Sensing Tension
Epithelial Sodium Channel/Acid-Sensing Ion Channel Proteins in Cardiovascular Homeostasis
Heather A. Drummond, Nikki L. Jernigan, Samira C. Grifoni

The epithelial sodium (Na\(^+\)) channel (ENaC) plays a critical role in blood pressure regulation by controlling renal salt and water reabsorption. Channel overactivity can lead to severe hypertension and underactivity to salt wasting and hypotension.\(^1\) In addition to their role in salt/water homeostasis, recent studies suggest that ENaC proteins, and their relatives, the acid-sensing ion channel (ASIC) proteins, may play more ubiquitous roles in cardiovascular regulation than considered previously. Recent evidence suggests that ENaC/ASIC proteins may act as mechanosensors and chemosensors in the cardiovascular system. ENaC/ASIC proteins are expressed in mechanosensing and chemosensing tissues, such as vascular smooth muscle cells (VSMCs), carotid body glomus cells, and sensory neurons innervating arterial baroreceptors, heart, and skeletal muscle. Disruption of the ENaC/ASIC channels alters myogenic constriction, arterial chemoreceptor and baroreceptor responses, and acid-induced responses in heart and skeletal muscle. This brief review summarizes the evidence supporting a role for ENaC and ASIC proteins in diverse systems of cardiovascular mechanosensing and chemosensing. Together, these studies suggest that ENaC/ASIC proteins contribute to cardiovascular homeostasis by mediating neural and local regulatory mechanisms.

The Degenerin/ENaC/ASIC Family
ENaC and ASIC proteins are members of a protein family termed the degenerin (DEG)/ENaC/ASIC family. Members of this family are expressed in a wide range of species (nematode Caenorhabditis elegans, Drosophila, and mammals) and participate in diverse biological functions, including neurodegeneration, acid sensation, taste, learning and memory, proprioception, Na\(^+\)/water transport, and mechanosensation. All of the members of the DEG/ENaC/ASIC family share a highly conserved structure: intracellular N and C termini and 2 membrane-spanning domains separated by a large extracellular domain. Most DEG/ENaC/ASIC proteins form amiloride sensitive, nonvoltage, gated cation channels.\(^1,2\)

C. elegans DEGs
Members were first identified in the nematode, where a chemically induced mutation caused a subset of neurons to swell and lyse. This phenotype led to the first name of the family, Deg, short for degeneration. Subsequently, other C. elegans DEG genes expressed in neurons and muscle have been identified after genetic screens for proteins involved in touch responsiveness and proprioception, responses dependent on mechanotransduction.\(^1,2\) These data provided the initial genetic link between the DEG/ENaC/ASIC channels and mechanotransduction.

Mammalian ENaC and ASIC Proteins
In vertebrates, there are \(\geq 2\) subgroups of DEG/ENaC/ASIC proteins: ENaC and ASIC. Gain-of-function and loss-of-function mutations in ENaC channels are manifested in 2 diseases, Liddle’s disease and pseudohypoaldosteronism type I, respectively. In Liddle’s disease, certain mutations disrupt normal channel degradation, resulting in increased channel density, excessive salt/water retention, and severe hypertension. In pseudohypoaldosteronism type I, underactive channels produce salt wasting and hypotension. At least 5 different ENaC proteins have been identified in mammals (\(\alpha\)ENaC, \(\beta\)ENaC, \(\gamma\)ENaC, \(\delta\)ENaC, and \(\varepsilon\)ENaC). \(\alpha\)ENaC, \(\beta\)ENaC, and \(\gamma\)ENaC proteins form a heteromultimeric channel critical in Na\(^+\) and water transport in the renal, colon, and lung epithelia.\(^1,2\) The \(\delta\)ENaC and \(\varepsilon\)ENaC subunits can substitute for \(\alpha\)ENaC or interact with \(\alpha\beta\gamma\)ENaC channels. Expression of the \(\delta\)ENaC subunit is limited to the brain, pancreas, testes, ovary, and retinal cells.\(^3,4\) Expression of the \(\varepsilon\)ENaC subunit is limited to the brain, skeletal muscle, kidney, and urinary bladder in Xenopus.\(^6\) ENaC channels are constitutively active, nonvoltage gated, and highly sensitive to amiloride (\(\alpha\beta\gamma\)ENaC IC\(_{50}\) \(\leq 100\) nmol/L; \(\alpha\beta\gamma\)ENaC IC\(_{50}\) \(= 1\) \(\mu\)mol/L; \(\delta\beta\gamma\)ENaC IC\(_{50}\) \(= 2.6\) \(\mu\)mol/L) and its lipophylic analog benzamil.\(^1\) Although \(\alpha\)ENaC protein is required to form the fully functional channel characteristic of the epithelial Na\(^+\) channel in renal epithelia, \(\beta\) and \(\gamma\)ENaC can form an Na\(^+\) conducting ion channel in the absence of \(\alpha\)ENaC.\(^7\)

