REVIEW

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Connexin 43, a new therapeutic target for cardiovascular diseases

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Junctional channels (JC) play essential roles in the normal function of the cardiovascular system, mediating the spread of the electrical impulse that triggers synchronized contraction of the cardiac chambers and contributing to the coordination of activities between cells of the arterial wall. In mammalian hearts, cells most prominently express JC built of Connexin40 (Cx40), Cx43 and Cx45, of which Cx43 is the predominant intercellular gap junction protein. Changes in cardiovascular Cx gene expression during development or in response to (patho)physiological signals are expected to be a crucial factor in normal cardiac development and functions, and several cardiac diseases, such as atrial fibrillation, hypertrophy, heart failure, atherosclerosis, etc. Although the underlying molecular mechanisms have not yet been elucidated, recent research has found a variety of novel potential therapies related to Cx43 that can help to learn more about the mechanism of those cardiovascular diseases and the signaling pathway.

1. Introduction

Gap junctions are specialized channels formed between the membranes of two adjacent cells. They permit the direct passage of small molecules from the cytosol of one cell to its neighbor, and thus form a system of cell-cell communication that exists alongside familiar secretion/receptor signaling. Because of the rich potential for regulation of junctional conductance, and directional and molecular gating, gap junctional communication plays a crucial role in many aspects of normal tissue physiology (Levin 2002).

Gap junction channels are located in the cell membrane. Each cell contributes a half channel (termed a connexon), with each half channel formed by the oligomerization of six protein subunits (connexins) in a hexameric torus. The connexons dock to provide direct cell-to-cell communication through channels, which are large enough for molecules of up to about 1000 MW to pass (Danesh-Meyer and Green 2008).

The connexins (Cx) are a multigene family of gap junction proteins, which has highly conserved transmembrane and extracellular regions. All connexins share a common architecture: four hydrophobic amino acid regions that are membrane-spanning domains, two extracellular loops and three cytoplasmic components; amino- and carboxy-terminal regions, and a cytoplasmic loop. Most cell types express several different connexin isoforms in a temporal-, spatial-, and differentiation-specific manner. As far as we know, 21 isoforms in humans have been described. Each connexin is characterized by its predicted molecular mass; for example, connexin 43 (Cx43) has a predicted mass of 43 kDa. Small molecules less than 1 kDa, such as cAMP, IP_3, K^+, and Ca^{2+} ions, are capable of traveling through gap junction channels. Cx43 has been identified in several tissues including heart muscle, central nervous system, renal tubules and bone, and provides communication between the intracellular and extracellular compartments. It is also involved in Ca^{2+} signaling and glutamate release in astrocytes, in transduction of cell survival signals in bone, and in promoting cell injury in response to metabolic inhibition in isolated ventricular myocytes, astrocytes and renal tubule cells (Hawat and Baroudi 2008). That's why alterations in the distribution and/or level of Cx expression can be found under many pathological conditions, especially cardiac diseases. This article reviews the physiological features of Cx43 and its complex role in the genesis, propagation, and potential therapeutics of cardiovascular diseases.

2. General features of connexin 43

In the connexins family, Cx26, Cx30, Cx36, Cx40, Cx43, Cx45 are the most common connexins in human body, and multiple Cxs are coexpressed in the heart. Three principal Cxs are found in cardiac myocytes, Cx43, Cx40 and Cx45. Cx43 predominates in the heart as a whole but is typically coexpressed in characteristic combinations and relative quantities with Cx40 and/or Cx45 in a chamber-related and myocyte type-specific manner (Despantez et al. 2007). The most ubiquitously expressed member of the

connexin family, Cx43, has a half-life of only 1∼3 h (in cardiac myocytes), from synthesis to degradation by internal digestion within proteasomes or lysosomes (Hawat and Baroudi 2008). Cx43 gap junctions contribute to local metabolic homeostasis and synchronization of cellular activities by allowing bidirectional, intercellular movement of ions, metabolites and second messengers. Following injury, a Cx43 mediated bystander effect allows the propagation of cell death and survival-modulating signals that modulate the fate of the surrounding cells, subsequently causes many serious diseases (Herve et al. 2007).

