Title
Studies on the regulation of fat metabolism during endurance exercise

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Abstract

Chapter 1

Moderate-intensity running (treadmill velocity, 21 m/min) increased the lactate and active transforming growth factor-β (TGF-β) concentrations in rat blood and cerebrospinal fluid (CSF), respectively. In contrast, low-intensity running (15 m/min) did not alter blood lactate and CSF TGF-β concentrations. Intraperitoneal (i.p.) administration of lactate to anesthetized rats increased blood lactate concentration to a value close to that observed after a 21 m/min running exercise and increased the level of active TGF-β in the CSF. In contrast, intraperitoneal administration of lactate at the same dose to awake and unrestricted rats decreased the respiratory exchange ratio, i.e., enhanced fatty acid oxidation and depressed spontaneous motor activity (SMA). Given that intracisternal administration of TGF-β to rats enhances fatty acid metabolism and depresses SMA, we surmise that the changes caused by i.p. lactate administration were mediated, at least in part, by TGF-β in the brain.

Chapter 2

Moderate-intensity exercise (above the blood lactate threshold) increased active TGF-β level in the CSF, and this increase enhanced fatty acid oxidation. The present study investigated whether MMP, integrins, plasmin, or thrombospondin-1 (TSP-1) is required for activation of TGF-β in the brain following i.p. administration of lactate and whether blockade of TGF-β activation in the brain by TSP-1 decreases whole-body fatty acid oxidation during physical exercise. The author showed that the increase in active TGF-β level in the brain following i.p. administration of lactate was mediated via TSP-1-dependent activation of TGF-β and that inhibition of TSP-1-dependent TGF-β activation in the brain reduced whole-body fatty acid oxidation during physical exercise. These findings support the hypothesis that increase in blood lactate concentration due to physical exercise induces TSP-1-mediated TGF-β activation in the brain, which in turn enhances whole-body fatty acid oxidation.

Chapter 3

Fatty acids (FAs) are an important energy source during exercise. In addition to their role as an energy source for skeletal muscle, FAs may activate signaling pathways that regulate gene expression. Cluster of differentiation 36 (CD36) and G protein-coupled receptor 120 (GPR120) are long-chain FA receptors. This study investigated the impact of deletion of CD36 or GPR120 on energy metabolism during
exercise. CD36 has been reported to facilitate cellular transport and FA oxidation during endurance exercise. Using a combination of $^{13}$C-labeled FA oxidation measurement and indirect calorimetry, the author showed that CD36 deletion decreased exogenous FA oxidation during exercise. In contrast, GPR120 deletion had no observable effect on energy metabolism during exercise. These results further substantiate that CD36-mediated FA transport plays an essential role in efficient FA oxidation during exercise.