Cannabinoid system and cyclooxygenases inhibitors

Păunescu H*, Coman OA*, Coman L**, Ghiță I*, Georgescu SR***, Drăghia E****, Fulga I*

*Department of Pharmacology and Pharmacotherapy, “Carol Davila” University of Medicine and Pharmacy, Bucharest
**Department of Physiology, “Carol Davila” University of Medicine and Pharmacy, Bucharest
***Department of Dermatology, “Carol Davila” University of Medicine and Pharmacy, Bucharest
****Department of Anatomy, “Carol Davila” University of Medicine and Pharmacy, Bucharest

Correspondence to: Păunescu Horia,
1-3 Poarta Albă Street, bl. 110, ap. 88, District 6, Bucharest, postal code: 061162
Phone: 0040723867286, Fax 0040213102115, E-mail: phpaunescu@yahoo.com

Received: November 28th, 2010 – Accepted: January 25th, 2011

Abstract

Rationale. The cannabinoid system consists of a complex array of receptors, substances with agonist/antagonist properties for those receptors, biosynthetic machineries and mechanisms for cellular uptake and degradation for endocannabinoids. This system is in interrelation with other systems that comprise lipid mediators like prostaglandins/leukotrienes systems. A clear antagonist, additive or synergic effect of nonsteroidal anti-inflammatory drugs (NSAIDs)-cannabinoid associations was not yet demonstrated. Aim. The present study tried to summarize the existent data on NSAIDS-cannabinoid system interactions.

Methods and results. A bibliographic research in Medline, Scirus, Embase was made using as keywords cannabinoid, nonsteroidal anti-inflammatory drugs, aspirin, ibuprofen, flurbiprofen, diclofenac, indomethacin, acetaminophen, coxibs, antinociceptive, antinociception, analgesia.

Discussions. A systematization of the results focusing on the NSAIDS drugs interaction with the cannabinoid system was presented. Out of all the substances analyzed in the present review, acetaminophen was studied the most regarding its interferences with the cannabinoid system, mainly due to contradictory results.

Conclusions. Some NSAIDs have additional influences on the cannabinoid system either by inhibiting fatty acid amide hydrolase (FAAH) or by inhibiting a possible intracellular transporter of endocannabinoids. All the NSAIDs that inhibit COX2 can influence the cannabinoid system because a possible important degenerative pathway for anandamide and 2-arachidonoyl glycerol might involve COX 2. One of the causes for the variety of experimental results presented might be due to pharmacokinetic mechanisms, depending on the route of administration and the dose.

Key words: cannabinoids; NSAIDs; cyclooxygenase; analgesia.

Abbreviations. A9 THC, (++)-(6R,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol; Δ9-THC-11-oic acid, 1-hydroxy-6,6-dimethyl-3-pentyl-6a,7,8,10a-tetrahydrobenzo[c]chromene-9-carboxylic acid; Anandamide, [(S,Z,8Z,11Z,14Z)-N-(2-hydroxyethyl)cyclohexyl]cyclohexyl-5,8,11,14-tetraenamide; Methanandamide, [(Z,2R)-1-hydroxypropan-2-yl]cyclohexyl-5,8,11,14-tetraenamide; 2-AG, 1,3-Dihydroxy-2-propanoyl (5Z,8Z,11Z,14Z)-5,8,11,14-eicosatetraenoe; HU 210, (6aR,10aR)-9-(Hydroxymethyl)-6,6-dimethyl-3-(2-methyloctan-2-yl)-6a,7,10,10a-tetrahydrobenzo[c]chromen-1-ol; SR141716A, 5-(4-Chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamid; SR144528, N-((1S)-endo-1,3,3-trimethyl bicyclo[2.2.1] heptan-2-yl)-1-(4-methylbenzyl)-3-(4-(chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide; AM251, 1-1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-N-(1-piperidinyl)pyrazole-3-carboxamide; AM 404, (5Z,8Z,11Z,14Z)-N-(4-hydroxyphenyl)cyclohexyl-5,8,11,14-tetraenamide; WIN 55,212-2, (R)-(2,3-Dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo[1,2,3-de]-1,4-benzoxazin-6-yl)-1-naphthalenylmethanone; AM 281, N-(morpholin-4-yl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide; AM 630, [6-Iodo-2-methyl-1-[2-(4-morpholinylethyl)-1H-indol-3-yl][4-methoxyphenyl)methanone; Ibuprofen, 5-[(3-methylpyridin-2-yl)-2-(4-isobutyrophenoxy)propionamide; CP 55, 940, 2-[(1R,2R,5R)-5-hydroxy-2-(3-hydroxypropoxy)cyclohexyl]-5-(2-methyloctan-2-yl)phenol; NS-398, N-[2-(Cyclohexyloxy)-4-nitrophenyl]methanesulfonamide; SC-560, 5-(4-chlorophenyl)-1-(4-methoxyphenyl)-3-trifluoromethylpyrazole; AM 1241, (3-iodo-5-nitrophenyl)-[1-[1-(methylpiperidin-2-yl)methyl]indol-3-yl]methanone; Met FAEA, 2-methyl-arachidonyl-2'-fluoro-ethylamide; PMSF, Phenylmethylsulfonyl fluoride; URB 597, [3-(3-carbamoylphenyl)phenyl] N-cyclohexylcarbamate; TRPV1, Transient receptor potential vanilloid type 1; CB1R, cannabinoid receptor type 1; CB2R, cannabinoid receptor type 2; FAAH, fatty acid amide hydrolase; NSAIDs, nonsteroidal anti-inflammatory drugs; p.o., per os; i.p., intraperitoneally; i.th., intrathecially; s.c., subcutaneously; i.pl., intraplantar; i.v., intravenously; CB cannabinoid.
Introduction

