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The brain's kv7 channel plays a new role in the development of hypertension

Yun Zhu*
Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan

INTRODUCTION

Multifactorial mechanisms play a role in the development of hypertension. Despite numerous findings from rodents and humans demonstrating that elevated sympathetic nerve activity is one of the major contributors to the onset, development, and maintenance of hypertension, the mechanisms underlying this phenomenon remain poorly understood. One way to treat resistant hypertension is to modify sympathetic overactivity. It has been shown that elevated sympathetic nerve activity is a major cause of resistant hypertension. Resistant hypertension, which is defined as hypertension that was resistant to three medications, one of which was a diuretic, was found in 9 to 18 percent of patients who received antihypertensive treatment. In prior research, the sympathetic outflow, which innervates the heart and blood vessels, was identified as a brain region involved in regulating cardiovascular functions. The rostral ventrolateral medulla (RVLM), which houses sympathetic promotor neurons that project to sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord, is an important part of the brain stem. In addition to receiving innervation from the hypothalamic paraventricular nucleus (PVN), the RVLM's premotor neurons also receive projections from other brain regions, such as the central nucleus of the amygdala (CeA). In hypertension, increased sympathetic vasomotor tone is a direct result of the activity of the neurons in these brain regions that are associated with cardiovascular health. Ion channels play a significant role in determining these neurons' intrinsic membrane properties[1].

DESCRIPTION

There are 78 known members of the voltage-dependent potassium channel (Kv) family, which are encoded by 40 genes and are broken down into 12 subfamilies. The activity of excitable cells like epithelial, muscle, neuron, and cardiac myocytes is controlled by a K+ channel encoded by KCNQ (Kv7).Kv7 subunits are encoded by five KCNQ genes (KCNQ 1–5) and form homotetrameric and heterotetrameric channels. The heart, smooth muscle, and inner ear all express Kv7.1 channels. Jervell and Lange-Nielsen syndrome is a life-threatening autosomal recessive disorder with a prolonged QT interval on electrocardiography (ECG) and congenital deafness that is linked to mutations in the KCNQ1 gene. The nervous system, smooth muscles, cochlear hair cells, and endothelial cells all express Kv7.2–7.5 channels. Despite the fact that Kv7 channels are expressed in a wide variety of cell types

Address for correspondence:

Yun Zhu
Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan
Email: yunzhu@yahoo.com

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in various organs, this review will focus on recent findings that suggest Kv7 channels in cardiovascular-related neurons control the activity of the sympathetic nerve and blood pressure in hypertension. Understanding the arising job of Kv7 in managing pulse gives the ability to unwind novel focuses for future therapeutics improvements to treat hypertension [2].

Nearly half of adults in the United States (47%) and millions of people worldwide suffer from hypertension, a chronic condition marked by persistently high blood pressure. There are no symptoms of hypertension by themselves; however, hypertension is a known risk factor for myocardial infarction and stroke, the first and third leading causes of death in Europe and the United States, respectively. Hypertension guidelines advise determining hypertension by observing persistently high arterial blood pressure. The International Society of Hypertension will publish global guidelines in 2020 that focus on essential and optimal standards of hypertension care. The Centers for Disease Control estimate that hypertension is a primary or contributing cause of 670,000 deaths in the United States, demonstrating the scope of the problem. This is due to the fact that the majority of patients receive treatment that is ineffective, including 15% of patients whose BP responses completely resist advancements in pharmacological therapies and lifestyle modifications that are utilized to treat hypertension. Around 200 million people worldwide who suffer from hypertension are unable to respond to standard pharmacological treatments, necessitating at least three medications for blood pressure control; Even with five medications, 5–10 million people do not achieve adequate blood pressure control. As a result, novel therapeutic approaches aimed at novel targets are urgently required for the treatment of hypertension. The majority of people with hypertension are either treated ineffectively or do not know what causes their condition [3].

The etiology of hypertension, a heterogeneous disease, remains exclusive and likely incorporates multiple mechanisms. The central nervous system (CNS) is implicated in the development of hypertension, according to recent research on the role of brain mechanisms in short- and long-term blood pressure control. Many examinations in people and creatures give proof that the mind directs the arrived at the midpoint of blood vessel circulatory strain and brokenness of cerebrum areas add to the turn of events and upkeep of hypertension, yet the hidden systems still need to be clarified. Since stimulation of the carotid baroreflex or renal denervation effectively lowers blood pressure in resistant hypertension, human hypertension is caused by elevated sympathetic nerve activity. Agents that block ganglionic neurotransmission between preganglionic and postganglionic sites in the sympathetic ganglions or 1- or -adrenergic receptors to reduce sympathetic outflow are another example. The adverse effects profile of these molecules' antihypertensive therapies frequently restricts their use. However, the mechanisms underlying the elevated activity of the sympathetic nerve in neurogenic hypertension are still poorly understood. Through cardiovascular reflexes, several brain nuclei and their circuits fine-tune the sympathetic vasomotor tone, including the hypothalamic paraventricular nucleus (PVN), the ventrolateral medulla (VLM), and the nucleus tractus solitaries (NTS) in the hindbrain. Post-ganglionic neurons in the spinal cord's intermedial cell column receive sympathetic efferent from neurons in those regions, which in turn send post-ganglionic sympathetic nerves to innervate the heart, blood vessels, kidney, and other peripheral organs. The cellular mechanisms underlying the elevated sympathetic outflow in hypertension have been the subject of numerous investigations [4].

