Activation of the nlrp3 inflammasome increases the il-1β level and decreases glut4 translocation in skeletal muscle during insulin resistance

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Abstract

Low-grade chronic inflammation plays a pivotal role in the pathogenesis of insulin resistance (IR), and skeletal muscle has a central role in this condition. NLRP3 inflammasome activation pathways promote low-grade chronic inflammation in several tissues. However, a direct link between IR and NLRP3 inflammasome activation in skeletal muscle has not been reported. Here, we evaluated the NLRP3 inflammasome components and their role in GLUT4 translocation impairment in skeletal muscle during IR. Male C57BL/6J mice were fed with a normal control diet (NCD) or high-fat diet (HFD) for 8 weeks. The protein levels of NLRP3, ASC, caspase-1, gasdermin-D (GSDMD), and interleukin (IL)-1β were measured in both homogenized and isolated fibers from the flexor digitorum brevis (FDB) or soleus muscle. GLUT4 translocation was determined through GLUT4myc-eGFP electroporation of the FBD muscle. Our results, obtained using immunofluorescence, showed that adult skeletal muscle expresses the inflammasome components. In the FDB and soleus muscles, homogenates from HFD-fed mice, we found increased protein levels of NLRP3 and ASC, higher activation of caspase-1, and elevated IL-1β in its mature form, compared to NCD-fed mice. Moreover, GSDMD, a protein that mediates IL-1β secretion, was found to be increased in HFD-fed-mice muscles. Interestingly, MCC950, a specific pharmacological NLRP3 inflammasome inhibitor, promoted GLUT4 translocation in fibers isolated from the FDB muscle of NCD-and HFD-fed mice. In conclusion, we found increased NLRP3 inflammasome components in adult skeletal muscle of obese insulin-resistant animals, which might contribute to the low-grade chronic metabolic inflammation of skeletal muscle and IR development. © 2021 by the authors. Licensee MDPI, Basel, Switzerland.

Author keywords

Caspase-1; GLUT4; GSDMD; High-fat diet; Inflammation; Myokines; NALP3