Progress in Neuro-Psychopharmacology & Biological Psychiatry 38 (2012) 59–67

Contents lists available at SciVerse ScienceDirect

Progress in Neuro-Psychopharmacology & Biological Psychiatry

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

Cannabinoid modulation of noradrenergic circuits: Implications for psychiatric disorders☆

Ana Franky Carvalho [a,b,c], Elisabeth J. Van Bockstaele [a,*]

[a] Neuroscience, Farber Institute for Neurosciences, Thomas Jefferson University, Philadelphia, PA, USA
[b] Life and Health Science Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal
[c] ICVS/3B's-PT Government Associate Laboratory, Braga/Guimarães, Portugal

ARTICLE INFO

Article history:
Received 14 September 2011
Received in revised form 17 January 2012
Accepted 17 January 2012
Available online 24 January 2012

Keywords:
Adrenergic receptor
Cannabinoid receptor type 1
Nucleus accumbens
Nucleus of the solitary tract
Sprague–Dawley

ABSTRACT

The interaction between the endocannabinoid system and catecholaminergic circuits has gained increasing attention as it is recognized that the development of synthetic cannabinoid receptor agonists/antagonists or compounds targeting endocannabinoid synthesis/metabolism may hold some therapeutic potential for the treatment of psychiatric disorders. The noradrenergic system plays a critical role in the modulation of emotional state, primarily related to anxiety, arousal, and stress. Recent evidence suggests that the endocannabinoid system mediates stress responses and emotional homeostasis, in part, by targeting noradrenergic circuits. This review summarizes our current knowledge regarding the anatomical substrates underlying regulation of noradrenergic circuitry by the endocannabinoid system. It then presents biochemical evidence showing an important effect of cannabinoid modulation on adrenergic receptor signaling. Finally, new evidence from behavioral pharmacology studies is provided demonstrating that norepinephrine is a critical determinant of cannabinoid-induced aversion, adding another dimension to how central noradrenergic circuitry is regulated by the cannabinoid system.

1. Introduction

For centuries, cannabis preparations have been used for their medicinal properties. However, psychotropic and mood altering properties are common and cannabis users have described "visions of devils" and "communication with spirits" (Zuardi, 2006). In the Western world, the use of cannabis for therapeutic purposes did not reach prominence primarily due to difficulties in obtaining reproducible effects in clinical studies, and because of the development of more effective medications. However, cannabis has been, and still is, used for recreational purposes and is exploited for its euphoric and sedative properties. Nevertheless, adverse effects, such as anxiety, panic and depression, are also commonly reported (Johns, 2001).

A link between cannabis use and the development of serious mental illnesses, including schizophrenia, bipolar disease and major depression, has been debated for several decades (Degenhardt et al., 2003; Johns, 2001; Strakowski et al., 2007; van Rossum et al., 2009). It is still not clear whether cannabis use can trigger or facilitate the onset of a psychiatric disorder or whether the genetic predisposition for mental illness leads to consumption of cannabis to compensate for any disturbance in the endocannabinoid system. In summary, there is a significant amount of evidence implicating the endocannabinoid system in psychiatric disorders (Degenhardt et al., 2003; Fernandez-Espejo et al., 2009; Parolaro et al., 2010; Viveros et al., 2005). Considering that the monoamine system is critically involved in the pathophysiology of depression, anxiety and post-traumatic stress disorder (PTSD), the goal of the present review is to explore the association between the endocannabinoid and noradrenergic systems with a particular emphasis on the pathophysiology of psychiatric disorders.

2. Cannabinoids, norepinephrine and mood regulation

There are a number of contradictory reports in the literature regarding the effects of cannabinoids on mood. For example, both cannabinoid type 1 receptor (CB1r) agonists (Gobbi et al., 2005; Hill and Gorzalka, 2005; Morrish et al., 2009) and antagonists (Griebel et al., 2005; Shearman et al., 2003; Tzavara et al., 2003) have been shown to exert an antidepressant-like effect in pre-clinical animal studies. Furthermore, cannabinoid receptor agonists/antagonists have been shown to exert anxiolytic effects in some studies but anxiogenic effects in others (Carvalho et al., 2010b; Degroot, 2008; Haller et al.,

Abbreviations: AR, adrenergic receptor; CB1r, cannabinoid type 1 receptor; Δ9-THC, Δ9-tetrahydrohydrocannabinol; FAAH, fatty acid amide hydrolase; LC, locus coeruleus; MAO, monoamine oxidase; NE, norepinephrine; NET, norepinephrine transporter; Acb, nucleus accumbens; NTS, nucleus of the solitary tract; PTSD, post-traumatic stress disorder; PFC, prefrontal cortex; TH, tyrosine hydroxylase.

☆ Grant support: NIDA DA020129.

* Corresponding author at: Neuroscience, Farber Institute for Neurosciences, Thomas Jefferson University, 900 Walnut Street, Suite 417, Philadelphia, PA 19107, USA. Tel.: +1 215 503 9147.
E-mail address: ejv101@jefferson.edu (E.J. Van Bockstaele).

