Role of the Endocannabinoid System in Depression: from Preclinical to Clinical Evidence

Chapter · January 2014

DOI: 10.1007/978-1-4939-2294-9_5

8 authors, including:

Vincenzo Micale
Masaryk University
81 PUBLICATIONS **2,189** CITATIONS
SEE PROFILE

Jana Ruda-Kucerova
Masaryk University
90 PUBLICATIONS **208** CITATIONS
SEE PROFILE

Filippo Drago
University of Catania
282 PUBLICATIONS **5,979** CITATIONS
SEE PROFILE

Chapter 5
Role of the Endocannabinoid System in Depression: from Preclinical to Clinical Evidence

Vincenzo Micale, Katarina Tabiova, Jana Kucerova and Filippo Drago

Abstract The endogenous cannabinoid system (ECS) works as pro-homeostatic and pleiotropic signaling system activated in a time- and tissue-specific way during physiological conditions, which include cognitive, emotional and motivational processes. It is composed of two G protein-coupled receptors (the cannabinoid receptors types 1 and 2 [CB1 and CB2] for marijuana's psychoactive ingredient Δ9-tetrahydrocannabinol [Δ9-THC]), their endogenous small lipid ligands (anandamide [AEA] and 2-arachidonoylglycerol [2-AG], also known as endocannabinoids), and the proteins for endocannabinoid biosynthesis and deactivation. Data from preclinical and clinical studies have reported that a hypofunction of the endocannabinoid signaling could induce a depressive-like phenotype; consequently, enhancement of endocannabinoid signaling could be a novel therapeutic avenue for the treatment of depression. To this aim there have been proposed cannabinoid receptor agonists or synthetic molecules that inhibit endocannabinoid degradation. The latter ones do not induce the psychotropic side effects by direct CB1 receptor activation, but rather elicit antidepressant-like effects by enhancing the monoaminergic neurotransmission, promoting hippocampal neurogenesis and normalizing the hyperactivity of hypothalamic-pituitary-adrenal axis, similarly as the standard antidepressants. The dysfunction of elements belonging to the ECS and the possible therapeutic use of endocannabinoid deactivation inhibitors and phytocannabinoids in depression is discussed in this chapter.

Keywords Endocannabinoid system · CB1 and CB2 receptors · TRPV1 channels · Animal models · Depression · Antidepressants · Δ9-THC · Cannabidiol

V. Micale (✉) · K. Tabiova · J. Kucerova
Department of Pharmacology, CEITEC (Central European Institute of Technology)
Masaryk University, Brno, Czech Republic
e-mail: vincenzomicale@inwind.it

F. Drago
Department of Clinical and Molecular Biomedicine, Section of Pharmacology and Biochemistry,
Medical School, University of Catania, Catania, Italy

P. Campolongo, L. Fattore (eds.), *Cannabinoids and Modulation of Emotion, Memory, and Motivation,* DOI 10.1007/978-1-4939-2294-9_5

Introduction

Current Pharmacological Approach for the Treatment of Depression

Depression is one of the most common mental illness with a lifetime prevalence of about 15–20 %, resulting in enormous personal suffering, as well as social and economic burden [1]. The major depressive disorder is characterized by episodes of depressed mood lasting for more than 2 weeks often associated with feelings of guilt, decreased interest in pleasurable activities and inability to experience pleasure (named anhedonia), low self-esteem and worthlessness, high anxiety, disturbed sleep patterns and appetite, impairment in memory and suicidal ideation [2].

The treatment of depression was revolutionized in the 1950s with the introduction of two classes of pharmacological agents to the clinical practice: the monoamine oxidase inhibitors "MAOIs" and the tricyclic antidepressants "TCAs". The discovery was based on the serendipitous finding that enhancement of the synaptic levels of monoamines improves the symptoms of depression, leading to the *monoamine hypothesis of depression* [3]. Thus, the introduction of antidepressant drugs had a profound impact on the way depression was viewed: if chemicals can reverse most depressive symptomatologies, then depression itself may be caused by chemical abnormalities in the brain. However first generation antidepressants, due to their toxic and poorly tolerated profile, were largely replaced by the selective serotonin reuptake inhibitors (SSRIs), norepinephrine reuptake inhibitors and serotonin norepinephrine reuptake inhibitors and by atypical antidepressants (i.e. nefazodone and mirtazapine), which are not more effective than MAOIs or TCAs but show an improved safety profile [4].

Recently, some atypical antipsychotics such as olanzapine, quetiapine or aripiprazole, used either as monotherapy or in combination with venlafaxine or sertraline, have also shown efficacy at ameliorating symptoms of bipolar disorder and treatment-resistant major depression and received approval from the FDA (US Food and Drug Administration) for these indications [5]. Since disruptions of circadian and sleep-wake cycles have been recognized as major contributor to mood disturbance, and agomelatine (a melatonergic agonist and a serotonin 5-HT_{2C} receptor antagonist) was found to be very effective in ameliorating depressive symptoms with a good tolerability and safety profile, a new concept for the treatment of mood disorders has recently emerged [6].

However, the past decade has witnessed a driven focus on the rational discovery of highly selective drugs, acting at novel non monoamine based targets such as GABAergic and glutamatergic neurotransmission, neuroendocrine system or neuropeptide signaling, which in turn could affect intracellular signal transduction pathways. Yet, except for the N-methyl-D-aspartate (NMDA) receptor antagonist ketamine [7], none of these drugs has reached the market [8–11]. Thus, the dominant hypothesis of depression is still based on the monoamine model, which comprises the primary target for current antidepressants. Although today's treatments are generally

safe and effective, 30% of depressed patients treated with the conventional antidepressants are pharmacoresistant. In addition, the medication has to be administered for weeks or months to see appreciable clinical benefit [12]. Therefore, there is still a great need to update the current level of knowledge with regard to the pathophysiological mechanisms underlying depressive disorders in order to develop safer, more effective, and faster acting pharmacotherapies. The partial efficacy of current drugs raises the central question to be addressed in this chapter: Does the alteration of the endocannabinoid system (ECS) have a crucial role in the pathophysiology of depressive disorders and is the ECS consequently able to provide a promising therapeutic approach for their treatment?

The Endocannabinoid System (ECS)

The ECS is a neuromodulatory system, which plays a role in a variety of physiological processes both in the central nervous system (CNS) and in the periphery, mediating the effects of the psychoactive constituent of Cannabis Δ9-tetrahydrocannabinol (Δ9-THC) [13]. Multiple lines of evidence have shown that its dysregulation is associated with several pathological conditions such as pain and inflammation [14, 15], obesity, metabolic [16, 17], gastrointestinal [18], hepatic [19], neurodegenerative [20–22] and psychiatric disorders [23–25]. However, the exact pathophysiological mechanisms through which the ECS controls these functions are not fully elucidated yet. The ECS is comprised of: (1) the cannabinoid receptors type CB1 and CB2 [26–28], (2) their endogenous ligands anandamide (N-arachidonoyl-ethanolamine, AEA) and 2-arachidonylglycerol (2-AG) [29, 30], (3) a specific and not yet identified cellular uptake mechanism [31, 32], and (4) the enzymes for endocannabinoid biosynthesis, N-acyl-phosphatidylethanolamine-selective phosphodiesterase or glycerophosphodiesterase E1 and diacylglycerol lipase α or β [33, 34], or their inactivation, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) [35, 36], respectively for AEA and 2-AG. However, additional "players" which are described as potential members of the ECS include the TRPV1 channels, the putative CB1 receptor antagonist peptides like hemopressins, peroxisome proliferator-activated receptor-α (PPAR-α) and γ (PPAR-γ) ligands, such as oleoylethanolamide (OEA) or palmitoylethanolamide (PEA), and N-arachidonoyl-dopamine (NADA), which activates both TRPV1 and CB1 receptors. Although the existence of a third cannabinoid receptor subtype has also been suggested [37], to date only CB1 and CB2 receptors are recognized as G protein-coupled receptors for endocannabinoids [38].

The cannabinoid CB1 and CB2 receptors are established as mediators of the biological effects induced by cannabinoids, either plant derived, synthetic, or endogenously produced. These receptors are encoded by two different genes on human chromosomes: 6q14-q15 (CNR1) and 1p36.11 (CNR2). They are 7 transmembrane Gi/o coupled receptors that share 44% protein identity and display different pharmacological profiles and patterns of expression, a dichotomy that provides a unique opportunity to develop pharmaceutical approaches.

The CB1 receptors are ubiquitously expressed in the CNS where they are predominantly found at high densities in the basal ganglia, frontal cortex, hippocampus and cerebellum. They are present at a moderate/low densities in the periaqueductal gray, amygdala, nucleus accumbens, thalamus and medulla. However, the CB1 receptors are also found in non-neuronal cells of the brain such as microglia, oligodendrocytes and astrocytes [39]. Within these cortical areas there are two major neuronal subpopulations expressing the CB1 receptors: the GABAergic interneurons (with high CB1 receptor levels) and glutamatergic neurons (with relatively low CB1 receptor levels) [40], which represent the two major opposing players regulating the excitation state of the brain, GABAergic interneurons being inhibitory and glutamatergic neurons being excitatory. CB1 receptors are also located in neurons of the dorsal raphe nucleus (DRN) and in the *locus coeruleus* (LC) which are the major sources of serotonin (5-HT) and noradrenalin (NE) in the brain [41, 42]. Thus, the direct or indirect modulation of monoamine activity or of GABA and glutamate neurons, respectively, could underlie the psychotropic and non-psychotropic effects of CB1 receptor activation.

The cannabinoid CB2 receptors, which are also activated by AEA and 2-AG, are mainly distributed in immune tissues and inflammatory cells, although they are also detected in glial cells, and to a much lesser extent, in neurons of several brain regions such as cerebral cortex, hippocampus, amygdala, hypothalamus and cerebellum [43, 44]. While their role in pain and inflammation has been extensively reported, recently their involvement in emotional processes has been suggested [45]. The observation that the elements belonging to the ECS are prevalent throughout the neuroanatomical structures and circuits implicated in emotionality, including prefrontal cortex (PFC), hippocampus, amygdala, hypothalamus and forebrain monoaminergic circuits, provides a rationale for the preclinical development of agents targeting this system to treat affective diseases.

Cannabis, Endocannabinoid System and Depression: Clinical and Preclinical Evidence

Cannabis sativa is the most commonly used illicit “recreational” drug worldwide, its popularity being due to its capacity to increase sociability, to induce euphoria and to alter sensory perception. Although the association between *Cannabis sativa* and psychopathologic conditions has been known for thousands of years, only in the last 50 years the identification of the chemical structure of marijuana components, the cloning of specific cannabinoid receptors and the discovery of the ECS in the brain have triggered an exponential growth of studies to explore its real effects on mental health [46].

The Cannabis plant contains over 100 terpenophenolic pharmacologically active compounds, known as cannabinoids. Of these, Δ9-THC, characterized in 1964 by Mechoulam’s team [47], was identified as the primary psychoactive component of Cannabis, and later shown to act as a direct agonist of CB1 and CB2 receptors. Oth-

er cannabinoids include cannabichromene, cannabigerol and cannabidiol (CBD), which do not seem to induce the psychotropic side effects of Δ9-THC. They act on several levels in the CNS, including modulation of endocannabinoid tone [48–50], interaction with transient receptor potential vanilloid 1 (TRPV1) channels [48] and serotonin 5-HT_{1A} receptors [51], and enhancement of adenosine signaling [52, 53]. The above mentioned mechanisms could underlie the positive effects induced by CBD treatment in preclinical studies of several psychiatric as well as other disorders [54, 55].

Although elevation of mood is one of the commonly cited motivations for the use of Cannabis, in addition to its recreational actions, data from clinical trials in the 1970's failed to show any antidepressant effects of Δ9-THC [56, 57]. Additionally, the hypothesis that depressed individuals use Cannabis as a mean of self-medication proposed by preclinical studies [58] has not been fully supported by clinical data yet [59, 60]. By contrast, some data support the hypothesis that Cannabis use precipitates depression [61–65], where genetic and environmental factors could play a pivotal role [66–68]. However, a recent study has shown that depressive symptoms are indirectly related to Cannabis use through positive, but not negative, expectancies [69]. It is not to be excluded that other factors such as the dose, route of administration, baseline emotional states, personality, environment and the setting, during which the drug is used, could be involved in Δ9-THC effects on mood.

Despite preclinical data supporting an altered endocannabinoid signaling as a molecular underpinning of several psychiatric disorders [70], to date only few direct investigations have assessed endocannabinoid activity in depressed patients, as reviewed in Table 5.1. A significant increase of CB1 receptor density has been found in the dorsolateral prefrontal cortex (dlPFC) of depressed suicide victims, possibly suggesting a hyperfunctionality of the ECS in this population [71]. By contrast, a down-regulation of the ECS activity was suggested by Koethe et al. [72] and Hill et al. [73, 74], showing a decreased CB1 receptor density in grey matter glial cells and lower serum concentration of 2-AG in patients with major depression. However, an increase of endocannabinoid tissue content in the dlPFC of alcoholic depressed patients as well as a significantly enhanced serum level of AEA in patients suffering of minor depression were also reported [73, 75]. Furthermore, in two recent clinical studies, a positive correlation was found among high blood pressure and serum contents of endocannabinoids in depressed females [76] and among intense physical exercise, AEA and brain-derived neurotrophic factor (BDNF) levels [77], suggesting that an interrelationship among endocannabinoids, depression and cardiovascular risk factors in women and an increase in peripheral BDNF levels could be a mechanism by which AEA intervenes in the neuroplastic and antidepressant effects of exercise.

