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Prospects for Cannabinoids as Anti-inflammatory Agents

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Abstract The marijuana plant (*Cannabis sativa*) and preparations derived from it have been used for medicinal purposes for thousands of years. It is likely that the therapeutic benefits of smoked marijuana are due to some combination of its more than 60 cannabinoids and 200–250 non-cannabinoid constituents. Several marijuana constituents, the carboxylic acid metabolites of tetrahydrocannabinol, and synthetic analogs are free of cannabimimetic central nervous system activity, do not produce behavioral changes in humans, and are effective antiinflammatory and analgesic agents. One cannabinoid acid in particular, ajulemic acid, has been studied extensively in in vitro systems and animal models of inflammation and immune responses. This commentary reviews a portion of the work done by investigators interested in separating the medicinal properties of marijuana from its psychoactive effects. Understanding the mechanisms of the therapeutic effects of nonpsychoactive cannabinoids should lead to development of safe effective treatment for several diseases, and may render moot the debate about ''medical marijuana''. J. Cell. Biochem. 88: 462–466, 2003.

Key words: cannabinoids; ajulemic acid; inflammation; immunosuppression

Preparations derived from *Cannabis sativa* have been the source of medicinal preparations since the earliest written records on pharmacobotany [Abel, 1980]. The Chinese emperor, Shen-nung, noted 4000 years ago, as later recorded in a work called Pen-tsao, many effects of *Cannabis* on the human body. Among these, it was claimed that *Cannabis* can "undo rheumatism" [Hui-Lin, 1975]. *Cannabis sativa* is a complex botanical. Therefore, it is not unlikely that the therapeutic benefits of marijuana are due to some combination of its more than 60 cannabinoids as well as the 200–250 noncannabinoid constituents of the plant. One noncannabinoid, the prenylated flavone cannflavin, is 30 times more potent than aspirin as an inhibitor of cyclo-oxygenase [Barrett et al., 1985, 1986]. These potentially important findings have been overlooked, as most attention in marijuana research has been directed to the analgesic effects of the plant and to mechanisms of psychoactivity. A further example that this line of inquiry has not been pursued vigorously is a series of papers published 30 years ago [Sofia et al., 1973a,b, 1974] which demonstrate potent antiinflammatory actions of a crude marijuana extract, of tetrahydrocannabinol (THC), and of the nonpsychoactive *Cannabis* constituents, cannabidiol (CBD), and cannabinol (CBN) in the carageenan induced paw edema model of acute inflammation in rats. In these studies, THC proved 80 times more potent than aspirin and twice as potent as hydrocortisone. In addition, the nonpsychoactive constituent, cannabichromene (CBCr) was reported to have antiinflammatory activity in the carageenan paw edema assay [Wirth et al., 1980; Turner and ElSohly, 1981]. More recently, CBD was shown to reduce joint inflammation in a murine model of collagen induced arthritis [Malfait et al., 2000]. Volatile oil components of the plant suppress cyclooxygenase-1 (COX-1) activity [Burstein et al., 1975, 1976], and pyrolysis products of CBD exhibit activity in COX-1 suppression assays [Spronck et al., 1978]. Since CBD is usually the most abundant nonpsychoactive cannabinoid in the plant, these pyrolysis products may add to the therapeutic properties

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of smoked marijuana. p-hydroxycinnamic acid is also moderately abundant in the plant, and its pyrolysis product p-vinyl phenol may have anti-inflammatory properties. Several of the most abundant cannabinoid (Fig. 1) and noncannabinoid (Fig. 2) constituents of marijuana are nonpsychoactive [Razdan, 1986].

It seems clear that smoked marijuana, whatever its health benefits, also imposes health risks, both psychological and physiological [Hollister, 1986]. Also, many physicians are reluctant to prescribe pure THC (Marinol®) for fear of substance abuse in vulnerable populations. The challenge before us is to determine which nonpsychoactive constituent or combination of constituents of the whole plant will provide safe effective therapy, and to uncover mechanisms responsible for those effects. In addition, development of nonpsychoactive cannabinoid analogs should be encouraged.

A major obstacle to broad acceptance of cannabinoids as therapeutic agents is their potent psychoactive effects. A class of cannabinoids, the carboxy THCs, shows promise as therapeutic agents since they are free of cannabimimetic central nervous system activity [Burstein, 1999]. These cannabinoid acids, which are

