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Central & Peripheral Nervous System

The cannabinoid CB_1 receptor and the endocannabinoid anandamide: possible antidepressant targets

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Background: Major depression has the highest rate of prevalence and incidence of morbidity among all mental disoders. The limited efficacies of current antidepressant treatments necessitate the development of alternative pharmacotherapies. Recent preclinical findings suggesting that cannabinoid CB_1 receptor agonists and endocannabinoid enhancers possess antidepressant-like properties, and clinical evidence that the CB_1 antagonist rimonabant increases the risk of depression and suicidality, support the notion that the endocannabinoid system represents a novel target in the treatment of mood disorders. *Objective/methods*: To compare the mechanism of endocannabinoid enhancers and CB_1 agonists with current antidepressants and provide a rationale for a role of the endocannabinoid system in the pathology and treatment of mood disorders. *Results/conclusion*: CB_1 agonists and fatty acid amide hdyrolase (FAAH) inhibitors share mechanisms with other antidepressants: the ability to enhance central serotonergic and noradrenergic transmission and promote neurogenesis in the hippocampus. FAAH inhibitors, compared with direct CB_1 agonists, exhibit distinct pharmacological properties that quell adverse cannabinoid effects and widen the therapeutic window. Since the endocannabinoid system also plays a role in peripheral functions, side effects need to be addressed.

Keywords: anandamide, antidepressant, cannabinoid CB_1 receptor, endocannabinoid, noradrenaline, serotonin

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1. Introduction

Even before cannabis-derived compounds (cannabinoids) could be subjected to extensive experimental scrutiny, the hemp plant (*Cannabis sativa*) had already been considered for medicating depression. It was advocated by the English cleric Robert Burton in his '*The Anatomy of Melancholy*', published in 1862 [1]. In 1845, the French psychiatrist Jacques-Joseph Moreau de Tours, having come back to Paris from a journey to India, attempted the first trials in western society, when he tried testing its psychotropic effects on his depressive patients. His initiative, however, yielded mixed results [2].

In recent years, a revitalization of this interest in the therapeutic potential of cannabinoids was inspired by several reports about their ability to improve mood in healthy individuals and mitigate depressive symptoms in patients being treated for some other illnesses (secondary depression). A still more provocative discovery stemming from preclinical and clinical research efforts was the

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involvement of mammalian cerebral endogenous cannabinoids (endocannabinoids), such as arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG), in emotional processing, mood and anxiety regulation, and in the pathophysiology of depression. These developments reached another turning point with the invention of innovative pharmacological and genetic approaches to amplifying brain endocannabinoid content by interfering with the biological (metabolic) processes responsible for its synaptic transport and degradation. Such approaches launched efforts on the investigation of their possible application for the development of new classes of antidepressant and antianxiety drugs. The aim of the present review is to provide a compendium of scientific research output indicating that endocannabinoid enhancers, such as inhibitors of the anandamide-degrading fatty acid amide hdyrolase (FAAH) and endocannabinoid transporter blockers, may be an alternative line in the development of novel antidepressant pharmacotherapy.

Finally, recent findings suggesting that the central cannabinoid receptor (CB_1) antagonist rimonabant, used for the treatment of obesity, poses a risk for depression and suicide in a subgroup of patients support a clinical and scientific framework suggesting that impairment of cannabinoid signaling influences mood regulation.

2. Major depression

The Diagnostic and Statistical Manual of Mental Disorders IV-TR [3] defines the symptomatology of major depressive disorder as involving a complex mix of cognitive, affective, vegetative, somatic and neuroendocrine manifestations that include depressed mood, diminished interest or pleasure in nearly all day-to-day activities, significant weight loss or weight gain, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue, feelings of worthlessness or guilt, diminished ability to think and concentrate, and suicidal ideation. Anxiety is also a common feature. As such, depression greatly debilitates affected individuals that comprise up to 20% of the general population [4,5]. Approximately half of them undergo a second episode, and more episodes increase the risk of relapse to a high 90% [6]. The condition is extremely disabling and at its worst, can lead to premature fatality, of which it ranks as a leading cause, just second to cardiovascular disease [7]. As the most prevalent psychiatric disorder, it uses up staggering amounts of health-care resources [8]. Also, controversy on the efficacy of antidepressant treatments plagues the scientific and medical community. All clinically used antidepressant drugs have slow onsets of action (2 – 3 weeks) [5,9]. Furthermore, under level 1 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, only about 30% of patients underwent remission after up to 12 weeks of therapy with the selective serotonin re-uptake inhibitor (SSRI) citalopram. In addition, 15.8% of patients developed an intolerable adverse event, 38.6% moderate-to-severe impairments due to an adverse event, 8.6% discontinued treatment due to adverse events, and 4% developed a serious adverse event [10], findings that underscore efficacy and tolerability limitations of treatment with a typical first-line antidepressant agent.

Since there remains a huge gap in our knowledge of the pathophysiology of depression, the discovery of more effective alternative targets is a great but extremely important challenge.

3. The neurobiology of depressive disorder

Major depression, having a complex heterogenous aggregate of symptoms that are apparently overlapping with those of other psychiatric disorders, is probably produced by dysfunctions of multiple, related neural substrates [5]. Although its pathophysiology is not completely understood, it is widely acknowledged that it is linked to several levels of impairments including neurodegenerative elements (hippocampal and prefrontocortical neural degeneration), neuroendocrine (hypothalamic–pituitary–adrenal axis) diturbances, and neurochemical deficits. One of the most established hypotheses concerns an impairment of central monoaminergic neurotransmission; this hypothesis originates from the discovery of the monoamine-enhancing mechanistic principle subserving first-generation antidepressants. A dampening of synaptic 5-hydroxytryptamine (5-HT) and/or norepinephrine (NE) levels disturbs normal synaptic activity, and compromises mood [5,9]. Expectedly, two of the major neurobiological loci of antidepressant action are the midbrain serotonergic dorsal raphe (DR) and noradrenergic nucleus locus coeruleus (LC), which supply 5-HT and NE, respectively, to limbic and cortical regions subserving various aspects of emotion and mood regulation. Drugs blocking monoamine re-uptake or inhibiting the monoamine-catabolyzing monoamine oxidase in presynaptic and terminal fields of these nuclei possess potent antidepressant properties. Indeed, the antidepressant response is reversed by the 5-HT synthesis inhibitor parachlorophenylalanine (PCPA) in animal models, and the dietary depletion of the 5-HT precursor L-tryptophan produces mild dysphoria especially in healthy volunteers who have had a history of depression [9,11]. Similarly, in rodents, administration of PCPA reduces 5-HT neuronal activity, NE synthesis [12], and alpha-1 adrenoceptor activity [13]. Numerous other genetic [14], brain imaging [15], tryptophan depletion [16] and postmortem studies [17] support the pathophysiological correlates of underactive 5-HT function in major depressive patients.

4. Mechanisms of antidepressant action

Different antidepressant classes modulate 5-HT or NE neurotransmission by differentially acting on diverse components including the 5-HT and/or NE transporters, alpha-2 adrenoceptor, 5-HT_{1A} receptors, noradrenaline release mechanisms (bupropion) and oxidative deaminating enzymes (inhibition by monoamine oxidase inhibitors (MAOIs)) [9].

4.1 Serotonergic mechanisms

SSRIs increase synaptic 5-HT availability by preventing its re-uptake. Acutely, this decreases the electrical activity of 5-HT neurons due to the increased activity of 5-HT on inhibitory 5-HT_{1A} autoreceptors located on DR 5-HT neuronal somatodendrites. Long-term treatment however desensitizes these autoreceptors, thereby enhancing 5-HT neuronal activity back to basal levels [9]. This event has been shown to increase 5-HT outflow in postsynaptic forebrain regions relevant to affective and mood regulation. Other classes of antidepressants, for example the alpha-2 blocker mirtazapine, increase 5-HT neuronal firing by blocking inhibitory alpha-2 autoreceptors located on NE terminals synapsing with DR 5-HT neurons [18]. A consequent increase in the net NE outflow leads to increased excitatory activity of alpha-1 heteroreceptors located on 5-HT perikarya [19]. Other lines of evidence implicate extra-5-HT systems including the neurokinin 1 (NK_1) receptor system, excitatory amino acids and sigma ligands and receptors [20]. A summary of the electrophysiological effects of 5-HT-acting antidepressants, compared with those of other classes, is outlined in **Table 1**. Here, it is evident that all classes of antidepressants ultimately enhance 5-HT neurotransmission although through different presynaptic or postsynaptic mechanisms.

