Nutrition, epigenetics and disease - Effects of a ketogenic diet and beta-hydroxybutyrate on crucial epigenetic signatures of the histone code. Analysis of their potential beneficial value in metabolic disorders

Diseases of the circulatory system, including type 2 diabetes, which is suffered by about 90% of diabetics, occupy the first place in the list of civilization diseases of the World Health Organization (WHO). At the base of type 2 diabetes is overweight and obesity, especially ventral, and related metabolic disorders. The pancreatic cells produce insulin, which works by regulating the rate of sugar consumption by tissues, but the amount of hormone is insufficient in relation to the body's needs, due to the fact that the cells have acquired insulin resistance and become less sensitive to the hormone. Recent studies on the etiology of type 2 diabetes indicate that metabolic memory can play a major role in the disease. The phenomenon of metabolic memory is defined as the persistence of adverse effects of metabolic dysfunctions, such as the production and accumulation of potentially harmful substances, even when key metabolic parameters are achieved to an acceptable level. It is believed that in diabetes this phenomenon mediates the long-term microvascular complications leading to the development of diabetic retinopathy, nephropathy or neuropathy, even after achieving sufficient glycemic control.

Diabetic ketoacidosis (DKA), where concentrations of ketone bodies are extremely high, is a serious complication of diabetes, whereby serum concentrations of ketone bodies attain high levels to compensate for the organ’s failure to utilize glucose. Therefore ketone bodies can be either a necessary nutrient or the reflection of a pathological status, depending on their plasmatic concentration. Based on this rationale, and on the recent data from the literature indicating that the ketone body beta-OHBut provides the chemical moiety for a novel histone post translational modification (i.e.: beta-hydroxybutyrylation), we propose to extend the study of this novel epigenetic modification in the endothelium and insulin responsive tissues / cell lines. The aim of the study is twofold: (i) to determine the epigenetic (and consequently transcriptional) effects of beta-OHBut on the endothelium, *via* histone lysine beta-hydroxybutyrylation; (ii) to investigate the hypothesis that physiological concentrations of beta-OHBut (i.e. in the low millimolar range) might protect from diabetic vascular complications.

The rationale for selecting the endothelium as a key target tissue for the action of beta-OHBut rests on the fact that endothelial cells participate to the inflammatory state of the vasculature in diabetes. As an experimental model we gonna use cells with silenced expression of SCOT transferase (OXT1 KDs), responsible for keton body production, as well as endothelial specific SCOT knock-out mice fed with the ketogenic diet scheme (E-SCOT KO).

We postulate that beta-OHBut may counteract endothelial dysfunction arising from exposure of endothelial cells to hyperglycaemia. If this will prove to be the case, our project will attempt at defining the molecular changes taking place on the epigenome to mediate such protection. As beta-OHBut is effective in reducing oxidative stress and inflammation, we believe it is of great interest to evaluate whether its use could prove beneficial in alleviating endothelial and vascular dysfunction.