National Academy of Sciences of Ukraine

INSTITUTE OF MOLECULAR BIOLOGY AND GENETICS

XVIII All-Ukrainian Conference of Young Scientists May 21-22, 2024

BOOK OF ABSTRACTS

The conference is devoted to the heroic work of Ukrainian scientists during the war

Kyiv 2024

Role of the glyoxylate shunt in metabolic processes and it's potential pharmacological modulation

M.O.Borimskyi, N.O.Posternak
O.O.Bogomolets National Medical University
bieniewskiborims@gmail.com

Introduction. The Glyoxylate Shunt (GS) is an anaplerotic deviation of the Tricarboxylic Acid (TCA) cycle that uses isocitrate and acetyl-CoA as substrates to produce succinate and malate, bypassing the formation of α-ketoglutarate. The main enzymes of the GS are isocitrate lyase (ICL) and malate synthase (MS), which are normally present in prokaryotic organisms and plants, but not in humans. Some research suggests the presence of peroxisomal ICL and MS in human hepatocytes (Davis and Goodman, 1992), but this conclusion is disputable. Several articles (Dean et al., 2009 and 2010) indicate that the GS operates differently in mammals compared to bacterial metabolism. While the GS has potential therapeutic benefits, comprehensive research is still needed for adequate conclusions. **Results**. The article "Resistance of Diet-Induced Obesity in Mice with Synthetic Glyoxylate Shunt" (Dean et al., 2009) accurately describes the results of implementing the GS in transgenic (aceA) mice. Unlike bacterial gluconeogenesis, in mammals, the GS bypasses malate into pyruvate via Malic Enzyme 1 and reduces NADP+. Three lines of human hepatocytes were transfected, and in a marked palmitate medium, transgenic cells absorbed it highly without changing the glucose state. Gluconeogenesis was not disrupted, but glucose consumption fell significantly, leading to reduced ATP levels due to the shortened TCA cycle. *In vivo* testing showed optimistic results. Female rodents were more susceptible to the GS than males. Levels of triacylglycerols, leptin, and adipokine hormones in blood serum fell dramatically without affecting food consumption. Levels of ketone bodies and cholesterol also decreased, potentially reducing LDL levels, although reducing atherogenicity this way is uncertain. Visceral fat was also reduced, which may weaken insulin resistance. Ensembl modeling (Dean et al., 2010) explored that not only sexual dimorphism but also phenotypical diversity could result in different effects of the GS. In some cases, it did not change the rate of fatty acid oxidation, while in others, it decreased glucose consumption by hexokinase inhibition and increased fatty acid oxidation. **Conclusions**. Despite the lack of research in this field, we can hypothesize the potential positive therapeutic effects of implementing the GS in treating diabetes mellitus, atherosclerosis, and obesity. To reduce the disadvantages of the GS, allosteric modulators of hexokinase may be useful. Additionally, different isoforms of GS enzymes and the inclusion of ICL-Kinase might also effectively modulate the action of the GS (Dolan and Welch, 2018).