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ASIC and ENaC proteins are closely related. ASIC proteins (ASIC1, ASIC2, ASIC3, and ASIC4) can form homomultimeric and heteromultimeric channels that generally conduct Na$^+$. Although ASIC channels are also sensitive to amiloride, they tend to require higher doses than ENaC (10- to 100-fold). A specific inhibitor for ASIC1a is available (psalmotoxin); however, specific inhibitors for other ASIC channels are not available. A drop in extracellular pH gates most ASIC channels. Until recently, ASICs were only identified in neuronal and neuroepithelial tissue, where they may contribute to acid taste, acid sensation, learning, and mechanosensation; however, recent evidence suggests that ASICs are also expressed in vascular smooth muscle.

Evidence of Mechanosensitivity and Chemosensitivity of ENaC/ASIC Channels in Isolated Systems and Epithelial Tissues

Mechanosensitivity
Early investigations into the mechanosensitivity of ENaC in heterologous and endogenous expression systems demonstrated that αENaC and αβγENaC channels could be activated by the application of negative hydrostatic pressure.\(^9–12\) Contrasting results were found in the *Xenopus* oocyte expression system in response to osmotic induced swelling and shrinking.\(^13–14\) However, using the oocyte expression system, ENaC can be activated by a different mechanical stimulus, shear stress. In the cortical distal tubule, shear stress may be the appropriate stimulus to mechanically gate ENaC channels.\(^15,16\) The reasons underlying the conflicting results in isolated expression systems are unknown; however, they may reflect several factors, including the following: (1) specificity of mechanical gating of αβγENaC to the stimulus (ie, shear stress versus osmotic stretch); (2) presence of inhibitory substances such as ATP;\(^12\) and (3) importance of the appropriate combination of intracellular and extracellular proteins necessary to gate the channel in response to stretch or strain. These findings suggest that, under certain conditions, mechanical forces can gate isolated ENaC channels. Currently, the mechanosensitivity of ASIC channels has not been addressed.

Chemosensitivity
Direct evidence of the chemosensitivity of homomeric and heteromeric ASIC channels is derived from studies in isolated expression systems, where extracellular acidosis (EC$_{50}$ pH range: 3.5 to 7.0) gates the channels, with the different channels having varying pH sensitivities. Although αβγENaC channels are not gated by pH, the presence of the δENaC subunit confers pH sensitivity with and EC$_{50}$ of pH 6.1 for δβγENaC and 6.5 for δαβγENaC channels.\(^1–17\) These findings suggest that ASIC channels, and ENaC channels containing δENaC, can be gated by protons. Because protons are thought to signal chemoreflex responses initiated in carotid chemoreceptors and peripheral chemoreceptors, ENaC/ASIC proteins are considered candidates for these receptors.

Contribution of Neuron and Vascular Smooth Muscle ENaC/ASIC Proteins to Cardiovascular Homeostasis
In addition to their role in salt and water reabsorption, evidence suggests that ENaC/ASIC proteins contribute to cardiovascular homeostasis by functioning as mechanoreceptors in arterial baroreceptor neurons and VSMCs and as acid sensors in arterial chemosensors (carotid body glomus cells), myocardial tissue, and skeletal muscle. In this section, we discuss evidence implicating ENaC/ASIC proteins as mechanosensors and chemosensors in cardiovascular tissue.

