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Research Paper

THE ROLE OF GAP JUNCTION IN REGULATING VASCULAR FUNCTION AND ITS RELATIONSHIP WITH HYPERTENSION

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ABSTRACT

Gap junction (GJ), also called as gap connection, communication connection, is a special membrane structure which consisted of connecting channels in two adjacent cells.

Intercellular communication can be divided into indirect and direct communication. Direct communication is a cell-to-cell communication mediated by GJ between adjacent cells. Direct communication is also called as gap junction intercellular communication (GJIC). Adjacent cells exchange information, energy, and substances by using direct communication. They participate in the metabolic coupling of cell-to-cell substances exchanges and the electrical coupling of electrical signals. They play important roles in regulating physiological processes including metabolism, homeostasis, proliferation, and vasodilation of vascular smooth muscle so on. This article will focus on introducing the progresses of studies on the morphology, structure and function of GJ in details. Blood pressure is the force exerted by the blood against the walls of the blood vessels. A blood pressure higher than 130 over 80 millimeters of mercury (mmHg) is defined as hypertension. Hypertension and heart disease are global diseases. Hypertension was correlated with many factors, which contributed to hypertension by many mechanisms including sodium, potassium, Gap junction and so on. The studies on GJ and hypertension were also introduced in details, such as hypertension and expression of Cx, Ca2+ and GJ, Genetic Polymorphism of Cx40 and Hypertension.

KEYWORDS :Gap Junctions, Connexins, Cardiovascular System, Hypertension.

INTRODUCTION

Gap junction (GJ), also called as gap connection, communication connection, is a special membrane structure which consisted of connecting channels in two adjacent cells. Gap junctions are a specialized intercellular connection between a multitude of animal cell-types. They directly connect the cytoplasm of two cells, which allows various molecules,ions and electrical impulses to directly pass through are gulated gate between cells. In this review, the morphology□structure and function of GJ were introduced. Roles of Gap junction in hypertension, such as expression of Cx and hypertension, GJ and Ca2+, Genetic Polymorphism of Cx40 and Hypertension were also described in detail.

2. The Morphology, Structure and Function of GJ

2.1. The Morphology and Structure of GJ

GJ is common in cells, whose unit is the connexin (Cx). GJ consists of two connexons in membranes of adjacent cells. The linker, also known as half-channel, is a hollow half-channel surrounded by six identical or different connexons in the cell membrane. Hydrophilic channel about 1.5 nm in diameter was formed by two linkers on adjacent cell membranes, which is also gap connection [1]. Under normal conditions, the half-channels in the cell membrane were closed. The half-channel is activated and opened at the special situation, which allowed some molecules to enter and exit the cell through the channel. Up to now, 20 kinds of Cx were found in mammalian cells [2], and were named as Cx26-Cx56 according to their molecular weight. Among them, Cx37, Cx40, Cx43, and Cx45 are highly expressed in the cardiovascular system and their expression is highly heterogeneous [3]. One GJ consists of four transmembrane hydrophilic fragments called M1-4 which formed a-2 helix, two extracellular loops (E1-2, one cytoplasmic loop, CL), the carboxyl and amino terminal positions of Cx are located in the cytoplasm. The amino terminal position is relatively conserved whereas carboxy terminal is significantly different. Phosphorylation/dephosphorylation level of threonine and tyrosine residues in amino-terminal filament can influence the formation and functional status of GJ and change the conformation by sensing intracellular information, thereby regulating the formation and conductance of GJ. GJ appears as clusters in the cytoplasmic membrane and forms gap junction plaques. These GJ channel are selective and transparent to different substances and the ratio of Cx expression is also closely related to the function of GJ [4].

2.2. Function of GJ

In addition to the mechanical connection between cells, GJ also mediates the electrical and chemical signal transmission between cells by electrical coupling and chemical coupling. GJ is currently found in membrane channels of many cells. GJ is the only kind of cell membrane channel which allows adjacent cells to directly exchange substances in the cytoplasm [5]. Electrical signals and ions or small molecules with a molecular mass below 1000 D or less than 1.0 nm in diameter, such as small molecule metabolites, water molecules, and second messengers (Ca2+, IP3, cAMP) were allowed to pass through GJ [6].

GJ was not only existed in same type cells but also in different type cells. The current study [7] showed that there are many types of GJ in the vessel wall, such as endothelial cell junctions, smooth muscle cell junctions and endothelial cell-smooth muscle cell junctions. GJs in different type cells and same type cells interweave into an information network, which were widely existed in the layers of the blood vessel wall to maintain the synchronization of electrical activity and mechanical activity in the longitudinal and lateral directions of the blood vessel wall, and make the entire blood vessel as a functional unit.