3. Cardiovascular diseases related to Cx43

3.1. Arrhythmia

As we know, alterations in conduction velocity may contribute to cardiac arrhythmias. Propagation of electrical activity between myocytes in the heart requires gap junction channels, which contribute to coordinated conduction of the heartbeat. Two overlapping forms of remodeling of GJs and Cx expression may occur: (1) structural remodeling, which involves changes in the arrangement or organization of GJs, (2) remodeling of Cx expression, in which the amount and/or types of Cx expressed are altered (Severs et al. 2006). Howarth et al. (2007) suggested that altered expression of gap junction connexin proteins may partly underlie heart rhythm disturbances. Other research shows similar results (Kanagaratnam et al. 2002). Altered expression of connexin43 and its phosphorylation also contribute to the arrhythmogenic substrate, which induced through an inhibition of cell-to-cell coupling, in early stage heart failure of cardiomyopathic hamster (Sato et al. 2008).

Acquired adult heart disease with an arrhythmic tendency is marked by remodeling of GJs and Cx expression. With regard to alterations in Cx expression, the most widely documented change is downregulation of Cx43 in the ventricle of patients with end-stage congestive heart failure. The expression of Cx43 and Cx40 mRNA in the left ventricle of patients with end-stage heart failure due to idiopathic dilated cardiomyopathy (nonischemic heart disease, N-IHD, or ischemic heart disease, IHD) was observed. Results show that Cx43 mRNA is markedly downregulated, and the loss of Cx43 could, in some instances, exceed 90%. Meanwhile, Cx40 is strongly up-regulated (up to four or five times) in the ischemic category (Despantez et al. 2004). These changes occur regardless of the primary cause of the condition (e.g., idiopathic dilated cardiomyopathy, ischemic cardiomyopathy, valvular aortic stenosis or other etiologies) (Kostin et al. 2003; Yamada et al. 2003; Kostin et al. 2004). The reduction in ventricular Cx43 appears to develop progressively during the course of disease, as suggested by the pattern of change observed in pressure-overloaded hearts with valvular aortic stenosis classified according to ejection fraction and the finding of reduced Cx43 in the nonfailing ventricles of coronary artery bypass patients (Kostin et al. 2004). Synchronously, an increased expression of Cx45 and Cx40 has been reported in the failing human ventricle (Kanagaratnam et al. 2002; Yamada et al. 2003). Thus, the Cx co-expression patterns of the diseased human ventricle involve a generalized increase in the ratio of Cx45 : Cx43 and, in ischemic heart disease, a localized increase in Cx40 : Cx43.

3.2. Ischemic heart disease

A recent study showed that Cx43 is also localized in the inner membrane of cardiomyocyte mitochondria and as a new player in the pathophysiology of myocardial ischaemia-reperfusion injury (Ruiz-Meana et al. 2008). Normal ventricular myocytes are extensively coupled by gap junctions and have the capacity to rapidly increase the amount of connexin within gap junction plaques to meet physiological demands for enhanced cell-cell communication. However, myocytes can also rapidly uncouple in response to injury or disease. Ischemic and non-ischemic heart disease is associated with changes in the expression of connexins and remodeling of gap junctions (Saffitz et al. 2007). In addition, Cx43 is also involved in the formation of reactive oxygen species, which are crucial to the signal transduction cascade of ischemic pre/post-conditioning's protection. One study shows that the heterozygous Cx43-deficiency abrogates the cardioprotection induced by ischemic preconditioning, although the 50% Cx43-deficiency mice do not exaggerate tissue damage under sustained ischemia (Schwanke et al. 2003). In another study, heterozygous connexin 43-deficient (Cx43+/−) mice were subjected to permanent coronary occlusion. Infarct size of area at risk was reduced significantly in Cx43 +/− mice compared with Cx43+/+ mice (Heusch et al. 2006).

3.3. Heart hypoplasia

Although Cx43 is expressed in various cell types during embryonic development, mice with a global inactivation of Cx43 survive until birth but die in the perinatal period, which is due to an obstruction of the right ventricular outflow tract of the heart, as well as narrowing of the ventricular outlet region and hypertrophy of ventricular myocardium.

