to tissues. Similarly, during exercise, the rise in arterial pressure necessitates a shift to a higher set point and a reversible resetting of arterial baroreceptors to operate over a higher pressure range[263]. One point of consideration for future device design is that set points are not static, but dynamic, and should allow the body to respond to changes in behavioural state. This characteristic emphasizes the need for not only closed-loop delivery, but also adaptive functions of devices permitting reversible shifts in set point control, and highlights the issue that sensory feedback from multiple sensors might be needed for the dynamic regulation of blood pressure in a state-dependent manner.

Establishing the stimulus threshold. Implantable stimulators use either constant current or voltage. Constant current takes into consideration changes in electrode and tissue impedance and adjusts the voltage accordingly to ensure that the current generated is maintained. Constant-voltage devices do not adjust voltage if impedance changes, meaning that power delivery will reduce if impedance increases, as might result from physical changes in the electrodes or tissue. For example, tissue injury can occur if stimulation intensities are too high, causing damage by the toxic products produced by electrolysis.

One advantage of the use of devices to modulate the cardiovascular system is that the parameter being controlled can be measured during device set-up, which allows the determination of the stimulus threshold to produce a desired response. Once the stimulus threshold is determined, and based on an agreed multiplier, the absolute intensity can be set. Such a process standardizes treatment. Importantly, the multiplier selected ensures that the stimulus intensity is supra-threshold but remains submaximal to protect and preserve the tissue being stimulated. Pulse width, frequency and pattern can also be preselected. Pulse width can be determined on the basis of the type of axon being targeted, with longer widths for small and unmyelinated fibres. The choice of frequency would ideally be related to that recorded either from preclinical studies or from humans; such data are becoming available for VNS[264], which is important given that the vagus nerve contains both sensory and motor fibres running to and from multiple organs. Future research is required to decode the endogenous neural signature that is specific to the function being emulated. Consideration of the pattern of stimulation is also important, given that autonomic activity is not just tonic but cyclical and is based on diurnal, respiratory or cardiac rhythms[38,265,266]. Certain patterns of stimulation are dependent on peripheral receptors, reinforcing the need for closed-loop control. Rhythmic patterned activity is crucial for maintaining transduction efficiency and the sensitivity of the end organ to the applied stimulus[267], which differs with age and sex[268], supporting the potential requirement for a degree of personalization of stimulation settings.

Considering sensors and what to sense. Devices with a closed-loop design will need a sensor to detect the variable being controlled. For carotid sinus baroreceptor stimulation (Figs. 2 and 3), an arterial pressure sensor is crucial. Solid-state transducers and implantable pressure transducers that allow continuous beat-by-beat pressure monitoring via radiotelemetry and fitted with induction power have been developed for animal models[269], but the devices available for humans measure only intracranial[270] and pulmonary artery[271] pressures. However, advances in miniaturization technology have led to the development of implantable leadless pressure devices that are inert and do not react with the surrounding tissue to induce an immune response, such as a borosilicate-glass-encapsulated micropressure implant[272]. This device requires induction power provided by an exterior wand that is placed manually over the device. Similarly, manipulating neural activity requires power, but typical power sources are bulky or dependent on wiring. Miniaturizing such devices and making them biocompatible would be highly desirable. A set of miniaturized ionic power sources has been developed by depositing lipid-supported networks of nanolitre hydrogel droplets that use internal ion gradients to generate energy[33]. These power sources are biocompatible and have been shown to generate ionic currents to modulate neuronal activity in human neural microtissues and mouse brain slices[34].

Future developments are needed to measure beat-by-beat blood pressure output with the use of power sources originating from a powerpack that allows induction charging or from the neuroceutical stimulating device. The pressure sensor might also detect, for example, pulmonary capillary wedge pressure as an index of HF and provide feedback to a cardiac pacemaker. Drawing from cardiac pacemaker technology, closed-loop blood-pressure-controlling devices might also benefit from accelerometers, intracardiac impedance monitors to measure the inotropic state of the heart[273,274], or detection of minute ventilation via thoracic impedance variation to physical activity and emotional stress[219] (Fig. 4b). The detection of respiration could be derived from the changes in chest impedance that occur with each breath, providing an immediate and sensitive readout of the onset and offset of exercise and, importantly, its intensity. For the devices to learn and adapt to patient-specific cardiovascular responses, these sensory signals would need to be integrated into computational descriptions of the dynamics of cardiovascular responses to neural stimuli, either by fine-tuning biophysical or physiological descriptions or via data-driven models using machine learning approaches, to enable closed-loop regulation of blood pressure and other cardiovascular parameters[155,275,276]. Fuzzy-logic-based and artificial-intelligence-based self-learning algorithms have been applied to in silico and in situ models for closed-loop vagus nerve stimulation on the basis of physiological parameters[155,156].

Anatomical and molecular considerations of the autonomic nervous system. Although the fascicular organization of somatic nerves has been well characterized, the viscerotopical organization of spatially distinct fascicles in the pig vagus nerve was only recognized in the past two years[277], and might provide an opportunity to stimulate distinct functionally specific axons. For example, the preganglionic cardiac motor nerves could be targeted without affecting other efferent or afferent nerves, as has been achieved in pigs using a circumferential multielectrode cuff designed to focus voltage or current into different sectors of the vagus nerve[129]. The relatively large diameter of the vagus nerve lends itself to this approach. Whether selectively driving functionally specific subpopulations of vagal preganglionic fibres is beneficial compared with stimulation of either the whole or a branch

