Neurosci. Bull. February, 2019, 35(1):98–112
https://doi.org/10.1007/s12264-018-0274-y

www.neurosci.cn
www.springer.com/12264

REVIEW

# Cellular and Molecular Mechanisms Underlying Arterial Baroreceptor Remodeling in Cardiovascular Diseases and Diabetes

**Huiyin Tu[1] · Dongze Zhang[1] · Yu-Long Li[1]**

Received: 15 March 2018 / Accepted: 31 May 2018 / Published online: 27 August 2018


**Abstract** Clinical trials and animal experimental studies have demonstrated an association of arterial baroreflex impairment with the prognosis and mortality of cardiovascular diseases and diabetes. As a primary part of the arterial baroreflex arc, the pressure sensitivity of arterial baroreceptors is blunted and involved in arterial baroreflex dysfunction in cardiovascular diseases and diabetes. Changes in the arterial vascular walls, mechanosensitive ion channels, and voltage-gated ion channels contribute to the attenuation of arterial baroreceptor sensitivity. Some endogenous substances (such as angiotensin II and superoxide anion) can modulate these morphological and functional alterations through intracellular signaling pathways in impaired arterial baroreceptors. Arterial baroreceptors can be considered as a potential therapeutic target to improve the prognosis of patients with cardiovascular diseases and diabetes.

**Keywords** Cardiovascular disease · Diabetes · Baroreflex · Baroreceptor · Vascular wall · Mechanosensitive ion channels · Voltage-gated ion channels · Angiotensin II · Superoxide · Nuclear factor-kappa B

## Introduction

With neurohormonal regulation, the cardiovascular system primarily transports substances such as amino-acids, electrolytes, $O_2$, $CO_2$, hormones, and other metabolic products to and from the cells in the body through the blood. Its function is to maintain homeostasis and provide adequate nourishment for fighting various types of diseases. The arterial baroreflex plays an important role in regulating the cardiovascular system [1, 2]. In general, when arterial vascular tension triggers a feedback signal, the arterial baroreflex reflexively decreases the excessive arterial blood pressure and heart rate to the normal physiological range. The arterial baroreflex arc is composed of an afferent limb (baroreceptor neurons), a central component (central nuclei), and an efferent limb (peripheral sympathetic and parasympathetic neurons). Arterial baroreceptors, including carotid and aortic baroreceptors, are key afferents of the baroreflex arc. The cell bodies of these baroreceptors are located in the nodose and petrosal ganglia and their terminals innervate arterial blood vessels in the carotid sinus and aortic arch. These terminals sense mechanical changes of the arterial vasculature in the carotid sinus and aortic arch and produce excitatory electrical signals, which are integrated and modulated in the arterial baroreceptors by local modulators. Then the integrated signal is conveyed to the dorsal medial region of the nucleus of the solitary tract (a central component of the baroreflex arc) in the dorsal medulla. Finally, this excitation evokes peripheral sympathoinhibitory and parasympathoexcitatory responses. Therefore, the consequence of arterial baroreceptor activation is to decrease heart rate, cardiac output, and peripheral vascular resistance, and to reflexively neutralize an increase in arterial blood pressure and heart rate [3–5].

Cardiovascular diseases (such as heart failure and hypertension) and diabetes are major health problems worldwide [6–8], especially cardiovascular diseases that are the number-one killer in the USA [6]. Attenuation of arterial baroreflex sensitivity is considered to be a common feature in cardiovascular diseases and diabetes [9–15].

✉ Yu-Long Li
yulongli@unmc.edu

[1] Department of Emergency Medicine, University of Nebraska Medical Center, Omaha, NE 68198, USA

Much evidence indicates that decreased baroreflex sensitivity leads to cardiac arrhythmogenesis and sudden cardiac death [1, 16, 17], and is linked with the prognosis and mortality in patients with cardiovascular diseases or diabetes [18–22]. The baroreflex can be modulated by regulatory circuitry at multiple levels including peripheral nerve afferents at the baroreceptors, central components, and efferent components (sympathetic and parasympathetic nerves). In the baroreflex arc, structural and functional changes in each component may attenuate the baroreflex sensitivity. However, two pieces of evidence should be considered. First, recent studies have confirmed that arterial baroreflex dysfunction is attributable to functional impairment of the baroreceptors under pathophysiological conditions [4, 23–28]. Second, both animal studies and clinical trials have demonstrated that baroreceptor activation therapy (direct electrical stimulation of the baroreceptor area) markedly attenuates the symptoms and improves the prognosis in cardiovascular diseases and diabetes [18, 20, 22, 29, 30]. Therefore, baroreceptor impairment might be an important factor in baroreflex dysfunction, including peripheral sympathetic over-activation and withdrawal of peripheral parasympathetic activity in cardiovascular diseases and diabetes. Direct electrical stimulation of the baroreceptor area is a novel therapeutic approach for patients with cardiovascular diseases or diabetes, and has a strong pathophysiological rationale. However, the surgical procedure for baroreceptor stimulation can have adverse complications, including nerve injury, hematoma, headache, worsening of existing heart failure, and hypertension [30–32]. Considering these sequelae, exploring the cellular and molecular mechanism(s) associated with the impairment of arterial baroreceptors and identifying effective therapeutic interventions are crucial for improving the development and prognosis of patients with cardiovascular diseases and diabetes. In this review, we mainly discuss the pathophysiological changes of arterial baroreceptors and related mechanisms in cardiovascular diseases and diabetes.

## Anatomy and Physiology of Arterial Baroreceptors

Baroreceptors are divided into high-pressure arterial baroreceptors and low-pressure baroreceptors. High-pressure arterial baroreceptors, also known as arterial baroreceptors, have stretch-sensitive terminals, and mainly innervate arterial vasculature in the aortic arch and carotid sinus. Arterial baroreceptors are an important part of the negative feedback regulation of blood pressure and heart rate, although low-pressure baroreceptors also influence blood pressure by adjusting blood volume and the retention of salt and water in the kidney. As the main receptors for the regulation of cardiopulmonary function or blood volume, low-pressure baroreceptors are located in the great systemic veins, pulmonary arteries, and walls of right and left atria.

Arterial baroreceptors, one type of pseudo-unipolar peripheral neurons, have a special structural feature. Each soma of the arterial baroreceptors in the nodose and petrosal ganglia has an initial axon segment that bifurcates into two processes [33, 34].

One process is defined as the central process, which terminates in the dorsomedial region of the nucleus of the solitary tract [33, 34], while the other is the peripheral process, which innervates the arterial vasculature in the aortic arch and carotid sinus [33, 34]. The structure of the aortic baroreceptor neuron is illustrated in Fig. 1.

The structure of the nerve terminals in the peripheral process innervating the arterial vasculature has been extensively studied using light and electron microscopic techniques [35–42]. Although there are subtle differences among species, the common morphological features are as follows [35, 36, 41]. First, unmyelinated and myelinated fibers in these nerve bundles form a network that pursues a roughly helical course in the adventitia, and also reaches

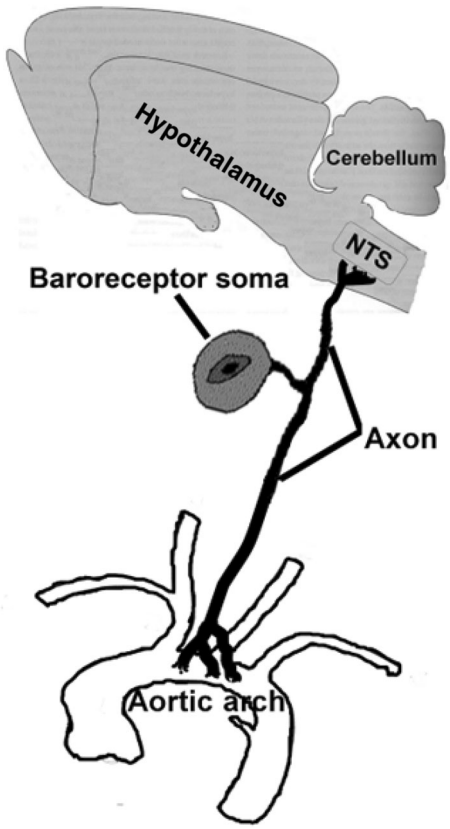


**Fig. 1** Cartoon of an aortic baroreceptor neuron including a soma, a central process to the NTS (nucleus of the solitary tract), and a peripheral process to the aortic arch.

the border of the media to form complex, irregular varicosities (rings or reticula). Second, the afferent axons contain abundant neurotubules. Third, densely-packed mitochondria occur in most of the nerve terminals. Fourth, axoplasmic organelles accumulate in varicosities of the lanceolate terminals, including granular vesicles, glycogen particles, lamellated bodies, and lysosomes. Considering the fast response of electrical impulses to pulsatile arterial expansion, the presence of numerous mitochondria in the nerve terminals supports the high metabolic rate of arterial baroreceptors [35, 36, 41]. Granular vesicles, neurotubules, glycogen particles, lamellated bodies, and lysosomes are possible markers of the continuous reorganization of baroreceptor terminals, which matches the repeated variation in arterial blood pressure [35, 41]. A recent study reported that these synaptic-like granular vesicles could be a part of a constitutive glutamate secretory system [43]. This special system may be involved in maintaining the stretch-sensitivity of arterial baroreceptors [43].

The nerve fibers of arterial baroreceptors are both myelinated (A-type) and unmyelinated (C-type) afferent fibers [44]. The different dynamic characteristics of sensory nerve activity are usually used to clarify both A-type and C-type baroreceptor afferents. Serving as the regulators of the arterial baroreflex sensitivity, A-type afferents are activated by lower pressure and present stable and rapid discharges [45]. On the other hand, C-type afferents primarily regulate tonic levels of arterial blood pressure because these afferents have a high pressure threshold with slow and irregular neural activity [46].

Both aortic and carotid sinus baroreceptors function as an input to the arterial baroreflex, providing afferent signals to the dorsomedial region of the nucleus of the solitary tract, and subsequently to maintain arterial blood pressure at the normal level through a negative feedback circuit. When arterial blood pressure increases, vascular distension-triggered excitation of these arterial baroreceptors results in reduction of the peripheral sympathetic outflow and activation of the peripheral parasympathetic outflow, and reflexively restores arterial blood pressure to normal levels. Conversely, when arterial blood pressure decreases, unloading arterial baroreceptor excitation leads to peripheral sympathetic over-activation and silencing of the peripheral parasympathetic activity, subsequently normalizing arterial blood pressure [3, 47, 48].

