Hydrogen Sulfide—a potent multichannel anti-arrhythmic drug

Guang-Zhen Zhong
Department of Cardiology, Beijing Chaoyang Hospital, Capital Medical University, Beijing, P.R.China 100020 zhongguangzhen@hotmail.com

ABSTRACT—Arrhythmia is a big headache for cardiologist for a long time. A new antiarrhythmic drug with good effects and few side effects should be explored. Hydrogen sulfide, a newly found gaseous transmitter, was found to have multi-effects on a variety of ion channels. It may be a promising antiarrhythmic drug. This article reviews the different effects of hydrogen sulfide on different ion channels.

Hydrogen sulfide—a potent multichannel acting antiarrhythmic drug

Recent studies\(^5,6\) showed that hydrogen sulfide (H\(_2\)S), a new gaseous transmitter, acted on several cardiac ion channels, inhibited arrhythmia and prevented ischemia-reperfusion injury. It is reasonable to think of it as a potential promising multichannel acting antiarrhythmic drug.

H\(_2\)S has been best known for decades as the toxic gas or ‘gas of rotten eggs’. It has been founded as a new gaseous transmitter only in recent years.\(^7\) And from 2003, H\(_2\)S has been widely studied in different pathological animals. Most of these studies showed that H\(_2\)S exerts its function through acting on different ion channels.\(^8,9\)

Effects of H\(_2\)S on ATP dependent potassium channel (K\(_{\text{ATP}}\))

The first study\(^10\) about the action of H\(_2\)S on ion channels was from Zhao’s study, and they studied the effects of H\(_2\)S on K\(_{\text{ATP}}\). They proved the opening effect of H\(_2\)S on K\(_{\text{ATP}}\) channel through three different levels. First, they found blood pressure decreasing effect of H\(_2\)S was antagonized by blockade of K\(_{\text{ATP}}\) channels. Then their results showed H\(_2\)S relaxed rat aortic in vitro through three different levels. First, they found blood pressure decreasing effect of H\(_2\)S was antagonized by blockade of K\(_{\text{ATP}}\) channels. Finally, they proved with patch Clamp technique that H\(_2\)S increased K\(_{\text{ATP}}\) channel currents.

After that, Geng et al\(^11\) found H\(_2\)S has negative inotropic effect through opening K\(_{\text{ATP}}\) channel. Zhang and colleagues\(^5\) did an even more interesting study. They made an ischemia-reperfusion model in vitro by Langendorff apparatus. They found H\(_2\)S had a cardioprotective effect against ischemia-reperfusion injury. Moreover, they found H\(_2\)S decreased arrhythmia score significantly in this model. Through patch-clamp technique, they also found that cardioprotective mechanism of H\(_2\)S was opening of K\(_{\text{ATP}}\) channel. Zhang’s results challenged the traditional point of view, i.e. shortening of repolarization of cardiac cells due to opening of potassium channel may shorten the refractory period and induce arrhythmia. This may be explained by the following mechanisms: 1) Although H\(_2\)S shortened refractory period of ventricular myocardial cells, it prolonged the effective refractory period relatively; 2) H\(_2\)S has greater effects on other ion channels.

Ion channels initiate and conduct electrical activity in the heart. The channels open and close in response to changes in membrane potential, and allow ionic permeation across the plasma membrane. The idea that defective ion channels might be responsible for cardiac arrhythmia has received indirect support from the anti- or proarrrhythmic actions of a host of drugs and toxins that are specific for Na\(^+\), Ca\(^{2+}\) and K\(^+\) channels. With the progress of the clinical trials, it is widely understood that drugs having multi-effects on various ion channels may be the promising antiarrhythmic drug.

Antiarrhythmic drugs today

Recently, cardiologists are more interested in devices and ablation techniques for arrhythmia treatment than in pharmacological treatment. However, pharmacological treatment is still very important especially in prevention of atrial fibrillation and sudden cardiac death.

It is well known that present antiarrhythmic drugs are not ideal. They induce another arrhythmia when treating one arrhythmia or increased the total death rate although inhibited arrhythmia. Therefore, new antiarrhythmic drugs are still welcome.

To date, the most popular antiarrhythmic drug classification is the system developed by Singh and Vaughan Williams\(^1\) in the early 1970s and subsequently modified by Singh and Hauswirth and by Harrison.\(^2\) In this system, antiarrhythmic drugs were divided into class I for sodium-channel blockade (with subclasses IA, IB and IC), class II for adrenergic antagonism, class III for action-potential prolongation, and class IV for calcium-channel blockade. Among these drugs, since the publication of studies demonstrating that certain drugs may increase mortality in high-risk post-infarction patients,\(^3\) basic science and clinical studies have focused on Class III antiarrhythmic drugs. However, Class III drugs prolong repolarization and cardiac refractoriness, and are sometimes associated with potentially lethal Torsades de pointes. Amiodarone, a multichannel blocker, may be the exception to this observation. Therefore, both cardiologists and pharmacologists are turning their interests towards developing new multichannel blocker, since amiodarone nevertheless fails to reduce total mortality compared with placebo in high-risk patients following myocardial infarction.\(^4\)
To further explore the mechanism of H$_2$S on K$_{ATP}$, Zhang et al. studied the effect of H$_2$S on gene and protein expression of K$_{ATP}$ (SUR2B mRNA and Kir 6.1mRNA). Their results showed that H$_2$S increased the gene expression of K$_{ATP}$ as well as the protein expression.