Thus, considering the recent preclinical evidence relating the effects of enhanced endocannabinoid signaling to the promotion of neurogenesis, it is not to exclude that its activation exerts antidepressant properties through mechanisms that resemble the ones triggered by conventional antidepressants on synaptic plasticity [78, 79]. However, the increasing interest concerning ECS dysfunction in depressive disorders was engendered after the clinical use of the CB1 receptor antagonist

Table 5.1 Schematic representation of the changes of the endocannabinoid system (ECS) elements in clinical studies of depression

ECS elements	Sex (number of cases)	Diagnosis	Tissue sample[a]	Molecular readout	References
CB1	♂♀ ($n=10$)	Major depression	dlPFC	↑ density	[71]
	♂♀ ($n=11$)	Alcohol dependence	dlPFC/occipital cortex	↑ density (dlPFC)	[75]
	♂♀ ($n=15$)	Major depression	Anterior-cingulate cortex	↓ density	[72]
AEA	♂♀ ($n=11$)	Alcohol dependence	dlPFC	↑ level	[75]
	♀ ($n=16$)	Major depression	Serum	No effect	[73]
	♀ ($n=12$)	Minor depression	Serum	↑ level	[73]
	♀ ($n=15$)	Major depression	Serum	↓ level	[74]
	♀ ($n=28$)	Major/Minor depression	Serum	↑ level	[76]
2-AG	♂♀ ($n=11$)	Alcohol dependence	dlPFC	↑ level	[75]
	♀ ($n=16$)	Major depression	Serum	↓ level	[73]
	♀ ($n=12$)	Minor depression	Serum	No effect	[73]
	♀ ($n=15$)	Major depression	Serum	↓ level	[74]
	♀ ($n=28$)	Major/Minor depression	Serum	↑ level	[76]
Palmitoylethanolamide (PEA)	♀ ($n=15$)	Major depression	Serum	No effect	[74]
Oleoylethanolamide (OEA)	♀ ($n=15$)	Major depression	Serum	No effect	[74]

[a] *dlPFC* dorsolateral prefrontal cortex

rimonabant for the treatment of obesity was interrupted. In line with the theory that a deficiency in CB1 receptor signaling could be involved in depression, rimonabant was withdrawn from the market because of undesirable psychiatric side effects such as anxiety, depression and suicidal ideations [80]. Although no controlled clinical trials concerning endocannabinoid signaling in depression are available, opposite changes in endocannabinoid activity could underlie the different forms of depressive illness.

As recently suggested, genetic variations in CB1 receptor function could also facilitate the development of mood disorders in humans [81]. The human CB1 receptor gene (CNR1), which is located on the chromosome 6q14–15, seems to play a role in a broad spectrum of psychiatric disorders such as substance abuse disorders, schizophrenia and autism spectrum conditions [82–84]. With regard to depression, while Barrero et al. [85] showed a significant association between polymorphisms in CNR1 and depression only in Parkinson's disease patients, recent studies support that genetic variations in CB1 receptor function and in FAAH could influence both

Table 5.2 Schematic representation of the antidepressants effects on the endocannabinoid system (ECS) elements

Drug class	Effective medication	Brain region[a]	Molecular readout	References
Tricyclic antidepressants	Desipramine	Hippocampus, Hypothalamus	↑ CB1 receptor binding	[95]
	Imipramine	Hypothalamus, Hippocampus, Midbrain, vStriatum, Amygdala	↓ CB1 receptor binding (Hypothalamus, Midbrain, vStriatum) ↑ CB1 receptor binding (Amygdala)	[96]
MAO (A-B) inhibitors	Tranylcypromine	PFC, Hippocampus, Hypothalamus	↑ CB1 receptor binding ↑ 2-AG content (PFC) ↓ AEA content	[92]
Selective serotonin reuptake inhibitors (SSRI)	Fluoxetine	PFC	↑ CB1 receptor binding	[92, 93]
	Citalopram	Hippocampus, Hypothalamic paraventricular nucleus	↓ CB1 receptor binding	[94]

[a] *PFC* prefrontal cortex, *vStriatum* ventral striatum

the development of depressive symptoms and the antidepressant treatment response [86–88]. However, a significant genetic interaction among the polymorphism in the serotonin transporter gene 5-HTTLPR, variants in the CNR1 gene, anxiety or stress adaptation have also been found [89, 90]. Thus, the identification of individuals with a high-risk of psychiatric disorders through genetic testing could be a promising strategy for the development of safer drugs [91].

The putative role of the ECS in depression is supported by evidence showing that the majority of available antidepressants also modify CB1 receptor expression and endocannabinoid content in brain regions related to mood disorders (Table 5.2). While fluoxetine increased CB1 receptor binding and/or signaling in the limbic region [92, 93], citalopram reduced CB1 receptor signaling in the hippocampus and hypothalamic paraventricular nucleus [94], suggesting a region-specific effect of SSRI on CB1 receptor-mediated signaling. Similarly, TCAs elicited different effects based on various brain regions: desipramine increased hippocampal and hypothalamic CB1 receptor binding [95], while imipramine reduced it within the hypothalamus, midbrain and ventral striatum and increased it within the amygdala [96]. However, no difference has been found in the AEA content. The MAOI tranylcypromine enhanced CB1 receptor binding and 2-AG level in PFC and hippocampus, while reducing AEA content within the PFC, hippocampus and hypothalamus [92]. Despite the conflicting panorama, these findings suggest that the antidepressants modify the endocannabinoid tone in different ways, depending both on the class of drugs and on the different brain regions considered.

Changes in ECS elements have also been reported in several stress related animal models (Table 5.3), in accordance with the clinical data described above. In

Table 5.3 Schematic representation of the changes of the endocannabinoid system (ECS) elements in preclinical studies of depression

ECS elements	Experimental model	Animals	Behavioural response[a]	Brain region[a]	Molecular readout	Positive control	References
CB1	CMS	Wistar rats	↓ sucrose preference ↓ body weight	PFC Midbrain	↑ expression ↓ expression	Imipramine	[97]
		Sprague-Dawley rats	↓ body weight ♂♀ ↓ sucrose preference ♂	Hippocampus	↓ expression ♂ ↑ expression ♀	ND	[102]
	Chronic unpredictable stress	Long-Evans rats	Cognitive deficit in the MWM	Hippocampus Limbic forebrain	↓ expression No effects	ND	[101]
			↓ sexual motivation	PFC Hippocampus Hypothalamus vStriatum	↑ binding ↓ binding ↓ binding ↓ binding	Imipramine	[96]
		Sprague-Dawley rats	↑ immobility time in the FST	vmPFC dmPFC	↑ binding (vmPFC)	ND	[100]
			↑ immobility time in the FST ↓ sucrose preference ↓ locomotor activity in the OFT	Hippocampus	↓ expression	Transcranial magnetic stimulation	[103]
	OBX	Sprague-Dawley rats	↑ locomotor activity in the OFT	PFC	↑ binding	Fluoxetine	[98]
	Restraint stress	Sprague-Dawley rats	ND	Amygdala Hippocampus PFC	↑ binding (adolescent) ↓ binding (adult) ↑ binding (adolescent/adult)	ND	[99]
CB2	Chronic unpredictable mild stress	Wild type mice of CB2 overexpressing mice	↑ immobility time in the FST ↓ sucrose preference	Hippocampus	↓ expression	ND	[106]

Table 5.3 (continued)

ECS elements	Experimental model	Animals	Behavioural response[a]	Brain region[a]	Molecular readout	Positive control	References
TRPV1	Restraint stress	Wistar rats	↑ immobility time in the FST	Hippocampus	↑ expression	Clomipramine	[158]
FAAH	Restraint stress	Wistar rats	↑ immobility time in the FST	Hippocampus	↑ expression	Clomipramine	[158]
AEA	CMS	Wistar rats	↓ sucrose preference ↓ body weight	PFC, Midbrain, Hippocampus, Striatum, Thalamus	No effect	Imipramine	[97]
	Restraint stress	ICR mice	ND	Amygdala	↓ content	ND	[108]
				Amygdala vStriatum, mPFC	↓ content (Amygdala and mPFC) ↑ content (vStriatum)	ND	[111]
		Sprague-Dawley rats	ND	PFC, Hippocampus, Hypothalamus, Amygdala	↓ content	ND	[109]
		Bl6 mice	ND	Amygdala	↓ content	ND	[110]
		Wistar rats	↑ immobility time in the FST	PFC, Hippocampus	No effect	Clomipramine	[158]
	Chronic unpredictable stress	Long-Evans rats	↓ sexual motivation	PFC, Hippocampus, Hypothalamus, vStriatum, Amygdala, Midbrain	↓ content	Imipramine	[96]

Table 5.3 (continued)

ECS elements	Experimental model	Animals	Behavioural response[a]	Brain region[a]	Molecular readout	Positive control	References
2-AG	Chronic unpredictable stress	Long-Evans rats	Cognitive deficit in the MWM	Hippocampus Limbic forebrain	↓ content No effect	ND	[101]
			↓ sexual motivation	PFC, Hippocampus, Hypothalamus, vStriatum, Amygdala, Midbrain	↑ content (Hypothalamus, Midbrain)	Imipramine	[96]
	Restraint stress	ICR mice	ND	Amygdala, Forebrain	↑ content	ND	[108]
	CMS	Wistar rats	↓sucrose preference ↓ body weight	PFC, Hippocampus, Striatum, Midbrain, Thalamus	↑ content (Thalamus)	Imipramine	[97]
	Restraint stress	ICR mice	ND	Amygdala, vStriatum mPFC	↑ content (Amygdala, mPFC) ↓ content (vStriatum)	ND	[111]
				Amygdala	↑ content	ND	[112]
		Sprague-Dawley rats	ND	Amygdala	↑ content	ND	[109]
		Bl6 mice	ND	Amygdala	No effect	ND	[110]
		Wistar rats	↑ immobility time in the FST	PFC, Hippocampus	No effect	Clomipramine	[158]

[a] *FST* forced swim test, *CMS* chronic mild stress, *MWM* Morris water maze, *ND* not determined, *OBX* bilateral olfactory bulbectomy, *OFT* open field test, *PFC* prefrontal cortex, *mPFC* medial prefrontal cortex, *dmPFC* dorsomedial prefrontal cortex, *vmPFC* ventromedial prefrontal cortex, *vStriatum* ventral striatum

well validated animal models of depression such as the chronic mild stress (CMS) paradigm or the bilateral olfactory bulbectomy (OBX) model, which produce behavioural and neurochemical changes similar to those in human depression, a significant increase of CB1 receptor density and binding has been found in the PFC [96–100], together with a significant decrease in the ventral striatum, hypothalamus [96], midbrain [97] and hippocampus [99, 101–103]. This latter seems to be associated with a significant alteration of the hippocampal endocannabinoid-mediated neurotransmission and synaptic plasticity [104]. Collectively, the effects of experimental stress procedures on brain CB1 receptor expression seem to be region dependent.

Although the presence of CB2 receptors in stress responsive brain regions suggests their involvement in the regulation of mood, to date there is no evidence concerning their modification in the brain of depressed patients. More data come from preclinical studies, which reported a reduction of CB2 receptors in the hippocampus, striatum and midbrain in animal models of depression. Similarly, an increase of CB2 receptor expression counteracts behavioural and neurochemical features related to a depressive-like state [105–107]. Other controversial data about the endocannabinoid brain content in depression have also been recorded. While Bortolato et al. [97] did not find a change in AEA levels in different brain regions of rats subjected to CMS, others reported a significant reduction of AEA content following different chronic stress paradigms [96, 108–111]. The effects of stress procedure on 2-AG levels are confusing as well, since a reduction in the hippocampus and an increase in thalamus, hypothalamus and amygdala has been shown [96, 97, 101, 109, 112], or no such effects [97, 110]. Although the discrepancy may be due to numerous factors, such as the nature and duration of the stress, the species (rats vs. mice) or strain (Wistar vs. Sprague-Dawley rats), differences in response to stress procedure, or the time and tissue of extraction, the data described above supports the general hypothesis that a deficiency in the functioning of the endocannabinoid signaling, both in depressed patients and in animal models of depression, may directly lead to a vulnerability in development of the illness. Thus, it seems reasonable to hypothesize that its pharmacological facilitation would produce certain antidepressant effects.

Current Status of Animal Models of Depression and Antidepressant Responsive Tests

Due to the limited efficacy of antidepressant treatments, a better understanding of the pathophysiology of mental health disorders and the development of novel, improved therapeutic treatments would fill a considerable unmet medical need [113]. Due to the enormous cost of clinical trials, pharmaceutical companies make all efforts at testing new chemicals designed to alter the function of a specific target of disease in a predictable and safe manner [114]. Thus, of central importance to this approach is the availability of valid preclinical animal models for the evaluation of

the potential efficacy of novel compounds and the further understanding of the neuropathology that underlies the idiopathic disease state of depression [115].

