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Fund “Nauka” Project № 11012 Resume

“Vitamin K status and indices of energy metabolism in experimental and clinical conditions”

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Osteocalcin (OC) is a bone derived vitamin K dependent protein. It can be found in the circulation as both the carboxylated (cOC) and undercarboxylated form (ucOC). Although it has been considered a bone forming protein, its skeletal function remain elusive. Current research interest has been focused on the role of OC in the regulation of energy metabolism. Preclinical data on genetically modified mice has revealed a hormonal function of OC. OC has been demonstrated to stimulate insulin release and to improve insulin sensitivity of peripheral tissues by increasing adiponectin secretion from adipocytes. In addition, behavioral and cognitive effects have been described for OC. These hormonal, as well as central nervous system effects have been attributed to the ucOC. High levels of ucOC would represent a low status of vitamin K, since this vitamin is involved in the gamma-glutamyl carboxylation of OC. At the same time, evidence points to beneficial effects of vitamin K itself on glucose homeostasis and on cognition.

This discrepancy triggered our interest and we designed experiments to test both effects of vitamin K and OC in a model of metabolic syndrome (MS) in rats as a species that has not been studied in this respect. We used a model that we developed in our department in which rats were fed high fat high fructose diet for 8-12 weeks to present features of MS typical for humans. We assessed parameters of energy metabolism and behavior in intact animals and in rats treated with vitamin K1 or vitamin K2.

We were also interested in the potential role of osteocalcin vitamin K status in regulating glucose homeostasis in humans. Therefore, we examined the levels of cOC and ucOC in children with metabolic syndrome compared to healthy peers.

What we found in the experimental part of our study was that the levels of ucOC were lower in the rats with metabolic syndrome compared to control rats. A negative correlation was established between ucOC and blood glucose, confirming the hormonal activity of ucOC in this animal species. The supplementation of rats with both forms of vitamin K did not alter significantly the levels of ucOC. Vitamin K improved some, but not all signs of MS. Vitamin K1 improved insulin sensitivity, which might have been due to its antioxidant action as revealed by the decrease of markers of oxidative stress in serum and liver. In a separate experimental setting vitamin K2 reduced the elevated blood sugar in rats with MS. In the test for anxiety, rats fed high fat high fructose diet had reduced social interactions and vitamin K2 normalized their behavior demonstrating anxiolytic activity. Both forms of vitamin K prevented the signs of depression in the forced swimming test. No effect was found in the test

assessing memory function. These results are compatible with both vitamin K and ucOC being involved in the regulation of metabolic and behavioral functions in rats with MS, though, possibly, via different and independent mechanisms.

In the clinical part of the project, we performed a cross-sectional study, in which we examined 89 children of both genders, divided according to their degree of metabolic derangement in three groups – healthy, overweight and obese. We measured both forms of osteocalcin – cOC and ucOC, adiponectin and leptin in addition to the conventional laboratory parameters characterizing the MS. The levels of cOC progressively declined with the degree of MS. They correlated negatively with blood glucose, HOMA-IR, triglycerides, leptin, BMI, body weight and waist circumference. Positive correlation was found between cOC and adiponectin concentrations. Low levels of cOC were associated with higher systolic and diastolic blood pressure. Overall, these results are in line with the beneficial impact of the good vitamin K status on the parameters of energy homeostasis and cardiovascular aspects of metabolic derangements in human.

Our data are supporting the hypothesis of hormonal activity of osteocalcin, but suggest a different contribution of its carboxylated and undercarboxylated forms in humans and rodents, possibly due to species biological differences.

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