Only in 1964 when Ganoi and Mechoulam identified ∆9 tetrahydrocannabinol (∆9 THC) being the main psychotropic agent from *Cannabis sativa* the researches in the “field” of cannabinoids gain scale. Many efforts to discover the substrate of psychotropic and analgesic effects of ∆9 THC were made. The discovery of cannabinoid receptors and endogenous cannabinoids (endocannabinoids) came about twenty years later. The two main endocannabinoids discovered were, in order, anandamide (arachidonoyl ethanolamine) and 2-arachidonoyl glycerol.

Cannabinoid system consists of a complex array of receptors, substances with agonist/antagonist properties for those receptors, biosynthetic machineries and mechanisms for cellular uptake and degradation for endocannabinoids. It might represent a new target for adverse reactions like alterations in cognition and muscle spasms/spasticity in multiple sclerosis and decreased intestinal motility.

The positive effects are often accompanied by adverse reactions like alterations in cognition and memory, dysphoria/euphoria, and sedation [1].

Endocannabinoids are rich in cannabinoid receptors and in cannabinoids (endocannabinoids). The cannabinoid receptors and endogenous cannabinoids are in interrelation with other systems that comprise lipid mediators like prostaglandins/leukotrienes systems [2]. Nowadays it is well known that cyclooxygenase type 2 (COX2) actions both on arachidonic acid, resulting prostaglandins and other eicosanoids, and on endocannabinoids (anandamide and 2-arachidonoyl glycerol), resulting prostanamides and prostaglandin glycerol esters. It is not surprising that these substances have different pharmacological properties than the amides or the esters from which they are derived. From this point of view the inhibition of cyclooxygenases, especially COX2, might have many influences at the level of central nervous system or in immune cells (two of the main domains that are rich in cannabinoid receptors and in cannabinoids). The cyclooxygenase products of endocannabinoids were reviewed elsewhere [3-7] and will not make a subject for this paper.

The cannabinoid receptors and endocannabinoids

The human cannabinoid receptor 1 (CB1R) was cloned by Gerrard et al. (1991). CB1 receptors are coupled with Gi/Go proteins and are serpentine receptors. Through G protein action the activity of adenylyl cyclase is diminished, which leads to a decrease of cAMP level. The activity of some ionic channels is also modulated. The human cannabinoid receptor 2 (CB2R) was first identified in man in 1993.

CB2 receptors are coupled with Gi/Gq type proteins. Unlike CB1 receptors, the CB2 ones do not seem to be coupled to ionic channels. They are coupled with intracellular signalization pathways associated to MAP kinase.

Another two serpentine receptors, classified among orphan receptors because, when discovered, there did not exist a specific ligand to bind them, are supposed to be cannabinoid receptors. These two receptors are still named GPR55 and GPR119. Another receptor for anandamide is the transient receptor potential vanilloid1 receptor (TRPV1), the receptor for capsaicin [1].

Anandamide and especially 2-arachidonoyl glycerol can function as retrograde synaptic messengers. They are released from postsynaptic neurons and travel backward across synapses, activating CB1 on presynaptic axons and suppressing neurotransmitter release. Cannabinoids may affect memory, cognition, and pain perception by means of this cellular mechanism [8].

Endogenous ligands for CB receptors discovered until now are eicosanoids: N-arachidonoylethanolamide (anandamide), 2-arachidonoyl glycerol, noladin ether, O-arachidonoylethanolamine (virodhamide) and N-arachidonoyldopamine.

Anandamide, 2-arachidonoyl glycerol, and N-arachidonoyldopamine are susceptible to degradation by fatty acid amide hydrolase (FAAH), although a second enzyme, monoacylglycerol lipase, catalyzes hydrolysis of 2-arachidonoylglycerol *in vivo* [1].