4.2 Noradrenergic mechanisms

Tricyclic antidepressants (TCA) and norepineprhine re-uptake inhibitors (NRI) directly interact with the central NE system. These drugs are also able to influence 5-HT function by taking advantage of the strong neuroanatomical cross-talk between the NE and 5-HT systems [21]. Hence, it is likely that their therapeutic effects are conveyed through this indirect action on the 5-HT system. However, since 5-HT-acting antidepressants (e.g., SSRIs) equally influence and modulate the NE system (**Table 2**), it may also be possible that the therapeutic effects of NE-acting antidepressants are mediated by NE-dependent processes distinct from those of 5-HT-acting antidepressants, and that some therapeutically relevant effects of 5-HT-acting antidepressants are explained at least in part by their secondary activity on the NE system. Basically, all classes of antidepressants modulate (increase or decrease) NE neuronal firing activity after acute or chronic treatment (**Table 2**). The precise clinical significance of this modulation is largely unknown. However, considering that NE function is neurobiologically linked to the control of vigilance, arousal and anxiety, one may hypothesize that drugs decreasing NE neuronal activity act favorably on anxiety symptoms. For example, the dual serotonin and noradrenaline re-uptake inhibitor (SNRI) venlafaxine, which decreases NE neuronal firing activity, has been approved for generalized anxiety, social phobia and panic attacks. On the other hand, the increase in NE neuronal activity induced by some drugs and somatic treatment approaches (e.g., vagus nerve stimulation (VNS)) may account for efficacies on depressive disorders with associated psychomotor retardation and impairments in executive function and motor speed [22]. More research in this area is warranted, in particular, in correlating basic and clinical information. It is equally important to identify whether NE-related subsystems differentially interact with corticosteroids (HPA system), cholecystokinin and the GABAergic system, all closely linked to anxiety, and to determine how these interactions are influenced by antidepressant treatments.

5. Antidepressants and the hippocampus

The hippocampus harbors neurochemical and neuromolecular systems highly sensitive to the aetiological and epigenetic elements in depression, most notably stress-related factors [23]. Indeed, adverse functional, morphological and ultrastructural changes in this structure may result from stress and depression. Conversely, antidepressant treatments may reverse these impairments probably through neurobiological mechanisms associated with increased tonic hippocampal 5-HT_{1A} receptor activity, upregulation of neurotrophic factors and enhancement of cell proliferation/neurogenesis.

5.1 Antidepressants increase tonic activity of hippocampal 5-HT1A receptors

The enhancement of 5-HT neurotransmission by antidepressants engenders various postsynaptic and downstream consequences, such as enhanced tonic 5-HT_{1A} receptor activty [24], downregulation of forebrain postsynaptic 5-HT_{1A} [25] and 5-$HT_{2A/C}$ receptors [26], regulation of alpha/beta adrenoceptors, 5-HT_4, 5-HT_6, 5-HT_7 receptors, second messenger systems and transcription and post-transcription processes [27].

The increase in tonic postsynaptic 5-HT_{1A} activity has been consistently and robustly demonstrated in the CA3 region of the dorsal hippocampus. Like presynaptic (DR) 5-HT_{1A} autoreceptors, hippocampal 5-HT_{1A} receptors are G_i protein-coupled metabotropic receptors, whose stimulation opens K^+ channels and hyperpolarizes the neuron [23]. Local agonist-activation of 5-HT_{1A} receptor activity in CA3 pyramidal neurons, for instance, can inhibit neuronal activity. In normosensitive conditions, systemic administration of the 5-HT_{1A} antagonist WAY100635 does not influence the activity of these neurons [24]. Haddjeri *et al.* [24], however, found that chronic antidepressant treatment (TCA impramine, SSRI paroxetine, reversible MAOI befloxatone, α_2-adrenergic receptor antagonist mirtazapine, 5-HT_{1A} agonist gepirone or multiple electroconvulsive shock (ECS)) markedly disinhibited pyramidal firing activity in response to WAY100635, indicating an increase in tonic activity of 5-HT_{1A} receptors. Compellingly, this effect is limited to chronically treated and therefore therapeutically relevant antidepressant regimens, and was not observed with acute antidepressant treatments, single ECS or the non-antidepressants haloperidol and chlorpromazine (**Table 3**) [24,28].

Table 1. Effects of long-term (subchronic or chronic, > 4 days, daily) treatment with antidepressants and cannabinoid drugs on the responsiveness of different 5-hydroxytryptamine (5-HT) and norepinephrine (NE) receptors, neuronal firing activity of raphe 5-HT neurons, and the consequent net effect on 5-HT neurotransmission.

Treatment	Responsiveness of somatodendritic 5-HT_{1A} autoreceptors	Function of terminal 5-HT_{1B} autoreceptors	Function of terminal a_2 adrenergic heteroreceptors	Responsiveness of postsynaptic 5-HT_{1A} receptors	5-HT neuronal firing activity	Net effect on 5-HT transmission	Ref.
MAOI	↓	↔	↓	↔↓	↔*	↑	[154]
TCA	↔	↔	↓	↑	↔*	↑	[154,155]
SSRI	↓	↓	↔	↔	↔*	↑	[154]
NRI	↔	↔	↓	↑	↔	↑	[21]
SNRI	↓	↓	↔	↔	↔*	↑	[156]
Bupropion	n.d.	n.d.	n.d.	n.d.	↔	↑	[157,158]
Mirtazapine	↓	↔	↓	↔	↑	↑	[18]
NK1 antagonist	↓	↔	↓	↔	↑	↑	[159,160,161]
Sigma agonist	n.d.	n.d.	n.d.	n.d.	↑	↑	[20]
ECS	↔	↔	↔	↑	↔	↑	[162]
VNS	↔	n.d.	↔	n.d.	↑	↑	[163]
Direct CB_1 agonist	n.d.	n.d.	n.d.	↓	↑↓	↑↓	[98,131]
CB_1 antagonist/inverse agonist	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	
FAAH inhibitor URB597	↔	n.d.	n.d.	↓	↑	↑	[102,131]

↑: Increase; ↓: Decrease; ↔: No change; n.d.: Not determined; *: Progressive recovery to normal.

All data are based on *in vivo* electrophysiological studies.

Table adapted from [9,19].

CB_1: Cannabinoid receptor type 1; ECS: Electroconvulsive shock; FAAH: Fatty acid amide hdyrolase; MAOI: Monoamine oxidase inhibitor; NK1: Neurokinin 1; NRI: Norepineprhine re-uptake inhibitor; SNRI: Serotonin and noradrenaline re-uptake inhibitor; SSRI: Selective serotonin re-uptake inhibitor; TCA: Tricyclic antidepressant; VNS: Vagus nerve stimulation.

Table 2. Effects of acute, subchronic (> 1 day, < 14 days, daily) and chronic (14 – 28 days, daily) treatments with antidepressants and cannabinoid drugs on spontaneous norepinephrine (NE) neuronal firing activity.

Treatment	Acute	Subchronic	Chronic	Ref.
MAOI	↓	↓	↓	[164]
TCA	↓	↓	↓	[164]
SSRI	↔	↓	↓	[164]
NRI	↓	↓	↓	[21,164]
SNRI	↓	↓	↓	[156]
Bupropion	↓	↓	↑ (only bursts)	[157,158]
Mirtazapine	↑	↑	↑	[18]
Neurokinin 1 antagonist	↑	↑	↑ (only bursts)	[161]
Sigma ligands	n.d.	n.d.	n.d.	–
ECS	↔	↔	↓	[165]
VNS	↑	↑	↑	[163]
Direct CB_1 agonist	↑	n.d.	n.d.	[121]
CB_1 antagonist/inverse agonist	↔↓	n.d.	n.d.	[121,102]
FAAH inhibitor URB597	↑	↑	n.d.	[102]

↑: Increase; ↓: Decrease; ↔: No change; n.d.: Not determined.
All data are based on *in vivo* electrophysiological studies.
Table adapted from [19].
CB_1: Cannabinoid receptor type 1; ECS: Electroconvulsive shock; FAAH: Fatty acid amide hdyrolase; MAOI: Monoamine oxidase inhibitor; NRI: Norepineprhine re-uptake inhibitor; SNRI: Serotonin and noradrenaline re-uptake inhibitor; SSRI: Selective serotonin re-uptake inhibitor; TCA: Tricyclic antidepressant; VNS: Vagus nerve stimulation.

