The Protective Effect of a Novel H_2s Donor Cys-S3 Against Liver Injury in Diabetic Mice Includes an Antiferroptotic Effect

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Abstract:

Ferroptosis, a form of regulated cell death characterized by iron-dependent lipid peroxidation, is involved in the development/progression of liver disease associated with diabetes. Although studies suggest that H2S protects cells from ferroptosis, it is unclear whether targeting ferroptosis through H2S signaling pathways could ameliorate diabetic liver injury. Therefore, T1D was induced with streptozotocin, and mice were treated with: GYY4137, the most studied slow-release H2S donor, the polysulfide donor Na2S4, and the in situ persulfide donor Cys-S3, or with liproxstatin-1 (Lip-1), an established ferroptosis inhibitor, for four weeks two months after the onset of T1D. H2S/RSS donors were found to improve biochemical parameters of glucose homeostasis, liver injury (ALT, AST) and histological indices (liver fibrosis, hepatocyte size, binucleation). The increased lipid peroxidation caused by diabetes (indicated by the increased 4-HNE positivity and iron accumulation) was reduced by treatment with H2S/RSS donors. Decreased activation of Nrf2, GSH-related antioxidant defence parameters (GPX4, GCLC, GSS) and expression of iron sequestering proteins (ferritin, ferroportin) were improved/increased by H2S/

RSS donors. In parallel, Lip-1 significantly attenuated the liver injury caused by diabetes. Overall, H2S/RSS donors, especially Cys-S3, exert a beneficial effect in the treatment of liver pathology caused by diabetes and have both antidiabetic and antiferroptotic effects.

Keywords:

Diabetes, ferroptosis, H2S/RSS donors, liver.