Numerous substances with cannabinoid properties were described. They might act as full or partial agonists, antagonists or inverse agonists, neutral antagonists [9], or may increase the endocannabinoids level (FAAH inhibitors, cellular uptake of cannabinoids inhibitors). Some of them are presented in table I [1].

Cyclooxygenases inhibitors or nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of substances that block either the cyclooxygenase site of enzyme cyclooxygenase type 1 or 2 (COX 1 and COX 2, respectively), or its peroxidase site [10,11]. In the first category can be mentioned ibuprofen, diclofenac, indomethacin, coxibs (rofecoxib, celecoxib) and in the second category might be included acetaminophen and metamizole sodium.

Methods

A systematic analysis of data from existing literature databases Medline, Pubmed, Embase, Scirus up to 31.08.2010 was performed. Initial selection of articles was made using as key words cannabinoid AND (nonsteroidal anti-inflammatory drugs OR aspirin OR ibuprofen OR flurbiprofen OR diclofenac OR indomethacin OR acetaminophen OR coxibs) taking into account articles in abstract and full text from clinical and preclinical studies. 225 articles, published after the year
1972 to date, out of which 199 in full text and 26 in abstract, were found. The search area was reduced by introducing new keywords: antinociceptive OR antinociception OR analgesia. References to all relevant articles were examined to include all relevant reports and review sites on the subject. The study included data in English and French. Following the final selection, 24 items were retained in the study considering the exclusion criteria (analytical interference in the determination of cannabinoids and NSAIDs). The 24 studies that emphasized the interactions between the endocannabinoid system or exogenous cannabinoids and NSAIDs, especially on the analgesic effect, were analyzed in terms of types of cannabinoid receptors or of the endocannabinoids involved. Another aim was to elucidate the mechanism of action of cyclooxygenase inhibitors and their interactions with exogenous cannabinoid agonists.

Results

A systematization of the data found in the articles studied are presented in table 2.

Discussions

We tried to systematize the results presented in the previous table by sorting the anti-inflammatory substances and their interactions with the cannabinoid system.

Indomethacin might interfere with the endocannabinoid system, as reported in some studies made by Burstein SH, et al. 1988 [12], Gühring H, et al. 2001[14], Anikwue R, et al. 2002 [15] and Bujalska M. 2008 [29]. Oral administration of indomethacin decreased the hiperalgesia produced by Δ9-THC – a cannabinoid agonist, but in intrathecal administration did not influence the analgesic effects of HU 210 – another cannabinoid agonist. In chronic oral administration Δ9-THC decreased the effects of indomethacin, possibly by a pharmacokinetic mechanism (Δ9-THC interfered the metabolism of indomethacin). The interference of indomethacin on the cannabinoid system is relatively controversial. Anikwue R, et al. 2002 [15] concluded that indomethacin might not react on the cannabinoid system, while Gühring H, et al. 2001 [14] showed that indomethacin acted by means of the CB receptors. In his study, Bujalska M. 2008 [29] showed that indomethacin might potentiate the low doses of CB1 and CB2 agonists in a neuropathic pain model. Taking into account these studies, we can conclude that indomethacin interfere the cannabinoid system either by the CB receptors or by a pharmacokinetic mechanism.

Fowler CJ, et al. 1997 [13], Seidel K, et al. 2003 [18] and Guindon J, et al. 2006 [22] in their studies with ibuprofen, ibu am5 and flurbiprofen showed that all these substances inhibited FAAH. Ibuprofen acted synergistically with anandamide. This effect of ibuprofen was highlighted in experimental models for acute pain and also for neuropathic pain. Guindon J, et al. 2006 [22] concluded that ibuprofen potentiated the exogenous cannabinoids. Flurbiprofen, an ibuprofen derivative, intrathechally administrated proved an analgesic effect mediated by the endocannabinoid system, as result from Ates M, et al. 2003 [17], Seidel K, et al. 2003 [18] and Bishay P, et al. 2010 [34]. Some nonselective COX inhibitors, such as sulindac, ketoprofen and naproxen had been tested by Anikwue R, et al. 2002 [15], who showed that these substances did not act directly or indirectly on CB1 or CB2 receptors. On the other hand, aspirin proved to potentiate the effect of HU-210, a CB1 and CB2 receptor agonist (Ruggieri V, et al. 2010, [33]). After Naidu PS, et al. 2009 [31] diclofenac acted synergistically with URB 597 (a potent inhibitor of FAAH).

Ketorolac, a selective inhibitor of COX1, had additive effects in association with WIN 55212-2, a nonselective cannabinoid agonist (Ulugöl A, et al. 2006 [20]). However, other authors, like Anikwue R, et al. 2002 [15], proved that ketorolac did not act directly or indirectly on cannabinoid receptors.

