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Palmitoylethanolamide: From endogenous cannabimimetic substance to innovative medicine for the treatment of cannabis dependence

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ABSTRACT

Palmitoylethanolamide (PEA) is a fatty acid amide showing some pharmacodynamic similarities with Δ^9-tetrahydrocannabinol, the principal psychoactive compound present in the cannabis plant. Like Δ^9-tetrahydrocannabinol, PEA can produce a direct or indirect activation of cannabinoid receptors. Furthermore, it acts as an agonist at TRPV1 receptor. The hypothesis is that PEA has anti-craving effects in cannabis dependent patients, is efficacious in the treatment of withdrawal symptoms, produces a reduction of cannabis consumption and is effective in the prevention of cannabis induced neurotoxicity and neuro-psychiatric disorders.

Introduction

Cannabis sativa L. is an annual dioecious plant belonging to the Cannabaceae family [1]. This plant, native to Central Asia, is legally or illegally cultivated worldwide as a source of hemp fibres and for medical or recreational purposes [2]. *C. sativa* L. contains over 420 different substances and among these, there are more than 60 psychoactive compounds [3]. Cannabis plant is the source of a number of drug products generally named cannabis [4]. In particular, herbal cannabis (or marijuana) consists of dried plant parts while cannabis resin (or hashish) is the resin secreted by the glandular hairs present all over the plant but principally around the flowers [4]. Finally, in addition to these two kinds of preparation used since time immemorial, most recently, through the use of solvents (e.g. acetone) and evaporation, is extracted from the plant the hashish oil [4]. The main active principle contained in all cannabis products is the terpenophenolic derivative Δ^9-tetrahydrocannabinol (THC) (Fig. 1) [5]. This substance is considered the principal responsible for the acute intoxication produced by cannabis in humans as well as for its chronic physiological and psychological effects [6]. THC exerts its effects via interaction with endogenous cannabinoid receptors [7]. In particular, CB1 receptor has been found in the brain, peripheral nerves, reproductive system, some glandular systems and in the microcirculatory system [8–10], while CB2 receptor has been identified in the spleen, macrophages and other immune cells [11–13]. Endogenous ligands interacting with cannabinoid receptors have been identified in a group of arachidonic acid derivatives conjugated with ethanolamine or glycerol collectively termed endocannabinoids [14,15]. The most abundant and potent endocannabinoids actually known are: anandamide (AEA) (Fig. 1), 2-arachidonoylglycerol (2-AG) and virodhamine [16,17]. These substances, structurally different from THC and similar to eicosanoids such as prostaglandins and leukotrienes [18], act as neuromodulators via interaction with intracellular G-proteins controlling cyclic adenosine monophosphate formation and through the regulation of ion channels activity (Ca and K) [19,20]. Their role of neuromodulators is exerted through the interaction with many neurotransmitters including opioids, monoamines and γ-aminobutiryc acid [21]. Despite being frequently considered a less dangerous drug of abuse, chronic use of cannabis has been associated with numerous and severe diseases including bronchitis, emphysema, increased risk of myocardial infarction in the hour after use and in patients with heart disease, cognitive impairment, psychotic disorders (especially in people with a history or family history of psychosis) [22]. Furthermore, cannabis consumption can induce tolerance, abuse, withdrawal symptoms and in about 9% of users, dependence [23]. In fact, cannabis produces an increase in dopamine release in the areas of reward similar to that produced by other drug of abuse such as cocaine, heroin and MDMA [24,25]. Although the rate of cannabis induced dependence is lower than that induced by other drugs, the high prevalence of cannabis consumption worldwide is cause of concern in medical community [26]. Despite pharmacological and non-pharmacological treatments currently available can produce some benefits in cannabis dependent patients, further therapeutic alternatives are needed for improving the outcomes in these patients [27,28]. Since many years, palmitoylethanolamide (PEA) (Fig. 1), oleylethanolamide (OEA) and other structure related lipid messengers belonging to the cannabimimetic group are investigated for their important physiological function on inflammation, pain control, feeding behaviour and lipid metabolism [29]. In particular, PEA is an

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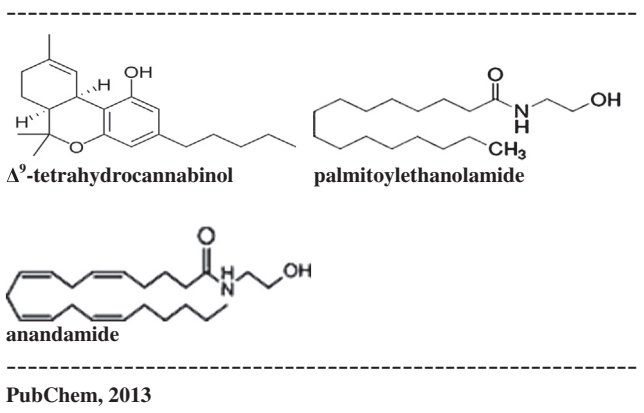

Fig. 1. chemical structure of anandamide, Δ^9-tetrahydrocannabinol, palmitoylethanolamide.

endogenous fatty acid amide known since the 1950s as an anti-inflammatory substance contained in egg yolk [30]. Furthermore, it was sold in the 1970s in Eastern Europe for the prevention of acute viral infections of the respiratory system [31,32]. Most recently, it has been investigated as anti-inflammatory, anti-nociceptive and neuroprotective agent [33]. Despite being considered inactive at CB1 and CB2 receptors, recent evidences have shown that the effects of PEA are mediated by the direct or indirect activation of CB1, CB2, peroxisome proliferator-activated receptor alpha (PPARα), peroxisome proliferator-activated receptor gamma (PPARγ), G protein-coupled receptor 55 (GPR55) and transient receptor potential cation channel subfamily V member 1 (TRPV1 or capsaicin or vanilloid receptor 1) receptors [34,35]. Pharmacodynamic comparison between PEA and THC suggests the hypothesis that PEA could be useful in the treatment of cannabis dependence.

