Published in final edited form as:

Prog Neuropsychopharmacol Biol Psychiatry. 2012 July 2; 38(1): 1–3. doi:10.1016/j.pnpbp.2012.01.002.

Cannabinoid receptor signaling and modulation of monoamines: implications for psychiatric and neurological disorders

Elisabeth J. Van Bockstaele

Department of Neuroscience, Farber Institute for Neurosciences, Thomas Jefferson University, Philadelphia, PA, USA

The past decade has seen a tremendous growth in knowledge related to cannabinoid receptor signaling in brain. In addition, new perspectives on the impact and consequences of cannabinoid modulation of monoaminergic circuits are steadily emerging demonstrating a significant interaction between these two systems in a variety of psychiatric (affective disorders) and neurological disorders (neurodegeneration, pain). The goal of the special issue is to provide current insights into cannabinoid receptor signaling and updated information regarding cannabinoid modulation of dopaminergic, noradrenergic and serotonergic circuitry with an emphasis on their putative role in psychiatric and neurological disorders.

It is now well recognized that the endocannabinoid system is involved in a variety of physiological functions due to abundant expression of its receptors and ligands in the central nervous system (Herkenham et al., 1991, Mackie, 2005, 2008). Endocannabinoids are lipophilic arachidonic acid derivatives that are released in an activity dependent fashion from the postsynaptic cell (Basavarajappa, 2007, Di Marzo et al., 2005, Piomelli, 2003, 2005, Piomelli et al., 1998). Two currently known endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), have been implicated in the control of emotional reactivity, motivated behaviors and energy homeostasis primarily by actions on brain cannabinoid (CB) type 1 receptors (CB1r)(Martin et al., 1999, Mechoulam et al., 1995, Mechoulam et al., 1998, Stella et al., 1997, Sugiura et al., 1995). In this special issue, **Console-Bram and colleagues** provide a summary of current receptor nomenclature for classifying a target as a cannabinoid receptor. Furthermore, the authors' review describes basic pharmacological definitions, principles and mechanisms underlying cannabinoid receptor activation. Finally, in light of the discovery of additional sites of action for endocannabinoids as well as synthetic cannabinoid compounds, the authors consider and discuss the existence of additional putative cannabinoid receptors. The complexity of the endocannabinoid system and its ubiquitous distribution presents challenges for the development of novel therapeutics. **Atwood and colleagues** review recent evidence for a novel class of therapeutics directed at the CB2 receptor that may hold promise for the treatment of chronic pain, neuroinflammation, immune suppression and osteoporosis. These authors discuss challenges associated with the development of this new class of drugs and possible explanations for the mismatch between promising preclinical data and disappointing clinical data.

While it is known that the endocannabinoid system and exogenous cannabinoid-based drugs interact with amino acid neuromodulatory systems (Kano et al., 2009), a neurochemical target at which cannabinoids interact to have global effects on behavior is brain monoaminergic circuitry. Accumulating evidence indicates a significant role of the cannabinoid system in the regulation of basal ganglia function, particularly with respect to reward, psychomotor function and motor control. Dysfunction in the endocannabinoid system is likely to impact dopamine- and basal ganglia related neuropsychiatric disorders, including drug addiction, psychosis, Parkinson's disease and Huntington's disease. The distribution of CB1r and the endocannabinoids, 2-AG and anandamide, within the dopamine-enriched basal ganglia networks suggest that the motivational and motor effects of endocannabinoids are modulated, in part, by dopamine transmission. **Fitzgerald and colleagues** summarize evidence indicating that cannabinoids modulate dopamine transmission through indirect mechanisms by inhibiting the presynaptic release of neurotransmitters onto midbrain dopamine neurons. The authors provide elegant neuroanatomical findings demonstrating that CB1rs are not co-expressed with markers of dopamine in midbrain dopamine neurons or their striatal targets, but rather that dopamine terminals converge on single neuronal targets with other axons containing the CB1r in striatal and cortical brain regions. Finally, the authors discuss receptor interactive mechanisms that enable cannabinoids to fine-tune the activity of mesocorticolimbic and nigrostriatal dopamine neurons with a consideration of the psychiatric and neurological implications of cannabinoid modulation of dopamine transmission within these networks.

