Editorial

Hyperglycemia and Tumor Energy Metabolism

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Precise and critical analysis of biomedical data is crucial in our understanding of the pathological metabolism and necessary elements in the progress of a new drug development. Therefore this new journal (Journal of Pharmacological & Biomedical Analysis) is an important and welcome initiative for a new communication platform of research community allowing the rapid exchange of the scientific data.

An evolution of our understanding of tumor energy metabolism is a good example how our knowledge is under the constant changes. It was Otto Warburg who in 1956 discovered that for the cancer cells, glycolysis, non-oxidative degradation of glucose is the main source of energy (ATP) [1]. Glucose is the only source of the basic building block for the growing cells eg. ribose source. It seems that hyperglycemia, up normal blood glucose concentration, as seen in diabetic patients, should be a serious risk factor for the cancer diseases. In fact several recent studies prove such conclusion [2-4]. On the cellular level it was reported that hyperglycemia has devastating influence on the cells and induce oxidative stress and ROS (reactive oxygen species) production [5]. Hyperglycemia decrease mitochondrial function and suppress oxidative phosphorylation pushing the cell energy metabolism towards glycolysis (Crabtree effect), and increase mutagenesis also [6,7]. Glucose modulate the mitochondrial adaptation in tumor cells caused an increase in IF1 (inhibitor factor of ATP synthase) expression level [8]. Even transient hyperglycemia causes persistent epigenetic changes and altered gene expression for at least 6 days [9]. Hyperglycemia stabilized hypoxia-inducible factor-1 alpha, crucial for the expression of enzymes from glycolytic pathway [10]. These data do not concern the cases of cancers where the mutation in mitochondrial DNA, resulting in impaired oxidative phosphorylation is observed, because by the definition, their survivals are completely dependent on the glycolysis. It becomes obvious to apply the low carbohydrate or the ketogenic diet as the preventive or therapeutic treatment for the cancer disease [11]. However, overall results from such studies provide only the evidence of limited efficacy. If Warburg hypothesis is right, seems we are missing some important point here. I would like to suggest again [12] that the key factor could be gluconeogenesis. Our body has two sources of glucose, one from the diet and other from the liver and kidney gluconeogenesis. The gluconeogenesis could be activated under certain circumstances despite of normal glucose and insulin level, resulting in the hyperglycemia, a serious risk factor for the cancer development. Such increase in the blood glucose level, could escape of our attention in diet-based treatment. Such circumstances include, fat [13], and growth hormone induced gluconeogenesis (eg. risk of the colorectal cancer [14], stimulation of renal gluconeogenesis by exogenous nucleotide [15], as well as somatostatin [16] and noradrenaline [17] stimulation in the kidney gluconeogenesis of animal models [17]. What is most intriguing, the fructose, being one of the main food carbohydrates induces gluconeogenesis also [18]. Epidermal growth factor stimulates gluconeogenesis at least in isolated rat hepatocytes [19]. It needs to be established in vivo, if some of these effects could lead to rise of glucose level to the stage of hyperglycemia. For the time being it could be advisable to inhibit gluconeogenesis, if we attend to apply the low carbohydrate or ketogenic diet as therapeutic treatment for the cancer. The metformin, a well known and safe inhibitor of gluconeogenesis is the best choice [12].

References


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