Arthritis

Excerpt from www.arthritis.ca:

Arthritis consists of more than 100 different condition which range from relatively mild forms of tendinitis and bursitis to crippling systemic forms, such as rheumatoid arthritis. It includes pain syndromes such as fibromyalgia and arthritis-related disorders, such as systemic lupus erythematosus, that involve every part of the body. Other forms of the disease, such as gout, are almost never thought of as arthritis, while osteoarthritis is often thought to be the only form of this disease.

JOINT PAIN IS THE MOST COMMON DENOMINATOR

The common denominator for all of these conditions is joint and musculoskeletal pain, which is why they are grouped together as 'arthritis.' Often this pain is a result of inflammation of the joint lining. Inflammation is involved in many forms of arthritis and is the body's natural response to injury. The warning signs presented by inflammation are redness, swelling, heat and pain. When a joint becomes inflamed, it may get any or all of these symptoms. This can prevent the normal use of the joint and therefore it can cause the loss of function of that joint.

ARTHRITIS CAN AFFECT ANYONE

Arthritis can affect babies and children, as well as people in the prime of their lives. Nearly three of every five people with arthritis are of working age (under 65).

Anesth Analg. 2012 Jun;114(6):1346-52. doi: 10.1213/ANE.0b013e31824c4eeb. Epub 2012 Mar 26.

The effects of peptide and lipid endocannabinoids on arthritic pain at the spinal level.

Petrovszki Z, Kovacs G, Tömböly C, Benedek G, Horvath G.
Source

Department of Physiology, Faculty of Medicine, University of Szeged, Szeged, Hungary.

Abstract
BACKGROUND:
Hemopressin, a nonapeptide (PVNFKFLSH: HP) derived from the α chain of hemoglobin was shown to interact specifically with brain cannabinoid CB(1) receptors. Therefore, it seems to be the only peptide structure with cannabinoid activities. Our goal in this study was to further characterize this peptide and to clarify the antinociceptive potency of the polyunsaturated fatty acid derivates, 2-arachidonoyl-glycerol (2-AG) and anandamide, by investigating their effects on mechanical allodynia at the spinal level.

METHODS:
HP was prepared on solid phase by in situ neutralization. After chronic intrathecal catheterization, mechanical hypersensitivity was produced in male Wistar rats by injection of carrageenan (300 μg/30 μL) into the tibiotarsal joint of one of the hind legs. Three hours after carrageenan administration, the ligands were administered intrathecally. The mechanical threshold was assessed using a dynamic aesthesiometer.

RESULTS:
2-AG (1-200 μg) and anandamide (10-200 μg) decreased carrageenan-induced mechanical allodynia in a dose-dependent manner, whereas HP had no antinociceptive effect in a wide dose range (0.3-30 μg). The effect of 2-AG was prevented by the CB(1) receptor antagonist AM 251, but not by the CB(2) antagonist SSR144528-2. HP (3 and 30 μg) also inhibited the effect of 2-AG. None of the ligands influenced the degree of edema.

CONCLUSIONS:
HP posttreatment had no effect on mechanical allodynia, whereas spinally injected 2-AG and anandamide were potent drugs.

PMID: 22451592 [PubMed - indexed for MEDLINE]

Tonic modulation of spinal hyperexcitability by the endocannabinoid receptor system in a rat model of osteoarthritis pain

. Devi Rani Sagar[1,*], Lydia E. Staniaszek[1], Bright N. Okine[1], Stephen Woodhams[1], Leonie M. Norris[1], Richard G. Pearson[1], Michael J. Garle[1], Stephen P. H. Alexander[1], Andrew J. Bennett[1], David A. Barrett[2], David A. Kendall[1], Brigitte E. Scammell[1], Victoria Chapman[1]

Article first published online: 30 NOV 2010

DOI: 10.1002/art.27698

Arthritis & Rheumatism
Volume 62, **Issue 12**, **pages 3666–3676**, **December 2010**

Abstract

Objective

To investigate the impact of an experimental model of osteoarthritis (OA) on spinal nociceptive processing and the role of the inhibitory endocannabinoid system in regulating sensory processing at the spinal level.