Although it is well accepted that cannabis, the endocannabinoid system and cannabinoid-based drugs increase dopamine neurotransmission, **Filbey** summarizes evidence from the literature underscoring the likelihood of both direct and indirect influences in cannabinoid-induced dopamine enhancement. Furthermore, Filbey discusses neural mechanisms of cannabis cue-elicited craving by highlighting activation of the reward neurocircuitry. She reviews evidence suggesting that cannabis cues, regardless of sensory modality, trigger subjective and physiologic craving for cannabis indicating that, in cannabis users, conditioned cues have increased motivational salience and trigger craving. Because the putative pathway for motivational salience is the dopaminergic reward pathway, it can be inferred that cue-elicited craving mechanisms are also associated with the reward neurocircuitry.

The use of synthetic cannabinoid receptor agonists/antagonists or compounds targeting endocannabinoid synthesis/metabolism in brain has received widespread attention as these approaches may hold some therapeutic potential for psychiatric disorders (Witkin et al., 2005a, Witkin et al., 2005b). Cannabinoid ligands have been shown to alleviate depressive- and anxiety-like behaviors in pre-clinical studies (Gobbi et al., 2005, Hill and Gorzalka, 2005). However, the cannabinoid receptor antagonist, rimonabant, was withdrawn from clinical trials due to an unacceptably high incidence of psychiatric side effects (Despres, 2009, Janero and Makriyannis, 2009, Nissen et al., 2008, Taylor, 2009). This has generated significant interest in understanding the regulation of endogenous cannabinoid signaling in psychiatric disorders and has stimulated investigations into manipulating endogenous cannabinoids for potential clinical benefit. **El Khoury and colleagues** highlight interactions

between cannabinoids, dopamine and glutamate in the basal ganglia and present how cannabinoid receptor antagonism might constitute an integrated pharmacotherapeutic approach that impacts the affective, cognitive, appetitive and motivational neuronal networks involved in mood disorders. The review highlights interactions between cannabinoids and dopamine, with respect to neurotransmitter release and synaptic plasticity in the context of drug addiction, psychosis and cognition. The authors discuss targeting the endocannabinoid system, as a plasticity-based therapeutic strategy, in the above pathologies with a particular focus on CB1r antagonists/inverse agonists. They further discuss the promise of CB1r antagonists as therapeutic approaches in disease states associated with hedonic dysregulation and with cognitive dysfunction, in particular in the context of psychosis. Finally, *El Khoury and colleagues* review evidence for the use of inhibitors of endocannabinoid catabolism in psychiatric disorders that may be CB1 receptor independent and involve TRPV1 receptors. *Giuffrida* elaborates on preclinical studies of endocannabinoid signaling and discusses a putative role of cannabinoid receptors in neurodegeneration and schizophrenia. The ability of cannabinoid agonists to enhance norepinephrine (NE) release plays a critical role in the mood altering properties and cognitive effects of cannabis-based compounds. The noradrenergic system continues to be an important target in the development of new therapies for affective disorders because of its critical role in the modulation of emotional state and regulation of arousal and stress responses (Ballenger, 2000, Carrasco and Van de Kar, 2003, Charney et al., 1989, Heninger and Charney, 1988). *Carvalho and Van Bockstaele* discuss anatomical, biochemical and behavioral evidence for cannabinoid modulation of noradrenergic circuits and discuss the role of norepinephrine in cannabinoid-induced behaviors, notably aversion.

Because the endocannabinoid system plays a role in the regulation of mood, accumulating evidence supports changes in the endocannabinoid system by chronic treatment with antidepressants, including serotonin and/or norepinephrine reuptake inhibitors as well as monoamine oxidase inhibitors. *Fisar* reviews mechanisms of action of cannabinoids on monoaminergic systems, with an emphasis on inhibition of monoamine oxidase. *Esteban and Garcia Sevilla* integrate findings from numerous experimental studies on the role of endocannabinoids and CB1rs in the modulation of brain monoaminergic systems: i.e., neuronal (spontaneous firing rate) activity and synthesis and release of the corresponding neurotransmitter. The authors also discuss the effects of cannabinoid drugs on the activity of presynaptic monoaminergic receptors (autoreceptors and heteroreceptors) that regulate the synthesis and release of classic neurotransmitters and participate in the mechanisms of action of antidepressant drugs. Finally, the review discusses the possible relevance of the endocannabinoid system and CB1rs in the pathophysiology and treatment of major depression and schizophrenia, with a special focus on evidence from postmortem human brain studies.