5.2 Antidepressants upregulate brain-derived neurotrophic factor (BDNF)

A growing body of literature increasingly supports the hypothesis that enhanced hippocampal 5-HT trasmission results in increased production of neurotrophic factors, such as brain derived neurotrophic factor (BDNF). Stimulation of hippocampal 5-HT_{1A} receptors activates the cAMP–protein kinase A (PKA)–cAMP response element binding protein (CREB) molecular pathways, eventually resulting in the phosphorylation of CREB. Increased CREB phosphorylation leads to increased BDNF production. The antidepressant-like effects demonstrated in animal models by intra-hippocampal infusions of BDNF [29] is enabled by BDNF's ability to protect the hippocampus from the adverse effects of stress-induced glucocorticoid overproduction and cell death. It is worth mentioning that in the ventral tegmental area (VTA)–nucleus accumbens (NAc) pathway, BDNF seems to promote depression-like behaviors [30].

5.3 Antidepressants increase hippocampal cell proliferation and neurogenesis (Table 3)

Malberg *et al.* [31] were some of the first to suggest that chronic treatment with several different classes of antidepressants but not with non-antidepressants boosts cell proliferation, measured as an increase in bromodeoxyuridine (BrdU)-labeled cells, particularly in the hippocampal dentate gyrus. Newly generated cells mature and differentiate into neurons, as determined by triple labeling for BrdU and neuronal- or glial-specific markers. Such a mechanism has been suggested to overcome stress-induced hippocampal atrophy (volume reduction) and the loss of neurons seen in depressed patients [32].

Santarelli *et al.* [33] demonstrated that an intact 5-HT_{1A} receptor system in wild type mice as opposed to its genetic deletion in 5-HT_{1A} knockout mice is necessary for the proliferative/neurogenic effects associated with antidepressant-like behavioral effects of the SSRI fluoxetine. On the other hand, the neurogenic abilities of the TCA imipramine and desipramine were not circumvented in 5-HT_{1A} receptor knockouts, which could mean that other antidepressant drug classes, TCAs for example, use a molecular pathway independent of the 5-HT_{1A} receptor.

On the other hand, blocking neurogenesis in animal models has not led to the emergence or worsening of depression-like behaviors [34]. Hence, the hypothesis that hippocampal neurogenesis or its blockade is a fundamental facet of the pathophysiology of depression and a final common mechanistic pathway of antidepressants remains a matter of debate [34]. Nevertheless, proponents

Table 3. Effects of subchronic (> 1 day, < 14 days, daily) or chronic (14 – 28 days, daily) treatments with antidepressants and cannabinoid drugs on the tonic activity of hippocampal 5-HT_{1A} receptors and on hippocampal cell proliferation/neurogenesis.

Treatment	Tonic activation of hippocampal 5-HT_{1A} heteroreceptors	Hippocampal cell proliferation and neurogenesis	Ref.
MAOI	↑	↑	[24,31]
TCA	↑	↑	[24]
NRI	↑	↑	[24,31,166]
Mirtazapine	↑	n.d.	[24]
SNRI	↑	↑	[156]
SSRI	↑	↑	[24,31]
Bupropion	n.d.	n.d.	–
Neurokinin 1 antagonist	↑	↑ (in knockouts)	[167,168]
Sigma agonist	n.d.	n.d.	–
ECS	↑	↑	[24,31]
VNS	n.d.	n.d.	–
Direct CB_1 agonist	↑	↑↔	[131,99,169]
CB_1 antagonist/inverse agonist	n.d.	↔	[134]
FAAH inhibitor URB597	↑	↑ (in knockouts)	[131,132]

↑: Increase; ↔: No change; n.d.: Not determined.
Table adapted from [19].
CB_1: Cannabinoid receptor type 1; ECS: Electroconvulsive shock; FAAH: Fatty acid amide hdyrolase; MAOI: Monoamine oxidase inhibitors; NRI: Norepineprhine re-uptake inhibitors; SNRI: Serotonin and noradrenaline re-uptake inhibitor; SSRI: Selective serotonin re-uptake inhibitor; TCA: Tricyclic antidepressants; VNS: Vagus nerve stimulation.

argue for the facilitative role of neurogenesis in the restructuring of depression-induced faulty neuronal circuits that may lead to improvements in information processing and consequently, mood [35]. Airan *et al.* [36] suggested that the neurogenic effects of antidepressants augment the activity propagation in the dentate gyrus and moderate the strength of hippocampal (CA1) output, therefore modulating the abnormal activity, evident in depression, of output targets, e.g., the amygdala and subgenual cortex.

6. Endocannabinoids

In the brain, CB_1 is the pharmacological target of the dibenzopyrane cannabis derivative (-)-*trans*-Δ^9-tetrahydrocannabinol (THC) [37]. In contrast, the cannabinoid type 2 receptor (CB_2) is expressed primarily in the periphery and is mainly involved in immunoregulation. CB_1 is the most abundant G-protein-coupled receptor in the mammalian brain, and its presence in the neocortex, hippocampus, basal ganglia, cerebellum, limbic system and brainstem is thought to account for most of the behavioral actions of cannabinoid drugs. CB_1 is a presynaptic receptor, mostly localized on GABAergic and glutamatergic axon terminals [38]. CB_1 activation depresses synaptic GABA and glutamate release in the hippocampus, cerebellum and other brain areas. The understanding of this suppression is still incomplete but it has been shown to be involved in long-term synaptic depression (LTD) [39] or potentiation (LTP) [40], as well as in cerebral developmental processes [41]. The brain produces at least two lipids that are the endogenous ligands for CB_1: anandamide and 2-AG. Anandamide is produced in a receptor-activation-dependent manner and released into the extracellular space through facilitated transport, where it activates CB_1 receptors located on neighboring cells or on the same cell producing anandamide [38,42]. It is transported back into neurons by a carrier-mediated transport system, whose molecular identity remains unknown. Once inside the cell, it is deactivated by the intracellular enzyme fatty acid amide hydrolase (FAAH), an intracellular membrane-bound serine hydrolase that breaks down anandamide into arachidonic acid and ethanolamine [42]. **Figure 1** shows a schematic representation of the life cycle of anandamide. On the other hand, 2-AG is degraded by monoglyceride lipase [42]. Because anandamide and 2-AG are released under different circumstances and degraded by different enzymes, they probably serve distinct functional roles.