The selective COX2 agonists: NS-398,respectively rofecoxib, potentiated the action of cannabinoid agonists in acute pain models (Ahn DK, et al. 2007 [27]) or in neuropathic pain models (Guindon J and Beaulieu P. 2006 [23]). Celecoxib might not have a cannabinoid effect in the Anikwue R, et al. 2002 [15] study, while nimesulide showed an effect on CB1 receptors (Staniszek LE, et al. 2010 [35]) without implication on anandamide or 2-AG levels.

Out of all the substances included in the NSAIDs group, acetaminophen was studied the most regarding its interferences with the cannabinoid system mainly due to contradictory results. Högestätt ED, et al. 2005 [19] showed that acetaminophen could be transformed in AM 404 in the central nervous system by FAAH. This metabolite is an agonist on TRPV1 receptors, a COX1 and COX2 inhibitor and inhibits the reuptake of anandamide, with an analgesic effect. There are some studies using acute pain models realized on animals performed by Ottani A, et al. 2006 [21] and Mallet C, et al. 2008 [30] and other studies conducted on neuropathic pain models performed by Dani M, et al. 2007 [28] and Hama AT and Sagen J. 2010 [32] which sustain the existence of cannabinoid effects for acetaminophen. Other studies (Anikwue R, et al. 2002 [15], Haller VL, et al. 2006 [24]) had opposite results. Hama AT and Sagen 2010 [21] and Costescu M, et al 2010 [36] studied the association between acetaminophen and gabapentin, morphine or ibuprofen. They concluded that CB receptor
blockers could antagonize the analgesic effects of these associations.

Conclusions

1. A clear antagonist, additive or synergic effect of NSAIDs-cannabinoid associations was not yet demonstrated. One of the causes for the variety of experimental results presented might be due to pharmacokinetic mechanisms, depending on the route of administration and the dose.

2. All the NSAIDs that inhibit COX2 can influence the cannabinoid system because a possible important degradative pathway for anandamide and 2-arachidonoyl glycerol might involve COX 2.

3. Some NSAIDs have additional influences on the cannabinoid system either by inhibiting FAAH (i.e. ibuprofen, indomethacin, flurbiprofen, ibu-am5), or by inhibiting a possible intracellular transporter of endocannabinoids (i.e. acetaminophen).

| Table I. Classification of substances that influence endocannabinoid system |
|-------------------------------------------------|-----------------|-----------------|
| **Cannabinoid receptor agonists**                |                  |                  |
| Classical cannabinoids                          | Δ9 THC           | partial agonist of CB1R and CB2R |
|                                                 | HU 210           | complete agonist of both CB1R and CB2R |
| Non-classical cannabinoids                     | CP-55, 940       | complete agonist of both CB1R and CB2R |
| Specific CB-2 receptor agonist                  | AM 1241          |                  |
| Aminoalkylindoles                               | WIN-55, 212-2    | complete agonist of both CB1R and CB2R, slightly selective for CB2R |
| Eicosanoids                                     | Anandamide (AEA) | partial agonist of both CB1R and CB2R and TRPV1 agonist |
|                                                 | R-(+)-methanandamide |                  |
|                                                 | Met F AEA        | full agonist of both CB1R and CB2R |
|                                                 | 2-AG             |                  |
| **Cannabinoid receptor antagonists/inverse agonists** |                  |                  |
| Diarylpyrazoles and other derivatives           | SR141716A [rimonabant], | selective CB1R blockers |
|                                                 | AM 251, AM281    |                  |
|                                                 | SR144528, AM 630 | selective CB2R blockers |
| Uptake blockers: AM 404                          |                  |                  |
| FAAH inhibitors: PMSF, URB 597                  |                  |                  |
### Table 2. Synopsis of data collected from 25 studies on NSAIDs and cannabinoid system interactions