When a mechanical change in the arterial vasculature needs to be translated into an excitatory signal and then transmitted to the dorsomedial region of the nucleus of the solitary tract, three successive functional processes must occur [49]. Vascular distension and the deformation of arterial baroreceptor terminals are the first step. In the adventitia and part of the media in the aortic arch and carotid sinus, sensory nerve terminals of the aortic and carotid baroreceptors are embedded in vascular wall components that include elastin, collagen, and smooth muscle cells. This specific structure ensures viscoelastic coupling between arterial vascular wall components and the terminals of arterial baroreceptors. Deformation of the baroreceptor terminals is triggered by mechanical distension of the arterial vasculature when blood pressure rises. Mechanoelectrical transduction is the second step: mechanosensitive ion channels are activated by deformation of the baroreceptor terminals, inducing their depolarization. This completes the conversion from mechanical to electrical energy in these terminals. The translation of membrane depolarization into action potentials is the third step: mechanosensitive ion channel-induced membrane depolarization reaches the voltage threshold (a specific voltage level for each excitable cell), and voltage-gated inward and outward ion channels (including $Na^+$, $Ca^{2+}$, and $K^+$ channels) are successively activated to generate action potentials. Finally, the action potentials generated in the terminals are conveyed along the peripheral and central processes to the dorsal medial region of the nucleus of the solitary tract.

## Influence of Arterial Vascular Wall on Arterial Baroreceptor Sensitivity

Arterial baroreceptor terminals are excited by deformation or strain of the arterial vascular wall but not by intra-vessel pressure *per se* [50, 51]. Multi-faceted experimental methodologies from whole-animal studies to cellular-molecular measurements have been used to evaluate the influence of the arterial vascular wall on baroreceptor sensitivity. Using *in-situ* and *in-vitro* preparations of carotid arteries, these studies have demonstrated that the alteration of circumferential strain is larger than that of axial strain when the pressure in the artery is kept in the physiological range [52]. These results indicate that circumferential deformation of the arterial vascular wall plays a predominant role in baroreceptor sensitivity. In these studies, however, the carotid arteries are usually isolated from surrounding tissues and cannulated in *in-situ* preparations, and a linear flow path is created by cannulating the brachiocephalic artery and descending aorta in *in-vitro* preparations [53–55]. It is possible that the role of axial deformation in the baroreceptor sensitivity has been downplayed, because these preparations cannot maintain the normal anatomical flow path and orientation of the arteries [56]. Feng *et al.* combined an *in-vitro* aortic arch preparation and a traditional three-dimensional finite element modeling method to maintain the normal anatomical flow path and orientation of aortic arteries [56]. They found that both axial and circumferential strains contribute

to pressure-triggered deformation of the arterial vasculature [56].

Regardless of the influence of axial and circumferential strains in the arterial baroreceptor sensitivity, alteration of the arterial vascular wall deforms the baroreceptor terminals [41, 57, 58]. This process is completed by vascular wall components comprising smooth muscle, elastin, and collagen in the tunica adventitia and the media-adventitia border of the aortic arch and carotid sinus [41, 57, 58]. Much evidence has demonstrated that the aortic and carotid baroreceptor areas are specialized, having more elastin and less smooth muscle in the tunica media than other areas of the arterial wall [35, 41, 57–60]. In the tunica media of the baroreceptor areas, the high levels of elastin make the vasculature easily distensible in response to changes in intraluminal pressure [57]. This responsiveness is accompanied by deformation of the baroreceptor terminals [57]. Both polarized light investigations and electron microscopic studies have revealed that a network of contacts among elastic and collagen fibers maintains the collagen in a folded configuration to terminate at the basement membrane and wrapping around the baroreceptor nerve endings [39, 57, 58, 61]. When the arterial vascular wall is stretched, this network modulates collagen unfolding to induce mechanical deformation of the baroreceptor terminals by traction on the basement membrane [39, 57, 58, 61].

Individual arterial baroreceptor nerve terminals have a wide spectrum of stimulus thresholds [62]. To explain this phenomenon, Rees [58] noted that the threshold of an individual baroreceptor terminal might depend on the ratio of the particular collagen/elastin admixture surrounding it. This explanation implies that baroreceptor terminals surrounded by more extensive elastic fibers would be more sensitive than those embedded in less extensive elastic fibers. However, studies have demonstrated that both myelinated and unmyelinated baroreceptor terminals form complex, irregular varicosities, and the latter directly contact the basement membrane [35, 36, 39, 41, 60]. In addition, physiological studies have shown that unmyelinated baroreceptor fibers in the aortic arch and carotid sinus have higher thresholds and lower sensitivity than myelinated baroreceptor fibers [63–65]. Therefore, the wide spectrum of thresholds for baroreceptor fibers could be associated with their intrinsic properties, irrespective of the ratio of the particular collagen/elastin admixture surrounding them.

Considering the role of vascular wall components (elastin, collagen, and smooth muscle cells) in the deformation of arterial baroreceptor nerve terminals, increased stiffness of large elastic arteries in the carotid sinus and aortic arch could be associated with a decrease in baroreceptor sensitivity. Earlier studies [66, 67] have demonstrated that arterial atherosclerosis in the human carotid sinus and hypertrophy of the aortic vasculature in chronic hypertension increase the stiffness of the arterial vasculature, and subsequently attenuate the arterial baroreceptor activity in response to a change of intravascular pressure. Clinical trials have demonstrated that increased arterial stiffness impairs arterial baroreflex sensitivity as an independent determinant [68–72]. These clinical observations assumed (but did not confirm) that the contribution of arterial stiffness to the arterial baroreflex dysfunction might occur *via* a decrease in baroreceptor sensitivity, because these clinical trials did not directly measure the baroreceptor sensitivity.

Using an *in-vitro* aortic arch-aortic nerve preparation and recording from single aortic baroreceptor fibers, Andresen *et al.* reported that the baroreceptor sensitivity is more closely associated with aortic distensibility when vessel stiffness occurs in spontaneously hypertensive rats [73, 74]. Thus far, there have been no reports on whether arterial stiffness is involved in the attenuation of baroreceptor sensitivity in diabetes and chronic heart failure. Based on the findings that arterial stiffness is a shared consequence of diabetes and chronic heart failure, and is an independent risk factor in these diseases [75–80], arterial stiffness is likely to be an important factor in baroreceptor sensitivity. In addition, circulating angiotensin (Ang) II levels are elevated in patients and animal models with hypertension, diabetes, or chronic heart failure [81–90]. A recent study reported that chronic infusion of exogenous Ang II activates $Ca^{2+}$/calmodulin-dependent kinase II (CaMKII) in vascular smooth muscle cells (VSMCs), and subsequently results in increased aortic stiffness and decreased baroreceptor activity [91]. Furthermore, transgenic expression of a CaMKII peptide inhibitor in VSMCs prevents the Ang II-induced increase in aortic stiffness and decrease in baroreceptor activity [91]. Therefore, alteration of the arterial vascular wall could be an important factor in modulating the arterial baroreceptor sensitivity in cardiovascular diseases and diabetes.

## Role of Mechanoelectrical Transduction in Arterial Baroreceptor Sensitivity

Mechanoelectrical transduction converts the mechanical deformation of arterial baroreceptor nerve terminals into baroreceptor membrane depolarization. Much evidence has confirmed the presence of mechanosensitive ion channels in aortic baroreceptors [92–96]. Usually, the opening of mechanosensitive ion channels constitutes mechanoelectrical transduction when arterial baroreceptor terminals are mechanically deformed.

In animal studies, direct recording of single-fiber or multi-fiber electrical activity is usually used to measure the function of the arterial baroreceptor afferent nerve and terminals in *in-vivo*, *in-situ*, or *in-vitro* aortic arch or carotid sinus preparations [53, 97–105]. The first study focusing on the role of mechanosensitive ion channels in arterial baroreceptor activation investigated the baroreceptor activity in the perfused isolated carotid sinus preparation before and after intraluminal injection of a mechanosensitive ion channel blocker [106]. This study demonstrated that the inhibition of mechanosensitive ion channels blunts the pressure-induced increase in the baroreceptor activity without changing the carotid sinus compliance [94]. However, clarifying the contribution of the terminals alone to the baroreceptor sensitivity is very difficult, because of the presence of endothelial cells, vascular smooth muscle cells, and other types of cells in the arterial vasculature. In addition, the baroreceptor nerve endings have a complex network structure, and are embedded in the arterial vasculature. These factors do not allow the direct measurement of membrane electrophysiology in the terminals. Nevertheless, an alternative preparation using the isolated somata of arterial baroreceptor neurons has been used as a substitute for terminals in electrophysiological recording [49, 107].

So far, it is unclear which type of mechanosensitive ion channel is the mechanoelectrical transducer in arterial baroreceptors. Many types of such channels have been reported to be expressed in sensory neurons, including epithelial $Na^+$ channels (ENaCs) [108–110], acid-sensing ion channels (ASICs) [111], transient receptor potential (TRP) ion channels [112], stretch-activated $K^+$ channels [113], mechanically-gated two-pore domain $K^+$ channels [114], and piezo-ion channels [113, 115, 116]. ENaCs, ASICs, and TRP channels have been considered possible candidates for mechanoelectrical transduction in arterial baroreceptor nerve terminals.

ENaCs are members of the amiloride-sensitive degenerin channel (DEG) superfamily identified in mammals [117–120]. ENaCs were first identified as mechanosensory in *Caenorhabditis elegans* [121–123]. Four subunits of ENaCs (α-, β-, γ-, and σ-ENaC) are expressed in many tissues, including brain, kidney, and aortic baroreceptors [124–129]. In polarized epithelial cells, they function as an obligate heteromultimer to direct the flow of $Na^+$ ions into the cytoplasm *via* the channel pore in the membrane [120, 130]. The function of ENaCs in epithelial cells can be blocked with amiloride [130]. As vectorial transcellular transporters of $Na^+$ ions, ENaCs play important roles in regulating extracellular fluids, and maintaining whole-body salt balance and water homeostasis [131]. Besides their expression as the $Na^+$ transporter in epithelial cells, ENaCs are considered to be mechanosensors in non-epithelial cells. In some mechanosensory neurons, the ENaC protein has the electrophysiological characteristics of a mechanosensory channel [118]. Experimental evidence has also demonstrated that inward $Na^+$ currents activated by membrane stretch or shear force occur in ENaC-expressing *Xenopus* oocytes [126]. These ENaC-like currents are totally blocked by amiloride and benzamil (specific ENaC blockers) [126]. These studies confirm that the ENaC is involved in mechanosensation in non-epithelial mechanosensitive tissues as a mechano/amiloride-sensitive channel [108, 110, 125, 126, 132]. Furthermore, studies have also reported the expression of ENaC subunits in baroreceptor cell bodies and nerve terminals [125, 133, 134]. More importantly, in arterial baroreceptors, only the β- and γ-ENaC subunits and not the α-ENaC subunit are expressed [125, 133, 134]. The role of ENaCs in arterial baroreceptor function has been extensively investigated by the application of ENaC blockers including amiloride and benzamil. In the isolated carotid sinus of rabbits, application of benzamil significantly attenuates carotid sinus nerve activity in a dose-dependent manner [133]. In isolated aortic baroreceptor neurons, amiloride selectively abolishes mechanical stimulation-induced membrane depolarization, while this drug does not attenuate depolarizing current-induced action potentials [133, 134].

