Karolinska Institutet

**Institutionen för molekylär medicin och kirurgi**

# THE ROLE OF STEROID HORMONES IN SKELETAL MUSCLE METABOLISM

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska Institutet offentligen försvaras i Farmakologens föreläsningssal, Nanna Svartz väg 2 på engelska språket

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# ABSTRACT

Steroid hormones play important roles in the regulation of whole body metabolism. Skeletal muscle is an insulin-responsive organ with a key role in overall substrate metabolism. Disturbances in skeletal muscle metabolism, as a result of hormonal imbalance may be an underlying defect in metabolic disease. Reduced insulin-responsive glucose disposal in skeletal muscle is a characteristic feature of metabolic syndrome. The overall aim of this thesis work is to identify the role of steroid hormones on glucose and lipid metabolism; and to dissect the impact of sex steroid hormones on insulin signaling pathways in human skeletal muscle. A further goal is to understand how sex differences impact on skeletal muscle metabolism.

Whole body metabolism differs between men and women, and sex-dependent differences in gene expression are evident in skeletal muscle biopsies. Some sex-dependent differences in gene expression are retained *in vitro* in cultured human skeletal muscle. In contrast, glucose and lipid metabolism did not show any sex-dependent differences. Chronic exposure of muscle cell cultures to physiological doses of testosterone or 17 β-estradiol resulted in sex-dependent responses. Exposure to testosterone enhanced palmitate oxidation, AMP dependent protein kinase phosphorylation and *IRS2* gene expression in myotubes from both sexes, while 17 β-estradiol exposure increased palmitate oxidation in myotubes from male donors only and *PDK4* gene expression from female donors only. Testosterone or 17 β-estradiol treatment enhanced insulin-stimulated glucose incorporation into glycogen and AKT phosphorylation only in myotubes from female donors. Acute supra-physiological doses of testosterone or 17 β-estradiol reduced glucose metabolism, independent of sex origin of the cells. Moreover, acute testosterone treatment increased basal palmitate oxidation and disrupted the insulin-suppressive effect on palmitate oxidation.

Increased glucocorticoid action leads to reduced whole body insulin action and may predispose to type 2 diabetes. Local conversion of cortisone to active cortisol by the enzyme 11β-hydroxysteroid dehydrogenase in target tissues may regulate tissue-specific roles of glucocorticoids in patho-physiological states. Chronic high dose exposure to cortisol or cortisone reduced glucose metabolism, and enhanced palmitate oxidation, via induction of PDK4 expression in myotubes. siRNA-mediated reduction or pharmacological inhibition of HSD1 prevented the effects of cortisone, but not cortisol, on metabolic responses.

In conclusion, steroid hormones exert diverse effects in a dose and time dependent manner. Modulation of steroid hormone actions at specific regulatory steps may provide potential therapeutic entry points for metabolic disease and Type 2 diabetes. Moreover, attention should be focused on understanding sex-dependent differences in metabolic disease, and sex-origin of cells is important to consider when assessing hormonal responses in culture.


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