# Cannabis and Eicosanoids: A Review of Molecular Pharmacology

John M. McPartland

**ABSTRACT.** Many constituents of cannabis exhibit beneficial anti-inflammatory properties, such as ? $^{9}$-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil. The effects of these cannabis constituents on eicosanoid metabolism is reviewed. THC and GLA modulate the arachidonic acid cascade, inhibiting the production of series 2 prostaglandins and series 4 leukotrienes. Cannabinoid receptor- as well as non-receptor-mediated signal transduction pathways appear to be involved. It is proposed that THC acts as a selective cyclooxygenase-2 (COX-2) inhibitor. *[Article copies available for a fee from The Haworth Document Delivery Service: 1-800-342-9678. E-mail address: <getinfo@haworthpressinc.com> Website: <http://www.HaworthPress.com>* 

**KEYWORDS.** Cannabis, cannabinoids, tetrahydrocannabinol, marijuana, anandamide, prostaglandins, thromboxanes, leukotrienes, phospholipase, cyclooxygenase, lipooxygenase

## *INTRODUCTION*

Eicosanoids are bioactive compounds derived from $C_{20}$ polyunsaturated fatty acids, and include the prostaglandins, thromboxanes, and leukotrienes. Many of these compounds originate from arachidonic

John M. McPartland, DO, MS, is Clinical Assistant Professor, Department of Family Practice, University of Vermont College of Medicine, 53 Washington Street Extension, Middlebury, VT 05753.

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acid (AA), via a series of enzymatic transformations. Eicosanoids play roles in the regulation of immunity, inflammation, and neurotransmission (Zurier 1993).

The AA cascade is circumfused by the metabolism of endogenous cannabimimetic ligands, including anandamide (ANA) and 2-arachidonyl glycerol (2-AG). Coincidentally, the AA cascade is modulated by many exogenous cannabis compounds, such as ? $^{9}$-tetrahydrocannabinol (THC) in marijuana and gamma-linolenic acid (GLA) in hemp seed oil.

Many studies concerning cannabis and eicosanoids report contradictory data. One fact seems certain: the release of AA from membrane phospholipids is stimulated by THC (Burstein and Hunter 1977) and by ANA (Wartman et al. 1995). The mechanism of this release may or may not involve cannabinoid (CB) receptors. CB receptors are proteins associated with cell membranes, consisting of single serpentine chains of amino acids, approximately 53 kiloDaltons (kDa) in size. The N-terminus of the protein is extracellular, the carboxyl terminus is intracellular, and the rest of the chain winds into seven transmembrane helices, with interconnecting loops of amino acids extending extra- and intracellularly (reviewed by Felder and Glass 1998). Two CB receptors have been identified. $CB_1$ receptors arise in neurons and some glial cells, primarily in the central nervous system, as well as in cells of the gut, uterus, and elsewhere. $CB_2$ receptors are found in immune cells (B-cells, monocytes, T-cells, etc.) and immune tissues (tonsils, spleen, etc.).

$CB_1$ receptors may mediate AA release, according to Hunter and Burstein (1997). These researchers attenuated THC-stimulated AA release by treating N18 mouse neuroblastoma cells with either $CB_1$ antisense probes or the $CB_1$ antagonist SR141716A. Contrarily, Felder et al. (1992,1993) reported that activated $CB_1$ receptors did not induce AA release. Felder and colleagues proposed that THC induced AA release by increasing intracellular calcium, a non-CB receptor effect. Increased intracellular calcium, in turn, induced AA release. Hunter and Burstein (1997) argued that Felder's transfected CHO cells may not express the signaling components required for AA release via receptors. Most recently, Pestonjamasp and Burstein (1998) decreased THC-stimulated AA release by treating murine monocyte cells with the $CB_2$ antagonist SR144528, suggesting the possible involvement of $CB_2$ receptors in THC-stimulated AA release.

Non-receptor mechanisms must be responsible for the activity promoted by cannabidiol (CBD). CBD is non-psychoactive and does not bind to CB receptors, yet it potently stimulated AA release, more so than THC (White and Tansik 1980). Similarly, cannabinol (CBN) and cannabigerol (CBG), with little receptor affinity, also stimulated AA release, at lower $EC_{50}$ concentrations than THC (Evans et al. 1987).

