VEGETAL MARIJUANA, ANIMAL MARIJUANA

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SUMMARY

Marijuana is the illicit drug most commonly used worldwide. The mechanisms by which this drug affects the brain have been studied exhaustively during the last 40 years, and better understood in the last decade. For example, the discovery of receptors to which marijuana binds, has been a major achievement in neurosciences and in the study of drug addiction. Moreover, the description of the endogenous ligands, the endocannabinoids, has shed light to the physiology of the brain regulating several behaviors: from pain to pleasure and from sex to thinking.

For all these exciting effects, endocannabinoids are an important target for therapeutic endeavors.

Key words: Oleamide, anandamide, acylethanolamides, mating, feeding, sleeping.

RESUMEN

La mariguana es uno de los productos ilícitos de abuso que más se usa en el mundo. Los mecanismos por los cuales afecta al cerebro se han estudiado exhaustivamente en los últimos 40 años, pero se han entendido mejor en la última década. Por ejemplo, conocer los receptores a los que se une la mariguana ha sido un gran descubrimiento en el área de las neurociencias. Asimismo, la descripción de ligandos endógenos, los endocanabinoides, ha arrojado luz para entender la fisiología cerebral que regula desde el dolor hasta el placer y desde el sexo hasta el pensamiento.

Por todos estos efectos, los endocanabinoides son un tema de estudio con fines terapéuticos.

Palabras clave: Oleamida, anandamida, aciletanolamidas, apareamiento, alimentación, sueño.

INTRODUCTION

Many drugs have the capacity to modify brain physiology. In doing so, these psychoactive agents alter consciousness, alertness, perception and behavioral performance, and its repeated administration can often produce addiction due to their pharmacological effects. In this review we discuss the action of marijuana and its receptors in the brain, and a group of fatty acid ethanolamides that are naturally produced by vertebrate and invertebrate Nervous Systems which bind to marijuana (cannabinoid) receptors. These molecules are the animal-produced marijuana: the endogenous cannabinoids, all of which have an impact on conscious behavior and sleep.

For centuries cannabinoids have been used for religious or mystical purposes, placing them in the type of drugs best described as "drugs of the spirit" (48). For example, the earliest reference to marijuana comes from the Chinese emperor Sheng Nung in the year 2 737 b.C., in which marijuana was termed "the liberator of sin" (48). Possibly influenced by this association, the first discovered endogenous molecule that binds to cannabinoid receptors in the brain of mammals has been called anandamide (10), a name coined from the Sanskrit word *Ananda,* which means bliss.

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Marihuana, mariguana, grass, weed, pot, refeer, hashish, charas, bhang, ganja, and dagga, all are names referring

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to the derivatives of the plant *Cannabis sativa,* a hemp plant consisting of two varieties: *indica* and *americana.* The entire plant harbors cannabinoids, the active pharmacological agent, but the highest concentration is found in its flowering tops. Although the hemp plant synthesizes at least 400 chemicals, only 60 are cannabinoid-like in structure. The representative active molecule is Δ9-tetrahydrocannabinol (Δ9-THC) (2) (fig. 1).

Effects in humans

Marijuana is by far the illicit drug most commonly used worldwide. In the U.S. about 55% of young adults admit having some experience with this drug (48). Δ9-THC induces several psychoactive effects after an oral dose of 20 mg/kg, or after smoking a cigarette containing 2% of Δ9-THC (2). Among other effects, a sensation of relaxation, promptness to hilarity, and to sexual activity are produced. Flavor perception is also increased, hence the user refers finding food more palatable. Some users experience hallucinations, such as listening to colors or seeing music. They also have a change in self-perception, remarking a particular sensation of "being part of the universe". All these effects may be taken as reinforcing effects, which facilitate marijuana-dependence. Accompanying the "pleasurable" effects, another gamma of "not so pleasurable effects" may appear, such as an impairment of short-term memory, motor coordination, cognitive ability, and attention. Also, a decrease in skin and core temperature, and an increase in subjective sleepiness, and slow-wave sleep (47). At higher doses Δ9-THC can elicit hallucinations associated with delusional and paranoid feelings. Thinking can be confusing and disorganized with profound loss of sense of time (48). Although acute administration of Δ9-THC can enhance sexual drive, the levels of testosterone are lowered, spermatogenesis is inhibited, and actually, impotence may be induced (21). Hormonal changes have also been described in women following both acute and chronic use of Δ9-THC. For example, suppression of luteinizing hormone during the luteal phase of the menstrual cycle (21). Δ9-THC may also have teratogenic actions (21).