ASICs are also members of the DEG/ENaC superfamily [130]. At least seven ASIC isoforms (ASIC-1a, -1b, -2a, -2b, -3, -4, and -5) are highly expressed in the mammalian central and peripheral nervous systems [111, 135, 136]. When the gene for ASIC-1a, -1, -2, or -3 is mutated, neurosensory mechanotransduction is deficient in peripheral tissues including muscle and skin, and in the gastrointestinal tract [135–143]. Therefore, these ASIC isoforms contribute to neurosensory mechanotransduction in different types of sensory nerves innervating all peripheral tissues and organs. Both ASIC mRNA and protein are also expressed in arterial baroreceptors [144]. Quantitative RT-PCR has shown that ASIC-1a, -1b, -2a, -2b, and -3 mRNAs are expressed in the cell bodies of nodose neurons [144]. In addition, immunofluorescent staining has demonstrated that ASIC-1, -2, and -3 proteins are present in the cell bodies, nerve fibers, and terminals of aortic baroreceptors [144]. To evaluate the role of ASIC2 in aortic baroreceptor sensitivity, baroreceptor activation has been measured *in vitro* in isolated aortic baroreceptor neurons and *in vivo* in the aortic depressor nerve [144]. In isolated primary aortic baroreceptor neurons, mechanical stimulation-induced membrane depolarization is markedly greater in mice with ASIC2 overexpression than in wild-type mice, while mechanical stimulation-induced membrane depolarization is abolished in ASIC2-null mice [144]. Similarly, *in vivo* aortic depressor nerve activity is attenuated in ASIC2-null mice compared to wild-type mice [144].

TRP ion channels are a superfamily of cellular sensors that respond to extra- and intra-cellular stimuli including light, temperature, pheromones, acidity, taste, pain, direct membrane stretching, and osmotic stress [145–150]. Recent studies reported seven subfamilies of mammalian TRP ion channels: TRPC (canonical 1-7), TRPV (vanilloid 1-6), TRPM (melastatin 1-8), TRPP (polycystin 2, 3, 5), TRPML (mucolipin 1-3), TRPA (ankyrin 1), and TRPN (NOMPC-like 1) [148–151]. Many tissues and cells express TRP channels [149]. Using immunocytochemical and immunofluorescent techniques, studies have demonstrated the expression of TRPV1 and several TRPC (TRPC1 and TRPC3-7) proteins in the somata of aortic baroreceptor neurons, while TRPV1, TRPC1, and TRPC3-5 proteins are expressed in aortic myelinated and unmyelinated axons and baroreceptor terminals [152–154]. A recent study demonstrated the stretch activation of TRPC5 channels and their involvement in whole-cell ion currents activated by hypo-osmolarity and arterial baroreceptor mechanosensation [152]. In cell bodies of rat aortic baroreceptor neurons, a mechanosensitive channel has been recorded using whole-cell and single-channel patch-clamp recordings [152]. This channel activation is antagonized by T5E3 (a TRPC5-blocking antibody) and T5DN (a dominant-negative TRPC5 construct) [152]. Similarly, this mechanosensitive channel recorded in wild-type mice is undetectable in TRPC5$^{-/-}$ mice [152]. In addition, hypo-osmolarity cannot activate whole-cell inward currents in TRPC5$^{-/-}$ animals, while it does so in the aortic baroreceptor neurons of wild-type animals [152]. These hypo-osmolarity-activated inward currents are inhibited by T5E3 and T5DN153. Furthermore, pressure-elevated arterial baroreceptor nerve activity is significantly blunted in lentiviral-T5DN-transfected and TRPC5$^{-/-}$ animals [152]. More importantly, knockdown of other TRPC isoforms (TRPC-1, -3, -4, and -6) does not change hypo-osmolarity-activated whole-cell currents and pressure-induced frequency increase in arterial baroreceptors [152]. These data indicate that TRPC5 may be a key mechanotransducer in arterial baroreceptors.

In contrast to studies focusing on the role of mechanosensitive ion channels as the mechanoelectrical transducers in arterial baroreceptors under normal conditions, scant information is available about changes in mechanosensitive ion channels in arterial baroreceptors under pathophysiological conditions. Using immunofluorescent staining and Western Blot analysis, Li *et al.* [107] demonstrated that the βENaC and γENaC subunit proteins are expressed, while the αENaC subunit protein is undetectable in aortic baroreceptor terminals and cell bodies. In particular, the expression of βENaC and γENaC proteins is decreased in aortic baroreceptor terminals and cell bodies from animals with chronic heart failure [107]. Whole-cell ENaC currents recorded by patch-clamp are also reduced in aortic baroreceptor neurons from animals with chronic heart failure [107]. The decrease in ENaC currents may contribute to attenuation of the pressure-stimulated aortic depressor nerve activity in animals with chronic heart failure [107]. Although the above evidence supports the potential involvement of stretch-activated ion channels in arterial baroreceptor sensitivity and their important clinical implications, further studies are needed to identify baroreceptor mechanosensors and the related regulatory mechanisms in cardiovascular diseases and diabetes.

## Involvement of Voltage-Gated Ion Channels in Arterial Baroreceptor Sensitivity

As noted above, after mechanically-induced membrane depolarization reaches threshold, voltage-gated inward and outward ion channels are successively activated to generate action potentials in baroreceptor terminals. Finally, the action potentials are conveyed to the dorsomedial region of the nucleus of the solitary tract. In 1952, Hodgkin and Huxley provided a fundamental framework for the initiation and propagation of the nerve impulse along axonal processes [155]. Voltage-gated ion channels [$Na^+$ (Nav), $Ca^{2+}$ (Cav), and $K^+$ (Kv)] are the basis of neuronal electrical excitability [156, 157]. Many studies have recorded voltage-gated ion currents in arterial baroreceptor neurons, and analyzed the modulation of voltage-gated ion channels and their contributions to the initiation and propagation of the nerve impulse under normal conditions [99, 102, 158–168]. Under pathophysiological conditions, however, only the roles and related modulation of Nav and hyperpolarization-activated cyclic nucleotide-gated (HCN) channels have been elucidated in detail in arterial baroreceptor neurons [4, 11, 12, 15, 23, 169–172].

### Role of Nav Channels in Arterial Baroreceptors in Chronic Heart Failure

Voltage-gated Nav channels are found in excitable cells and other types of cells. In excitable cells, including primary viscerosensory neurons, voltage-gated Nav channels are essential for the initiation and propagation of action potentials [173, 174]. Based on the characteristics of a pore-forming α-subunit, voltage-gated Nav channels are divided into nine functional isoforms (Nav1.1–1.9) [174]. These isoforms are located in specific tissues, and each isoform has a different function in mammalian physiology [174]. Tetrodotoxin (TTX) is a voltage-gated Nav channel blocker. Based on the TTX-sensitivity of Nav channels,

they have also been separated into TTX-sensitive (Nav-1.1, -1.2, -1.3, -1.4, -1.6, and -1.7) and TTX-resistant (Nav-1.5, -1.8, and -1.9)[175–177]. In primary viscerosensory neurons in the nodose ganglia, Nav-1.7, -1.8, and -1.9 are abundantly expressed [23, 165, 176, 177]. Based on the expression of Nav-1.7, -1.8, and -1.9 channels, aortic baroreceptor neurons in the nodose ganglia are divided into A-type and C-type [166]. Neurons with only TTX-sensitive Nav channels (Nav-1.7) are defined as A-type, whereas neurons with both TTX-sensitive (Nav-1.7) and TTX-resistant Nav channels (Nav-1.8 and -1.9) are defined as C-type [23, 165, 176, 177].

To evaluate the role of Nav channels in arterial baroreflex sensitivity, it was measured in conscious dogs with chronic heart failure before and after treatment with a Nav channel enhancer [178] and the attenuation of sensitivity was normalized by the enhancer [178]. This was the first evidence for a contribution of Nav channels to the maintenance of arterial baroreflex sensitivity under pathophysiological conditions such as chronic heart failure. However, this study did not reveal which component(s) of the arterial baroreflex arc is the target of the enhancer. Using multi-faceted techniques (real-time RT-PCR, Western blot analysis, and immunofluorescent staining), Tu *et al.* measured the expression of Nav channel mRNAs and proteins in the nodose ganglia, including aortic baroreceptor neurons [23]. Their study demonstrated the mRNA and protein expression of Nav-1.7, -1.8, and -1.9 channels in the nodose ganglia, and especially their low expression in rats with chronic heart failure [23]. In addition, decreases in Nav currents (both TTX-sensitive and TTX-resistant) and cell excitability have been found in isolated aortic baroreceptor neurons from rats with chronic heart failure [23]. In such rats, attenuation of the arterial baroreflex sensitivity is normalized by direct injection of rATX II (a Nav channel activator) into the nodose ganglia [23]. Similarly, application of rATX II to aortic baroreceptor neurons also restores Nav current density and cell excitability in rats with chronic heart failure [23]. The results of the above studies demonstrate that neuronal remodeling of arterial baroreceptors, including changes in Nav channel expression and activation, could be involved in attenuated arterial baroreceptor function and the resultant arterial reflex dysfunction in chronic heart failure.

Ang II-superoxide-NFκB signaling is a common signal pathway in a variety of pathophysiological conditions [5, 179–182]. This signaling has also been reported to modulate Nav channel expression and activation in arterial baroreceptors in chronic heart failure [4, 5, 172]. A common endogenous peptide, Ang II is involved in many physiological actions through its binding with Ang II receptors expressed on cell membranes [183–185]. Circulating and local tissue Ang II levels are increased in experimental animal models and patients with chronic heart failure [81, 86–88]. In particular, a recent study found that AT1R mRNA and protein are overexpressed and local tissue Ang II concentration is elevated in the nodose ganglia including aortic baroreceptors from rats with chronic heart failure [15]. In sham rats, Nav currents in isolated aortic baroreceptor neurons are inhibited by acute treatment with exogenous Ang II [15]. The inhibitory effect of exogenous Ang II on Nav currents is completely counteracted by pretreatment with losartan (an AT1R blocker) [15]. In rats with chronic heart failure, however, application of losartan to isolated aortic baroreceptor neurons does not affect Nav currents [15]. Possible explanations include: (1) chronic heart failure-reduced expression of Nav channels is not modulated by acute treatment with losartan; and (2) acute isolated aortic baroreceptor neurons lose *in-vivo* environments including elevation of endogenous Ang II levels and paracrine release of Ang II from other adjacent cells after aortic baroreceptor neurons are acutely associated from animals [15]. Therefore, high levels of endogenous Ang II combined with AT1R overexpression during the progression of chronic heart failure should be considered to modulate Nav channel expression and activation in aortic baroreceptor neurons in chronic heart failure.