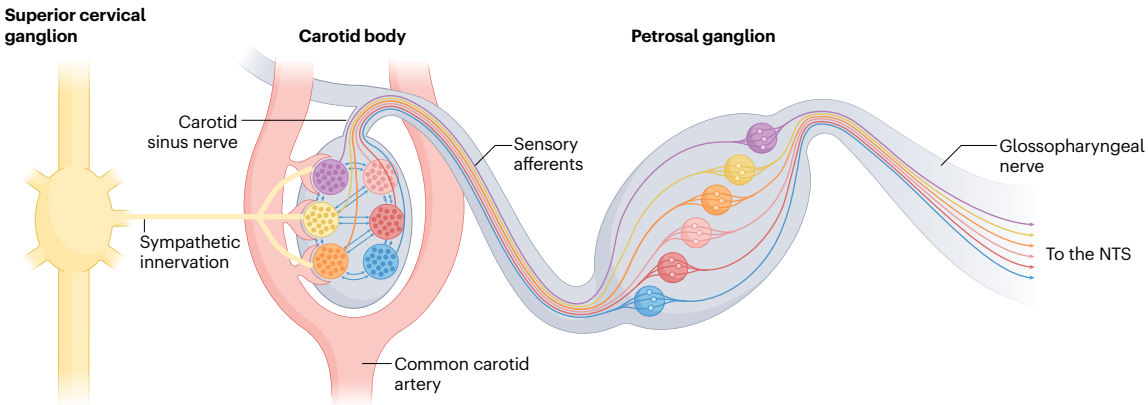


Fig. 5 | Phenotypically distinct afferents from carotid body driving the sympathetic nervous system. The carotid body has become a novel target for regulating sympathetic activity, but it is a multimodal sensor that regulates many systems (respiration, osmoregulation, blood glucose, and hormonal and higher brain function systems). Thus, whether phenotypically unique afferents that relay to drive the sympathetic system exist needs to be established before the development of targeted therapy of the carotid body to control sympathetic activity. Studies have shown that afferents might be phenotypically distinct and that these circuits relay through separate central reflex pathways to alter different motor functions[249]. The P2X purinoceptor 3 has been associated with carotid afferents that regulate vasomotor sympathetic outflows[18,336]. NTS, nucleus of the tractus solitarius. This figure is reproduced from ref. 337, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

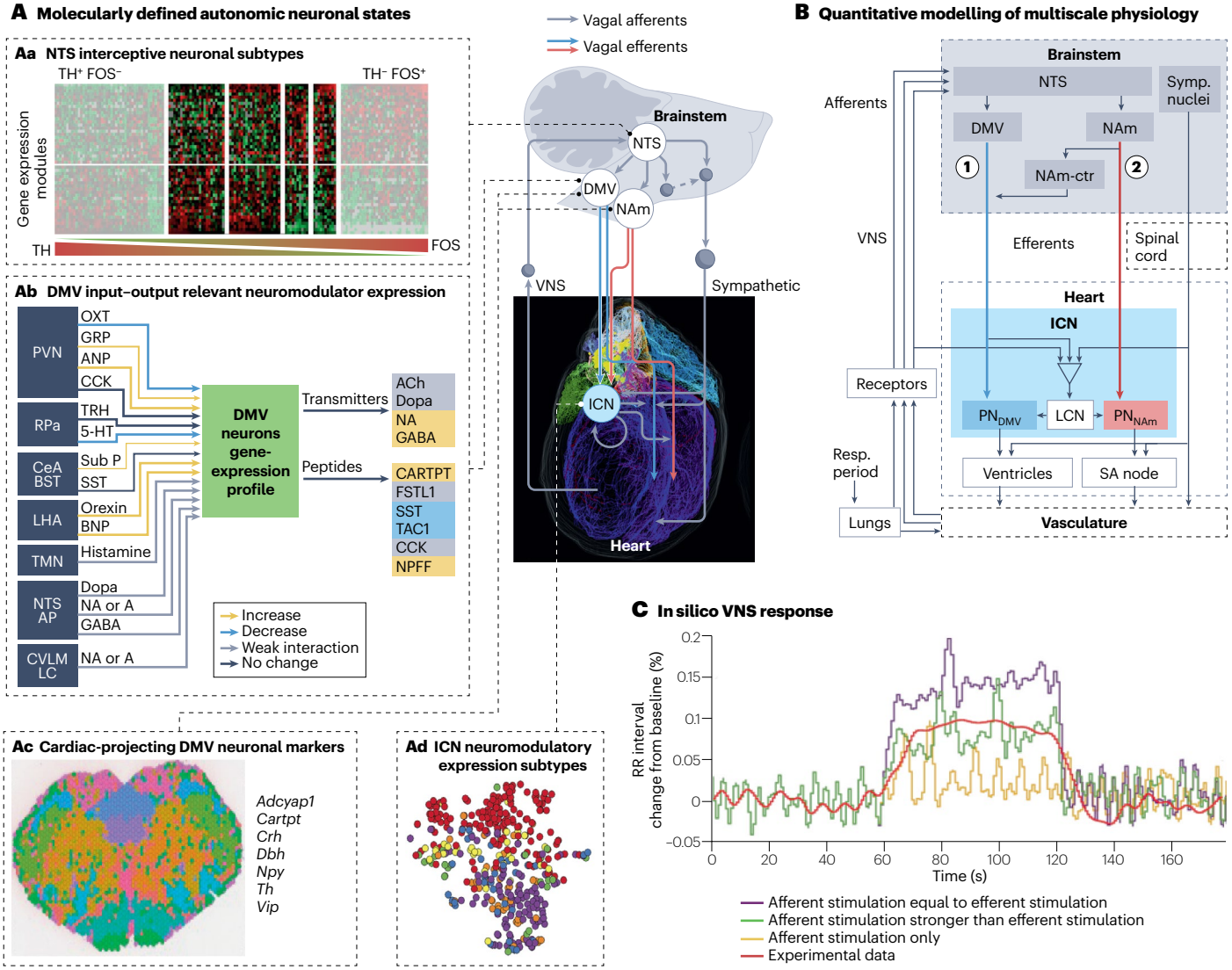
of the vagus nerve (such as the tragus) remains to be determined. Theoretically, activation of the cardiac vagal nerves might provide therapeutic benefit with anti-arrhythmic (ventricular) and coronary vasodilatory responses[278].

