The role of estrogen in hypothalamic regulation of hypothalamus-pituitary-adrenal axis activity, energy homeostasis and bone metabolism
Liu, Ji

Citation for published version (APA):
Liu, J. (2013). The role of estrogen in hypothalamic regulation of hypothalamus-pituitary-adrenal axis activity, energy homeostasis and bone metabolism

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Summary
Summary

Sex differences have been found in many homeostatic domains, including the stress response, energy metabolism and fat distribution. In the present thesis, I studied the involvement of the female hormone estrogen in the occurrence of these sex-differences, more specifically I focused on the brain-mediated effects of estrogen on the regulation of a number of neuroendocrine responses.

In the first Chapter, I shortly reviewed the current knowledge on the synthesis of endogenous estrogen in the central nervous system, the estrogen signal transduction cascade and hypothalamo-pituitary-gonadal (HPG) axis regulation. In the hypothalamus, estrogen is locally produced from testosterone by the enzyme aromatase. Local estrogen levels in the brain may therefore fluctuate independently from circulating estrogen levels in plasma. In addition, I discussed the distribution of the different estrogen receptors within hypothalamus and the possible functional connection between brain estrogen on the one hand, and HPA-axis activity, energy expenditure, body fat distribution and bone metabolism on the other hand.

In Chapters 2 and 3, I presented experimental evidence that central estrogen influences HPA-axis activity during both basal and stress conditions. In Chapter 2 we show that exposure to stress affects local hypothalamic estrogen production and estrogen receptor expression. These findings drove us to unlock further the details of this interaction in Chapter 3. We found that under basal conditions stimulation of the estrogen receptor alpha exerts a positive effect on HPA-axis activity, while during stress conditions both estrogen receptor alpha and beta activation modulate HPA-axis activity. Therefore, the final output of the HPA-axis is determined by the opposite effects of estrogen receptor alpha and beta activation.

In Chapters 4 and 5 I studied the hypothalamic effects of estrogen on glucose metabolism and fat distribution. We revealed for first time the direct effects of hypothalamic estrogen on glucose metabolism. The stimulatory effect of estrogen in the ventromedial hypothalamus (VMH) on hepatic glucose production is mediated via the sympathetic nervous input to the liver. Most likely also the effects of estrogen in the PVN and VMH on glucose uptake are mediated via the autonomic nervous system, although we have not been able to prove this in our current series of experiments. The modulatory effects of estrogen on glucose metabolism may ultimately also affect energy metabolism, and result in altered fat deposition and body weight gain. These findings led me to investigate further the effects of hypothalamic estrogen on body fat distribution and gene expression in adipose tissue in Chapter 5. We showed that hypothalamic estrogen is sufficient to change body fat distribution, to activate brown adipose tissue, and to up-regulate lipolytic gene expression within white adipose tissue.

Bone loss is a well-known consequence of the decline of endogenous estrogen levels during the female menopause. In Chapter 6, we investigated possible regulatory effects of
Summary

hypothalamic estrogen on bone formation and found the first evidence that hypothalamic estrogen may be a determinant of bone formation. Finally, in chapter 7 I discussed the implications and limitations of the results presented in this thesis as well as their clinical relevance.