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Title

P54 Hydrogen sulfide inhibits activation of the renin-angiotensin system in diabetic heart

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and CSE knockout (KO) mice were fed a high-fat diet (HFD) for 8 weeks. We determined the effects of CSE knockout on beta-cell function and mass in islets from these mice. After 8 weeks of HFD, blood glucose levels were markedly increased in middle-aged KO mice, insulin responses were significantly reduced, and DNA fragmentation of the islet cells was increased. In order to assess the effects of HFD on 6-month-old mice, we analyzed changes in gene expression in the islets. As a result, we found that expression of thioredoxin binding protein-2 (TBP-2, also known as Txnip) was increased in middle-aged KO mice. Administration of NaHS (a hydrogen sulfide donor) reduced TBP-2 gene levels in isolated islets from KO mice. The gene levels were elevated when islets were treated with the CSE inhibitor DL-propargylglycine (PPG). These results provide evidence that CSE-produced hydrogen sulfide protects beta-cells from glucotoxicity via regulation of TBP-2 expression levels and thus prevents the onset/development of type 2 diabetes.

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P53

Promoted interaction of nuclear factor-kappa B with demethylated cystathionine-beta-synthetase gene contributes to gastric hypersensitivity in diabetic rats

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The present study was designed to investigate roles for NF-kappa B and the endogenous H₂S producing enzyme cystathionine-beta-synthetase (CBS) signaling pathways in adult rats with experimental diabetes. Here, we showed that injection of STZ produced gastric hypersensitivity in female rats in response to gastric balloon distention in association with upregulation of CBS and p65 expression in gastric DRGs. Treatment with CBS inhibitor AOAA attenuated gastric hypersensitivity. AOAA treatment also reversed hyperexcitability of gastric-specific DRG neurons in diabetic rats. Blockade of NF-kappa B signaling using PDTC reversed upregulation of CBS expression. STZ treatment led to a significant demethylation of CpG island in *cbs* gene promoter region determined by methylation specific PCR and bisulfite sequencing. STZ treatment significantly enhanced *cbs* ability to bind DNA at p65 consensus site by CHIP assays. Our findings suggest that upregulation of *cbs* expression is attributed to *cbs* promoter DNA demethylation and p65 activation and that the enhanced interaction of *cbs* gene and p65 would contribute to gastric hypersensitivity in diabetes.

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P54

Hydrogen sulfide inhibits activation of the renin-angiotensin system in diabetic heart

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Diabetic cardiomyopathy is a major contributing factor to morbidity in diabetics. A significant role of the cardiac renin-angiotensin

system (RAS) in diabetic cardiomyopathy has been demonstrated clinically. Plasma levels of hydrogen sulfide (H₂S), which have been demonstrated to inhibit plasma renin and endothelial ACE activity, are reduced in diabetic patients. The interaction between H₂S and the RAS in the heart is unclear. We hypothesize that cardiac H₂S levels are reduced in diabetes, resulting in cardiac RAS activation. Type 1 diabetes was induced in mice by streptozotocin. We observed that the expression of cystathionine gamma-lyase (CGL) in the heart was reduced significantly as diabetes progressed, whereas the cardiac RAS was activated. By using a fluorescent probe specific for H₂S, we determined that H₂S production was significantly impaired in neonatal rat ventricular myocytes (NRVM) cultured in high glucose medium (HG, 30 mM). In addition, DL-propargylglycine (PAG), a CGL inhibitor, increased the expression of angiotensinogen (AGT) in NRVM, suggesting that endogenous H₂S is inhibitory to the cardiac RAS. HG significantly upregulated AGT expression in NRVM, which was further potentiated by PAG. GYY4137, a slow H₂S releasing compound, completely abolished the effect of HG on RAS activation. Currently, we are using the transgenic mouse with cardiac specific over-expression of CGL to confirm these findings. In conclusion, downregulation of H₂S synthesis may contribute to cardiac RAS activation in diabetes. Replenishing the H₂S level in the diabetic heart, using an H₂S donor, might provide a potential treatment for diabetic cardiomyopathy.

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Overexpression of cystathionine gamma-lyase suppresses spinocerebellar ataxia type 3-associated neurodegeneration in *Drosophila*

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Spinocerebellar ataxia type 3 (SCA3) is a polyglutamine disorder caused by a CAG repeat expansion in the ataxin3 gene resulting (amongst others) in toxic protein aggregation. Inflammation and oxidative stress are secondary factors contributing to the progression of the disease. There is no cure that halts or reverses the symptoms of SCA3. The transsulfuration pathway has been implicated in diverse crucial physiological processes, among which are those in the central nervous system. Activation of this pathway leads to biosynthesis of hydrogen sulfide (H₂S), which is produced by cystathionine gamma-lyase (CSE), cystathionine beta-synthase and 3-mercaptopyruvate sulfurtransferase. This gas has anti-oxidative and anti-inflammatory properties, making it an attractive candidate to intervene in damaging processes of SCA3. Here, we show that overexpression of the H₂S-producing enzyme, CSE, suppresses SCA3-associated degeneration in *Drosophila*. This decrease in degeneration is associated with reduced oxidative stress and a dampened immune response. Treatment of SCA3-bearing flies with an H₂S donor, sodium thiosulfate, resulted in similar protective effects, suggesting that the beneficial effects of CSE overexpression are due to an increased production of H₂S. In humans, we observed expression of CSE in SCA3-relevant brain regions and a decreased CSE expression in

¹ Equally contributed.