Citation: IBMS BoneKEy **9,** Article number: 202 (2012) | doi:10.1038/bonekey.2012.202

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COMMENTARY

Estrogen-BDNF signalling in neuronal cells: toward a brain-centric approach to the cure of aging and osteoporosis

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IBMS BoneKEy **9**, Article number: 202 (2012) | doi:10.1038/bonekey.2012.202; published online 10 October 2012

Commentary on: Ohlsson C, Engdahl C, Borjesson AE, Windahl SH, Studer E, Westberg L, Eriksson E, Koskela A, Tuukkanen J, Krust A, Chambon P, Carlsten H, Lagerquist MK. Estrogen receptor-α expression in neuronal cells affects bone mass. *Proc Natl Acad Sci USA*. 2012; **109**: 983-988.

Ohlsson *et al.*[1] in a recently published *PNAS* paper explored the possible role of central estrogens receptor (ER-α) signalling on bone mass and found that the deletion of ER-α signalling in nestin-ERα$^{-/-}$ mice brain results in high bone mass phenotype. The authors propose that the balance between the well-known peripheral stimulatory ER action and the newly discovered central inhibitory ER-α action determine bone mass with the contribution of the anabolic effect of peripheral leptin on bone. Interestingly, the nestin-ERα$^{-/-}$ mice phenotype appears closely related to the recently reported brain-derived neurotrophic factor (Bdnf)$^{2lox/2lox}$/93 mice, in which BDNF has been selectively deleted from neuronal cells.[2] Which could be the implications of these findings on the whole-organism approach to physiology, can we give new identities to old molecules? The mirror images of this physiological process can be found in disease symptoms and their contributions can be used as a new therapeutic platform toward a brain-centric approach to the cure of aging and osteoporosis.

Several neurotransmitters and hormones are involved in bone homeostasis; one of the top factor as bone regulator is leptin, which regulates food intake and energy expenditure in human and animals.[3] It is also accepted that the sympathetic signalling has a negative impact on bone mass, and the central leptin action on bone is mediated by the sympathetic signalling.[3,4] Despite the observed central catabolic action of leptin on bone, peripheral leptin increases osteoblast differentiation leading to bone formation, thereby suggesting that leptin has opposite central vs peripheral effects on bone.[5] Two other substances, oxytocin and serotonin, have been implicated as regulators of both body weight and bone mass through the leptin-sympathetic transmission showing opposite central vs peripheral effects on bone mass.[6–10] Cytokines and T lymphocytes also have a role in the bone homeostasis as first demonstrated by Lacey *et al.*[11]

The role of estrogens as important endocrine regulators of skeletal growth and maintenance is well known. The physiological effects of estrogens are mediated by two nuclear estrogen receptor, ER-α and ER-β. The protective action against OVX-induced trabecular bone loss is exerted thought ER-α signalling, whereas ER-β is not essential for this bone-protective effect of estrogens.[12] ER are present both peripherally and centrally, and ER-α and leptin are co-expressed in the same hypothalamic areas related to reproductive function and energy metabolism.[13] Whereas peripheral estrogens are known to benefit bone maintenance, our knowledge of effects of central estrogens on bone mass is emerging. An attempt to compare central and peripheral action of estrogens has been addressed, administrating estradiol intracerebroventricularly and subcutaneously, but it failed because estradiol easily pass the blood–brain barrier accrual.[14] To further investigate this point, Ohlsson *et al.*[1] generated Nestin-Cre mice in which ER-α is selectively ablated in the nervous system of female animals. This genetic manipulation led to a significant reduction of ER-α in the hypothalamous and no compensatory effects in the expression of ER-β in other tissues. Prevention of ER-α signalling in the nervous system significantly affects bone mass in both cortical and trabecular districts and in both the appendicular and axial skeleton leading to increased bone mineral density and increased bone strength due to an increased bone formation.

What is the physiological mechanism underling the nestin-ERα$^{-/-}$ phenotype in mice?

A possible disturbed hormonal negative feedback was excluded in the case in nestin-ERα$^{-/-}$ mice as serum levels of sex steroids, estradiol and testosterone, luteinizing hormone and follicle-stimulating hormone show no significant increase. The immune system was also not involved in the regulation of bone mass in nestin-ERα$^{-/-}$ mice, as well as serotonergic and/or adrenergic centrally mediated mechanism.

