The role of glucocorticoid receptor signaling in metabolic disease: a matter of time and sex

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6

English Summary

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List of publications

Curriculum vitae

Acknowledgement

ENGLISH SUMMARY

Glucocorticoids are essential modulators of the stress response and metabolic homeostasis. However, their long-term elevation can lead to many adverse effects, including muscle atrophy, glucose intolerance and obesity. This dissertation addresses differential aspects of glucocorticoid signaling in metabolic diseases, focusing on how sex differences and circadian rhythm influence glucocorticoid effects. We focused on how GR signaling differs between sexes and how circadian timing modulates glucocorticoid-induced metabolic dysregulation.

In **Chapter 1,** a general introduction to the physiological importance of glucocorticoid signaling and the pathological outcome arising from its dysregulation was given. This chapter points out how widely synthetic glucocorticoids are used in the medical treatment of a wide range of inflammatory and autoimmune diseases and that their long-term use causes metabolic side effects. It also outlines that understanding the involvement of sex-specific differences and the circadian rhythm may improve therapeutic strategies.

In **Chapter 2**, we investigate sex differences in glucocorticoid-induced muscle atrophy using a mouse model. Muscle atrophy has been well documented in patients with prolonged use of synthetic glucocorticoids and Cushing Syndrome. We found that female mice show greater loss in muscle function after chronic exposure to corticosterone as compared to male mice, while both sexes exhibit similar muscle mass loss. Transcriptomic analysis reveals that male skeletal muscle undergoes more pronounced transcriptional changes as compared to female muscle, suggesting that sex hormones including androgens may play a protective role. These findings highlight the importance of sex in glucocorticoid-induced muscle atrophy.

The circadian rhythm refers to the biological processes that occur within a cycle of 24 hours. In humans, glucocorticoids levels peak in the early morning, and the timing of administration has significant biological consequences. **Chapter 3** highlights that the circadian rhythm affects the outcome of synthetic glucocorticoid treatment. We found that administering synthetic glucocorticoids at te wrong time of the day (misaligned with the circadian rhythm) exacerbated insulin resistance and hyperinsulinemia. In contrast, the administration of glucocorticoids aligned with the endogenous circadian rhythm results in fewer metabolic side effects. These findings suggest that glucocorticoid chronotherapy can potentially minimize metabolic complications and thereby improving treatment outcomes.

Polycystic ovary syndrome (PCOS) is a prevalent endocrine disorder in women, which is characterized by increased levels of androgens like testosterone in women, and by symptoms including insulin resistance and obesity. In **Chapter 4**, we investigated if glucocorticoid signaling plays a role in the metabolic symptoms associated with PCOS. We found that chronic exposure of female mice to androgens resulted in hyperglycemia and glucose intolerance. Androgens also upregulate the glucocorticoid receptor, and other factors involved in glucocorticoid signaling. For this reason we investigated if blockade of the glucocorticoid receptor is a promising approach for PCOS, and we found that preventive but not therapeutic treatment mitigated the metabolic abnormalities associated with PCOS. This study supports recent findings indicating significant overlap between androgen and glucocorticoid signaling pathways in various metabolic tissues and shows a possible role of glucocorticoids in PCOS

Chapter 5 is the general discussion in which the implications of the studies in this thesis are discussed. This chapter underlines the importance of considering sex and timing in glucocorticoid therapies to minimize adversity and maximize therapeutic efficacy. Further studies will be necessary for the molecular mechanisms which determine sex differences in the glucocorticoid sensitivity in metabolic tissues. This thesis contributes to our understanding if the complex interactions between glucocorticoid signaling, sex steroids, and circadian rhythm. These studies highlight the sexually dimorphic responses and the critical role of treatment timing, offering valuable insights for the optimizing glucocorticoid therapies and provide important guidance for developing novel strategies in the management of metabolic diseases.