Ideally, an experimental animal model should reflect the human psychiatric disease in terms of face validity (i.e. reproduce the symptoms of depression observed in humans), construct validity (the same neurochemical mechanisms in humans as in the animal model) and predictive validity (chronic antidepressant treatment must reverse the phenotype of the animal model) [116]. In the case of depression, an animal model which perfectly includes the etiology, the pathophysiology and the symptoms of depression whilst allowing evaluating the responses to treatments remains impossible to fully envisage. However, different models, each with specific limitations, are able to reproduce most of the etiological factors and many symptoms of depression or possess a satisfactory predictive value for identifying new compounds. For this purpose, the forced swim test (FST) or the tail suspension test (TST) and the CMS or the OBX seem to be good experimental approaches for screening potential new antidepressants and shape the underlying disease etiology [117].

The most widely used paradigm to assess antidepressant-like behaviour is the FST also known as Porsolt's test [118]. In the FST rodents are forced to swim in an inescapable cylinder filled with water and eventually adopt a characteristic immobile posture which is interpreted as a passive stress-coping strategy or depressive-like behaviour (behavioural despair). The FST has shown its ability to detect a broad spectrum of substances with antidepressant efficacy, as these drugs shift from passive stress-coping towards active coping, which is detected as reduced immobility. Furthermore, the quantity of different movements such as climbing and swimming behaviour has predictive value to differentiate between NEergic and 5-HTergic activity. Some of the most representative potential antidepressants with different mechanisms of action have been submitted to this test [23, 119].

Similar assumptions and interpretations as the FST is the TST [120]. In this test, mice are suspended by their tails for a defined period of time and their immobility is decreased by several antidepressants. A major drawback of the TST is that its application is restricted to mice and limited to strains which do not tend to climb their tail, a behaviour that would otherwise confuse the interpretations of the results [121]. The test however is sensitive to acute treatment only and its validity for non-monoamine antidepressants is uncertain [119, 122].

A different model is the CMS paradigm, which is based on reduced sweet fluid intake as an index of anhedonia, induced by repeated (at least 2 weeks) exposure to unpredictable stressors (i.e. wet bedding, disruption of dark-light cycle and food or water deprivation) [123]. This model induces various long-term behavioural and neurochemical alterations resembling some of the dysfunctions observed in depressed patients, which are reversed only by chronic treatment with a broad spectrum of antidepressants. As compared to other experimental models of depression, it has been evaluated as a high perspective research approach, despite its procedural complexity and poor inter-laboratory reliability.

The OBX, a lesion model of depression is based on surgical removal of olfactory bulbs by aspiration [124] and results in a disruption of the limbic hypothalamic axis

followed by neurochemical (i.e. changes in all major neurotransmitter systems) and behavioural (e.g. hyperactive response in the open field paradigm and anhedonia) alterations, which resemble changes seen in depressed patients and are reversed only by chronic administration of antidepressants [125, 126]. In most of the models described above, locomotor activity in the open field test must be also monitored to ensure that motor depression rather than emotional behaviour is not influencing animal responses [126].

Although none of the available experimental paradigms are able to model all aspects of depression disorders in terms of etiological factors and symptoms, and most likely never will, the paradigms described above have proven extremely useful both in the identification of potential new antidepressants and in the validation of neurobiological concepts. More specifically, they have been extensively used for assessing the potential antidepressant-like activity of compounds modulating the endocannabinoid signaling in rodents.

Effects of Pharmacological Manipulation of the Endocannabinoid Signaling in Preclinical Studies of Depression

After discovering the ECS members (CB1 and CB2 receptors, endocannabinoids AEA and 2-AG and enzymes for their degradation, FAAH and MAGL) several pharmacological tools, which vary from direct agonists or antagonists (Fig. 5.1) to endocannabinoid enhancers have been evaluated in several *in vitro* and *in vivo* studies to assess their therapeutic potential in stress-related neuropsychiatric disorders [23] (Table 5.4). Based on the hypothesis that a reduction of endocannabinoid signaling could underlie depressive disorders, it has been seen that acute or repeated treatment with different compounds which activate directly cannabinoid receptors, such as the main pharmacologically active principle of *Cannabis sativa* Δ9-THC [98, 127–130], the endogenous cannabinoid AEA [131, 132], the synthetic nonspecific CB1/CB2 receptor agonists CP55,940 [133], WIN55,212–2 [134, 135] and HU-210 [136–139] or the selective CB1 receptor agonist arachidonoyl 2'-chloroethylamide (ACEA) [140, 141] elicited antidepressant-like effects through CB1 and 5-HTergic or NEergic receptor-mediated mechanisms.

However, chronic exposure to Δ9-THC or WIN55,212–2 in adolescence led to a depressive-like phenotype in adulthood, further supporting the fact that adolescence is a critical period in which protracted direct CB1 receptor activation may influence mood control [142–146] (see also Chap. 12). Although the CB1 receptor antagonist rimonabant, which was introduced into clinical practice as antiobesity agent, was withdrawn from the market due to the higher incidence of psychiatric side effects [147], preclinical studies have reported an antidepressant-like activity of rimonabant in rodents [129, 130, 148–151]. Using a genetic approach controversial results regarding the effects of CB1 receptor signaling inhibition on stress coping

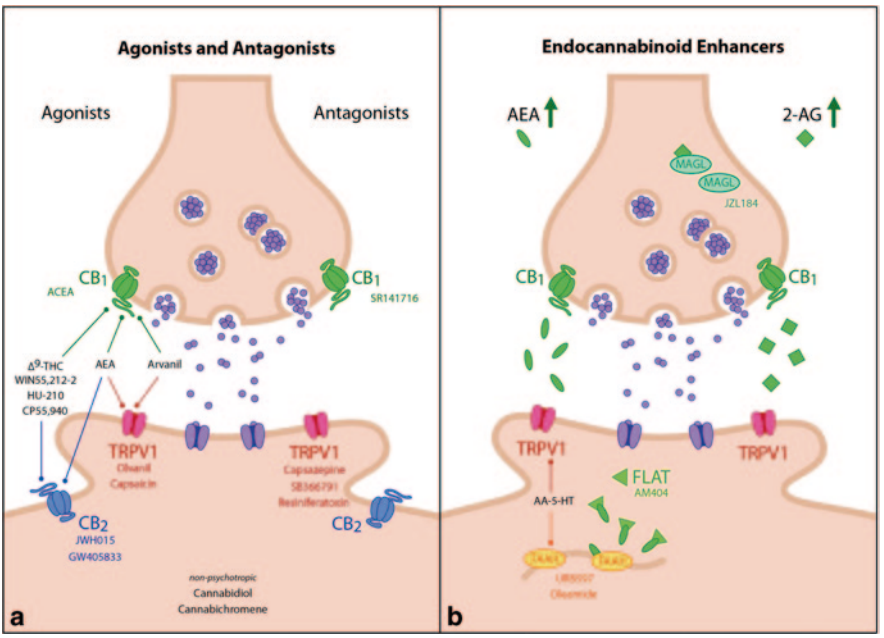

Fig. 5.1 Schematic illustration of the pharmacological modulation (i.e. agonists, antagonists and endocannabinoid enhancers) of the endocannabinoid system in preclinical studies of depression. For details about the different drugs see the main text and Table 5.4

behaviour have been obtained indicating that they could depend on specific deletion of CB1 receptors in some neuronal subpopulations [129, 152, 153]. However, compensatory mechanisms which develop in mutant mice could underlie the discrepancies between pharmacological and genetic inhibition of CB1 receptor signaling.

Although CB2 receptor ligands might be potentially safer due to the lack of psychoactive effects, controversial evidence concerning the effects of CB2 receptor signaling modulation on depressive-like behaviour has been recently described [23]. Thus, further clinical and preclinical investigations are required to define the role of CB2 receptors in the pathophysiology and treatment of depression. Despite the fact that vanilloid TRPV1 channels, due to their co-localization with CB1 receptors in several brain regions [154], seem to represent "the other side of the coin" in the regulation of anxiety, a similar function in depression is still ambiguous, since both TRPV1 agonists [155, 156] and pharmacological [155–158] or genetic TRPV1 blockade [159] elicited antidepressant-like effects. Thus, further studies are necessary to assess the role of TRPV1 channels as additional ECS "players" in mood regulation. Based on the assumption that direct activation of CB1 receptors elicited psychotropic side effects, several compounds have been developed that reinforce the effects of AEA and 2-AG by inhibiting their degradative enzymes FAAH and MAGL, or by blocking their cellular reuptake. Since CB1 receptors, FAAH and MAGL are not equally distributed in the brain; the indirect stimulation of CB1 receptors by endocannabinoid breakdown blockers could modulate the endocannabinoid signaling in selected brain areas which control mood [160].

Table 5.4 Schematic representation of the effects of the pharmacological modulation of the endocannabinoid system (ECS) in preclinical studies of depression

Drugs	Mechanism of action	Experimental model[a]	Animals	Behavioural response[a]	Positive control	References
Δ9-THC	Non selective CB1/CB2 receptor agonist	OBX	Sprague-Dawley rats	↓ locomotor activity	Fluoxetine	[98]
			Lister hooded rats	↓ locomotor activity	ND	[130]
		FST/TST	Swiss-DBA/2 mice	↓ immobility time	Fluoxetine, Desipramine	[127]
			Sprague-Dawley rats	↓ immobility time	Citalopram	[128]
			Bl6N mice	↓ immobility time	ND	[129]
AEA	Non selective CB1/CB2 receptor agonist	FST/TST/CMS	ICR mice	No effect on immobility time/↑ sucrose consumption	Clomipramine	[131]
		FST	Swiss mice	↓ immobility time	Fluoxetine	[132]
CP,55940	Non selective CB1/CB2 receptor agonist	FST	Wistar rats	↓ immobility time	ND	[133]
WIN55,212–2	Non selective CB1/CB2 receptor agonist	FST	Sprague-Dawley rats	↓ immobility time	Citalopram, Desipramine	[134]
		CMS	Sprague-Dawley rats	↓ immobility time/↑ extinction of avoidance behaviour/ No effect on sucrose consumption	ND	[135]
HU-210	Non selective CB1/CB2 receptor agonist	FST	Long-Evans rats	↓ immobility time	Desipramine	[136]
					ND	[137]
			Sprague-Dawley rats	↓ immobility time	ND	[138]
					Desipramine	[139]
Arachidonoyl 2'-chloro-ethylamide (ACEA)	Selective CB1 receptor agonist	FST	BALB/c mice	↓ immobility time	Fluoxetine	[140]
		CMS	Sprague-Dawley rats	↑ extinction of aversive memories	ND	[141]

Table 5.4 (continued)

Drugs	Mechanism of action	Experimental model[a]	Animals	Behavioural response[a]	Positive control	References
JWH015	Selective CB2 receptor agonist	CMS	BALB/c mice	↑ sucrose consumption	ND	[105]
GW405833	Selective CB2 receptor agonist	FST	Wistar rats	↓ immobility time	Desipramine	[224]
Olvanil	Selective TRPV1 agonist	FST/TST	ICR mice	↓ immobility time	ND	[156]
Capsaicin	Selective TRPV1 agonist	FST/TST	ICR mice	↓ immobility time	ND	[156]
			Swiss mice	↓ immobility time	Fluoxetine	[155]
Arvanil	Nonselective TRPV1/CB1 receptor agonist	FST/TST	ICR mice	↓ immobility time	ND	[156]
Rimonabant (SR141716)	Selective CB1 receptor antagonist/inverse agonist	FST	Swiss mice	↓ immobility time	ND	[148]
		CMS/FST	Wistar rats/BALB/c mice	↓ immobility time	Fluoxetine	[149]
		FST	Bl6 N mice	↓ immobility time	ND	[129]
					Desipramine	[150]
			ICR mice	↓ immobility time	Imipramine	[151]
		OBX	Lister hooded rats	↓ locomotor activity	ND	[130]
Capsazepine	selective TRPV1 antagonist	FST/TST	Swiss mice	↓ immobility time	Fluoxetine	[155]
Resiniferatoxin	selective TRPV1 antagonist	FST	Swiss mice	↓ immobility time (26 °C) ↑ immobility time (41 °C)	Amitriptyline, Ketamine	[157]
SB366791	selective TRPV1 antagonist	FST	Wistar rats	↓ immobility time in STR rats	Clomipramine	[158]

Table 5.4 (continued)

