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Anti-degradative and pro-chondrogenic properties of liraglutide, a Glucagon-Like-Peptide 1 Receptor agonist: evidence from preclinical studies and implication for osteoarthritis

Francis Berenbaum*[1], Coralie Meurot[2], Jerome Breton[2], Laure Sudre[3], Carole Bougault[3], Revital Rattenbach[2], Celine Martin[2], Claire Jacques[3]

[1]APHP, Sorbonne University, Rheumatology Department, INSERM UMRS_938, CDR St-Antoine Paris, Paris, France, *[2]4P-Pharma, Lille, France*, *[3]Sorbonne University, INSERM UMRS_938, CDR St-Antoine Paris, Paris, France*

Background:

Osteoarthritis (OA) is a degenerative joint disease affecting millions of individuals worldwide. Its development has been reported to be associated with cartilage degradation and inflammatory responses leading to pain, swelling and reduced function. Although OA is a disorder of the whole joint, the progressive destruction of cartilage extracellular matrix is considered as its hallmark. To date, approved OA treatments are only symptomatic. Therefore, there is an urgent need to explore disease-modifying OA drugs (DMOADs) that can mitigate, stop, or even reverse the development of OA.

Objectives:

In this context, the objective of this study was to assess the effect of liraglutide, a Glucagon-Like-Peptide 1 Receptor (GLP-1R) agonist approved for type 2 diabetes, on chondrogenesis, catabolism/inflammation and cartilage protection in *in vitro* and *in vivo* preclinical models of OA.

Methods:

The capacity of liraglutide to induce chondrogenesis was evaluated using primary human mesenchymal stem cells (hMSCs). Alcian blue staining was used to assess differentiation of hMSC into chondrocyte spheroids. IL-1β-stimulated mouse articular chondrocytes were treated with different concentrations of liraglutide for 24h. Production of matrix metalloproteinase MMP-13, prostaglandin E2 (PGE2) and nitrite was measured by ELISA and Griess reaction, respectively. Exendin 9-39, a GLP-1R antagonist, was used to confirm target engagement in the *in vitro* experiments. Intra-articular (IA) injections of liraglutide or vehicle were performed in the type II collagenase rat model. Histopathological analyses (OARSI scores[1]) were conducted blindly by one investigator.

Results:

Liraglutide induced the differentiation of hMSCs into chondrocytes. Indeed, 21 days after differentiation initiation, 5/6 and 4/6 alcian-blue positive spheroids were observed for 10 and 100nM liraglutide, respectively, versus 0/6 for vehicle. Liraglutide significantly reduced dose-dependently the IL-1β-induced production of PGE2 (5808±178 for vehicle vs 4560±140, 2933±171 and 2365±85 pg/ml for liraglutide 10, 100 and 500nM, respectively, $p \leq 0.001$), nitrite

(24.9±0.4 for vehicle vs 20.9±1.5, 19.1±0.9 and 16.5±0.5 µM for liraglutide 10, 100 and 500nM, respectively, p≤0.001) and MMP-13 (686±9 for vehicle vs 553±3, 402±5 and 297±8 pg/ml for liraglutide 10, 100 and 500nM, respectively, p≤0.001) in murine chondrocytes. Effects of liraglutide were GLP-1R dependent since exendin 9-39 significantly counteracted both chondrogenesis and inflammation/catabolism markers expression. Histological assessment of rat collagenase-injected knee joint revealed a significant (p≤0.05) decrease of the total joint score in the IA Liraglutide treated group (8±4) compared to vehicle (11±4).

Conclusion:

Liraglutide induced chondrogenesis, decreased metalloproteinase and inflammatory mediators production by chondrocytes and protected cartilage in *in vitro* and *in vivo* preclinical OA models, opening the way for repositioning this drug as a potential DMOAD.

References:

[1] Osteoarthritis Cartilage. 2010 Oct;18 Suppl 3:S24-34

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