AA release from membrane phospholipids is catalyzed by three enzymes, phospholipases A, C, and D. Each of these enzymes will be reviewed.

## *PHOSPHOLIPASE $A_2$*

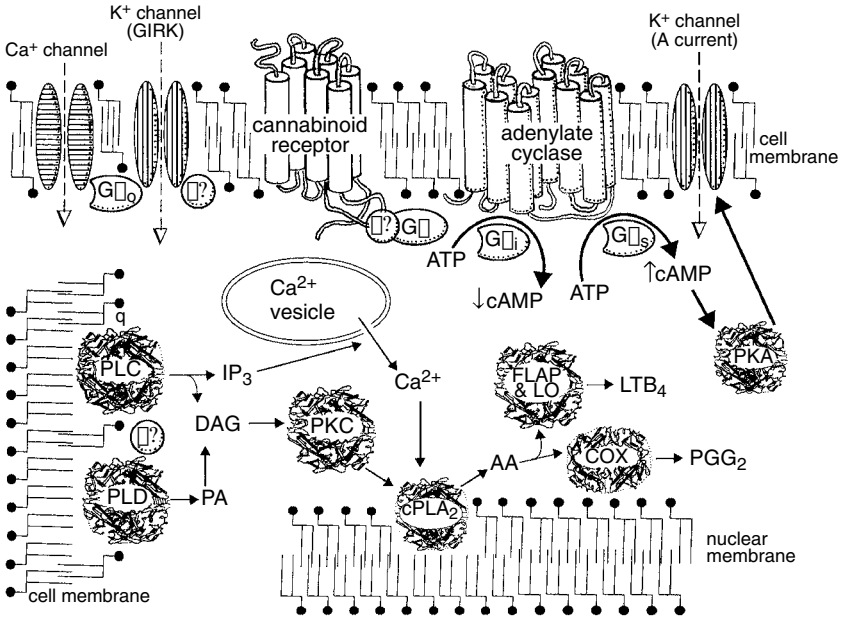
Phospholipase $A_2$ ($P1A_2$) activity increases in cells exposed to THC (Evans et al. 1987) and ANA (Wartmann et al. 1995). This enzyme hydrolyzes membrane phospholipids, particularly phosphatidylcholine and phosphatidylethanolamine, into two products–a lysophospholipid and a free fatty acid. If the fatty acid at the *sn* (stereospecific numbering)-2 position is AA, then $P1A_2$ releases AA in a single-step reaction. Various forms of $P1A_2$ have been identified. One $P1A_2$ specifically implicated in AA release is cytosolic $P1A_2$ ($cP1A_2$), a soluble 85 kDa protein. Upon activation, $cP1A_2$ translocates from the cytoplasm to the nuclear membrane, where it hydrolyzes phospholipids.

Felder et al. (1992) reported that cannabinoid-enhanced $P1A_2$ activity was not a receptor-mediated event. Felder et al. (1993) repeated their results using ANA. A nonreceptor mechanism must also be responsible for the potent stimulation of $P1A_2$ activity by CBD (White and Tansik 1980), and CBN and CBG (Evans et al. 1987).

Although currently unproven, CB receptors could indirectly enhance $P1A_2$ activity via G-proteins. G-proteins couple to many kinds of receptors, including those for cannabinoids, eicosanoids, opioids, epinephrine ( - and -adrenergic receptors), acetylcholine (muscarinic but not nicotinic receptors), serotonin, dopamine, ACTH, CCK, VIP, FSH, LH, TSH, parathyroid hormone, calcitonin, somatostatin, glucagon, angiotensin II, oxytocin, vasopressin, and substance P.

G-proteins are composed of three subunits: an  subunit and a ? subunit complex (Figure 1). At least three families of G-proteins are associated with CB receptors–Gi, Go, and Gs (Glass and Felder 1997).

