A molecular basis of the therapeutic and psychoactive properties of cannabis (Δ9-tetrahydrocannabinol)

Gabriel Nahas*a, David J. Harveyb, Kenneth Sutina, Herman Turndorfa, Robert Cancroc

aDepartment of Anesthesiology, New York University School of Medicine, New York, NY, USA
bDepartment of Biochemistry, University of Oxford, South Parks Road, Oxford, UK
cDepartment of Psychiatry, New York University School of Medicine, New York, NY, USA

Abstract

All of the therapeutic properties of marihuana (analgesic, antiemetic, appetite stimulant, antiglaucoma) have been duplicated by the tetrahydrocannabinol (THC) molecule or its synthetic derivatives. Today, the molecular mechanisms of action of these compounds have led to a general understanding of the pharmacological effects of marihuana and of its therapeutic properties. These mechanisms involve the specific binding of THC to the 7-transmembrane (7TM) domain G protein-linked receptor, a molecular switch which regulates signal transduction in the cell membrane. The natural ligand of the 7TM receptor is an eicosanoid, arachidonylethanolamide (AEA), generated in the membrane and derived from arachidonic acid. THC acts as a substitute ligand to the 7TM receptor site of AEA. THC would deregulate the physiological function of the 7TM receptor and of its ligand AEA. As a result, the therapeutic effects of the drug may not be separated from its adverse psychoactive and cardiovascular effects. The binding of THC to the 7TM receptor site of AEA induces allosteric changes in the receptor sites of neurotransmitter and opiates resulting in variable interactions and pharmacological responses. The pharmacokinetics of THC with its prolonged storage in fat and its slow release result in variable and delayed pharmacological response, which precludes precise dosing to achieve timely therapeutic effects. The experimental use of THC and of its synthetic analogues, agonists, and antagonists has provided novel information in the nature of molecular signaling in the cell membrane. As a result, the relationships between allosteric receptor responsiveness, molecular configuration of proteins, and physiological regulation of cellular and organ function may be further investigated. © 2002 Elsevier Science Inc. All rights reserved.

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1. Introduction

There has been much discussion over the last year (Select Committee on Science and Technology, 1998; Joy et al., 1999; Nahas et al., 1999b) on the use of psychoactive cannabinoids of marihuana (tetrahydrocannabinol or THC) for medical purposes, particularly with respect to the treatment of neurological disorders (multiple sclerosis), glaucoma, and pain. However, little of this discussion appears to reflect the true nature of this drug that contains many active components, present in varying amounts. These compounds affect the body through a number of mechanisms that can, in some cases, produce opposing effects. Of particular importance are the developing theories of signal transduction within the membrane and the emerging evidence that suggests that marihuana interferes with a basic regulation of cell function at the molecular level with unforeseen consequences. This paper reviews the molecular mechanisms by which THC produces its effects and presents a unified theory of membrane signaling transduction, which could account for the therapeutic properties of THC and its associated adverse effects.

2. Cannabinoids

Marihuana is a product of the plant Cannabis sativa L. that contains some 60 unique terpenoid-containing mole-
molecules known as cannabinoids [cannabidiol (CBD) and cannabinoi1 (CBN)]. CBD, for example, inactivates certain iso7ymes of the cytochrome P-450 drug-metabolizing enzyme system (Bornheim et al., 1993)] which, in turn, alters the relative amount of psychoactive metabolites produced from Δ9-THC. It can be seen that marihuana from uncontrolled sources could produce inconsistent pharmacological effects. Furthermore, the high lipophilicity of THC (Garrett and Hunt, 1977; Leuschner et al., 1986] produces a long half-life and results in substantial accumulation in body tissues after chronic use (Cridland et al., 1983; Ellis et al., 1985) Cannabinoids and their metabolites (Harvey, 1991) are classified into two major categories, psychoactive and nonpsychoactive, corresponding to particular chemical structures and pharmacological effects. The psychoactive cannabinoids, Δ9-THC, Δ8-THC (a synthetic analogue), and their 11-hydroxy derivatives bind stereospecifically to unique receptors and have pharmacologic activity in nanomolar concentrations. The nonpsychoactive cannabinoids, which consist of both natural compounds such as CBD and metabolites such as Δ9-THC-11-oic acid, exert their actions at other sites. While not psychoactive, these latter compounds nevertheless possess other biological activities and, as first emphasized by Paton et al. (1972), target the lipid bilayer. The membrane and its integral receptors closely interact; THC partitions into the membrane, alters membrane fluidity (increases the molecular disorder of the bilipid layer), and affects membrane-bound enzymes and receptors.