If ENaC/ASIC proteins are to be considered as mechanosensors or chemosensors, then ≥2 criteria must be met. First, ENaC/ASIC proteins must be expressed at the site of mechanotransduction or chemoreception. Second, inhibition or disruption of ENaC/ASIC activity should inhibit the mechanosensitive or chemosensitive response. Because ENaC null mice are very ill or die shortly after birth, genetic evidence for ENaC involvement in mechanotransduction is lacking.\(^18–20\) ASIC null mice thrive and have provided evidence for their involvement in mechanoreception and chemoreception. As an alternative to ENaC null mice, selective ENaC inhibitors, such as amiloride and benzamil, have been useful tools in determining ENaC involvement, because αβγENaC can be blocked by as little as 100 nmol/L.\(^1–21\) Thus, low doses of amiloride can discern the importance of ENaC channels from other transporters and ion channels.

Role in Neural Cardiovascular Mechanosensation
ENaC and ASIC molecules are expressed in specific sensory neuron populations in the dorsal root, trigeminal and nodose ganglia, and the afferent nerve terminals innervating certain somatic and visceral receptors.\(^1,2,22–25\) One of these sites includes arterial baroreceptor nerve endings located in the aortic arch and carotid sinus. Arterial baroreceptors discharge in response to pressure-induced vessel wall stretch and play an important role in the beat-to-beat control of the cardiovascular system. Four lines of evidence suggest that ENaC/ASIC channels participate in arterial baroreceptor activation. First, baroreceptor neurons express at least βENaC, γENaC, and ASIC2 molecules.\(^22,26\) Second, ENaC inhibition prevents mechanically activated membrane depolarization and Ca$^{2+}$ transients in baroreceptor neurons.\(^22,27\) Third, ENaC inhibition blocks pressure-induced changes in carotid baroreceptor activity and reflex-induced changes in systemic blood pressure. Fourth, ASIC2 null mice have reduced spontaneous baroreflex sensitivity.\(^28\) Taken together these findings suggest that at least βENaC, γENaC, and ASIC2 are expressed in baroreceptor neurons, where they may mediate mechanically initiated responses in vitro and in vivo. It is unknown whether βENaC, γENaC, and ASIC2 associate to form a homogenous population of heteromorphic channels (ie, all of the channels are composed of βENaC, γENaC, and ASIC2) or if the subunits associate to form multiple heteromorphic channels (ie, channels are composed of βENaC/γENaC, γENaC/ASIC, or βENaC/ASIC channels) or homomorphic channels (ie, βENaC, γENaC, or ASIC only). Although ENaC/ASIC proteins are expressed in nonbaroreceptor neurons in sensory ganglia, it is unknown whether ENaC/ASIC proteins act as mechanoreceptors in...
nonbaroreceptor cardiovascular mechanoreceptors, such as cardiopulmonary receptors.

**Local Control of Vascular Resistance:**

**Pressure-Induced Vasconstriction**

In addition to neural mechanisms, ENaC/ASIC proteins may contribute to cardiovascular homeostasis by participating in local mechanisms regulating vascular resistance. Pressure-induced, or myogenic, constriction is an inherent response of certain vessels that allows resistance arteries to adjust tone in response to luminal pressure; vessels constrict to increases and dilate to decreases in pressure. The response is initiated by vessel wall stretch and is, thus, activated by a mechanical stimulus. The response may play a critical role in preventing the transmission of pressure waves to small, fragile microvessels, particularly in the renal and cerebral circulations, and, thus, may protect against hypertension-induced injury.29,30

The importance of ENaC/ASIC proteins in pressure-induced vasconstriction has been examined in cerebral and renal arteries. VSMCs express βENaC, γENaC, and ASIC2.31–34 In these VSMCs, ENaC/ASIC2 proteins are expressed at or near the cell surface, the predicted site of mechanotransduction of a VSMC stretch into a cellular signaling event (Figure 1A). Pharmacological inhibition of ENaC with amiloride or benzamil inhibits pressure-mediated constriction (at submicromolar and low micromolar concentrations) in the middle cerebral artery, renal interlobar, and renal afferent arterioles.31,32,35,36 In a follow-up study, Jermigan and Drummond32 used gene-specific silencing approaches, small-interfering RNA, and dominant negatives to determine the importance of βENaC and γENaC in pressure-induced constriction (Figure 1B). Both approaches inhibited protein expression and pressure-induced vasoconstriction in isolated renal interlobar segments. Constriction in response to the α-adrenergic receptor phenylephrine was not altered after ENaC inhibition or gene silencing, suggesting that vasoconstriction, per se, was not altered after ENaC inhibition.32,33 Although these findings suggest that certain ENaC proteins may mediate pressure-induced constriction, the role of ASIC proteins has not been thoroughly examined. However, preliminary studies suggest that pressure-induced constriction is absent in cerebral vessels of ASIC2 heterozygous null mice.34 When we consider that ASIC2, βENaC, and γENaC are expressed in similar VSMC populations; ASIC2 biochemically interacts with γENaC in other systems; and the loss of ASIC2, βENaC, and γENaC produces the same phenotype (loss of pressure-induced constriction), the speculation that these proteins form a heteromultimeric channel seems reasonable.22,31–34,37,38