FIGURE 1




When a cannabinoid agonist binds to the extracellular face of a CB receptor, there is a change in the conformation of the intracellular domain of the receptor, which permits coupling of the G-protein. Coupling activates the G-protein, which quickly uncouples from the receptor and splits into its Gα and Gα? subunits. Each goes its own way, thus bifurcating the receptor signal; the signal is further amplified by the fact that each CB receptor can activate many G-proteins. Uncoupled subunits diffuse along cell membranes and influence multiple effector systems (Figure 1). Gα and Gα? subunits directly regulate ion channels, such as N-, Q-, and L-type $Ca^{2+}$ channels, and G-protein-coupled inwardly rectifying K+ (GIRK) channels. Gβ subunits also interact with adenylate cyclase, thus modulating the rate of cyclic AMP (cAMP) synthesis. By this mechanism, Gβ subunits regulate the activity of cAMP-dependent protein kinase A (PKA). PKA in turn modulates the activity of transcription factors in the CREB protein family, and the transcription of genes in the nucleus.

CB receptor activation decreases cAMP production (Devane et al.

1988). Since cAMP inhibits $cP1A_2$, a CB receptor-mediated decrease in cAMP may result in a net release of AA (Di Marzo et al. 1997). Alternatively, CB receptors may act through ras and mitogen-activated protein kinase (MAPK), which phosphorylates and activates $cPlA_2$ (Wartmann et al. 1995, Di Marzo et al. 1997). Lastly, diacylglycerol (DAG), a product of other CB-receptor-mediated pathways, may activate $cP1A_2$ via protein kinase C (PKC) and MAPK.

THC actually modulates $P1A_2$ in a biphasic manner (Evans et al. 1987); low concentrations stimulate enzyme activity ($EC_{50}$ range of 2-6 □g/ml), whereas high concentrations inhibit the enzyme ($IC_{50}$ range of 17-48 □g/ml). To explain biphasic activity, Sulcova et al. (1998) proposed that different concentrations of ANA and THC may invoke CB receptors to couple to different G-proteins–low concentrations may activate Gs proteins (stimulatory), whereas high concentrations activate Gi proteins (inhibitory). Glass and Northup (1999) demonstrated that different agonists (THC, ANA, HU-210, and WIN 55,212-2) induced different G-protein coupling of CB receptors (Gi versus Go).

## *PHOSPHOLIPASE C*

One type of phospholipase C (PLC) hydrolyzes a specific phospholipid, phosphatidylinositol 4,5-biphosphate, into two products that serve as second messengers: diacylglycerol (DAG) and inositol 1,4, 5-triphosphate ($IP_3$). DAG activates PKC, as mentioned previously, whereas $IP_3$ releases $Ca^{2+}$ from intracellular stores (Figure 1). DAG can subsequently be hydrolyzed into AA and monoacylglycerol.

Felder et al. (1992) did not find CB receptors had any effect on PLC activity. This was corroborated by Glass and Northup (1999), who found CB receptors did not couple with G□q subunits; G□q subunits normally stimulate PLC□ activity.

## *PHOSPHOLIPASE D*

Phospholipase D (PLD), a 100 kDa protein, hydrolyzes phospholipids into phosphatidic acid and a polar head. Phosphatidic acid is subsequently hydrolized by a phosphatase enzyme into DAG plus

phosphate. DAG can subsequently enter the DAG lipase pathway described above. Burstein et al. (1994) reported THC activated PLD, as measured by increased levels of phosphatidic acid, and they suggested the activation may be a receptor-mediated process.

AA released by phospholipase enzymes does not have a long half-life. It quickly becomes metabolized or becomes reincorporated back into phospholipids. THC, however, inhibits the reuptake of free AA into phospholipids (Reichman et al. 1991); this does not appear to be a CB-receptor-mediated phenomenon (Felder et al. 1993).

AA may be metabolized into a variety of oxygenated products via several enzymes, including (1) cycloxygenases, (2) lipoxygenases, (3) cytochrome P450 enzymes, and perhaps (4) fatty acid amide hydrolase (FAAH). Only the first two enzymes will be addressed in this review. For reviews of the latter two enzymes, see Bornheim et al. (1993) and Felder and Glass (1998), respectively.

