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Betulin Rescues Elevated SREBP Expression in Heart of Rats Exposed to Chronic Sulfur Dioxide

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Editorial

Sulfur dioxide (SO_2) is a colourless gas with a sharp, irritating odor. It is produced by burning fossil fuels and by the smelting of mineral ores that contain sulfur. Exposure to SO_2 produces toxic symptoms such as thickening of the mucous layer of the respiratory tract, pneumonia, nasopharyngitis, fatigue [1]. Epidemiological investigations suggest that SO_2 exposure increases morbidity and mortality, particularly among subjects with respiratory diseases and cardiopulmonary disease [2,3]. However, the underlying molecular mechanism remains unclear. Our previous study indicated that chronic SO_2 exposure led to increased free-fatty acid levels in the serum and enhanced lipogenic gene sterol regulatory element-binding proteins gene expression (SREBP1 and SREBP2) in the heart [4], suggesting a risk of lipotoxicity in the heart.

SREBP1 and SREBP2 are major transcription factors that activate the expression of genes involved in biosynthesis of fatty acid and cholesterol. Betulin, a small molecule that specifically inhibits the activation of SREBP, has been shown to decrease the lipid contents in serum and tissues in vivo [5,6]. Thiazolidinedione (TZD) is a widely used diabetic mediation and acts by activating peroxisome proliferator-activated receptor gamma (PPARγ), a key regulator of fatty acids oxidation and glucose-lipid metabolism. In animal models, PPARγ agonist treatment improves lipotoxic cardiomyopathy [7]. In the current study, we aimed to elucidate whether inhibiting fatty acid synthesis or promoting fatty acid oxidation would ameliorate SO_2 inhalation-induced lipid accumulation program in heart.

Results and Conclusions

Consistent with our previous finding, real-time RT-qPCR analysis revealed that the mRNA expression of both SREBP1 and SREBP2 were stimulated by chronic SO_2 inhalation in rat hearts. Administration of streptozotocin (STZ), a compound that has a preferential toxicity toward pancreatic β cells, successfully induced diabetic rats as indicated by hyperglycemia (data not shown). STZ treatment greatly increased SREBP1 levels but not SREBP2. In addition, SO_2 exposure in STZ-induced diabetic rats did not further increased the expression of SREBP1 or SREBP2 compared with single treatment, indicating there is no synergistic effect of SO_2 on STZ. Treating rats with TZD had no effect on SO_2-induced SREBP1 or SREBP2 expression, but ameliorated the STZ-induced SREBP1 expression in heart. Betulin gavage treatment markedly diminished both SO_2-induced and STZ-induced elevation of SREBP1 expression and suppressed SO_2-induced SREBP2 expression. Taken together, these data suggested that betulin could rescue SO_2-induced lipid and cholesterol overproduction and partially mitigated the effect of STZ on lipid synthesis, however TZD treatment cannot improve SO_2 inhalation-induced lipid metabolism disturbance (Figure 1).

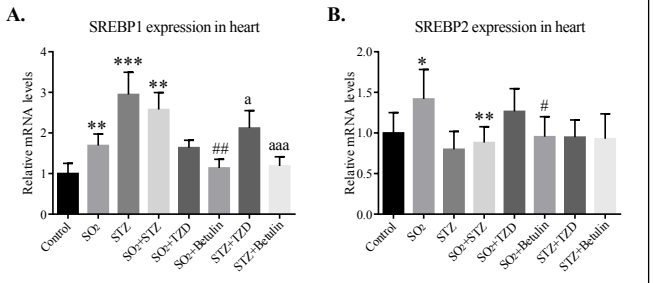

Figure 1: SREBP1 and SREBP2 gene mRNA expression in heart. Data are presented as mean ± SD (n=6/group). *P<0.05, **P<0.01 and ***P<0.001 (relative to SO_2 group); #P<0.05 and ##P<0.01 (relative to STZ group); a P<0.01 and P<0.001 (relative to STZ group) by one-way ANOVA.

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