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Invited Plenary Abstract
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Is calcitonin a novel treatment for osteoarthritis?

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Objective: Osteoarthritis (OA) is the most common form of degenerative joint diseases and a major cause of disability and impaired quality of life in the elderly. Experimental and clinical observations suggest that the structural integrity of articular cartilage is dependent on normal subchondral bone turnover, intact chondrocyte function and ordinary biomechanical stresses. Because there is a strong inter-relationship between the subchondral bone and the articular cartilage, an ideal therapeutic agent, in the face of normal biomechanical stresses, might logically be directed at regulating the metabolic activity of both bone and cartilage.
Calcitonin has well-established effects on bone resorption. We have investigated whether calcitonin has direct effect on articular cartilage chondrocytes ex vivo, and in vivo investigated whether a novel oral formulation of calcitonin would improve cartilage health in a non-traumatic model of OA.
Methods: The localisation and expression of the calcitonin receptor in articular chondrocytes was investigated by immunhistochemistry and RT-PCR. Potential direct effects was tested in the articular cartilage explants model, where cartilage degradation was induced by cytokine stimulation of TNF-α [20ng/ml] + oncostatin M (OSM) [10ng/ml], and cultured with salmon or human calcitonin simultaneously [0.0001-1μM]. The changes in cartilage degradation were investigated in the conditioned medium by quantification of C-terminal telopeptides of collagen type II (CTX-II). The effect of calcitonin was investigated *in vivo* using the OVX rats. Rats were administered with an oral dose of calcitonin (2 mg/kg) bound to the carrier 5-CNAC (150 mg/kg) once daily for 9 weeks. Collagen type II degradation was quantified in serum by measuring the released CTX-II. Cartilage erosion in knee joints was evaluated by histology. .
Results: The calcitonin receptor was identified on articular chrondrocytes, both mRNA and protein forms. Culturing articular cartilage explants in the presence of TNF-α and OSM resulted in a marked, 100-fold increase in CTX-II release compared to vehicle-treated controls ($p<0.001$). Addition of salmon calcitonin to the explants culture [0.0001-1μM] in the concomitant presence of TNF-α and OSM resulted in a significant and dose dependent inhibition of CTX II release ($p<0.01$). At 100 nm and 1 μM of calcitonin treatment in the presence of OSM and TNF-α, calcitonin very nearly abrogated collagen type II release, at day 13,16 and 19 of culture. Proteolytic activity was investigated by zymography. TNF-α and OSM resulted in a strong up regulation of MMP-9 activity and expression. This increase in MMP activity was strongly attenuated by calcitonin at 100 nM and 1 μM, and the positive control GM6001 [25 μM], a the general MMP inhibitor, Under *in vivo* conditions, oral treatment with calcitonin induced a 95% decrease in serum CTX-II levels, i.e. chondrocyte-mediated cartilage degradation, and restored cartilage degradation in OVX animals to below sham operated animals.
Conclusions: These results suggest that 1) calcitonin act directly on articular chondrocytes; 2) calcitonin inhibits MMP expression and the related collagen type II degradation, thereby providing direct chondroprotective effects; 3) calcitonin carries potentials for becoming a useful therapeutical option for patients with degenerative joint diseases.