## *CYCLOXYGENASE*

Cycloxygenase (COX) enzymes are globular, 72 kDa proteins that associate with membrane surfaces. AA released from membranes enters a channel within COX that leads to the active catalytic site. When AA reaches the catalytic site, COX inserts two oxygen molecules and extracts a free radical from AA, resulting in the five-carbon ring that characterizes prostaglandin $G_2$ ($PGG_2$). $PGG_2$ is subsequently metabolized to other prostaglandins (e.g., $PGE_2$), prostacyclins (e.g., $PGI_2$), and thromboxanes (e.g., $TXB_2$). Note that prostaglandins derived from AA have two double bonds, indicated by the subscript 2. Prostagiandins with one or three double bonds are derived from other fatty acids (e.g., $PGE_1$ from dihomo-gamma-linolenic acid, and $PGE_3$ from eicosapentaenoic acid).

THC blocks the conversion of AA to $PGE_2$, presumably by inhibiting COX activity (Burstein and Raz 1972). But in subsequent studies, THC exhibited a biphasic, dose-related effect on $PGE_2$ release, namely, inhibition at doses of 0.016-0.16 □M and stimulation at 1.6 □M (Burstein and Hunter 1977). This biphasic activity was probably due to the release of AA by THC; i.e., increased substrate overcame COX inhibition.

Cannabinoid structures that do not activate $CB_1$ receptors also in-

hibit the metabolism of AA to $PGE_2$, including CBD, CBN, and CBC (Burstein et al. 1973). Even noncannabinoid constituents in marijuana can inhibit COX activity and $PGE_2$ synthesis, such as essential oils (Burstein et al. 1975), phenols (Burstein et al. 1976), and flavonoids (Evans et al. 1987). The flavonoid cannflavin A was more potent an inhibitor than THC or CBD, with an $IC_{50}$ of 7.0 mg/ml (Evans et al. 1987). But on a weight basis, crude marijuana extracts were more inhibitory than any single constituent, suggesting that synergy occurs with individual compounds (Evans et al. 1987).

The mechanism by which cannabinoids inhibit COX remains unclear. Pro-inflammatory cytokines may be involved, such as interferon ? (INF?), interleukin-1 (IL-1), and tumor necrosis factor a (TNF). COX is activated by these cytokines, and cannabinoids are known to inhibit INF? production (Klein et al. 1998a), and inhibit IL-1 and TNF (Zurier et al. 1998). Inhibition of INF? by THC appears to be mediated by $CB_2$ receptors rather than $CB_1$ receptors (Klein et al. 1998a). Whereas and IL-1 and TNF are inhibited by a cannabinoid without receptor affinity (Zurier et al. 1998). TNF is also inhibited by noncannabinoids present in cannabis, such as apigenin, a flavonoid (McPartland and Pruitt 1999).

The modulation of cytokines by cannabinoids is complex, and biphasic effects are seen (Klein et al. 1998b). Evidence suggests that cannabinoids may directly inhibit COX without involving the cytokine network.

## *COX ISOFORMS*

Two COX isoforms exist, dubbed COX-1 and COX-2. Although they both synthesize prostaglandins, they appear to serve different functions. COX-1 is constitutively expressed, localized in the endoplasmic reticulum, and it produces prostaglandins that protect the gastric mucosa, renal parenchyma, vascular endothelium, and platelet function COX-2 is found on the nuclear envelope, it is activated during inflammatory reactions, and by proinflammatory cytokines. COX-2 activation potentiates the pain and inflammation caused by bradykinin, histamine, and leukotrienes. Lastly, COX-2 prostaglandins are manufactured by malignant cells in the colon (Sheehan et al. 1999).

The obvious goal, at least as far as pain and inflammation is concerned, is to develop drugs that block COX-2 without affecting COX-1. Standard non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin and ibuprofen, inhibit COX-2 and COX-1. Thus, NSAIDs inhibit inflammation but also predispose people to stomach ulcers and renal disease. Recently, however, ''selective COX-2 inhibitors'' have become available, such as celecoxib (Celebrex®) and rofecoxib (Vioxx®).

