The role of estrogen receptor α in the regulation of bone mass

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 11 januari 2019, klockan 09:00

av Helen Farman
Fakultetsopponent:
Professor Mustapha Kassem
Klinisk institut, Syddansk Universitet, Odense, Danmark

Avhandlingen baseras på följande delarbeten


The role of estrogen receptor $\alpha$ in the regulation of bone mass

Helen Farman
Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.

Abstract
Estrogens are major regulators of skeletal growth and maintenance in both females and males. Estrogen receptor $\alpha$ (ER$\alpha$) is the main mediator of estrogenic effects in bone. Thus, estrogen signaling via ER$\alpha$ is a target for treatment of estrogen-related bone diseases including osteoporosis. However, treatment with estrogen leads to side effects in both genders. The aim of this thesis was to characterize different ER$\alpha$ signaling pathways in order to increase the knowledge regarding the mechanisms behind the protective effects of estrogen on bone mass versus adverse effects in other organs.

We have evaluated the role of ER$\alpha$ expression in two distinct hypothalamic nuclei. Female mice lacking ER$\alpha$ expression in proopiomelanocortin (POMC) neurons, mainly found in the arcuate nucleus, displayed substantially enhanced estrogenic response on cortical bone mass while lack of ER$\alpha$ in the ventromedial nucleus revealed no effects on bone mass. We therefore propose that the balance between inhibitory effects of central ER$\alpha$ activity in hypothalamic POMC neurons and stimulatory peripheral ER$\alpha$-mediated effects in bone determines cortical bone mass in female mice.

We have also evaluated the role of ER$\alpha$ signaling pathways in males. We found that the ER$\alpha$ activation function (AF)-2 was required for the estrogenic effects on all evaluated parameters. In contrast, the role of ER$\alpha$AF-1 was tissue specific, where trabecular bone was dependent on ER$\alpha$AF-1, while effects on cortical bone did not require ER$\alpha$AF-1. In addition, all evaluated effects of the selective estrogen receptor modulators (SERMs) were dependent on a functional ER$\alpha$AF-1.

In addition to nucleus, ER$\alpha$ is also located at the plasma membrane, where it can initiate extra-nuclear signaling. We found that extra-nuclear ER$\alpha$ signaling affects cortical bone mass in males and that this effect is dependent on a functional ER$\alpha$AF-1.

To further determine the role of membrane-initiated ER$\alpha$ signaling, we used a mouse model lacking an ER$\alpha$ palmitoylation site, which is crucial for membrane localization of ER$\alpha$. We showed that membrane ER$\alpha$ signaling is essential for normal development and maintenance of trabecular and cortical bone, and is crucial for normal estrogen response in both trabecular and cortical bone in male mice.

The studies presented in this thesis have increased our knowledge regarding estrogen signaling pathways in both females and males and may contribute to the design of new, bone-specific treatment strategies that maintain the protective effects of estrogen but minimize the adverse effects.

Keywords: estrogen receptor $\alpha$, bone, estrogen

ISBN 978-91-7833-252-6 (PDF)