REVIEW

Hydrogen sulfide therapy: a narrative overview of current research and possible therapeutic implications in future

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Abstract

Diabetic nephropathy is one of the most important comorbidities in the diabetic population. In China, more and more young patients are showing an increasing prevalence of diabetes. As a gas molecule, hydrogen sulfide (H_2S) has some unique chemical and physiological functions. In recent years, it has been studied in various fields. These effects are manifested in the induction of renal vasodilation and anti-renal vascular fibrosis. The ball clearing function is improved. Therefore, increasing prospective studies have focused on how H_2S protects diabetic nephropathy and how to obtain H_2S by modern means to treat diabetic nephropathy.

Key words: clinical research; diabetic nephropathy; experimental research; future application; hydrogen sulfide; kidney; pathological mechanism; renal hypertension; renal protection

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Introduction

Diabetic nephropathy, one of the most common complications of diabetes, is mainly caused by poor long-term glycemic control. Excessive blood sugar and blood pressure in the body will continue to damage the blood vessels of the kidneys. With the increase of kidneys to filter blood, it will eventually lead to the kidney disease.[1] When the metabolic function of the kidney is lost by more than 90%, it becomes uremia.[2] Once diabetic nephropathy occurs, it will be developed and treated without timely control and treatment. And it will contribute to the end-stage renal disease, which often causes irreversible damage to the kidney. Although it has many complicated mechanisms for this pathological change, the etiology and mechanism are not completely clear.[3] It is currently believed that multiple factors are involved. Diabetic nephropathy is characterized by abnormal renal hemodynamics, which is manifested in glomerular hyperperfusion and hyperfiltration, increased renal blood flow and glomerular filtration rate.[4] And the degree of increased protein after ingestion is more pronounced. Hyperglycemia mainly causes renal damage through renal hemodynamic changes and metabolic abnormalities.[5] The mechanism of renal damage caused by metabolic abnormalities mainly includes: Firstly, local glucose metabolism disorder in kidney tissue, which can form glycosylation terminal metabolism through non-enzymatic glycosylation.[6] Secondly, in a high concentration of glucose environment, it will destroy the basal cells by activation of the polyol pathway. Thirdly, it can also lead to renal fibrosis through the activation of the diacylglycerol-protein kinase c pathway. Last but not least, abnormal metabolism of the glycosylation pathway will damage renal tubular cells.[7] In addition to participating in early hyperfiltration, the above-mentioned metabolic abnormalities are more important to thicken the glomerular basement membrane and accumulate the extracellular matrix. Thereby it leads to stenosis of the glomerular blood vessels.[8] With the development of modern society and the improvement of living standards, people are increasingly lacking attention to the control of diet and the laws of living habits, leading to an increasing prevalence of diabetes. Therefore, we must pay attention to this issue in a timely manner. People should carry out diabetes education and instill sports concept.[9] Many studies have shown that hydrogen sulfide (H_2S) has protective and therapeutic properties for renal blood vessels, so we can use these physiological characteristics to solve the kidney disease caused by diabetes.[10]

Mechanism of Hydrogen Sulfide in Diabetic Nephropathy

As a widely studied gas, H_2S can cause various biological effects in different tissues of human body, and the concentration is also different in different tissues. H_2S molecules mediate a series of pathophysiological changes through different ion channels or signal proteins in the body.[11] As we all know, things are two-sided, H_2S is neurotoxic and tissue damage to human tissues at high concentrations, and it may have a potential protective effect on blood vessels at low concentrations.[12] Therefore, we will be able to explore how H_2S at low concentrations protects against renal vascular diseases caused by diabetes and the feasibility of its clinical use in the future. At present, the mechanism of high glucose-induced renal vascular injury is not fully explained. The relevant theory holds that H_2S molecules are composed of cystathionine γ-lyase, cystathionine β-synthase and 3-mercaptopyruvate thioltransferase. A physiologically relevant gas transmitter synthesized

