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A novel cardioprotective drug Methyl-GBB decreases long chain fatty acid oxidation and protects against acute myocardial infarction and atherosclerosis

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In the heart, a nutritional state (fed or fasted) is characterized by a unique energy metabolism pattern determined by the availability of substrates. In fed-state physiology an insulin-activated glucose and lactate utilization is increased. We have shown that the increased level of glucose oxidation or reduction of fatty acid load in the fed state provides the basis for protection against myocardial infarction in an experimental rat model of ischemia-reperfusion. Further experiments provided evidence that the changes in long chain acylcarnitine contents orchestrate the interplay between the metabolism of pyruvate-lactate and long chain fatty acids, and thus determine the pattern of energy metabolism in cardiac mitochondria. The accumulation of L-carnitine and its fatty acid esters, acylcarnitines, in tissue or plasma have been linked to the development of type 2 diabetes mellitus and atherosclerosis.

Recently, we discovered a potent inhibitor of L-carnitine biosynthesis and transport, methyl-γ-butyrobetaine (Methyl-GBB), which significantly decreases contents of L-carnitine and acyl-carnitines in heart tissue. As a result, in Methyl-GBB-treated isolated rat hearts, the uptake and oxidation rates of labeled palmitate were significantly decreased by 40%, while glucose oxidation was significantly increased 2-fold. Methyl-GBB at dose 5 mg/kg and 20 mg/kg decreased the infarct size by 45 and 48%, respectively. In vivo pretreatment with Methyl-GBB attenuated the infarct size by 45% and improved 24 h survival of rats by 30%. In apolipoprotein E knockout (apoE-/-) mice Methyl-GBB treatment at a dose of 10 mg/kg decreased the acylcarnitine and L-carnitine levels in the aortic tissues by seventeen- and ten-fold, respectively. This resulted in reduced size of atherosclerotic plaques and decreased accumulation of macrophages and monocytes in the atherosclerotic lesions.

In conclusion, the reduction of L-carnitine and long chain acyl-carnitine content by the inhibition of L-carnitine biosynthesis and transport represents an effective strategy to protect against ischemia–reperfusion-induced damage and atherosclerosis. Methyl-GBB treatment leads to cardioprotective effects by limiting long chain fatty acid oxidation and facilitating glucose metabolism.

Curriculum Vitae

Dr. pharm. Maija Dambrova is the Head of the Laboratory of Pharmaceutical Pharmacology (LPP) of the Latvian Institute of Organic Synthesis and Associated Professor in Riga Stradins University. She has a PhD in Pharmaceutical biosciences from Uppsala University (Sweden) and she also holds a Master of Business Administration degree from Riga International School of Economics and Business Administration. LPP is an outstanding laboratory for biological activity testing and pharmacological investigations with a dedicated research group and up-to-date equipment. Dr. pharm. M. Dambrova is specializing in investigation of the molecular action mechanisms of drugs and newly synthesised compounds for applications in CNS and cardiovascular fields in collaboration with partners in pharmaceutical industry. **Dr. Pharm. Edgars Liepinsh** and **Dr. Pharm. Reinis Vilskersts** are Leading Researchers in the LPP. Their research interests include cardiovascular pharmacology and medicinal chemistry related to the anti-ischemic drugs with novel mechanisms of action, cellular energy metabolism, atherosclerosis and inflammation.

Recent publications:

1. Liepinsh E, Makrecka M, Kuka J, Makarova E, Vilskersts R, Cirule H, Sevostjanovs E, Grinberga S, Pugovics O, Dambrova M, The heart is better protected against myocardial infarction in the fed state compared to the fasted state, *Metabolism Clinical and Experimental*, **2014**, 63:127-136. doi: 10.1016/j.metabol.2013.09.014
2. Liepinsh E, Makrecka M, Kuka J, Cirule H, Makarova E, Sevostjanovs E, Grinberga S, Vilskersts R, Lola D, Loza E, Stonans I, Pugovics O, Dambrova M. Selective inhibition of OCTN2 is more effective than inhibition of Gamma-butyrobetaine dioxygenase to decrease the availability of L-carnitine and to reduce myocardial infarct size. *Pharmacological Research*, **2014**; 85:33-38. doi: 10.1016/j.phrs.2014.05.002.
3. Makrecka M, Kuka J, Volska K, Antone U, Sevostjanovs E, Cirule H, Grinberga S, Pugovics O, Dambrova M, Liepinsh E. Long chain acylcarnitine content determines the pattern of energy metabolism in cardiac mitochondria. *Molecular and Cellular Biochemistry*, **2014**, 395(1-2):1-10. doi:10.1007/s11010-014-2106-3.