Methods

Experimental OA was induced in rats by intraarticular injection of sodium mono-iodoacetate (MIA), and the development of pain behavior was assessed. Extracellular single-unit recordings of wide dynamic range (WDR) neurons in the dorsal horn were obtained in MIA-treated rats and saline-treated rats. The levels of endocannabinoids and the protein and messenger RNA levels of the main synthetic enzymes for the endocannabinoids (*N*-acyl phosphatidylethanolamine phospholipase D [NAPE-PLD] and diacylglycerol lipase α [DAGLα]) in the spinal cord were measured.

Results

Low-weight (10 gm) mechanically evoked responses of WDR neurons were significantly ($P < 0.05$) facilitated 28 days after MIA injection compared with the responses in saline-treated rats, and spinal cord levels of anandamide and 2-arachidonoyl glycerol (2-AG) were increased in MIA-treated rats. Protein levels of NAPE-PLD and DAGLα, which synthesize anandamide and 2-AG, respectively, were elevated in the spinal cords of MIA-treated rats. The functional role of endocannabinoids in the spinal cords of MIA-treated rats was increased via activation of cannabinoid 1 (CB_1) and CB_2 receptors, and blockade of the catabolism of anandamide had significantly greater inhibitory effects in MIA-treated rats compared with control rats.

Conclusion

Our findings provide new evidence for altered spinal nociceptive processing indicative of central sensitization and for adaptive changes in the spinal cord endocannabinoid system in an experimental model of OA. The novel control of spinal cord neuronal responses by spinal cord CB_2 receptors suggests that this receptor system may be an important target for the modulation of pain in OA.

http://onlinelibrary.wiley.com/doi/10.1002/art.27698/abstract

Future Med Chem. 2012 Apr;4(6):713-25. doi: 10.4155/fmc.12.20.

Cannabinoids: novel therapies for arthritis?

Dunn SL, Wilkinson JM, Crawford A, Le Maitre CL, Bunning RA.
Source

Biomedical Research Centre, Faculty of Health and Wellbeing, Sheffield Hallam University, Sheffield, S1 1WB, UK.

Abstract

A key feature of osteoarthritis and rheumatoid arthritis is the loss of articular cartilage. Cartilage breakdown is mediated by complex interactions of proinflammatory cytokines, such as IL-1, inflammatory mediators, including nitric oxide and prostaglandin E(2), and proteases, including matrix metalloproteinases and aggrecanases, such as ADAMTS-4 and -5. Cannabinoids have been shown to reduce joint damage in animal models of arthritis. They have also been shown to prevent IL-1-induced matrix breakdown of collagen and proteoglycan, indicating that cannabinoids may mediate chondroprotective effects. Cannabinoids produce their effects via several cannabinoid receptors and it is important to identify the key cannabinoids and their receptors that are involved in chondroprotection. This review aims to outline the current and future prospects of cannabinoids as anti-arthritic therapeutics, in terms of their ability to prevent cartilage breakdown.

PMID: 22530636 [PubMed - indexed for MEDLINE]

J Pharm Pharmacol. 2006 Mar;58(3):351-8.

Arthritis and cannabinoids: HU-210 and Win-55,212-2 prevent IL-1alpha-induced matrix degradation in bovine articular chondrocytes in-vitro.

Mbvundula EC, Bunning RA, Rainsford KD.
Source

Biomedical Research Centre, Sheffield Hallam University, Sheffield, S1 1WB, UK.