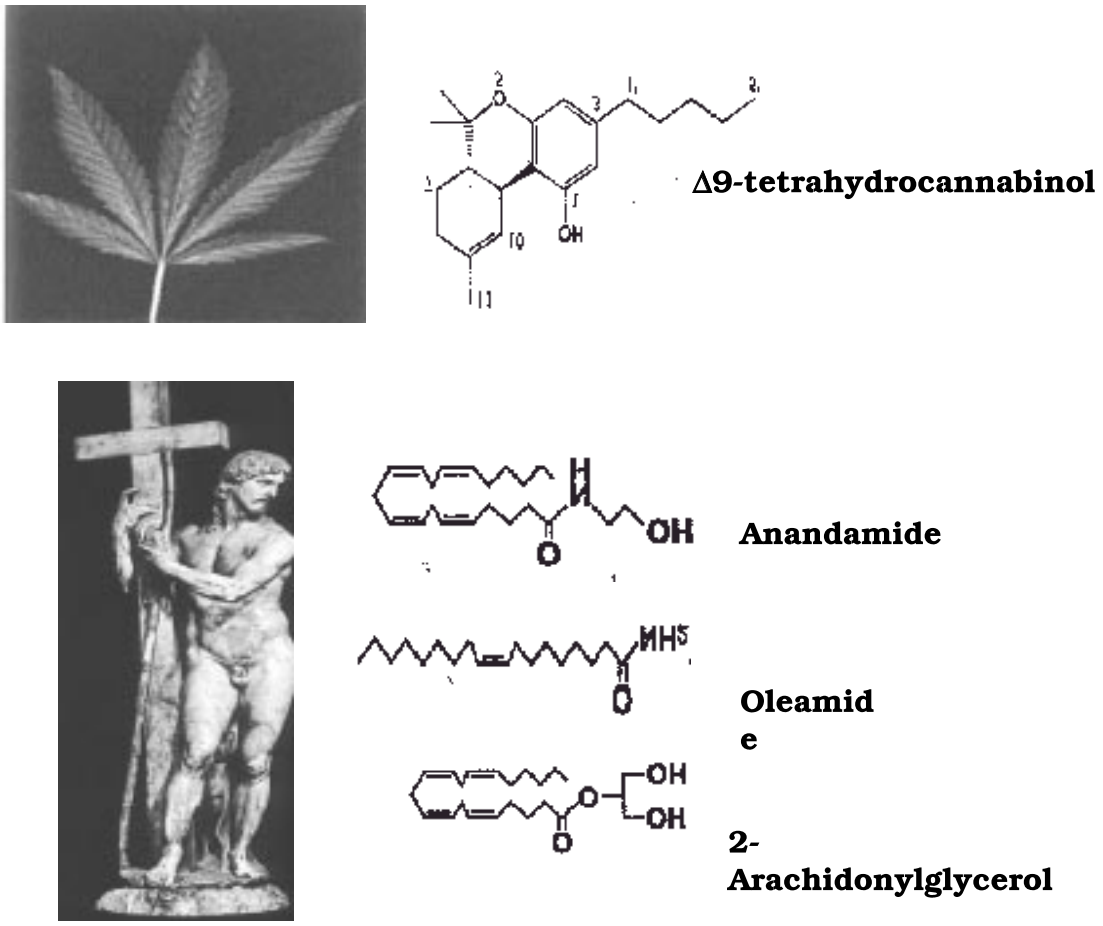

Figure 1. Illustration of both types of marijuana known: the vegetal marijuana in use since several centuries before our era, and the new discovered animal marijuanas.