In mitochondria, the electron transport chain is mainly involved in ATP production through transferring electrons to molecular oxygen under physiological conditions [186, 187]. During the process of electron transport, 1%–2% of the electrons are leaked from mitochondrial complex enzymes (complexes I–IV) to produce a low level of the superoxide anion [186–191]. Under pathophysiological conditions, imbalance of the mitochondrial oxidative and anti-oxidative systems occurs [187, 190, 192, 193]. The levels of the mitochondria-derived superoxide anion are elevated due to the inhibition of mitochondrial complex enzymes and/or the inactivation of manganese superoxide dismutase (MnSOD) [187, 190, 192, 193]. In animals with chronic heart failure, the mitochondria-derived superoxide anion in the nodose ganglia is overproduced through inhibition of the mitochondrial oxidative and anti-oxidative systems [172]. In this study, the adenoviral MnSOD gene was injected into the nodose ganglia in animals with chronic heart failure to overexpress the MnSOD protein [172]. This *in vivo* gene transfection not only reduced the levels of the mitochondria-derived superoxide anion, but also normalized aortic baroreceptor function (such as expression and activation of Nav channels and cell excitability) in rats with chronic heart failure [172]. Therefore, mitochondria-derived superoxide overproduction triggers a downstream signal to inhibit the expression and activation of Nav channels, and reduce cell excitability in aortic baroreceptor neurons in chronic heart failure.

NFκB is a transcription factor in all types of cells. Although it has 5 structurally-related proteins (RelA (p65), RelB, c-Rel, p50, and p52) the p65/p50 heterodimer is the most important functional form [194]. In the resting state, a silent form of NFκB exists in the cytosol, because a specific inhibitor of κBα (IκBα) tightly binds with NFκB to limit its activation [194, 195]. When multiple stimuli activate IKKβ kinase, IKKβ kinase-phosphorylated IκB is ubiquitinated and degraded [196–198]. Finally, liberated NFκB is activated in the cytoplasm and translocated to the nucleus [195]. Once phosphorylated NFκB binds with specific sites on target DNAs, it induces the transcription of numerous target genes [195]. The IKK–IκB–NFκB signaling pathway is also present in rat nodose ganglia [4]. More importantly, chronic heart failure increases IKK phosphorylation, IκBα degradation, NFκB p65 phosphorylation, and the binding of NFκB p65 to the Nav1.7 promoter in rat nodose ganglia [4]. In addition, lentiviral NFκB p65 shRNA transfected into the nodose ganglia *in vivo* normalizes the phosphorylation of the NFκB p65 protein, and markedly increases the expression and activation of Nav channels and neuronal excitability in aortic baroreceptor neurons isolated from rats with chronic heart failure [4]. The above results confirm that downregulation of Nav1.7 channels and suppression of neuronal excitability are attributable to a cascade of the IKK–IκB–NFκB signaling pathway in aortic baroreceptors in chronic heart failure.

As discussed above, either the adenoviral MnSOD gene or lentiviral NFκB p65 shRNA transfected into nodose neurons *in vivo* reverses the attenuation of Nav channel expression and activation and reduction of the neuronal excitability in aortic baroreceptor neurons isolated from animals with chronic heart failure [4, 172]. In addition, in animals with chronic heart failure, adenoviral MnSOD gene transfection inhibits the over-phosphorylation of NFκB p65 in the nodose ganglia, while lentiviral NFκB p65 shRNA does not change the levels of the mitochondria-derived superoxide anion in the nodose ganglia [4]. Therefore, NFκB p65 is downstream of the superoxide anion to mediate aortic baroreceptor dysfunction in chronic heart failure.

Many studies have demonstrated that Ang II is an endogenous biological trigger to stimulate the overproduction of mitochondria-derived superoxide [199, 200]. Based on the above, a reasonable conclusion is that the Ang II-superoxide-NFκB signaling pathway contributes to lower expression and inactivation of Nav channels and suppression of the neuronal excitability in aortic baroreceptor neurons in chronic heart failure. This viewpoint is supported by data from other studies, in which Ang II-hydrogen peroxide-NFκB signaling induces down-transcription of Nav1.5 channels in cardiac myocytes [201].

## Role of HCN Channels in Arterial Baroreceptors in Diabetes

HCN channels were first reported in the sinoatrial node of the heart and are composed of four homologous members (HCN-1, -2, -3, and -4) in mammals [4, 99, 202–207]. During the hyperpolarization phase, inward ions pass through HCN channels to modulate cell automaticity [202, 205]. The mRNA and protein expression of the four HCN isoforms are found in cell bodies and nerve terminals of aortic baroreceptor neurons [11, 99, 171]. Measurements by immunofluorescent staining have demonstrated that the proteins of all four isoforms are expressed in A-type nodose neurons, while the proteins of HCN-2, -3, and -4 isoforms are expressed in C-type nodose neurons [11, 171]. Usually HCN channels initiate pacemaker excitation in the heart [50, 208, 209] and generate sustained rhythmic oscillation in various brain regions [210–212]. However, HCN channel activation decreases neuronal excitability of aortic baroreceptors by affecting membrane rectification [158], because HCN channel blockers significantly enhance this excitability [11]. More importantly, in the streptozotocin-induced type-1 diabetic animal model, HCN channel expression and activation are increased, while excitability is decreased in aortic baroreceptor neurons [11, 171]. These data confirm that upregulation of HCN channels decreases the excitability of arterial baroreceptors in diabetes.

Usually, endogenous substances can chronically modulate the expression of ion channels and acutely influence their electrophysiological properties. A whole-cell patch-clamp study has demonstrated that the application of exogenous Ang II to isolated nodose neurons acutely affects their electrophysiological activity *via* AT1 receptors [213]. Using radioimmunoassay, single-cell RT-PCR, and western blot analysis, a recent study found a high level of endogenous Ang II and overexpression of AT1 receptor mRNA and protein in nodose neurons from streptozotocin-induced type 1 diabetic rats [169]. Both exogenous Ang II and diabetes activate HCN channels and suppress the excitability of isolated aortic baroreceptor neurons [168, 169]. The effects of exogenous Ang II and diabetes on HCN channels and neuronal excitability are totally inhibited by AT1 receptor antagonists [168, 169]. In addition, chronic application of exogenous Ang II to cultured primary nodose neurons induces overexpression of HCN channels [170]. These experimental data indicate that high levels of endogenous Ang II with overexpression of AT1 receptors modulate HCN channel expression and activation and subsequently attenuate the excitability of aortic baroreceptors in diabetes.

NADPH oxidase is a membrane-bound enzyme with multiple components (gp91phox, P22phox, p40phox,

p47phox, and p67phox) [185, 214]. This enzyme is thought to be a key downstream target of Ang II-AT1 receptors to produce superoxide in many tissues [170, 185, 214–219]. These NADPH oxidase subunits are overexpressed in the nodose ganglia from type-1 diabetic animals [169]. Both NADPH oxidase inhibitors and superoxide scavengers markedly blunt either exogenous Ang II or diabetes-induced high levels of superoxide production, HCN channel over-activation, and the suppression of excitability in aortic baroreceptors [168, 169]. These studies strongly suggest that Ang II-NADPH oxidase-superoxide signaling is associated with the modulation of HCN channel expression and activation, and the resultant suppression of excitability in aortic baroreceptors in diabetes.

## Perspectives and Future Directions

This review summarizes potential mechanisms underlying arterial baroreceptor remodeling in cardiovascular diseases and diabetes (Fig. 2). As a major part of the arterial baroreflex arc, arterial baroreceptors are impaired in cardiovascular diseases and diabetes. The impairment of arterial baroreceptors is attributed to alterations in the arterial walls, mechanosensitive ion channels, and voltage-gated ion channels. Endogenous substances (such as Ang II and superoxide anion) modulate these changes through intracellular signaling pathways. These findings are helpful for identifying effective therapeutic interventions, which are crucial for improving the prognosis of cardiovascular diseases and diabetes and reducing their mortality. Although these findings can provide potential therapeutic strategies for improving the prognosis in patients with cardiovascular diseases and diabetes, further studies are needed to address the involvement of other ion channels and endogenous substances.

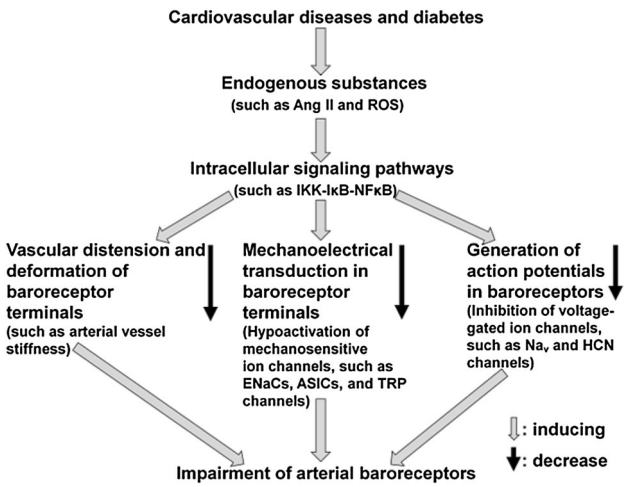


**Fig. 2** Schematic of potential mechanisms responsible for the impairment of arterial baroreceptors in cardiovascular diseases and diabetes. Ang II, angiotensin II; ROS, reactive oxygen species; IKK, IκB kinase; IκB, inhibitor of κB; NFκB, nuclear factor kappa B; ENaC, epithelial $Na^+$ channel; ASIC, acid-sensing ion channel; TRP, transient receptor potential; Nav, voltage-gated $Na^+$; HCN, hyperpolarization-activated cyclic nucleotide-gated.

**Acknowledgements** This review was supported by the American Heart Association (0730108N) and the National Institute of Health's National Heart, Lung, and Blood Institute (R01HL-098503 and R01HL-137832), USA.