Despite increasing evidence from preclinical data suggesting that therapeutic use of cannabinoid-based drugs may outweigh any potential risks in certain serious medical conditions, the debate surrounding its widespread utility continues as regulatory concerns preclude a smooth transition of promising preclinical studies into clinical trial testing. This may persist in the near future as state and federal governments debate over regulation of

medicinal application of cannabis. Applications for medicinal cannabinoids that are already under investigation include the treatment of nausea, anorexia, neurodegeneration, inflammation, excitotoxicity and pain. The appetitive and anti-emetic properties of cannabinoids have led to the approval of their use in chemotherapy and AIDS patients. There is growing evidence for therapeutic cannabinoid effects on inflammatory and excitotoxic cellular processes that are linked to epilepsy, Parkinson's disease, amyotrophic lateral sclerosis, spasticity, and central nervous system injury. **Bambico and colleagues** discuss antidepressant-like properties of (-)-trans-9-tetrahydrocannabinol (delta-9-THC) and its potential efficacy by modulation of serotonin transmission in the dorsal raphe nucleus and hippocampus. Since few studies have been undertaken to test the antidepressant-like property of the phytocannabinoid delta-9-THC, these authors examined the effects of single or repeated delta-9-THC administration on behavioral despair in the forced swim test and investigated the modulation of presynaptic 5-HT transmission and enhanced tonic hippocampal 5-HT_{1A} receptor activity under these conditions. These authors, however, highlight challenges associated with distinguishing the neural underpinnings of delta-9-THC's therapeutic potential against those underlying its adverse liabilities.

Although challenges exist with medicinal cannabis, the current Special Issue highlights the potential for the development of compounds designed to modulate endocannabinoid levels or the use of synthetic cannabinoids with well-defined pharmacological properties that may provide significant clinical benefit. Considering the important role of cannabinoid receptor compounds in mediating anti-nociception and anti-hyperalgesia, potential clinical applications of cannabinoid-based drugs to the management of chronic pain may be on the horizon. **Dogrul and colleagues** summarize the involvement of descending serotonergic pathways in cannabinoid-mediated anti-nociception. The authors provide an overview of descending modulatory pathways in cannabinoid-induced analgesia as well as the involvement of descending serotonergic and noradrenergic pathways in CB₁ receptor-mediated anti-nociception.

The CB₁r is one of the most plentiful G protein coupled receptors within the brain, and cannabinoid signaling through this receptor mediates a wide variety of peripheral and central processes. Like many pharmacological therapeutics, the use of cannabinoid-based compounds may not come without side effects and as acknowledged in many of the articles within this Special Issue determining the therapeutic efficacy in clinical populations will be extremely important. Ultimately, the knowledge gained from preclinical and clinical research offers important and exciting new avenues for the development of novel cannabinoid-based therapeutics that provide a new tool in the treatment of a number of psychiatric and neurological disorders.

References

- Ballenger JC. Anxiety and Depression: Optimizing Treatments. Primary care companion to the Journal of clinical psychiatry. 2000; 2:71–79.
- Basavarajappa BS. Neuropharmacology of the endocannabinoid signaling system-molecular mechanisms, biological actions and synaptic plasticity. Curr Neuropharmacol. 2007; 5:81–97. [PubMed: 18084639]

