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MEETING ABSTRACT

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Protective effects of pharmacologically decreased long-chain acylcarnitine contents in the preclinical models of diabetes and its complications

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Background: Incomplete fatty acid oxidation and subsequent accumulation of fatty acid intermediates long-chain acylcarnitines have been linked to development of insulin resistance and cardiovascular diseases. We hypothesised that decreasing the long-chain acylcarnitine content may represent an effective strategy for the treatment of diabetes and cardiovascular complications related to diabetes.

Objective: To investigate the protective effects of the acylcarnitine concentration-lowering drug methyl-GBB in experimental animal models of diabetes, cardiac ischemia-reperfusion injury and atherosclerosis.

Methods: Female apolipoprotein E knockout (apoE$^{-/-}$) mice, C57BL/6 male mice fed with high-fat diet, male CD-1 mice, diabetic db/db mice, non-diabetic db/lean male mice and male Wistar rats were used for the experiments. To lower long-chain acylcarnitine contents, chronic methyl-GBB treatment was used. In diabetic mice models, glucose and insulin tolerance tests were performed. In apoE$^{-/-}$ mice, the TNFα concentration in the plasma, the amount of atherosclerotic lesions and the number of immune cells in atherosclerotic lesions were analysed. The effects of methyl-GBB treatment on infarct size were investigated in an isolated rat heart infarction model.

Results: Methyl-GBB treatment induced a substantial decrease in tissue and plasma long-chain acylcarnitine concentrations in both fed and fasted states of animals in all experimental models. Both in db/db and high-fat-diet-fed C57BL/6 mice methyl-GBB administration (5 mg/kg) improved insulin sensitivity and significantly reduced blood glucose and insulin levels. In apoE$^{-/-}$ mice, treatment with methyl-GBB at a dose of 10 mg/kg reduced the TNFα concentration in the plasma 2.4-fold and decreased the infiltration of macrophages and monocytes into the aortic lesions of the aortic root. Furthermore, methyl-GBB treatment reduced the size of atherosclerotic plaques by 36%. The methyl-GBB (20 mg/kg) pretreatment-induced decrease in acylcarnitine content protected against acute ischaemia-reperfusion-induced damage in the isolated rat heart model by decreasing the infarct size by 44%.

Conclusions: Methyl-GBB treatment decreases the acylcarnitine contents and attenuates the development of insulin resistance, atherosclerosis and diminishes the damage induced by ischemia-reperfusion. The pharmacologically reduced long-chain acylcarnitine content represents an effective strategy to improve insulin sensitivity and to protect the heart against ischemia-reperfusion-induced damage and development of atherosclerosis.

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Keywords: long-chain acylcarnitine – methyl-GBB – diabetes mellitus – atherosclerosis – ischemia-reperfusion injury

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