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Endocannabinoid system and mood disorders: Priming a target for new therapies

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ABSTRACT

The endocannabinoid system (ECS), comprising two G protein-coupled receptors (the cannabinoid receptors 1 and 2 [CB1 and CB2] for marijuana's psychoactive principle Δ^9-tetrahydrocannabinol [Δ^9-THC]), their endogenous small lipid ligands (namely anandamide [AEA] and 2-arachidonoylglycerol [2-AG], also known as endocannabinoids), and the proteins for endocannabinoid biosynthesis and degradation, has been suggested as a pro-homeostatic and pleiotropic signaling system activated in a time- and tissue-specific way during physiopathological conditions. In the brain activation of this system modulates the release of excitatory and inhibitory neurotransmitters and of cytokines from glial cells. As such, the ECS is strongly involved in neuropsychiatric disorders, particularly in affective disturbances such as anxiety and depression. It has been proposed that synthetic molecules that inhibit endocannabinoid degradation can exploit the selectivity of endocannabinoid action, thus activating cannabinoid receptors only in those tissues where there is perturbed endocannabinoid turnover due to the disorder, and avoiding the potential side effects of direct CB1 and CB2 activation. However, the realization that endocannabinoids, and AEA in particular, also act at other molecular targets, and that these mediators can be deactivated by redundant pathways, has recently led to question the efficacy of such approach, thus opening the way to new multi-target therapeutic strategies, and to the use of non-psychotropic cannabinoids, such as cannabidiol (CBD), which act via several parallel mechanisms, including indirect interactions with the ECS. The state of the art of the possible therapeutic use of endocannabinoid deactivation inhibitors and phytocannabinoids in mood disorders is discussed in this review article.

Abbreviations: 5-HT, 5-Hydroxytryptamine or serotonin; AA-5-HT, N-arachidonoyl-serotonin; ACEA, arachidonoyl 2′-chloroethylamide; AEA, N-arachidonoylethanolamine; 2-AG, 2-arachidonoylglycerol; AM251, *N*-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide; AM281, 1-(2,4-dichlorophenyl)-5-(4-iodophenyl)-4-methyl-*N*-4-morpholinyl-1*H*-pyrazole-3-carboxamide; AM404, *N*-(4-hydroxyphenyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide; AM630, [6-iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1*H*-indol-3-yl](4-methoxyphenyl) methanone (6-iodopravadoline); AM3506, 5-(4-hydroxyphenyl)pentanesulfonyl fluoride; AM4113, N-piperidin-1-yl-2,4-dichlorophenyl-1H-pyrazole-3-carboxamide; AMY, amygdala; Bl6, C57Bl6; BLA, basolateral amygdala; BNST, bed nucleus of the stria terminalis; CBC, cannabichromene; CBD, cannabidiol; CBG, cannabigerol; CBDV, cannabidivarin; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; CDP, chlordiazepoxide; CIT, citalopram; CNR1, human CB1 receptor gene; CNS, central nervous system; CMS, chronic mild stress; CP55940, (-)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol; CREM, cremophor; dlPAG, dorsolateral periaqueductal gray; DMI, desipramine; DMSO, dimethylsulfoxide; DW, distilled water; DZP, diazepam; EPM, elevated plus-maze; ECS, endocannabinoid system; ETOH, ethanol; FAAH, fatty acid amide hydrolase; FC, fear conditioning task; FLU, fluoxetine; FST, forced swim test; GABA, γ-aminobutyric acid; HPβCD, hydroxypropyl-β-cyclodextrin; HU-210, (6a*R*)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy- 6,6-dimethyl-6*H*-dibenzo[*b*,*d*]pyran-9-methanol; I.C.V., intracerebroventricular route of administration; IMI, imipramine; I.P., intraperitoneal route of administration; JWH-015, (2-methyl-1-propyl-1*H*-indol-3-yl)-1-naphthalenylmethanone; JWH-133, (6a*R*,10a*R*)-3-(1,1-dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6*H*-dibenzo[*b*,*d*]pyran; JZL184, 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate; KO, knock-out mice; LD, light-dark avoidance task; LE, long evans; MAGL, monoacylglycerol lipase; MAOI, monoamine oxidase inhibitor; MBB, marble burying behavior; MDZ, midazolam; NADA, N-arachidonoyl-dopamine; NE, noradrenalin; NRI, norepinheprine reuptake inhibitor; NST, non-stressed group; OBX, olfactory bulbectomy; OEA, oleoylethanolamide; PAR, paroxetine; PEA, palmitoylethanolamide; PEG, polyethyleneglycol; PFC, prefrontal cortex; PND, postnatal day; P.O., *per os* route of administration; PPAR, peroxisome proliferator-activated receptor; SAL, saline; S.C., subcutaneous route of administration; SD, sprague dawley; SNRI, serotonin norepinheprine reuptake inhibitor; SPT, sucrose preference test; SSRI, selective serotonin reuptake inhibitor; SR144528, *N*-((1*S*)-endo-1,3,3-trimethyl bicyclo heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide); STR, stressed group; Tw80, tween 80; TCA, tricyclic antidepressant; Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; TRPV1, transient receptor potential vanilloid 1 channel; TST, tail suspension test; URB597, cyclohexylcarbamic acid 3_-carbamoyl-biphenyl-3-yl ester; vHPC, ventral hippocampus; vmPFC, ventromedial prefrontal cortex; WIN55,212-2, [3H]norepinephrine,(R)-(þ)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo [1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanonemesylate; WT, wild type mice.