Ongoing studies are characterizing the molecular specificity of visceral circuits both centrally[31,32] and peripherally, such as those defining vagal sensory versus motor neurons[25]. Functionally defined afferents that regulate the airways[23,28] and food intake[29,30] have been described. Transcriptomic assessment of cardiac vagal postganglionic neurons might lead to the definition of subclasses of neurons that, for example, regulate rate versus contraction force versus conduction[19]. Additionally, afferents from the carotid body might use a different transmitter–receptor mechanism for inducing sympathetic versus respiratory responses[18] (Fig. 5). Collectively, these exciting data now provide the evidence supporting the potential for discrete neuromodulation of functionally defined visceral afferent circuits. One technical challenge will be how to modulate these pathways therapeutically in humans, which could perhaps be achieved using optogenetics or pharmacogenetics or via the development of site-specific viral vectors, which have been previously used to target sympathetic neurons[279], although not choline acetyltransferase-positive neurons specifically[280,281].

Intersection of cardiac neuron phenotyping with neuroceutical devices

The molecular characterization of visceral afferents has led to the mapping of the molecular signatures of brainstem circuits mediating cardiac reflexes (Fig. 6). The transcriptional state of these neurons relates to their function and responses to synaptic inputs, giving rise to heterogeneity and organization into distinct subtypes and circuits[282,283]. Changes in state affect the transcription profiles of these neurons; for example, dorsal vagal and nucleus ambiguus neurons show diurnal variability in gene expression[284] as well as variability in response to hormones and inflammatory mediators released after cardiac ischaemic injury. Myocardial ischaemia has been shown to change the transcriptomic profile of dorsal vagal neurons, leading to reduced synaptic inhibition and increased neurosecretory function for cardioprotection[20]. We note that cardiac-projecting dorsal vagal neurons express a unique pattern of proteins, such as the pituitary adenylate cyclase-activating polypeptide (PACAP) and the cocaine- and amphetamine-regulated transcript (CART), in addition to non-pathological synucleins, catecholamines and acetylcholine[285]. Notably, PACAP has been shown to be cardioprotective in ischaemia–reperfusion injury[286], to be neuroprotective[287] and to potentiate cholinergic transmission[288] in preclinical models. Functionally, CART exerts neuroprotective effects by preserving mitochondrial function and preventing energy failure after ischaemia–reperfusion injury[289]. PACAP and CART both have anti-inflammatory effects, and their release after the stimulation of dorsal vagal motor neurons might provide cardioprotection after myocardial infarction[290]. These data support the therapeutic potential of devices that can stimulate the cervical vagus nerve and adopt parameter optimization and biofeedback based on the detection of PACAP, CART and synucleins.

Regarding the intrinsic cardiac neurons, their anatomical locality has been well documented, with anatomically correct 3D heart scaffolds providing insights into their precise location in the heart and their interganglionic connectivity[291,292] (Fig. 7). These neurons are predominantly localized to the heart, with the majority located on the posterior or dorsal surface of both atria, but more prominently on the left side. The pattern, distribution and clustering of these neurons is highly conserved between male and female rats, with the exception that female rats have fewer neurons[293]. This highly conserved nature allows the precise placement of electrophysiological recording and ablation catheters, as well as medical actuators and sensors. The molecular characteristics of individual neurons are diverse, and their functional specificity is defined by these characteristics as well as by their location and connectivity to other neurons and cardiac targets (Figs. 5, 8 and 9). Findings from neural-tracing experiments indicate that the vagal motor pathways originating in the dorsal motor nucleus of the vagus nerve and the nucleus ambiguus are distinct at the cardiac postganglionic targets, suggesting anatomically distinguishable ‘lanes’



of vagal control of cardiac physiology[294]. Whether this postganglionic neuronal heterogeneity relates to cardiac physiological functions of chronotropy, dromotropy, ionotropy and lusitropy (Fig. 6 and Fig. 8), and thus whether neurons can be selectively targeted to modulate specific aspects cardiac function, remains to be seen. Intrinsic cardiac neurons contain tyrosine hydroxylase, which can be co-expressed with the vesicular acetylcholine transporter or NPY[291], indicating numerous potential cell phenotypes. A single-cell quantitative polymerase chain reaction study supported the finding that the right atrial ganglionic plexus neurons co-expresses both cholinergic and catecholaminergic phenotypes[19]. The additional presence of NPY, galanin and somatostatin with their respective receptors suggested paracrine modulation within the plexus, overlaid with PACAP, CART and synucleins released from preganglionic terminals. Given this complexity, we propose that future studies considering electrical stimulation of the cardiac vagus nerve to treat disease should first establish the optimal site of stimulation (for example, cervical vagus versus ganglionic plexus), the functional role of the transmitter substances released, and the correct stimulation parameters required to release relevant transmitters for optimal therapeutic effect. Optogenetic stimulation of the dorsal motor nucleus of the vagus in rats showed that VNS induced substantial transcriptional changes in the heart in genes related to pathways that regulate autonomic signalling, inflammation, fibrosis and hypertrophy, indicating the potential for long-term effects of VNS on cardiac physiology[295]. Whether these ventricular effects will persist with chronic VNS and whether the dynamics of ventricular gene expression remodelling are sensitive to the type and pattern of electrical stimulation remain to be determined.