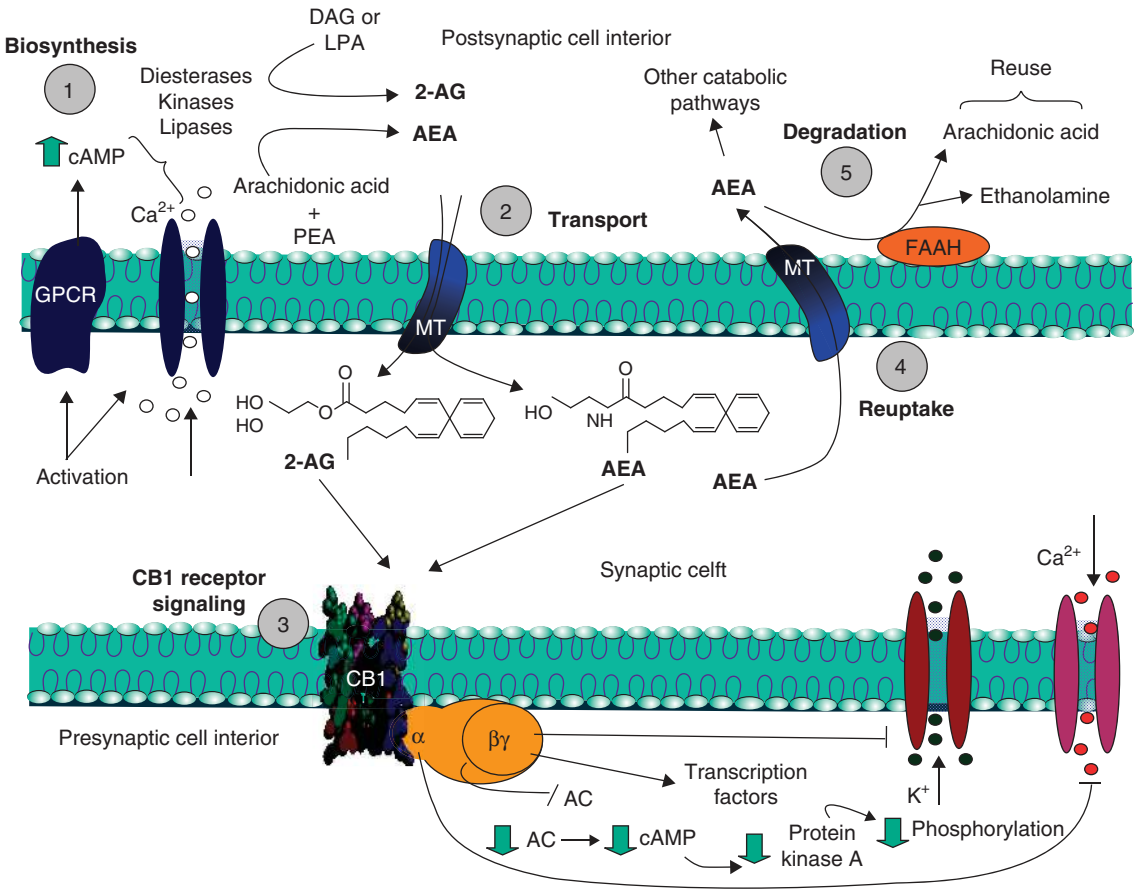

Figure 1. A simplified schematic diagram illustrating the life cycle of the endocannabinoid anandamide (AEA). 1. AEA, as well as 2-AG, are synthesized on demand through the action of multiple diesterases, kinases and lipases. Upon stimulation of postsynaptic G protein-coupled receptors (GPCR) (increased adenylyl cyclase/AC activity) and calcium (Ca^{2+}) channels, the increased levels of cyclic adenosine monophosphate (cAMP) and calcium facilitate production and/or conversion of the endocannabinoid precursor *N*-arachidonoylphosphatidylethanolamine (from arachidonic acid and phosphatidylethanolamine/PEA) or diacylglycerol (DAG) (or 2-arachidonoyl lysophosphatidic acid/LPA through an alternative pathway) into AEA and 2-AG, respectively. 2. AEA and 2-AG are transported into the synaptic cleft through non-vesicular trafficking that involves a yet uncharacterized membrane transporter (MT). 3. AEA and 2-AG act as agonists on the metabotropic CB_1 that may be localized on either or both presynaptic or/and postsynaptic membranes. Increased endocannabinod–CB_1 signaling hyperpolarizes the presynaptic membrane (shown) by activating G protein-regulated inwardly rectifying potassium (GIRK) channels via reduced phosphorylation by protein kinase A (through the Gi/o protein α subunit and AC), and by inhibiting L, N and P/Q-type calcium channels (through the Gi/o protein α subunit). CB_1 receptor activity can also activate mitogen-activated protein kinases and influence transcription factors. 4. AEA and 2-AG are transported back into the cell via a yet uncharacterized endocannabinoid MT. In the cell, AEA and 2-AG go through different catabolic pathways. AEA is degraded by the membrane-bound serine hydrolase, fatty acid amide hydrolase (FAAH) into arachidonic acid ethanolamine. Other parallel AEA-catabolic pathways exist.
↑: Stimulation; ⊤ or ↓: Inhibition.

7. The mood-elevating and antidepressant properties of cannabis and exogenous cannabinoids: epidemiological and clinical evidence

7.1 Pros

In the last ten years, although the medical use of cannabis has been applied to various medical conditions from cancer metastatis to bone diseases, the main motivations attributed to smoking cannabis remain related to mood-altering, particularly pleasant and tension/anxiety-dissipating experiences. However, no large-scale double-blind study, to date, has been carried out to directly test the anxiolytic and antidepressant effects of cannabis on patients with mood disorders.

THC constitutes ~ 5 – 10% of dry weight in marijuana, and is probably responsible for most of the psychoactive effects experienced from smoking cannabis. Anecdotal reports of healthy users refer to the early stage of cannabinoid intoxication as a complex state of fatuous euphoria, consisting of uncontrollable fits of laughter, sharpened sense of humour, enhanced sociability, heightened sensory experience and imagination, distortion of time perception and feelings of

depersonalization. This is followed by a generally favorable emotional experience characterized by relief from stress, relaxation, profound sense of well-being, good mood, introspection and entry into dream-like disconnection from reality [43], reports that were confirmed by cross-sectional epidemiological analyses [44]. Kotin *et al.* [45] reported that studies of the therapeutic effects of THC on severely depressed patients failed to yield significant results, probably due to the small number of participants, low oral dose used (0.3 mg/kg) and the limited time it was administered (every 12 h for 1 week). A few years later, however, Regelson *et al.* [46] published findings about the antidepressant effects of THC among cancer patients. They reported that the drug decreased the incidence (but not severity) of depression, reduced apprehensive feelings, produced tranquility/relaxation and moved patients towards self-reliance. More recently, Gruber *et al.* [47] reviewed five cases in which cannabis clearly showed direct antidepressant effects. Up to now, reports on the self-medicative use of cannabis for both primary and secondary depression continue to accumulate. Over 95% of patients surveyed in the UK believed to have obtained various medicinal benefits from cannabis [48], and European surveys indicated that depression was one of the most frequently mentioned illnesses for which it was used [49]. Among multiple sclerosis patients, emotional or mood dysfunction [50,51], depression [52,53], anxiety [52], appetite or weight loss, stiffness, pain [51,53], stress, and sleep disturbance [51] were symptoms reported to be chiefly relieved by cannabis. Likewise, cannabis use appears to ameliorate appetite loss, pain, depression and anxiety-related symptoms associated with HIV infection [54,55]. More recent highly controlled clinical studies on both chronically ill patients and healthy volunteers have provided more informative results. A placebo-controlled double-blinded clinical experiment on the tolerability and effects of marijuana and dronabinol (THC synthetic analog) on eating behavior, mood, cognitive performance, physiological measures and sleep were conducted among HIV-positive marijuana smokers. Marijuana and dronabinol were similar in producing a positively-rated (pleasurable) subjective high and increases in caloric intake without engendering significant discomfort or cognitive impairments, measured using a battery of tests for various aspects of learning, memory, vigilance and psychomotor ability. On visual analog scales, both drugs improved mood while marijuana also improved ratings of sleep [56].

The cloning of CB_1 [57] and the subsequent discovery of selective agonists and antagonists have led to the discovery that the acute subjective and physiological components of cannabinoid-induced mood changes are mediated by the selective activation of CB_1. An elegant randomized, placebo-controlled, double-blind experiment by Huestis *et al.* [58] involved healthy male marijuana users. An acute oral dose of the CB_1 antagonist rimonabant (90 mg/kg) was proven to be effectively sufficient in blocking the effect of a marijuana cigarette (2.64% THC) smoked 2 h later. These include the subjective feeling of drug high along with its physiological components (heart rate), feelings of being stoned, and perception of the extent of marijuana intoxication as assessed by visual analog scales and questionnaires.

7.2 Cons and caveats

Despite the aforementioned reports on the mood-related effects of CB_1 agonists, certain challenges need to be met head-on. First, it is known that the experience associated with cannabis intoxication is highly variable and dependent on baseline emotional states, personality and expectations of the user, environmental setting, frequency of use and dose (e.g., low versus high THC content) [43,59]. Moreover, exposure to high doses may produce anxiety, panic and psychotomimetic effects [43,60]. The complex variable and bidirectional effects typically associated with cannabinoids would present an unstable therapeutic window under the influence of many factors. Second, since cannabis is globally the most abused illicit substance accessible for recreational use and has been hypothesized to serve as gateway for the use of other drugs of abuse [43,61,62], findings need to be interpreted carefully against the history of cannabis use and substance abuse. This becomes more important upon considering indications that heavy use, particularly among adolescents, is paradoxically associated with increased risks of contracting depressive symptoms that persist in adulthood [63,64]. A constellation of maladaptive behaviors including diminished drive and ambition, increased apathy, dysphoria, decreased capacity to carry out long-term plans, and a difficulty dealing with frustration – referred to as amotivational syndrome – is suggested to be caused by long-term exposure to marijuana. Interestingly, these component symptoms overlap with those of depression, suggesting that long-term use of cannabis could have a negative effect on mood and motivation [61,62]. A reevaluation of the 1980 Baltimore Epidemiological Catchment Area study participants found a fourfold likelihood of contracting depressive symptoms (anhedonia and suicidal ideation) in those who initially had a diagnosis of cannabis abuse [63]. In another longitudinal study, Fergusson *et al.* [65] determined a significant association between heavy cannabis use and illicit drug use, crime, depression and suicidal behaviors among adolescents and young adults. Interestingly, while males may seem to be more receptive to the antidepressant effects of cannabis [51], female adolescent cannabis consumers were five times more likely to develop depression and anxiety compared to non-users [64]. Furthermore, empirical evidence implicates cannabis use as a risk factor for schizophrenia in susceptible subpopulations, and its heavy use was linked to the first episode of psychosis [66,67].

In summary, anecdotal reports and epidemiological and clinical investigations seem to converge on the hypothesis that enhancement of the activity of brain CB_1 receptors by cannabis and cannabinoids affects mood regulation. However, positive psychotropic effects are apparently mixed with unwanted effects probably due to the indiscriminate activation

of many brain structures that express CB_1. Therefore, alternative routes of selectively harnessing therapeutically relevant effects are of the utmost clinical value.