Abstract

Cannabinoids have analgesic, immunomodulatory and anti-inflammatory properties and attenuate joint damage in animal models of arthritis. In this study the mechanisms of action of the synthetic cannabinoid agonists, HU-210 and Win-55,212-2, were studied to determine if they affected interleukin-1 alpha (IL-1alpha)-induced proteoglycan and collagen degradation in bovine nasal cartilage explant cultures and prostaglandin E2 (PGE2) production in primary cultures of bovine articular chondrocytes. The effects of the inactive enantiomer, Win-55,212-3, were compared with those of the active enantiomer, Win-55,212-2, to determine if the effects were cannabinoid (CB)-receptor mediated. The chondrocytes and explants were stimulated by IL-1alpha (100 U mL(-1) identical with 0.06 nM and 500 U mL(-1) identical with 0.3 nM, respectively). Proteoglycan breakdown was determined as sulfated glycosaminoglycan (sGAG) release using the dimethylmethylene blue assay. Collagen degradation was determined as hydroxyproline in the conditioned culture media and cartilage digests. PGE2 was determined by ELISA. Expression of cannabinoid receptors, CB1 and CB2; cyclooxygenase-1 and -2 (COX-1 and COX-2); inducible nitric oxide synthase (iNOS); as well as activation of nuclear factor-kappa B (NF-kappaB) in chondrocytes were studied using immunoblotting techniques and immunofluorescence. The results showed that HU-210 and Win-55,212-2 (5-15 microM) significantly inhibited IL-1-alpha stimulated proteoglycan ($P < 0.001$) and collagen degradation ($P < 0.001$). Win-55,212-2 (5-10 microM) also significantly inhibited PGE2 production ($P < 0.01$). At 5 microM, Win-55,212-2 inhibited the expression of iNOS and COX-2 and activation of NF-kappaB. Chondrocytes appeared to constitutively express cannabinoid receptors CB1 and CB2. It is concluded that biologically stable synthetic cannabinoids protect cartilage matrix from degradation induced by cytokines and this effect is possibly CB-receptor mediated and involves effects on prostaglandin and nitric oxide metabolism. Cannabinoids could also be producing these effects via inhibition of NF-kappaB activation.

PMID: 16536902 [PubMed - indexed for MEDLINE]

Arthritis Res Ther. 2008;10(2):R43. doi: 10.1186/ar2401. Epub 2008 Apr 16.

Characterisation of the cannabinoid receptor system in synovial tissue and fluid in patients with osteoarthritis and rheumatoid arthritis.

Richardson D, Pearson RG, Kurian N, Latif ML, Garle MJ, Barrett DA, Kendall DA, Scammell BE, Reeve AJ, Chapman V.
Source

Centre for Analytical Bioscience, School of Pharmacy, University of Nottingham, Nottingham, NG7 2RD, UK. denise.richardson@pfizer.com

Abstract

INTRODUCTION:

Cannabis-based medicines have a number of therapeutic indications, including anti-inflammatory and analgesic effects. The endocannabinoid receptor system, including the cannabinoid receptor 1 (CB1) and receptor 2 (CB2) and the endocannabinoids, are implicated in a wide range of physiological and pathophysiological processes. Pre-clinical and clinical studies have demonstrated that cannabis-based drugs have therapeutic potential in inflammatory diseases, including rheumatoid arthritis (RA) and multiple sclerosis. The aim of this study was to determine whether the key elements of the endocannabinoid signalling system, which produces immunosuppression and analgesia, are expressed in the synovia of patients with osteoarthritis (OA) or RA.

METHODS:

Thirty-two OA and 13 RA patients undergoing total knee arthroplasty were included in this study. Clinical staging was conducted from x-rays scored according to Kellgren-Lawrence and Larsen scales, and synovitis of synovial biopsies was graded. Endocannabinoid levels were quantified in synovial fluid by liquid chromatography-mass spectrometry. The expression of CB1 and CB2 protein and RNA in synovial biopsies was investigated. Functional activity of these receptors was determined with mitogen-activated protein kinase assays. To assess the impact of OA and RA on this receptor system, levels of endocannabinoids in the synovial fluid of patients and non-inflamed healthy volunteers were compared. The activity of fatty acid amide hydrolase (FAAH), the predominant catabolic endocannabinoid enzyme, was measured in synovium.

RESULTS:

CB1 and CB2 protein and RNA were present in the synovia of OA and RA patients. Cannabinoid receptor stimulation of fibroblast-like cells from OA and RA patients produced a time-dependent phosphorylation of extracellular signal-regulated kinase (ERK)-1 and ERK-2 which was significantly blocked by the CB1 antagonist SR141716A. The endocannabinoids anandamide (AEA) and 2-arachidonyl glycerol (2-AG) were identified in the synovial fluid of OA and RA patients. However, neither AEA nor 2-AG was detected in synovial fluid from normal volunteers. FAAH was active in the synovia of OA and RA patients and was sensitive to inhibition by URB597 (3'-(aminocarbonyl) [1,1'-biphenyl]-3-yl)-cyclohexylcarbamate).

