HYDROGEN SULFIDE (H2S) GAS SIGNALING IN THE BODY

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INTRODUCTION

- Hydrogen sulfide (H_2S) is a well-known toxic gas with the smell of rotten eggs.
- Since the first description of the toxicity of H_2S in 1713, most studies about H_2S have been devoted to its toxic effects.
- Excessive exposure to H_2S could lead to cellular toxicity, orchestrate pathological process, and increase the risk of various diseases
- Recently, H_2S has been proposed as a physiologically active messenger

ROLE IN THE BODY

- H2S is produced in response to neuronal excitation, and alters hippocampal long-term potentiation (LTP), a synaptic model for memory. can also regulate the release of corticotropin-releasing hormone (CRH) from hypothalamus
- Interestingly, under physiological status, H2S plays a critical role in maintaining cellular physiology and limiting damages to tissues.
- The protective role of H2S in the development of fibrosis is primarily attributed to its
- antioxidation, antiapoptosis, anti-inflammation, proangiogenesis, and inhibition of fibroblasts activities. Future studies might focus on the potential to intervene fibrosis by targeting the pathway of endogenous H2S-producing enzymes and H2S itself.

PRODUCTION OF H2S IN THE BODY

- Three groups discovered In mammalian species, the generation of H2S is catalyzed by
- cystathionine beta-synthase (CBS),
- cystathionine gamma-lyase (CSE),
- And 3-mercaptomethylthiopyruvate aminotransferase (3MST) and cysteine aminotransferase (CAT).

H2S PRODUCTION IN THE BODY

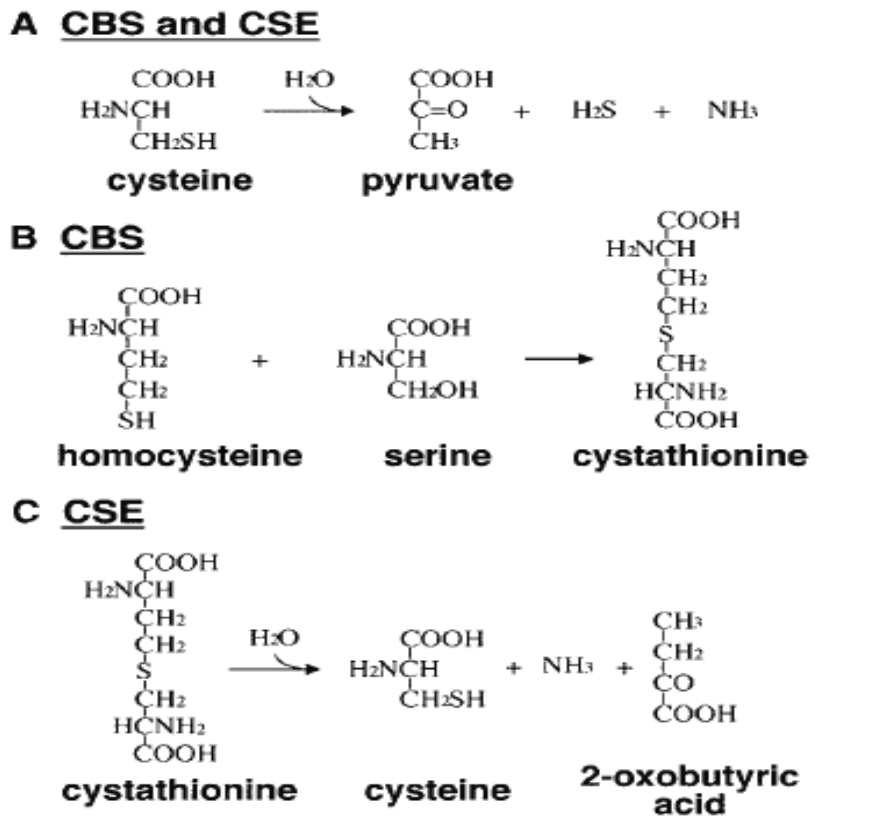


Fig. 1. Cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) catalyze two metabolic reactions. (**A**) is a common reaction for CBS and CSE to produce H_2S. (**B**) is the specific reaction for CBS and C for CSE (6–9).