**Compliance with Ethical Standards**

**Conflict of interest** All authors claim that there are no conflicts of interest.

## References

1. Palma JA, Benarroch EE. Neural control of the heart: recent concepts and clinical correlations. Neurology 2014, 83: 261–271.
2. Talman WT, Kelkar P. Neural control of the heart. Central and peripheral. Neurol Clin 1993, 11: 239–256.
3. Benarroch EE. The arterial baroreflex: functional organization and involvement in neurologic disease. Neurology 2008, 71: 1733–1738.
4. Zhang D, Liu J, Tu H, Muelleman RL, Cornish KG, Li YL. *In vivo* transfection of manganese superoxide dismutase gene or nuclear factor kappaB shRNA in nodose ganglia improves aortic baroreceptor function in heart failure rats. Hypertension 2014, 63: 88–95.
5. Zhang D, Muelleman RL, Li YL. Angiotensin II-superoxide-NFkappaB signaling and aortic baroreceptor dysfunction in chronic heart failure. Front Neurosci 2015, 9: 382.
6. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, *et al.* Heart Disease and Stroke Statistics-2017 Update: A report from the American Heart Association. Circulation 2017, 135: e146–e603.
7. Redon J, Tellez-Plaza M, Orozco-Beltran D, Gil-Guillen V, Pita FS, Navarro-Perez J, *et al.* Impact of hypertension on mortality and cardiovascular disease burden in patients with cardiovascular risk factors from a general practice setting: the ESCARVAL-risk study. J Hypertens 2016, 34: 1075–1083.
8. Stokes A, Preston SH. Deaths Attributable to diabetes in the United States: Comparison of data sources and estimation approaches. PLoS One 2017, 12: e0170219.
9. Dauphinot V, Kossovsky MP, Gueyffier F, Pichot V, Gosse P, Roche F, *et al.* Impaired baroreflex sensitivity and the risks of new-onset ambulatory hypertension, in an elderly population-based study. Int J Cardiol 2013, 168: 4010–4014.
10. de Moura-Tonello SC, Porta A, Marchi A, de Almeida FA, Francisco CO, Rehder-Santos P, *et al.* Cardiovascular variability analysis and baroreflex estimation in patients with type 2 diabetes in absence of any manifest neuropathy. PLoS One 2016, 11: e0148903.
11. Li YL, Tran TP, Muelleman R, Schultz HD. Blunted excitability of aortic baroreceptor neurons in diabetic rats: involvement of hyperpolarization-activated channel. Cardiovasc Res 2008, 79: 715–721.
12. Li YL. Elevated angiotensin II in rat nodose ganglia primes diabetes-blunted arterial baroreflex sensitivity: involvement of

NADPH oxidase-derived superoxide. J Diabetes Metab 2011, 2: 1000135.
13. Martiniskova Z, Kucera P, Sykora M, Kollar B, Goldenberg Z, Turcani P. Baroreflex sensitivity in patients with type I diabetes mellitus. Neuro Endocrinol Lett 2009, 30: 491–495.
14. Ruttanaumpawan P, Gilman MP, Usui K, Floras JS, Bradley TD. Sustained effect of continuous positive airway pressure on baroreflex sensitivity in congestive heart failure patients with obstructive sleep apnea. J Hypertens 2008, 26: 1163–1168.
15. Zhang D, Liu J, Zheng H, Tu H, Muelleman RL, Li YL. Effect of angiotensin II on voltage-gated sodium currents in aortic baroreceptor neurons and arterial baroreflex sensitivity in heart failure rats. J Hypertens 2015, 33: 1401–1410.
16. Fukuda K, Kanazawa H, Aizawa Y, Ardell JL, Shivkumar K. Cardiac innervation and sudden cardiac death. Circ Res 2015, 116: 2005–2019.
17. Shen MJ, Zipes DP. Role of the autonomic nervous system in modulating cardiac arrhythmias. Circ Res 2014, 114: 1004–1021.
18. Alnima T, Kroon AA, de Leeuw PW. Baroreflex activation therapy for patients with drug-resistant hypertension. Expert Rev Cardiovasc Ther 2014, 12: 955–962.
19. Chen HS, Hwu CM, Kuo BI, Chiang SC, Kwok CF, Lee SH, *et al.* Abnormal cardiovascular reflex tests are predictors of mortality in Type 2 diabetes mellitus. Diabet Med 2001, 18: 268–273.
20. Gronda E, Vanoli E. Autonomic modulation with baroreflex activation therapy in heart failure. Curr Heart Fail Rep 2016, 13: 273–280.
21. Sanya EO, Brown CM, Dutsch M, Zikeli U, Neundorfer B, Hilz MJ. Impaired cardiovagal and vasomotor responses to baroreceptor stimulation in type II diabetes mellitus. Eur J Clin Invest 2003, 33: 582–588.
22. Wallbach M, Lehnig LY, Schroer C, Luders S, Bohning E, Muller GA, *et al.* Effects of baroreflex activation therapy on ambulatory blood pressure in patients with resistant hypertension. Hypertension 2016, 67: 701–709.
23. Tu H, Zhang L, Tran TP, Muelleman RL, Li YL. Reduced expression and activation of voltage-gated sodium channels contributes to blunted baroreflex sensitivity in heart failure rats. J Neurosci Res 2010, 88: 3337–3349.
24. Madias JE. Baroreceptor dysfunction, diabetes mellitus, and takotsubo syndrome: An intricate triangle needing exploration. Int J Cardiol 2015, 184: 517–518.
25. Rowaiye OO, Jankowska EA, Ponikowska B. Baroreceptor sensitivity and diabetes mellitus. Cardiol J 2013, 20: 453–463.
26. Bechir M, Enseleit F, Chenevard R, Muntwyler J, Luscher TF, Noll G. Folic Acid improves baroreceptor sensitivity in hypertension. J Cardiovasc Pharmacol 2005, 45: 44–48.
27. Sforza E, Martin MS, Barthelemy JC, Roche F. Is there an association between altered baroreceptor sensitivity and obstructive sleep apnoea in the healthy elderly? ERJ Open Res 2016, 2:pii: 00072–2016.
28. Shimoura CG, Lincevicius GS, Nishi EE, Girardi AC, Simon KA, Bergamaschi CT, *et al.* Increased dietary salt changes baroreceptor sensitivity and intrarenal renin-angiotensin system in goldblatt hypertension. Am J Hypertens 2017, 30: 28–36.
29. de Leeuw PW, Bisognano JD, Bakris GL, Nadim MK, Haller H, Kroon AA. Sustained reduction of blood pressure with baroreceptor activation therapy: results of the 6-year open follow-up. Hypertension 2017, 69: 836–843.
30. Weaver FA, Abraham WT, Little WC, Butter C, Ducharme A, Halbach M, *et al.* Surgical experience and long-term results of baroreflex activation therapy for heart failure with reduced ejection fraction. Semin Thorac Cardiovasc Surg 2016, 28: 320–328.
31. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. J Clin Neurophysiol 2001, 18: 415–418.
32. Oparil S, Schmieder RE. New approaches in the treatment of hypertension. Circ Res 2015, 116: 1074–1095.
33. Ducreux C, Reynaud JC, Puizillout JJ. Spike conduction properties of T-shaped C neurons in the rabbit nodose ganglion. Pflugers Arch 1993, 424: 238–244.
34. Kalia M, Mesulam MM. Brain stem projections of sensory and motor components of the vagus complex in the cat: I. The cervical vagus and nodose ganglion. J Comp Neurol 1980, 193: 435–465.
35. Bock P, Gorgas K. Fine structure of baroreceptor terminals in the carotid sinus of guinea pigs and mice. Cell Tissue Res 1976, 170: 95–112.
36. Abdel-Magied EM. Ultrastructure of carotid baroreceptors in the goat. Tissue Cell 1992, 24: 681–687.
37. Taha AA, Abdel-Magied EM, King AS. Ultrastructure of aortic and pulmonary baroreceptors in the domestic fowl. J Anat 1983, 137: 197–207.
38. Abdel-Magied EM, Taha AA, King AS. An ultrastructural investigation of a baroreceptor zone in the common carotid artery of the domestic fowl. J Anat 1982, 135: 463–475.
39. Kimani JK. Electron microscopic structure and innervation of the carotid baroreceptor region in the rock hyrax (Procavia capensis). J Morphol 1992, 212: 201–211.
40. Shin HS, Hulbert WC, Biggs DF. Observations on the fine structure of the baroreceptors and adrenergic innervation of the guinea-pig carotid sinus. J Morphol 1987, 194: 65–74.
41. Krauhs JM. Structure of rat aortic baroreceptors and their relationship to connective tissue. J Neurocytol 1979, 8: 401–414.
42. Aumonier FJ. Histological observations on the distribution of baroreceptors in the carotid and aortic regions of the rabbit, cat and dog. Acta Anat (Basel) 1972, 82: 1–16.
43. Bewick GS. Synaptic-like vesicles and candidate transduction channels in mechanosensory terminals. J Anat 2015, 227: 194–213.
44. Yamasaki M, Shimizu T, Miyake M, Miyamoto Y, Katsuda S, Ishi H, *et al.* Effects of space flight on the histological characteristics of the aortic depressor nerve in the adult rat: electron microscopic analysis. Biol Sci Space 2004, 18: 45–51.
45. Seagard JL, Hopp FA, Drummond HA, Van Wynsberghe DM. Selective contribution of two types of carotid sinus baroreceptors to the control of blood pressure. Circ Res 1993, 72: 1011–1022.
46. Thoren P, Munch PA, Brown AM. Mechanisms for activation of aortic baroreceptor C-fibres in rabbits and rats. Acta Physiol Scand 1999, 166: 167–174.
47. Czachurski J, Lackner KJ, Ockert D, Seller H. Localization of neurones with baroreceptor input in the medial solitary nucleus by means of intracellular application of horseradish peroxidase in the cat. Neurosci Lett 1982, 28: 133–137.
48. Thrasher TN. Unloading arterial baroreceptors causes neurogenic hypertension. Am J Physiol Regul Integr Comp Physiol 2002, 282: R1044–R1053.
49. Chapleau MW, Lu Y, Abboud FM. Mechanosensitive ion channels in blood pressure-sensing baroreceptor neurons. Curr Top Membr 2007, 59: 541–567.
50. Brown AM. Receptors under pressure. An update on baroreceptors. Circ Res 1980, 46: 1–10.
51. James JE, Daly MB. Comparison of the reflex vasomotor responses to separate and combined stimulation of the carotid sinus and aortic arch baroreceptors by pulsatile and non-pulsatile pressures in the dog. J Physiol 1970, 209: 257–293.

