Anti-Osteoporotics for New Century: Now and Then

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Summary: In 2003, WHO compiled its final evaluation of the clinical effectiveness of the 20th century drugs prescribed for post-menopausal osteoporosis (1). Four criteria selected for evaluation were increase in bone mineral density (BMD), and decrease in each fracture rate of vertebral, non-vertebral and hip. Among 16 types of drug intervention, only estrogens and two N-bisphosphonates (alendronate and risedronate)scored positive evidence in every criterion, Ca + vitamin D in three (except vertebral), and raloxifene only in BMD and vertebral. Prevention trials by Ca + vitamin D tends to give variable results (2). All of these drugs are intrinsically bone-protective and not bone-anabolic. Intervention by PTH(1-34), a classical bone anabolic drug, was not available in the old century. The WHO evaluation in general agrees well with the one by the WHI group, indicating that our society still needs more understanding of bone biology in one hand and development of novel drugs, the other.

Recently we have synthesized various series of raloxifene analogs, aiming at, first of all, separating each biological action of estradiol from the other (e.g. bone protective action from thrombogenic, anti-lipemic and/or neuron-protective) and found that, in one of such analogs, MU314, the bone protective action is separable from the anti-lipemic action (3).

In our past search on the mechanism of bone anabolic effect of PTH(1-34), we identified the cAMPpacRap1B-Raf MEKERK signaling route for non-cancer osteoblastic and/or osteocytic lineages of cells (4). Quite recently, Kulkarni et al. noted possible participation of Wnts signaling pathway in the PTH action (5).

Our future prospects are presented for understanding how timely interactions of type 1 PTH/PTHrP receptor with its exogenous and endogenous ligands (PTH and PTHrP)(6) are scheduled to take place for control of normal skeleton formation and maintenance under the influences of novel lines of signaling systems including SOST (7) and mechanical stress (8), and also how estrogen signal basically supports such controling processes.

References:

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