The use of reflexogenic mathematical models might assist with making predictions[276] for subsequent validation in animal experiments and potential extension to human studies[282] (Fig. 6b). Such mathematical models provide a promising platform for in silico testing of precisely targeted VNS by considering the effects of blood pressure and heart rate on the closed-loop response. These computational models can be used to estimate the relative proportion of sensory and motor fibres that are being stimulated by the electrical devices to yield the observed physiological changes in blood pressure and heart rate[276] (Fig. 6c), and accordingly inform optimal device parameters.

Fig. 6 | High-resolution and high-fidelity computational model of closed-loop control of cardiac physiology incorporating molecular, anatomical and connectome details of the central and peripheral autonomic nervous circuits. **A**, Schematic of the autonomic control circuit highlighting vagal afferent and efferent pathways, the intrinsic cardiac nervous (ICN) system, and the brainstem nuclei relevant to vagally mediated cardiac control. The insets illustrate emerging data and concepts relating to the composition and distribution of neuronal states in the corresponding circuit loci. Gene-expression modules in neurons of the nucleus of the tractus solitarius (NTS) are tuned along a continuum of subtypes between the second-order glutamatergic neurons receiving vagal afferent inputs and the A2 catecholaminergic neurons known to control the blood pressure set point[283] (panel **Aa**). States of the dorsal motor nucleus of the vagus (DMV) are characterized by specific combinations of cellular receptors linking these neurons to other brain regions and distinct neuropeptides and neurotransmitters that these vagal motor neurons might release at their peripheral targets[20] (panel **Ab**). Cardioprotective physiological stimuli, such as remote ischaemic preconditioning, can induce the upregulation and downregulation of multiple receptors (inputs) and neuromodulatory systems (outputs). The colours indicate the putative alteration of the interaction strength of input information flow or output signals[20]. Spatial transcriptomics of the brainstem and single-cell transcriptomics of retrogradely traced, cardiac-projecting DMV neuronal markers revealed distinct expression of the genes encoding neuromodulatory proteins[285] (panel **Ac**). Spatially resolved single-cell transcriptomics demonstrated extensive heterogeneity of gene expression in the postganglionic neurons in the heart[19] (panel **Ad**). Clustering revealed five neuronal subtypes based on the gene expression of neuromodulators and their receptors, including those for cholinergic, catecholaminergic, neuropeptide Y (NPY), somatostatin (SST) and other pathways. The varying colours in the panel indicate different neuronal subtypes. **B**, Molecular, anatomical and physiological data can be used to develop multiscale quantitative models that span from the cellular scale, accounting for neuronal electrophysiology and neuromodulation, to the circuit scale that captures the integration of various neuronal and cardiac components into a closed-loop physiological control system[276,282]. In the scheme presented here, the overall circuit can be broken down into brainstem, heart and vasculature modules, which are connected by the afferent and efferent nerve signals and blood flow. The afferent signals from the vasculature and lungs are integrated in the NTS, which projects to the DMV and nucleus ambiguus (NAm). The activation of the NAm is gated based on the phase of the respiratory cycle to account for respiratory sinus arrhythmia (not shown). The block labelled NAm-ctr represents the NAm activity affecting ventricular elastance (a surrogate for contractility) together with DMV. The numbers (1) and (2) refer to the relatively slower and faster lanes of vagal control of the heart, mediated by the DMV and NAm, respectively. The two vagal outflow lanes innervate the ICN at the heart and target separate populations of principal neurons (PN). In addition to direct input from the brainstem, PNs receive input from local circuit neurons (LCN) within the ICN, which integrate local cardiac afferent feedback and sympathetic input. ICN activity regulates the sinoatrial (SA) node and ventricles, modulating heart rate and blood pressure, respectively. Details of model structure, parameters and governing equations are available from refs. 276,282. **C**, A simulation of the multiscale closed-loop cardiac control model to evaluate the combination of afferent and efferent vagal activation required to account for observed experimental effects of vagus nerve stimulation (VNS). Data presented in this graph were derived from ref. 276. 5-HT, serotonin; A, adrenaline; ACh, acetylcholine; ADCYAP1, adenylate cyclase activating polypeptide 1; ANP, atrial natriuretic peptide; AP, area postrema; AP-1 transcription factor subunit; BNP, brain natriuretic peptide; BST, bed nucleus of the stria terminalis; CARTPT, cocaine- and amphetamine-regulated transcript protein; CCK, cholecystokinin; CeA, central amygdala; CRH, corticotropin-releasing hormone; CVLM, caudal ventrolateral medulla; DBH, dopamine β-hydroxylase; Dopa, dopamine; FOS, Fos proto-oncogene, FSTL1, follistatin-related protein 1; GABA, gamma-aminobutyric acid; GRP, gastrin-releasing peptide; LC, locus coeruleus; LCN, local circuit neuron; LHA, lateral hypothalamus; NA, noradrenaline; NPFF, pro-FMRFamide-related neuropeptide FF; OXT, oxytocin; PN_{DMV}, principal neuron with inputs from the dorsal motor nucleus of the vagus; PN_{NAm}, principal neuron with inputs from the nucleus ambiguus; PVN, paraventricular nucleus; Resp. period, respiratory period; RPa, raphe pallidus; RR interval, period between two consecutive electrocardiographic R waves; Sub P, substance P; SA, sinoatrial; Symp. nuclei, sympathetic nuclei; TAC1, tachykinin precursor 1; TH, tyrosine hydroxylase; TMN, tuberomammillary nucleus; TRH, thyrotropin-releasing hormone; VIP, vasoactive intestinal peptide; VNS, vagal nerve stimulation. Panel **A** adapted from refs. 19–21,283,285,292, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/); panel **B** adapted from ref. 21, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/); panel **C** adapted with permission from ref. 276, CC BY-NC-ND 4.0 (https://creativecommons.org/licenses/by-nc-nd/4.0/).