| No. | Cyclooxygenase pathway (prostaglandins precursors, prostaglandins, COX inhibitors) | Cannabinoid (agonists, antagonists) administered | Experimental method used | The results of the study | Discussion | Authors |
|-----|----------------------------------------------------------------------------------|-------------------------------------------------|-------------------------|--------------------------|------------|---------|
| 1   | Indomethacin (p.o.) | Δ9-THC, Δ9-THC-11-oic acid (p.o.) | The hot plate test (in mice) | 10 min after Δ9-THC administration, a pronounced hyperalgesia was seen. Hyperalgesia could be inhibited by prior administration of either indomethacin or Δ9-THC-11-oic acid. | The metabolite Δ9-THC-11-oic acid inhibited eicosanoid synthesis whereas the parent drug (Δ9-THC) elevated tissue levels of prostaglandins. | Burstein SH, et al. FASEB J. 1988 Nov;2(14):3022-6. |
| 2   | Ibuprofen, aspirin, sulindac, acetaminophen, ketoprofen, naproxen | | Rat cerebellar membrane preparation | The potency of ibuprofen as an inhibitor of anandamide metabolism was of the same magnitude as required for inhibition of COX2. Aspirin, sulindac, acetaminophen, ketoprofen and naproxen did not inhibit the anandamide metabolism. | The metabolism of anandamide might be affected, following the therapeutic doses of ibuprofen. | Fowler CJ, et al. Pharmacol Toxicol. 1997 Feb;80(2):103-7 |
| 3   | Indomethacin (i.th.) | HU-210 (p.o. and i.th.) | Tail flick and formalin test (in mice) | Indomethacin reduced the HU 210 effect on pronociceptive prostaglandins production but did not potentiate the analgesic effect of HU-210 | HU-210 showed analgesic properties that are independent of its influence on the prostaglandin pathway. | Gühring H, et al. Eur J Pharmacol. 2001 Oct 19;429(1-3):127-34 |
| 4   | Aspirin, indomethacin, celecoxib, ketorolac, acetaminophen diclofenac (p.o.) | Δ9-THC, anandamide, arachidonic acid, ethanolamine, methanandamide, SR141716A, SR144528 (i.p.) | The phenylbenzoquinone writhing test (in mice) | After chronic treatment with Δ9-THC the analgesic effect of diclofenac and acetaminophen decreased while the effect of aspirin, indomethacin, celecoxib, ketorolac was not detected. Chronic treatment with methanandamide did not alter the analgesic effects of the NSAIDs tested. Neither SR141716A, SR144528 blocked the effects of the NSAIDs tested. | The alteration of NSAIDs effects was not due to chronic administration of Δ9-THC and might be due to pharmacokineti mechanisms (some metabolites of Δ9-THC might interfere with NSAIDs). Also it was stated that NSAIDs are not acting directly or indirectly at either the CB1R or CB2R. | Anikwue R, et al J Pharmacol Exp Ther. 2002 Oct;303(1):340-6 |
|   | Indomethacin-induced analgesia was reversed by co-administration of AM251, but not by co-infusion of prostaglandin E2. | Flurbiprofen-induced analgesia was reversed by co-administration of AM251, but not by co-infusion of prostaglandin E2. | The analgesic effect of flurbiprofen (i.th.) was reversed by the co-administration of AM-251, but not by prostaglandin E2. | The formalin test (in spinally microdialyzed mice) | The formalin test (in rats) | The spinal superfusion model (in rats) | The hot plate test (in mice) | The formalin test (in rats) | The hot plate test (in rats) | The acetic acid-induced –writhing test (in mice) | The evaluation of mechanical allodynia and thermal hyperalgesia in neuropathic rats |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 5 | Indomethacin | AM251 | (i.th.) | AM251 | (i.th.) | AM251 | (i.th.) | AM251 | (i.th.) | AM251 | (i.th.) | AM251 | (i.th.) |
| 6 | Prostaglandin E2 | Flurbiprofen | (i.th.) | Flurbiprofen | (i.th.) | Flurbiprofen | (i.th.) | Flurbiprofen | (i.th.) | Flurbiprofen | (s.c.) | Flurbiprofen | (p.o.) |
| 7 | Flurbiprofen | Prostaglandin E2 | (i.th.) | Prostaglandin E2 | (i.th.) | Prostaglandin E2 | (i.th.) | Prostaglandin E2 | (i.th.) | Prostaglandin E2 | (s.c.) | Prostaglandin E2 | (s.c.) |
| 8 | Δ9-THC inhibited capsaicin induced CGRP release. Similarly, flurbiprofen inhibited spinal CGRP release. This inhibition was reversed by AM-251, but not by co-administration of prostaglandin E2. | Δ9-THC inhibited capsaicin induced CGRP release. Similarly, flurbiprofen inhibited spinal CGRP release. This inhibition was reversed by AM-251, but not by co-administration of prostaglandin E2. | The mechanism for flurbiprofen inhibitory effect on spinal CGRP release might be the shift of arachidonic acid metabolism towards endocannabinoids formation. | The formalin test (in rats) | The spinal superfusion model (in rats) | The hot plate test (in mice) | The formalin test (in rats) | The hot plate test (in rats) | The acetic acid-induced –writhing test (in mice) | The evaluation of mechanical allodynia and thermal hyperalgesia in neuropathic rats |
| 9 | Acetaminophen | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) |