NSAIDs inhibit COX by a simple blockade of the channel that leads to the active catalytic site within COX. Selective COX-2 inhibitors exploit small differences in the shapes of COX-1 and COX-2 tunnels (Hawkey 1999). The difference between the COX isoforms is a single amino acid substitution, which produces a sidepocket in the channel of COX-2. Selective COX-2 inhibitors are bulky molecules; they fit in the COX-2 channel sidepocket, but cannot fit in the narrower channel of COX-1.

Zurier et al. (1998) studied COX inhibition by THC-11-oic acid, a metabolite of THC that is non-psychoactive and has little affinity for CB receptors. Zurier and coworkers substituted the pentyl side chain of THC-11-oic acid for a dimethylheptyl side chain. The synthetic product, termed ajulemic acid, demonstrated highly selective COX-2 activity.

It is proposed here that the bulky tricyclic ring structure of THC, like that of ajulemic acid, may provide selective COX-2 inhibition, assuming THC can gain access to cytoplasmic COX enzymes. Mechanical blockade of the COX-2 channel would not be a CB-receptor-mediated event. The hypothesis that THC and perhaps all cannabinoids selectively inhibit COX-2 is supported by the clinical observation that chronic marijuana use does not damage the gastric mucosa, unlike NSAIDs which inhibit COX-1 as well as COX-2.

Lack of gastric toxicity by cannabinoids, however, may be due to enhanced production of nitric oxide (NO). NO protects the gastric mucosa by stimulating COX-1 enzymes (Hawkey 1999), and some researchers report that cannabinoids stimulate release of NO (Stefano et al. 1996), although stimulation is not observed in all cell lines (Waksman et al. 1999).

## *LIPOXYGENASE*

AA released by $cP1A_2$ can also be metabolized by lipoxygenase (LO) enzymes. Three types of LO enzymes, 5-LO, 12-LO, and 15-LO, are known in humans; they are associated with membranes and weigh about 75 kDa.

The 5-LO enzyme catalyzes the insertion of an oxygen molecule into AA at carbon 5, forming 5-hydroperoxy-eicosatetraenoic acid (5-HPETE), an unstable intermediate which can be further metabolized into a series of leukotrienes ($LTB_4$, $LTC_4$, $LTD_4$, $LTE_4$). Leukotrienes cause epithelial inflammation, mucus secretion, smooth muscle contraction, and bronchoconstriction, leading to symptoms of asthma and ulcerative colitis (Drazen et al. 1999). The 15-LO enzyme converts AA into 15-HPETE, which is further metabolized to 15-hydroxy-eicosatetraenoic acid (15-HETE) or a series of lipoxins ($LX_A$, $LX_b$, etc.). These products are potential mediators of airway inflammation, and they induce hyperalgesia by increasing the sensitivity of pain fibers in the skin (Riccio et al. 1997). The 12-LO enzyme converts AA into 12-HPETE, which is subsequently reduced to 12-HETE. These products modulate neurotransmission and may have neuroprotecuve properties, as well as cardioprotective ''ischemic preconditioning'' effects, but 12-HETE also promotes tumor cell adhesion, an important factor in metastasis (Chen et al. 1997).

In a noncellular soybean LO assay, THC and CBD inhibited 15-LO activity, with $IC_{50}$ values around 3 □M (Evans et al. 1987). Noncannabinoid constituents of cannabis, such as cannflavin, did not inhibit LO at pharmacologically relevant concentrations. Subsequently, the same research group studied the effects of THC and CBD on the 5-LO enzyme. CBD produced a 100% inhibition of $LTB_4$ production in human polymorphonuclear (PMN) cells, with an $IC_{50}$ = 5.4 □M; THC was only capable of producing a 90% inhibition, with an $IC_{50}$ = 8.2 □M (Formukong et al. 1991). This degree of inhibition is comparable to the new pharmaceutical drug zileuton (Zyflo®); a single 800 mg dose blocks $LTB_4$ production by 80%, although the $IC_{50}$ = 0.5 □M (McGill and Busse 1996).