CONCLUSION:

Our data predict that the cannabinoid receptor system present in the synovium may be an important therapeutic target for the treatment of pain and inflammation associated with OA and RA.

PMID: 18416822 [PubMed - indexed for MEDLINE] PMCID: PMC2453762

Arthritis Rheum. 2004 Mar;50(3):985-98.

A novel synthetic, nonpsychoactive cannabinoid acid (HU-320) with antiinflammatory properties in murine collagen-induced arthritis.

Sumariwalla PF, Gallily R, Tchilibon S, Fride E, Mechoulam R, Feldmann M.
Source

Kennedy Institute of Rheumatology, Imperial College London, London, UK.

Abstract

OBJECTIVE:

To explore the antiarthritic potential of a novel synthetic cannabinoid acid, Hebrew University-320 (HU-320), in the DBA/1 mouse model of arthritis, and to investigate in vitro antiinflammatory and immunosuppressive effects of HU-320 on macrophages and lymphocytes.

METHODS:

DBA/1 mice were immunized with bovine type II collagen (CII) to induce arthritis and then injected intraperitoneally daily with HU-320. The effects of treatment on arthritic changes in hind feet were assessed clinically and histologically, and draining lymph node responses to CII were assayed. Murine splenic and human blood lymphocytes were cultured to study the effect of HU-320 on polyclonal mitogenic stimulation. Macrophage cultures were set up to evaluate in vitro effects of HU-320 on production of tumor necrosis factor alpha (TNF alpha) and reactive oxygen intermediates (ROIs). The effect of HU-320 administration on lipopolysaccharide-induced serum TNF levels was assayed using C57BL/6 mice. Bioactive TNF production was measured using BALB/c clone 7 target cells. Evaluation of HU-320 psychoactivity was performed using established laboratory tests on Sabra mice.

RESULTS:

Systemic daily administration of 1 and 2 mg/kg HU-320 ameliorated established CII-induced arthritis. Hind foot joints of treated mice were protected from pathologic damage. CII-specific and polyclonal responses of murine and human lymphocytes were down-modulated. HU-320 inhibited production of TNF from mouse macrophages and of ROIs from RAW 264.7 cells and suppressed the rise in serum TNF level following endotoxin challenge. HU-320 administration yielded no adverse psychotropic effects in mice.

CONCLUSION:

Our studies show that the novel synthetic cannabinoid acid HU-320 has strong antiinflammatory and immunosuppressive properties while demonstrating no psychoactive effects. The profound suppressive effects on cellular immune responses and on the production of proinflammatory mediators all indicate its usefulness as a novel nonpsychoactive, synthetic antiinflammatory product.

PMID: 15022343 [PubMed - indexed for MEDLINE]

http://www.ncbi.nlm.nih.gov/pubmed/15022343

J Neurosci. 2016 Jan 20;36(3):837-50. doi: 10.1523/JNEUROSCI.4047-15.2016.

Rescue of Impaired mGluR5-Driven Endocannabinoid Signaling Restores Prefrontal Cortical Output to Inhibit Pain in Arthritic Rats.

Kiritoshi T[1], Ji G[1], Neugebauer V[2].