| 10 | Ketorolac | SR141716A | (p.o.) | SR141716A | (p.o.) | SR141716A | (p.o.) | SR141716A | (p.o.) | SR141716A | (p.o.) | SR141716A | (p.o.) |
| 11 | Ibuprofen | AM281 | (i.p.) | AM281 | (i.p.) | AM281 | (i.p.) | AM281 | (i.p.) | AM281 | (i.p.) | AM281 | (i.p.) |
| 12 | Ibuprofen | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) | WIN55,212-2 | (s.c.) |
| Article Number | Protocol/Compound | Results/Findings |
|----------------|-------------------|------------------|
| 13             | Acetaminophen (i.p.) | SR141716A and SR144528 (i.p.) | The analgesic effects of acetaminophen were not blocked by SR141716A and SR144528. |
| 14             | Arachidonic acid (i.v.) | Anandamide (i.v.) | SR141716A (i.p.) | The failure of SR141716A to antagonize the in vivo effects of anandamide suggested that non-CB1R might be involved. |
| 15             | Ibu am-5 (the 6-methyl-pyridin-2-yl analogue of ibuprofen) | Tissue homogenate experiments or intact cell assays (in rats) | The compound Ibu am-5 inhibited rat brain anandamide hydrolysis by FAAH in a non-competitive manner. Ibu am-5 inhibited the binding of [3H]-CP55,940 to rat brain CB1Rs and to human CB2Rs more potently than ibuprofen. |
| 16             | NS-398, indomethacin, acetaminophen, SC-560 (intracisternal) | WIN55,212-2 (intracisternal) | Intra-articular injection of formalin in temporomandibular joint (in rats) | An ineffective dose of WIN 55,212-2 in producing analgesia by intracisternal administration became effective following intracisternal administration of NS-398, indomethacin, acetaminophen, but not following SC-560. |
| 17             | Acetaminophen (i.p.) | AM251 AM630 (i.p.) | Evaluation of mechanical allodynia and hyperalgesia in neuropathic rats | Acetaminophen decreased mechanical allodynia and hyperalgesia dose-dependently. These effects were inhibited by the administration of AM251 and AM630. |
| 18             | Indomethacin (chronic treatment) (s.c.) | WIN55,212-2 and AM1241 (s.c.) | Met-F-AEA (i.p.) | Chronic pretreatment with indomethacin progressively increased the analgesic effects of low doses of WIN 55,212-2, AM1241 and Met-F-AEA. |
| 19             | Acetaminophen (p.o) | AM251 (i.p.) | URB597 (i.p.) and PMSF (s.c.) | AM251 abolished the analgesic action of acetaminophen; inhibition of FAAH suppressed the analgesic effect of acetaminophen. |
| 20             | Diclofenac (s.c.) | URB597 (s.c.) | The acetic acid-induced writhing test (in mice) | Combinations of URB597 and diclofenac showed synergistic analgesic interactions. |
| 21 | Acetaminophen (i.p.), morphine (s.c.), gabapentin(s.c.) and their combination | AM251 AM630 (s.c.) | The measure of hind paw hypersensitivity after acute compression of the mid-thoracic spinal cord hot-plate and formalin tests (in rats) | Pre-treatment with AM251 significantly diminished the analgesic effect of the acetaminophen + gabapentin combination. Both AM251 and AM630 reduced the efficacy of the acetaminophen + morphine combination. | Modulation of the endocannabinoid system might mediate the synergistic analgesic effects of acetaminophen combinations. Hama AT and Sagen J. Neuropharmacology. 2010 Mar-Apr;58(4-5):758-66. [32] |
| 22 | Aspirin (i.p.) | HU210 (i.p.) | Low doses of HU210 significantly increased the analgesic effect of the sub-active dose of aspirin. SR141716A was ineffective per se and failed to modify analgesia induced by the HU210 plus aspirin combination. | Mutual potentiation of the analgesic effects of HU210 and aspirin might depend on an indirect participation of cannabinoid mechanism. Ruggieri V, et al. Life Sci. 2010 Mar 27;86(13-14):510-7 [33] |
| 23 | R-flurbiprofen | Spinal cord microdialysis, after sciatic nerve injury in rats | R-flurbiprofen reduced glutamate release in the dorsal horn of the spinal cord evoked by sciatic nerve injury; also inhibited FAAH activity. | R-flurbiprofen improved the endogenous mechanisms to fend off the chronic neuropathic pain. Bishay P, et al. PLoS One. 2010 May 13;5(5):e10628. [34] |
| 24 | Nimesulide (i.th.) | AM251 (i.th.) | Evoked responses of rat dorsal horn neurons in rats Spinal microdialysis | Spinal, but not peripheral, injection of nimesulide significantly reduced mechanically evoked responses of dorsal horn neurons that were blocked by AM251. Spinal levels of endocannabinoids were not elevated. | Responses to nimesulide were dependent on CB1R, without an implication of anandamide or 2-AG. Staniaszek LE, et al. Br J Pharmacol. 2010 Jun;160(3):669-76. [35] |
| 25 | Ibuprofen (i.p.) associated with acetaminophen (p.o) | AM281 (i.p.) | Acetic acid writhing test and hot plate test (in mice) | Additive analgesic effect in writhing test and potentiation in hot plate test. Adding AM281 the additive effect in writhing test is decreased and the potentiation in hot plate test disappeared | Influencing the cannabinoid system might be responsible for a part of analgesic effect of acetaminophen-ibuprofen combinations. Costescu M, et al Basic and Clinical Pharmacology & Toxicology. 2010, 107, Suppl. 1, 1: 243 [36] |
References

