

## Abstract

Studies on endurance exercise training adaptation and endurance performance in mice under different pharmacological, physiological, and dietary conditions

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Endurance training leads to changes in whole-body metabolism, phenotype and endurance improvements through the activation of contraction-induced signals. Downstream to these signals are transcription factors that control genes that regulate cellular metabolism and overall adaptation to increased energy demand brought about by exercise. As these transcription factors are also activated by non-contraction signals e.g. pharmacological metabolic activators, and nutrients such as fatty acids and carbohydrates, it goes to say that endurance training together with pharmacological or dietary manipulation could influence downstream adaptations. Likewise, genetic background which could influence the chemical milieu of cells, particularly the muscle could also affect training-induced adaptations. In this doctoral thesis, adaptations that occur in training with pharmacological, genetic or physiological, and dietary environment was investigated.

Pharmacological agents that activate the AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor delta (PPAR $\delta$ ) have been considered as exercise mimetics. Their individual use causes changes on muscle physiology and endurance performance that are somewhat similar to that of exercise training. However, their simultaneous administration with endurance exercise training have not been investigated. The author determined the effects of their combined pharmacological activation with endurance exercise training in this chapter. Four (4) weeks of daily administration of the AMPK activator AICAR and PPAR $\delta$  selective agonist GW0742 with training on alternate days greatly improved performance than training alone. This could be attributed to increased mRNA expression of the substrate utilization switch pyruvate dehydrogenase kinase 4 (PDK4), preference for fat oxidation during exercise and muscle glycogen accumulation. AMPK

activation with training also improved endurance but modestly relative to training. Increased citrate synthase activity was increased indicating mitochondrial biogenesis. Likewise, muscle glycogen was spared with AICAR administration. These imply that while pharmacological activation of AMPK can potentiate endurance, greater potentiation could be achieved with combined pharmacological activation of AMPK and PPAR $\delta$ .

The uptake of long-chain fatty acids (LCFAs) in cells are mediated by different fatty acid transporters on cell membranes. The major fatty acid transporter in the muscle is CD36. While it has been general knowledge that LCFAs are utilized for energy production, their significant role in fatty-acid mediated signaling by the PPAR family have been recognized in the past decades. Because fatty acid uptake is increased by muscle contraction during training, this could also influence the exercise-training adaptations by influencing PPAR-mediated signaling. In this chapter, the author determined how CD36 influences exercise training adaptations and endurance in chronically trained mice. Exercise training failed to ameliorate endurance in CD36 knock-out (KO) mice despite having similar adaptations in mitochondrial biogenesis and intact albeit lower glycogen accumulation with training as wild-type (WT) mice. Likewise, exercise training-induced whole-body metabolism changes at rest and during exercise, as well as transcriptional increases in PPAR $\alpha$  and PPAR target genes observed in WT mice were absent in KO mice. These findings show the importance of CD36 not only in endurance but also in exercise training-induced adaptive changes in substrate metabolism and PPAR-related transcriptional regulation.

Different fat sources contain varying composition of fatty acids. Fatty acids classified broadly on chain length have been demonstrated to influence metabolism differently. Medium-chain fatty acids (MCFAs) are easily metabolized in cells attributed to their lack of dependence on fatty acid transport proteins unlike LCFAs. Increased endurance in swimming exercise in mice fed with diet supplemented with purified MCFAs were observed in comparison to LCFAs. Also, MCFAs increase mitochondrial biogenesis in the muscle. However, the influence of MCFAs on training adaptations on a treadmill particularly on endurance, whole-body metabolism, substrate handling and transcriptional changes in the muscle and liver remained unexplored. Also, the use of coconut oil as a source of MCFAs and its comparison to diets with different fat content has yet to be studied. In this chapter, the

author compared the effects of low-fat diet and medium-fat diets containing coconut oil and soybean oil on exercise training adaptations. Coconut oil modestly improved endurance attributed to increased fatty acid oxidation markers in the muscle. With training, all diet groups increased endurance likely through increased mitochondrial functions, and exercise efficiency. Despite this, coconut oil showed inhibition of training-induced increase in transcription of PPAR $\delta$  and its targets in the muscle. In the liver, coconut oil increased fatty acid oxidation markers likely through PPAR $\alpha$  activation. Furthermore, while glycogen accumulation was inhibited by coconut oil with training, compensatory mechanisms by glycogen sparing through ketogenesis and ketolysis possibly prevented impairment of endurance in this group. These findings show that training improves endurance by generally improving muscle mitochondrial biogenesis however, transcriptional and metabolic adaptations in the muscle and liver are diet-dependent.

Overall, this thesis explored the complex interaction of non-contraction stimuli and contraction with exercise on different training adaptations in endurance, whole-body metabolism and local adaptations in the muscle and liver. Results presented in this thesis show that in a healthy and genetically intact state, training primarily determines the endurance performance of mice. Furthermore, pharmacological compounds that alter metabolism as well as natural compounds commonly found in food can variably impact adaptations that occur during endurance exercise training. Data from this thesis may suggest a potential use of nutritional supplementation or alteration in the diet for the improvement of endurance of genetically compromised individuals predisposed with impaired metabolism.