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Anti-arthritic actions of relaxin, in combination with estrogens, in joint and bone tissue

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Summary

The incidence and severity of rheumatoid arthritis decline during pregnancy. However, the role of hormones of pregnancy, including estrogens and relaxin, in attenuating the symptoms of rheumatoid arthritis, including joint inflammation and bone destruction is unknown. In rat adjuvant-induced arthritis, a model for rheumatoid arthritis, relaxin in combination with estrogens, reduced joint inflammation and circulating levels of pro-inflammatory, tumor necrosis factor α. In addition, relaxin together with estrogens, altered systemic levels of bone remodeling markers receptor activator of nuclear factor-kappa B, its ligand and osteoprotegerin to improve bone health when compared with arthritic controls. *In vitro* studies using primary rat osteoblasts and an osteoblast cell line showed a similar bon-saving response to treatment with estrogens in combination with relaxin.

Key words

Relaxin, estrogens, arthritis, joint, bone

Rheumatoid arthritis (RA) is a systemic autoimmune disorder marked by joint inflammation and bone destruction. Symptoms of RA diminish during pregnancy and estrogens are reported to decreases RA progression in humans and rodent models of arthritis. Relaxin (RLX) targets connective tissue and remodels the extracellular matrix in both reproductive and non-reproductive tissues. Estrogen priming can enhance the effects of RLX in target organs. Relaxin, alone and to a greater extent, in combination with estrogens, reduced joint inflammation in a rat model of adjuvant-induced arthritis (Santora et al., 2007). A pregnancy-related increase in joint laxity has been reported that coincides with elevated estrogens and RLX. Bone remodeling is regulated at the molecular level by receptor activator of nuclear factor-kappa B (RANK), its ligand (RANKL) and osteoprotegerin (OPG), the decoy receptor for RANKL. The RANKL/OPG ratio controls the balance between bone formation and resorption and is a marker of RA progression and treatment (Catrina et al., 2006). Thus, the effects of RLX, in combination with estrogens, on bone remodeling were studied *in vivo*, in a rodent model of RA and *in vitro* by studying primary rat osteoblast cells and a murine osteoblast cell line. Treatment with estradiol valerate (E) and RLX reduced disease severity in rats with adjuvant-induced arthritis (AIA). Treatment with E or RLX alone decreased adjuvant-induced inflammation in the injected

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paw and the combination treatment was more effective than either hormone alone in blocking secondary (non-injected) paw inflammation. The reduction in radiographic joint changes was associated with lower systemic tumor necrosis factor (TNF)-α, a pro-inflammatory cytokine, in hormone-treated arthritic rats. The combination of E and RLX resulted in a greater decline in circulating TNF-α than treatment with either hormone alone. Likewise, E and RLX treatment of AIA rats altered systemic levels of bone remodeling markers resulting in a decrease in the RANKL/OPG ratio indicative of improved bone health, when compared to untreated arthritic controls. RLX family peptide receptor 1 gene expression (RXFP1) increased in response to E and E + RLX both *in vivo* in joints of AIA rats and *in vitro* in the UMR-106-01 osteoblast cell line. In primary rat osteoblasts E and RLX increased OPG protein and reduced the RANKL/OPG protein ratio. Together these results indicate that estrogens and RLX contribute to the antiarthritic effects on joints and bone by reducing joint inflammation and decreasing systemic and local proinflammatory cytokines and proteins involved in bone degradation.

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References

Catrina AI et al (2006) Anti-tumor necrosis factor therapy increases synovial osteoprotegerin expression in rheumatoid arthritis. Arthritis Rheum 54:76-81.

Santora et al (2007) Antiarthritic effects of relaxin, in combination with estrogen, in rat adjuvant-induced arthritis. J Pharmacol Expt Therapeutics 322:887-893.