52. Dobrin PB, Canfield TR. Elastase, collagenase, and the biaxial elastic properties of dog carotid artery. Am J Physiol 1984, 247: H124–H131.
53. Andresen MC, Yang M. Arterial baroreceptor resetting: contributions of chronic and acute processes. Clin Exp Pharmacol Physiol Suppl 1989, 15: 19–30.
54. Angell James JE. The effects of altering mean pressure, pulse pressure and pulse frequency on the impulse activity in baroreceptor fibres from the aortic arch and right subclavian artery in the rabbit. J Physiol 1971, 214: 65–88.
55. Angell James JE, Daly MB. Effects of graded pulsatile pressure on the reflex vasomotor responses elicited by changes of mean pressure in the perfused carotid sinus-aortic arch regions of the dog. J Physiol 1971, 214: 51–64.
56. Feng B, Li BY, Nauman EA, Schild JH. Theoretical and electrophysiological evidence for axial loading about aortic baroreceptor nerve terminals in rats. Am J Physiol Heart Circ Physiol 2007, 293: H3659–H3672.
57. Kimani JK. Elastin and mechanoreceptor mechanisms with special reference to the mammalian carotid sinus. Ciba Found Symp 1995, 192: 215–230.
58. Rees PM. Observations on the fine structure and distribution of presumptive baroreceptor nerves at the carotid sinus. J Comp Neurol 1967, 131: 517–548.
59. Bagshaw RJ, Fischer GM. Morphology of the carotid sinus in the dog. J Appl Physiol 1971, 31: 198–202.
60. Kimani JK, Mungai JM. Observations on the structure and innervation of the presumptive carotid sinus area in the giraffe (Giraffa camelopardalis). Acta Anat (Basel) 1983, 15: 117–133.
61. Coulson WF, Weissman N, Carnes WH. Cardiovascular studies on copper–deficient swine. VII. Mechanical properties of aortic and dermal collagen. Lab Invest 1965, 14: 303–309.
62. Bronk DW, Stella G. Afferent impulses in the carotid sinus nerve. J Cell Comp Physiol 1932, 1: 113–130.
63. Thoren P, Jones JV. Characteristics of aortic baroreceptor C-fibres in the rabbit. Acta Physiol Scand 1977, 99: 448–456.
64. Yao T, Thoren P. Characteristics of brachiocephalic and carotid sinus baroreceptors with non-medullated afferents in rabbit. Acta Physiol Scand 1983, 117: 1–8.
65. Coleridge HM, Coleridge JC. Cardiovascular afferents involved in regulation of peripheral vessels. Annu Rev Physiol 1980, 42: 413–427.
66. Aars H. Relationship between aortic diameter and aortic baroreceptor activity in normal and hypertensive rabbits. Acta Physiol Scand 1969, 75: 406–414.
67. Angell–James JE, Lumley JS. The effects of carotid endarterectomy on the mechanical properties of the carotid sinus and carotid sinus nerve activity in atherosclerotic patients. Br J Surg 1974, 61: 805–10.
68. Chesterton LJ, Sigrist MK, Bennett T, Taal MW, McIntyre CW. Reduced baroreflex sensitivity is associated with increased vascular calcification and arterial stiffness. Nephrol Dial Transplant 2005, 20: 1140–1147.
69. Jensen-Urstad K, Reichard P, Jensen-Urstad M. Decreased heart rate variability in patients with type 1 diabetes mellitus is related to arterial wall stiffness. J Intern Med 1999, 245: 57–61.
70. Lage SG, Polak JF, O'Leary DH, Creager MA. Relationship of arterial compliance to baroreflex function in hypertensive patients. Am J Physiol 1993, 265: H232–H237.
71. Okada Y, Galbreath MM, Shibata S, Jarvis SS, VanGundy TB, Meier RL, *et al.* Relationship between sympathetic baroreflex sensitivity and arterial stiffness in elderly men and women. Hypertension 2012, 59: 98–104.
72. Tomiyama H, Matsumoto C, Kimura K, Odaira M, Shiina K, Yamashina A. Pathophysiological contribution of vascular function to baroreflex regulation in hypertension. Circ J 2014, 78: 1414–1419.
73. Andresen MC, Kuraoka S, Brown AM. Baroreceptor function and changes in strain sensitivity in normotensive and spontaneously hypertensive rats. Circ Res 1980, 47: 821–828.
74. Andresen MC. Short- and long-term determinants of baroreceptor function in aged normotensive and spontaneously hypertensive rats. Circ Res 1984, 54: 750–759.
75. Prenner SB, Chirinos JA. Arterial stiffness in diabetes mellitus. Atherosclerosis 2015, 238: 370–379.
76. de Oliveira AR, Santos PCJL, Musso MM, de Sa CR, Krieger JE, Mill JG, *et al.* Impact of diabetes mellitus on arterial stiffness in a representative sample of an urban Brazilian population. Diabetol Metab Syndr 2013, 5: 45.
77. Yeboah K, Antwi DA, Gyan B. Arterial stiffness in nonhypertensive type 2 diabetes patients in ghana. Int J Endocrinol 2016, 2016: 6107572.
78. Chow B, Rabkin SW. The relationship between arterial stiffness and heart failure with preserved ejection fraction: a systemic meta-analysis. Heart Fail Rev 2015, 20: 291–303.
79. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial dysfunction, arterial stiffness, and heart failure. J Am Coll Cardiol 2012, 60: 1455–1469.
80. Pandey A, Khan H, Newman AB, Lakatta EG, Forman DE, Butler J, *et al.* Arterial stiffness and risk of overall heart failure, heart failure with preserved ejection fraction, and heart failure with reduced ejection fraction: the health ABC study (Health, aging, and body composition). Hypertension 2017, 69: 267–274.
81. Liu JL, Irvine S, Reid IA, Patel KP, Zucker IH. Chronic exercise reduces sympathetic nerve activity in rabbits with pacing–induced heart failure: A role for angiotensin II. Circulation 2000, 102: 1854–1862.
82. Sechi LA, Griffin CA, Schambelan M. The cardiac renin–angiotensin system in STZ–induced diabetes. Diabetes 1994, 43: 1180–1184.
83. Catt KJ, Cran E, Zimmet PZ, Best JB, Cain MD, Coghlan JP. Angiotensin II blood–levels in human hypertension. Lancet 1971, 297: 459–464.
84. Huskova Z, Vanourkova Z, Erbanova M, Thumova M, Opocensky M, Mullins JJ, *et al.* Inappropriately high circulating and intrarenal angiotensin II levels during dietary salt loading exacerbate hypertension in Cyp1a1-Ren-2 transgenic rats. J Hypertens 2010, 28: 495–509.
85. Sowers JR. Hypertension, angiotensin II, and oxidative stress. N Engl J Med 2002, 346: 1999–2001.
86. van de Wal RM, Plokker HW, Lok DJ, Boomsma F, van der Horst FA, Van Veldhuisen DJ, *et al.* Determinants of increased angiotensin II levels in severe chronic heart failure patients despite ACE inhibition. Int J Cardiol 2006, 106: 367–372.
87. Cardin S, Li D, Thorin-Trescases N, Leung TK, Thorin E, Nattel S. Evolution of the atrial fibrillation substrate in experimental congestive heart failure: angiotensin-dependent and -independent pathways. Cardiovasc Res 2003, 60: 315–325.
88. Roig E, Perez-Villa F, Morales M, Jimenez W, Orus J, Heras M, *et al.* Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. Eur Heart J 2000, 21: 53–57.
89. Frustaci A, Kajstura J, Chimenti C, Jakoniuk I, Leri A, Maseri A, *et al.* Myocardial cell death in human diabetes. Circ Res 2000, 87: 1123–1132.
90. Shimoni Y, Liu XF. Gender differences in ANG II levels and action on multiple $K^+$ current modulation pathways in diabetic rats. Am J Physiol Heart Circ Physiol 2004, 287: H311–H319.
91. Prasad AM, Morgan DA, Nuno DW, Ketsawatsomkron P, Bair TB, Venema AN, *et al.* Calcium/calmodulin–dependent kinase

II inhibition in smooth muscle reduces angiotensin II–induced hypertension by controlling aortic remodeling and baroreceptor function. J Am Heart Assoc 2015, 4: e001949.
92. Chapleau MW, Hajduczok G, Sharma RV, Wachtel RE, Cunningham JT, Sullivan MJ, *et al.* Mechanisms of baroreceptor activation. Clin Exp Hypertens 1995, 17: 1–13.
93. Cunningham JT, Wachtel RE, Abboud FM. Mechanosensitive currents in putative aortic baroreceptor neurons *in vitro*. J Neurophysiol 1995, 73: 2094–2098.
94. Hajduczok G, Chapleau MW, Ferlic RJ, Mao HZ, Abboud FM. Gadolinium inhibits mechanoelectrical transduction in rabbit carotid baroreceptors. Implication of stretch-activated channels. J Clin Invest 1994, 94: 2392–2396.
95. Kraske S, Cunningham JT, Hajduczok G, Chapleau MW, Abboud FM, Wachtel RE. Mechanosensitive ion channels in putative aortic baroreceptor neurons. Am J Physiol 1998, 275: H1497–H1501.
96. Sullivan MJ, Sharma RV, Wachtel RE, Chapleau MW, Waite LJ, Bhalla RC, *et al.* Non-voltage-gated $Ca^{2+}$ influx through mechanosensitive ion channels in aortic baroreceptor neurons. Circ Res 1997, 80: 861–867.
97. Chapleau MW, Li Z, Meyrelles SS, Ma X, Abboud FM. Mechanisms determining sensitivity of baroreceptor afferents in health and disease. Ann N Y Acad Sci 2001, 940: 1–19.
98. do Carmo JM, Huber DA, Castania JA, Fazan VP, Fazan R, Jr., Salgado HC. Aortic depressor nerve function examined in diabetic rats by means of two different approaches. J Neurosci Methods 2007, 161: 17–22.
99. Doan TN, Stephans K, Ramirez AN, Glazebrook PA, Andresen MC, Kunze DL. Differential distribution and function of hyperpolarization-activated channels in sensory neurons and mechanosensitive fibers. J Neurosci 2004, 24: 3335–3343.
100. Fazan R, Jr., Ballejo G, Salgado MC, Moraes MF, Salgado HC. Heart rate variability and baroreceptor function in chronic diabetic rats. Hypertension 1997, 30: 632–635.
101. McDowell TS, Hajduczok G, Abboud FM, Chapleau MW. Baroreflex dysfunction in diabetes mellitus. II. Site of baroreflex impairment in diabetic rabbits. Am J Physiol, 266: H244–H249.
102. Reynolds PJ, Yang M, Andresen MC. Contribution of potassium channels to the discharge properties of rat aortic baroreceptor sensory endings. Brain Res 1994, 665: 115–122.
103. Reynolds PJ, Fan W, Andresen MC. Aortic baroreceptor function in long term streptozotocin diabetic rats. Soc Neurosci 1999, 16: 221.
104. Xiao L, Wu YM, Wang R, Liu YX, Wang FW, He RR. Hydrogen sulfide facilitates carotid sinus baroreceptor activity in anesthetized male rats. Chin Med J (Engl) 2007, 120: 1343–1347.
105. Zhang H, Liu YX, Wu YM, Wang ZM, He RR. Capsaicin facilitates carotid sinus baroreceptor activity in anesthetized rats. Acta Pharmacol Sin 2004, 25: 1439–1443.
106. Yang XC, Sachs F. Block of stretch-activated ion channels in Xenopus oocytes by gadolinium and calcium ions. Science 1989, 243: 1068–1071.
107. Li YL, Zhang D, Tu H, Muelleman RL. Altered ENaC is associated with aortic baroreceptor dysfunction in chronic heart failure. Am J Hypertens 2016, 29: 582–589.
108. Simon A, Shenton F, Hunter I, Banks RW, Bewick GS. Amiloride-sensitive channels are a major contributor to mechanotransduction in mammalian muscle spindles. J Physiol 2010, 588: 171–185.
109. Du S, Araki I, Mikami Y, Zakoji H, Beppu M, Yoshiyama M, *et al.* Amiloride-sensitive ion channels in urinary bladder epithelium involved in mechanosensory transduction by modulating stretch-evoked adenosine triphosphate release. Urology 2007, 69: 590–595.
110. Drummond HA, Gebremedhin D, Harder DR. Degenerin/epithelial $Na^+$ channel proteins: components of a vascular mechanosensor. Hypertension 2004, 44: 643–648.
111. Chen CC, Wong CW. Neurosensory mechanotransduction through acid-sensing ion channels. J Cell Mol Med 2013, 17: 337–349.
112. Sharif–Naeini R, Dedman A, Folgering JH, Duprat F, Patel A, Nilius B, *et al.* TRP channels and mechanosensory transduction: insights into the arterial myogenic response. Pflugers Arch 2008, 456: 529–540.
113. Nilius B, Honore E. Sensing pressure with ion channels. Trends Neurosci 2012, 35: 477–486.
114. Lembrechts R, Pintelon I, Schnorbusch K, Timmermans JP, Adriaensen D, Brouns I. Expression of mechanogated two-pore domain potassium channels in mouse lungs: special reference to mechanosensory airway receptors. Histochem Cell Biol 2011, 136: 371–385.
115. Xu XZ. Demystifying Mechanosensitive Piezo ion channels. Neurosci Bull 2016, 32: 307–309.
116. Xiao R, Xu XZ. Mechanosensitive channels: in touch with Piezo. Curr Biol 2010, 20: R936–R938.
117. Ben-Shahar Y. Sensory functions for degenerin/epithelial sodium channels (DEG/ENaC). Adv Genet 2011, 76: 1–26.
118. Corey DP, Garcia-Anoveros J. Mechanosensation and the DEG/ENaC ion channels. Science 1996, 273: 323–324.
119. Horisberger JD. Amiloride-sensitive Na channels. Curr Opin Cell Biol 1998, 10: 443–449.
120. Kellenberger S, Schild L. Epithelial sodium channel/degenerin family of ion channels: a variety of functions for a shared structure. Physiol Rev 2002, 82: 735–767.
121. Hong K, Driscoll M. A transmembrane domain of the putative channel subunit MEC-4 influences mechanotransduction and neurodegeneration in C. elegans. Nature 1994, 367: 470–473.
122. Huang M, Chalfie M. Gene interactions affecting mechanosensory transduction in *Caenorhabditis elegans*. Nature 1994, 367: 467–70.
123. O'Hagan R, Chalfie M, Goodman MB. The MEC-4 DEG/ENaC channel of *Caenorhabditis elegans* touch receptor neurons transduces mechanical signals. Nat Neurosci 2005, 8: 43–50.
124. Amin MS, Wang HW, Reza E, Whitman SC, Tuana BS, Leenen FH. Distribution of epithelial sodium channels and mineralocorticoid receptors in cardiovascular regulatory centers in rat brain. Am J Physiol Regul Integr Comp Physiol 2005, 289: R1787–R1797.
125. Drummond HA, Welsh MJ, Abboud FM. ENaC subunits are molecular components of the arterial baroreceptor complex. Ann N Y Acad Sci 2001, 940: 42–47.
126. Fronius M, Clauss WG. Mechano-sensitivity of ENaC: may the (shear) force be with you. Pflugers Arch 2008, 455: 775–785.
127. Ito K, Hirooka Y, Sunagawa K. Cardiac sympathetic afferent stimulation induces salt-sensitive sympathoexcitation through hypothalamic epithelial $Na^+$ channel activation. Am J Physiol Heart Circ Physiol 2015, 308: H530–H539.
128. Krueger B, Schlotzer-Schrehardt U, Haerteis S, Zenkel M, Chankiewitz VE, Amann KU, *et al.* Four subunits (alpha-betagammadelta) of the epithelial sodium channel (ENaC) are expressed in the human eye in various locations. Invest Ophthalmol Vis Sci 2012, 53: 596–604.
129. Loffing J, Schild L. Functional domains of the epithelial sodium channel. J Am Soc Nephrol 2005, 16: 3175–3181.
130. Hanukoglu I. ASIC and ENaC type sodium channels: conformational states and the structures of the ion selectivity filters. FEBS J 2017, 284: 525–545.
131. Hanukoglu I, Hanukoglu A. Epithelial sodium channel (ENaC) family: Phylogeny, structure-function, tissue distribution, and associated inherited diseases. Gene 2016, 579: 95–132.