8. The endocannabinoid system in depression

The endocannabinoid system has recently been postulated to be involved in the etiology and pathophysiology of depression. Alterations at the level of receptors and in circulating and brain extracellular levels of endocannabinoids in the disease state have been supported by both clinical studies on depressed patients and preclinical studies that have used animal models of depression [68,69].

8.1 Human studies

At the genetic level, polymorphic mutation of the cannabinoid receptor gene (CNR1) was found to be associated with impulsivity [70]. This gene was also linked to depressive symptoms in patients with Parkinson's disease. A decrease in the prevalence of depression from among these patients occurs in those who were genotyped with two long alleles with more than 16 repeated AAT trinucleotides in the CNR1 gene [71].

At the level of the CB_1 receptor, quantitative immunohistochemical and radiobinding postmortem analyses have provided evidence for aberrant receptor density associated with depressive disorders. Koethe *et al.* [72] found a significant decrease in glial but not neuronal CB_1 density in the anterior cingulate cortices of patients with major depression from among patients that included manic-depressives and schizophrenics. Furthermore, those that received antidepressant medication had more pronounced reduction in glial CB_1. In the dorsolateral subregions of the prefrontal cortex (PFC), Hungund *et al.* [73] reported elevated CB_1 density and activity of associated G proteins (G_i) observed in depressed suicide victims in comparison with healthy controls. These observations were replicated in chronic alcoholics who died by suicide in comparison with matched alcoholic controls that died by other causes [74]. Several independent studies on schizophrenics, whose negative symptoms overlap with those of major depressives, have also shown increased CB_1 density in the dorsolateral PFC [75] and anterior [76] and posterior cingulate cortices [77]. This was paralleled by increased cerebrospinal fluid (CSF) levels of anandamide. 2-AG levels for both schizophrenic and control groups were below detection levels. Since anandamide levels were inversely correlated with the severity of psychotic symptoms, its increase was conjectured to represent an adaptive mechanism in response to abnormal neurochemical signaling underlying psychoses [78-80]. Recently, a preliminary clinical report by Canadian researchers documented that female ambulatory medication-free patients diagnosed with major depression in comparison with matched controls exhibited a significant reduction in serum levels of endocannabinoids, particularly 2-AG. They also reported a strong negative correlation between serum anandamide levels and measures of cognitive and somatic anxiety in the Hamilton Depression Scale [81]. No data on males are available to date. In summary, it may be hypothesizied that an upregulation of cortical CB_1 may serve to compensatorily adapt to neurochemical alterations in the disease state. In particular, this could very well be in response to reduced endocannabinoid signaling in major depression. Interestingly, physiological processes, such as those associated with moderately intense exercise that counter depressive disorders [82] significantly increase anandamide levels (with a non-significant increase of 2-AG) [83].

8.2 Animal studies

Consistent with data from human depressives, experimental animals subjected to different stress-related behavioral paradigms to model depression have also exhibited perturbations in the endocannabinoid system. Chronic mild stress (CMS) or chronic unpredictable stress (CUS) led to an upregulation of CB_1 receptors [84] and mRNA [85] in rat PFC and CB_1 mRNA in mice PFC [84], resembling patterns observed in human depressives. Bortolato *et al.* [85] also found that CB_1 mRNA was significantly decreased in the midbrain of CMS-exposed rats while mRNA levels in the hippocampus were unaffected. In contrast, Hill *et al.* [86] and Hillard *et al.* [84] maintained that hippocampal CB_1 receptor density is diminished by CUS, observed also in the amygdala, hypothalamus and ventral striatum. This negative effect on CB_1 density may be due to long-term exposure to high levels of glucocorticoids [87] that is also associated with chronic stress. In addition, whereas Bortolato *et al.* [85] found no change in endocannabinoid levels in the PFC, midbrain, hippocampus and striatum of chronically stressed animals (except for an increase in 2-AG in the thalamus), Hill *et al.* [86] reported a significant attenuation of hippocampal 2-AG following chronic stress. Patel *et al.* [88], on the other hand, showed that merely an acute exposure to a 30 min restraint stress can reduce hypothalamic 2-AG below control levels, coinciding with an increase in serum corticosterone concentration. Remarkably, this decrease in 2-AG and increase in corticosterone were reversed after 5 days of exposure, this was suggested to result from adaptive adjustments or habituation to the repeated homotypic stress exposures [89].

The preclinical data indicating a decrease in CB_1 receptor density and/or endocannabinoid levels in depression models are consistent with the physiological and behavioral consequences of genetic or pharmacological deletion of CB_1 that have been shown to exhibit enhanced depressive/anxiety-like behaviors and physiological abnormalities associated with mood dysfunction. CB_1-null-mutant mice have been seen to contract impairments in the extinction of aversive memories [90], in habituating to fear reactivity [91], and to exhibit increased anxiety-like (e.g., in the light/dark test and elevated plus maze) [92-94] or anhedonia-like (decreased sucrose preference/intake induced by CMS) as well as aggressive, antagonistic behaviors in the resident–intruder

test [93], and to manifest a dysregulated HPA axis with abnormally enhanced hypothalamic and plasma corticosteroid levels [95].

9. Antidepressant-like activity of cannabinoids in animal models

Several animal models and tests of depression/antidepressant-like activity have also supported clinical indications of the antidepressant potential of enhancing the function of the endocannabinoid system.

9.1 Behavioral despair (FST and TST)

Among the first-stage screens predicting antidepressant activity, the rat/mouse forced swim test (FST) and the mouse tail suspension test (TST) measure the capacity of putative agents to reverse learned behavioral despair, a depressive-like behavior. A 15-minute pre-exposure to an inescapable water-filled bin is sufficient to increase the duration and decrease the latency of immobility (passive floating) on the second 5-min exposure 24 h later. Antidepressant drugs in comparison to vehicle decrease immobility and increase active coping. Similarly, the direct CB_1 agonists WIN55,212-2 [96-98], HU-210 [99], ACEA [100], the anandamide re-uptake inhibitor AM404 [101] and the inhibitor of the anandamide-degrading fatty acid amide hydrolase (FAAH) URB597 [102] all decrease immobility. The endocannabinoids anandamide and virodhamine have also been tested to curtail the exaggerated increase in immobility induced by nicotine treatment [103]. The genetic deletion of FAAH in mice showed positive and negative results depending on the experimental context [104,105].

In the TST, mice are suspended by the tail, after which they normally give up struggling within a few minutes. Antidepressant drugs in comparison to vehicle increase struggling behavior across time. The pharmacological and genetic blockade of FAAH has also yielded mixed positive and negative results, which were also dependent on experimental contexts [102,104,105].

9.2 Novelty-suppressed feeding task (NSF)

The NSF measures the latency of unexposed food-deprived rats or mice to eat chow pellets made available in a novel open field chamber. Chronic but not acute antidepressant drug treatment in comparison to vehicle reduces the anxiety induced by the novelty, increases the motivation to feed and consequently decreases the latency to approach the chow pellets. HU-210 (0.1 mg/kg, intraperitoneal, twice per day for 10 days) has been shown to similarly decrease feeding latency even after 1 month of drug treatment [99].

9.3 Social interaction test (SI)

SI, which examines the extent to which two previously uncoupled conspecifics investigate each other and exhibit agonistic or antagonistic (aggression) behavior towards each other, can also be used to predict the effects of putative antidepressant drugs. Acute antidepressant treatment decreases aggressive and antagonistic behaviors while chronic treatment increases social interaction and aggressive behaviors. THC has been found to decrease aggressive behavior in this test [106]. Cassano *et al.* (unpublished results) reported that the genetic deletion of FAAH increases social interaction, an effect similar to chronic antidepressant treatment.

9.4 Chronic unpredictable mild stress (CMS)

CMS possesses a high degree of external validity since it mimics in humans the risk of vulnerability associated with exposure to chronic stressful life events. Both repeated restraint stress and chronic unpredictable mild stressors in rodents progressively diminish the consumption and preference for a sapid sucrose solution. This observation is analogous to one core symptom of depressive disorder: the blunting of interest for pleasureable activities (anhedonia). Anhedonia-like behaviors in stress-exposed rodents are associated with a reduction in neurogenesis and impaired 5-HT neurotransmission. Chronic but not acute antidepressant treatment reverses these behaviors (FR Bambico, N Nguyen, G Gobbi, unpublished results). Likewise, acute treatment with the direct CB_1 agonist CP55,940 or the FAAH inhibitor URB597 [107] as well as chronic URB597 treatment [85,108] completely reverse anhedonia-like responses and normalize stress-induced stunting of body weight gain [108].