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Contents

1. Introduction

1.1. Current pharmacological approach for the treatment of the major mood disorders

The two major mood disorders such as depression and anxiety are the most prevalent forms of mental illness with 17% lifetime prevalence, resulting in enormous personal suffering, as well as social and economic burden (Lopez & Murray, 1998; Kessler et al., 2005; Wittchen et al., 2010). The major depressive disorder is characterized by episodes of depressed mood lasting for more than 2 weeks often associated with feelings of guilt, low-self esteem and worthlessness and high anxiety. It is also accompanied by additional symptoms including disturbed sleep and appetite, impairment in memory and suicidal thoughts (American Psychiatric Association, 2000). The treatment of depression was revolutionized more than 50 years ago with the discovery—by serendipity—that pharmacological agents such as the tricyclic antidepressants "TCAs" and the monoamine oxidase inhibitors "MAOIs", by enhancing the synaptic levels of monoamines, improved the symptoms of depression, leading to the *monoamine hypothesis of depression* (Schildkraut, 1965). Thus, the introduction of antidepressant drugs had a profound impact on the way depression is viewed: if chemicals can reverse most of depressive symptomatology, then depression itself may be due to chemical abnormalities in the brain. However, due to their toxic and poorly tolerated profile, first generation antidepressants were largely replaced by the selective serotonin reuptake inhibitors (SSRIs), norepinheprine reuptake inhibitors (NRIs) and serotonin norepinheprine reuptake inhibitors (SNRIs) and by atypical antidepressants (i.e. mirtazapine and nefazodone), which show an improved side effects profile but are not more effective than TCAs or MAOIs (Li et al., 2012). Recently, some atypical antipsychotics such as quetiapine, olanzapine or aripiprazole, used either as monotherapy or in combination with sertraline or venlafaxine have also shown efficacy at ameliorating symptoms of bipolar depression and treatment-resistant major depression and received FDA approval for these indications (Kupfer et al., 2012). Since a dysregulation of circadian rhythm has been recognized as a major contributor or a sequel of mood disturbance, agomelatine, a melatonergic agonist and a 5-HT_{2C} antagonist elicited antidepressant activity with a relatively mild side-effect profile, representing a new concept for the treatment of mood disorders (Sansone & Sansone, 2011).

However, the past decade has witnessed a driven focus on the rational discovery of highly selective drugs, acting at innovative non monoaminergic targets such as glutamatergic and GABAergic neurotransmission, neuropetide signalling or neuroendocrine system, which in turn, could affect intracellular signal transduction pathways; but—except for the NMDA receptor antagonist ketamine (Duman & Aghajanian, 2012)—none of these drug has reached the market (Machado-Vieira et al., 2009; Kehne & Cain, 2010; Wong et al., 2010; Engin et al., 2012). Thus, the dominant model of depression is still the monoamine model, which alterations are the primary target for current antidepressant medications. Although today's treatments are generally safe and effective, 30% of depressed patients treated with antidepressants available already on the market are resistant to these drugs. In addition, it is necessary to administer these drugs for weeks or months to see clinical benefit (Connolly & Thase, 2012). Therefore, there is still a great need for faster acting, safer and more effective treatments for depressive disorders.

The anxiety disorders, including panic disorder, social anxiety disorder, generalized anxiety disorder, obsessive–compulsive disorder and post-traumatic stress disorder, share the features of apprehension about future events (associated with symptoms of anxiety) and avoidance behavior (American Psychiatric Association, 2000). With the introduction of chlordiazepoxide as a psychotherapeutic agent in 1960 (Tobin & Lewis, 1960), benzodiazepines, which act to enhance the actions of γ-aminobutyric acid (GABA) neurotransmission, replaced barbiturates and became the mainstay of pharmacotherapy for anxiety disorders. In the late 80s buspirone emerged as the first non-benzodiazepine anxiolytic drug approved for the treatment of generalized anxiety disorder. However, buspirone did not replace the use of benzodiazepines in the clinical management of anxiety, partly because of ongoing concerns about its efficacy (Rickels et al., 1982). An important development in the pharmacotherapy of anxiety disorders was the introduction of antidepressant treatment, which was based on the recognition that a degree of neurobiological commonality exists between depressive and anxiety disorders, as implied by their high degree of co-occurrence (Morilak & Frazer, 2004). Actually, several guidelines argue that SSRIs or SNRIs are first-line pharmacotherapy for a number of anxiety disorders (Baldwin et al., 2012). Although benzodiazepines, SSRIs, and SNRIs are often effective, it is clear there is a need for improvement in the development of rapidly acting, better tolerated medications with a greater and more sustained response.

Therefore, the comorbidity and symptomatic overlap between depressive and anxiety disorders, along with the partial efficacy of actual pharmacological armamentarium, raises the central question to be addressed in this review: Should the pharmacological exploitation of the endocannabinoid system (ECS) be a promising future option to treat the behavioral dimensions which are dysregulated in both depressive and anxiety disorders, and account for the high degree of comorbidity and overlapping symptomatology between these two affective disorders?

1.2. Cannabis and mental illness: clinical evidence on depression and anxiety

Cannabis (or marijuana) is the most frequently abused illicit "recreational" substance in the Western society, its popularity being due to its capacity to alter sensory perception, to induce euphoria and to increase sociability. Although the association between *Cannabis sativa* and psychopathologic conditions has been known for thousands of years before the Christian era, 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 has triggered an exponential growth of studies to explore its real effects on mental health (Pacher et al., 2006). The *Cannabis* plant contains over 100 terpenophenolic pharmacologically active compounds, known as cannabinoids. Of these, Δ-9-tetrahydrocannabinol (Δ^9-THC), characterized in 1964 (Gaoni & Mechoulam, 1964), was identified as the main psychoactive component of *Cannabis*, and later shown to act as a direct agonist of cannabinoid CB1 and CB2 receptors. Other cannabinoids

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