Lack of skeletal muscle IL-6 influences hepatic glucose metabolism in mice during prolonged exercise

The liver is essential in maintaining and regulating glucose homeostasis during prolonged exercise. IL-6 has been shown to be secreted from skeletal muscle during exercise and has been suggested to signal to the liver. Therefore, the aim of this study was to investigate the role of skeletal muscle IL-6 on hepatic glucose regulation and substrate choice during prolonged exercise. Skeletal muscle-specific IL-6 knockout (IL-6 MKO) mice (age, 12-14 wk) and littermate lox/lox (Control) mice were either rested (Rest) or completed a single bout of exercise for 10, 60, or 120 min, and the liver was quickly obtained. Hepatic IL-6 mRNA was higher at 60 min of exercise, and hepatic signal transducer and activator of transcription 3 was higher at 120 min of exercise than at rest in both genotypes. Hepatic glycogen was higher in IL-6 MKO mice than control mice at rest, but decreased similarly during exercise in the two genotypes, and hepatic glucose content was lower in IL-6 MKO than control mice at 120 min of exercise. Hepatic phosphoenolpyruvate carboxykinase mRNA and protein increased in both genotypes at 120 min of exercise, whereas hepatic glucose 6 phosphatase protein remained unchanged. Furthermore, IL-6 MKO mice had higher hepatic pyruvate dehydrogenase (PDH) Ser232 and PDH Ser300 phosphorylation than control mice at rest. In conclusion, hepatic gluconeogenic capacity in mice is increased during prolonged exercise independent of muscle IL-6. Furthermore, skeletal muscle IL-6 influences hepatic substrate regulation at rest and hepatic glucose metabolism during prolonged exercise, seemingly independent of IL-6 signaling in the liver.
Mellemkødet sladrer om skadelige kemikalier

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Lack of skeletal muscle IL-6 affects pyruvate dehydrogenase activity at rest and during prolonged exercise

Pyruvate dehydrogenase (PDH) plays a key role in the regulation of skeletal muscle substrate utilization. IL-6 is produced in skeletal muscle during exercise in a duration dependent manner and has been reported to increase whole body fatty acid oxidation, muscle glucose uptake and decrease PDHa activity in skeletal muscle of fed mice. The aim of the present study was to examine whether muscle IL-6 contributes to exercise-induced PDH regulation in skeletal muscle. Skeletal muscle-specific IL-6 knockout (IL-6 MKO) mice and floxed littermate controls (control) completed a single bout of treadmill exercise for 10, 60 or 120 min, with rested mice of each genotype serving as basal controls. The respiratory exchange ratio (RER) was overall higher (P<0.05) in IL-6 MKO than control mice during the 120 min of treadmill exercise, while RER decreased during exercise independent of genotype. AMPK and ACC phosphorylation also increased with exercise independent of genotype. PDHa activity was in control mice higher (P<0.05) at 10 and 60 min of exercise than at rest but remained unchanged in IL-6 MKO mice. In addition, PDHa activity was higher (P<0.05) in IL-6 MKO than control mice at rest and 60 min of exercise. Neither PDH phosphorylation nor acetylation could explain the genotype differences in PDHa activity. Together, this provides evidence that skeletal muscle IL-6 contributes to the regulation of PDH at rest and during prolonged exercise and suggests that muscle IL-6 normally dampens carbohydrate utilization during prolonged exercise via effects on PDH.
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