- Carrasco GA, Van de Kar LD. Neuroendocrine pharmacology of stress. *European journal of pharmacology*. 2003; 463:235–272. [PubMed: 12600714]
- Charney DS, Woods SW, Heninger GR. Noradrenergic function in generalized anxiety disorder: effects of yohimbine in healthy subjects and patients with generalized anxiety disorder. *Psychiatry research*. 1989; 27:173–182. [PubMed: 2540501]
- Despres JP. Pleiotropic effects of rimonabant: clinical implications. *Current pharmaceutical design*. 2009; 15:553–570. [PubMed: 19199981]
- Di Marzo V, De Petrocellis L, Bisogno T. The biosynthesis, fate and pharmacological properties of endocannabinoids. *Handb Exp Pharmacol*. 2005:147–185. [PubMed: 16596774]
- Gobbi G, Bambico FR, Mangieri R, Bortolato M, Campolongo P, Solinas M, et al. Antidepressant-like activity and modulation of brain monoaminergic transmission by blockade of anandamide hydrolysis. *Proc Natl Acad Sci U S A*. 2005; 102:18620–18625. [PubMed: 16352709]
- Heninger GR, Charney DS. Monoamine receptor systems and anxiety disorders. *The Psychiatric clinics of North America*. 1988; 11:309–326. [PubMed: 2843838]
- Herkenham M, Groen BG, Lynn AB, De Costa BR, Richfield EK. Neuronal localization of cannabinoid receptors and second messengers in mutant mouse cerebellum. *Brain Res*. 1991; 552:301–310. [PubMed: 1913192]
- 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; 15:593–599. [PubMed: 15916883]
- Janero DR, Makriyannis A. Cannabinoid receptor antagonists: pharmacological opportunities, clinical experience, and translational prognosis. *Expert opinion on emerging drugs*. 2009; 14:43–65. [PubMed: 19249987]
- Kano M, Ohno-Shosaku T, Hashimoto-dani Y, Uchigashima M, Watanabe M. Endocannabinoid-mediated control of synaptic transmission. *Physiol Rev*. 2009; 89:309–380. [PubMed: 19126760]
- Mackie K. Distribution of cannabinoid receptors in the central and peripheral nervous system. *Handb Exp Pharmacol*. 2005:299–325. [PubMed: 16596779]
- Mackie K. Cannabinoid receptors: where they are and what they do. *J Neuroendocrinol*. 2008; 20(Suppl 1):10–14. [PubMed: 18426493]
- Martin BR, Mechoulam R, Razdan RK. Discovery and characterization of endogenous cannabinoids. *Life Sci*. 1999; 65:573–595. [PubMed: 10462059]
- Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, et al. Identification of an endogenous 2-monoglyceride, present in canine gut, that binds to cannabinoid receptors. *Biochem Pharmacol*. 1995; 50:83–90. [PubMed: 7605349]
- Mechoulam R, Fride E, Di Marzo V. Endocannabinoids. *Eur J Pharmacol*. 1998; 359:1–18. [PubMed: 9831287]
- Nissen SE, Nicholls SJ, Wolski K, Rodes-Cabau J, Cannon CP, Deanfield JE, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: the STRADIVARIUS randomized controlled trial. *Jama*. 2008; 299:1547–1560. [PubMed: 18387931]
- Piomelli D. The molecular logic of endocannabinoid signalling. *Nat Rev Neurosci*. 2003; 4:873–884. [PubMed: 14595399]
- Piomelli D. The endocannabinoid system: a drug discovery perspective. *Curr Opin Investig Drugs*. 2005; 6:672–679.
- Piomelli D, Beltramo M, Giuffrida A, Stella N. Endogenous cannabinoid signaling. *Neurobiol Dis*. 1998; 5:462–473. [PubMed: 9974178]
- Stella N, Schweitzer P, Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. *Nature*. 1997; 388:773–778. [PubMed: 9285589]
- Sugiura T, Kondo S, Sukagawa A, Nakane S, Shinoda A, Itoh K, et al. 2-Arachidonoylglycerol: a possible endogenous cannabinoid receptor ligand in brain. *Biochem Biophys Res Commun*. 1995; 215:89–97. [PubMed: 7575630]
- Taylor D. Withdrawal of Rimonabant--walking the tightrope of 21st century pharmaceutical regulation? *Current drug safety*. 2009; 4:2–4. [PubMed: 19256104]

- Witkin JM, Tzavara ET, Davis RJ, Li X, Nomikos GG. A therapeutic role for cannabinoid CB1 receptor antagonists in major depressive disorders. *Trends Pharmacol Sci.* 2005a; 26:609–617. [PubMed: 16260047]
- Witkin JM, Tzavara ET, Nomikos GG. A role for cannabinoid CB1 receptors in mood and anxiety disorders. *Behav Pharmacol.* 2005b; 16:315–331. [PubMed: 16148437]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript