Progress in Neuro-Psychopharmacology & Biological Psychiatry 38 (2012) 88–96

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Effect of delta-9-tetrahydrocannabinol on behavioral despair and on pre- and postsynaptic serotonergic transmission

Francis Rodriguez Bambico, Patrick R. Hattan, Jean-Philippe Garant, Gabriella Gobbi *

Neurobiological Psychiatry Unit, Dept. Psychiatry, McGill University, Montréal, Québec, Canada

ARTICLE INFO

Article history:
Received 9 November 2011
Received in revised form 2 February 2012
Accepted 13 February 2012
Available online 22 February 2012

Keywords:
Behavioral despair
Cannabinoids
CB_1 receptor
Delta-9-THC
Serotonin

ABSTRACT

Preclinical and clinical studies suggest that direct and indirect cannabinoid agonists, including enhancers of endocannabinoids, engender stress-relieving, anxiolytic and antidepressant effects, mediated by central CB_1 receptors (CB_1Rs). The effect of the main pharmacologically active principle in cannabis, (−)-trans-Δ^9-tetrahydrocannabinol (delta-9-THC), on depressive behavior and on the serotonin (5-HT) system, which is implicated in the mechanism of action of antidepressants, has not been extensively clarified. Here, we showed that repeated (5 days), but not single (acute) intraperitoneal (ip) treatment with delta-9-THC (1 mg/kg) exerts antidepressant-like properties in the rat forced swim test (FST). This effect was CB_1R-dependent because it was blocked by the CB_1R antagonist rimonabant (1 mg/kg, ip). Using in vivo electrophysiology, we demonstrated that delta-9-THC modulated dorsal raphe (DR) 5-HT neuronal activity through a CB_1R-dependent mechanism. Acute intravenous delta-9-THC administration (0.1–1.5 mg/kg) elicited a complex response profile, producing excitatory, inhibitory and inert responses of 5-HT neurons. Only excitatory responses were blocked by rimonabant. Finally, repeated but not single delta-9-THC administration (1 mg/kg, ip) enhanced tonic 5-HT_{1A} receptor activity in the hippocampus, a postsynaptic event commonly elicited by standard antidepressants. These results suggest that delta-9-THC, like other CB_1R agonists and endocannabinoid enhancers, may possess antidepressant properties at low doses, and could modulate 5-HT transmission in the DR and hippocampus as standard antidepressants such as selective serotonin reuptake inhibitors.

1. Introduction

Major depression is one of the most prevalent and debilitating psychiatric afflictions. It is characterized by pervasive and recurrent episodes of low mood and motivation, despair and anhedonia. Despite the availability of several classes of antidepressants, more than a third of patients are either unremitting or relapsing (Bambico and Gobbi, 2008; Zisook et al., 2008). Antidepressants that are known to act on the brain's monoamine systems are limited by a delayed onset of therapeutic action. Moreover, the pathophysiology of depression is far from being fully elucidated. Multiple levels of dysfunction have been proposed, including impaired synaptic transmission of the monoamine 5-hydroxytryptamine (5-HT or serotonin) (Bambico et al., 2009a), which is produced by the midbrain raphe 5-HT neurons (Dahlström and Fuxe, 1964; Descarries et al., 1982), and known to regulate emotional, vegetative and neuroendocrine functions (Holmes, 2008). Not surprisingly, drugs that augment 5-HT transmission, such as selective serotonin reuptake inhibitors (SSRIs), are most preferred first-line treatments (Vaswani et al., 2003). Their chronic application facilitates exocytosis of 5-HT and/or increases 5-HT synaptic availability in corticolimbic regions extensively innervated by the raphe. Many of these forebrain structures, including the prefrontal cortex, hippocampus and amygdala are implicated in mood regulation and stress adaptation (Holmes, 2008). On the other hand, chronic stress that is known to be a risk factor for depression impairs presynaptic and postsynaptic 5-HT transmission (Bambico et al., 2009b). Also, acute or repeated 5-HT or tryptophan depletion precipitates anxiety/depression-like behaviors in animals (Blokland et al., 2002) and mood-lowering effects in humans (for review, Young and Leyton, 2002), exacerbates anxiogenic responses in human subjects (Miller et al., 2000), and triggers relapse in depressive patients (for review, Van der Does, 2001).

The role of the 5-HT_{1A} receptor in the antidepressant response is well established. The therapeutic onset of many antidepressants has been attributed to gradual neuroplastic adaptations of these receptors, such as to the desensitization of presynaptic dorsal raphe (DR) 5-HT_{1A} auto-inhibitory receptors and to the enhancement of the tonic activity of postsynaptic hippocampal 5-HT_{1A} receptors (for review, Bambico and Gobbi, 2008; Bambico et al., 2009a). Such has been hypothesized to result from the progressive augmentation in 5-HT activity, and that could be linked to the neurogenic effects on hippocampal cells,

Abbreviations: 5-HT, 5-hydroxytryptamine, serotonin; CB1R, cannabinoid CB1 receptor; Delta-9-THC, (-)-trans-delta(9)-tetrahydrocannabinol; DR, dorsal raphe; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; FST, forced swim test; OFT, open field test; WAY100, 635, N-[2-[4-(2-methoxyphenyl-1-piperazinyl] ethyl]-N-(2-pyridyl)cyclohexanecarboxamide.

* Corresponding author at: 1033 Pine Avenue West, Neurobiological Psychiatry Unit, Department of Psychiatry Research and Training Building, McGill University, Montréal, Québec, Canada H3A 1A1. Tel.: +1 514 398 1290; fax: +1 514 398 4866.
E-mail address: gabriella.gobbi@mcgill.ca (G. Gobbi).

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doi:10.1016/j.pnpbp.2012.02.006

observed after chronic antidepressant treatment. In addition to 5-HT-specific modes of action, agents that enhance the transmission of norepinephrine (NE) have also been shown effective in alleviating depressive symptoms, likely due to the interplay of 5-HT and NE neurotransmission in correcting or in compensating for deficiencies produced by the disease (for review, Bambico and Gobbi, 2008).

The main pharmacologically active cannabinoid principle in cannabis, (−)-trans-Δ^9-tetrahydrocannabinal (delta-9-THC), likely mediates most of its psychoactive and mood-related effects (Huestis et al., 2001). This is known to be achieved by activation of cannabinoid CB_1 receptors (CB_1R), one of two well-characterized, and the most abundant G-protein coupled receptor in the mammalian brain. Although heavy or high-dose cannabis use has been associated with escalated risks for mood disorders, anxiety, psychosis and cognitive impairment, especially among teen-agers, its continued use for self-medicating depressive symptoms suggests possible therapeutic benefits in primary and secondary depression (for review, Bambico and Gobbi, 2008).

Recently, the lipid endocannabinoid molecules N-arachidonoylethanolamide (anandamide) and 2-arachidonoylglycerol (2-AG)- along with their native receptor, the CB_1R; and their catabolic enzymes, fatty acid amide hydrolase (FAAH) mainly for anandamide, and monoacylglycerol lipase (MAGL) mainly for 2-AG- have been found to be present in 5-HT neurons in the DR (Egertova et al., 1998; Häring et al., 2007; Moldrich and Wenger, 2000). In addition to their localization in monoaminergic neurons, these endocannabinoid elements are also expressed in excitatory (glutamatergic) and inhibitory (GABAergic) neurons throughout the cerebral cortex (for review, Esteban and Garcia-Sevilla, 2011). CB_1R signaling in the DR 5-HT system has been shown to modulate 5-HT transmission. Direct CB_1R agonists modulate DR 5-HT neural firing in brain slices (Mendiguren and Pineda, 2009) and in a bidirectional manner in vivo (Bambico et al., 2007), inhibit 5-HT reuptake ex vivo (Johnson et al., 1976; Steffens and Feuerstein, 2004) and decrease 5-HT synthesis in vivo (Moranta et al., 2004). Pharmacological or genetic deactivation of FAAH also stimulates DR 5-HT neural firing likely by increasing endocannabinoid-CB_1R signaling (Bambico et al., 2010a; Gobbi et al., 2005). Interestingly, repeated CB_1R activation does not seem to induce tolerance to its modulatory action on monoamine neurons, including 5-HT activity, in contrast to its many other cannabimimetic effects (Esteban and García-Sevilla, 2011). This could be related to progressive modifications in the function of monoamine-regulating presynaptic or postsynaptic receptors, such as $5\text{-}HT_{1A}$ (upregulated) and α_2-adrenoceptors (downregulated) (Esteban and García-Sevilla, 2011).

Consistent with these 5-HT-augmenting mechanisms, synthetic cannabinoid agonists (Bambico et al., 2007) and endocannabinoid enhancement through FAAH inhibition (Gobbi et al., 2005) elicit antidepressant and anxiolytic effects detected in a wide range of behavioral tests and animal models (Bambico and Gobbi, 2008; Bambico et al., 2009a). Since few studies have been undertaken to test the antidepressant-like property of the phytocannabinoid delta-9-THC and its effect on 5-HT neurotransmission, here we examined the effects of single and repeated delta-9-THC administration on behavioral despair in the forced swim test (FST). We then examined whether this would be paralleled by neurobiological adaptations known to be associated with antidepressant activity, including the modulation of 5-HT neural firing activity in the DR and enhanced tonic hippocampal $5\text{-}HT_{1A}$ receptor activity, a common neurobiological hallmark of antidepressant treatments (Haddjeri et al., 1998).

2. Materials and methods

2.1. Maintenance and preparation of animals

The experiments were mainly carried out on male adult Sprague–Dawley rats (Charles Rivers, Ste. Constant, Quebec, Canada) weighing approximately 300 g. All animals were kept in pairs or trios in standard polycarbonate cages and maintained under standard conditions (12:12 light–dark cycle, lights on at 07:30; temperature at 20 ± 2 °C; 50–60% relative humidity, ad libitum access to food and water). All experiments were initiated after 1 week of acclimatization, and a 30–60 minute habituation to the testing laboratory was observed prior to each experimental run. All procedures were undertaken in compliance to the standards and ethical guidelines mandated by the Canadian Institutes of Health Research and the Canadian Council on Animal Care.

2.2. Drugs

The dose of delta-9-THC (1 mg/kg) used in this study was chosen on the basis of initial intravenous administration results in electrophysiological experiments. This intraperitoneal delta-9-THC dose of 1 mg/kg corresponded to 10 times more than the minimum pharmacologically active intravenous dose (0.1 mg/kg). Moreover, a dose range of 1.0–1.5 mg/kg also represents a dose that has been reported to induce changes in intracellular transduction cascades, mRNA and protein expression, as well as mild to moderate physiological and behavioral reactions in rodents (Butovsky et al., 2005; Derkinderen et al., 2003; Nahas et al., 2002a). Furthermore, this amount is the usual dose contained in about 2 puffs ("hit") of a marijuana joint that generally produces mild to moderate psychoactive effects (common dose of 0.67 g in humans). All drugs except for the CB_1R antagonist/inverse agonist rimonabant (SR141716A, a kind gift from Dr. Daniele Piomelli) and the antidepressant citalopram HBr (kindly provided by Lundbeck, Copenhagen, Denmark) were obtained from Sigma-Aldrich Canada Ltd. Rimonabant and the CB_1R/CB_2R agonist delta-9-THC were dissolved in 5% Tween 80, 5% polyethylene glycol and 90% saline (0.9% NaCl solution) to a final concentration of 3 mg/ml. All other drugs were dissolved in physiological saline (0.9% NaCl solution), the $5\text{-}HT_{1A}$ receptor antagonist N-[2-[4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridyl)cyclohexanecarboxamide (WAY100,635) was dissolved to a final concentration of 75 μg/ml, and citalopram HBr to 30 mg/ml. Chloral hydrate was the anesthesia used in electrophysiological experiments. The pH of vehicles and solutions was adjusted to 7.2.

2.3. Effect of delta-9-THC on coping behavior in the forced swim test (FST)

The FST examines the dynamics of transition from an active to a passive mode of coping in an inescapable water-filled bin. An enhancement of immobility normally ensues after exposure, a phenomenon argued to reflect learned behavioral despair, a depressive-like behavior that is prevented by antidepressant treatment (Porsolt et al., 1977). First, rats were each immersed for a 15 minute-pre-test in Plexiglas cylindrical bins (20 cm diameter, 50 cm high) filled with water (at 25–27 °C) to a depth of 20 cm, which did not allow the tail and hind paws to touch the floor of the bin. The main test was conducted 24 h later wherein rats were re-exposed for 5 min under conditions identical to the pre-test, and during which the frequency and duration of immobility, swimming and climbing episodes were encoded. We used an automated behavioral tracking system (Videotrack system, View Point Life Sciences, Montreal, Quebec, Canada) in this test as with all subsequent behavioral tests. For single drug administrations, rats received intraperitoneal injections of either delta-9-THC (1 mg/kg), the vehicle or citalopram (10 mg/kg) 45 min before the main test. For repeated administrations, delta-9-THC, citalopram or the vehicle, was injected once daily for 4 days. On the 5th day, drugs were injected 5 h and 45 min prior to the main test (modified from Page et al. (1999)). In addition, some animals receiving delta-9-THC (1 mg/kg) were injected with rimonabant (1 mg/kg, intraperitoneal) 15 min prior to each delta-9-THC administration. All tests were conducted toward the end of the light phase, in a dim environment and under minimal anxiogenic conditions (Kelliher et al., 2000). Custom-made plates arrayed with infrared light-emitting diodes