LEVELS INSIDE THE BODY

- Endogenous concentrations of H2S have also been measured in human and bovine brain .
- The relatively high concentrations of H2S in the brain (50–160 μM) suggest that it has a physiological function.

EFFECT ON EYE

- H2S-releasing compounds could act on adenylyl cyclase and ATP sensitive potassium channels (KATP) channels in eyes, thus increase cAMP concentrations in porcine ocular anterior segments and help mediate the outflow of Aqueous Humour.
- H2S donors exert vasodilator effects on pre-contracted posterior ciliary arteries (PCAs), which are crucial to OBF.

BRAIN COGNATIVE FUNCTION

- The CBS gene is encoded on chromosome 21q22.3 , a region associated with Down syndrome, and it has been proposed that H2S may be involved in the cognitive dysfunction associated with Down syndrome.
- Loss of CBS activity causes homocystinurea, an autosomal recessive disease characterized, in part, by mental retardation.
- CBS interacts with Huntingtin (a neurodegenerative disease), mutants of which cause Huntington's disease.
- Finally polymorphisms of CBS gene is significantly underrepresented in children with high IQ compared with those with average IQ, suggesting that CBS activity may be involved in the cognitive function.

- H2S also hyperpolarizes smooth muscle by activating KATP channels. Based on these observations, it is likely that H2S may also regulate cerebral blood flow.
- Production and function of H2S in the central nervous system. When the electrical signals descend to the axon terminal, Ca2+ enters into the nerve terminal and interacts with calmodulin. The Ca2+/calmodulin activates CBS to produce H2S. H2S can pass through the membrane and reach the postsynaptic membrane to modify the activity of the NMDA receptor, allowing greater Ca2+ influx. H2S also can modulate the release of transmitters and hormones . When the NMDA receptor is activated, Ca2+ enters through NMDA receptors and Ca2+/calmodulin activates CBS to produce H2S.
- H2S can regulate NMDA receptor activity and modulate the induction of long-term potentiation (LTP), a synaptic model of learning and memory

H2S AND DIABETIC RETINOPATHY (DR) REDUCTION OF THE EFFECTS OF ADVANCED GLYCATION END PRODUCTS (AGES) IN DR

- Mechanistically, H2S reduces ROS production and lipid peroxidation, while enhancing the expression of superoxide dismutase (SOD) and glutathione peroxidase (GPX), two endogenous antioxidant enzymes.
- In addition, H2S could reverse high glucose induced increase in the expression of aldehyde oxidase 1(AOX-1) and decrease in glutathione synthetase (GSS) level, ultimately to antagonize the AGEs-induced oxidative stress in cells.