3. The interaction of cannabinoids with the membrane lipid bilayer

Lawrence and Gill (1975) first demonstrated that THC in micromolar concentration increases the molecular disorder of the liposome. At higher concentrations, the effect levels off and does not increase as the molecular ratio of THC to lecithin is increased. The maximum degree of fluidization (disordering) produced by THC does not approach that of Δ9-THC-11-oic acid, exert their actions at other sites. While not psychoactive, these latter compounds nevertheless possess other biological activities and, as first emphasized by Paton et al. (1972), target the lipid bilayer. The membrane and its integral receptors closely interact; THC partitions into the membrane, alters membrane fluidity (increases the molecular disorder of the bilipid layer), and affects membrane-bound enzymes and receptors.

It was reported (Leuschner et al., 1984) that the disordering effect of THC actually occurred in vivo: There was an equilibrium between the concentration of the drug in erythrocytes and plasma. A disordering effect in the membrane was also reported after chronic treatment of mice with ethanol (Wing et al., 1982), which led the authors to suggest that tolerance might be associated with changes in the membrane lipid composition. By contrast, the nonpsychoactive cannabinoids, CBN and CBD, produce an effect opposite to that of Δ9-THC by decreasing the molecular disorder of the lipid bilayer (Lawrence and Gill, 1975), and one could expect that CBN and CBD would antagonize, in part, the effect of THC in vivo, a prediction that has been documented by experimental observations (Borgen and Davis, 1974). These results could contribute, in part, to the variability of observed effects in studies which use different cannabinoids.

4. Effects of cannabinoids on neurotransmitter receptors

THC has been reported to affect the activity of several neurotransmitter receptor systems. THC, however, does not interact directly with the active site of the receptors, but causes an allosteric modification of the receptor, which in turn modifies its response to other agonists and antagonists. After THC administration, the effects of subsequent exposure to the receptor agonists acetylcholine (Domino, 1981; Gessa et al., 1997), opioids (Vaysse et al., 1987) and N-methyl-D-aspartate (NMDA) (Hampson et al., 1998) are decreased, while the effects of THC on catecholamines (Bloom et al., 1978) and gamma aminobutyric acid (GABA) are biphasic (Pryor et al., 1977). Bloom and Hillard (1984) conclude that, since THC alters membrane fluidity, its effect on constituent receptors is due to changes in the membrane environment, which in turn, affect membrane receptors. “Although some differences exist in the interactions with specific proteins, the fact remains that psychoactive cannabinoids affect a broad range of membrane-bound receptors, which supports the concept of a direct influence on the membrane lipid bilayer, rather than an embedded receptor specific for Δ9-THC on each of these very different receptor molecules to neurotransmitters.”

5. Interaction of THC with specific receptors

As a result of these general interactions with membrane-bound receptors, it was concluded that while THC altered, in a specific fashion, the physicochemical organization of the membrane, this effect alone could not account for the stereospecific psychoactive properties of this cannabinoid. These are exerted at lower nanomolar concentrations, and are more typical of drugs acting at specific receptors.

A receptor to THC was identified in rat brain (Devane et al., 1988) and called cannabinoid-1 (CB-1 receptor). It has been identified to a nucleotide regulatory (G) protein-linked 7-transmembrane (7TM) receptor. Receptors are unevenly distributed, with highest concentrations in the globus pallidus, substantia nigra, cerebral cortex, striatum, and the molecular layers of the cerebellum and hippocampus (Herkenham et al., 1990) A second receptor called (CB-2), has 44% sequence homology with the CB-1 receptor and is also a G protein-linked 7TM receptor (Munro et al., 1993). Although the CB-2 receptors appear to be in the periphery, CB-1 receptors are found both centrally and peripherally (Pertwee, 1995).
5.1. Functional correlates of THC receptor binding and signaling alterations