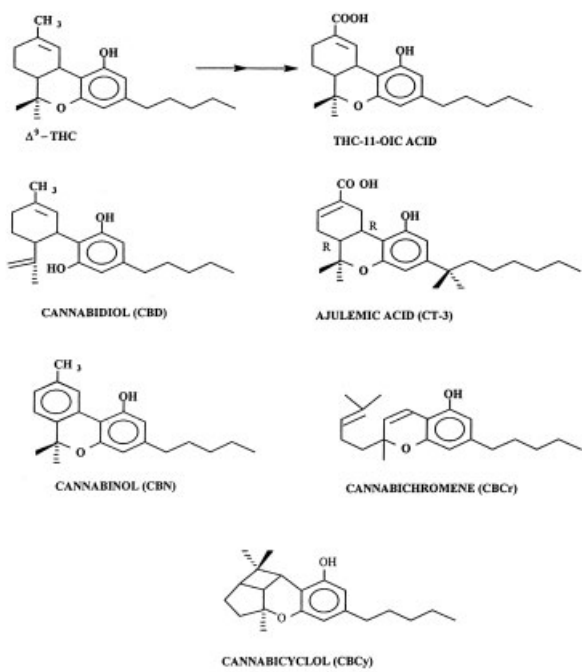

Fig. 1. Structures of the most abundant cannabinoids found in *Cannabis* (THC, CBD CBN, CBCr, and CBCy), the principal metabolite of THC (THC-11-oic acid), and its synthetic analog (ajulemic acid; CT3).

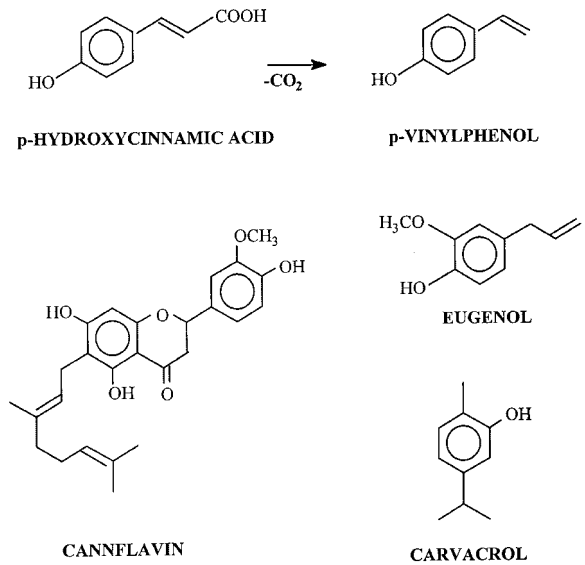

Fig. 2. Structure of available noncannabinoid *Cannabis* constituents, and of cannflavin which can be isolated from whole plant extracts. p-vinylphenol is a pyrolysis product of p-hydroxycinnamic acid.

metabolites of THC, the psychoactive agent of *Cannabis*, do not produce behavioral changes in humans at doses several times greater than THC doses given to the same volunteers [Perez-Reyes, 1985]. The term cannabinoid acid includes all the carboxylic acid metabolites of the cannabinoids, and their synthetic analogs. The principal metabolite in this series, THC-11 oic acid (Fig. 1), is effective in animal models of inflammation and pain at oral doses of 20–40 mg/kg [Burstein et al., 1986; Doyle et al., 1990]. THC-11 oic acid also suppresses both the cyclooxygenase and lipoxygenase activities of cells in tissue culture [Burstein et al., 1986]. However, more potent activity is needed for clinical use.

It has been known for some time that specific modifications of the pentyl side chain of THC increase its potency [Loev et al., 1993]. In particular, extending the chain length to seven carbons and introducing branching close to the ring leads to compounds with potencies that are 50–100 times greater than THC. This strategy was employed in designing the structure of 1′1′-dimethylheptyl-THC-11 oic acid (trivial name ajulemic acid:AjA) [Burstein et al., 1992]. This analog (AjA; Fig. 1) of THC-11 oic acid is a potent antiinflammatory and analgesic agent in several animal models [Burstein, 1999]. In rats, AjA is equipotent to

morphine as an analgesic but has a longer duration of action [Dajani et al., 1999]. AjA also suppresses 5-lipoxygenase and cyclooxygenase-2 activities, but unlike the nonsteroidal anti-inflammatory drugs currently used, AjA is not ulcerogenic [Dajani et al., 1999]. Moreover, pharmacologically meaningful physical dependence was not evident in rats treated with doses up to 40 mg/kg/day AjA. In addition, AjA is not psychoactive; indeed, AjA suppresses THC induced catalepsy in mice [Burstein, 1999]. We have shown [Zurier et al., 1998] that oral administration of AjA at a dose of 0.1 mg/kg three times weekly reduces significantly the severity of adjuvant-induced polyarthritis in rats, although periarticular inflammation did occur in treated rats. Histomorphological evaluation of the joints suggested that synovial inflammation also occurred in AjA treated animals, but that it did not progress to cartilage degradation, bone erosion, and distortion of joint architecture (crippling), as was observed in rats given placebo.