Despite all these adverse effects, marijuana possesses potential therapeutic effects. The drug was used in ancient China as a pain reliever, to control gout, malaria and other diseases (48). However, several effects are still of contemporary interest. For example, attenuation of the nausea and vomiting caused by cancer therapy, decrease of bronchial constriction associated with asthma, decrease of intraocular pressure in glaucoma, antipyretic actions, treatment of convulsant disorders, appetite stimulation and decrease of the intestinal motility increased by diarrhea (21).

Effects in animals

Δ9-THC produces several effects in rats including short-term and spatial memory impairment and aversion in both place and taste preference tasks (33,35,42). These effects can be elicited by either systemic or intrahippocampal administration of this drug (35,37). Complementary, the synthetic CB1 antagonist, SR141716A improves memory (51). Other effects include hypermotility and hyperreactivity to several stimuli at low doses; while hypomotility, hypothermia, rigid immobility and antinociception are observed at higher doses. Regarding the last effect, it has been observed that the CB1 receptor is upregulated in rats with chronic neuropathic pain (49). On the other hand, in spite of the reported aphrodisiac effects induced by marijuana in humans, Δ9-THC and synthetic cannabinoids, such as HU 210, inhibit copulatory behavior in rats (14,40). It has also been documented that marijuana increases food ingestion in humans and rats. In this context, SR141716A, reduces food ingestion in food-deprived rats (17), further supporting that marijuana stimulation of feeding is mediated by the CB1 receptor.

Marijuana receptors

Interestingly enough, most of the symptoms caused by marijuana are mediated by at least two subtypes of cannabinoid receptors, CB1 and CB2 (2,16,26). Receptor CB1 has a preferential distribution in the brain, with the highest concentration in the hippocampus (24,25), although its mRNA has also been found in testis (19). The gene encoding this receptor (CNR1) has been located in the human chromosome 6q14-q15 (28).

In contrast, the CB2 receptor, encoded by the CNR2 gene, located in the human chromosome 1, has a more peripheral distribution with no apparent expression of either protein or mRNA in the brain (38). The action of cannabinoid molecules in the brain via CB1 receptor is apparently mediated by Gi/Go-proteins which inhibit adenylyl cyclase and voltage-gated L, N, and P/Q Ca^{2+} channels (2,7,15,16,27), while activating K^+

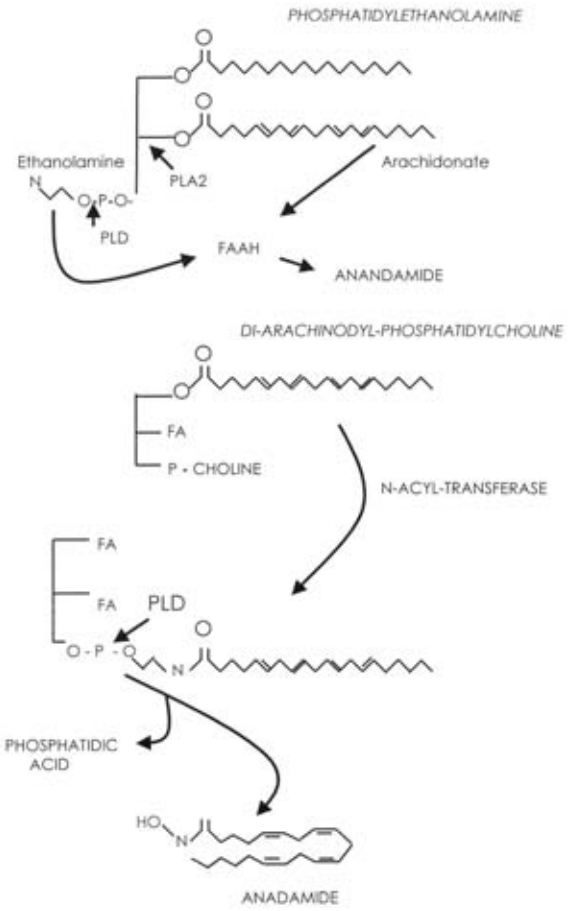

Figure 2. Illustration of the cannabinoid receptor (VB1) most basic mechanism of intracellular signaling transduction.

