Evaluation of the molecular basis of ß-hydroxy-ß-methylbutyrate as a tool to support the medical treatment of muscular dystrophies- studies in vivo and in vitro

Muscular dystrophies are neuromuscular degenerative disorders resulting from mutations in the dystrophin gene. Duchenne muscular dystrophy (DMD) is the most frequent of genetic muscular dystrophies. In humans and animals it is characterized by progressive muscle weakness and chronic muscle degeneration, eventually resulting in death. The disease is caused by the absence of dystrophin- a protein responsible for the stability of cellular membrane in muscular fibers. Our research group since early 90-s is involved in the studies on ß-hydroxy-ß-methylbutyrate (HMB) , a metabolite of leucine. We observed that HMB decreases muscle protein breakdown in humans and animals. Protective effects on muscle mass result from the observation that HMB is a source of de novo cholesterol synthesis for new cell membranes or damaged membranes of existing cells. These membranes are becoming more resistant to any potential damage. This could also explain why certain cholesterol synthesis inhibitors can cause severe muscle myopathy. The main objective of the project is to search molecular mechanisms of HMB action in cells isolated from dystrophic patients (humans with Duchenne muscular dystrophy, DMD mutated rats, dogs) and in vivo studies where HMB will be given to DMD mutated rats. We plan to collect blood from DMD rats for the metabolomic studies using our new advanced high resolution mass spectrometer. In all animal and human models HMB will be offered eather as a dietary supplement or as a component added to the incubation medium There are following research tasks in the project: effect of HMB on protein metabolism including changes in gene expression, effect of HMB on autophagy, apoptosis and regulation of death pathways, effect of HMB on mitochondrial biogenesis and skeletal muscle health, HMB role in myogenic cell proliferation, HMB role in cholesterol synthesis and its impact on cellural membrane stability and CK activity, comparison of the rat dystrophy and canine dystrophy with the human Duchenne dystrophy. Our studies, however basic in their nature, may have potentially practical future implications in the treatment of muscular dystrophy, in addition to the standard corticosteroid treatment. We are inspired by our observations that children with DMD receiving HMB for a long time improved their muscle strength and performance. Parents of sick kids reported an improvement in the motion of their children, slower progression of a disease, better tolerance to exercise and improved walking ability. In all HMB-treated children there was significant decrease in the activity of serum creatine phosphokinase (CPK) when compared with patients not treated with HMB. All these observations has not been published yet and in the available literature there are no data about the use of HMB in DMD kids and dystrophic dogs and rats. So proposed project would be the first attempt to study various molecular mechanisms of HMB action in dystrophic rats as well as in human and animal cells from dystrophic patients.