Drugs	Mechanism of action	Experimental model[a]	Animals	Behavioural response[a]	Positive control	References
URB597	FAAH inhibitor	FST	Long-Evans rats	↓ immobility time	ND	[161]
			Wistar rats	↓ immobility time	ND	[133]
			Swiss mice	↓ immobility time	Fluoxetine	[132]
			Sprague-Dawley rats	↓ immobility time	ND	[162]
		TST	Bl6J mice	↓ immobility time	Desipramine	[163]
		CMS	Wistar rats	↑ sucrose consumption	Imipramine	[97]
			ICR mice	↑ sucrose consumption	ND	[164]
Oleamide	FAAH inhibitor	FST	Long-Evans rats	↓ immobility time	Desipramine	[136]
			Albino mice	↓ immobility time	ND	[166]
AA-5-HT	FAAH inhibitor/TRPV1 antagonist	FST	Wistar rats	↓ immobility time in STR rats	Clomipramine	[158]
AM404	AEA uptake inhibitor	FST	Long-Evans rats	↓ immobility time	Desipramine	[136]
			Wistar rats	↓ immobility time	Imipramine	[133]
			Swiss mice	↓ immobility time	ND	[172]
			Swiss mice	↓ immobility time	Fluoxetine	[132]
JZL184	MAGL inhibitor	Chronic unpredictable mild stress	Bl6J mice	↑ sucrose consumption ↓ immobility time	ND	[176]
Cannabidiol	CB1-CB2 receptor antagonist/inverse agonist, 5-HT1 A receptor agonist, TRPV1 agonist, AEA uptake inhibitor, FAAH inhibitor	FST	Swiss mice	↓ immobility time	Fluoxetine, Desipramine	[127]
			Swiss mice	↓ immobility time	Imipramine	[180]
Cannabichromene	TRPV1 agonist, AEA uptake inhibitor	FST/TST	Swiss-DBA/2 mice	↓ immobility time	Fluoxetine, Desipramine	[127]

[a] *CMS* chronic mild stress, *FST* forced swim test, *ND* not determined, *OBX* bilateral olfactory bulbectomy, *TST* tail suspension test, *STR* stressed group

The FAAH inhibitor URB597 has shown CB1 receptor-mediated antidepressant-like effects by enhancing AEA signaling in several experimental models such as FST [132, 133, 161, 162], TST [163], CMS paradigm [97, 164], adolescent Δ9-THC exposure [146] and tail-pinch test [165]. Another FAAH inhibitor, oleamide, elicited antidepressant-like effects through a CB1 receptor-mediated mechanism [136, 166]. In agreement with the pharmacological approach, transgenic mice lacking FAAH, which exhibit more than 10-fold higher levels of AEA as compared to wild-type mice, have shown a less depressive-like phenotype [145].

A particularly innovative approach in the treatment of mood disorders could be the use of compounds with the capability to combine inhibition of AEA hydrolysis with antagonism of TRPV1 channels. One such dual FAAH/TRPV1 blocker is N-arachidonoyl-serotonin (AA-5-HT) [167, 168], which elicited anxiolytic- [169–171] and antidepressant-like activity [158], suggesting the potential therapeutic use of dual FAAH/TRPV1 inhibitors in stress-related disorders. A different strategy to enhance AEA signaling at the receptor is to block its uptake into pre- and/or post-synaptic terminals, thereby promoting the indirect activation of CB1 receptors. The prototypical endocannabinoid transport inhibitor AM404 has improved the behavioural performance of rodents in the FST, through a CB1 receptor-mediated mechanism [132, 133, 136, 172]. However, the exact mechanism of action of endocannabinoid uptake inhibitors as well as the molecular identity of the transporter itself still remains to be characterized. Therefore, further biomolecular studies will have to be performed in this direction.

Collectively, this evidence supports the clinical potential of endocannabinoid level modulators as new therapeutic tools for the treatment of mood disorders. Recent data have suggested that 2-AG could act in the brain modulating behavioural responses in stress-related conditions [173–175]. In this context the prototypical MAGL inhibitor JZL184, by inducing an 8-fold increase in 2-AG, but not AEA, brain content reversed the depressive-like behaviour via activation of both CB1 receptor and mTor signaling [176]. However, contrary to FAAH blockade, a potential drawback in the use of MAGL inhibitors could be the development of tetrad effects which are typical of CB1 receptor agonists [177] as well as of tolerance with chronic use [178, 179].

In conclusion, while endocannabinoids are rapidly metabolized in vivo, limiting the potential efficacy of their exogenous administration, the data described above supports more FAAH than MAGL as a potential therapeutic target for the identification of new pharmacotherapies for affective disorders [160]. In addition to the pharmacological modulation of the endocannabinoid signaling, a different approach to reduce the psychotropic side effects of Cannabis is the use of plant-derived cannabinoids with very weak or no psychotropic effects such as CBD, cannabichromene, cannabigerol, cannabidivarin and Δ9-Tetrahydrocannabinol, some of which show potential as therapeutic agents in preclinical models of CNS disorders [55]. Special emphasis is given to CBD, which exerts several positive pharmacological effects in preclinical and clinical studies to the point of making it a highly attractive therapeutic entity in several diseases. We still do not know the exact mechanism(s) of action underlying the mood-elevating effect of CBD, as it may act not only through

the ECS, but also by directly or indirectly activating the metabotropic receptors for 5-HT or adenosine or by targeting nuclear receptors of the PPAR family as well as modulating ion channels including TRPV1 [18]. Contrary to the extensive research done regarding the potential therapeutic effects of CBD in anxiety [23] or schizophrenia [24], only few studies have examined its antidepressant-like effects. In the FST, which represents a standard preclinical test to assess the effects of potential antidepressants, cannabichromene and CBD decreased the immobility time, the latter acting through a 5-HT1 A receptor–mediated mechanism [127, 180]. However, further studies are necessary to establish the efficacy and safety profile of phytocannabinoids for the treatment of stress-related disorders.

Endocannabinoid Signaling and Antidepressant-Like Effects: Potential Molecular Underpinning

As described above, based on the monoaminergic hypothesis of depression, the actual antidepressants act by enhancing the central 5-HTergic and/or NEergic neurotransmission through the inhibition of the synaptic re-uptake or enzymatic degradation, and the desensitization or sensitization of specific receptors [4]. Several lines of evidence suggest that modulation of endocannabinoid signaling could facilitate 5-HTergic neurotransmission through an enhancement of 5-HT neuronal activity, an increased 5-HT efflux or modulation of 5-HT receptors (i.e. 5-HT_{1A} and 5-$HT_{2A/C}$). Both direct and indirect activation of CB1 receptors (the latter acting through pharmacological or genetic inhibition of FAAH activity) increased firing activity of 5-HTergic neurons in the DRN [128, 134, 162, 181], and enhanced basal 5-HT efflux in several brain regions such as nucleus accumbens, striatum, hippocampus and PFC [181–183]. However, chronic exposure to the CB1 receptor agonist WIN55,212–2 during adolescence attenuated 5-HTergic activity and elicited a depressive-like phenotype in adulthood, further supporting the importance of adolescence as a highly sensitive developmental window within which the disruptive effects of cannabinoid exposure increase the risk for developing psychiatric disorders [145]. Interestingly, inhibition of CB1 receptor signaling induced a depressive-like phenotype in mice, which was mediated by an impairment of 5-HTergic neural activity [152, 153, 184–186], strenghening the role of the endocannabinoid tone in emotional behaviour through the modulation of the 5-HTergic neurotransmission. As described for conventional antidepressants, which induce a desensitization of the 5-$HT_{2A/C}$ autoreceptors and/or an enhancement of the tonic activity of 5-HT_{1A} receptors [187], the antidepressant-like effects elicited by cannabinoids could be due to changes in the expression and function of these receptors [128, 188]. However, further 5-HT receptor subtypes (i.e. 5-HT_3 or 5-HT_4) could also be involved in the emotional responses induced by the endocannabinoid tone modulation [189–192].

A dysregulation of NEergic system seems to be implicated in the pathophysiology of depression, as supported by the primary action of antidepressants to enhance central NEergic transmission. In this context, a strong interaction between

the endocannabinoid and NEergic systems could participate in the antidepressant effects of endocannabinoid signaling enhancement, based on the expression of CB1 receptors in the LC (the major NEergic nucleus). More specifically, CB1 receptor activation could directly or indirectly, by modulating inhibitory and/or excitatory inputs to LC, increase the firing activity of NEergic neurons and consequently the release of NE in the forebrain. This indicates the existence of a functional interaction between these two systems in the action of antidepressants [181, 193, 194]. However, *in vitro* studies have shown the capacity of cannabinoids to inhibit monoamine reuptake and metabolism, sharing some pharmacological properties with antidepressants [195–198].

Increasing evidence links stress to depression and antidepressant action, and suggests that stressors act by inducing a disruption in cellular mechanisms governing neuronal plasticity and disturbances in the hypothalamic-pituitary adrenal (HPA) axis [199, 200]. Hence, current and potential antidepressants exert neurotrophic activity, by increasing the hippocampal expression of factors such as cyclic adenosine monophosphate-response element binding protein (CREB) and BDNF, and also affect HPA axis hyperactivity [201–205]. The endogenous cannabinoids AEA and 2-AG [206] and the synthetic nonspecific cannabinoid CB1/CB2 receptor agonists HU-210 [137] or WIN55,212–2 [207, 208] stimulate neurogenesis, which is inhibited by pharmacological [151, 206] or genetic [209–212] CB1 receptor blockade. The enhanced AEA signaling also stimulates hippocampal cell proliferation, through a CB1 receptor-mediated mechanism [158, 213, 214]

Based on the recent detection of CB2 receptors in the brain [43], their potential mechanisms underlying emotional responses are under investigation. So far, it has been seen that pharmacological activation or genetic inactivation of CB2 receptors enhanced or reduced hippocampal neuronal plasticity, respectively [215, 216]. Similarly, the CMS procedure did not alter BDNF expression in mice overexpressing CB2 receptors [106], suggesting their potential protective role. On one hand the controversial *in vivo* data does not give us a coherent picture concerning the role of CB2 receptors in depression, on the other hand, however, the molecular data further strengthens the rationale for the development of selective CB2 receptor agonists as promising candidates to target neurogenesis, thus bypassing the undesired psychoactive effects of central CB1 receptor activation.

Taken together the data presented herein suggests that facilitation of the endocannabinoid signaling through CB1 and/or CB2 receptors activation seems to mimic the effects of current antidepressants on hippocampal neuroplasticity. The HPA axis acts as a neuroendocrine bridge, regulating the stress response by controlling the secretion of corticotrophin-releasing hormone, adrenocorticotropic and glucocorticoidhormones. Additionally, it is controlled by a negative feedback inhibition loop which involves mineralocorticoid and glucocorticoid receptors [217]. Depressive disorders are also characterized by an inability of glucocorticoids to bind their receptors, which in turn can lead to HPA axis hyperactivity and increased levels of circulating glucocorticoids. Treatment with the current antidepressants results in reduction of glucocorticoid release, suggesting that the attenuation of HPA axis hyper-responsivity could be one of the long-term adaptations in response to

antidepressants that contributes to their therapeutic efficacy [218]. Several evidence highlights the role of the endocannabinoid signaling to regulate the HPA axis both during basal conditions and after stress exposure [133, 219] (see also Chap. 1). While CB1 receptor activation inhibits HPA axis activity, as a part of the HPA axis negative feedback inhibition loop, impairment in the CB1 receptor signaling increases HPA axis activity under both basal conditions and following stress exposure [152, 220–222]. Collectively the data described above suggests that the antidepressant-like effects of different classes of cannabinoids may in part be due to molecular mechanisms which resemble the ones triggered by antidepressants.

Future Perspective and Conclusive Remarks

In conclusion, the current evidence suggests a strong link between ECS and depressive disorders. A deficiency in the endocannabinoid tone leads to a depressive-like phenotype in experimental animal models of depression (Table 5.3), which is in line with clinical findings where depressed patients have reduced levels of endogenous cannabinoids (Table 5.1). Hence, facilitation of the endocannabinoid signaling could be the target for developing potential new antidepressants. Supporting this hypothesis is preclinical data which has shown that elevated endocannabinoid signaling is able to produce behavioural and biochemical effects as the conventional antidepressant treatment (Table 5.4), and that many antidepressants alter endogenous cannabinoid tone (Table 5.2). However, whilst the direct activation of CB1 receptors is hampered by unwanted psychotropic effects, and the possibly safer direct modulation of CB2 receptors still lacks sufficient experimental evidence to justify its use, the indirect activation of cannabinoid receptors with agents that inhibit endocannabinoids deactivation has produced very promising results in experimental animal models of depression. Yet, this approach is not devoid of intrinsic problems, mostly due to the fact that endocannabinoid-deactivating proteins also recognize other non-endocannabinoid mediators as substrates which then activate different receptors—a property also shared to some extent by endocannabinoids like AEA and NADA. Thus, inhibition of enzymes like FAAH or of the putative endocannabinoid transporter might lead to the activation of these alternative receptors. This complication and the possible compensatory action of co-occurring deactivation routes and enzymes for endocannabinoids [223] may render this approach not sufficiently efficacious or safe. In view of these potential problems and of the fact that genetic studies have revealed a relationship between depression and polymorphisms of cannabinoid receptors and/or degradative enzymes, only time will tell if targeting the ECS may result in effective pharmacotherapies for major depression and other affective-related disorders.

Acknowledgments The research of the authors is supported by the project “CEITEC—Central European Institute of Technology” (CZ.1.05/1.1.00/02.0068) from European Regional Development Fund. We thank Caitlin Riebe (independent scientific illustrator, Vancouver, Canada) for the artwork and Vanessa Raileanu (Toronto, Canada) for the proof-reading.