The binding of THC to its CB-1 or CB-2 G protein-7TM coupled receptors is associated with changes in functions of the brain, the immune system, and the reproductive organs. In the brain, binding of THC to CB-1 receptors is associated with marked changes of sensory perception. These changes were first described in 1845 by Moreau, who emphasized alterations of visual, auditory, and “body image” perceptions. Subsequently, these self-reported alterations were correlated with functional markers used to estimate visual, auditory, and somatosensory perceptions: Cannabis intoxication induces an illusion of visual perception characterized by binocular depth inversion that is also observed in unmedicated persons with schizophrenia (Emrich et al., 1997). It is also associated with a delay in the P-300 response to auditory-evoked potentials, a dysfunction that may persist for weeks after THC or marihuana administration. (Solowij et al., 1995) Distortion of somatosensory perception reported by Moreau was also observed in a controlled clinical setting (Perez-Reyes et al., 1991). Lowering of thermal pain perception has also been measured in heavy marihuana smokers (Clark et al., 1981). Such perceptual alterations may be related to the persistent binding of THC to the “CB-1” receptors in areas of the brain where sensory perceptions are transduced.

Binding of THC to peripheral CB-2 7TM receptors induces alterations of signaling in the immune system and the reproductive organs. The binding to CB-2 receptors on lymphocytes and macrophages impairs their signaling function (Cabral, 1999). Binding of THC to receptors on sperm cells and ovum interferes with the acrosomal reaction (Schuel et al., 1994), fertilization, and ovum implantation (Paria et al., 1995). These signaling alterations could account for the clinical and experimental observations reporting a decreased spermatogenesis, decreased sperm motility, and increase of abnormal forms of sperm in rodents and humans exposed to marihuana smoke or THC (Hembrée et al., 1999).

6. Endogenous membrane-derived ligands of the cannabinoid receptor

The discovery of receptors with an affinity for THC suggested the occurrence of endogenous ligands for these receptors. The first such compound to be discovered was an eicosanoid, N-arachidonylthanolamide (AEA) (Devane et al., 1992), also named “anandamide” after the Sanskrit word “ananda” meaning bliss. Biosynthesis of AEA occurs from membrane phosphatidylethanolamine, which becomes esterified by free arachidonic acid or, by acyltransferase (ACE), from the 1-position of phosphatidylcholine (Di Marzo, 1998, 1999; Di Marzo et al., 1999). AEA is then released by the action of a phosphodiesterase (Sugiura et al., 1996a,b) identified in neuroblastoma cells as phospholipase (PPL)-D (Di Marzo et al., 1996). Degradation of AEA occurs within the membrane by the action of the amidase, anandamide amidohydrolase (Ueda et al., 1996; Bisogno et al., 1997a,b). AEA has a lower affinity for the 7TM receptor than THC, a much shorter duration of activity and is rapidly metabolized like most signaling and second messenger molecules. It is not stored in cells, but accumulates in the brain following hypoxia or cellular death (Schmid et al., 1995). Like THC, AEA has been found to fluidize the cell membrane (Bloom et al., 1997), and one might expect that AEA might play a role in the regulation of membrane function.

The full profile of AEA has activity yet to be elucidated and there are conflicting theories (Stanford and Mitchell, 1999), AEA, like THC may be a long-acting endothelium-derived vasorelaxant, known as endothelium-derived hyperpolarizing factor, or EDHF, which is independent of NO. This mechanism has been discussed, although AEA has been shown to cause a dose-dependent vasodilatation in the perfused rat mesenteric bed (Wagner et al., 1999), which appears to act through CB-1 or CB-2 receptors (Wagner et al., 1999; Niederhofer and Szabo, 1999).

A second ligand of both CB-1 and CB-2 receptors has subsequently been identified as 2-arachidonylglycerol (2-AG). It was first isolated from canine gut (Mechoulam et al., 1995) and was later found in higher concentrations in brain cells (Sugiura et al., 1995; Stella et al., 1997). Its affinity for the receptors parallels that of AEA. Two mechanisms for its biosynthesis have been proposed (Di Marzo, 1998, 1999). The first involves cleavage of inositol phosphate from phosphatidylinositol by a phosphatidylinositol-specific PPL-C followed by removal of the acyl-group from the 1-position. The second pathway involves the removal of the fatty acid from the 1-position of sn-arachidonic acid-containing diacylglycerides which, in turn, can originate from hydrolysis of triglycerides, phosphatidic acid, phosphatidylinositol, or phosphatidylcholine.