channels and the extracellular-signal-regulated kinase (ERK) cascade, the focal adhesion kinase (FAK) and immediate early genes, as well as the nitric oxide synthase (NOS) (27). Regarding the CB2 receptor, less is known. However, it has been documented that the activation of CB2 receptors also inhibits the generation of cAMP and activates the MAPK signaling pathway (2,16) (fig. 2).

Cannabinoids

As mentioned before, the hemp plant synthesizes about 60 cannabinoids, most of them have no psychomimetic actions. However, those that are active mimic to a degree the action of Δ9-THC (41). The great extent of cannabinoid pharmacology is mediated by CB1 and CB2 receptors (2,15,27). However, some of these effects may not be receptor specific, but actually a result of cannabinoid binding in a non-saturable fashion to the membrane. Also, some of the cannabinoid effects may be mediated by interactions with other neurotransmitters and their receptors. For example, the

description of a putative endogenous cannabinoid, anandamide (10), suggests that some arachidonic acid derivatives may be the endogenous ligands of the cannabinoid receptor. One group of these derivatives is the prostaglandin family (PGs). Several *in vitro* studies have suggested that Δ9-THC hampers the synthesis of PGs in the rodent brain, e.g., PGE and PGF_4. In this context, there is an extensive literature supporting the fact that PGE_2 modulates wakefulness, while PGD_2 facilitates SWS (23). Therefore, the cannabinoid sedation-inducing effect may be a result of a blockade of PGE_2 synthesis. It is also possible that cannabinoids bind to PGE_2 receptor, due to the great homology between the two molecules. However, since it has been described that prostaglandine levels increase after the performance of a learning task, in particular, PGE_2, the deleterious effect on memory caused by cannabinoids may also be partially explained by a blockade of these receptors (50).

Cannabinoids also interact directly with monoamine systems. For example, Δ9-THC binds to serotonin (5-HT) receptors (13), resulting in inhibition of serotonin activity (1,2,47). Moreover, Δ9-THC can block neurotransmission mediated by glutamate (45). Both actions may count for the deleterious effects exerted on the mnemonic processes. Other additional effects are an enhancement of norepinephrine synthesis (2) and the inhibition of DNA, RNA and protein synthesis. Moreover, Δ9-THC increases dopamine release in the *nucleus accumbens*, very likely through an indirect yet efficient mechanism (36), to induce a rewarding effect.

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The molecules we are calling animal marijuana are more properly name endocannabinoids (fig. 1). There are at least two, produced by the brain, and some others that have cannabinoid-like activity, but which do not bind to the cannabinoid receptor. One of them, oleamide, binds to this receptor only at high concentrations. All these molecules are lipid in nature and differ from the classical and peptide neurotransmitters in several ways including how they participate in neurotransmission. For example, classical neurotransmitters are synthesized by neurons and stored in vesicles, and then they are released when the neuron is excited. In the case of these lipids, they seem to be synthesized from membrane lipid precursors, as a response to the activation of membrane receptors, and then released by neurons immediately after their synthesis. With all, the most fascinating part of these molecules is the potential behaviors they are regulating in the normal subject. If we have to admit that vegetal marijuana is