The closed-loop computational models can also be used for in silico testing of the effect of shifting the VNS activation site, for example, by considering differences in cervical versus auricular VNS: the cervical VNS could activate sensory and motor fibres, whereas the auricular VNS would primarily activate sensory fibres. A detailed accounting of vagal sensory processing in the brainstem to integrate information from multiple peripheral loci has not yet been performed, limiting the capability of the closed-loop computational models to consider alternative sites and modalities of vagal stimuli. Computational models also allow for personalization of neuroceuticals by adjusting the parameters of the model based on patient-specific responses to VNS (Fig. 6c). Integrating patient-specific anatomical and physiological features with the known heterogeneous features in the molecular and cellular parameters is crucial to systematically evaluating the distribution of model-predicted physiological dynamics and to matching them against clinical observations.

Bridging neuroceuticals with targeted cell therapy

Although animal studies have yielded important findings that have guided research on therapeutic interventions targeting the cardiac–neural axis, animal models cannot fully recapitulate human pathophysiology, especially given the patient-specific variability in disease presentation. This point is especially evident in inherited cardiac arrhythmia syndromes, in which activation of the sympathetic nervous system can cause sudden cardiac death[296–298]. Advances in stem cell research (Fig. 8), single-cell transcriptomics (Fig. 6) and bioengineering techniques provide an opportunity to bridge neuroceuticals with targeted cell therapy (Fig. 9). Given the current technical challenges of generating cholinergic neurons in vitro[299], research efforts have focused on generating catecholamine-synthesizing neurons with a major emphasis on correcting their hyperexcitability phenotype.

Emerging work using ‘omic’ approaches and cell research combined with advances in molecular imaging[14,39,300–302] has demonstrated the presence of bidirectional signalling between sympathetic neurons and cardiomyocytes both in vitro[303–305] and in vivo[306]. Studies using co-culture models of neurons and cardiomyocytes[307,308] (Fig. 8) combined with high-resolution imaging have revealed that the neuro-cardiac junction has nonrandom connections that might constitute a structural basis for a retrograde communication system[304]. Of interest, neurons seem to survive longer in co-culture with cardiomyocytes than in monoculture, suggesting a biological synergy between these cell types[305,309] and reinforcing the need for site-specific targeting.

Functionally, culturing sympathetic stellate neurons from healthy rats onto cardiomyocytes from hypertensive rats has been shown to