7. Effect of psychoactive cannabinoids on phospholipid enzymes and arachidonic acid biosynthesis and membrane molecular signaling

A phospholipid messenger system constitutes a major function of the lipid bilayer and involves signal-mediated hydrolysis of phospholipids within the membrane. The best characterized of these systems is that originating from arachidonic acid, which is released from phospholipids following activation by a PPL. Psychoactive cannabinoids and some of their nonpsychoactive acid metabolites also release arachidonic acid from phosphatidylcholine in a dose-related manner (Hunter et al., 1985; Burstein et al., 1986). Arachidonic acid has been associated with biosynthesis of prostaglandins and other eicosanoids such as leukotrienes and platelet activation factors (PAF). Its meta-
bolism has been shown to be inhibited by steroids, non-steroidal anti-inflammatory drugs (NSAIDs) (Burstein et al. 1986), and by the THC metabolite, THC-11-oic acid (Zurier et al., 1998). In direct contrast to the stimulation of prostaglandin production by THC-induced arachidonic acid release, an inhibitory effect is produced by the non-psychoactive THC metabolite THC-11-oic acid, which suppresses cyclooxygenase (COX) activity and inhibits prostaglandin production.

It is proposed that an alternative pathway of arachidonic acid metabolism, namely the formation of AEA, involved in a molecular signaling system of the cell (Nahas, 2001; Nahas et al., 2000). Protein receptor interaction with lipid ligands like AEA would regulate signaling between boundary lipids and receptors or enzymes of the membrane. Boundary lipids surrounding the membrane proteins transduce signals from AEA to the integral membrane receptors. The change of configuration of the 7TM receptor, caused by the lipid mediators, would produce allostERIC changes of the protein, modulating or fine-tuning of membrane-bound protein activity. According to this hypothesis, AEA and 2-AG, are indirect modulators of membrane and enzyme activity. THC, a lipid molecule, permeates the lipid bilayer of the membrane and would disorder its “fluidity,” activating membrane-bound PPL and ACE. These enzymes control the biosynthesis of signaling molecules, derived from membrane phospholipids, like arachidonic acid and its cascade of eicosanoids which include, besides prostaglandins, AEA. It is suggested that AEA, the natural intracellular lipid ligand of the G protein-linked 7TM domain receptor, is a molecular switch which controls membrane signal transduction. THC would alter in an allosteric fashion the responses of neurotransmitter and neuromodulator receptor sites related to the 7TM receptor (opiate, NMDA, 5-HT, nicotinic). THC is the only natural cannabinoid which binds to same 7TM receptor site as AEA and for which it
has a greater affinity. It is proposed that THC might act as a surrogate ligand of AEA and alter the physiological function of the 7TM receptor. This change in shape of the 7TM receptor would be imparted by “molecular transmission” of THC to the receptor proteins. This change in configuration results in an adiabatic amplification of the molecular signal transmitted by the lipid molecule to the receptor protein and its allosteric sites. The proposed mechanism of membrane signaling would fall within the category of molecular transmission of intracellular communication.

