Roles of membrane estrogen receptor alpha in bone sparing effects of estrogens

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Introduction and objective

Estrogen bone-sparing effects are mediated via Estrogen Receptor alpha (ERα), which stimulates transcriptional action through its two transactivating functions (AF1 and AF2) [3, 4]. Whereas ERα AF-1 plays a crucial role in trabecular bone, not in cortical bone, ERα AF-2 is necessary for the estrogen effects in both types of bone [5]. In addition to these nuclear effects, a fraction of this receptor is targeted to the plasma membrane where it triggers membrane initiated steroid signaling (MIS). A pharmacological approach using an estrogen dendrimer conjugate suggested that the selective activation of membrane ERα is sufficient to elicit a sparing effect in cortical but not trabecular bone [4]. The aim of this study was to define the role of ERαMIS on the beneficial actions of estrogens on bone in vivo, using a mouse model in which ERα membrane localization is abrogated due to a point mutation of the palmitoylation of ERα (C451A-ERα).

ERα expression is preserved in bone tissue of C451A-ERα mice

E2 effects on bone mineral density is partially lost in C451A mice

E2 effects on trabecular bone are mediated in part by ERαMIS

ERαMIS is involved in E2 effects on cortical bone

ERαMIS of medullar compartment is not involved in E2 effects on cortical and trabecular bone

E2 effects on osteoclasts are preserved in C451A mice whereas they are altered in osteoblasts

Conclusion

Using a genomic approach, we demonstrate here that ERαMIS is necessary to elicit a full beneficial effect of estrogens on both trabecular and cortical bone. The use of bone marrow grafts showed that these MISE effects are not mediated by ERα of bone marrow compartment, including osteoclasts and lymphocytes, known to play a role in bone metabolism [5,6]. Accordingly, similar numbers of osteoclasts were found between WT and C451A mice treated by E2 but osteoblasts activity is significantly reduced in C451A mice as revealed by less osteoprogerin level and alkaline phosphatase activity. In accordance with Bartell et al. [4], our results demonstrate that ERαMIS is not only sufficient but also necessary to induce an optimal beneficial effect on trabecular bone. In addition, although selective activation of ERαMIS is not sufficient to induce E2 effect on cortical bone, we show here that ERαMIS is involved in this beneficial action, probably through a crosstalk of nuclear and membrane ERα activities.

References

1 - Bord S et al., J Clin Endocrinol Metab 2001 ; 86 : 3290-94
2 - Sims N et al., J Clin Invest 2003 ; 111 : 1319-27
3 - Botrye-Ass A et al., PLoS One 2003 ; 10 : 6288-93
4 - Bartell S et al., Mol Endocrinol 2013 ; 27 : 649-56
5 - Oral M et al., J Bone Miner Res 2012 ; 27 : 2965-60
6 - Khosla et al., Trends Endocrinol Metab 2012 ; 23 : 576-81