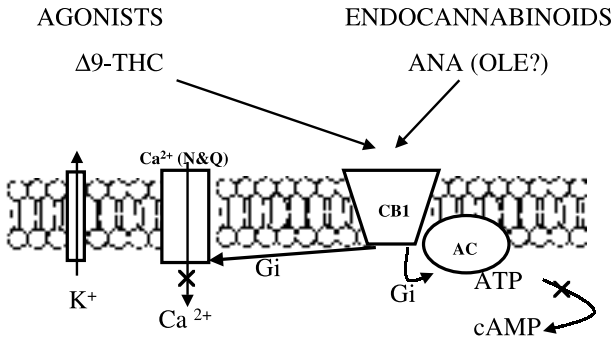

Figure 3. Potential biosynthetic pathways for anandamide. Neurons may be using both pathways.

activating this pathway, therefore, disclosing the neurophysiological mechanisms and behaviors endocannabinoids regulate, what they seem to regulate is from pain to feeding, and from mating to thinking. Let us discuss in the next section the specific effects endocannabinoids produce.

Arachidonylethanolamide (anandamide)

This lipid is the bio-synthetic product of arachidonic acid and ethanolamine, a process catalyzed by phospholipase D (45) (fig. 3). The original studies indicated that anandamide exists in the porcine brain and binds to cannabinoid receptors (10,18). Further work has shown that anandamide can also be isolated from human and rat brains as well as peripheral tissues (16). It is noteworthy that anandamide binds to cannabinoid receptors at all stages of development. Degradation of anandamide depends on the activity of an enzyme known as fatty acid amide hydrolyze (FAAH) (9). Interestingly, the highest enzymatic activity of FAAH is observed in the cerebral cortex and the hippocampus. This activity correlates with the CB1 receptor distribution.

Anandamide cellular effects are similar to those induced by Δ9-THC, such as inhibition of the adenylyl cyclase activity and inhibition of N and L type Ca^{2+} channels (2,27). In addition, anandamide activates the ERK signaling pathway (52) and increases arachidonic acid release and PGE_2 synthesis (47). Anandamide also stimulates vanilloid receptors, VR (44), transient changes in intracellular Ca^{2+} and disruption of gap junctions (27).

Anandamide effects on behavior are similar to those induced by Δ9-THC, although with shorter duration (2). For example, anandamide produces analgesia (45,53). This effect seems to be mainly regulated by CB2 receptors, at least at the early stages of nociception. Analgesia seems to be induced by systemic but not by intracerebroventricular administration (39), further supporting that this effect may be mediated by CB2.

In addition, anandamide may substitute for Δ9-THC and CP 55,940 (a cannabimimetic drug) in a discriminative stimulus task (43,54). Anandamide also induces hypothermia, hypomotility and catalepsy (18,50). Likewise, overeating in rats treated with rather low doses (0.5 to 10 mg/kg) (55). In our laboratory, we have observed that anandamide increases rapid eye movement (REM) sleep in rats, whether it is injected into the lateral ventricle (39) or injected into the pons (unpublished observations).

Due to all these effects and to the capacity to bind the cannabinoid receptor, anandamide is definitively considered as the first endogenous marijuana described.

2-Arachidonylglycerol (2-AG)

This endocannabinoid binds to CB1 and CB2 receptors. 2-AG binds the CB1 receptor with an affinity close to that of anandamide (400 nM). It seems to be synthesized by phospholipase C (PLC), which by acting on phosphatidylinositol (4,5)-biphosphate, generates diacylglycerol (DAG), which is then converted to 2-AG by the DAG lipase. 2-AG can be synthesized from other sources, for example, from lysophospholipids or triacylglycerols. This molecule has not been thoroughly investigated, hence its effects on behavior and neurophysiological processes remain unclear. At the cellular level, it is now fairly clear that 2-AG increases Ca^{++} conductance (2,27).