8. Membrane signaling and molecular transmission (Fig. 1)

The terms wiring transmission (WT) and volume transmission (VT) were introduced to provide for a “systematic categorization of intracellular communication in the brain” (Zoli et al., 1999) (Fig. 1). WT (voltage) is a quantifiable measurement, while VT is not. This VT has been referred to as hormonal messengers in “brain extracellular space and cerebrospinal fluid.” In the membrane bilayer intracellular signaling, VT might also occur and be more clearly defined as molecular transmission. A signal transmission carried by a lipid molecule occurring in the fluid milieu of the lipid bilayer will induce a volume change. This change in the lipid bilayer volume is imparted through a molecular transmission of the lipid signaling molecule to the 7TM receptor protein, and, in turn, will affect the configuration of the receptor. A change in receptor configuration will result in an adiabatic amplification of the original signal; the pressure-volume relationships of the protein would be modulated by the recycling of the natural physiological lipid ligand AEA. Signaling through the lipid bilayer falls within the science of fluidics, which uses the technology of fluid pressure-volume relationships of fluid dynamics to study signal amplification and transduction mechanisms. THC deregulates this putative membrane signaling in three ways: (1) by altering the physicochemical organization of the boundary lipid bilayer which THC permeates, as a surrogate lipid signaling molecule; (2) by inducing or promoting AEA synthesis through release of arachidonic acid; (3) by persistent binding to the CB receptors. The persistent deregulation by THC of this ubiquitous membrane signaling system is associated in a time- and dose-related fashion with measurable function alterations of the brain and cerebellum, impairing visual, auditory, somatosensory perceptions, coordination, memory, and consciousness (Munro et al., 1993; Pertwee, 1995; Moreau, 1845; Emrich et al., 1997). While binding to central and peripheral cannabinoid receptors and displacing their natural ligands, THC alters central and peripheral cardiovascular regulations inducing tachycardia (Trouve and Nahas, 1999) and vasodilatation (Stanford and Mitchell, 1999; Fulton and Quilley, 1998; Wagner et al., 1999; Niederhofer and Szabo, 1999).

9. Biosynthesis of membrane lipid mediators

The fundamental nature of the AEA and 2-AG lipid mediators in controlling membrane signaling function is supported, in the case of AEA, by at least two biosynthetic mechanisms: direct enzyme-mediated esterification of phosphatidylethanolamine by free arachidonic acid and a trans-esterification reaction from phosphatidylcholine. The first of these processes probably works to compensate, or fine-tune, the effects of the products of arachidonic acid oxidation (prostaglandins and the eicosanoid cascade), whereas the second, transferase-eicosanoid formation, could be a mechanism by which the cell produces AEA independently of eicosanoid production.

AEA and 2-AG receptors systems have been discovered in primitive organisms such as the leech (Stefano et al., 1997), Mytilus (Sepe et al., 1998), Hydra (De Petrocellis et al., 1999), and sea urchin (Bisogno et al., 1997a,b) attesting to the fundamental and ubiquitous nature of this signaling mechanism. Even in organisms with a primitive nervous system, it appears this system plays a fundamental role in controlling behavior (De Petrocellis et al., 1999) and may even predate the nervous system in unifying aggregations of single cells into a single functioning organism. Consequently, the AEA and 2-AG signaling pathways should be thought of as an important physiological control systems in contrast to the current emphasis on an “endogenous” cannabinoid system. We suggest that “cannabinoid” receptors should be renamed to reflect their in vivo function, rather than to their binding to exogenous cannabinoid ligands. Moreover, the CB-1 receptors have been shown to exhibit a significant degree of sequence homology with that of another phospholipid-derived bioactive mediator, lysophosphatidic acid (Piomelli et al., 1998). This similarity suggests that all of these lipid-mediator receptors should be classified together rather than in separate groups, one of which the “cannabinoid receptor” is classified as the result of interaction with an exogenous agonist which does not reflect its fundamental role.

10. Physiological implications for medicine and therapeutics

Most therapeutic properties of cannabinoids have been attributed to natural psychoactive Δ9-THC and to its 11-hydroxy metabolite, which binds stereospecifically to the G protein-coupled 7TM receptors. A similar mode of action has been attributed to the synthetic analogues of Δ9-THC, like nabilone and levonantradol, and it is difficult or impossible to dissociate their therapeutic from their psychoactive effects because both these properties are mediated by the same molecular mechanism, an alteration of 7TM molecular configuration. In addition, as discussed above, the highly lipophilic THC, together with its nonpsychoactive metabolites and its synthetic derivatives, interacts with
the membrane lipid bilayer. The drugs also accumulate in
the fatty tissues, maintaining blood levels during chronic
administration, but making it difficult to titrate the precise
therapeutic level in patients, especially in those with
impaired drug metabolism. The persistence of this drug in
lipid membranes induces a persistent state of neuronal
membrane dysfunction, and continued use impairs the
mental ability of the chronic user. The capability of THC
to disrupt fundamental membrane signaling pathways must
be considered when evaluating the full spectrum of mar-
ihuana’s therapeutic potential.

