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"Targeted Activation of Cannabinoid 2 Receptor to Attenuate Painful Synovitis"

Background: Osteoarthritis (OA) causes painful joint stiffness, reducing quality of life and imposing a significant economic burden. The functional limitations associated with OA arise from cartilage degradation, inflammation, fibrosis, osteophytes, and muscle weakening around the joint. The synovial membrane produces joint fluid and is a significant source of sensory nerves that intensify pain during inflammation (synovitis). Synovitis severity is graded based on the amount of inflammatory cell foci in the synovial subintima. Underpinned by the critical need for innovative, longer-lasting anti-inflammatory therapies, non-surgical treatments for OA include opioids, steroids, and hyaluronic acid, which pose risks such as addiction and accelerated disease progression with short-term relief. Interleukin (IL)-1β promotes enzyme-mediated cartilage degradation and initiates inflammation in OA. The cannabinoid 2 receptor (CB2R), highly expressed in synoviocytes, has been associated with anti-inflammatory responses. JWH133 is a CBD analog designed for targeted activaiton of CB2R with 200-fold higher binding affinity than endocannabinoids and CBD. We aim to assess the response of inflammatory synoviocytes to JWH133 compared to CBD. We predict that JWH133 will more effectively reduce the concentration of IL-6 secreted by IL-1β-stimulated synoviocytes compared to CBD.

Methods: Synovial tissue from banked knee OA patients (n=15), stratified into high (n=10) and low (n=5) self-reported pain groups based on microscopic synovitis scores, was processed for histological assessment (H&E) and CB2R immunofluorescence (IIF). CB2R IIF signal was quantified using confocal microscopy and normalized to cell number and tissue area using Slidebook™(3i). Cultured human fibroblast-like synoviocytes (HFLS) were serum-starved, stimulated with IL-1β (4 ng/mL), and treated with 20 μM CBD or JWH133 (dissolved in Cyrene). IL-6 levels in conditioned media were measured by ELISA and normalized to total protein content. Statistical analyses included Student's t-tests for histological comparisons, Pearson's correlation to assess associations, and one-way ANOVA to evaluate in vitro treatment effects with $\alpha = 0.05$.

Results: The mean CB2R expression in the synovium of the low inflammation group (7.62% ± 1.2%) was significantly higher ($p=0.0009$) than in the high inflammation group (3.23% ± 0.41%). An inverse, moderate, yet significant correlation between synovitis and CB2R expression was found ($R = -0.051$; $p < 0.001$). Compared to the cells pre-stimulated with IL-1β and treated with Cyrene vehicle, IL-6 levels were 44% lower in the HFLS pre-stimulated with IL-1β and treated with 20 μM of JWH133 ($p = 0.0198$). CBD decreased IL-6 by 24.65% compared to stimulated Cyrene vehicle controls but without calculated significance.

Discussion: The inverse relationship between CB2R expression and synovitis highlights a therapeutic need in patients with heightened painful inflammation. JWH133 has shown superior efficacy in suppressing IL-6 production compared to CBD, positioning it as a potential anti-inflammatory agent for synovitis. Ongoing evaluation of knee OA patient-derived synoviocytes will further elucidate its therapeutic potential. Future studies should investigate its broader effects on inflammatory pathways, mechanisms of action, and interaction with pain receptors in the synovium. Because the anti-inflammatory effect of CB2R helps modulate cartilage-degrading proteases and fibrous collagen deposition, JWH133 must be evaluated in animal models of OA.