The physiological function of GJ in blood vessels is received extensive attention. In large arteries and vascular smooth muscles, GJ is mainly involved in the intercellular calcium transfer and achieves synchronization of smooth muscle cell (SMC) contraction. In addition, long-range communication of the GJ along the longitudinal axis of the blood vessel may be involved in regulating mitosis in the vascular SMC. In knockout mice of Cx43 gene in vascular SMC, loss of Cx43 promoted proliferation of SMC, which may be related to the amount of GJ, as reducing half of the Cx43 level inhibits proliferation of SMC [8]. There is abundant GJ in endothelial cells and SMCs of small blood vessels and these GJs are called as myoendothelial junction (MEJ). More studies [9] showed that MEJ is involved in vasodilation mediated by endothelial-derived hyperpolarization factor (EDHF). EDHF is the main factor that causes relaxation of smooth muscle in small blood vessels. Acetylcholine and bradykinin can increase synthesis of EDHF in endothelial cells, which enters smooth muscle cells through MEJ, activates calcium dependent potassium channels, hyperpolarizes cell membranes, and causes relaxation of blood vessels. In addition, SMC can also affect the function of endothelial cells through MEJ. In SMCs, IP3 can enter endothelial cells through MEJs, increase endothelial Ca2+ levels and promotes release of NO in endothelial cell. Recent studies showed that under inflammatory conditions, the expression of Cx43 in the pulmonary vascular endothelial cells was increased and the intercellular communication was enhanced. The permeability of pulmonary blood vessels was increased, which plays an important role in the pathogenesis of acute respiratory distress syndrome [10].

The regulation of gap junction function is significant for cell communication. Cytoplasmic pH, Ca2+, voltage, oncogenes, nucleotides, hormones, neurotransmitters, lipids, growth factors, and many exogenous chemicals can regulate function of gap junction by different levels including transcription, translation and post-translation modification, which is achieved by a variety of mechanisms [11-14].

3. GJ and Hypertension

Studies showed that gap junctions are involved in the regulation of blood pressure in the body, and different gap junction proteins play different roles in blood pressure.

3.1. Hypertension and Expression of Cx

Changes of Cx expression are closely related to hypertension [15, 16]. Studies [17] showed that mechanical stretch not only increased the expression of Cx43 in smooth muscle cells, but also improved the gap junction cell-cell communication. The expression of Cx in spontaneous hypertensive rats (SHRs) or hypertensive animal models was changed compared to normal. Some of these parameters, such as mechanical load, bioavailability of NO, shear stress, angiotensin II, etc were also changed, which may be involved in the change of Cx expression [18, 19]. Moreover, GJ exerted different functions on blood, sometimes even opposite functions such as vasodilation and contraction. Due to different experimental models, animal species or detection methods, there are still some controversies about the dynamic changes and effects of Cx on the development of hypertension [3]. Therefore, Cx expression cannot determine whether Cx has a role in the development of hypertension, or change of Cx expression cannot predict the development of hypertension.

Knockout techniques used in mice confirm that there is a relationship between GJ and regulation of blood pressure. Cx40 gene was associated with the regulation of the vascular diameter. All Cx40-deficient mice develop hypertension and their vascular regulation doesn't work [20]. The blood pressure of Cx40 knockout mice continued to increase significantly, which was related to the contraction and irregular movement of the small arteries,suggesting that there is a direct relationship between Cx40 and peripheral resistance,blood pressure. Recent study [21] found that expression levels of Cx40 can influence secretion of renin. Synthesis and secretion of renin were significantly increased in Cx40 knockout mice.It was also found that the number of renin-secreting cells was also increased, and that the distribution in the afferent arterioles was also changed.

It is well known that the connexin is involved in the formation of hypertension by controlling the release of renin. Cx37, Cx40, and Cx43 are expressed in the endothelial cells of the renal afferent arteriole, renin-producing cell and the juxtaglomerular apparatus (JGA) cells [22]. Cx40 and Cx37 were highly expressed in JGA cells [23]. Recent studies confirmed that Cx40 expression in JGA cells but not in endothelial cells can improve hypertension and reduce levels of renin [24]. Deletion of Cx40 leads to increase renin production and plasma renin levels [25,26]. Further specific deletion of Cx40 in JGA cells results in excessive secretion of renin and hypertension, while restoration of Cx40 expression in JGA cells can improve hypertension and reduce renin levels [24]. All these may be due to lose of GJ between JGA cells and afferent arterioles. Gap junctions cannot be formed between JGA cells and afferent arterioles, which damage function of the renal baroreceptor [27]. It can be speculated that Cx40 plays an important role in the stress repression of the renin system.

Schmidt et al. [28] found that the absence of Cx45 in vascular smooth muscle cell is not essential for the transduction of vasoconstrictive responses in arterioles. Function of Cx45 may be replaced by other Cx. Cx45 in renin does not seem to affect the arterial blood pressure in mice. However, endothelial cell communication mediated by Cx43 play a key role in controlling secretion of renin [29]. The study also found that Cx43 expression was significantly downregulated in SHRs, and that telmisartan significantly reduced angiotensin II and blood pressure and increased expression of Cx43 [30].