In its smoked form, marihuana contains some 60
cannabinoids (Turner et al., 1980) with variable agonist
and antagonist properties. Smoke is toxic to the lung,
impairs macrophage function, and smoked marihuana or
cannabis is not a medically acceptable medium for THC
delivery. Oral administration results in erratic uptake (Ohls-
son et al., 1980) and hepatic first-pass metabolism.

10.1. Analgesic effects (Fig. 2)

Over thousands of its consumption, pain
relief and sedation were not the primary therapeutic prop-
erties attributed to marihuana (Fig. 2). Cannabis prepara-
tions were recommended as general-purpose medications to
relieve a wide variety of ailments including asthma, urinary
tract infection, inflammation, and headache. Opium has for
several millennia been the medication of choice for the relief
of pain and was prescribed preferentially over all other
substances This unique role was confirmed by Sydenham in
the 17th century, when opium preparations (laudamum)
became available in Europe. During the 19th century, after
cannabis was introduced into the British and US medicinal
formularies, opium remained the drug of choice for the
relief of pain.

Since the discovery of Δ⁹-THC, it has been claimed that
this cannabinoid and its synthetic derivatives possess
marked pain-relieving properties, however, the role of
marihuana and cannabinoids as analgesics has never been
clearly defined in modern clinical medicine. Although THC
and its synthetic derivatives have been shown to be
effective in some antinociceptive tests in laboratory ani-
mal, results in man have been inconclusive or sometimes
negative (Martin and Lichtman, 1998; Waser and Martin,
1999). A controlled clinical trial of smoked marihuana to
evaluate the analgesic effect of the drug separately from its
intoxicating effects concluded that marihuana enhanced
pain perception (Clark et al., 1981). The authors point out
that changes in reported pain probably reflect subjective
sensation or reduced anxiety. In experimental studies,
results are also inconsistent (Waser and Martin, 1999).
THC exerts antalgic effects by interacting with the two
major biochemical pathways that control pain: the opiate
pathway of acute pain and the prostaglandin pathway of
inflammatory pain. The opioid and prostaglandin pathways
interact, yet are separately targeted by the two major
categories of pain mediation, opiates and NSAIDs, which
have well-defined molecular mechanisms of action. A new
family of NSAIDs and antalgic molecules targeted to
inhibit cyclooxygenase-2 (COX-2) is widely available for
this purpose in current therapeutics.

10.2. “Opiate pathway” (acute pain)

The effect of THC and of other psychoactive canna-
binoids in relieving pain has been documented in some

Fig. 2. Receptor and nonreceptor-mediated analgesic effects of THC. Acute traumatic pain is not relieved by THC. Inflammatory or chemical pain has been
relieved in experimental animals treated with 11-THC-oic acid, a cannabinoid which inhibits COX-2. From Nahas et al. (1999b) [Marihuana and Medicine,
p. 576, with permission].

experimental studies on animals but not in controlled observations of marihuana smokers. The acute analgesic effect of THC and other psychoactive cannabinoids has been attributed to their interaction with the opioid–endorphin system by a mechanism yet to be determined. The euphoriant property of THC, which cannot be measured with objective markers, may contribute to analgesia, and makes it difficult to assess the pain-relieving properties of this drug. The combination of opiates or barbiturates and THC is also undesirable because their combination significantly increases the undesirable side effects of both medications (Johnstone et al., 1975). Either marihuana smoking or THC administration is not suitable for the relief of acute pain; opiates remain the drugs of choice. Attempts to dissociate acute analgesic properties of THC from its unwanted psychoactive effects are problematic since these two properties appear to be related to the interaction of THC with the same 7TM receptor.

10.3. Inflammatory pain

Some nonpsychoactive cannabinoids, especially metabolites of THC such as THC-11-oic acid and certain synthetic derivatives, inhibit COX-2 and, consequently, prostaglandin production. They are effective in relieving inflammatory pain in rodents (Zurier et al., 1998) by the same mechanism of older and newly developed anti-inflammatory agents (NSAIDs). This effect is independent of the CB receptors, and is not associated with psychoactive effects. Cannabinoids increase arachidonic acid release, and exert a dual releasing and inhibiting effect on prostaglandin metabolism. A clinical comparison of nonpsychoactive cannabinoids, such as THC-11-oic acid, with currently used COX-2 inhibitors in the treatment of inflammatory pain, has not been performed. Cannabinoids might be considered “weak” analgesics (anodynes) that fail to control directly the major pathways of nociceptive pain.