References

1. Wittchen HU, Jacobi F, Rehm J, Gustavsson A, Svensson M, Jönsson B, Olesen J, Allgulander C, Alonso J, Faravelli C, Fratiglioni L, Jennum P, Lieb R, Maercker A, van Os J, Preisig M, Salvador-Carulla L, Simon R, Steinhausen H-C. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011;21(9):655–79.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 5th ed. A.P. Publishing: Arlington;2013.
3. Schildkraut JJ. The catecholamine hypothesis of affective disorders: a review of supporting evidence. Am J Psychiatry. 1965;122(5):509–22.
4. Li X, Frye MA, Shelton RC. Review of pharmacological treatment in mood disorders and future directions for drug development. Neuropsychopharmacology. 2012;37(1):77–101.
5. Han C, Wang S-M, Kato M, Lee S-J, Patkar AA, Masand PS, Pae C-U. Second-generation antipsychotics in the treatment of major depressive disorder: current evidence. Expert Rev Neurother. 2013;13(7):851–70.
6. Srinivasan V, De Berardis D, Shillcutt SD, Brzezinski A. Role of melatonin in mood disorders and the antidepressant effects of agomelatine. Expert Opin Investig Drugs. 2012;21(10):1503–22.
7. Krystal JH, Sanacora G, Duman RS. Rapid-acting glutamatergic antidepressants: the path to ketamine and beyond. Biol Psychiatry. 2013;73(12):1133–41.
8. Machado-Vieira R, Salvadore G, Diazgranados N, Zarate CA Jr. Ketamine and the next generation of antidepressants with a rapid onset of action. Pharmacol Ther. 2009;123(2):143–50.
9. Kehne JH, Cain CK. Therapeutic utility of non-peptidic CRF1 receptor antagonists in anxiety, depression, and stress-related disorders: evidence from animal models. Pharmacol Ther. 2010;128(3):460–87.
10. Wong EHF, Tarazi FI, Shahid M. The effectiveness of multi-target agents in schizophrenia and mood disorders: Relevance of receptor signature to clinical action. Pharmacol Ther. 2010;126(2):173–85.
11. Engin E, Liu J, Rudolph U. α2-containing GABA(A) receptors: a target for the development of novel treatment strategies for CNS disorders. Pharmacol Ther. 2012;136(2):142–52.
12. Connolly KR, Thase ME. Emerging drugs for major depressive disorder. Expert Opin Emerg Drugs. 2012;17(1):105–26.
13. Isbell H, Gorodetzsky CW, Jasinski D, Clausseln U, von Spulak F, Korte F. Effects of (—) delta-9-trans-tetrahydrocannabinol in man. Psychopharmacologia. 1967;11(2):184–8.
14. Luongo L, Maione S, Di Marzo V. Endocannabinoids and neuropathic pain: focus on neuron-glia and endocannabinoid-neurotrophin interactions. Eur J Neurosci. 2014;39(3):401–8.
15. Starowicz K, Makuch W, Korostynski M, Malek N, Slezak M, Zychowska M, Petrosino S, De Petrocellis L, Cristino L, Przewlocka B, Di Marzo V. Full inhibition of spinal FAAH leads to TRPV1-mediated analgesic effects in neuropathic rats and possible lipoxygenase-mediated remodeling of anandamide metabolism. PLoS ONE. 2013;8(4):e60040.
16. Di Marzo V. "De-liver-ance" from CB(1): a way to counteract insulin resistance? Gastroenterology. 2012;142(5):1063–6.
17. Silvestri C, Di Marzo V. The endocannabinoid system in energy homeostasis and the etiopathology of metabolic disorders. Cell Metab. 2013;17(4):475–90.
18. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther. 2010;126(1):21–38.
19. Silvestri C, Ligresti A, Di Marzo V. Peripheral effects of the endocannabinoid system in energy homeostasis: adipose tissue, liver and skeletal muscle. Rev Endocr Metab Disord. 2011;12(3):153–62.
20. Mazzola C, Micale V, Drago F. Amnesia induced by beta-amyloid fragments is counteracted by cannabinoid CB1 receptor blockade. Eur J Pharmacol. 2003;477(3):219–25.
21. Micale V, Mazzola C, Drago F. Endocannabinoids and neurodegenerative diseases. Pharmacol Res. 2007;56(5):382–92.

22. Micale V, Cristino L, Tamburella A, Petrosino S, Leggio GM, Di Marzo V, Drago F. Enhanced cognitive performance of dopamine D3 receptor "knock-out" mice in the step-through passive-avoidance test: assessing the role of the endocannabinoid/endovanilloid systems. Pharmacol Res. 2010;61(6):531–6.
23. Micale V, Di Marzo V, Sulcova A, Wotjak CT, Drago F. Endocannabinoid system and mood disorders: priming a target for new therapies. Pharmacol Ther. 2013;138(1):18–37.
24. Kucerova J, Tabiova K, Drago F, Micale V. Therapeutic potential of cannabinoids in schizophrenia. Recent Pat CNS Drug Discov. 2014;9(1):13–25.
25. Terzian ALB, Micale V, Wotjak CT. Cannabinoid receptor type 1 receptors on GABAergic vs. glutamatergic neurons differentially gate sex-dependent social interest in mice. Eur J Neurosci. 2014;40(1):2293–8.
26. Howlett AC, Bidaut-Russell M, Devane WA, Melvin LS, Johnson MR, Herkenham M. The cannabinoid receptor: biochemical, anatomical and behavioral characterization. Trends Neurosci. 1990;13(10):420–3.
27. Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature. 1990;346(6284):561–4.
28. Munro S, Thomas KL, Abu-Shaar M. Molecular characterization of a peripheral receptor for cannabinoids. Nature. 1993;365(6441):61–5.
29. Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, Gibson D, Mandelbaum A, Etinger A, Mechoulam R. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science. 1992;258(5090):1946–9.
30. Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, Gopher A, Almog S, Martin BR, Compton DR. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. Biochem Pharmacol. 1995;50(1):83–90.
31. Lovinger DM. Endocannabinoid liberation from neurons in transsynaptic signaling. J Mol Neurosci. 2007;33(1):87–93.
32. Marnett LJ. Decoding endocannabinoid signaling. Nat Chem Biol. 2009;5(1):8–9.
33. Di Marzo V Petrosino S. Endocannabinoids and the regulation of their levels in health and disease. Curr Opin Lipidol. 2007;18(2):129–40.
34. Liu J, Wang L, Harvey-White J, Huang BX, Kim H-Y, Luquet S, Palmiter RD, Krystal G, Rai R, Mahadevan A, Razdan RK, Kunos G. Multiple pathways involved in the biosynthesis of anandamide. Neuropharmacology. 2008;54(1):1–7.
35. Cravatt BF, Giang DK, Mayfield SP, Boger DL, Lerner RA, Gilula NB. Molecular characterization of an enzyme that degrades neuromodulatory fatty-acid amides. Nature. 1996;384(6604):83–7.
36. Dinh TP, Carpenter D, Leslie FM, Freund TF, Katona I, Sensi SL, Kathuria S, Piomelli D. Brain monoglyceride lipase participating in endocannabinoid inactivation. Proc Natl Acad Sci USA. 2002;99(16):10819–24.
37. Begg M, Pacher P, Bátkai S, Osei-Hyiaman D, Offertáler L, Mo FM, Liu J, Kunos G. Evidence for novel cannabinoid receptors. Pharmacol Ther. 2005;106(2):133–45.
38. Pertwee RG. Receptors and channels targeted by synthetic cannabinoid receptor agonists and antagonists. Curr Med Chem. 2010;17(14):1360–81.
39. Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol. 2005;(168):299–325.
40. Marsicano G, Lutz B. Expression of the cannabinoid receptor CB1 in distinct neuronal subpopulations in the adult mouse forebrain. Eur J Neurosci. 1999;11(12):4213–25.
41. Häring M, Marsicano G, Lutz B, Monory K. Identification of the cannabinoid receptor type 1 in serotonergic cells of raphe nuclei in mice. Neuroscience. 2007;146(3):1212–9.
42. Oropeza VC, Mackie K, Van Bockstaele EJ. Cannabinoid receptors are localized to noradrenergic axon terminals in the rat frontal cortex. Brain Res. 2007;1127(1):36–44.
43. Van Sickle MD Duncan M Kingsley PJ Mouihate A Urbani P Mackie K Stella N Makriyannis A Piomelli D Davison JS Marnett LJ Di Marzo V Pittman QJ Patel KD Sharkey KA. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005;310(5746):329–32.

44. Gong JP, Onaivi ES, Ishiguro H, Liu QR, Tagliaferro PA, Brusco A, Uhl GR. Cannabinoid CB2 receptors: immunohistochemical localization in rat brain. Brain Res. 2006;1071(1):10–23.
45. Marco EM, García-Gutiérrez MS, Bermúdez-Silva F-J, Moreira FA, Guimarães F, Manzanares J, Viveros M-P. Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects. Front Behav Neurosci. 2011;5:63.
46. Pacher P, Bátkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58(3):389–462.
47. Gaoni Y, Mechoulam R. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc. 1964;86(8):1646–7.
48. Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, Brandi I, Moriello AS, Davis JB, Mechoulam R, Di Marzo V. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. Br J Pharmacol. 2001;134(4):845–52.
49. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. Proc Natl Acad Sci USA. 2006;103(20):7895–900.
50. De Petrocellis L Ligresti A Moriello AS AllarÃ M Bisogno T Petrosino S Stott CG Di Marzo V. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. Br J Pharmacol. 2011;163(7):1479–94.
51. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005;30(8):1037–43.
52. Magen I, Avraham Y, Ackerman Z, Vorobiev L, Mechoulam R, Berry EM. Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation. J Hepatol. 2009;51(3):528–34.
53. Cascio MG, Gauson LA, Stevenson LA, Ross RA, Pertwee RG. Evidence that the plant cannabinoid cannabigerol is a highly potent alpha2-adrenoceptor agonist and moderately potent 5HT1 A receptor antagonist. Br J Pharmacol. 2010;159(1):129–41.
54. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30(10):515–27.
55. Hill AJ, Williams CM, Whalley BJ, Stephens GJ. Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacol Ther. 2012;133(1):79–97.
56. Ablon SL, Goodwin FK. High frequency of dysphoric reactions to tetrahydrocannabinol among depressed patients. Am J Psychiatry. 1974;131(4):448–53.
57. Kotin J, Post RM, Goodwin FK. 9-Tetrahydrocannabinol in depressed patients. Arch Gen Psychiatry. 1973;28(3):345–8.
58. Amchova P, Kucerova J, Giugliano V, Babinska Z, Zanda MT, Scherma M, Dusek L, Fadda P, Micale V, Sulcova A, Fratta W, Fattore L. Enhanced self-administration of the CB1 receptor agonist WIN55, 212–2 in olfactory bulbectomized rats: evaluation of possible serotonergic and dopaminergic underlying mechanisms. Front Pharmacol. 2014;5:44.
59. Patton GC, Coffey C, Carlin JB, Degenhardt L, Lynskey M, Hall W. Cannabis use and mental health in young people: cohort study. BMJ. 2002;325(7374):1195–8.
60. Arendt M, Rosenberg R, Fjordback L, Brandholdt J, Foldager L, Sher L, Munk-Jørgensen P. Testing the self-medication hypothesis of depression and aggression in cannabis-dependent subjects. Psychol Med. 2007;37(7):935–45.
61. Bovasso GB. Cannabis abuse as a risk factor for depressive symptoms. Am J Psychiatry. 2001;158(12):2033–7.
62. Rey JM, Sawyer MG, Raphael B, Patton GC, Lynskey M. Mental health of teenagers who use cannabis. Results of an Australian survey. Br J Psychiatry. 2002;180:216–21.
63. Degenhardt L, Hall W, Lynskey M. Exploring the association between cannabis use and depression. Addiction. 2003;98(11):1493–504.
64. Harder VS, Morral AR, Arkes J. Marijuana use and depression among adults: testing for causal associations. Addiction. 2006;101(10):1463–72.