Brain regions directly innervating and regulating sympathetic outflow have been identified through retrograde labeling with the pseudorabies virus. Additionally, a distinct population of presympathetic neurons in the PVN is responsible for controlling the sympathetic outflow to various organs, according to this study. PVN neurons that control renal sympathetic outflow are distinct from those that control cardiac sympathetic outflow, supporting this idea. Additionally, these presympathetic neurons may contain oxytocin, vasopressin, corticotropin-releasing hormone, or a variety of other neuropeptides, resulting in distinct differences in their neurochemical properties. Additionally, a number of PVN presympathetic neurons provide collateral innervation to various organs, including the heart and adrenal medulla. In the spinal cord, some PVN neurons project collaterally to the RVLM and intermediolateral (IML) cell column. Premotor neurons in the RVLM receive projections from the central nucleus of the amygdala (CeA), in addition to receiving innervation from the hypothalamic PVN. One of the crucial brain regions involved in regulating autonomic and behavioral responses to stress, fear, and pain is the CeA. In this regard, the CeA neurons directly project to the RVLM and form synaptic connections with the region's adrenergic (C1) neurons.

In cells like neurons, cardiac myocytes, and vascular smooth muscle cells, voltage-gated potassium (K+) channels are essential for controlling excitability. Critically regulating the excitability of excitable cells like neurons, muscles, and myocytes are the K+ channel Q subfamily members Kv7.1–Kv7.5 channels that are encoded by KCNQ 1–5 genes. Positional cloning was the first method used to find the KCNQ1 gene, which is on chromosome 11p15 in families with long QT syndrome type 1.There are six transmembrane segments (S1–S6) in each Kv7 subunit. There is a voltage-sensing domain in each of those, with the S4 serving as the primary voltage-sensor. For K+ ion selectivity, the flanking pore loop that is formed by the S5 and S6 is crucial.PIP2 is required for the opening of Kv7 channels because it acts as a cofactor for many ion changes and transporters, including Kv7, through coupling to the channel pore module. All of the homomeric and heteromeric subunits of KCNQ channels are highly sensitive to PIP2 in the plasma membrane. The possible sites to which PIP2 binds or acts allosterically to exert its strong influence on the M channel have been the

subject of numerous structure-function studies. The S2–S3 and S4–S5 linkers, as well as the junction between S6 and the C-terminal domain, are clusters of these PIP2-bound sites. In addition, it has been demonstrated that PIP2 is coupled to the pore domain in Kv7.1 by the voltage-sensing domain. Controlling the excitability of KCNQ-expressing cells requires PIP2-mediated regulation of KCNQs. Acetylcholine's excitatory action, for instance, is primarily mediated by PIP2 depletion caused by muscarinic acetylcholine receptor activation. Neuronal M-current, which is produced by Kv7.2/Kv7.3 heteromers, is reduced and neuronal depolarization is triggered when PIP2 is depleted. [5].

CONCLUSION

Each Kv7 subunit has a short intracellular domain at the N-terminus and a long intracellular tail at the C-terminus with four helices (helices A–D) that bind to CaM and mediate subunit assembly. CaM alters the operation of Kv7 channels in the Apo/CaM and Ca2+/CaM forms. This is accomplished by acting as a calcium sensor. CaM regulates the movement of Kv7 channels toward the plasma membrane and facilitates channel interaction with PIP2. Kv7 subunits are contacted by CaM's C-terminal helix A and B. Other accessory proteins, including protein phosphatase 1, protein phosphatase 2B, protein kinase A, protein kinase C, and protein kinase CK2, have been found to bind to the Kv7.2 subunit. CaM's Ca2+-containing N-lobe interacts with Kv7's helix B, whereas CaM's Ca2+-free C-lobe does not. A-kinase anchoring proteins (AKAPs), which are involved in second messenger signaling events, bind enzymes to plasma membrane target substrates like Kv7 channels.

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