10.4. Anesthetic action

THC possesses mild anesthetic properties as shown by its ability to increase barbiturate sleeping time in rodents and enhance sedation. THC also enhances the respiratory depression of opiates (Johnstone et al., 1975) and alters cardiovascular function while increasing their side effects. Infiltration of tissues with local anesthetics and $\alpha_2$ agonists offers another therapeutic intervention to relieve acute pain by a direct action on C fibers. THC does not possess a local anesthetic effect.

10.5. Antiemetic effects

The antiemetic effect of marihuana was first reported in patients who smoked marihuana and were receiving cancer chemotherapy. This effect was subsequently duplicated in patients who were prescribed THC or other psychoactive cannabinoids. The antiemetic property of marihuana was attributed to an effect of THC on its receptor since nonpsychoactive cannabinoids were not effective in relieving nausea. There are two main categories of antiemetic drugs with known mechanisms of action on the chemoreceptor trigger zone of the area postrema: the phenothiazines, (prochlorperazine) and substituted benzamides, (metoclopramide), which are D$_2$ (dopamine) receptor antagonists and drugs such as ondansetron which are 5-HT$_3$ receptors antagonists (Brunton, 1996). THC affects indirectly and partially these specific 5-HT$_3$ and D$_2$ receptors and may be considered a limited antiemetic for mild to moderate chemotherapy; its administrations are associated with dose-related adverse psychoactive effects (Brunton, 1996).

10.6. Antiglaucoma effects

Psychoactive cannabinoids, either smoked or ingested, decrease intraocular pressure in patients with glaucoma. To be maintained, this effect requires repetitive daily exposure to marihuana smoking. THC may not be topicaly applied like other antiglaucoma medications because of its ocular irritating property. The mechanism of action of cannabinoids on glaucoma appears to be mediated by their interaction with prostaglandins. Psychoactive and nonpsychoactive cannabinoids stimulate arachidonic acid production and the eicosanoid cascade, including prostaglandin synthesis. At the same time, the nonpsychoactive metabolite of THC, THC-11-oic acid, inhibits COX and biosynthesis of prostaglandins (Burstein et al., 1986). THC may be considered an indirect anti-glucoma medication by the action of its metabolite on aqueous outflow pathways. The role of prostaglandins in glaucoma treatment has led to the development of the prostaglandin analogue PGE$_2$-tromethamine that has proved to be highly effective in local application for the management of open-angle glaucoma with minimal side effects (Camras et al., 1996). Topical beta blockers (timolol) and carbonic anhydrase inhibitors like brinzolamide are also available for the effective management of glaucoma (Silver, 1998). The use of cannabinoids, with their dual stimulation and inhibition of prostaglandin production and their acute and chronic side effects, is not recommended in modern ophthalmology.

10.7. Appetite stimulation

Open studies in cancer patients and healthy volunteers treated with marihuana smoking or with oral THC for appetite stimulation have reported conflicting results. Anecdotal information and case reports suggest that smoking marihuana is beneficial for treatment of AIDS patients with wasting syndrome. Studies comparing oral THC to megestrol acetate are inconclusive (Bennett and Bennett, 1999). In this case, the most likely molecular mechanism of action of THC is related to the receptor-mediated euphoriant effect of
the drug. The property of THC to produce apoptosis of lymphocytes is an added contradiction to its use in patients with AIDS (Nahas, 2001).

11. Neurological disorders

These disorders involve many alterations of signal transmission in the brain and spinal cord that are displayed by symptomatic disturbances of sensory and motor function. Present symptomatic medications attempt to target the major molecular causes of these ailments. Psychoactive cannabinoids are no substitute for these medications such as COX-2 inhibitors. Properties of destabilization of membrane- and receptor-regulating mechanisms by THC may add to the poor prognosis of the ailments they are supposed to alleviate. For instance, THC and marijuana smoking have been used as potential therapy for multiple sclerosis patients with symptoms of spasticity, ataxia, tremor, pain, and bladder dysfunction. Clinical studies are inconclusive and not supportive of benefits: ataxia and tremors appear to worsen and spasticity is not favorably affected (Francis, 1999). A similar lack of consistent therapeutic effects is also observed in studies of marijuana use for management of epilepsy and spasticity following spinal injury.