132. Drummond HA, Jernigan NL, Grifoni SC. Sensing tension: epithelial sodium channel/acid-sensing ion channel proteins in cardiovascular homeostasis. Hypertension 2008, 51: 1265–1271.
133. Drummond HA, Price MP, Welsh MJ, Abboud FM. A molecular component of the arterial baroreceptor mechanotransducer. Neuron 1998, 21: 1435–1441.
134. Snitsarev V, Whiteis CA, Abboud FM, Chapleau MW. Mechanosensory transduction of vagal and baroreceptor afferents revealed by study of isolated nodose neurons in culture. Auton Neurosci 2002, 98: 59–63.
135. Page AJ, Brierley SM, Martin CM, Price MP, Symonds E, Butler R, *et al.* Different contributions of ASIC channels 1a, 2, and 3 in gastrointestinal mechanosensory function. Gut 2005, 54: 1408–1415.
136. Price MP, McIlwrath SL, Xie J, Cheng C, Qiao J, Tarr DE, *et al.* The DRASIC cation channel contributes to the detection of cutaneous touch and acid stimuli in mice. Neuron 2001, 32: 1071–1083.
137. Bielefeldt K, Davis BM. Differential effects of ASIC3 and TRPV1 deletion on gastroesophageal sensation in mice. Am J Physiol Gastrointest Liver Physiol 2008, 294: G130–G138.
138. Drew LJ, Rohrer DK, Price MP, Blaver KE, Cockayne DA, Cesare P, *et al.* Acid-sensing ion channels ASIC2 and ASIC3 do not contribute to mechanically activated currents in mammalian sensory neurones. J Physiol 2004, 556: 691–710.
139. Jones RC, III, Xu L, Gebhart GF. The mechanosensitivity of mouse colon afferent fibers and their sensitization by inflammatory mediators require transient receptor potential vanilloid 1 and acid-sensing ion channel 3. J Neurosci 2005, 25: 10981–10989.
140. Kang S, Jang JH, Price MP, Gautam M, Benson CJ, Gong H, *et al.* Simultaneous disruption of mouse ASIC1a, ASIC2 and ASIC3 genes enhances cutaneous mechanosensitivity. PLoS One 2012, 7: e35225.
141. Lin SH, Cheng YR, Banks RW, Min MY, Bewick GS, Chen CC. Evidence for the involvement of ASIC3 in sensory mechanotransduction in proprioceptors. Nat Commun 2016, 7: 11460.
142. Page AJ, Brierley SM, Martin CM, Martinez-Salgado C, Wemmie JA, Brennan TJ, *et al.* The ion channel ASIC1 contributes to visceral but not cutaneous mechanoreceptor function. Gastroenterology 2004, 127: 1739–1747.
143. Price MP, Lewin GR, McIlwrath SL, Cheng C, Xie J, Heppenstall PA, *et al.* The mammalian sodium channel BNC1 is required for normal touch sensation. Nature 2000, 407: 1007–1011.
144. Lu Y, Ma X, Sabharwal R, Snitsarev V, Morgan D, Rahmouni K, *et al.* The ion channel ASIC2 is required for baroreceptor and autonomic control of the circulation. Neuron 2009, 64: 885–897.
145. Clapham DE. TRP channels as cellular sensors. Nature 2003, 426: 517–524.
146. Desai BN, Clapham DE. TRP channels and mice deficient in TRP channels. Pflugers Arch 2005, 451: 11–18.
147. Liedtke W, Kim C. Functionality of the TRPV subfamily of TRP ion channels: add mechano–TRP and osmo–TRP to the lexicon. Cell Mol Life Sci 2005, 62: 2985–3001.
148. Nilius B, Owsianik G, Voets T, Peters JA. Transient receptor potential cation channels in disease. Physiol Rev 2007, 87: 165–217.
149. Nilius B, Owsianik G. The transient receptor potential family of ion channels. Genome Biol 2011, 12: 218–212.
150. Pedersen SF, Nilius B. Transient receptor potential channels in mechanosensing and cell volume regulation. Methods Enzymol 2007, 428: 183–207.
151. Li H. TRP channel classification. Adv Exp Med Biol 2017, 976: 1–8.
152. Lau OC, Shen B, Wong CO, Tjong YW, Lo CY, Wang HC, *et al.* TRPC5 channels participate in pressure-sensing in aortic baroreceptors. Nat Commun 2016, 7: 11947.
153. Sun H, Li DP, Chen SR, Hittelman WN, Pan HL. Sensing of blood pressure increase by transient receptor potential vanilloid 1 receptors on baroreceptors. J Pharmacol Exp Ther 2009, 331: 851–859.
154. Glazebrook PA, Schilling WP, Kunze DL. TRPC channels as signal transducers. Pflugers Arch 2005, 451: 125–130.
155. Hodgkin AL, Huxley AF. A quantitative description of membrane current and its application to conduction and excitation in nerve. J Physiol 1952, 117: 500–544.
156. Zakon HH. Adaptive evolution of voltage-gated sodium channels: the first 800 million years. Proc Natl Acad Sci U S A 2012, 109: 10619–10625.
157. Kole MH, Ilschner SU, Kampa BM, Williams SR, Ruben PC, Stuart GJ. Action potential generation requires a high sodium channel density in the axon initial segment. Nat Neurosci 2008, 11: 178–186.
158. Doan TN, Kunze DL. Contribution of the hyperpolarization-activated current to the resting membrane potential of rat nodose sensory neurons. J Physiol 1999, 514: 125–138.
159. Li BY, Glazebrook P, Kunze DL, Schild JH. KCa1.1 channel contributes to cell excitability in unmyelinated but not myelinated rat vagal afferents. Am J Physiol Cell Physiol 2011, 300: C1393–C1403.
160. Li DP, Chen SR. Nitric oxide stimulates glutamatergic synaptic inputs to baroreceptor neurons through potentiation of Cav2.2-mediated Ca(2+) currents. Neurosci Lett 2014, 567: 57–62.
161. Li Z, Lee HC, Bielefeldt K, Chapleau MW, Abboud FM. The prostacyclin analogue carbacyclin inhibits Ca(2+)-activated K+ current in aortic baroreceptor neurones of rats. J Physiol 1997, 501: 275–87.
162. Li Z, Chapleau MW, Bates JN, Bielefeldt K, Lee HC, Abboud FM. Nitric oxide as an autocrine regulator of sodium currents in baroreceptor neurons. Neuron 1998, 20: 1039–49.
163. Matsumoto S, Takahashi M, Iwasaki K, Ide R, Saiki C, Takeda M. Direct inhibition of the transient voltage-gated K(+) currents mediates the excitability of tetrodotoxin-resistant neonatal rat nodose ganglion neurons after ouabain application. Eur J Pharmacol 2011, 659: 130–138.
164. Mendelowitz D, Kunze DL. Characterization of calcium currents in aortic baroreceptor neurons. J Neurophysiol 1992, 68: 509–517.
165. Schild JH, Kunze DL. Differential distribution of voltage-gated channels in myelinated and unmyelinated baroreceptor afferents. Auton Neurosci 2012, 172: 4–12.
166. Tatalovic M, Glazebrook PA, Kunze DL. Expression of the P/Q (Cav2.1) calcium channel in nodose sensory neurons and arterial baroreceptors. Neurosci Lett 2012, 520: 38–42.
167. Wladyka CL, Feng B, Glazebrook PA, Schild JH, Kunze DL. The KCNQ/M-current modulates arterial baroreceptor function at the sensory terminal in rats. J Physiol 2008, 586: 795–802.
168. Zhang L, Tu H, Li YL. Angiotensin II enhances hyperpolarization-activated currents in rat aortic baroreceptor neurons: involvement of superoxide. Am J Physiol Cell Physiol 2010, 298: C98–C106.
169. Li YL, Zheng H. Angiotensin II-NADPH oxidase-derived superoxide mediates diabetes-attenuated cell excitability of aortic baroreceptor neurons. Am J Physiol Cell Physiol 2011, 301: C1368–C1377.
170. Liu J, Zhang L, Tu H, Li YL. Angiotensin II induces protein overexpression of hyperpolarization-activated cyclic nucleotide-gated channels in primary cultured nodose neurons. Neurosci Lett 2012, 515: 168–173.

