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Strategies to invent cardiovascular drugs targeting cardiac gap junctions

Review article

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Abstract: In order to prevent and treat cardiac diseases, the author proposed strategies to invent cardiovascular drugs targeting cardiac gap junctions through summarizing the functions, physiology and pathophysiology of cardiac gap junctions. The 5 principle strategies to invent cardiovascular drugs that are suggested have great potentialities to be used as novel proposals to treat and prevent cardiac diseases.

Keywords: *Cardiac gap junctions • Cardiovascular • Pharmacology*

1. Introduction

More and more research has been done on the gap junctions' structure, functions, physiology and pathophysiology. The gap junctions as pharmacological targets for clinical treatments become an important topic in medical science. Although many tissues have gap junctions, the cardiac gap junctions are the most important gap junctions in the human body. Research on cardiac gap junctions' structure, functions, physiology and pathophysiology has had many good achievements. But the cardiac gap junctions' clinical applications as targets to invent cardiovascular drugs have not yet developed good results.

There are no reports about the cardiac gap junctions' clinical applications as targets to invent cardiovascular drugs. This fact was discovered through a MEDLINE search of the English-language literature on "Strategies to Invent Cardiovascular Drugs by Cardiac Gap Junctions," on the key words of this paper or only on the title of the paper. One of the topics has been addressed by Wit A.L. et al. recently in the article "*Drug Development for Treatment of Cardiac Arrhythmias. Targeting the Gap Junctions*" [1].

According to cardiac gap junctions' structure, functions, physiology, pathophysiology characteristics and recent research achievements about cardiac gap junctions, the author summarized his ideas as to how cardiac gap junctions should be targeted to invent cardiovascular drugs in the following five strategies.

2. Cardiac gap junction blockers or mediators for clinical usages

Researching and selecting cardiac gap junction blockers or mediators to block or mediate cardiac gap junction channels, so as to block or mediate the ions and small molecules flowing through cardiac gap junctions and therefore block or mediate electrical activation of the heart's cell-cell transfer of current via gap junctions. The gap junction blocker had been invented for clinical prevention and treatment of the nervous system; the cardiac gap junction mediators have a bright future. These strategies may be easy to accomplish.

In 2002, Rozental et al. had invented a gap junction blocker for clinical prevention and treatment, which has been in the process of being patented in the United States of America. This invention relates to methods of preventing and treating hypoxic-ischemic injury and the consequences of that condition in the

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newborn utilizing a class of drugs known as the gap junction blockers. The invention provides a method for treating a preterm or term newborn infant with suspected or diagnosed hypoxic-ischemic injury with a gap junction blocker either before or after delivery. The present invention also provides a method for preventing seizures in term or preterm newborn infants. The method for treating and preventing the consequences of head injury is also described in this invention.

Therefore it is relatively easy to create the strategy to invent cardiovascular drugs by researching and selecting cardiac gap junction blockers or mediators.

3. Modulating gap junction protein expression

Since cardiac gap junction channels are predominantly composed of connexin40 (Cx40) or connexin43 (Cx43) proteins, specially selected molecules to mediate connexin40 or connexin43 protein expression, transcription, and translation or proteins catabolism are also bright ways to mediate the cardiac gap junction channels' functions, physiology, and pathophysiology. These strategies may affect gap junction conductance chronically.

It is clear that the proteins of cardiac gap junction channels are much too important to their intrinsic functions. Because the normal protein production of cardiac gap junction channels needs protein expression, transcription, and translation or proteins catabolism, this group of strategies is created.

Research has found that the some kinds of proteins catabolism are correlated with cardiovascular diseases [2,3].

4. Modulating protein kinases

Substances which activate protein kinase C, protein kinase A or protein kinase G may alter Cx43 gap junction conductance. Therefore, some selected substances when modulating protein kinase C, A or G, can also alter cardiac gap junction conductance. These selected substances may become cardiovascular drugs. These strategies can be a possible breakthrough to the invention of cardiovascular drugs.

The strategies were supported by the research done by Dhein S. et al. [4].

5. Reformed mediators like endothelin-1, angiotensin-II, transforming growth factor beta (TGF-beta), vascular endothelial growth factor (VEGF), and cAMP to mediate cardiac gap junction conductance

Mediators like endothelin-1, angiotensin-II, TGF-beta, VEGF, and cAMP have been shown to increase Cx43 [4]. Pharmacologically changing endothelin-1, angiotensin-II, TGF-beta, VEGF, and cAMP et al. into positive substances to mediate cardiac gap junction conductance for the treatment and prevention of cardiac diseases is also a good strategy.

6. Modification of gap junction communication in special conditions for the prevention cardiac diseases

Research has found that some substances can prevent cardiac diseases from developing into their critical stages through the modification of gap junction communications [5]. The studies suggest that gap junction-mediated intercellular communication (GJMIC) may still allow synchronization of the onset of ischemic rigor contracture and of the progression of ischemic injury beyond rigor onset. During reperfusion, GJMIC has been shown to mediate cell-to-cell propagation of hypercontracture and cell death. Finally, there is increasing evidence that gap junctions or their protein components are involved in the genesis of the protective effect of ischemic preconditioning. Modifications of gap junction communication in these special conditions for the prevention of cardiac diseases are additional ways to treat and prevent cardiac diseases, which may be the best but most difficult way. The selected substances to modify the gap junction communication in these special conditions can become good cardiovascular drugs. These strategies may be another breakthrough method for the invention of cardiovascular drugs.

There are many other methods to treat cardiac diseases. Cardiac diseases still have high mortality and incidence rates, so it is important to develop new aspects of research to treat and prevent cardiac diseases. More and more research has been done on the gap junctions' structure, functions, physiology and pathophysiology. The gap junctions

as pharmacological targets for clinical treatments become an important topic in medical science. The five suggested principle strategies to invent cardiovascular drugs targeting cardiac gap junctions have great potentialities to be used as principles for inventions of cardiovascular drugs to treat and prevent cardiac diseases.

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