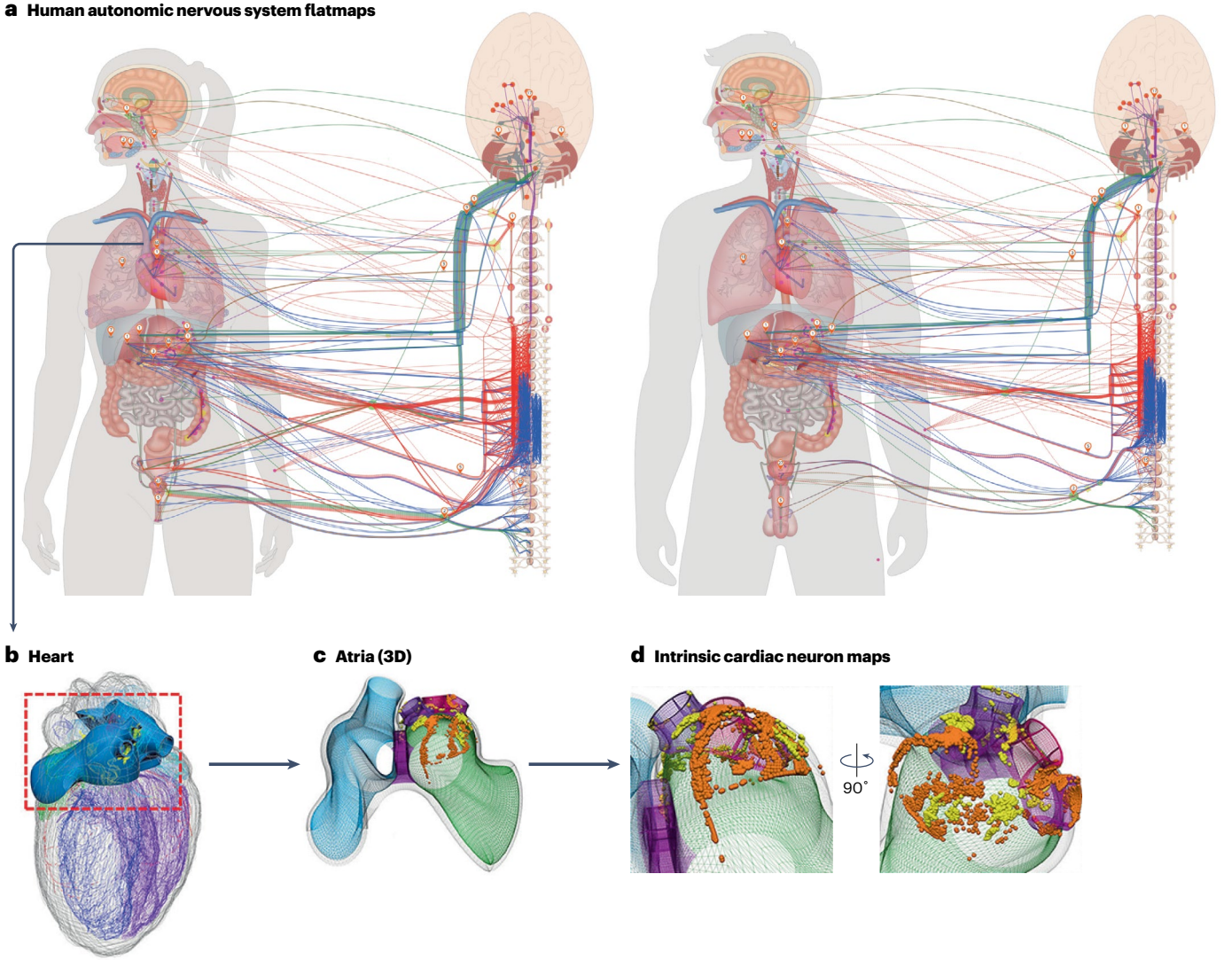


Fig. 7 | Global data repository of autonomic nervous system data for high resolution mapping on common cardiovascular scaffolds. a, A flatmap of men and women from the SPARC portal is presented. When accessed online, the resolution can be increased and reference to the data source can be visualized. **b**, A detailed example of the autonomic nervous system flatmap for the heart is shown, and, based on this model, a generic three-dimensional (3D) scaffold of the atria has been generated (panel **c**), including mapping of the intrinsic cardiac neurons (represented by yellow or orange dots), with views of their specific locations from different angles (panel **d**). This online tool allows investigators to combine their data with existing data to increase the cellular and molecular detail of the flatmaps. Such data are immensely powerful for informing the design and placement of medical devices. Part **a** is reproduced from ref. 11. Parts **b**–**d** are reproduced from ref. 17, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

restore the aberrant cyclic AMP response of diseased cardiomyocytes to that observed in cardiomyocytes from healthy rats, highlighting the capacity of the neuron to drive cardiac phenotypes[303]. Conversely, neurons from hypertensive rats cultured onto cardiomyocytes from healthy rats partially recapitulated the aberrant cyclic AMP response observed in cardiomyocytes from hypertensive rats. Although this study highlighted a unidirectional communication signal, the cardiomyocyte itself can alter the excitability of the sympathetic neuron in a retrograde fashion. For example, co-culture of cardiomyocytes from healthy rats with neurons from a rat model of dysautonomia reduced the hyperexcitability of the neurons[305]. Furthermore, when monocultures of the diseased neurons were treated with conditioned media from healthy cardiomyocytes, neuronal excitability decreased. Whether diseased cardiomyocytes could induce an increase in excitability in healthy neurons has not been established. Nevertheless, these findings suggest that bidirectional communication might be an important homeostatic controller of neuro-cardiac function. Indeed, paracrine agents released from cardiomyocytes (such as nerve growth factor from sympathetic-coupled cardiomyocytes) can activate neuronal tropomyosin receptor kinase A[304]. These trophic factors are known to regulate synaptic plasticity and neuronal survival[310,311].

Whether transplantation of healthy sympathetic neurons can provide physiological support to the diseased heart remains to be established (Fig. 9). In people who have received a heart transplant, those

with restoration of sympathetic innervation in the transplanted heart showed improved heart rate responses and better cardiac performance during exercise compared with recipients with no reinnervation[312], supporting the functional importance of reinnervation in transplanted hearts. To establish the translational potential of cell–cell communication pathways, in vitro human cell models (for example, neurons or cardiomyocytes) must be developed to provide physiological and pathophysiological contexts, and these model systems must demonstrate that the key transcripts and proteins involved in neurotransmission and excitability are conserved and analogous to those seen in animal cell-based systems. Furthermore, technical and biological reproducibility will be crucial in demonstrating the proof of principle that healthy neurons can have a beneficial effect on cardiac function before clinical utility can be established.

'Disease-in-a-dish' models have been developed to predict the safety and efficacy of targeted therapy. This technology is based on the Nobel-winning discovery by Takahashi and Yamanaka in 2016, whereby human adult somatic cells can be reprogrammed to their immature state and then differentiated into other cell types of interest[35,313,314]. Therefore, replacing defective sympathetic neurons to regenerate and restore normal autonomic balance is technically feasible (Fig. 8). These models have led to the successful phenotyping of inherited arrhythmia syndromes. The most dominant cardiac channelopathies are long-QT syndrome type 1 (caused by variants in *KCNQ1*, which encodes a channel subunit for the I_{Ks} current), long-QT syndrome type 2 (caused by variants in *KCNH2*, which encodes a channel subunit for the I_{Kr} current) and CPVT (caused by a gain-of-function variant in *RYR2*). Both channelopathies have a propensity to be triggered by the activation of the sympathetic nervous system during exercise, emotional stress and rapid eye movement (REM) sleep[296]. hiPSC-derived cardiomyocytes from people with long-QT syndrome type 1 show prolonged action potential duration with a reduction in the slow component of the delayed rectifier potassium I_{Ks} current compared with cells from control individuals[315].

To model the sympathetic triggering of arrhythmia, two-dimensional cocultures of hiPSC-derived neurons with hiPSC-derived cardiomyocytes have been successful in driving cardiomyocyte excitability[36,296,309,316–319]. Moreover, emerging data from monocultures of hiPSC-derived sympathetic neurons from people with long-QT syndrome type 1[320] or CPVT[36] demonstrate increased neuronal excitability and heightened intracellular calcium transients, suggesting that these cardiac channelopathies might also be diseases of the sympathetic nervous system and potential therapeutic targets.