171. Tu H, Zhang L, Tran TP, Muelleman RL, Li YL. Diabetes alters protein expression of hyperpolarization-activated cyclic nucleotide-gated channel subunits in rat nodose ganglion cells. Neuroscience 2010, 165: 39–52.
172. Tu H, Liu J, Zhu Z, Zhang L, Pipinos II, Li YL. Mitochondria-derived superoxide and voltage-gated sodium channels in baroreceptor neurons from chronic heart-failure rats. J Neurophysiol 2012, 107: 591–602.
173. Chang W, Berta T, Kim YH, Lee S, Lee SY, Ji RR. Expression and role of voltage–gated sodium channels in human dorsal root ganglion neurons with special focus on Nav1.7, species differences, and regulation by paclitaxel. Neurosci Bull 2018, 34: 4–12.
174. Yu FH, Catterall WA. Overview of the voltage-gated sodium channel family. Genome Biol 2003, 4: 207.
175. Catterall WA, Goldin AL, Waxman SG. International Union of Pharmacology. XLVII. Nomenclature and structure-function relationships of voltage-gated sodium channels. Pharmacol Rev 2005, 57: 397–409.
176. Waxman SG, Dib–Hajj S, Cummins TR, Black JA. Sodium channels and pain. Proc Natl Acad Sci U S A 1999, 96: 7635–7639.
177. Cummins TR, Sheets PL, Waxman SG. The roles of sodium channels in nociception: Implications for mechanisms of pain. Pain 2007, 131: 243–257.
178. Shen W, Gill RM, Zhang JP, Jones BD, Corbly AK, Steinberg MI. Sodium channel enhancer restores baroreflex sensitivity in conscious dogs with heart failure. Am J Physiol Heart Circ Physiol 2005, 288: H1508–H1514.
179. Kang YM, Ma Y, Zheng JP, Elks C, Sriramula S, Yang ZM, *et al.* Brain nuclear factor-kappa B activation contributes to neurohumoral excitation in angiotensin II-induced hypertension. Cardiovasc Res 2009, 82: 503–512.
180. Li L, Xu T, Du Y, Pan D, Wu W, Zhu H, *et al.* Salvianolic acid A attenuates cell apoptosis, oxidative stress, Akt and NF–kappaB activation in angiotensin-II induced murine peritoneal macrophages. Curr Pharm Biotechnol 2016, 17: 283–290.
181. Rius C, Abu-Taha M, Hermenegildo C, Piqueras L, Cerda-Nicolas JM, Issekutz AC, *et al.* Trans- but not cis-resveratrol impairs angiotensin-II-mediated vascular inflammation through inhibition of NF-kappaB activation and peroxisome proliferator-activated receptor-gamma upregulation. J Immunol 2010, 185: 3718–3727.
182. Ziypak T, Halici Z, Alkan E, Akpinar E, Polat B, Adanur S, *et al.* Renoprotective effect of aliskiren on renal ischemia/reperfusion injury in rats: electron microscopy and molecular study. Ren Fail 2015, 37: 343–354.
183. Allen AM, Lewis SJ, Verberne AJ, Mendelsohn FA. Angiotensin receptors and the vagal system. Clin Exp Hypertens A 1988, 10: 1239–1249.
184. Mehta PK, Griendling KK. Angiotensin II cell signaling: physiological and pathological effects in the cardiovascular system. Am J Physiol Cell Physiol 2007, 292: C82–C97.
185. Touyz RM, Berry C. Recent advances in angiotensin II signaling. Braz J Med Biol Res 2002, 35: 1001–1015.
186. McCord JM. Human disease, free radicals, and the oxidant/antioxidant balance. Clin Biochem 1993, 26: 351–357.
187. Cadenas E, Davies KJ. Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med 2000, 29: 222–230.
188. Adam-Vizi V, Chinopoulos C. Bioenergetics and the formation of mitochondrial reactive oxygen species. Trends Pharmacol Sci 2006, 27: 639–645.
189. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell 2005, 120: 483–495.
190. Murphy MP. How mitochondria produce reactive oxygen species. Biochem J 2009, 417: 1–13.
191. Turrens JF. Mitochondrial formation of reactive oxygen species. J Physiol 2003, 552: 335–344.
192. Robinson BH. The role of manganese superoxide dismutase in health and disease. J Inherit Metab Dis 1998, 21: 598–603.
193. Wallace DC. A mitochondrial paradigm for degenerative diseases and ageing. Novartis Found Symp 2001, 235: 247–263.
194. Hoffmann A, Baltimore D. Circuitry of nuclear factor kappaB signaling. Immunol Rev 2006, 210: 171–186.
195. Israel A. The IKK complex, a central regulator of NF-kappaB activation. Cold Spring Harb Perspect Biol 2010, 2: a000158.
196. Hacker H, Karin M. Regulation and function of IKK and IKK-related kinases. Sci STKE 2006, 2006: re13.
197. Kabe Y, Ando K, Hirao S, Yoshida M, Handa H. Redox regulation of NF-kappaB activation: distinct redox regulation between the cytoplasm and the nucleus. Antioxid Redox Signal 2005, 7: 395–403.
198. Karin M, Ben-Neriah Y. Phosphorylation meets ubiquitination: the control of NF–[kappa]B activity. Annu Rev Immunol 2000, 18: 621–663.
199. Case AJ, Li S, Basu U, Tian J, Zimmerman MC. Mitochondrial-localized NADPH oxidase 4 is a source of superoxide in angiotensin II-stimulated neurons. Am J Physiol Heart Circ Physiol 2013, 305: H19–H28.
200. Yin JX, Yang RF, Li S, Renshaw AO, Li YL, Schultz HD, *et al.* Mitochondria-produced superoxide mediates angiotensin II-induced inhibition of neuronal potassium current. Am J Physiol Cell Physiol 2010, 298: C857–C865.
201. Shang LL, Sanyal S, Pfahnl AE, Jiao Z, Allen J, Liu H, *et al.* NF-kappaB-dependent transcriptional regulation of the cardiac scn5a sodium channel by angiotensin II. Am J Physiol Cell Physiol 2008, 294: C372–C379.
202. Brown HF, DiFrancesco D, Noble SJ. How does adrenaline accelerate the heart? Nature 1979, 280: 235–236.
203. Ishii TM, Takano M, Xie LH, Noma A, Ohmori H. Molecular characterization of the hyperpolarization-activated cation channel in rabbit heart sinoatrial node. J Biol Chem 1999, 274: 12835–12839.
204. Ludwig A, Zong X, Jeglitsch M, Hofmann F, Biel M. A family of hyperpolarization-activated mammalian cation channels. Nature 1998, 393: 587–591.
205. Noma A, Irisawa H. Membrane currents in the rabbit sinoatrial node cell as studied by the double microelectrode method. Pflugers Arch 1976, 364: 45–52.
206. Santoro B, Liu DT, Yao H, Bartsch D, Kandel ER, Siegelbaum SA, *et al.* Identification of a gene encoding a hyperpolarization-activated pacemaker channel of brain. Cell 1998, 93: 717–729.
207. Vaccari T, Moroni A, Rocchi M, Gorza L, Bianchi ME, Beltrame M, *et al.* The human gene coding for HCN2, a pacemaker channel of the heart. Biochim Biophys Acta 1999, 1446: 419–425.
208. DiFrancesco D. Pacemaker mechanisms in cardiac tissue. Annu Rev Physiol 1993, 55: 455–472.
209. Kaupp UB, Seifert R. Molecular diversity of pacemaker ion channels. Annu Rev Physiol 2001, 63: 235–257.
210. Notomi T, Shigemoto R. Immunohistochemical localization of Ih channel subunits, HCN1-4, in the rat brain. J Comp Neurol 2004, 471: 241–276.
211. Pape HC. Queer current and pacemaker: the hyperpolarization-activated cation current in neurons. Annu Rev Physiol 1996, 58: 299–327.
212. Robinson RB, Siegelbaum SA. Hyperpolarization-activated cation currents: from molecules to physiological function. Annu Rev Physiol 2003, 65: 453–480.

213. Widdop RE, Krstew E, Jarrott B. Electrophysiological responses of angiotensin peptides on the rat isolated nodose ganglion. Clin Exp Hypertens A 1992, 14: 597–613.
214. Griendling KK, Sorescu D, Ushio-Fukai M. NAD(P)H oxidase: role in cardiovascular biology and disease. Circ Res 2000, 86: 494–501.
215. Cifuentes ME, Rey FE, Carretero OA, Pagano PJ. Upregulation of p67(phox) and gp91(phox) in aortas from angiotensin II-infused mice. Am J Physiol Heart Circ Physiol 2000, 279: H2234–H2240.
216. Franco MC, Akamine EH, Di Marco GS, Casarini DE, Fortes ZB, Tostes RC, *et al.* NADPH oxidase and enhanced superoxide generation in intrauterine undernourished rats: involvement of the renin–angiotensin system. Cardiovasc Res 2003, 59: 767–775.
217. Gao L, Wang W, Li YL, Schultz HD, Liu D, Cornish KG, *et al.* Superoxide mediates sympathoexcitation in heart failure: roles of angiotensin II and NAD(P)H oxidase. Circ Res 2004, 95: 937–944.
218. Li YL, Gao L, Zucker IH, Schultz HD. NADPH oxidase-derived superoxide anion mediates angiotensin II-enhanced carotid body chemoreceptor sensitivity in heart failure rabbits. Cardiovasc Res 2007, 75: 546–554.
219. Schieffer B, Luchtefeld M, Braun S, Hilfiker A, Hilfiker-Kleiner D, Drexler H. Role of NAD(P)H oxidase in angiotensin II-induced JAK/STAT signaling and cytokine induction. Circ Res 2000, 87: 1195–1201.