Congenital Diaphragmatic Hernia (CDH), one of the typical heart hypoplasia diseases, is one of the fatal diseases found in the newborn. The main symptom of CDH is heart hypoplasia and conotruncal defects as well as great vessel malformations that are likely related to disturbed neural crest developmental control. The latest study suggests that the main natural cause of CDH is the altered expression of Cx43, leading to the disturbance of GJ, which suggested that Cx43 might be a promising target of the CDH therapy (Levin 2002; Eckardt et al. 2006).

3.4. Vessel injury/repair

Endothelial dysfunction is thought to play a pivotal role in the initiation, progression, and occurrence of clinical complications of atherosclerosis. Maintenance of the functional integrity of the endothelial monolayer requires direct intercellular communication via gap junctions between individual cells. In mammalian vascular tissues, endothelial cells mainly express Cx37, Cx40, and Cx43, which is by far the predominant connexin (Chou et al. 2007). In human endothelial cells, different isoforms of connexins are subjected to different ways of regulation (Haussing et al. 2008). Studies showed that decreases in endothelial connexins occur in a variety of vascular disorders, closely related to atherosclerosis, such as hypertension and hyperlipidemia (Chou et al. 2007).

Tobacco abuse is still among the most important cardiovascular risk factors in modern society. Haussig et al. (2008) set an example to investigate whether sub-chronic nicotine exposure could induce endothelial dysfunction

and communication failure. Results showed that the levels of endothelial gap junction proteins Cx37 and Cx43 were significantly reduced. This indicated that nicotine induced functional intercellular communication failure in endothelial cells probably resulting from the down-regulation of Cx37 and Cx43 expression.

4. Novel potential therapies on cardiovascular disease with regulating connexin 43

Modulation of Cx43 expression has the potential to have widespread therapeutic applications to some cardiovascular disease. Although many mechanisms are far from clear, and moreover, the regulation of connexins and gap junctional conductance is very complex and differs between species, between cells from different tissues and between the connexin isoforms themselves, some novel potential therapies related to regulation of connexins have already been proposed as treatments of cardiovascular diseases.

4.1. Regulation of the phosphorylation of connexin 43

Phosphorylation of Cx43 subunits is known to be an important regulatory mechanism of Cx43 channels. Activation of protein kinases and protein phosphatases has been correlated with a reduction or increase of gap junction, since connexins could be phosphorylated by proteins kinases and dephosphorylated by protein phosphatases. The different phosphorylation form of connexins has different effects on gap juntional intercellular communication (GJIC). Suitable phosphorylation of connexin enhances GJIC, dephosphorylation or superphosphorylation of connexin restrains the GJIC. Alterations of phosphorylation state of Cx43 are related to cardiac function injury after hypoxia or reoxygenation. Detection of dephosphorylated Cx43 may serve as a diagnostic tool for examing ischemic heart disease (Matsushita et al. 2006; Wang et al. 2007).

Many enzymes, such as PKA, PKC, CK, MAPK, non-receptor tyrosine kinase, PP (PP1, PP2A, PP2B and PP2C), involved in the protein phosphorylation have effects on the regulation of Cx43 expression. Okadaic acid, a PP1/PP2 inhibitor, decreases ischemia-induced Cx43 dephosphorylation and the accumulation of non-phosphorylated Cx43 at the intercalated discs of myocytes in the whole heart (Jeyaraman et al. 2003). Thus, it shows a potent protection of cadiocytes under ischemia. Calyculin, which decreases ischemia-induced Cx43 dephosphorylation, showed similar results in the same experiment. It is concluded that isolated adult myocytes respond to ischemia in a manner similar to whole hearts and that ischemia-induced dephosphorylation of Cx43 is mediated, at least in part, by PP1-like phosphatase(s) (Jeyaraman et al. 2003; Ai and Pogwizd 2005).