65. Tziraki S. [Mental disorders and neuropsychological impairment related to chronic use of cannabis]. Rev Neurol. 2012;54(12):750–60.
66. Fu Q, Heath AC, Bucholz KK, Nelson E, Goldberg J, Lyons MJ, True WR, Jacob T, Tsuang MT, Eisen SA. Shared genetic risk of major depression, alcohol dependence, and marijuana dependence: contribution of antisocial personality disorder in men. Arch Gen Psychiatry. 2002;59(12):1125–32.
67. Lynskey MT, Heath AC, Nelson EC, Bucholz KK, Madden PAF, Slutske WS, Statham DJ, Martin NG. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. Psychol Med. 2002;32(2):195–207.
68. Lynskey MT, Glowinski AL, Todorov AA, Bucholz KK, Madden PAF, Nelson EC, Statham DJ, Martin NG, Heath AC. Major depressive disorder, suicidal ideation, and suicide attempt in twins discordant for cannabis dependence and early-onset cannabis use. Arch Gen Psychiatry. 2004;61(10):1026–32.
69. Farris SG, Zvolensky MJ, Boden MT, Bonn-Miller MO. Cannabis use expectancies mediate the relation between depressive symptoms and cannabis use among cannabis-dependent veterans. J Addict Med. 2014;8(2):130–6.
70. Parolaro D, Realini N, Vigano D, Guidali C, Rubino T. The endocannabinoid system and psychiatric disorders. Exp Neurol. 2010;224(1):3–14.
71. Hungund BL, Vinod KY, Kassir SA, Basavarajappa BS, Yalamanchili R, Cooper TB, Mann JJ, Arango V. Upregulation of CB1 receptors and agonist-stimulated [35S]GTPgammaS binding in the prefrontal cortex of depressed suicide victims. Mol Psychiatry. 2004;9(2):184–90.
72. Koethe D, Llenos IC, Dulay JR, Hoyer C, Torrey EF, Leweke FM, Weis S. Expression of CB1 cannabinoid receptor in the anterior cingulate cortex in schizophrenia, bipolar disorder, and major depression. J Neural Transm. 2007;114(8):1055–63.
73. Hill MN, Miller GE, Ho W-SV, Gorzalka BB, Hillard CJ. Serum endocannabinoid content is altered in females with depressive disorders: a preliminary report. Pharmacopsychiatry. 2008;41(2):48–53.
74. Hill MN, Miller GE, Carrier EJ, Gorzalka BB, Hillard CJ. Circulating endocannabinoids and N-acyl ethanolamines are differentially regulated in major depression and following exposure to social stress. Psychoneuroendocrinology. 2009;34(8):1257–62.
75. Vinod KY, Arango V, Xie S, Kassir SA, Mann JJ, Cooper TB, Hungund BL. Elevated levels of endocannabinoids and CB1 receptor-mediated G-protein signaling in the prefrontal cortex of alcoholic suicide victims. Biol Psychiatry. 2005;57(5):480–6.
76. Ho WS, Hill MN, Miller GE, Gorzalka BB, Hillard CJ. Serum contents of endocannabinoids are correlated with blood pressure in depressed women. Lipids Health Dis. 2012;11:32.
77. Heyman E, Gamelin F-X, Goekint M, Piscitelli F, Roelands B, Leclair E, Di Marzo V, Meeusen R. Intense exercise increases circulating endocannabinoid and BDNF levels in humans—possible implications for reward and depression. Psychoneuroendocrinology. 2012;37(6):844–51.
78. Duman RS, Monteggia LM. A neurotrophic model for stress-related mood disorders. Biol Psychiatry. 2006;59(12):1116–27.
79. Hill MN, Hillard CJ, Bambico FR, Patel S, Gorzalka BB, Gobbi G. The therapeutic potential of the endocannabinoid system for the development of a novel class of antidepressants. Trends Pharmacol Sci. 2009;30(9):484–93.
80. Moreira FA, Crippa JAS. The psychiatric side-effects of rimonabant. Rev Bras Psiquiatr. 2009;31(2):145–53.
81. Lazary J, Juhasz G, Hunyady L, Bagdy G. Personalized medicine can pave the way for the safe use of CBâ receptor antagonists. Trends Pharmacol Sci. 2011;32(5):270–80.
82. Levinson DF, Holmans P, Straub RE, Owen MJ, Wildenauer DB, Gejman PV, Pulver AE, Laurent C, Kendler KS, Walsh D, Norton N, Williams NM, Schwab SG, Lerer B, Mowry BJ, Sanders AR, Antonarakis SE, Blouin JL, DeLeuze JF, Mallet J. Multicenter linkage study of schizophrenia candidate regions on chromosomes 5q, 6q, 10p, and 13q: schizophrenia linkage collaborative group III. Am J Hum Genet. 2000;67(3):652–63.

83. Chen X, Williamson VS, An S-S, Hettema JM, Aggen SH, Neale MC, Kendler KS. Cannabinoid receptor 1 gene association with nicotine dependence. Arch Gen Psychiatry. 2008;65(7):816–24.
84. Chakrabarti B, Baron-Cohen S. Variation in the human cannabinoid receptor CNR1 gene modulates gaze duration for happy faces. Mol Autism. 2011;2(1):10.
85. Barrero FJ, Ampuero I, Morales B, Vives F, de Dios Luna Del Castillo J, Hoenicka J, García Yébenes J. Depression in Parkinson's disease is related to a genetic polymorphism of the cannabinoid receptor gene (CNR1). Pharmacogenomics J. 2005;5(2):135–41.
86. Domschke K, Dannlowski U, Ohrmann P, Lawford B, Bauer J, Kugel H, Heindel W, Young R, Morris P, Arolt V, Deckert J, Suslow T, Baune BT. Cannabinoid receptor 1 (CNR1) gene: impact on antidepressant treatment response and emotion processing in major depression. Eur Neuropsychopharmacol. 2008;18(10):751–9.
87. Juhasz G, Chase D, Pegg E, Downey D, Toth ZG, Stones K, Platt H, Mekli K, Payton A, Elliott R, Anderson IM, Deakin JFW. CNR1 gene is associated with high neuroticism and low agreeableness and interacts with recent negative life events to predict current depressive symptoms. Neuropsychopharmacology. 2009;34(8):2019–27.
88. Monteleone P, Bifulco M, Maina G, Tortorella A, Gazzerro P, Proto MC, Di Filippo C, Monteleone F, Canestrelli B, Buonerba G, Bogetto F, Maj M. Investigation of CNR1 and FAAH endocannabinoid gene polymorphisms in bipolar disorder and major depression. Pharmacol Res. 2010;61(5):400–4.
89. Lazary J, Lazary A, Gonda X, Benko A, Molnar E, Hunyady L, Juhasz G, Bagdy G. Promoter variants of the cannabinoid receptor 1 gene (CNR1) in interaction with 5-HTTLPR affect the anxious phenotype. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(8):1118–27.
90. Agrawal A, Nelson EC, Littlefield AK, Bucholz KK, Degenhardt L, Henders AK, Madden PAF, Martin NG, Montgomery GW, Pergadia ML, Sher KJ, Heath AC, Lynskey MT. Cannabinoid receptor genotype moderation of the effects of childhood physical abuse on anhedonia and depression. Arch Gen Psychiatry. 2012;69(7):732–40.
91. Mitjans M, Gastó C, Catalán R, Fañanás L, Arias B. Genetic variability in the endocannabinoid system and 12-week clinical response to citalopram treatment: the role of the CNR1, CNR2 and FAAH genes. J Psychopharmacol. 2012;26(10):1391–8.
92. Hill MN, Ho W-SV, Hillard CJ, Gorzalka BB. Differential effects of the antidepressants tranylcypromine and fluoxetine on limbic cannabinoid receptor binding and endocannabinoid contents. J Neural Transm. 2008;115(12):1673–9.
93. Mato S, Vidal R, Castro E, Díaz A, Pazos A, Valdizán EM. Long-term fluoxetine treatment modulates cannabinoid type 1 receptor-mediated inhibition of adenylyl cyclase in the rat prefrontal cortex through 5-hydroxytryptamine 1 A receptor-dependent mechanisms. Mol Pharmacol. 2010;77(3):424–34.
94. Hesketh SA, Brennan AK, Jessop DS, Finn DP. Effects of chronic treatment with citalopram on cannabinoid and opioid receptor-mediated G-protein coupling in discrete rat brain regions. Psychopharmacology (Berl). 2008;198(1):29–36.
95. Hill MN, Ho W-SV, Sinopoli KJ, Viau V, Hillard CJ, Gorzalka BB. Involvement of the endocannabinoid system in the ability of long-term tricyclic antidepressant treatment to suppress stress-induced activation of the hypothalamic-pituitary-adrenal axis. Neuropsychopharmacology. 2006;31(12):2591–9.
96. Hill MN, Carrier EJ, McLaughlin RJ, Morrish AC, Meier SE, Hillard CJ, Gorzalka BB. Regional alterations in the endocannabinoid system in an animal model of depression: effects of concurrent antidepressant treatment. J Neurochem. 2008;106(6):2322–36.
97. Bortolato M, Mangieri RA, Fu J, Kim JH, Arguello O, Duranti A, Tontini A, Mor M, Tarzia G, Piomelli D. Antidepressant-like activity of the fatty acid amide hydrolase inhibitor URB597 in a rat model of chronic mild stress. Biol Psychiatry. 2007;62(10):1103–10.
98. Rodríguez-Gaztelumendi A, Rojo ML, Pazos A, Díaz A. Altered CB receptor-signaling in prefrontal cortex from an animal model of depression is reversed by chronic fluoxetine. J Neurochem. 2009;108(6):1423–33.
99. Lee TTY, Hill MN. Age of stress exposure modulates the immediate and sustained effects of repeated stress on corticolimbic cannabinoid CBâ receptor binding in male rats. Neuroscience. 2013;249:106–14.

100. McLaughlin RJ, Hill MN, Dang SS, Wainwright SR, Galea LAM, Hillard CJ, Gorzalka BB. Upregulation of CBâ receptor binding in the ventromedial prefrontal cortex promotes proactive stress-coping strategies following chronic stress exposure. Behav Brain Res. 2013;237:333–7.
101. Hill MN, Patel S, Carrier EJ, Rademacher DJ, Ormerod BK, Hillard CJ, Gorzalka BB. Downregulation of endocannabinoid signaling in the hippocampus following chronic unpredictable stress. Neuropsychopharmacology. 2005;30(3):508–15.
102. Reich CG, Taylor ME, McCarthy MM. Differential effects of chronic unpredictable stress on hippocampal CB1 receptors in male and female rats. Behav Brain Res. 2009;203(2):264–9.
103. Wang H, Wang L, Zhang R, Chen Y, Liu L, Gao F, Nie H, Hou W, Peng Z, Tan Q. Antidepressive mechanism of repetitive transcranial magnetic stimulation in rat: the role of the endocannabinoid system. J Psychiatr Res. 2014;51:79–87.
104. Reich CG, Mihalik GR, Iskander AN, Seckler JC, Weiss MS. Adolescent chronic mild stress alters hippocampal CB1 receptor-mediated excitatory neurotransmission and plasticity. Neuroscience. 2013;253:444–54.
105. Onaivi ES, Ishiguro H, Gong JP, Patel S, Meozzi PA, Myers L, Perchuk A, Mora Z, Tagliaferro PA, Gardner E, Brusco A, Akinshola BE, Liu Q-R, Chirwa SS, Hope B, Lujilde J, Inada T, Iwasaki S, Macharia D, Teasenfitz L, Arinami T, Uhl GR. Functional expression of brain neuronal CB2 cannabinoid receptors are involved in the effects of drugs of abuse and in depression. Ann N Y Acad Sci. 2008;1139:434–49.
106. García-Gutiérrez MS, Pérez-Ortiz JM, Gutiérrez-Adán A, Manzanares J. Depression-resistant endophenotype in mice overexpressing cannabinoid CB(2) receptors. Br J Pharmacol. 2010;160(7):1773–84.
107. Zoppi S, Madrigal JL, Caso JR, García-Gutiérrez MS, Manzanares J, Leza JC, García-Bueno B. Regulatory role of the cannabinoid CB2 receptor in stress-induced neuroinflammation in mice. Br J Pharmacol. 2014;171(11):2814–26.
108. Patel S, Roelke CT, Rademacher DJ, Hillard CJ. Inhibition of restraint stress-induced neural and behavioural activation by endogenous cannabinoid signalling. Eur J Neurosci. 2005;21(4):1057–69.
109. Hill MN, McLaughlin RJ, Bingham B, Shrestha L, Lee TTY, Gray JM, Hillard CJ, Gorzalka BB, Viau V. Endogenous cannabinoid signaling is essential for stress adaptation. Proc Natl Acad Sci USA. 2010;107(20):9406–11.
110. Hill MN, Kumar SA, Filipski SB, Iverson M, Stuhr KL, Keith JM, Cravatt BF, Hillard CJ, Chattarji S, McEwen BS. Disruption of fatty acid amide hydrolase activity prevents the effects of chronic stress on anxiety and amygdalar microstructure. Mol Psychiatry. 2013;18(10):1125–35
111. Rademacher DJ, Meier SE, Shi L, Ho WV, Jarrahian A, Hillard CJ. Effects of acute and repeated restraint stress on endocannabinoid content in the amygdala, ventral striatum, and medial prefrontal cortex in mice. Neuropharmacology. 2008;54(1):108–16.
112. Patel S, Kingsley PJ, Mackie K, Marnett LJ, Winder DG. Repeated homotypic stress elevates 2-arachidonoylglycerol levels and enhances short-term endocannabinoid signaling at inhibitory synapses in basolateral amygdala. Neuropsychopharmacology. 2009;34(13):2699–709.
113. Millan MJ. Dual- and triple-acting agents for treating core and co-morbid symptoms of major depression: novel concepts, new drugs. Neurotherapeutics. 2009;6(1):53–77.
114. DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. J Health Econ. 2003;22(2):151–85.
115. Micale V, Kucerova J, Sulcova A. Leading compounds for the validation of animal models of psychopathology. Cell Tissue Res. 2013;354(1):309–30.
116. McKinney WT Jr, Bunney WE Jr. Animal model of depression. I. Review of evidence: implications for research. Arch Gen Psychiatry. 1969;21(2):240–8.
117. Nestler EJ, Gould E, Manji H, Buncan M, Duman RS, Greshenfeld HK, Hen R, Koester S, Lederhendler I, Meaney M, Robbins T, Winsky L, Zalcman S. Preclinical models: status of basic research in depression. Biol Psychiatry. 2002;52(6):503–28.

