SEPSIS-INDUCED CHANNELOPATHY IN SKELETAL MUSCLES IS ASSOCIATED WITH EXPRESSION OF NON-SELECTIVE CHANNELS

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Abstract

Skeletal muscles (similar to 50% of the body weight) are affected during acute and late sepsis and represent one sepsis associate organ dysfunction. Cell membrane changes have been proposed to result from a channelopathy of yet unknown cause associated with mitochondrial dysfunction and muscle atrophy. We hypothesize that the channelopathy might be explained at least in part by the expression of non-selective channels. Here, this possibility was studied in a characterized mice model of late sepsis with evident skeletal muscle atrophy induced by cecal ligation and puncture (CLP). At day seven after CLP, skeletal myofibers were found to present de novo expression (immunofluorescence) of connexins 39, 43, and 45 and P2X7 receptor whereas pannexin1 did not show significant changes. These changes were associated with increased sarcolemma permeability (similar to 4 fold higher dye uptake assay), similar to 25% elevated in intracellular free-Ca2+ thorn concentration (FURA-2), activation of protein degradation via ubiquitin proteasome pathway (Murf and Atrogin 1 reactivity), moderate reduction in oxygen consumption not explained by changes in levels of relevant respiratory proteins, similar to 3 fold decreased mitochondrial membrane potential (MitoTracker Red CMXRos) and similar to 4 fold increased mitochondrial superoxide production (MitoSox). Since connexin hemichannels and P2X(7) receptors are permeable to ions and small molecules, it is likely that they are main protagonists in the channelopathy by reducing the electrochemical gradient across the cell membrane resulting in detrimental metabolic changes and muscular atrophy.

Palabras clave

Palabras clave de autor: Cecal ligature; connexin; connexon; hemichannel; mitochondrial dysfunction; muscle waste; P2X(7) receptor; pannexin

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