4.2. Regulation of C43 by stimulating some related receptors

Certain receptors also have an effect on the Cx43 expression when they are activated. A typical example is the alpha-1-adrenoceptor subtype, whose activation selectively up-regulates the expression of connexin 43 in rat cardiomyocytes (Salameh et al. 2008), while Cx40, Cx45 are not influenced. Furthermore, the up-regulation of Cx43 expression could be inhibited by α_{1A}-adrenoceptor agonists, such as prazosin (Rojas et al. 2008). However, the role of α_1-adrenoceptor subtypes in the regulation of Cx43 remained unclear until now. The physiological meaning of this regulation could be that in case of adaptation of the heart muscle to higher exercise (hypertrophy), the electrical communication is regulated independently, which might provide a possibility to separate between contractility adaptation and establishment of electrical pathways for conduction. However, at present, this just remains a hypothesis.

Another example is that the activation of M_3 receptor improves GJIC and structural remodeling of Cx43. The mRNA level of Cx43 could be recovered from down-regulation level under pathologic conditions, such as ischemia (Yu et al. 2007). M3 receptor agonist treatment before ischemia occurrence could abrogate the down-regulation of Cx43 (Yue et al. 2006). Another report showed that Cx43 and M_3 receptor are co-located in the cardiac myocyte, which makes both M_3 and Cx43 potential therapeutic targets in cardiovascular diseases, such as arrhythmia (Zhang et al. 2006).

4.3. Actions of hormones

Stress impacting the heart and the renin-angiotensin-aldosterone system (RAAS) causes changes in cellular structure and electrophysiology. Modulation of intercellular coupling through gap junctions could lead to an alteration in conduction velocity and conduction block. Aldosterone (Ald) shows a complex influence on the Cx43 expression. A significant down-regulation of Cx43 in neonatal rat cardiac myocytes is induced when exposed to 10^{-4} M Ald, but a significant up-regulation of Cx43 is induced with 10^{-8} M Ald. These results suggest that Ald affects gap junction remodeling in a dose dependent manner by modulating Cx43 synthesis through different receptors, which results in a concomitant change of conduction velocity (Shyu et al. 2001). AngII facilitates Cx43 synthesis, up-regulates Cx43 expression and increases the number and size of gap junction profiles in cardiac cells via AT1 receptor and ERK and p38 signal pathway (Polontchouk et al. 2002). Therefore, an effective prevention of RAAS activation during development of gap junction remodeling, including angiotension-converting enzyme inhibitors, angiotensin receptor blockers, aldosterone receptor antagonists, etc, might be a new therapeutic strategy for the treatment of arrhythmias (Murray et al. 2007).

T3, a thyroid hormone, up-regulates Cx43 and accelerates gap junction formation in cultured neonatal cardiac myocytes. Thyroid status not only modulates the mechanical function of cardiomyocytes but also cell-to-cell communication which is essential for myocardial electrical and metabolic synchronizations (Tribulova et al. 2004).

4.4. Anti-cancer drugs

Cx43 also plays a crucial role in the growth, differentiation and proliferation of tumor cells. Many anti-cancer drugs show a certain influence on the expression of Cx43 which has the potential to be used in the treatment of cardiovascular diseases.

Recent reports studied the ability of Coleusin Factor (CF, also named FSK88), a new anti-cancer drug, on regulating the Cx43 expression and GJIC level in rat osteosarcoma UMR106 cells. Results demonstrated that CF increased the mRNA and protein expression of Cx43 in a dose- and time-dependent manner and up-regulated the diminished GJIC level in UMR106 cells by dye transfer experiments. In addition, Cx43 distribution in the plasma membrane was also dramatically enhanced by CF treatment. These

results provide the first evidence that CF could regulate connexin and GJIC, indicating that Cx43 may be a target of CF which could be used to exert cadioprotection as well as its anti-tumor effects (Geng et al. 2007).

As_2O_3, an anti-cancer drug, regulates the endothelial gap junctions. Cx43 transcripts and gap junctions in human aortic endothelial cells (HAEC) are reduced with gap-junction communication attenuated by As_2O_3. The reduction of Cx43 involves both down-regulation at the transcriptional level and an increase of degradation. This indicates that gap-junction communication in the vascular endothelium is inhibited by As_2O_3, which might be useful for the therapy of vascular dysfunction (Chou et al. 2007).