Abstract

The medial prefrontal cortex (mPFC) serves executive functions that are impaired in neuropsychiatric disorders and pain. Underlying mechanisms remain to be determined. Here we advance the novel concept that metabotropic glutamate receptor 5 (mGluR5) fails to engage endocannabinoid (2-AG) signaling to overcome abnormal synaptic inhibition in pain, but restoring endocannabinoid signaling allows mGluR5 to increase mPFC output hence inhibit pain behaviors and mitigate cognitive deficits. Whole-cell patch-clamp recordings were made from layer V pyramidal cells in the infralimbic mPFC in rat brain slices. Electrical and optogenetic stimulations were used to analyze amygdala-driven mPFC activity. A selective mGluR5 activator (VU0360172) increased pyramidal output through an endocannabinoid-dependent mechanism because intracellular inhibition of the major 2-AG synthesizing enzyme diacylglycerol lipase or blockade of CB1 receptors abolished the facilitatory effect of VU0360172. In an arthritis pain model mGluR5 activation failed to overcome abnormal synaptic inhibition and increase pyramidal output. mGluR5 function was rescued by restoring 2-AG-CB1 signaling with a CB1 agonist (ACEA) or inhibitors of postsynaptic 2-AG hydrolyzing enzyme ABHD6 (intracellular WWL70) and monoacylglycerol lipase MGL (JZL184) or by blocking GABAergic inhibition with intracellular picrotoxin. CB1-mediated depolarization-induced suppression of synaptic inhibition (DSI) was also impaired in the pain model but could be restored by coapplication of VU0360172 and ACEA. Stereotaxic coadministration of VU0360172 and ACEA into the infralimbic, but not anterior cingulate, cortex mitigated decision-making deficits and pain behaviors of arthritic animals. The results suggest that rescue of impaired endocannabinoid-dependent mGluR5 function in the mPFC can restore mPFC output and cognitive functions and inhibit pain.

SIGNIFICANCE STATEMENT:

Dysfunctions in prefrontal cortical interactions with subcortical brain regions, such as the amygdala, are emerging as important players in neuropsychiatric disorders and pain. This study identifies a novel mechanism and rescue strategy for impaired medial prefrontal cortical function in an animal model of arthritis pain. Specifically, an integrative approach of optogenetics, pharmacology, electrophysiology, and behavior is used to advance the novel concept that a breakdown of metabotropic glutamate receptor subtype mGluR5 and endocannabinoid signaling in infralimbic pyramidal cells fails to control abnormal amygdala-driven synaptic inhibition in the arthritis pain model. Restoring endocannabinoid signaling allows mGluR5 activation to increase infralimbic output hence inhibit pain behaviors and mitigate pain-related cognitive deficits.

PMID:
26791214
[PubMed - in process]
PMCID:
PMC4719019
[Available on 2016-07-20]

Arthritis Res Ther. 2014 Sep 27;16(5):437. doi: 10.1186/s13075-014-0437-9.

Tapping into the endocannabinoid system to ameliorate acute inflammatory flares and associated pain in mouse knee joints.

Krustev E, Reid A, McDougall JJ.

Abstract

INTRODUCTION:

During the progression of rheumatoid arthritis (RA), there are frequent but intermittent flares in which the joint becomes acutely inflamed and painful. Although a number of drug therapies are currently used to treat RA, their effectiveness is variable and side effects are common. Endocannabinoids have the potential to ameliorate joint pain and inflammation, but these beneficial effects are limited by their rapid degradation. One enzyme responsible for endocannabinoid breakdown is fatty acid amide hydrolase (FAAH). The present study examined whether URB597, a potent and selective FAAH inhibitor, could alter inflammation and pain in a mouse model of acute synovitis.

METHODS:

Acute joint inflammation was induced in male C57BL/6 mice by intra-articular injection of 2% kaolin/2% carrageenan. After 24 hr, articular leukocyte kinetics and blood flow were used as measures of inflammation, while hindlimb weight bearing and von Frey hair algesiometry were used as measures of joint pain. The effects of local URB597 administration were then determined in the presence or absence of either the cannabinoid (CB)1 receptor antagonist AM251, or the CB2 receptor antagonist AM630.

RESULTS:

URB597 decreased leukocyte rolling and adhesion, as well as inflammation-induced hyperaemia. However, these effects were only apparent at low doses and the effects of URB597 were absent at higher doses. In addition to the anti-inflammatory effects of URB597, fatty acid amide hydrolase (FAAH) inhibition improved both hindlimb weight bearing and von Frey hair withdrawal thresholds. The anti-inflammatory effects of URB597 on leukocyte rolling and vascular perfusion were blocked by both CB1 and CB2 antagonism, while the effect on leukocyte adherence was independent of cannabinoid receptor activation. The analgesic effects of URB597 were CB1 mediated.

CONCLUSIONS:

These results suggest that the endocannabinoid system of the joint can be harnessed to decrease acute inflammatory reactions and the concomitant pain associated with these episodes.

PMID:
25260980
[PubMed - indexed for MEDLINE]
PMCID:
PMC4201700