**Effects of H$_2$S on Calcium channel**

The first study that may involve L-Calcium channel is from Geng’s work. Both in vivo and in vitro experiments in this study proved that H$_2$S had a negative inotropic effect on rat heart. This may suggest the effect of H$_2$S on L-calcium channel, although the authors did not perform any related experiments. As researchers focused on the effect of H$_2$S on K$_{ATP}$ channel, Xiao et al. noticed another channel—L-calcium channel was also involved in the acute mechanism of H$_2$S. They studied the effect of H$_2$S on the functional curve of baroreflexes. The results showed H$_2$S facilitated the carotid sinus baroreceptor. Pretreatment with a K$_{ATP}$ channel blocker, abolished the above effects while pretreatment with Bay K8644 (an agonist of calcium channels) eliminated the effect of H$_2$S on carotid sinus baroreceptor. Therefore, they concluded that H$_2$S opened K$_{ATP}$ channels and further closed the calcium channels.

The above study is on carotid sinus baroreceptor, which may be quite different from myocardial cells. Yet, Xu and colleagues studied the effect of H$_2$S on L-calcium channel on guinea pig papillary muscles. Their data showed that pretreatment with L-type Ca$^{2+}$ channel agonist Bay K8644 partially blocked the effects of NaHS (a H$_2$S donor), which suggested that the reduction of calcium influx may also contribute to the effects of H$_2$S. Furthermore, they found that pretreatment with Ca$^{2+}$-free K-H solution containing Glibenclamide completely blocked the effects of H$_2$S, which indicated that the effects of H$_2$S guinea pig papillary are due to the changes of potassium and calcium currents.

Step further, Sun et al. studied the effects of H$_2$S on L-Calcium channel directly, and stated definitely that Hydrogen sulphide is an inhibitor of L-type calcium channels. Sun and colleagues found a concentration-dependent inhibition of peak IC$_{a,L}$ on cardiomyocytes by NaHS (a H$_2$S donor). It becomes clear that H$_2$S has an inhibitory effect on L-Calcium channel. However, the mechanism needs further study.

Although, no study was reported about the H$_2$S on T type Calcium channel on cardiomyocytes, Nagasawa et al. studied the effect of H$_2$S on T-type calcium channels on NG 108-15 cells (which may be differentiated into neuronal cells). Their study showed H$_2$S could stimulate the T-type calcium channels. Therefore, it is reasonable to think of H$_2$S as having an effect on T-type calcium channels, which needs further exploration.

**Effects of H$_2$S on chloride channel**

Chloride channels are important for setting cell resting membrane potential and maintaining proper cell volume. These channels conduct Cl$^-$ as well as other anions such as HCO$_3^-$, I$^-$, SCN$^-$, and NO$_3^-$. Chloride channels display a variety of important physiological and cellular roles that include regulation of pH, volume homeostasis, organic solute transport, cell migration, cell proliferation and differentiation. Recent studies have identified several chloride (Cl$^-$) channel genes in the heart, including CFTR, CIC$^{-2}$, CIC$^{-3}$, CLCA, Bestrophin, and TMEM16A. It has been shown that Cl$^-$ channels may contribute to cardiac arrhythmogenesis, myocardial hypertrophy and heart failure, and cardioprotection against ischaemia–reperfusion.

Since the reason above, we are concerned of the effect of H$_2$S on chloride channel. The effect is reported on June 2009 by Malekova et al., where they derived single chloride channels from the rat heart lysosomal vesicles incorporated into a bilayer lipid membrane. Their results showed that H$_2$S inhibited the chloride channels by decreasing the channel open probability in a concentration-dependent manner. Since they incorporated the single chloride channels into the bilayer lipid membrane, they measured the IC$_{50}$ for tans and the cis sides, respectively and got the different results (42uM vs. 75uM).

**Beneficial cardiac effects from H$_2$S**

With the results of the famous CAST clinical trial,$^3$ people realized that benefits for the patient’s prognosis is more important than antiarrhythmia itself. So the effect of H$_2$S on the whole heart may be more important.

The effect on the whole heart was first described in Geng’s study.$^{15}$ Their results showed that administration of exogenous H$_2$S effectively protects cardiomyocytes and contractile activity from isoproterenol injury. Then, Zhang et al. isolated rat heart, then made an ischemia-reperfusion model with langendorff apparatus. The results showed that the treatment of hearts with a H$_2$S donor during reperfusion resulted in a significant improvement in heart function and the arrhythmia scores was also improved. Furthermore, Sivarajah et al. found in the ischemia-reperfusion model that the antiapoptotic effect of NaHS (H$_2$S donor) may be in part due to the opening of the putative mitochondrial adenine triphosphate-sensitive potassium channels.

