【博士論文本文の要約】Protective effects of estrogen replacement on glucose metabolism via insulin-signaling pathway and the complementary effect of endurance running exercise in postmenopausal model rats

Abstract of Doctoral Thesis

Protective effects of estrogen replacement on glucose metabolism via insulin-signaling pathway and the complementary effect of endurance running exercise in postmenopausal model rats.

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ABSTRACT

Menopause predisposes women to impaired glucose or lipid metabolism, but the role of estrogen (E2) remains unclear. This study was designed to investigate in protective effects of E2 replacement on glucose metabolism via insulin-signaling pathway and the complementary effect of endurance running exercise (Ex) training in postmenopausal model rats. In addition, effects of E2 replacement and Ex training on fatty acid synthesis and oxidation were also investigated. These thesis consists of three chapters.

In chapter 1, I examined the effects of chronic E2 replacement on whole-body insulin sensitivity and insulin signaling in ovariectomized (OVX) rats. In the OVX model, some studies have reported the effects of estrogen on insulin signaling intermediates related to insulin sensitivity. However, the insulin signaling pathway components involved in estrogen's action is not clear and could be possibly influenced by the experimental setting. In this study, Four weeks after OVX, rats were separated into E2 group implanted with pellets containing 17β-estradiol and placebo (Pla) group. Hyperinsulinemic-euglycemic clamp analysis and intravenous glucose tolerance test revealed that whole body insulin sensitivity was significantly lower in the Pla group than in the E2 group. In addition, *in vivo* insulin-stimulated phosphorylation of protein kinase B (Akt)2 and its substrate of 160 kDa (AS160) expression were higher in gastrocnemius muscle of the E2 group than the Pla group. These results suggest that estrogen replacement improves insulin sensitivity by activating Akt2/AS160 pathway in the insulin-stimulated muscle of OVX rats.

In chapter 2, I investigated complementary effects of endurance running Ex training

on hyperglycemia under E2 deficiency in OVX rats in comparison with E2 replacement. The general efficacy and safety of hormone replacement therapy (HRT) for postmenopausal women have been controversial in HRT trials by the Women's Health Initiative. Therefore, it is essential to develop alternative treatments that restore the positive effects of E2 on glucose metabolism. Several human studies show that aerobic Ex is insulin-sensitizing and that training is an effective substitute or adjunct for HRT. However, to my knowledge, mechanisms underlying the abilities of endurance running Ex training to improve glucose metabolism under reduced E2 function are not fully understood. In this study, OVX rats were separated into four groups: E2 group implanted with 17β-estradiol pellets, Pla, Pla/Ex trained by treadmill for 5 weeks, and Pla/ pair-feeding (PF) groups pair-fed to the E2 group for 4 weeks. The Pla/Ex group showed similar body weights to Pla group, which was attenuated in E2 and Pla/PF groups. The endurance running Ex training for 5 weeks attenuated plasma glucose concentration and enhanced phosphorylation of TBC1 (Tre-2, BUB2, CDC16) domain family member 1 (TBC1D1), and glucose transporter 4 (GLUT4) protein level in the muscle compared to the Pla groups. These results suggest that endurance Ex prevents hyperglycemia through the TBC1D1/GLUT4 pathway in muscle by an alternative mechanism to E2 replacement.

In chapter 3, I examined the effects of E2 replacement on lipid metabolism in OVX rats in comparison with endurance running Ex or PF to E2-replaced rat. Menopause and ageing are especially associated with the accumulation of abdominal fat. However, the molecular mechanisms underlying the metabolic actions of estrogen on ovariectomy-induced adiposity are poorly understood. In this study, OVX rats were separated into four groups similar to chapter 2. E2 replacement did not alter lipid metabolism-related proteins in Acetyl-CoA carboxylases (ACC)/ fatty acid synthase (FAS) or ACC/ carnitine palmitoyltransferase I (CTP1) pathway. Similarly, endurance running Ex had no effects on the pathway, though PF enhanced the FAS protein level which might activate a synthesis of fatty acid.

In conclusion, these results suggest that E2 replacement improves insulin sensitivity by activating Akt2/AS160 pathway in the insulin-stimulated muscle and that endurance running Ex training may compensate the preventing effect of E2 on hyperglycemia by

activating TBC1D1/GLUT4 pathway in the muscle of OVX rats. In addition, I showed that E2 replacement and endurance running Ex training had no effects on signaling proteins related to fatty acid synthesis and oxidation in the muscle and mesenteric adipose tissues of OVX rats. In contrast, food restriction might have an adverse effect on lipid metabolism in the muscle. These results provide insights into the protective effects of estrogen and the alternative effects of endurance Ex on impaired glucose metabolism under reduced E2 function in postmenopausal women.