Advances in bioengineering techniques, in particular in biomaterials and microfluidics, have helped to capture the cellular complexity

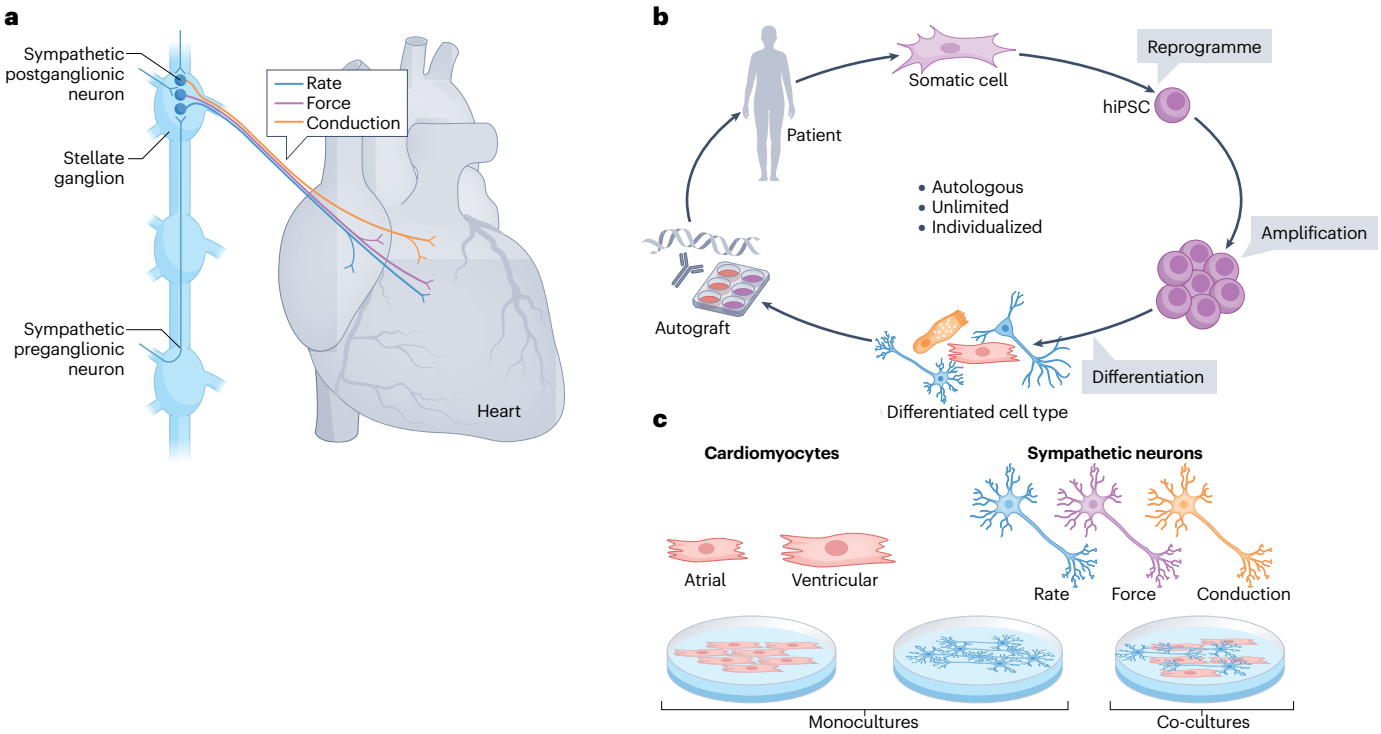


Fig. 8 | Novel targeting of multifunctional cardiac sympathetic neurons in inherited cardiac arrhythmias. The figure shows a targeting strategy involving the suppression of postganglionic cardiac sympathetic activity to alleviate arrhythmias. **a**, People with familial arrhythmias (such as catecholaminergic polymorphic ventricular tachycardia, long-QT syndrome or idiopathic ventricular fibrillation) have a substantial elevation of cardiac sympathetic activity contributing to disturbances in heart rate, force, conduction and filling. Such aberrant activity can induce changes in cardiomyocytes, resulting in an increased predisposition to arrhythmia. **b**, Both sympathetic neurons and cardiomyocytes can be derived in vitro from human induced pluripotent stem cells (hiPSCs) generated from somatic cells isolated from skin biopsy samples. **c**, Cocultures of hiPSC-derived neurons and cardiomyocytes from healthy individuals or people with disease are being used to identify novel targets for subsequent testing in vivo. These approaches might provide opportunities for the development of autograft cell therapy using hiPSC-derived sympathetic neurons and cardiomyocytes. Future research should aim to identify functionally specific (rate versus force versus conduction) sympathetic neurons to allow a high degree of targeting. Such approaches will lessen sympathetic drive and reduce co-transmitter release, and thereby remove the need for stellectomy, which carries the usual risks associated with surgery as well as other adverse effects, such as the development of Horner's syndrome.

