ORAL PRESENTATION



Non-genomic thyroid hormone signaling through NO/cGMP/PKGII

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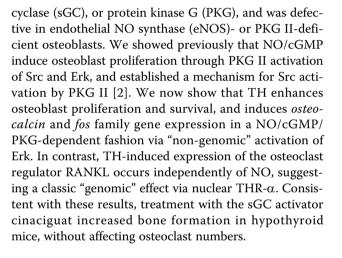
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Background

Skeletal integrity requires continuous bone remodelling by osteoblasts and osteoclasts, and thyroid hormone (TH) is a key regulator of bone remodelling. Excess TH (hyperthyroidism) causes net bone loss, resulting in osteoporosis and increased fracture risk; lack of TH (hypothyroidism) also increases fracture risk because bones become brittle from decreased bone turnover [1]. TH stimulates bone formation and resorption through processes that are only partly defined; it enhances osteoblast proliferation and differentiation, and induces osteoblast production of the osteoclast differentiation factor RANKL (receptor activator of nuclear factor- κ B ligand). Nuclear TH receptors (THR- α and THR- β) act as transcriptional regulators and generate the hormone's classic "genomic" effects [1]. In different cell types, TH also has transcription-independent ("non-genomic") effects, including stimulation of the MEK/Erk and PI3K/Akt/mTOR kinase cascades, but the molecular mechanisms mediating these non-genomic effects are largely unknown.

Results

We found that physiological concentrations of 3,5,3'triiodo-L-thyronine (T3, 10^{-9} to 10^{-11} M), but not reverse-T3, rapidly increase NO production, and activate Src, Erk, and Akt in osteoblasts. These TH effects required THR- α , but were independent of THR- β . We identified a novel, membrane-bound THR- α isoform that mediates T3-induced Erk/Akt activation, but does not affect transcription from TH response element-containing promoters. Signalling via the newly-discovered THR- α isoform was blocked by inhibitors of NO synthase, guanylate



Conclusion

We conclude that anabolic effects of TH in osteoblasts are mediated predominantly by non-genomic TH signalling, via activation of a novel, membrane-bound THR- α isoform, with subsequent activation of eNOS, sGC, PKGII, Src, Erk, and Akt. Our results are consistent with the phenotype of THR- α knockout mice and the role of NO in bone biology.

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