9.5 Antidepressant-like effects of CB_1 antagonists/inverse agonists

Overall, the results obtained from behavioral (animal) studies are complex since CB_1 antagonists/inverse agonists, such as rimonabant and AM251, have also been demonstrated to elicit antidepressant-like behaviors in the TST, FST and CMS [109-111]. Whether these apparently contradictory observations are due to inadequacies and insensitivities of the animal models/tests used or bonafide properties of the drugs themselves is not clear; more research is needed to clarify underlying neural processes. These aspects are beyond the scope of this review.

10. Effects of cannabinoids on 5-HT neurotransmission

The mechanistic principles underlying the antidepressant-like activity of CB_1 agonists and FAAH inhibitors remain by and large unexplored. Since conventional as well as putative/experimental antidepressant treatments increase 5-HT neurotransmission, it is reasonable to hypothesize that cannabinoid drugs also behave like antidepressants in affecting the 5-HT system. Several indications support this hypothesis, including the observation that 5-HT-acting agents and SSRI antidepressants potentiate some behavioral and physiological effects of cannabinoids, such as THC-induced hypothermia [112] and aggressiveness in REM sleep-deprived rats [113]

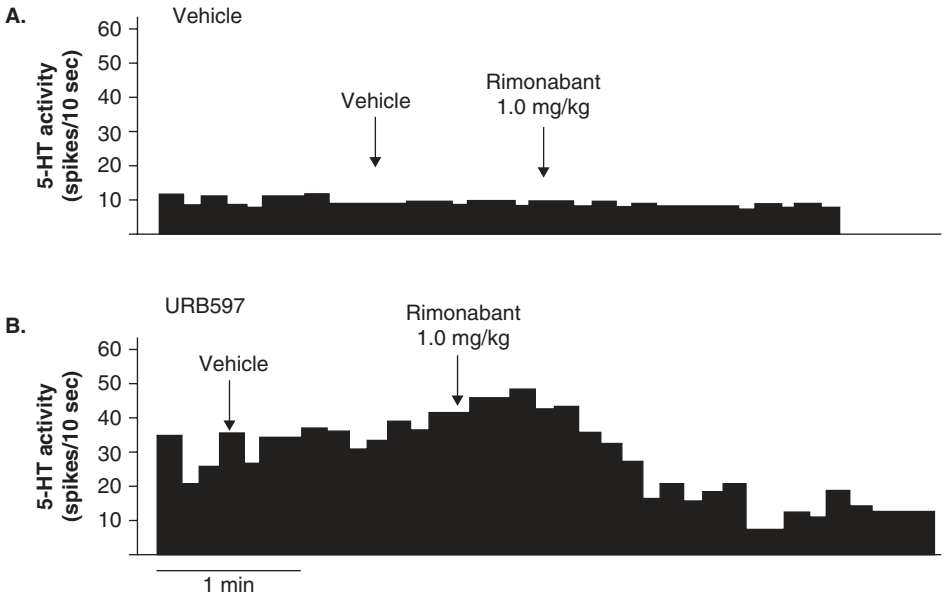

Figure 2. Effect of rimonabant on dorsal raphe nucleus 5-hydroxytryptamine (5-HT) neuronal firing activity. Integrated firing rate histograms showing that acute intravenous injection of rimonabant (1 mg/kg) does not influence spontaneous 5-HT neuronal firing rate in animals subchronically (4 days, once daily) treated with vehicle (intraperitoneal, ip) (**A**) but dramatically decreases, to below preinjection levels, that of animals subchronically treated with URB597 (0.1 mg/kg, intraperitoneal) (**B**). Each bar of the histogram corresponds to 10 s of recording. Calibration line below histograms = 1 min. Results published in [102].

10.1 Effects of CB_1 agonists and FAAH inhibitors on 5-HT neuronal firing activity (see Table 1)

The effect of cannabinoid CB_1 agonists on 5-HT neuronal excitability can be directly measured using the classic extracellular single-unit recordings of 5-HT neurons in the DR. Our experiments [98] have shown that acute intravenous and sequential intraperitoneal administration of WIN55,212-2 produced a dose-dependent excitatory enhancement in the spontaneous firing and burst activity of DR 5-HT neurons (67% of recorded) in chloral hydrate-anesthetized rats within a low dose range of 0.05 – 0.3 mg/kg (ED_{50} ~ 0.1 mg/kg, intravenous). Sequential doses applied 23, 1 and 0.75 h before electrophysiological recordings improved at least twofold the 5-HT response to acute injections, paralleled by a stronger antidepressant-like behavior in the FST. This was accompanied by an increase in the number of 5-HT neurons recorded per electrode descent, which served as an indirect index of the density of actively discharging neurons [102]. 5-HT neuronal firing activity following higher doses of WIN55,212-2 (0.3 – 0.8 mg/kg, intravenous) was significantly decreased below control levels, thus revealing a biphasic (bidirectional) profile in response to varying doses of WIN55,212-2. The FAAH inhibitor URB597 (subacute, intraperitoneal) (ED_{50} ~ 0.5 mg/kg, intraperitoneal) also excited 5-HT neurons, with significant increases in burst activity as well as in the number of 5-HT neurons recorded per electrode descent. In keeping with the slow pharmacokinetics of anandamide build-up following FAAH deactivation, which eventually leads to enhanced anandamide-CB_1 transmission, the excitatory response of 5-HT neurons followed a gradual increase that peaked 1.5 – 2 h postinjection. Indeed, mass spectrometric detection showed increased anandamide levels in the PFC, hippocampus and midbrain [102]. Chronic (5 weeks) treatment however did not maintain elevated anandamide levels in the PFC and the hippocampus, although high anandamide levels persisted in the midbrain, thalamus and striatum [85]. In contrast to the much delayed peak effect of URB597, intraperitoneal administration of excitatory doses of WIN55,212-2 showed a peak effect 7 – 15 min postinjection. A higher dose of URB597 (1 mg/kg, intraperitoneal) still produced an enhanced 5-HT neuronal activity significantly higher than control levels (FR Bambico, G Gobbi, unpublished data). In contrast to the biphasic response to WIN55,212-2, URB597 assumed the classic sigmoidal dose-response curve that may be indicative of a wider therapeutic window for FAAH inhibitors as compared to direct CB_1 agonists. Furthermore, FAAH-null-mutant mice also exhibited an endophenotypic augmentation of spontaneous 5-HT neuronal discharge activity, which could be explained by enhanced anandamide–CB_1 signaling due to increased basal levels of anandamide. In all these experiments, the 5-HT excitatory response was mediated by enhanced CB_1 activation since it was blocked or reversed by rimonabant (1 mg/kg, intravenous or intraperitoneal) that by itself did not induce any change in 5-HT neuronal activity.

Table 4. Differences and similitudes in the electrophysiological and neurobehavioral effects of fatty acid amide hdyrolase (FAAH) inhibitors and direct canabinoid receptor 1 (CB_1) agonists.

Parameter	FAAH Inhibitor	CB_1 agonist	Ref.
5-HT neuronal firing activity	↑ Sigmoidal, after 20 min	↑↓ Biphasic	[98,102]
NE neuronal firing activity	↑ After 20 min	↑ Rapid onset	[102,121]
Antidepressant-like activity	+	+ At low doses	[98,102]
Addiction liability (CPP)	-	+	[102,170]

↑: Increase; ↓: Decrease; +: Positive; -: Negative.
CPP: Conditioned place preference; 5-HT: 5-Hydroxytryptamine; NE: Neropinephrine.

Table 4 summarizes these effects of CB_1 agonists and FAAH inhibitors on 5-HT neuronal firing activity.

Recently Aso *et al.* [114] presented data on the enhancement of phenylephrine-evoked 5-HT neuronal firing accompanied by $5\text{-}HT_{1A}$ desensitization in DR slices (*in vitro*), as well as decreased 5-HT transporter (5-HTT) binding and increased basal 5-HT levels in the PFC, observed in CB_1-null-mutant mice; these mice paradoxically show increased depressive-like [115] and anxiety-like behaviors [92]. These findings were interpreted as compensatory mechanisms to counterbalance deficits in other systems induced by CB_1 deletion. Such mechanisms are not uncommon since other validated animal models of depression/anxiety have also been found to instigate at least one of these changes. For instance, $5\text{-}HT_{1A}$ autoreceptor desensitization/downregulation was found after chronic unpredictable stress (FR Bambico, N Nyugen, G Gobbi unpublished), 5-HTT genetic deletion [116] and neonatal clomipramine treatment [117].

11. Effects of cannabinoids on noradrenergic neurotransmission

For many years, studies on the influence of cannabinoids on the catecholaminergic systems were initially focused within the context of reward and addiction. In particular, the ability of CB_1 agonists to enhance dopamine (DA) neurotransmission by stimulating DA neuronal activity and release in the VTA–NAc pathway seemed to validate cannabis dependence in humans and the activity of cannabinoid drugs in animal models of drug craving [118]. Interestingly, unlike CB_1 agonists, solo treatment with URB597 increases neither DA levels in the NAc shell [119] nor VTA DA neuronal firing [120], and does not produce any indication of rewarding effects in the conditioned place preference paradigm [102]. Clearly, this difference can be capitalized on for the antidepressant potential of this drug.