Ohlsson *et al.*[1] attribute the skeletal phenotype of nestin-ERα$^{-/-}$ to the peripheral effect of leptin on bone. To state so, the author presents the following sequence of evidences:

(i) Serum levels of leptin are increased in these mice, as well as mRNA leptin levels in white adipose tissue (WAT), (ii) retroperitoneal WAT results increased, (iii) hypothalamic mRNA level of leptin receptor was decreased in nestin-ER$\alpha^{-/-}$ mice while the same parameter was unchanged in bone, (iv) the expression of SOCS3 and PTP1b, both negative downstream regulators of leptin signalling,[15] was unaffected in the hypothalamous of nestin-ER$\alpha^{-/-}$ mice indicating that the effect is on the receptor level and not on downstream signalling mechanism. Ohlsson *et al.*[1] conclude that the high bone mass phenotype of nestin-ER$\alpha^{-/-}$ mice is mediated by the anabolic action of leptin on bone and this is explained by the following sequence of events: (i) Prevention of ER-α signalling in the brain leads to decreased expression of leptin receptors in the hypothalamous, (ii) reduced central leptin sensitivity, (iii) increased secretion of leptin from WAT, (iv) elevated serum leptin levels and augmented bone mass for the direct effect of peripheral leptin on bone. Leptin is adipocytes derived; and increased body fat following increased caloric intake is often related to increased circulating leptin levels, which above a physiological threshold can bring to a state of resistance to the hormone that results from impaired central leptin receptor signalling. Of particular note is the fact that in spite of high serum leptin levels and increased retroperitoneal WAT, the authors did not address the measurement of food intake in the nestin-ER$\alpha^{-/-}$ mice. This is not obvious as in a previous murine model likening the human condition of obesity and leptin resistance, and displaying an high bone mass phenotype, as the ob/ob mice, a dramatic increase in food consumption was also reported,[3] whereas in another case of leptin resistance as the murine model of Oxt deficiency, an increased WAT and high bone mass in spite of no changes in food intake has been observed.[7,8] The expression of oxytocin and oxytocin receptor in central and peripheral tissues is ER-α dependent[16] then it is plausible to speculate that the genetic manipulation of ER-α signalling in neuronal cells could also lead to the failure of oxytocin signal in the brain. This could have contributed to the high bone mass reported in nestin-ER$\alpha^{-/-}$ mice. The authors conclude that the effect of ER-α on bone mass is the result of the fine balance between peripheral stimulatory and central inhibitory effect, and that the central and peripheral effects of ER on bone are opposite.

One intriguing part of this study relates to the observation that this genetic manipulation could lead to develop a bone-specific estrogen therapy that separate the peripheral effects of estrogens from the central ones strategically addressing the delivery challenge. This should be aimed to design an ER-α-specific agonist with low penetrance in the blood–brain barrier, thus excluding the negative effects of estrogen therapy on organs others than bone.

Interestingly the bone phenotype of the nestin-ER$\alpha^{-/-}$ appears similar to the one recently reported for the Bdnf$^{2lox/2lox}$/93 in which BDNF has been selectively deleted from the brain,[2] thereby leading to a possible estrogen–BDNF signalling interaction in the regulation of bone mass in these mice.

BDNF is a neurotrophin that promotes synaptic plasticity and is involved in the regulation of food intake and energy expenditure.[17]

The estrogen–BDNF interaction has been extensively demonstrated in hippocampus and hypothalamic neurons and contributes to the neuroprotective effects of estrogen, as well as effects on anxiety, aggression and fear or metabolism.[18,19] At least two possible models have been proposed to explain the estrogen–BDNF interaction: first, the ER-α and BDNF receptors activate a common signalling cascade in neurons; second, estradiol induces the expression of BDNF in hippocampus and hypothalamic neurons. In this context, BDNF has a role as a downstream factor in the estrogen-dependent neurotrophic and metabolic actions.[18]

Similarly to estrogens, peripheral BDNF has a positive effect on bone,[20–22] whereas its deletion in neuronal cells results in augmented bone mass, together with increased abdominal WAT and increased leptin levels in spite of no changes in UCP-1 expression possibly for the anabolic action of peripheral leptin on bone.[2]

The therapeutic implication of these findings relates to the possible actions of peripherally administered BDNF that is hypothesized to exert dual beneficial effects through reversal of low bone mass and obesity crossing the blood–brain barrier and circumventing leptin resistance.[23,24] These data, showing the interaction between central ER-α and BDNF signalling, add further credence that bone mass, metabolism and reproduction are linked.

It has been postulated that, to relieve the symptoms of postmenopausal cognitive decline, as an alternate approach, rational drug design would suggest BDNF therapy, not only because of its potential to activate the signalling pathways normally attributed to estrogens[18] but it also would avoid the health risk associated with estrogens therapy. Cognitive impairment is linked with lower bone mineral density in postmenopausal women.[25] In this context, it is plausible that the therapeutic use of BDNF in association with estrogens replacement could augment the benefit of classical anti-osteoporosis treatment and relief obesity and increase mental capacity.

Conflict of Interest

The author declares no conflict of interest.

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