1. Coman OA, Paunescu H, Coman L, Badarau A, Fulga I. Recent data on cannabinoids and their pharmacological implications in neuropathic pain. J Med Life. 2008 Oct-Dec;1(4):365-75.

2. Huwiler A, Pfeilschifter J. Lipids as targets for novel anti-inflammatory therapies. Pharmacol Ther. 2009 Oct;124(1):96-112.

3. Burstein SH, Rossetti RG, Yagen B, Zierer RB. Oxidative metabolism of anandamide. Prostaglandins Other Lipid Mediat. 2000 Apr;61(1-2):211-20.

4. Kozak KR, Marnett LJ. Oxidative metabolism of endocannabinoids. Prostaglandins Leukot Essent Fatty Acids. 2002 Feb-Mar;66(2-3):211-20.

5. Matias I, Chen J, De Petrocellis L, Bisogno T, Ligresti A, Fezza F, Krauss AH, Shi L, Protzman CE, Li C, Liang Y, Nieves AL, Kedzie KM, Burk RM, Di Marzo V, Woodward DF. Prostaglandin ethanolamines (prostamides): in vitro pharmacology and metabolism. J Pharmacol Exp Ther. 2004 May;309(2):745-57.

6. Guindon J, Hohmann AG. A physiological role for endocannabinoid-derived products of cyclooxygenase-2-mediated oxidative metabolism. Br J Pharmacol. 2008 Apr;153(7):1341-3.

7. Sagar DR, Gaw AG, Okine BN, Woodhams SG, Wong A, Kendall DA, Chapman V. Dynamic regulation of the endocannabinoid system: implications for analgesia. Mol Pain. 2009 Oct 8:59.

8. Wilson RI, Nicoll RA. Endocannabinoid signaling in the brain. Science. 2002 Apr 26;296(5568):679-82.

9. Sink KS, McLaughlin PJ, Wood JA, Brown C, Fan P, Vemuri VK, Peng Y, Olszewska T, Thakur GA, Makriyannis A, Parker LA, Salamone JD. The novel cannabinoid CB1 receptor neutral antagonist AM4113 suppresses food intake and food-reinforced behavior but does not induce signs of nausea in rats. Neuropsychopharmacology. 2008 Mar;33(4):946-55. Erratum in: Neuropsychopharmacology. 2008 Jun;33(7):1776. Pang, Yan [corrected to Peng, Yan]; Olszewska, Teresa [corrected to Olszewska, Teresa].

10. Aronoff DM, Oates JA, Boutaud O. New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two prostaglandin H2 synthases. Clin Pharmacol Ther. 2006 Jan;79(1):9-19.

11. Pierre SC, Schmidt R, Brenneis C, Michaelis M, Geisslinger G, Scholich K. Inhibition of cyclooxygenases by dipyrone. Br J Pharmacol. 2007 Jun;151(4):494-503.

12. Burstein SH, Hull K, Hunter SA, Latham V. Cannabinoids and pain responses: a possible role for prostaglandins. FASEB J. 1988 Nov 2; (14):3022-6. PubMed PMID:2846397.

13. Fowler CJ, Stenström A, Tiger G. Ibuprofen inhibits the metabolism of the endogenous cannabimimetic agent anandamide. Pharmacol Toxicol. 1997 Feb; 80 (2) :103-7.

14. Gühring H, Schuster J, Hamza M, Ates M, Kotalla CE, Brune K. HU-210 shows higher efficacy and potency than morphine after intrathecal administration in the mouse formalin test. Eur J Pharmacol. 2001 Oct 19; 429 (1-3) :127-34.

15. Anikwue R, Huffman JW, Martin ZL, Welch SP. Decrease in efficacy and potency of nonsteroidal anti-inflammatory drugs by chronic administration. J Pharmacol Exp Ther. 2002 Oct; 303 (1):340-6.

16. Gühring H, Hamza M, Sergejeva M, Ates M, Kotalla CE, Ledent C, Brune K. A role for endocannabinoids in indomethacin-induced spinal antinociception. Eur J Pharmacol. 2002 Nov 15; 454 (2-3):153-63.

17. Ates M, Hamza M, Seidel K, Kotalla CE, Ledent C, Gühring H. Intrathecally applied flurbiprofen produces an endocannabinoid-dependent antinociception in the rat formalin test. Eur J Neurosci. 2003 Feb; 17 (3) :597-604.

18. Seidel K, Hamza M, Ates M, Gühring H. Flurbiprofen inhibits capsaicin-induced calcitonin gene related peptide release from rat spinal cord via an endocannabinoid dependent mechanism. Neurosci Lett. 2003 Feb 27; 338 (2) :99-102.