Although a variety of mediators contribute to inflammatory responses, it seems clear that the actions of interleukin-1β (IL-1β) and tumor necrosis factorα (TNFα) are central to progression of joint tissue injury in patients with rheumatoid arthritis. Major advances in the treatment of rheumatoid arthritis have been made recently because of development of agents that block the actions of IL-1β [Arend and Dayer, 1995] and TNFα [Bathon et al., 2000; Lipsky et al., 2000]. Animal models continue to be instructive in determining the relation of inflammatory cytokines to joint tissue injury. In a series of elegant experiments, van den Berg and his colleagues reported that blockade or elimination of IL-1β does not prevent joint swelling, but it is effective in reducing joint cartilage degradation and bone erosion. In contrast, blockade or elimination of TNF-α prevents joint swelling but not cartilage and bone damage [Joosten et al., 1999]. Results of our own animal study noted above [Zurier et al., 1998] in which AjA reduces clinical inflammation (joint redness and swelling) only modestly, but prevents joint cartilage and bone damage may be explained by differential effects of AjA on IL-1β and TNFα. We have observed [Zurier et al., 2002] that addition of AjA to human peripheral blood and synovial fluid monocytes in vitro suppresses production of IL-1β by activated cells. In contrast, AjA does not have an appreciable effect on TNFα production by activated cells. AjA reduces steady state levels of IL-1β mRNA and subsequent secretion from activated cells of IL-1β. The reduction in IL-1β gene expression is not due to altered mRNA stability.

Using two murine models of arthritis, Campbell and colleagues showed that TNF is important but is not obligatory for development of acute inflammatory and chronic autoimmune arthritis [Campbell et al., 2001]. A dual role (pro-inflammatory and immunosuppressive) for TNF has been proposed in several experimental models of autoimmune disease [Kassiotis and Kollias, 2001]. These animal models may provide answers to why IL-1 or TNF blockade is not successful in all patients with rheumatoid arthritis.

Cannabinoid acids, including AjA, exhibit only modest affinity for either CB1 or CB2, the two known cannabinoid receptors. Although possible, it is unlikely that the effects of AjA are mediated by either of these receptors. Little evidence exists for a third member of the family of heteromeric G-protein coupled cannabinoid receptors. It is of course possible that other, perhaps intracellular, high affinity binding sites mediate some actions of AjA. Other cannabinoids also block production of inflammatory cytokines.

Identification of four endocannabinoids which may modulate neuronal, vascular, and immune cell function, reinforces the need for research into the regulatory activities of these and similar molecules. Endocannabinoids are endogenous compounds capable of binding to and functionally activating the two known cannabinoid receptors, CB1 and CB2 [DiMarzo et al., 2002]. The four known endocannabinoids include anandamide (arachidonylethanolamide), 2-arachidonoyl glycerol, 2-arachidonyl glyceryl ether, and *O*-arachidonoyl ethanolamine [Porter et al., 2002]. Recent observations suggest that the endocannabinoids also interact with non-CB1, non-CB2 G protein coupled receptors and several ion channels [DiMarzo et al., 2002]. Since anandamide is a ligand for the CB1 receptor, which binds THC, it was named for the Sanskrit word ananda, meaning internal bliss. The most recently discovered endocannabinoid, *O*-arachidonoyl ethanolamide is arachidonic acid and ethanolamine joined by an ester linkage, the opposite of the amide linkage found in anandamide. Thus, the latest endocannabinoid

is named virodhamine from the Sanskrit word virodha, which means opposition.

Immune/inflammatory responses are of course designed to be protective, and are extremely redundant. It follows that successful therapy of chronic inflammatory diseases will require modification of several aspects of host defense responses with agents that can be given safely for long periods of time. The cannabinoids reduce pain, modulate several aspects of immune/inflammatory responses, and have a long history of safety in vivo. Many different preparations of *Cannabis* have been used since antiquity as medicinal agents by a number of societies. These substances are still important therapeutic agents in countries such as China, India, and in certain West Indian nations. It seems reasonable to assume that a rational basis exists for the persistent use of this plant over several millennia that justifies further research into the scientific basis for this phenomenon. A strong bias against the use of "medical marijuana" was introduced into our society in the middle of the 20th century. However, recent pubic opinion polls and the actions of a number of state legislative bodies indicate that a shift in sentiment has occurred toward the reinstatement of *Cannabis* as an approved medication. Accurate data are needed to address the issue objectively. Virtually all the published research on herbal *Cannabis* addresses its analgesic and mood altering properties. Experiments should be designed to examine possible anti-inflammatory properties of *Cannabis*. In addition to anecdotal information, data on cannabinoids suggest the presence of such activities. That *Cannabis* and the cannabinoids are characterized by their low toxicities when compared with other drugs and herbal preparations reinforces the notion that further investigation of their medicinal properties should be undertaken.

Now that psychoactivity can be separated from the medicinal properties of *Cannabis* products and pure constituents are available or can be isolated from the plant, it is very important to understand which constituents or combination of constituents of marijuana are responsible for the biological and pharmacological activities of the whole plant. Such knowledge, and synthesis of analogs of plant constituents, might lead to development of new, more benign treatment for diseases characterized by acute and chronic inflammation. Also, if nonpsychoactive constituents of marijuana and/or cannabinoid acid analogs proved equivalent or superior to the whole plant as antiinflammatory agents, that might stimulate similar studies for conditions such as glaucoma, pain, wasting, and cancer that could reduce the time and energy and money spent in debates about legalization of marijuana.

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