## *THE HEMP CONNECTION*

Not all prostaglandins and leukotrienes are derived from AA. One

group of non-AA-derived eicosanoids utilizes dihomo-?-linolenic acid (DGLA) as a substrate. Prostaglandins derived directly from DGLA have one double bond, and carry the subscript 1, such as $PGE_1$. Another group of prostaglandins, with three double bonds, carries the subscript 3, such as $PGE_3$.

$PGE_1$ and $PGE_3$, unlike their $PGE_2$ cohorts, actually provide antiinflammatory benefits. They shift the prostaglandin cascade away from series 2 products (e.g., $PGE_2$), suppress monocyte production of inflammatory cytokines, suppress synovial cell hyperplasia, decrease platelet aggregation, and protect the gastric mucosa against NSAID-induced injury (reviewed by DeLuca et al. 1995).

$PGE_1$ synthesis can be enhanced by consuming ?-linolenic acid (GLA), the precursor to DGLA. GLA is derived from the seed oil of evening primrose (*Oenothera biennis*, with 7-9% GLA), borage (*Borago officinalis*, 17-23% GLA), black currant (*Ribes nigrum*, 15-19% GLA), and hemp (*Cannabis sativa*, 2-6% GLA).

$PGE_3$ synthesis is enhanced by consuming omega-3 fatty acids: eicosapentaenoic acid and docosahexaenoic acid are found in fish oils (especially cold water fish like sardines, mackerel, salmon, bluefish, herring, and, to a lesser extent, tuna); □-linolenic acid (ALA) is found in the seed oil of certain plants, such as flax (*Linum usitatissimum*, containing 58% ALA), hemp (*C. sativa*, containing 15-25% ALA), and black currant (*R. nigrum*, containing 12-15% ALA).

Only hemp oil and black currant oil contain the precursors to both $PGE_1$ and $PGE_3$. Hemp oil alone has the added benefit of containing the precursors in a 3:1 ratio, the optimal ratio for human nutrition (Pate 1999).

## *CONCLUSIONS*

This review of eicosanoids and cannabis has been limited to molecular pharmacology. Taken together, *in vitro* studies suggest that cannabinoids act as antiinflammatory agents, inhibiting the AA cascade at several levels. Antiinflammatory activity is mediated by both CB-receptor and non-receptor mechanisms.

Clinical trials concerning eicosanoids and cannabis will be surveyed in a future review. Extracts of cannabis have long been known to decrease pain and inflammation in experimental animal models and

human subjects (O'Shaugnessy 1839). Traditional healers from Eurasian cultures have used cannabis to alleviate pain and inflammation for a very long time (Mechoulam 1986). For the same purposes, cannabis tinctures were prescribed by European and North American physicians, from O'Shaugnessy's era until Anslinger's era. Modern research has documented the molecular efficacy of cannabis products. As Graham (1976) predicted, ''The drug has been frowned upon, officially banned . . . but the interest of the medical profession is slowly reviving. It is not impossible that a limited but respectable niche will be established for it in therapeutics by the end of the century.''

## REFERENCES

Bornheim, L.M., E.T. Everhart, J.M. Li, and M.A. Correia. 1993. Characterization of cannabidiol-mediated cytchhrome P450 inactivation. *Biochem Pharmacol* 45: 1323-1331.

Burstein, S., J. Budrow, M. DeBatis, S.A. Hunter, A. Subramanian. 1994. Phospholipase participation in cannabinoid-induced release of free arachidonic acid. *Biochem Pharmcol* 48:1253-64.

Burstein, S., and S.A. Hunter. 1977. Prostaglandins and *Cannabis*–VI. Release of arachidonic acid from HeLa cells by ? $^{1}$-tetrahydrocannabinol and other cannabinoids. *Biochem Pharmacol* 27:1275-1280.

Burstein, S., E. Levin, and C. Varanelli. 1973. Prostaglandins and *Cannabis*–II. Inhibition of biosynthesis by the naturally occurring cannabinoids. *Biochem. Pharmacol* 22:2905-2910.