by the synergistic metabolism of cysteine by cysteine aminotransferase.[13] It has been found that cystathionine β-synthase is the most abundant in the brain, while cystathionine γ-lyase is dominant in human peripheral tissues, while pyruvate thioltransferase exists in brain and peripheral tissues similarly.[14] In the pathogenesis of diabetic nephropathy, due to the increase in the amount of sugar in the blood, accompanied by an increase in homocysteine, vascular endothelial cells induce the synthesis of related high glycoproteins under the action of high glucose, resulting in increased matrix protein, narrowing of blood vessels.[15] At the same time, recent studies have also shown that hyperhomocysteinemia can cause renal vascular endothelial cell injury and arteriolar ischemia in small arteries, which further lead to renal vascular sclerosis and fibrosis, aggravating the ischemic nature of renal blood vessels. Eventually it leads to a progressive decline in renal function.[16] H_2S is an endogenous regulator of tissue function in human body. Its production and decomposition rate is very fast, so it is often maintained at a lower concentration. On the one hand, H_2S is oxidized and metabolized to sodium sulfide in intracellular mitochondria, which improves the accumulation of matrix proteins in renal vascular cells.[17] On the other hand, H_2S can produce diastolic blood vessels by mediating the opening of potassium channels and blocking of voltage-gated calcium.[18] At the same time, it has recently been confirmed that H_2S has an antioxidant effect.[19] It is well known that in the process of metabolism, the human body produces reactive oxygen species, which can be divided into free radicals and non-free radicals and reactive nitrogen. In our normal activities, reactive oxygen is essential for the existence of immune mechanisms. But when it is too much, it will cause irreversible damage to our human tissues.[20] Studies have found that superoxide can be produced by NOX oxidase, endothelial nitric oxide synthase and other enzyme complexes. When superoxide is produced too much, it causes damage to vascular endothelial cells, and H_2S gas molecule that the unique chemical properties can transfer its own single electron or hydrogen atom to remove superoxide. At the same time, it has been reported that H_2S gas can inhibit the production of superoxide dismutase in vascular endothelial cells by reducing the activity of NOX oxidase. Thereby it reduces the damage caused by oxidation reaction on vascular endothelial cells, but the mechanism of action is not completely clear.[21] Thus, H_2S has been shown to protect diabetic renal blood vessels.[22]

Experimental Studies of Hydrogen Sulfide in Diabetic Nephropathy

In animal research, a rat model of diabetic nephropathy has been successfully established, and the disease model is intervened by H_2S, and then the changes of diabetic renal blood vessels after intervention are observed. So we can discuss the possible treatment mechanism of H_2S for diabetic nephropathy.[23] Animal experiments are based on pre-medical research and basic medical research. The most important thing is to explore the possible mechanism of action of H_2S in diabetic nephropathy and the possibility of future application in human body.

As far as we all know, we have to make a large number of animal experiments before clinical application. So as for achieving animal experiments, we have successfully established animal models of diabetic nephropathy. In this regard, we searched for experimental studies of rats related with diabetic nephropathy. We classified their different experimental results. H_2S has a significant effect on alleviation of renal fibrosis in diabetic rats, and its possible mechanism is to reduce the release of pro-inflammatory factors, and downgrade the expression of transforming growth factor-β1.[23] Thereby it inhibits the excessive production of type IV collagen in the kidney and alleviate diabetic renal fibrosis.[24] H_2S also reverses the damage of renal fibrosis caused by hyperhomocysteinemia caused by diabetic nephropathy.[21] H_2S has a significant improvement in the symptoms of proteinuria caused by diabetic nephropathy. The possible mechanism is to inhibit the activation of senescence-associated secretory phenotype in the kidney through H_2S, thereby inhibiting the activation of mammalian target of rapamycin (mTOR).[25] H_2S significantly reduced the expression of renal basement membrane and collagen type II, thus alleviating the process of renal fibrosis.[26] The down-regulation of cystathionine γ-lyase expression in podocytes of diabetic nephropathy by H_2S is an important mechanism to alleviate podocyte injury.[27]

The amusing conclusion of these animal studies may be different attributing to various experimental situations and methods. Here, we review and analyze these recent experimental studies regarding this gas for the treatment of diabetic nephropathy treatment (**Table 1**), and summarize the results.