118. Porsolt RD, Le Pichon M, Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. Nature. 1977;266(5604):730–2.
119. Cryan JF, Valentino RJ, Lucki I. Assessing substrates underlying the behavioral effects of antidepressants using the modified rat forced swimming test. Neurosci Biobehav Rev. 2005;29(4–5):547–69.
120. Steru L, Chermat R, Thierry B, Simon P. The tail suspension test: a new method for screening antidepressants in mice. Psychopharmacology (Berl). 1985;85(3):367–70.
121. Cryan JF, Mombereau C, Vassout A. The tail suspension test as a model for assessing antidepressant activity: review of pharmacological and genetic studies in mice. Neurosci Biobehav Rev. 2005;29(4–5):571–625.
122. Berrocoso E, Ikeda K, Sora I, Uhl GR, Sánchez-Blázquez P, Mico JA. Active behaviours produced by antidepressants and opioids in the mouse tail suspension test. Int J Neuropsychopharmacol. 2013;16(1):151–62.
123. Willner P, Towell A, Sampson D, Sophokleous S, Muscat R. Reduction of sucrose preference by chronic unpredictable mild stress, and its restoration by a tricyclic antidepressant. Psychopharmacology (Berl). 1987;93(3):358–64.
124. Kelly JP, Wrynn AS, Leonard BE. The olfactory bulbectomized rat as a model of depression: an update. Pharmacol Ther. 1997;74(3):299–316.
125. Song C, Leonard BE. The olfactory bulbectomised rat as a model of depression. Neurosci Biobehav Rev. 2005;29(4–5):627–47.
126. Cryan JF, Markou A, Lucki I. Assessing antidepressant activity in rodents: recent developments and future needs. Trends Pharmacol Sci. 2002;23(5):238–45.
127. El-Alfy AT, Ivey K, Robinson K, Ahmed S, Radwan M, Slade D, Khan I, ElSohly M, Ross S. Antidepressant-like effect of delta9-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L. Pharmacol Biochem Behav. 2010;95(4):434–42.
128. Bambico FR, Hattan PR, Garant JP, Gobbi G. Effect of delta-9-tetrahydrocannabinol on behavioral despair and on pre- and postsynaptic serotonergic transmission. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38(1):88–96.
129. Häring M, Grieb M, Monory K, Lutz B, Moreira FA. Cannabinoid CBâ receptor in the modulation of stress coping behavior in mice: the role of serotonin and different forebrain neuronal subpopulations. Neuropharmacology. 2013;65:83–9.
130. Elbatsh MM, Moklas MAA, Marsden CA, Kendall DA. Antidepressant-like effects of Δ9-tetrahydrocannabinol and rimonabant in the olfactory bulbectomised rat model of depression. Pharmacol Biochem Behav. 2012;102(2):357–65.
131. Hayase T. Depression-related anhedonic behaviors caused by immobilization stress: a comparison with nicotine-induced depression-like behavioral alterations and effects of nicotine and/or “antidepressant” drugs. J Toxicol Sci. 2011;36(1):31–41.
132. Umathe SN, Manna SS, Jain NS. Involvement of endocannabinoids in antidepressant and anti-compulsive effect of fluoxetine in mice. Behav Brain Res. 2011;223(1):125–34.
133. Adamczyk P, Gołda A, McCreary AC, Filip M, Przegaliński E. Activation of endocannabinoid transmission induces antidepressant-like effects in rats. J Physiol Pharmacol. 2008;59(2):217–28.
134. Bambico FR, Katz N, Debonnel G, Gobbi G. Cannabinoids elicit antidepressant-like behavior and activate serotonergic neurons through the medial prefrontal cortex. J Neurosci. 2007;27(43):11700–11.
135. Segev A, Rubin AS, Abush H, Richter-Levin G, Akirav I. Cannabinoid receptor activation prevents the effects of chronic mild stress on emotional learning and LTP in a rat model of depression. Neuropsychopharmacology. 2014;39(4):919–33.
136. Hill MN, Gorzalka BB. Pharmacological enhancement of cannabinoid CB1 receptor activity elicits an antidepressant-like response in the rat forced swim test. Eur Neuropsychopharmacol. 2005;15(6):593–9.
137. Jiang W, Zhang Y, Xiao L, Van Cleemput J, Ji SP, Bai G, Zhang X. Cannabinoids promote embryonic and adult hippocampus neurogenesis and produce anxiolytic- and antidepressant-like effects. J Clin Invest. 2005;115(11):3104–16.

138. McLaughlin RJ, Hill MN, Morrish AC, Gorzalka BB. Local enhancement of cannabinoid CB1 receptor signalling in the dorsal hippocampus elicits an antidepressant-like effect. Behav Pharmacol. 2007;18(5–6):431–8.
139. Morrish AC, Hill MN, Riebe CJN, Gorzalka BB. Protracted cannabinoid administration elicits antidepressant behavioral responses in rats: role of gender and noradrenergic transmission. Physiol Behav. 2009 Aug 4;98(1–2):118–24.
140. Rutkowska M, Jachimczuk O. Antidepressant—like properties of ACEA (arachidonyl-2-chloroethylamide), the selective agonist of CB1 receptors. Acta Pol Pharm. 2004;61(2):165–7.
141. Reich CG, Iskander AN, Weiss MS. Cannabinoid modulation of chronic mild stress-induced selective enhancement of trace fear conditioning in adolescent rats. J Psychopharmacol. 2013;27(10):947–55.
142. Rubino T, Vigano' D, Realini N, Guidali C, Braida D, Capurro V, Castiglioni C, Cherubino F, Romualdi P, Candeletti S, Sala M, Parolaro D. Chronic delta9-tetrahydrocannabinol during adolescence provokes sex-dependent changes in the emotional profile in adult rats: behavioral and biochemical correlates. Neuropsychopharmacology. 2008;33(11):2760–71.
143. Rubino T, Realini N, Braida D, Alberio T, Capurro V, Viganò D, Guidali C, Sala M, Fasano M, Parolaro D. The depressive phenotype induced in adult female rats by adolescent exposure to THC is associated with cognitive impairment and altered neuroplasticity in the prefrontal cortex. Neurotox Res. 2009;15(4):291–302.
144. Rubino T, Zamberletti E, Parolaro D. Adolescent exposure to cannabis as a risk factor for psychiatric disorders. J Psychopharmacol. 2012;26(1):177–88.
145. Bambico FR, Nguyen N-T, Katz N, Gobbi G. Chronic exposure to cannabinoids during adolescence but not during adulthood impairs emotional behaviour and monoaminergic neurotransmission. Neurobiol Dis. 2010;37(3):641–55.
146. Realini N, Vigano' D, Guidali C, Zamberletti E, Rubino T, Parolaro D. Chronic URB597 treatment at adulthood reverted most depressive-like symptoms induced by adolescent exposure to THC in female rats. Neuropharmacology. 2011;60(2–3):235–43.
147. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rössner S, RIO-Europe Study Group. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet. 2005;365(9468):1389–97.
148. Tzavara ET, Davis RJ, Perry KW, Li X, Salhoff C, Bymaster FP, Witkin JM, Nomikos GG. The CB1 receptor antagonist SR141716 A selectively increases monoaminergic neurotransmission in the medial prefrontal cortex: implications for therapeutic actions. Br J Pharmacol. 2003;138(4):544–53.
149. Griebel G, Stemmelin J, Scatton B. Effects of the cannabinoid CB1 receptor antagonist rimonabant in models of emotional reactivity in rodents. Biol Psychiatry. 2005;57(3):261–7.
150. Steiner MA, Marsicano G, Nestler EJ, Holsboer F, Lutz B, Wotjak CT. Antidepressant-like behavioral effects of impaired cannabinoid receptor type 1 signaling coincide with exaggerated corticosterone secretion in mice. Psychoneuroendocrinology. 2008;33(1):54–67.
151. Lee S, Kim DH, Yoon SH, Ryu JH. Sub-chronic administration of rimonabant causes loss of antidepressive activity and decreases doublecortin immunoreactivity in the mouse hippocampus. Neurosci Lett. 2009;467(2):111–6.
152. Steiner MA, Marsicano G, Wotjak CT, Lutz B. Conditional cannabinoid receptor type 1 mutants reveal neuron subpopulation-specific effects on behavioral and neuroendocrine stress responses. Psychoneuroendocrinology. 2008;33(8):1165–70.
153. Steiner MA, Wanisch K, Monory K, Marsicano G, Borroni E, Bächli H, Holsboer F, Lutz B, Wotjak CT. Impaired cannabinoid receptor type 1 signaling interferes with stress-coping behavior in mice. Pharmacogenomics J. 2008;8(3):196–208.
154. Cristino L, de Petrocellis L, Pryce G, Baker D, Guglielmotti V, Di Marzo V. Immunohistochemical localization of cannabinoid type 1 and vanilloid transient receptor potential vanilloid type 1 receptors in the mouse brain. Neuroscience. 2006;139(4):1405–15.

155. Manna SS, Umathe SN. A possible participation of transient receptor potential vanilloid type 1 channels in the antidepressant effect of fluoxetine. Eur J Pharmacol. 2012;685 (1–3):81–90.
15. Hayase T. Differential effects of TRPV1 receptor ligands against nicotine-induced depression-like behaviors. BMC Pharmacol. 2011;11:6.
157. Abdelhamid RE, Kovács KJ, Nunez MG, Larson AA. Depressive behavior in the forced swim test can be induced by TRPV1 receptor activity and is dependent on NMDA receptors. Pharmacol Res. 2014;79:21–7.
158. Navarria A, Tamburella A, Iannotti FA, Micale V, Camillieri G, Gozzo L, Verde R, Imperatore R, Leggio GM, Drago F, Di Marzo V. The dual blocker of FAAH/TRPV1 N-arachidonoylserotonin reverses the behavioral despair induced by stress in rats and modulates the HPA-axis. Pharmacol Res. 2014;87:151–9.
159. You IJ, Jung YH, Kim MJ, Kwon SH, Hong SI, Lee SY, Jang CG. Alterations in the emotional and memory behavioral phenotypes of transient receptor potential vanilloid type 1-deficient mice are mediated by changes in expression of 5-HTâA, GABA(A), and NMDA receptors. Neuropharmacology. 2012;62(2):1034–43.
160. Petrosino S, Di Marzo V. FAAH and MAGL inhibitors: therapeutic opportunities from regulating endocannabinoid levels. Curr Opin Investig Drugs. 2010;11(1):51–62.
161. Hill MN, Karacabeyli ES, Gorzalka BB. Estrogen recruits the endocannabinoid system to modulate emotionality. Psychoneuroendocrinology. 2007;32(4):350–7.
162. McLaughlin RJ, Hill MN, Bambico FR, Stuhr KL, Gobbi G, Hillard CJ, Gorzalka BB. Prefrontal cortical anandamide signaling coordinates coping responses to stress through a serotonergic pathway. Eur Neuropsychopharmacol. 2012;22(9):664–71.
163. Naidu PS, Varvel SA, Ahn K, Cravatt BF, Martin BR, Lichtman AH. Evaluation of fatty acid amide hydrolase inhibition in murine models of emotionality. Psychopharmacology (Berl). 2007;192(1):61–70.
164. Rademacher DJ, Hillard CJ. Interactions between endocannabinoids and stress-induced decreased sensitivity to natural reward. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31(3):633–41.
165. Haller J, Goldberg SR, Pelczer KG, Aliczki M, Panlilio LV. The effects of anandamide signaling enhanced by the FAAH inhibitor URB597 on coping styles in rats. Psychopharmacology (Berl). 2013;230(3):353–62.
166. Akanmu MA, Adeosun SO, Ilesanmi OR. Neuropharmacological effects of oleamide in male and female mice. Behav Brain Res. 2007;182(1):88–94.
167. Bisogno T, Melck D, De Petrocellis L, Bobrov MYu, Gretskaya NM, Bezuglov VV, Sitachitta N, Gerwick WH, Di Marzo V. Arachidonoylserotonin and other novel inhibitors of fatty acid amide hydrolase. Biochem Biophys Res Commun. 1998;248(3):515–22.
168. Maione S, De Petrocellis L, de Novellis V, Moriello AS, Petrosino S, Palazzo E, Rossi FS, Woodward DF, Di Marzo V. Analgesic actions of N-arachidonoyl-serotonin, a fatty acid amide hydrolase inhibitor with antagonistic activity at vanilloid TRPV1 receptors. Br J Pharmacol. 2007;150(6):766–81.
169. Micale V, Cristino L, Tamburella A, Petrosino S, Leggio GM, Drago F, Di Marzo V. Anxiolytic effects in mice of a dual blocker of fatty acid amide hydrolase and transient receptor potential vanilloid type-1 channels. Neuropsychopharmacology. 2009;34(3):593–606.
170. Micale V, Cristino L, Tamburella A, Petrosino S, Leggio GM, Drago F, Di Marzo V. Altered responses of dopamine D3 receptor null mice to excitotoxic or anxiogenic stimuli: Possible involvement of the endocannabinoid and endovanilloid systems. Neurobiol Dis. 2009;36(1):70–80.
171. John CS, Currie PJ. N-arachidonoyl-serotonin in the basolateral amygdala increases anxiolytic behavior in the elevated plus maze. Behav Brain Res. 2012;233(2):382–8.
172. Mannucci C, Navarra M, Pieratti A, Russo GA, Caputi AP, Calapai G. Interactions between endocannabinoid and serotonergic systems in mood disorders caused by nicotine withdrawal. Nicotine Tob Res. 2011;13(4):239–47.