**Lack of Direct Electrophysiological Evidence of ENaC/ASIC Channels in VSMCs**

Direct electrophysiological evidence of ENaC/ASIC channels in VSMCs is not available; however, one report of an epithelial-like Na⁺ current in VSMCs was found.39 Similar to αβγENaC, the channel reported in VSMCs is nonvoltage gated and has a 10 pS conductance and high Na⁺:K⁺ selectivity. Unlike αβγENaC, the channel is insensitive to amiloride (100 μmol/L). Although the amiloride characteristics of this channel are not consistent with the reported amiloride sensitivity of αβγENaC and βγENaC channels in heterologous expression systems, this finding supports the potential presence of an ENaC-like Na⁺ channel in VSMCs. It is not clear why there is so little electrophysiological evidence of ENaC; however, one possibility is that investigators have not looked for them. Another possibility is the channels are electrically silent until gated by mechanical stimuli.40,41

**Can βENaC and γENaC Form a Channel in the Absence of αENaC?**

In VSMCs and sensory neurons, βENaC and γENaC appear to be the predominant ENaC proteins expressed, whereas αENaC is rare. Because αENaC is required to generate the fully functional, constitutively active ENaC channel found typically in epithelial tissue, are βENaC and γENaC capable of forming a channel in the absence of αENaC? Evidence from Bonny et al7 suggest that αENaC is not required for β and γENaC to form a channel. Bonny et al7 demonstrated oocytes expressing βENaC and γENaC generate amiloride...
sensitive currents in the absence of αENaC, when provided a longer incubation period (≈6 days). Channels formed by βENaC and γENaC have a greater selectivity for Na⁺ and conduct less current. In addition, βγENaC channels have a 10-fold higher inhibition constant for amiloride (≈2 μmol/L in βγENaC versus 0.2 μmol/L in αβγENaC). Thus, channels formed by βγENaC are not the same as channels formed by αβγENaC. The finding by Jernigan and Drummond that ≈40% of myogenic constrictor responses are blocked with 1 μmol/L of amiloride is consistent with the amiloride inhibition constant for βγENaC channels.

Compared with αβγENaC channels, trafficking of βγENaC channels to the surface membrane in *Xenopus* oocytes is delayed, which results in protein localization in the intracellular compartment. This may be the basis for the lack of current generated by βγENaC in heterologous expression systems. In freshly dissociated VSMCs, trafficking of β and γENaC does not appear impaired because they are expressed at or near the cell surface (Figure 1). The mechanism(s) mediating membrane localization of βENaC and γENaC in the absence of αENaC is unknown; however, there are a few possible explanations. First, VSMCs may express another protein that associates with and stabilizes βENaC and γENaC. Second, another pore-forming subunit may interact with βENaC and γENaC, such as δENaC or an ASIC protein. Third, αENaC may be expressed in VSMCs, but we are unable to detect it, and the small amount expressed is sufficient to stabilize the channel. Lastly, the presence of proteins within the dense extracellular matrix of blood vessels may help stabilize βγENaC channels that reach the membrane. Regardless of the mechanism, in the absence of detectable levels of αENaC, βENaC and γENaC appear to traffic to the cell surface of VSMCs in vivo and remain there after enzymatic dissociation.