Therefore, we can analyze the results of these experiments and find that in the animal model, the effect of H_2S on diabetic nephropathy is positive to a certain extent. The study found

Table 1: The renal protective effect of H_2S in diabetic nephropathy

Type of disease	Method	Results	Animals
Diabetic nephropathy	DM + NaHS	The thickness of glomerular basement membrane was significantly improved, the proliferation of mesangial matrix was reduced, and the degree of foot process fusion was significantly reduced.	Rats
		H_2S significantly reduced the expression of renal basement membrane and collagen type II, thus alleviating the process of renal fibrosis.	
		H_2S has protective effect on podocyte injury induced by high glucose.	
		H_2S can reduce urinary albumin excretion and retain renal clearance function in aging mice.	Mice
Chronic kidney diseases	Hhcy + NaHS	H_2S reduced the glomerulosclerosis and interstitial fibrosis deficit.	Mice

Note: CKD: Chronic kidney diseases; DM: diabetes mellitus; H_2S: hydrogen sulfide; Hhcy: hyperhomocysteinemia; NaHS: sodium hydrosulfide.

that when the level of homocysteine in the blood rises, it often accompanied by the occurrence of high blood pressure.[28] In diabetic nephropathy, due to a decrease in the activity of endothelial nitric oxide synthase, the function of homocysteine detachment is lowered, resulting in the occurrence of hypertension. H_2S can reduce the activity of tissue inhibitors of metalloproteinase-1, -2 and -4 by inhibiting the activation of matrix metallopeptidase-2, -9 and -13 induced by hyperhomocysteinemia, thereby increasing the activity of endothelial nitric oxide synthase to lower the blood pressure.[21] In addition, when blood sugar in the renal blood vessels rises, Kasinath found that adenosine monophosphate-activated protein kinase is inhibited, which may be involved in catalytic activation of mTORC1.[10] When mTORC1 is activated, it induces an increase in the synthesis of endothelial cell matrix proteins, which further leads to changes in renal fibrosis. H_2S can further promote H_2S release by binding to phosphodiesterase-5, and can inhibit the expression of mTORC1 by stimulating the adenosine monophosphate-activated protein kinase pathway, thereby improving renal vascular fibrosis induced in a high glucose environment.[17] Through the above experimental studies, it is found that under the condition of low concentration of H_2S, it is of practical significance to improve diabetic nephropathy, although the range of low concentration and treatment time window are not clear.

Although there is currently no direct clinical trial of H_2S for diabetic nephropathy, recent evidence has suggested that hyperhomocysteinemia plays a very important role in the development of hypertension, leading to renal fibrosis.[29] In the above controlled experimental study, we can find that the development of diabetic nephropathy is almost accompanied by an increase in the concentration of hyperhomocysteinemia, so that the degree of reduction of hyperhomocysteinemia by H_2S can be used as an indicator to improve the blood vessels of diabetic nephropathy.[30] There is also evidence that the synthesis of H_2S in the blood vessels of diabetic nephropathy is impeded, and treatment with exogenous H_2S may be useful. Its possible mechanism is that H_2S can inhibit transforming growth factor-β1 through the extracellular signal-regulated protein kinases 1 and 2 pathway to induce renal fibrosis, which is another important pathway for diabetic nephropathy. However, whether this protection can be applied in clinical practice is still debatable.[31] Although there are many theories discussing the relationship between H_2S and diabetic nephropathy, there is currently no consensus on their relationship. More importantly, H_2S is closely related to diabetic nephropathy. Further exploration on the potential related mechanism is required.[32]

Clinical Studies of Hydrogen Sulfide in Diabetic Nephropathy

H_2S, as an endogenous gas signal molecule after carbon dioxide, nitric oxide, carbon monoxide, has been studied by humans in various tissues in recent years, and has extensive physiological effects in different organs.[33] In the past, H_2S has been considered as a neurotoxic gas, which may cause harm to the human body. However, it is worth mentioning that when the concentration of H_2S exceeds the physiological dose, and it will cause harm to the human body. At low concentrations, H_2S often shows the opposite therapeutic effect.[34,35] H_2S has not been applied in clinical practice, and its dose of use, concentration and frequency requires a lot of experimental research to prove its effectiveness, and the potential mechanism of action in human organs remains to be further explored in clinical trials.

Possible Therapeutic Implications

Through the introduction of H_2S gas above, we can find that H_2S has potential therapeutic effects in diabetic nephropathy. Although the current theory does not agree, the signaling pathways formed by gas molecules often exert their physiological characteristics to jointly build a complex physiological activity through different gas molecules. We should comprehensively analyze the use of H_2S from a dialectical angle, although it is a realistic problem for how to produce H_2S on a large scale and low cost. But we believe that H_2S will create a new chapter to protect diabetic nephropathy.

Author contributions
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