Experimental evidence on the interaction of CB_1 agonists with the NE neurotransmission has also started to abound in the literature as discussed in the following section.

11.1 Increase in LC NE neuronal activity by CB_1 agonists and FAAH inhibitors

Our electrophysiological recordings from the LC of chloral hydrate-anesthetized rats have shown that systemic URB597 (0.1 mg/kg, intraperitoneal or intravenous) enhanced the spontaneous firing activity of NE neurons twofold in comparison to vehicle [102]. Rimonabant (1 mg/kg, intraperitoneal) injected 15 min prior to recordings prevented this enhancement indicating a CB_1-dependent mechanism underlying this effect. These findings corroborate those of Muntoni *et al.* [121] on the dose-dependent modulatory effect of WIN55,212-2 (0.0625 – 1.0 mg/kg, cumulative intravenous doses, maximal at 1.0 mg/kg) and THC (0.0625 – 1.0 mg/kg, cumulative intravenous doses) on LC NE spontaneous firing activity of chloral-hydrate-anesthetized rats, with WIN55,212-2 having more efficacy than THC. They mimicked these effects with an ipsilateral intracerebroventricular (10 or 25 µg/10 µl) infusion of these drugs. In all cases, rimonabant (1 mg/kg, intravenous) attenuated the cannabinoid-induced neuronal stimulation, and slightly but significantly reduced NE spontaneous neuronal activity when given alone systemically, pointing to an endocannabinoid tonus on NE neuronal activity or to the inverse agonistic property of rimonabant.

Remarkably, the results obtained with WIN55,212-2 and URB597 on NE neurons show some similarities and differences with the results obtained on 5-HT neurons. WIN55,212-2 induced an immediate increase in NE firing activity, and URB597 increased the firing after 20 min peaking at 2 h; this time course was similar to that observed in 5-HT-neuron recordings and it is compatible with the pharmacokinetics of the two compounds. On the other hand, increasing doses of WIN55,212-2 produced a steep dose-response curve in NE neurons firing activity and not a biphasic curve as observed in 5-HT neurons. The meaning of this discrepancy is unknown. However, it may be related to the anxiogenic effects of cannabis at higher doses. Interestingly, the NE firing activity stimulation following URB597 administration seems to reach a plateau at higher doses and after subchronic treatment, suggesting that URB597 may not exert anxiogenic effects at higher doses (FR Bambico, G Gobbi unpublished observations).

Mendiguren and Pineda [122] also reported a dose-dependent modulatory effect of cumulative intravenous doses (0.03 – 0.05 mg/kg) of WIN 55,212-2 or CP55940, which were prevented by rimonabant (2 mg/kg, intraperitoneal) injected 30 min prior to recording. Autoradiographic binding [123] and immunostaining studies [124,125] of the LC revealed moderate CB_1 density. CB_1 has been found to be localized in NE axon terminals. A third of CB_1-immunopositive axon terminals in the frontal cortex were found to exhibit dopamine-beta-hydroxylase labeling and hence, were NE

terminals [125]. Single systemic (intraperitoneal) administration of WIN55,212-2 at 3.0 mg/kg and 15.0 mg/kg has been found to increase NE outflow in the rat frontal cortex coincident with an increase in c-Fos immunoreactivity in the LC, an effect that was blocked by a silent dose of rimonabant (0.2 mg/kg, intraperitoneal) injected 30 min prior to WIN55,212-2 injection [124]. THC (5 mg/kg, intraperitoneal) also increased NE turnover in the ppc [126], and THC (5, 10 and 20 mg/kg, intraperitoneal) and WIN55,212-2 (2 and 4 mg/kg, intraperitoneal) produced a 40 – 70% increase in NE synthesis in the neocortex, hippocampus, hypothalamus and other brain regions [127]. These effects were CB_1-mediated. On the other hand, Schlicker *et al.* [128] reported that the electrically or Ca^{2+}-evoked tritium ([^{3}H]NE) overflow in guinea-pig hippocampal slices, representing quasi-physiological NE release, was reduced by WIN55,212-2, while rimonabant increased it. While this latter phenomenon is probably due to CB_1 activation in NE axonal terminals in local (e.g., hippocampal) circuits, the net increase in NE outflow observed in the aforementioned studies may be explained by presynaptic CB_1 activation that leads to cannabinoid-induced NE neuronal excitation, nothwithstanding the actual input responsible for it. **Table 2** summarizes these effects of CB_1 agonists and FAAH inhibitors on NE neuronal firing activity.

12. Cannabinoid agonists, the hippocampus and neurogenesis

The hippocampus is one of the limbic regions enriched with CB_1 receptors that are sensitive to chronic stress exposure [129] and antidepressant treatment [86], by which they are downregulated and upregulated, respectively. Interestingly, FAAH inhibitors and CB_1 agonists appear to exhibit different mechanisms when administered locally in the hippocampus. Indeed, URB597 (0.5 and 1 µg) failed to elicit antidepressant-like coping in the FST, while the CB_1 agonist HU-210 (1 and 2.5 µg) was positive [130].

12.1 Cannabinoid agonists and hippocampal 5-HT_{1A} transmission

As with all other conventional antidepressant treatments, we have demonstrated that subchronic treatment with URB597 (0.3 mg/kg, intraperitoneal) or THC (1.0 mg/kg, intraperitoneal) produced an increase in hippocampal 5-HT_{1A} tonic activity, evidenced by disinhibition of CA3 pyramidal neuron firing activity upon systemic administration of the 5-HT_{1A} antagonist WAY100635 [131].

12.2 Cannabinoid agonists and FAAH inhibitors increase hippocampal neurogenesis

Cannabinoids, like antidepressants, also promote hippocampal neurogenesis. Jiang *et al.* [99] posited that the antidepressant/anxiolytic like action of chronic HU-210 treatment (0.1 mg/kg, intraperitoneal, twice daily for 10 days) in the rat forced swim test and novelty-suppressed feeding task (tested 1 month later) were probably mediated by enhanced neurogenesis in the dentate gyrus brought about by the activation of CB_1 receptors present in both embryonic and adult hippocampal neural stem/progenitor cells. In another study, Aguado *et al.* [132] found not only CB_1 receptors but also FAAH in neural progenitor cells. Activation of these receptors promoted cell proliferation and neurosphere generation. Not surprisingly, FAAH knockout mice exhibited increased cell proliferation in the hippocampus [132]. Furthermore, the compensatory adaptive increase *in vivo* in neural progenitor proliferation and neurogenesis, as well as of basic fibroblast growth factor (bFGF), brain-derived neurotrophic factor (BDNF) and epidermal growth factor (EGF) induced by excitotoxicity were found to be dependent on CB_1 activity and were accordingly blocked in CB_1 knockout mice and by rimonabant treatment in wild type mice [133]. All these findings are in agreement with those of Jin *et al.* [134], who found a reduction of about 50% in the number of BrdU-positive cells (decreased neurogenesis) in CB_1 null-mutant mice, which supports a role of enhanced CB_1 activation in fostering neurogenesis. However, THC administered acutely (1, 3, 10, 30 mg/kg, intraperitoneal), sequentially (two doses of 10 or 30 mg/kg, intraperitoneal, with a 5 h interval), or chronically (escalating doses of 20 – 80 mg/kg, orally for 3 weeks.) as well as acutely administered WIN55,212-2 (5 mg/kg, intraperitoneal) failed to produce changes in cell proliferation (BrdU labeling) in the adult mouse dentate gyrus. Also, *in vitro* and *in vivo* experiments conducted by Rueda *et al.* [135] indicated an inhibition of cortical neuron progenitor differentiation by anandamide, and of adult dentate gyrus neurogenesis by its synthetic analog, methanandamide. In contrast, another group has shown that WIN55,212-2 (100 nM) increased BrdU-labeling in mice cerebral cortical cultures [136]. It is still not known whether URB597, like other antidepressants, increases neurogenesis.