3.2. Ca2+ and GJ

GJ has the characteristics of ion channels. It is easy for Ca2+ to pass through GJ. Ca2+ is an important messenger of signal transduction pathway in cells. Therefore, Ca2+ is one of the important carriers of GJ-mediated intercellular signaling. In hypoxia-glucose (OGD) conditions, the conductance of Cx43, Cx40, and Cx45 gap junctions was reduced by 53%, 64%, and 85%, respectively. Phosphate buffer was used to limit intracellular Ca2+, pH changes and block the conductance of the gap junction channel. OGD regulates the uncoupling of the GJ channel mainly by increasing intracellular Ca2+ and decreasing pH. Cx43 is the most tolerant to OGD whereas Cx45 is the most sensitive to OGD [31]. Studies found that mechanical stimulation can induce calcium waves in rat mesenteric primary smooth muscle cells (pSMCs) and 6B5N cells (Cx43/Cx40-overexpressing A7r5 clonal cells) to spread to neighboring cells, whereas intracellular calcium in A7r5 cells cannot be transmitted to neighboring cells. Studies confirm that GJ with function consists of Cx43 was involved in the regulation of calcium wave between cells. Study also showed that ratio of both Cx43 and Cx40 is different, which can interfere with the functional GJ formed by Cx43, thereby changed communication of the gap junctions [32]. GJ calcium signaling is involved in the regulation of blood vessel tension. NO can inhibit the gap junctional communication of Hex cells (Hela-Cx37) which only expressed Cx37 while NO cannot inhibit the gap junctional communication of Hela-Cx40 or Hela-Cx43. In human umbilical vein endothelial cells (HUVEC) or human smooth muscle cells (HUVSMC), NO does not affect the Ca2+ signal transduction of GJ. In the co-culture of HUVEC and HUVSMC, NO can reduce the Ca2+ signal transmission of the myoepithelial junction by 60% [33]. Studies have also found that phosphorylation and dephosphorylation of proteins are regulated by cytosolic calcium oscillations, and that overload of calcium can activate phosphatases, which can cleave cells [34].

3.3. Genetic Polymorphism of Cx40 and Hypertension

Both mice with extensive lack of Cx40 and mice with specific deficiencies Cx40 in renin-secreting cells exhibit elevated levels of plasma renin and significant hypertension [25, 26]. Furthermore, ARB and ACEI reduced Cx40-/-mouse blood pressure although levels of plasma renin were higher in these animals than untreated Cx40-/- mice [25, 26]. In C57BL6 mice, mutation of the Cx40 A96S results in a renin-dependent increase in blood pressure, which is similar to Cx40-/- mice [25, 26, 35]. All these suggest that CJ40 mediates the release of renin in renin-producing cells GJIC. However, Kurtz et al. found that the mechanism of elevated renin levels in Cx40-deficient mice was the alteration of the JGA structure in Cx40-/- mice rather than reduce of the GJICs number [22].

Consistent with the important role of Cx40 in controlling secretion of renin and coordinating vascular tone, two closely linked polymorphisms (-44A and +71G) in promoter region of the human Cx40 gene are associated with an increased risk of hypertension in men [36, 37]. This gender difference may be related to the situation that the vasodilatory response of female animals is more dependent on the EDHF pathway. These polymorphisms appear to change the promoter activity of the Cx40 gene, as reporter gene analysis in vitro revealed that the Cx40 single-44A/+71G reduced the expression of luciferase by 50% and the polymorphism of -44A was negatively regulated by the transcription factors Sp1 and GATA4 [36-38].

Enalapril [26] or candesartan [39] can reduce but not restore the normal blood pressure of these experimental animals. Therefore, the hypertension observed in Cx40 knockout mice cannot be completely explained by secret of renin. Loss of Cx40 is associated with impaired transduction of irregular microvascular vasomotion and vasodilation signals [39, 40]. Therefore, in addition to renin-angiotensin II, the lack of Cx40-induced hypertension may be a disorder of control and coordination of vascular wall cells, suggesting that Cx may directly interact with signal molecules secreted by endocrine and paracrine of the vascular endothelium and SMC and lead to hypertension.

CONCLUSION

The expression and abnormal function of GJ can lead to hypertension. The mechanism may be the reason that the cell-mediated communication mediated by GJ is involved in the regulation of vasomotor movement, changes in the expression of connexin, regulation of renin secretion, resulting in increase of vascular tone and occurrence hypertension. Although it is very complex for GJ to be involved in vascular function, the development of Cx knockout animals has helped us to understand how these proteins work in the vasculature. Analog peptide of Cx is an effective tool for analyzing the role of GJ in vascular function. With the application of transgenic animals, more specific inhibitors, and proteomics technology in these new areas, pathogenesis of hypertension will be revealed soon.

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