**CONCLUSION**

In summary, H$_2$S has various effects on various ion channels from cardiomyocytes. Not only can it improves heart arrhythmia score, but also can protect heart from ischemia-reperfusion injury and has beneficial effects on the heart function. We have reasons to think of it as a promising antiarrhythmic drug. Since it was a newly found endogenous gaseous signaling molecule, the risk, safety issues, dosage, proposed delivery methods and so on are therefore a big field to be explored.

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**REFERENCES**

1. Vaughan WEM. Classification of antidyrsylnhmic drugs. Pharmacol Ther B. 1975; 1(1):115–38.
2. Harrison DC. Antiarrhythmic drug classification: new science and practice. Eur J Cardiovasc Dis. 1985. 56(1):185–7.
3. Hallstrom A, Friedman L, Denes P, Rizo-Patron C, Morris M. Do arrhythmia patients improve survival by participating in randomized clinical trials?
Guang-Zhen Zhong J. Cardiovasc. Dis. Res. 2010; 1(1): 37–39

Observations from the Cardiac Arrhythmia Suppression Trial (CAST) and the Antiarrhythmics Versus Implantable Defibrillators Trial (AVID). Control Clin Trials. 2003. 24(3):341–52.

4. Jafri SM, Borzak S, Goldberger J, Gheorghiade M. Role of antiarrhythmic agents after myocardial infarction with special reference to the EMIAT and CAMIAT trials of amiodarone. European Myocardial Infarct Amiodarone Trial. Canadian Amiodarone Myocardial Infarction Trial. Prg Cardiovasc Dis. 1998. 41(1):65–70.

5. Zhang Z, Huang H, Liu P, Tang C, Wang J. Hydrogen sulfide contributes to cardioprotection during ischemia-reperfusion injury by opening K_ATP channels. Can J Physiol Pharmacol. 2007. 85(12):1248–53.

6. Zhu YZ, Wang ZJ, Ho P, et al. Hydrogen sulfide and its possible roles in myocardial ischemia in experimental rats. J Appl Physiol. 2007. 102(1):261–8.

7. Wang R. Two's company, three's a crowd: can H2S be the third endogenous gaseous transmitter.

8. Tang G, Wu L, Liang W, Wang R. Direct stimulation of K_ATP channels by exogenous and endogenous hydrogen sulfide in vascular smooth muscle cells. Mol Pharmacol. 2005. 68(6):1757–64.

9. Malekova L, Krizanova O, Ondrias K. H(2)S and HS(-) donor NaHS inhibit its intracellular chloride channels. Gen Physiol Biophys. 2009. 28(2):190–4.

10. Zhao W, Zhang J, Lu Y, Wang R. The vasorelaxant effect of H2S as a novel endogenous gaseous K_ATP channel opener. EMBO J. 2001. 20(21):6008–16.

11. Geng B, Yang J, Qi Y, et al. H2S generated by heart in rat and its effects on cardiac function. Biochem Biophys Res Commun. 2004. 313(2):562–8.

12. Zhang RY, Jin HF, Tang CS, Du JB. Effects of Hydrogen Sulfide on Gene Expression of Adenosine Triphosphate Sensitive Potassium Channel of Aortic Vascular Smooth Muscle Cells in Rats? J Appl Clin Pediatr. 2009. 24(1):21–23.

13. Xiao L, Wu YM, Zhang H, Liu YX, He RR. Hydrogen sulfide facilitates carotid sinus baroreflex in anesthetized rats. Acta Pharmacol Sin. 2006. 27(3):294–8.

14. Xu M, Wu YM, Li Q, Wang FW, He RR. Electrophysiological effects of hydrogen sulfide on guinea pig papillary muscles in vitro. Sheng Li Xue Ban. 2007. 59(2):215–20.

15. Sun YG, Cao YX, Wang WW, Ma SF, Yao T, Zhu YC. Hydrogen sulphide is an inhibitor of L-type calcium channels and mechanical contraction in rat cardiomyocytes. Cardiovasc Res. 2008. 79(4):632–41.

16. Nagasawa K, Tarui T, Yoshida S, et al. Hydrogen sulfide evokes neurite outgrowth and expression of high-voltage-activated Ca2+ currents in NG108-15 cells: involvement of T-type Ca2+ channels. J Neurochem. 2009. 108(3):676–84.

17. Duan D. Phenomics of cardiac chloride channels: the systematic study of chloride channel function in the heart. J Physiol. 2009. 587(Pt 10):2163–77.

18. Geng B, Chang L, Pan C, et al. Endogenous hydrogen sulfide regulation of myocardial injury induced by isoproterenol. Biochem Biophys Res Commun. 2004. 318(3):756–63.

19. Sivarajah A, Collino M, Yasin M, et al. Anti-apoptotic and anti-inflammatory effects of hydrogen sulfide in a rat model of regional myocardial I/R. Shock. 2009. 31(3):267–74.