13. Why does CB_1 antagonism induce depression?

Clinical trials on the use of the CB_1 antagonist rimonabant as a treatment for obesity revealed that it induced depression and suicidal behavior. Christensen *et al.* [137] performed a meta-analysis of four of these published randomised controlled trials and found that although rimonabant led to a marked reduction in weight, triglycerides and high-density lipoprotein cholesterol [138], the adverse psychiatric consequences were alarming. Despite excluding people who have had severe neuropsychiatric illnesses, patients assigned to rimonabant were 2.5 times (odds ratio) more likely than were those receiving placebo (3 versus 1.4%) to discontinue the trial because of emergent depressive symptoms. Examining the same four studies, the US FDA committee found that 26% of participants who were taking 20 mg rimonabant have had

an adverse psychiatric event (mainly anxiety or depression) compared with 14% of those who were taking placebo [139]. This increase in psychiatric complications (relative risk 1.9) was significant compared with placebo (95% CI 1.5 – 2.3). Adverse events developed early in treatment. The FDA even identified substantial evidence for an increased risk of suicide attempts or suicidality (odds ratio 1.9, 95% CI 1.1 – 3.1) [139].

We lay out here a possible framework explaining this prodepressant effect of a CB_1 antagonist.

Animal behavioral studies have thus far reported that treatment with rimonabant alone at relatively low doses (< 2 mg/kg) does not change the basal activity of 5-HT neurons and also produce no effect in the FST and TST [98,102]. Although some studies have reported antidepressant-like properties at higher doses (> 2 mg/kg) of rimonabant and enhanced PFC monoamine transmission [109-111,140], other researchers have shown that similar doses of rimonabant were anxiogenic in several behavioral tests of anxiety [141,142] without effects on 5-HT transmission in the hypothalamus [142]. Also, CB_1-null-mutant mice were phenotyped to have higher sensitivities in exhibiting depressive-like and anxiety-like behaviors in several animal models/tests [93,143].

Electrophysiological recordings with low-dose rimonabant (1 mg/kg) revealed that in naive (control) animals, its solo administration produced a light but significant decrease in NE neuronal firing activity [121]. Our own experiments showed that the same dose of rimonabant did not modulate 5-HT neuronal firing activity in rats receiving single or repeated injections of vehicle, indicating that under control conditions, the endocannabinoid system does not exert a tonic activity over 5-HT neurons. However, in those repeatedly injected with URB597, 1 mg/kg of rimonabant dramatically decreased 5-HT neuronal firing activity below control levels (**Figure 2**). A probable explanation would be that subchronic URB597 administration led to an increase in both tonic anandamide-CB_1 activity and sustained 5-HT tonic activity. Within this milieu, the low dose of rimonabant may have dramatically blocked CB_1 activity that consequently caused a strong, abrupt drop in 5-HT transmission. Remarkably, underactivity of 5-HT function in rodents and humans is associated with dampening of mood and increased suicidality [144]. In parallel, one may hypothesize that in a subgroup of obese patients with heightened endocannabinoid tonus and increased tonic 5-HT activity, rimonabant could similarly induce an abrupt drop in 5-HT electrical activity, leading to depressive symptoms and suicidality. In support of this hypothesis, Engeli *et al.* [145] found that in the obese patient population, the endocannabinoid system is hyperactivated, with a 35% increase in the plasma levels of anandamide.

Another factor that should also be taken into consideration is that a decrease in cholesterol level is associated with decreased 5-HT, and higher risks of impulsivity and suicidality [146].

Also noteworthy, in these clinical antiobesity trials with rimonabant [137], no reports of potential antidepressant effects were ever made. This may be difficult to reconcile with its purported antidepressant-like properties reported in rodent studies (see Section 9.5 of this review). It is also worth mentioning that high doses of rimonabant were used in these animal studies. Although a matter of conjecture, at such doses, rimonabant could act on other receptor systems (e.g., the TRPV1 vanilloid receptor), or could induce hyperarousal or hyperemotionality as well as anxiety [141], possible sources of confounding results in behavioral tests for antidepressant-like effects. Further research is needed to better characterize the relationships among the endocannabinoid system, 5-HT, fat levels and depression.

14. Expert opinion

Research on new antidepressant drug targets represents a major challenge not only due to the high prevalence of depression but also because currently available antidepressants are effective in but a limitated percentage of patients according to extensive clinical trial reports [10], meta-analyses [147] and naturalistic studies [148,149].

In the last ten years, more than 50 preclinical studies have been published on the potential role of the endocannabinoid system in the pathophysiology and treatment of mood disorders. Behavioral (animal) studies, using well-validated and reliable animal paradigms for depression suggest that the FAAH inhibitor URB597 and the anandamide transport blocker AM404 possess antidepressant-like effects similar to those of other classes of clinically used antidepressants.

Electrophysiological and biochemical studies have indicated that subacute, subchronic and chronic treatments with URB597 share common features with chronic antidepressant treatment: i) increased 5-HT neurotransmission; ii) increased NE neurotransmission; iii) increased tonic activity of postsynaptic $5\text{-}HT_{1A}$ receptors, documented in the CA3 region of the dorsal hippocampus; and iv) FAAH genetic blockade promotes neurogenesis in the hippocampus (**Table 3**). These data are particularly compelling with respect to the notion that modulating the endocannabinoid system by FAAH inhibition holds promise as a novel pharmacological strategy for treating depression without producing secondary effects associated with SSRIs and the addiction liability associated with exogenous direct CB_1 agonists. Indeed, preclinical studies suggest that FAAH inhibitors possess mechanisms of action distinct from direct CB_1 agonists. First, due to slow kinetics, FAAH inhibitors produce a temporal progression in modulating 5-HT neuronal firing activity and transmission different from that of direct CB_1 agonists. CB_1 agonists more rapidly increase 5-HT neuronal activity. In addition, the fact that anandamide is released 'on demand' may already convey differences in spatio-temporal dynamics between FAAH inhibitors and CB_1 agonists. Second, increasing doses of FAAH inhibitors produce a

sigmoidal response profile in modulating 5-HT neuronal activity, whereas CB_1 agonists increase 5-HT neuronal activity at low doses but decrease it below basal levels at higher doses. This effect of CB_1 agonists on 5-HT neuronal activity may explain, at least in part, the biphasic psychotropic effects of cannabis within a narrow pharmacological window. Similarly in the FST, increasing doses of URB597 maintain a progressive reduction in behavioral despair (time spent in immobility). On the other hand, CB_1 agonists such as WIN55,212-2 reduce immobility at low doses, and this antidepressant-like effect is nullified by higher doses. Third, FAAH inhibitors, unlike CB_1 agonists fail to exhibit rewarding properties in the conditioned place preference test or produce generalization to the discriminative effects of THC [102], predictive of a low addictive liability in humans (**Table 4**). Furthermore, FAAH inhibitors, compared to CB_1 agonists, do not induce memory impairment but may rather improve cognitive function [150], and they do not seem to induce psychotic-like behaviors. Why do FAAH inhibitors and direct CB_1 agonists yield different effects if they ultimately act on the same receptor? Although insufficient information is available to readily address this question, several lines of evidence raise possible hypotheses. First, FAAH inhibitors primarily increase brain levels of anandamide which, compared to full CB_1 agonists, is a partial agonist at the CB_1 receptor, exerting a partial pharmacological efficacy. Second, the spatio-temporal differences in CB_1 activity enhancement by FAAH inhibitors and direct CB_1 agonists may also serve as contributing factors. Indeed, FAAH and CB_1 receptors do not have topographically equivalent histological localizations [151]. Consequently, whereas direct CB_1 agonists indiscriminately activate CB_1 receptors abundantly expressed in many brain regions, FAAH inhibitors increase anandamide-CB1 signaling in select brain regions that co-express FAAH and CB_1 receptors.

To date, all research efforts are still at the preclinical stage; the FAAH inhibitors URB597 (Shering-Plough) and SR144528 (Sanofi-Synthelabo) have not gone to clinical phases of testing. Consequently, the efficacies of these drugs on humans are yet to be determined. Endocannabinoid enhancers could also present hazards. Indeed, endocannabinoids also act peripherally, and their function implicated in many other conditions, e.g., pain, neurodegenerative disorders, gastrointestinal inflammation, obesity, metabolic dysfunctions, cardio-vascular and liver diseases, and reproductive dysfunctions [152]. The consequences of endocannabinoid enhancement in other systems is still unknown. Moreover, FAAH inhibitors may also increase other lipidic substances, e.g., *N*-palmithoylethanolamide and *N*-oleoylethanolamide, which may in turn act on other receptor systems, such as the nuclear receptor PPAR, which is involved in lipid and neuroimmune regulation. This needs to be clarified, and the physiological significance of these effects determined.

Unfortunately, economic issues and business investments limit research on new antidepressant drugs mainly because Phase II and III clinical trials have proven to engender the highest risk of failure for antidepressant drugs. This may be attributed, in part, to the difficulty of differentiating placebo and active drug effects, especially during the first weeks of treatment [153]. Nevertheless, considering the effects of major depression on public health and society, research on new antidepressant drug targets should remain a priority in drug development.

Declaration of interest

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