**How Do ENaC/ASIC Proteins Transduce Mechanical Stimuli?**

Although the studies presented in this review demonstrate that ENaC/ASIC proteins play a significant role in the mechanondependent responses, it is not entirely clear how ENaC/ASIC proteins transduce mechanical stimuli. A universal or “all-purpose” mechanotransducer model has been developed in the nematode for related DEG proteins. In this model, the mechanosensor is a large heteromultimeric channel complex consisting of 5 basic components: (1) extracellular matrix proteins, (2) extracellular linking proteins, (3) pore-forming channels, (4) intracellular linking proteins, and (5) cytoskeleton proteins (Figure 2). Nematode members of the DEG/ENaC/ASIC family form the ion-conducting unit of the complex. The application of a mechanical force is transduced through the extracellular matrix to gate the channel. Thus, the interaction between the pore-forming proteins and the extracellular matrix is critical to channel gating. The cytoskeleton may also participate in transduction of the applied force, and, along with other extracellular proteins, may also stabilize the pore at the cell surface. We speculate that a similar model also applies to ENaC/ASIC proteins in mammalian mechanosensors. When the channel is gated open, Na⁺ and possibly Ca²⁺ entry leads to membrane depolarization and subsequent activation of downstream signaling events, leading to smooth muscle cell contraction or neuronal action potential generation.

**Role in Cardiovascular Chemosensation**

In addition to their role in mechanosensing, ENaC/ASIC proteins may contribute to cardiovascular homeostasis via chemosensing mechanisms. A well-established characteristic of ASIC channels is their activation by drops in extracellular pH, which has made them very attractive candidates for chemosensing processes in arterial chemoreceptors and muscle metaboreceptors in skeletal and cardiac tissue.

Several lines of evidence support a potential role for ASIC channels in arterial chemoreceptors. First, carotid body glomus cells express ASIC1 and ASIC3 and, to a lesser extent, ASIC2. Second, carotid body glomus cells have pH-gated currents that resemble ASIC channels and are partially amiloride sensitive. Third, cardiovascular responses to chemoreceptor stimulation with carotid artery occlusion are attenuated in ASIC3 and ASIC1/ASIC3 double-null mice. Together these findings suggest that ASIC proteins may participate in pH sensing in arterial chemoreceptors.

Some investigators have suggested that ASIC proteins may be chemotransducers in muscle tissue that signal ischemic pain. In cardiac tissue, ischemia-induced extracellular acidosis is part of the signaling event leading to the sensation of pain. Activation of cardiac sympathetic afferents leads to a sympathetic inhibitory/vagal stimulatory effect to reduce cardiac work. The first study to address the role of ASIC proteins in...
ischemic pain demonstrated that cardiac sensory neurons have substantial extracellular acid–evoked Na⁺ currents that resemble ASIC currents and are sensitive to amiloride.⁴⁴ Follow-up studies suggest an important role for ASIC3, because ASIC3 is highly sensitive to lactic acid, a mediator of ischemic pain, and acid-gated currents in cardiac sensory neurons are nearly identical to acid gated currents of ASIC3 homomultimers.⁴⁵,⁴⁹ Studies of cardiovascular responses to cardiac ischemia in genetically modified mice are needed to confirm the importance of ASIC proteins in sensing cardiac ischemia.

A similar role for ASIC3, as well as other ASIC proteins, in sensing changes in skeletal muscle pH has been proposed.²⁵,⁴⁶,⁴⁷ Similar to cardiac tissue, fine sensory afferents in skeletal muscle are activated with lactic acid, a byproduct of anaerobic muscle activity. Activation of these skeletal muscle afferents contributes to the cardiovascular and respiratory response to exercise. There are 3 lines of evidence supporting involvement of ASIC channels in this response. First ASIC proteins are localized in populations of small nociceptive neurons innervating skeletal muscle.²⁵,⁵⁰ In particular, ASIC3 is expressed in fine nerve endings innervating skeletal muscle blood arterioles.²⁵ In addition, amiloride inhibits increases in blood pressure and heart rate to muscle contraction and intramuscular injection of lactic acid.⁴⁶,⁴⁷ Although these findings support a role for ASIC proteins as pH sensors in muscle tissue and potential mediators of ischemic pain, involvement of ENaC channels cannot be ruled out, because βENaC can confer pH sensitivity to ENaC channels, and ENaC proteins can interact with ASIC proteins to form channels. Future studies on ASIC/ENaC null mice are needed to elucidate the importance of specific ASIC (and possibly ENaC) proteins in muscle ischemic responses.