173. Sütt S, Raud S, Areda T, Reimets A, Kõks S, Vasar E. Cat odour-induced anxiety—a study of the involvement of the endocannabinoid system. Psychopharmacology. 2008;198(4):509–20.
174. Suárez J, Rivera P, Llorente R, Romero-Zerbo SY, Bermúdez-Silva FJ, de Fonseca FR, Viveros M-P. Early maternal deprivation induces changes on the expression of 2-AG biosynthesis and degradation enzymes in neonatal rat hippocampus. Brain Res. 2010;1349:162–73.
175. Eisenstein SA, Clapper JR, Holmes PV, Piomelli D, Hohmann AG. A role for 2-arachidonoylglycerol and endocannabinoid signaling in the locomotor response to novelty induced by olfactory bulbectomy. Pharmacol Res. 2010;61(5):419–29.
176. Zhong P, Wang W, Pan B, Liu X, Zhang Z, Long JZ, Zhang H, Cravatt BF, Liu Q. Monoacylglycerol lipase inhibition blocks chronic stress-induced depressive-like behaviors via activation of mTOR signaling. Neuropsychopharmacology. 2014;39(7):1763–76.
177. Long JZ, Li W, Booker L, Burston JJ, Kinsey SG, Schlosburg JE, Pavón FJ, Serrano AM, Selley DE, Parsons LH, Lichtman AH, Cravatt BF. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. Nat Chem Biol. 2009;5(1):37–44.
178. Schlosburg JE, Blankman JL, Long JZ, Nomura DK, Pan B, Kinsey SG, Nguyen PT, Ramesh D, Booker L, Burston JJ, Thomas EA, Selley DE, Sim-Selley LJ, Liu Q, Lichtman AH, Cravatt BF. Chronic monoacylglycerol lipase blockade causes functional antagonism of the endocannabinoid system. Nat Neurosci. 2010;13(9):1113–9.
179. Busquets-Garcia A, Puighermanal E, Pastor A, de la Torre R, Maldonado R, Ozaita A. Differential role of anandamide and 2-arachidonoylglycerol in memory and anxiety-like responses. Biol Psychiatry. 2011;70(5):479–86.
180. Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SRL. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1 A receptors. Br J Pharmacol. 2010;159(1):122–8.
181. Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, Cassano T, Morgese MG, Debonnel G, Duranti A, Tontini A, Tarzia G, Mor M, Trezza V, Goldberg SR, Cuomo V, Piomelli D. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. Proc Natl Acad Sci USA. 2005;102(51):18620–5.
182. Bambico FR, Duranti A, Tontini A, Tarzia G, Gobbi G. Endocannabinoids in the treatment of mood disorders: evidence from animal models. Curr Pharm Des. 2009;15(14):1623–46.
183. Cassano T, Gaetani S, Macheda T, Laconca L, Romano A, Morgese MG, Cimmino CS, Chiarotti F, Bambico FR, Gobbi G, Cuomo V, Piomelli D. Evaluation of the emotional phenotype and serotonergic neurotransmission of fatty acid amide hydrolase-deficient mice. Psychopharmacology (Berl). 2011;214(2):465–76.
184. Martin M, Ledent C, Parmentier M, Maldonado R, Valverde O. Involvement of CB1 cannabinoid receptors in emotional behaviour. Psychopharmacology (Berl). 2002;159(4):379–87.
185. Aso E, Renoir T, Mengod G, Ledent C, Hamon M, Maldonado R, Lanfumey L, Valverde O. Lack of CB1 receptor activity impairs serotonergic negative feedback. J Neurochem. 2009;109(3):935–44.
186. Burokas A, Martín-García E, Gutiérrez-Cuesta J, Rojas S, Herance JR, Gispert JD, Serra MÁ, Maldonado R. Relationships between serotonergic and cannabinoid system in depressive-like behavior: a PET study with [(11) C]-DASB. J Neurochem. 2014;130(1):126–35.
187. Mahar I, Bambico FR, Mechawar N, Nobrega JN. Stress, serotonin, and hippocampal neurogenesis in relation to depression and antidepressant effects. Neurosci Biobehav Rev. 2014;38:173–92.
188. Bambico FR, Nguyen NT, Gobbi G. Decline in serotonergic firing activity and desensitization of 5-HT1 A autoreceptors after chronic unpredictable stress. Eur Neuropsychopharmacol. 2009;19(3):215–28.

189. Höfelmann D, di Benedetto B, Azad SC, Micale V, Wotjak CT, Rammes G. Lack of interaction of endocannabinoids and 5-HT(3) neurotransmission in associative fear circuits of the amygdala: evidence from electrophysiological and behavioural experiments. Brain Res. 2013;1527:47–56.
190. Walstab J, Rappold G, Niesler B. 5-HT(3) receptors: role in disease and target of drugs. Pharmacol Ther. 2010;128(1):146–69.
191. Chegini HR, Nasehi M, Zarrindast MR. Differential role of the basolateral amygdala 5-HT3 and 5-HT4 serotonin receptors upon ACPA-induced anxiolytic-like behaviors and emotional memory deficit in mice. Behav Brain Res. 2014;261:114–26.
192. Xiong W, Koo B, Morton R, Zhang L. Psychotropic and nonpsychotropic cannabis derivatives inhibit human 5-HT(3A) receptors through a receptor desensitization-dependent mechanism. Neuroscience. 2011;184:28–37.
193. Muntoni AL, Pillolla G, Melis M, Perra S, Gessa GL, Pistis M. Cannabinoids modulate spontaneous neuronal activity and evoked inhibition of locus coeruleus noradrenergic neurons. Eur J Neurosci. 2006;23(9):2385–94.
194. Esteban S, García-Sevilla JA. Effects induced by cannabinoids on monoaminergic systems in the brain and their implications for psychiatric disorders. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38(1):78–87.
195. Steffens M, Feuerstein TJ. Receptor-independent depression of DA and 5-HT uptake by cannabinoids in rat neocortex—involvement of Na(+)/K(+)-ATPase. Neurochem Int. 2004;44(7):529–38.
196. Velenovská M, Fisar Z. Effect of cannabinoids on platelet serotonin uptake. Addict Biol. 2007;12(2):158–66.
197. Fisar Z, Hroudová J, Raboch J. Inhibition of monoamine oxidase activity by antidepressants and mood stabilizers. Neuro Endocrinol Lett. 2010;31(5):645–56.
198. Fišar Z. Cannabinoids and monoamine neurotransmission with focus on monoamine oxidase. Prog Neuropsychopharmacol Biol Psychiatry. 2012;38(1):68–77.
199. Kunugi H, Hori H, Adachi N, Numakawa T. Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression. Psychiatry Clin Neurosci. 2010;64(5):447–59.
200. Schmidt HD, Duman RS. The role of neurotrophic factors in adult hippocampal neurogenesis, antidepressant treatments and animal models of depressive-like behavior. Behav Pharmacol. 2007;18(5–6):391–418.
201. Pittenger C, Duman RS. Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology. 2008;33(1):88–109.
202. Grady MM, Stahl SM. Novel agents in development for the treatment of depression. CNS Spectr. 2013;18(Suppl 1):37–40.
203. Tamburella A, Micale V, Navarria A, Drago F. Antidepressant properties of the 5-HT4 receptor partial agonist, SL65.0155: behavioral and neurochemical studies in rats. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(7):1205–10.
204. Tamburella A, Micale V, Leggio GM, Drago F. The beta3 adrenoceptor agonist, amibegron (SR58611 A) counteracts stress-induced behavioral and neurochemical changes. Eur Neuropsychopharmacol. 2010;20(10):704–13.
205. Tamburella A, Leggio GM, Micale V, Navarria A, Bucolo C, Cicirata V, Drago F, Salomone S. Behavioural and neurochemical changes induced by stress-related conditions are counteracted by the neurokinin-2 receptor antagonist saredutant. Int J Neuropsychopharmacol. 2013;16(4):813–23.
206. Aguado T, Carracedo A, Julien B, Velasco G, Milman G, Mechoulam R, Alvarez L, Guzmán M, Galve-Roperh I. Cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis. J Biol Chem. 2007;282(9):6854–62.
207. Aguado T, Monory K, Palazuelos J, Stella N, Cravatt B, Lutz B, Marsicano G, Kokaia Z, Guzmán M, Galve-Roperh I. The endocannabinoid system drives neural progenitor proliferation. FASEB J. 2005;19(12):1704–6.

208. Marchalant Y, Brothers HM, Wenk GL. Cannabinoid agonist WIN-55,212–2 partially restores neurogenesis in the aged rat brain. Mol Psychiatry. 2009;14(12):1068–9.
209. Jin K, Xie L, Kim SH, Parmentier-Batteur S, Sun Y, Mao XO, Childs J, Greenberg DA. Defective adult neurogenesis in CB1 cannabinoid receptor knockout mice. Mol Pharmacol. 2004;66(2):204–8.
210. Kim SH, Won SJ, Mao XO, Jin K, Greenberg DA. Molecular mechanisms of cannabinoid protection from neuronal excitotoxicity. Mol Pharmacol. 2006;69(3):691–6.
211. Aso E, Ozaita A, Valdizán EM, Ledent C, Pazos A, Maldonado R, Valverde O. BDNF impairment in the hippocampus is related to enhanced despair behavior in CB1 knockout mice. J Neurochem. 2008;105(2):565–72.
212. Beyer CE, Dwyer JM, Piesla MJ, Platt BJ, Shen R, Rahman Z, Chan K, Manners MT, Samad TA, Kennedy JD, Bingham B, Whiteside GT. Depression-like phenotype following chronic CB1 receptor antagonism. Neurobiol Dis. 2010;39(2):148–55.
213. Derkinderen P, Valjent E, Toutant M, Corvol JC, Enslen H, Ledent C, Trzaskos J. Regulation of extracellular signal-regulated kinase by cannabinoids in hippocampus. J Neurosci. 2003;23(6):2371–82.
214. Ferreira-Vieira TH, Bastos CP, Pereira GS, Moreira FA, Massensini AR. A role for the endocannabinoid system in exercise-induced spatial memory enhancement in mice. Hippocampus. 2014;24(1):79–88.
215. García-Gutiérrez MS, Ortega-Álvaro A, Busquets-García A, Pérez-Ortiz JM, Caltana L, Ricatti MJ, Brusco A, Maldonado R, Manzanares J. Synaptic plasticity alterations associated with memory impairment induced by deletion of CB2 cannabinoid receptors. Neuropharmacology. 2013;73:388–96.
216. Avraham HK, Jiang S, Fu Y, Rockenstein E, Makriyannis A, Zvonok A, Masliah E, Avraham S. The cannabinoid CBâ receptor agonist AM1241 enhances neurogenesis in GFAP/Gp120 transgenic mice displaying deficits in neurogenesis. Br J Pharmacol. 2014;171(2):468–79.
217. De Kloet ER Sibug RM Helmerhorst FM Schmidt MV Schmidt M. Stress, genes and the mechanism of programming the brain for later life. Neurosci Biobehav Rev. 2005;29(2):271–81.
218. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31(9):464–8.
219. Riebe CJ, Wotjak CT. Endocannabinoids and stress. Stress. 2011;14(4):384–97.
220. Patel S, Roelke CT, Rademacher DJ, Cullinan WE, Hillard CJ. Endocannabinoid signaling negatively modulates stress-induced activation of the hypothalamic-pituitary-adrenal axis. Endocrinology. 2004;145(12):5431–8.
221. Hill MN, Tasker JG. Endocannabinoid signaling, glucocorticoid-mediated negative feedback, and regulation of the hypothalamic-pituitary-adrenal axis. Neuroscience. 2012;204:5–16.
222. Roberts CJ, Stuhr KL, Hutz MJ, Raff H, Hillard CJ. Endocannabinoid signaling in hypothalamic-pituitary-adrenocortical axis recovery following stress: effects of indirect agonists and comparison of male and female mice. Pharmacol Biochem Behav. 2014;117:17–24.
223. Piscitelli F, Di Marzo V. "Redundancy" of endocannabinoid inactivation: new challenges and opportunities for pain control. ACS Chem Neurosci. 2012;3(5):356–63.
224. Hu B, Doods H, Treede RD, Ceci A. Depression-like behaviour in rats with mononeuropathy is reduced by the CB2-selective agonist GW405833. Pain. 2009;143(3):206–12.