Palmitoylethanolamide information

PEA is a fatty acid amide belonging to the family of *N*-acylethanolamines [36]. This AEA congener is produced on-demand within the lipid bilayer via *N*-acylphosphatidylethanolamine phospholipase D (NAPEPLD) [37], and its signal is quickly terminated through its degradation catalysed by at least two enzymes: the fatty acid amide hydrolase (FAAH) [38] and the ethanolamine-hydrolyzing acid amidase (NAAA) [39]. Numerous evidence have shown that PEA can produce anti-inflammatory activity [40], analgesia in inflammatory and neuropathic pain [41,42], inhibition of food intake [43], reduction of gastrointestinal motility [44], inhibition of cancer cell proliferation [45], anti-pruritic effect [46], anti-epileptic action [47], and neuroprotective activity through the activation of some kinases such as ERK1/2 MAP kinase and Akt proteins involved in the antioxidative mechanisms [48]. Neurobiological mechanisms underlying the effects produced by PEA are not yet fully understood, however, three synergistic mechanisms of action have been proposed. The first mechanism of action hypothesized, named Autacoid Local Inflammation Antagonism (ALIA), consists in a local antagonism on inflammation via a down-regulation of mast-cell degranulation [49]. The second mechanism of action proposed suggests that PEA directly or indirectly actives the cannabinoids receptors [50]. The third mechanism of action hypothesized, termed entourage effect hypothesis, suggests that the anti-inflammatory and antinociceptive effects of PEA are in part due to the enhancement of the endocannabinoid and endovanilloid activity exerted by AEA and other related compound [51].

The hypothesis

Like cannabis, several evidences suggest that, PEA, an endogenous fatty acid, can produce anti-inflammation and anti-nociceptive activity in humans [52–54]. This anandamide congener appears to be able to activate cannabinoids receptors through two principal ways: directly, via CB1 and/or CB2 agonism or indirectly via AEA mediated cannabimimetic activity [55]. The hypothesis is that PEA has anti-craving effects in cannabis dependent patients, is efficacious in the treatment of withdrawal symptoms, produces a reduction of cannabis consumption and is effective in the prevention of cannabis induced neurotoxicity and neuro-psychiatric disorders.

Evaluation of the hypothesis

To date, no study has evaluated the effect of PEA in cannabis dependent patients. However, pharmacological similarities with THC suggest that PEA can produce anti-craving activity, and that it could be useful in the treatment of cannabis withdrawal symptoms. In addition, PEA could cause a reduction of cannabis consumption in cannabis dependent patients. Furthermore, considering its neuroprotective effect, PEA could protect cannabis dependent patients from both neurotoxicity and neuro-psychiatric disorders related with chronic consumption of cannabis. Like THC, PEA could produce a direct or indirect activation of CB1 and CB2 receptors [56]. Furthermore, it acts as an agonist at PPARα, PPARγ, GPR55 and TRPV1 receptors [57].

Activity at CB1 receptors

CB1 receptors are G protein-coupled receptors largely distributed throughout the central and peripheral nervous system [58]. They are highly concentrated around the cortex, cerebellum, hippocampus, olfactory areas and spinal cord while they are poorly present in the brainstem justifying the lack of respiratory depression associated with the consumption of CB1 agonists [59,60]. Increased dopamine release in the areas of reward via the activation of CB1 receptors is considered the neurobiological mechanism underlying the cannabis induced dependence [61]. Although PEA exhibits poor affinity for CB1 receptor in vitro, in vivo studies have shown that the CB1 receptor antagonist SR141716 can partially counteract the anti-hyperalgesic effect of PEA [62]. This discrepancy between data obtained in vitro and those obtained in vivo could be explained by an activity at CB1 receptor mediated by an enhancement of the levels of the endogenous CB1 receptor agonist AEA [63]. AEA is primarily degraded by FAAH through hydrolysis into arachidonic acid ethanolamine and the inhibition of FAAH activity enhances or prolongs responses to AEA in vitro and in vivo [64]. Since PEA is a substrate for the primary degradation enzyme for AEA, FAAH, it could compete with AEA for FAAH leading to a reduction in AEA hydrolysis [64]. In fact, studies in rat brain membranes have shown that 10 μM of PEA can produce an inhibition of AEA hydrolysis by 40–50% [64]. Despite the limited evidences, the competitive inhibition of the catabolism of AEA induced by PEA could be a possible point of interaction between AEA and its congener PEA. This pharmacodynamic interaction could be responsible for increased activity of AEA induced by PEA [64].

Activity at CB2 receptors

CB2 receptors are G protein-coupled receptors located peripherally and closely linked with cells in the immune system, predominantly the spleen and macrophages [65]. Although cannabinoid