Mitochondrial dysfunctions in inflammation and sepsis

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Sepsis is the leading cause of death in medical intensive care units. In most fatal cases of sepsis the patient experiences the multiple organ dysfunction syndrome (MODS) and tissue hypoxia has long been considered the putative mechanism of MODS. However, enhancement of tissue oxygenation during severe sepsis have proved ineffective and evidences indicate that mitochondria contribute decisively to the pathogenesis of MODS. In addition to dysregulation of oxygen metabolism (‘cytopathic hypoxia’), sepsis-induced mitochondrial dysfunction contributes to organ injury through accelerated oxidant production and cell death. Here, we investigated the changes in mitochondrial functions in three models of inflammation or sepsis: cultured RAW macrophages exposed to LPS, brain mitochondria from a model of sepsis in mice through caecal ligation and puncture (CLP) and peripheral blood monocytic cells from septic human patients at an intensive care unit. Firstly, we observed in RAW macrophages that just 60 minutes of exposure to 0.2 ?g/mL LPS caused a significant increase in oligomycin-induced state 4 respiration, which led to a reduction in respiratory control ratio (RCR), indicating a true uncoupling of oxidative phosphorylation. Sepsis in mice, 24h of CLP, caused major changes in brain mitochondria such as increase in state 4 respiration, which affected both RCR and ADP:O ratio. Moreover, we observed a significant delay in ??m repolarization upon state 3 induced by 200 ? M ADP in brain mitochondria of CLP mice. PBMCs isolated from blood of human septic patients showed a drastic reduction in both state 3 respiration and RCR. Interestingly, we observed an inverse relationship between the state 3 respiration and the norepinephrine requirement of PBMCs from septic patients, suggesting that a reduction in mitochondrial electron flux was correlated with severity of sepsis. Taken together, these data indicate that during inflammation and sepsis, a mitochondrial dysfunction is observed (i.e. uncoupling or impairment of electron transport chain) in a time and tissue dependent manner, which could be involved in the bioenergetic ‘shutdown’ observed in these conditions.

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