Burstein, S., and A. Raz. 1972. Inhibition of prostaglandin $E_2$ biosynthesis by ? $^{1}$-tetrahydrocannabinol. *Prostaglandins* 2:369-375.

Burstein, S., P. Taylor, F.S. El-Feraly, and C. Turner. 1976. Prostaglandins and *Cannabis*–V. Identification of p-vinylphenol as a potent inhibitor of prostaglandin synthesis. *Biochem Pharmacol* 25:2003-2004.

Burstein, S., C. Varanelli, and L.T. Slade. 1975. Prostaglandins and *Cannabis*–III. Inhibition of biosynthesis by essential oil components of marihuana. *Biochem Pharmacol* 24:1053-1054.

Chen, Y.Q., W. Hagmann, and K.V. Honn. 1997. Regulation of 12(S)-HETE production in tumor cells. *Adv Exp Med Biol* 400:159-166.

DeLuca, P., D. Rothman, and RB. Zurier. 1995. Marine and botanical lipids as immunomodulatory and therapeutic agents in the treatment of rheumatoid arthritis. *Rheumatic Disease Clinics North America* 21:759-777.

Devane, W.A., F.A. Dysarz, M.R. Johnson, L.S. Melvin, A.C. Howlett. 1988. Determination and characterization of a cannabinoid receptor in rat brain. *Molecular Pharmacol* 34:605-613.

Di Marzo, V., L. De Petrocellis, T. Bisogno, and S. Maurelli. 1997. The endogenous cannabimimetic eicosanoid, anandamide, induces arachidonate release in J774 mouse macrophages. *Advan Exp Med Biol* 407:341-6.

Drazen, J.M., E. Israel E, and M. O'Byrne. 1999. Treatment of asthma with drugs modifying the leukotriene pathway. *New England J Med*. 340:197-206.

Evans, A.T., E.A. Formukong, and F.J. Evans. 1987. Actions of cannabis constituents on enyzmes of arachidonate metabolism: anti-inflammatory potential. *Biochem Pharmacol* 36:2035-2037.

Felder, C.C., J.S. Velus, H.L. Williams, E.M. Briley, and L.A. Matsuda. 1992. Cannabinoid agonists stimulate both receptor–and non-receptor-mediated signal transduction pathways in cells transfected with and expressing cannabinoid receptor clones *Molecular Pharmacol* 42:838-845.

Felder, C.C., E.M. Briley, J. Axelrod, J.T. Simpson, K. Mackie, and W.A. Devane. 1993. Anandamide, an endogenous cannabimimetic eicosanoid, binds to the cloned human cannabinoid receptor and stimulates receptor-mediated signal transduction. *Proc Natl Acad Sci USA* 90:7656-7660.

Felder, C.C., and M. Glass. 1998. Cannabinoid receptors and their endogenous agonists. *Annu Rev Pharicol Toxicol* 38:179-200.

Formukong, E.A., A.T. Evans, F.J. Evans, and L.G. Garland. 1991. Inhibition of A23187-induced release of leukotriene $B_4$ in mouse whole blood *ex vivo* and human polymorphonuclear cells *in vitro* by the cannabinoid analgesic cannabidiol. *Phytotherapy Research* 5:258-261.

Glass, M., and C.C. Felder. 1997. Concurrent stimulation of cannabinoid CB1 and dopamine D2 receptors augments cAMP accumulation in striatal neurons: evidence for a Gs linkage to the CB1 receptor. *J Neuroscience* 17:5327-5333.

Glass, M., and J.K. Northup. Agonist selective regulation of G-proteins by cannabinoid CB1 and CB2 receptors. *Molecular Pharmacology* 1999, in press.

Graham, J.D.P. 1976. If Cannabis were a new drug. In: Graham JDP, editor. *Cannabis and Health*. London: Academic Press: p. 417-437.

Hawkey, C.J. 1999. COX-2 inhibitors. *Lancet* 353:307-314.

Hunter, S.A., and S.H. Burstein. 1997. Receptor mediation in cannabinoid stimulated arachidonic acid mobilization and anandamide synthesis. *Life Sciences* 18: 1563-1573.