Cis-9-10-Octadecenoamide (oleamide)

This lipid was detected in cerebrospinal fluid obtained from sleep deprived cats (5,34). The original report indicated that this fatty-amide was able to induce sleep in rats when administered systemically (5,46). Its synthetic pathway or the regional and cellular distribution in the brain is still under study. However, it is known that FAAH, the enzyme that degrades anandamide, also degrades oleamide (6). This observation suggests that oleamide may be part of an extended cannabinoid family. In fact, oleamide exhibits some effects similar to those caused by cannabinoids and anandamide. In our laboratory, we have observed that oleamide increases slow-wave sleep, impairs memory evocation, produces hypomotility, analgesia, and a decrease in body temperature. We have also observed that oleamide decreases c-FOS positive neuron expression in the hippocampus.

Other groups have documented an immuno-suppressing effect, indicating that oleamide, like cannabinoids, possesses the capacity to affect the immune system (31). Despite all these effects, oleamide binds poorly to the cannabinoid receptors and only at high concentrations (4). In contrast, oleamide binds to 5-HT receptors (4), but unlike cannabinoids and anandamide, enhances serotonin activity (29). Oleamide seems to have no interaction with glutamatergic transmission (29). We do not postulate oleamide as another endogenous marijuana, however, we do believe it shares several cannabinoid properties.

Acylethanolamides

Some other saturated and monounsaturated acylethanolamides (AEs), such as palmitylethanolamide (PEA) and oleylethanolamide (OEA) possess cannabinoid activity. These molecules have been poorly studied. However, a few studies have indicated that they may be involved in pain perception regulation (11). Surely, they are involved in the regulation of many other neurophysiological processes, and very likely, they also modulate the expression of several behaviors. This is definitely a promising area full of surprises for the study of behavior and consciousness.

In brief, endocannabinoids and their receptors, which were described about a decade ago, are well characterized in the brain of several mammals, including man. As we know, cannabinoids not only activate specific receptors to elicit pharmacological effects, but they also interact with several other neurotransmitter systems. One of the most important interactions appears to be involving serotonin as much as dopamine and their extended circuits (2,3,20). This observation may be crucial in explaining the hallucinogenic and rewarding effects of cannabinoids. One example is that the serotoninergic system may be involved in the generation of hallucinations (47), while the dopaminergic system participate in the rewarding effect caused by these drugs (8,30). These two systems interact with each other as well as other systems, i.e., the cholinergic system, making a highly complex resulting addictive behavior.

DISCUSSION

The continuous use of psychedelic drugs since ancient times suggests that there is a human desire to self-impose drug-induced altered states, and this desire prompts some individuals to seek methods for obtaining them. At present, it is clear that these altered states of consciousness depend on specific brain molecules, receptors and interconnected brain circuits. For example, one of the hedonic systems described, includes the ventral tegmental area (VTA), where dopaminergic fibers project to the *nucleus accumbens* (NAcc) (30). Serotoninergic as much as GABAergic neurons regulate the dopamine release in the NAcc. Most of the drugs of abuse, from nicotine to cocaine and, of course, marijuana, increase the release of

dopamine in the NAcc (30). In addition, most of the pleasurable behaviors, such as feeding, drinking, mating, also increase dopamine release. Interestingly, during rapid-eye movement (REM) sleep there is an increase in the activity of the NAcc cells, although nobody has shown an increase in dopamine release in this area of the brain.

On the other hand, some diseases that affect thinking processes may result from the malfunctioning of these systems. Recently, an increase in anandamide concentration in the cerebrospinal fluid of schizophrenics has been reported. Moreover, chromosome 6 has been involved in the generation of schizophrenia (12). For example, proteins have been implicated in schizophrenia, some of them, such as the diazepam binding inhibitor, have their genes mapping in the chromosome 6q12-q21. This mapping overlaps with the CB1 receptor gene mapping (6q14-q15) (28). Of course, this is not a definitive evidence postulating the CB1 receptor as one of the causing proteins, but this kind of finding encourages us to further explore such a possibility.

In conclusion, we believe this exciting research will lead us, in the near future, to have an explanation, partial and limited at the beginning, of thinking and cognitive processes as well as the processes subserving marijuana addiction.

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