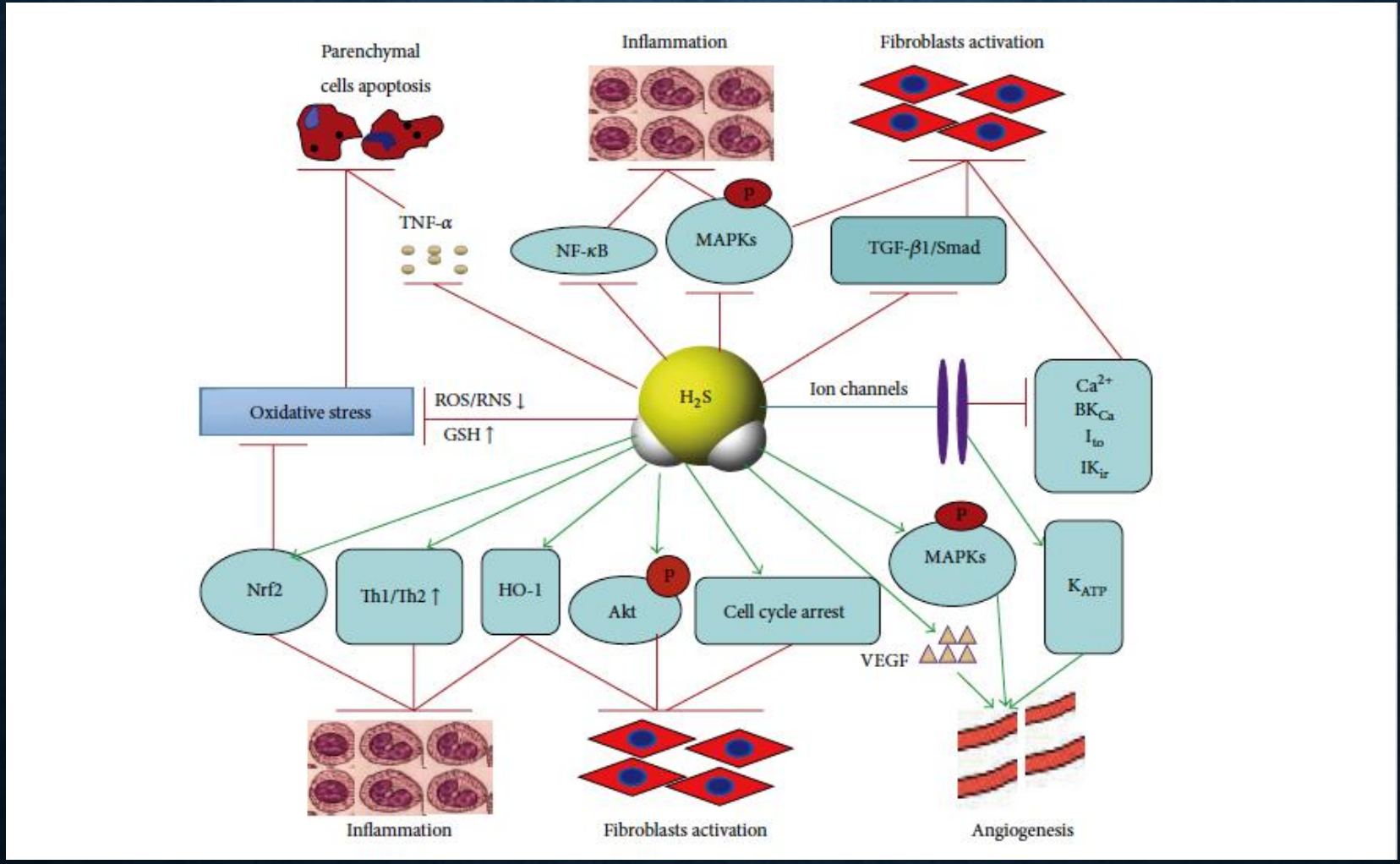
INHIBITION OF OXIDATIVE STRESS AND INFLAMMATION

- H2s decrease the levels of TNF-α, IL-8 and IFN-γ, while increasing the levels of cyclooxygenase (COX)-2 and eicosanoids. Similarly, H2S donors has been reported to inhibit Lipopolysaccharide-induced production of inflammatory mediators by macrophages, and to upregulate the release of anti-inflammatory cytokine, IL-10. Such regulation on inflammatory cytokine production can be attributed to the suppressive function of H2S on NF-κB activation.

INHIBITION OF OXIDATIVE STRESS AND INFLAMMATION

- Investigations on the regulation of H2S on myocardium in type 1 diabetic rat model has revealed that H2S interferes with the inducible NOS (iNOS)/NO system, inhibits iNOS activity and its catabolite mediated oxidative stress.
- However, the anti-inflammatory function by H2S is not always achieved. In low dose, H2S donor inhibits the inflammatory response, while high doses of H2S donor achieves controversial results.

POTENTIAL THERAPEUTIC TARGET



POTENTIAL THERAPEUTIC TARGET

- Administration of GYY4137 to diabetic mice ameliorated decrease in H_2S and prevented the development of histopathology, characteristic of diabetic retinopathy. Diabetes-induced increase in oxidative stress, MMP-9 activation, and mitochondrial damage were also attenuated in mice receiving GYY4137.Results from isolated retinal endothelial cells confirmed the results obtained from diabetic mice.

thanks for listening!