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Short Communication

Atherosclerosis is Lessened by Glycine-Based Therapy that Stimulates Glutathione Production

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Abstract

Lower circulating glycine levels are frequently linked to cardiovascular disease (CVD); however it is still unknown whether glycine has a causal or therapeutic function in atherosclerosis, the primary factor in most CVDs. Following the discovery that individuals with severe coronary artery disease (sCAD) had lower levels of circulating glycine, we looked into the possibility that glycine plays a causal role in atherosclerosis by altering the availability of glycine in atheroprone mice. We also assessed DT-109's potential for atheroprotection, a newly discovered glycine-based molecule with dual lipid and glucose-lowering characteristics. In apolipoprotein E-deficient (Apoe/) mice, glycine deprivation accelerated atherosclerosis development whereas glycine supplementation slowed it down (Rom O et al., 2016). The most notable atheroprotective benefits were shown with the use of DT-109, which also decreased superoxide levels and atherosclerosis across the whole aortic tree and aortic sinus. With no lipid-lowering effects, DT-109 therapy dramatically decreased aortic superoxide and atherosclerosis in Apoe/ animals with advanced atherosclerosis. Studies on the kinetics and targeted metabolomics of DT-109 have shown that it causes mononuclear cells to produce glutathione. Glycine and DT-109 reduced the production of superoxide in bone marrow-derived macrophages (BMDMs) in response to glycine deprivation. This was eliminated in glutamate-cysteine ligase modifier subunit-deficient (Gclm/-) animals, which have a problem with glutathione production. Glycine deficit reduces glutathione production in BMDMs, but glycine-based therapy stimulates de novo glutathione biosynthesis, according to metabolic flow and carbon tracing tests. We showed that glycine plays a causal role in atherosclerosis and identified glycine-based therapy as a strategy through investigations in patients with CAD, in vivo studies using atherosclerotic mice, and in vitro studies utilizing macrophages.

Keywords: Amino acids, Atherosclerosis, Glutathione, Glycine, Macrophages

INTRODUCTION

The simplest of the 20 natural amino acids, glycine, is regarded as a nonessential amino acid since it may be produced endogenously. But prior research suggests that glycine production could not be enough to satisfy the organism's metabolic requirements, indicating that glycine is just a conditionally necessary amino acid. In addition to its numerous biochemical and physiological functions, glycine is required for the production of numerous vital compounds, including glutathione, heme, creatine, and purines. Acute myocardial infarction, obesity, type 2 diabetes (T2D), metabolic syndrome, non-alcoholic fatty liver disease (NAFLD), coronary heart disease, and other cardio metabolic disorders have all been linked to lower circulating levels of glycine. We and others have shown that low glycine availability is a barrier to glutathione production. Glycine supplementation corrects this, which reduces oxidative stress in NAFLD and T2D. Although putative pathways by which glycine protects against NAFLD and T2D have been found, it is still unknown what function glycine plays in the development of atherosclerosis, the underlying condition that underlies the majority of CVDs (Hampton T, 2017).

Atherosclerosis is a chronic artery disease caused by abnormal immune response, uneven lipid metabolism, and deregulated redox homeostasis. The biological

consequences of underlying risk factors such as dyslipidemia, T2D, obesity, and NAFLD lead to the development of atherosclerosis. The risk of cardiovascular events and mortality is dramatically decreased when certain risk factors are reduced. Due to its recognized significance in atherosclerotic cardiovascular disease, current treatment guidelines concentrate on lowering circulating cholesterol, especially low-density lipoprotein cholesterol (LDL-C) (CVD). However, several clinical trials with statins, non-statins, and combination therapy have revealed persistent residual risk of atherosclerotic CVD, which remains a top cause of mortality globally, despite impressive advancements in LDL-C-lowering medications (Rom O, 2018). This is probably because current cholesterol-lowering treatments have little to no effect—or perhaps have negative effects—on cardio metabolic risk variables other than LDL-C. For example, although significantly decreasing LDL-C, statin medication increases the chance of newly developing T2D, causes a rise in body weight, and has no discernible benefit for NAFLD (Caldow MK et al., 2016). In order to lessen the burden of CVD, it is crucial to find novel metabolic pathways that may be targeted for the treatment of atherosclerosis without rising, and ideally while lowering, other cardio metabolic risk factors (Heresco-Levy U et al., 1999). There is a compelling case for examining the causal role of glycine in atherosclerosis as well as its therapeutic potential given the numerous publications associating reduced circulating glycine with a variety of cardio metabolic illnesses and its protective benefits in NAFLD and T2D.

DISCUSSION

We investigated a lower dosage of DT-109 (0.5 mg/g body weight/day), which we previously showed to improve advanced NAFLD in mice, and 2) employed an experimental technique to imitate established atherosclerosis followed by a lipid-lowering regimen to increase the translational relevance of the current investigation. Using this method, we were able to assess DT-109's atheroprotective potential without taking into account its lipid- or glucose-lowering capabilities. In fact, we discovered that switching Apoe/- animals from the WD to a low-fat SD did not further reduce the levels of circulating cholesterol and glucose after DT-109 therapy. DT-109 dramatically decreased atherosclerosis in the whole aortic tree and in the aortic sinus despite the lack of lipid/glucose-lowering effects (Rom O et al., 2017).

Additionally, DT-109 dramatically reduced superoxide in the aortic sinus of Apoe-animals with existing atherosclerosis without having any lipid or glucose-lowering effects, indicating that antioxidant defence is a key mechanism by which glycine-based therapy prevents atherosclerosis.

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