It is important to make a cautionary note: ENaC/ASIC channels are probably not the only cardiovascular mechanosensors and chemosensors. This protein family probably represents one of multiple signaling mechanisms for mechanosensing and pH sensing. Other ion channels are also involved, such as members of the 2-pore K⁺ channels and transient receptor potential channel families.⁵¹

**Aldosterone Regulation and Hypertension-Related Organ Injury**

Results of recent clinical trials, Randomized Aldactone Evaluation Study and Eplerenone Heart Failure Efficacy and Survival Study, demonstrate the protective effect of aldosterone inhibition on cardiovascular function.⁵²,⁵³ However, mechanisms of this protection are still unclear. One might consider, in the context of this review, a possible role for ENaC proteins. Aldosterone stimulates ENaC activity in epithelial tissue, yet its effect on vascular/neuronal ENaC expression is unknown.¹ Although sensory neurons and VSMCs might be expected to respond to aldosterone in a manner similar to epithelial tissue, this may not necessarily be true. Based on published studies and preliminary studies from our laboratory, we suspect that aldosterone may be a negative regulator of ENaC expression in sensory neurons and VSMCs.

Preliminary data from our laboratory suggest that aldosterone (1 nmol/L to 100 μmol/L) inhibits expression of βENaC and γENaC in cultured sensory neurons. The effect is blocked by the aldosterone antagonists spironolactone and RU752. In addition, indirect evidence suggests that aldosterone inhibits ENaC in sensory neurons and VSMCs. Several investigations have linked elevated plasma aldosterone to reduced arterial baroreflex sensitivity and inhibition of myogenic tone in cerebral vessels. The studies discussed in this review suggest that baroreflex and myogenic control are mediated by ENaC.⁵⁴–⁵⁶ Thus, aldosterone may suppress baroreflex and myogenic responses by inhibiting ENaC expression. These factors increase blood pressure lability and pressure transmission to the delicate microvasculature, which may result in susceptibility to pressure-related end-organ injury (Figure 3). We speculate that part of the cardioprotective effect of aldosterone antagonism in clinical trials may be because of its stimulatory effect on ENaC expression in sensory neurons and VSMCs, which may augment baroreflex sensitivity and prevent swings in systemic pressure and augment myogenic responsiveness and prevent the transmission of systemic pressure to the microvasculature.

How might aldosterone inhibit ENaC expression? Biochemical evidence suggests that aldosterone is capable of activating ≥1 negative regulatory pathway, the epidermal growth factor receptor-mitogen activated protein kinase pathway.⁵⁷ Recent studies suggest that aldosterone-mineralocorticoid binding leads to transactivation of the epidermal growth factor receptor, which acts as a “brake” that prevents overactivation of ENaC in epithelial tissue.⁵⁸ We speculate that this negative pathway is favored in VSMCs and sensory neurons, which results in the net inhibition of ENaC expression. Thus, aldosterone-mediated transactivation of the epidermal growth factor receptor is one mechanism that could mediate aldosterone inhibition of ENaCs in VSMCs and sensory neurons.

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**Figure 3.** Possible mechanism of aldosterone action on nonepithelial targets. Aldosterone inhibition of ENaC in neurons and VSMCs may suppress baroreflex sensitivity and myogenic constriction. These actions increase blood pressure lability and pressure transmission to delicate microvessels in the brain and kidney and, thus, increase susceptibility to end-organ injury. Protection against injury may contribute to the beneficial effect of aldosterone antagonism in clinical trials (Randomized Aldactone Evaluation Study and Eplerenone Heart Failure Efficacy and Survival Study).
Perspectives
A growing body of evidence suggests that ENaC/ASIC proteins play a more diverse role in cardiovascular homeostasis than recognized previously. Certain ENaC and ASIC proteins may also influence cardiovascular homeostasis by acting as mechanosensors that mediate arterial baroreflex responses and local control of vascular resistance. ASIC proteins may influence cardiovascular homeostasis by acting as chemosensors, detecting changes in arterial pH to mediate arterial chemoreflex and ischemic responses in cardiac and skeletal muscle and mechanosensors in baroreceptors. This is a very exciting time for this area of research; we are just beginning to understand the importance of ENaC/ASIC proteins as sensors in cardiovascular mechanoreception and chemoreception. How these channels interact with neighboring proteins to signal mechanical and chemical stimuli, contribute to the neural and local cardiovascular reflex responses, and contribute to the progression of cardiovascular disease, such as hypertension, remain to be determined.

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References


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