4.5. Active compounds

There are some active compounds that regulate the expression of connexins, for instance, nitrofen. Cx43 mRNA was overexpressed in the hearts of nitrofen-exposed embryonal rats, which could be normalized by vitamin A. The underlying mechanism of action deserves further investigation (Gonzalez-Reyes et al. 2006).

Recent experiments investigated that heptanol, as a reversible gap junction inhibitor, could down-regulate the connexins, consequently impair gap junction. This down-regulation, which has little selectivity on connexins family, at least including Cx40, Cx43 and Cx45, etc., diminishes soon after removal of heptanol (Keevil et al. 2000).

Some antipsychotic drugs, such as thioridazine and its active metabolite, mesoridazine, have well-known cardiac conduction side-effects that have resulted in fatal or nearly fatal clinical consequences. The physiological mechanisms responsible for these cardiac side-effects are unclear. Matesic et al. (2006) observed the effect of thioridazine and mesoridazine on gap junction-mediated intercellular communication between cells that express the major cardiac gap junction subtype Cx43. In light of the fact that the concentrations of thioridazine and mesoridazine used in these experiments are in the range of those used clinically in patients, the results suggest that inhibition of gap junction intercellular communication may be one factor contributing to the cardiac side-effects observed in some patients taking these medications.

5. Summary

Together with the above-mentioned studies, alterations of intercellular communication through gap junctional connections are likely contributing factors to the occurrence of many cardiovascular diseases. Such alterations may be as simple as microfibrosis interrupting gap junctional communication without a change in connexin quantity or distribution or as complex as remodeling of the three different connexin isoforms (Cx40, Cx43, Cx45) to change the makeup of heteromeric/heterotypic gap junctions.

Dramatic increase in the understanding of the molecular mechanisms of normal and abnormal cellular physiology led to the development of exciting new theories of cardiovascular disease. But there are still many things remaining unkown about Cx43 and a lot of research needs to be done. However, Cx43 certainly is a promising target in cardiovascular diseases, which will lead to novel therapy options in the future.

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ERRATUM

Key Laboratory of Organism Functional Factors of the Changbai Mountain (Yanbian University)[1], Ministry of Education, Yanji; College of Pharmacy[2], Yanbian University, Yanji; College of Medicine[3], Jilin, P.R. China

Evaluation of anticonvulsant activity of QUAN-0806 in various murine experimental seizure models

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Unfortunately, in the contribution by Li-Ping Guan et al. published in PHARMAZIE 2009, 64: 248–251 (doi: 10.1691/ph.2009.8738) the species of experimental animals was misprinted. In fact, Kunmimg mice were used instead of C57B/6 mice, as has erroneously been stated. Thus, the respective paragraph should read as follows:

4. Experimental

4.1 Animals

Kunming mice of either sex (obtained from the Laboratory of Animal Research, College of Pharmacy, Yanbian University) weighing from 18 to 25 g were used in these studies. The ratio of male and female mice in the control and drug-treated groups was kept same to avoid variation in responses due to sex differences. The animals were housed in plastic cages and were maintained on a 12 : 12 h light-dark (7 : 00 A.M. to 7 : 00 P.M.) schedule in a temperature-controlled (21 ± 2 °C) animal room and relative humidity (about 40–50%). The animals had free access to standard rodent chow and water and were acclimatized to their environment for one week prior to experimentation. The animals were randomly distributed into different groups. Each experimental group comprised of a minimum of 10 animals. Mice were moved from the animal care facility to the testing laboratory room; each animal was caged separately after recording its body weight and was randomized to receive the treatments according to a random number table. Each mouse was used only once. The MES test and the rotarod test were carried out by the standard described in the Antiepileptic Drug Development Program (ADD), Epilepsy Branch, National Institutes of Health, Bethesda, MD, U.S.A. (Hester 1979a; Hester 1980b). All animal procedures conform to the Provision and General Recommendations of Chinese Experimental Animal Administration Legislation.