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"Targeting arthralgia in knee osteoarthritis via non-psychoactive cannabinoid mechanisms"

Abstract

Background. Before total knee arthroplasty (TKA), the current non-surgical standard of care for knee osteoarthritis (KOA) involves using drugs like non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and opioids. However, these treatments often provide short-term pain relief and may even worsen KOA in the long term. As TKA procedures are projected to exceed 3.4 million annually by 2040, it is crucial to develop non-addictive, long-lasting, and cost-effective methods to manage KOA arthralgia. The activation of the transient receptor potential vanilloid 1 (TRPV1) channel plays a role in KOA-related pain and inflammation when bound by ligands such as capsaicin and 12-HETE, with CGRP as a byproduct of the binding. Co-activation of TRPV1 and the cannabinoid 2 receptor (CB2R) has been observed in neurodegenerative diseases and painful arthropathy. By exploring novel CB2R analogs and TRPV1 desensitization through cross-activation, we aim to enhance the effectiveness of cannabidiol (CBD) analogs without psychoactive effects. Assessing TRPV1 levels in synovial material, alongside knee injury and osteoarthritis outcome scores (KOOS), can help identify individuals with severe arthralgia who may benefit from cannabinoid-related treatment.

Methods. Immunofluorescence analysis quantifying TRPV1 and PGP9.5 co-expression was performed on 59 synovium samples, as well as 44 separate samples quantifying CB2R. The samples were randomly selected from end-stage knee osteoarthritis (KOA) patients based on pain levels. Expression was assessed using specific antibodies and quantified with SlidebookTM software. Immunofluorescence staining and quantification were performed using confocal microscopy. Statistical analysis involved a two-tailed Student's t-test (α=0.05) to compare mean expression levels between high and low pain groups for TRPV1, PGP9.5, and CB2R.

Results. Significant increases were observed in TRPV1 and PGP9.5 expression in high KOOS pain groups in comparison to low ($p<0.0001$). CB2R expression was mainly observed in synoviocytes of the synovium, with higher expression in the low pain (high KOOS) group compared to the high pain (low KOOS) group ($p<0.0001$). Patients with low pain exhibited 118.70% higher CB2R expression compared to patients with high pain.

Conclusion. The results support the hypothesis that TRPV1 and PGP9.5 levels correlate with KOOS score, indicating their potential as predictors of patient responsiveness to CB2R-specific analogs for synovial modulation. The use of CB2R agonists, such as JWH133, through an intra-articular injection route of delivery may selectively target CB2R and dysregulate TRPV1, offering analgesic effects while minimizing psychotropic effects associated with CB1 receptor activation.