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MEETING ABSTRACT

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Identification of targets in the energy metabolism pathways for possible treatment of sepsis

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Background: Sepsis, a life-threatening organ dysfunction induced by infection, is a leading cause of death among critically ill patients. Current immunological pathways cannot fully explain the mechanisms of cellular dysfunction and organ failure in sepsis. Significant impairments in energy metabolism and mitochondrial dysfunction are associated with morbidity in sepsis. However, the role of energy metabolism and mitochondrial function in the progression of sepsis-induced multi-organ dysfunction is not fully understood.

Objectives: The aim of the study was to identify the energy metabolism pathways responsible for sepsis-induced multi-organ dysfunction in the experimental model of endotoxemia.

Methods: A single injection of LPS (10 mg/kg, i.p.) was used to induce endotoxemia in CD1 male mice. The control animals received a saline injection. During the experiment the animals were deprived of food. The plasma biochemical parameters, energy substrate uptake, mitochondrial function and gene expression in heart, brain and kidneys were determined 4 and 24 h after LPS injection.

Results: In LPS-induced mice model of sepsis the hypoglycemia and hyperinsulinemia were observed. In heart, brain and kidneys, the fatty acid uptake was decreased by 43%, 31% and 34%, respectively, while glucose uptake was decreased by 59%, 26% and 51%. 4 h after administration of LPS, the mitochondrial dysfunction was observed in kidney, but not in heart or brain. Moreover, increase in markers related to kidney function (blood urea and creatinine) also indicated on kidney damage. The LPS injection induced a decrease in mitochondrial fatty acid oxidation in heart, while electron transfer system oxidative phosphorylation capacity was similar to the control group. The gene expression measurements demonstrated that the genes related to inflammation (*IL1β, IL6, TNFα, iNOS*) are upregulated in all studied tissues, and particularly, in brain tissues. The genes related to energy metabolism (*CPT1A, CPT1B, PDHx*) and to mitochondrial function and biogenesis (*ATP5O, PGC1a*) were downregulated particularly in heart and kidneys.

Conclusions: The obtained results demonstrate that endotoxemia induces tissue-specific and multicomponent failure of energy metabolism pathways. The main strategy for energy metabolism correction for improvement of sepsis outcome could be simultaneous activation of fatty acid oxidation, reduction of hyperinsulinemia and protection of mitochondria.

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Keywords: sepsis – energy metabolism – mitochondrial dysfunction

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