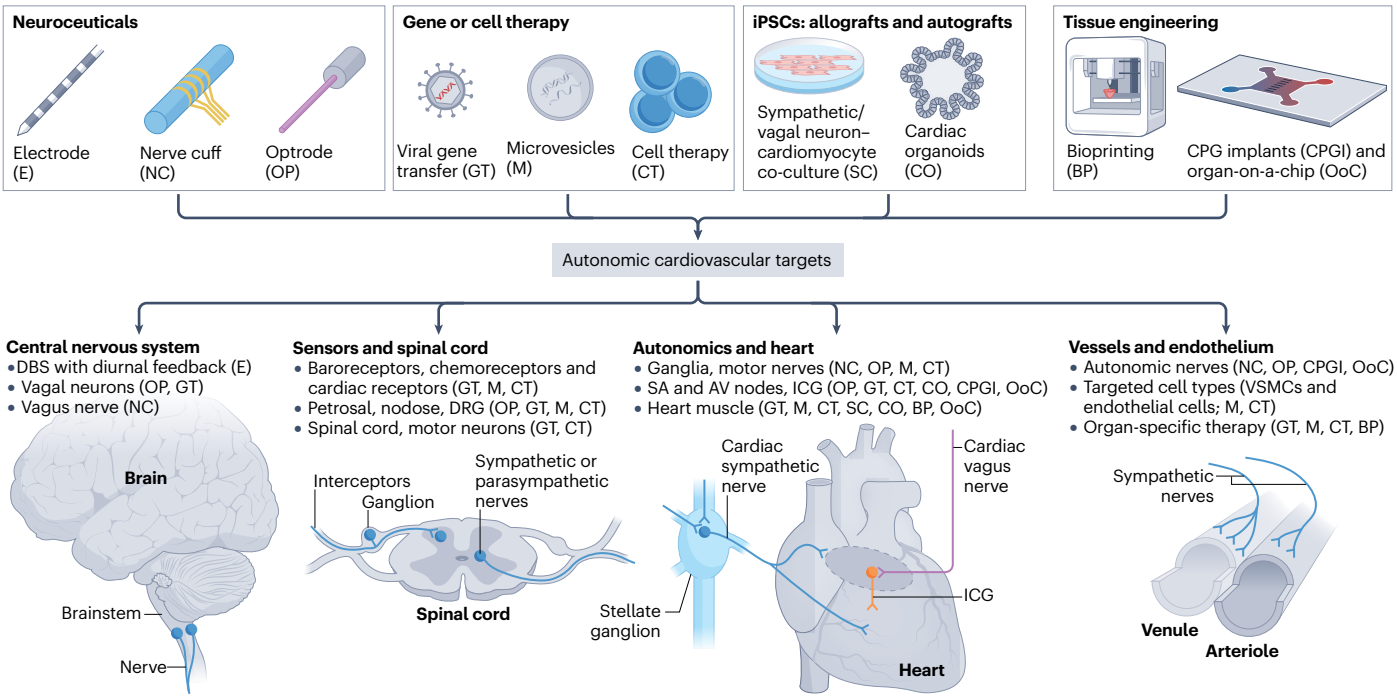


Fig. 9 | Future interventional approaches and targets for restoring autonomic imbalance in cardiovascular disease. Summary of the possible interventions and how they might be used on autonomic cardiovascular targets. Contemporary modulators include electrical stimulation of peripheral nerves, ganglia and brain structures (such as deep brain stimulation, DBS). We propose that these approaches should be fitted with sensors for physiological feedback, as exemplified in Figs. 2, 3 and 4. Stimulation of peripheral nerves might assist in the control of cardiac function, arterial and venous resistance, and venous capacity to regulate preload and/or afterload. The ability to conduct viral gene transfer (GT) will allow cell-type-specific upregulation or downregulation of receptors or transmitters, as well as the expression of opsins for optogenetic and chemogenetic excitatory or inhibitory modulation. Cell therapy (CT) can facilitate the replacement of damaged cells caused by infarcts, as well as the use of cells as shuttles for the secretion of neurotransmitters and modulators in target organs. Microvesicles (M) can be directed to specific organs using surface protein recognition on endothelial cells, for example, to deliver genetic material to either upregulate or downregulate receptors. Induced pluripotent stem cells (iPSCs) can be differentiated into any type of cardiovascular cell and genetically manipulated for therapeutic gain. Cells taken from a person who is also the recipient have the advantage that the autograft does not induce rejection. Cardiac organoids (CO), tissue engineering and bioprinting (BP) offer the option of bulk cell transplants for both the heart and sympathetic and parasympathetic nervous systems at multiple levels to correct autonomic imbalances. Organ-on-a-chip (OoC) technologies might permit neural network control system implants interfacing with, for example, the sinoatrial (SA) node, atrioventricular (AV) node or intracardiac ganglia (ICG). Microelectronic central pattern generator implants (CPGI) could offer correction of arrhythmias (such as atrial fibrillation), chronotropic support and ionotropic control. DRG, dorsal root ganglia; VSMC, vascular smooth muscle cell.

with the use of 3D cell models (Fig. 9). Integration of sensory neurons[321] and immune cells[322] alongside sympathetic and parasympathetic neurons[14] into 3D structures will improve the physiological utility of 'disease-in-a-dish' models. Organoids can be generated using biological hydrogels that act as cell scaffolds to reconstruct cardiac architecture[323–325]. Moreover, in hiPSC-derived cardiomyocyte in vitro models, 3D hydrogels provide a more realistic anatomical organization of sarcomeres and contractile proteins than two-dimensional monolayers[326]. Combined with microfluidic devices to aid in the differentiation and maturation of hiPSC-derived cardiomyocytes[327–329], 3D hydrogels have improved the efficacy of human cell models to help to refine neuromodulation therapies.

Conclusions

The emerging field of neuroceuticals is based on the site-specific targeting of autonomic circuits to develop a bioelectronic strategy to treat CVDs such as HF and arrhythmias. However, the bioelectronic modalities that have been tested have several limitations that preclude their clinical application. Device miniaturization[330] will assist in the development of more efficient devices and use of machine learning and artificial intelligence technologies will permit devices to learn set points and to train the devices to respond physiologically to feedback within a closed-loop system or to inputs from multiple sensors; together, these advances will facilitate device personalization[331]. Furthermore, physiological sensing requires further development of novel implantable detectors of pressure, blood gases, transmitter substances, blood biomarkers and respiration. The state-dependent adaptability of actuators will require multiple inputs and an improved capacity of the devices for parallel processing and integration in real time. Finally, cell therapy via autografting with biomaterials into the autonomic nervous system or the end organ, such as the heart, to alter excitability holds promise for the treatment of arrhythmias. Use of transcriptomics to understand whether visceral reflex pathways are associated with distinct phenotypes might enable highly selective

functional neuromodulation via optogenetics, pharmacogenetics or viral vectors. Taken together, these technological advances in bioelectronic medicine will pave the way for the delivery of viable therapies targeting the cardiovascular autonomic nervous system.

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