19. Högestätt ED, Jönsson BA, Ermund A, Andersson DA, Björk H, Alexander JP, Cravatt BF, Basbaum AI, Zygmun M. Conversion of acetaminophen to the bioactive N-acylphenolamine AM404 via fatty acid amide hydrolase-dependent arachidonic acid conjugation in the nervous system. J Biol Chem. 2005 Sep 9; 280 (36):31405-12.

20. UlugöI A, Ozyigit F, Yesilyurt O, Dogrul A. The additive antinociceptive interaction between WIN 55,212-2, a cannabinoid agonist, and ketorolac. Anesth Analg. 2006 Feb; 102 (2) :443-7.

21. Ottani A, Leone S, Sandrini M, Ferrari A, Bertolini A. The analgesic activity of paracetamol is prevented by the blockade of cannabinoid CB1 receptors. Eur J Pharmacol. 2006 Feb 15; 531 (1-3):280-1.

22. Guindon J, De Léan A, Beaulieu P. Local interactions between anandamide, an endocannabinoid, and ibuprofen, a nonsteroidal anti-inflammatory drug, in acute and inflammatory pain. Pain. 2006 Mar; 121 (1-2) :85-93.

23. Guindon J, Beaulieu P. Antihyperalgesic effects of local injections of anandamide, ibuprofen, rofecoxib and their combinations in a model of neuropathic pain. Neuropharmacology. 2006 Jun; 50 (7) :814-23.

24. Haller VL, Cichewicz DL, Welch SP. Non-cannabinoid CB1, non-cannabinoid CB2 antinociceptive effects of several novel compounds in the PPQ stretch test in mice. Eur J Pharmacol. 2006 Sep 28; 546 (1-3):60-8.

25. Wiley JL, Razzan RK, Martin BR. Evaluation of the role of the arachidonic acid cascade in anandamide’s in vivo effects in mice. Life Sci. 2006 Dec 3; 80 (1):24-35.

26. Holt S, Paylor B, Boldrup L, Alajakku K, Van devoorde A, Sundström A, Cocco MT, Onnis V, Fowler CJ. Inhibition of fatty acid amide hydrolase, a key endocannabinoid metabolizing enzyme, by analogues of ibuprofen and indomethacin. Eur J Pharmacol. 2007 Jun 22; 565 (1-3):26-36.
27. Ahn DK, Choi HS, Yeo SP, Woo YW, Lee MK, Yang GY, Jeon HJ, Park JS, Mokha SS. Blockade of central cyclooxygenase (COX) pathways enhances the cannabinoid-induced antinociceptive effects on inflammatory temporomandibular joint (TMJ) nociception. Pain. 2007 Nov; 132 (1-2):23-32.

28. Dani M, Guindon J, Lambert C, Beaulieu P. The local antinociceptive effects of paracetamol in neuropathic pain are mediated by cannabinoid receptors. Eur J Pharmacol. 2007 Nov 14; 573 (1-3):214-5.

29. Bujalska M. Effect of cannabinoid receptor agonists on streptozotocin-induced hyperalgesia in diabetic neuropathy. Pharmacology. 2008; 82 (3):193-200.

30. Mallet C, Daulhac L, Bonnefont J, Ledent C, Etienne M, Chapuy E, Libert F, Eschalier A. Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. Pain. 2008 Sep 30; 139 (1):190-200.

31. Naidu PS, Booker L, Cravatt BF, Lichtman AH. Synergy between enzyme inhibitors of fatty acid amide hydrolase and cyclooxygenase in visceral nociception. J Pharmacol Exp Ther. 2009 Apr; 329 (1):48-56.

32. Hama AT, Sagen J. Cannabinoid receptor-mediated antinociception with acetaminophen drug combinations in rats with neuropathic spinal cord injury pain. Neuropharmacology. 2010 Mar-Apr; 58 (4-5):758-66.

33. Ruggieri V, Vitale G, Filaferro M, Frigeri C, Pini LA, Sandrini M. The antinociceptive effect of acetylsalicylic acid is differently affected by a CB1 agonist or antagonist and involves the serotonergic system in rats. Life Sci. 2010 Mar 27; 86 (13-14):510-7.

34. Bishay P, Schmidt H, Marian C, Häußler A, Wijntvoort N, Ziebell S, Metzner J, Koch M, Myrczek T, Bechmann I, Kuner R, Costigan M, Dehghani F, Geisslinger G, Tegeder I. R-flurbiprofen reduces neuropathic pain in rodents by restoring endogenous cannabinoids. PLoS One. 2010 May 13; 5 (5):e10628.

35. Staniaszek LE, Norris LM, Kendall DA, Barrett DA, Chapman V. Effects of COX-2 inhibition on spinal nociception: the role of endocannabinoids. Br J Pharmacol. 2010 Jun; 160 (3):669-76.