12. Interactions of THC with other drugs

The molecular mechanisms of THC on the lipid bilayer and its integral receptors are also targeted by other therapeutic and nontherapeutic drugs. The resulting interactions (Nahas, 1984; Sutin and Nahas, 1999) have been reported experimentally and clinically. THC increases the effects of psychodepressants (alcohol, barbiturates, benzodiazepine anesthetics and opiates) and decreases the effects of stimulants such as amphetamines and cocaine. These clinical effects are not dose-related and are more often biphasic, first enhancing stimulation and subsequently depression or vice versa. The variability in individual responses of these interactions is also related to the genetic polymorphism of cytochrome P-450 present in the brain, mainly the CYP2D6 family of alleles (Britto and Wedlund, 1992). The metabolism of THC (Watanabe et al., 1988) by brain microsomal oxidation is a major source of pharmacokinetic variation and of variability of drug effect. The genetic polymorphism of P-450 oxidative enzymes contributes to the variability of drug effects on different subjects. The pharmacokinetics of THC and its storage in fat and subsequent slow release account for its prolonged and cumulative effects on brain function.

Marijuana or THC do not qualify as modern effective medications comparable to those presently available or in the advanced process of development. The reintroduction of THC into modern pharmacopoeia, from which cannabis preparations were eliminated in the first part of this century and replaced by more effective and dependable medications, is unwarranted today.

The experimental use of THC and of its synthetic analogues in molecular pharmacology has provided invaluable information leading to a better understanding of membrane signaling. As a result, the relationship between allosteric receptor responsiveness, molecular configuration of proteins, and regulations of cellular function should be reevaluated (Nahas et al., 1999b). Membrane enzymes and receptors are integrated in the lipid bilayer of the membrane and have lateral mobility. Lipids may be considered the solvent of the protein (Makriyannis, 1995). The proposed hypothesis of molecular transmission (Zoli et al., 1999) of lipid ligands in the membrane bilayer deserves additional investigation. The major difficulty of such studies resides in the measurement of volume changes in the membrane and its receptors of the order of the Angstrom (Skou, 1992). The interaction of lipid ligands like THC or eicosanoids with protein molecules and their structural effects on protein configuration remains a most important area for future research.

13. Conclusions

The therapeutic properties attributed to THC may be related to the simultaneous molecular interactions of this drug in the lipid bilayer and its integral G protein-linked 7TM receptors. Similar mechanisms account for the drug’s adverse effects, which may not be dissociated from its therapeutic properties. Genetic polymorphism of brain P-450 oxidative enzymes contributes to the variability of drug effects on different subjects. The pharmacokinetics of THC and its storage in fat and subsequent slow release account for its prolonged and cumulative effects on brain function.

Marijuana or THC do not qualify as modern effective medications comparable to those presently available or in the advanced process of development. The reintroduction of THC into modern pharmacopoeia, from which cannabis preparations were eliminated in the first part of this century and replaced by more effective and dependable medications, is unwarranted today.

The experimental use of THC and of its synthetic analogues in molecular pharmacology has provided invaluable information leading to a better understanding of membrane signaling. As a result, the relationship between allosteric receptor responsiveness, molecular configuration of proteins, and regulations of cellular function should be reevaluated (Nahas et al., 1999b). Membrane enzymes and receptors are integrated in the lipid bilayer of the membrane and have lateral mobility. Lipids may be considered the solvent of the protein (Makriyannis, 1995). The proposed hypothesis of molecular transmission (Zoli et al., 1999) of lipid ligands in the membrane bilayer deserves additional investigation. The major difficulty of such studies resides in the measurement of volume changes in the membrane and its receptors of the order of the Angstrom (Skou, 1992). The interaction of lipid ligands like THC or eicosanoids with protein molecules and their structural effects on protein configuration remains a most important area for future research.

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