Klein, T.W., C. Newton, and H. Friedman. 1998a. Cannabinoid receptors and the cytokine network. *Adv Exper Biol Med* 437:215-222.

Klein, T.W., H. Friedman, and S. Specter. 1998b. Marijuana, immunity and infection. *J Neuroimmunology* 83:102-115.

McGill, K.A., and W.W. Busse. 1996. Zileuton. *Lancet* 348:519-524.

McPartland, J.M., and F.L. Pruitt. 1999. Side effects of pharmaceuticals not elicited by comparable herbal medicines: the case of tetrahydrocannabinol and marijuana. *Alternative Therapies in Health & Medicine* 5(4):57-62.

Mechoulam, R. 1986. *Cannabinoids as Therapeutic Agents*. CRC Press: Boca Raton, FL. 186 pp.

O'Shaughnessy, W.B. 1839. On the preparations of the Indian hemp, or gunjah (*Cannabis indica*). *Transactions Medical and Physical Society of Bengal* 1838-1840:421-461.

Pate, D. 1999. Hemp seed: a valuable food source, pp. 243-255 in *Advances in Hemp Research*, P. Ranalli, ed. The Haworth Press, Inc.: Binghamton, NY.

Pestonjamasp, V.K., and S.H. Burstein. 1998. Anandamide synthesis is induced by

arachidonate mobilizing agonists in cells of the immune system. *Biochimica Biophysica Acta* 1394:249-260.

Reichman, M., W. Nen, and L.E. Hokin. 1991. ? $^{9}$-tetrahydrocanflabinol inhibits arachidonic acid acylation of phospholipids and triacylglycerols in guinea pig cerebral cortex slices. *Molec Pharmacol* 40:547-555.

Riccio, M.M., T. Matsumoto, J.J. Adcock, G.J. Douglas, D. Spina, and C.P. Page. 1997. The effect of 15-HPETE on airway responsiveness and pulmonary cell recruitment in rabbits. *Br J Pharmacol* 122:249-256.

Sheehan, K.M., K. Sheahan, D.P. O'Donoghue, F. MacSweeney, R.M. Conroy, D.J. Fitzgerald, and F.E. Murray. 1999. The relationship between cyclooxygenase-2 expression and colorectal cancer. *JAMA* 282:1254-1257.

Stefano, G.B., Y. Liu, and M.S. Goligorsky. 1996. Cannabinoid receptors are coupled to nitric oxide release in invertebrate immunocytes, microglia, and human monocytes. *J Biological Chem* 271:19238-19242.

Sulcova, E., R. Methoulam, and E. Fride. 1998. Biphasic effects of anandamide. *Pharmacol Biochem Behav* 59:347-352.

Waksman, Y., J.M. Olson, S.J. Carlisle, and G.A. Cabral. 1999. The central cannabinoid receptor (CB1) mediates inhibition of nitric oxide production by rat microglial cells. *J. Pharmacol. Exp. Therap*. 288:1357-1366.

Wartmann, M., D. Campbell, A. Subramanian, S.H. Burstein, and R.J. Davis. 1995. The MAP kinase signal transduction pathway is activated by the endogenous cannabinoid anandamide. *FEBS Letters* 359:133-136.

White, H.L., and R.L. Tansik. 1980. Effects of delta-9-tetrahydrocannabinol and cannabidiol on phospholipase and other enzymes regulating arachidonate metabolism. *Prostaglandins & Medicine* 4:409-417.

Zurier, R.B. 1993. Prostaglandins, leukotrienes, and related compounds, pp. 201-212 in *Textbook of Rheumatology*, 4th ed., Vol. 1., eds: WN Kelly, ED Harris, S Ruddy, CB Sledge. W.B. Saunders Co.: Philadelphia, PA.

Zurier, R.B., R.G. Rossetti, J.H. Lane, J.M. Goldberg, S.A. Hunter, and S.H. Burstein. 1998. Dimethylheptyl-THC-11-oic acid–a nonpsychoactive antiinflammatory agent with a cannabinoid template structure. *Arthritis & Rheumatism* 41:163-170.

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