0278-5846/$ – see front matter © 2012 Elsevier Inc. All rights reserved.
doi:10.1016/j.pnpbp.2012.01.008

2004b; Moreira and Lutz, 2008). In human studies, dual effects have been reported. Occasional users often report that cannabis increases well-being, euphoria and contentment (Velez et al., 1989). However, increased anxiety, dysphoria and depressive mood have been reported following moderate cannabis use (Reilly et al., 1998). The use of cannabis seems to exacerbate psychotic symptoms, such as delusions and hallucinations (Baigent et al., 1995; Cleghorn et al., 1991; Negrete et al., 1986), as well as increase anxiety and symptoms of psychosis (Morrison et al., 2009). Adverse effects of cannabis have been linked to potential toxic effects induced by the consumption of high doses of the drug as, unlike other drugs of abuse, cannabis rarely induces life-threatening events and, thus, users may consume extremely high doses.

Dysregulation of the noradrenergic system has been implicated in several mood disorders, including hyperarousal, anxiety, depression and PTSD (Friedman et al., 1999; Itoi and Sugimoto, 2010; Nutt, 2002, 2006; Southwick et al., 1999; Anand and Charney, 2000). The noradrenergic system, together with the serotonergic, cholinergic and dopaminergic systems, is typically viewed as a neuromodulatory system (Sara, 2009). The noradrenergic system, in particular, has its cell bodies grouped in nuclei in the brainstem, namely the locus coeruleus (LC) and the nucleus of the solitary tract (NTS) (Foote et al., 1983; Itoi and Sugimoto, 2010; Weinshenker and Schroeder, 2007). While the LC is a homogeneous nucleus in which most cells are noradrenergic (Foote et al., 1983), the NTS contains several other neurotransmitters (Barraco et al., 1992). The noradrenergic neurons of the NTS are distributed throughout the caudal NTS (subpostremal and commissural NTS) (Barraco et al., 1992). The LC, located within the dorsal wall of the rostral pons, in the lateral floor of the fourth ventricle, is the largest noradrenergic nucleus in the brain (Foote et al., 1983) and is the sole source of norepinephrine (NE) in the forebrain (Sara, 2009). The LC is seen as the "arousal" center, important for regulation of sleep and vigilance, and activation of the LC is important for selective attention (Sara, 2009; Southwick et al., 1999). On the other hand, the NTS works as relay station for sensory signals arising from the viscera, integrating visceral information with other regulatory information coming from the brainstem, diencephalon and forebrain (Barraco et al., 1992; Itoi and Sugimoto, 2010). The NTS is known to send efferents to autonomic centers in the brainstem but also to send ascending efferents to higher levels of the neuroaxis (Barraco et al., 1992).

NE can interact with three families of adrenergic receptors (ARs): α1, α2 and β(1–3) receptors that exhibit different signal transduction. For example, α1 receptors are coupled to Gq proteins, activating phospholipase C and the phosphotidyl inositol intracellular pathway, resulting in activation of protein kinase C and release of intracellular calcium (Duman and Nestler, 1995). In contrast, α2-ARs, found pre- and postsynaptically (MacDonald et al., 1997), are coupled to Gi proteins, which can lead to a decrease in intracellular cAMP (Duman and Nestler, 1995). Presynaptically distributed α2-ARs are considered autoreceptors, since activation of these receptors will decrease intracellular cAMP and Ca^{2+}, thereby inhibiting neurotransmitter release. Finally, β-ARs are coupled to Gs proteins, activating adenylyl cyclase and increasing intracellular cAMP (Duman and Nestler, 1995). Several studies have revealed alterations in the levels of adrenergic receptor expression in depressed suicide victims. The density of α2-ARs is increased in brains of depressed suicide victims (Callado et al., 1998; De Paermentier et al., 1997; Meana et al., 1992), while β1-AR density is decreased (De Paermentier et al., 1990). These changes are not widespread suggesting that specific areas of the brain may contribute to the pathophysiology of mood disorders. Moreover, pharmacological depletion of monoamines, using reserpine, for example, produces depressive-like behaviors in animal models, suggesting a role for monoamines (including NE) in the pathophysiology of depression (Nutt, 2006). Additionally, most antidepressants drugs act by increasing the levels of synaptic monoamines suggesting that low levels of NE account for the expression of depressive-like symptoms. Interestingly, higher levels of plasma NE were correlated with longer periods of remission to a new depressive episode in patients that had suffered their first major depression episode, suggesting a protective effect of NE (Johnston et al., 1999). However, it has also been described that patients with melancholic depression show dysregulation of the hypothalamic–pituitary–adrenal axis, with high levels of plasma cortisol and cerebrospinal fluid NE being reported (Wong et al., 2000). Thus, although the molecular mechanisms underlying depression are still largely unclear, abnormalities in noradrenergic transmission certainly play an important part in its pathophysiology.

3. The interplay between the endocannabinoid and noradrenergic systems

Manipulation of the endocannabinoid system results in effects on mood and cognition that share similarities with the noradrenergic system. Briefly, increasing endocannabinoid tone has been shown to improve mood similar to increasing noradrenergic tone with antidepressants. This has been shown in preclinical studies, where the antidepressant effects of chronic CB1r agonist administration implicate a role for NE (Morrish et al., 2009). Moreover, over-activation of the endocannabinoid system can cause mania (Henquet et al., 2006), a side effect that has been reported by patients using antidepressants (Bond et al., 2008; Peet, 1994; Tondo et al., 2010). Taken together, the effects of manipulating the endocannabinoid system and modulating noradrenergic transmission suggest that the two systems may interact or share some common signaling pathways. Consistent with this, a study performed in human subjects revealed that administration of the β-AR blocker, propranolol, before consumption of marijuana prevented cannabinoid-induced cardiovascular effects and prevented cannabinoid-induced learning impairment (Sulkowski et al., 1977). In agreement with this, early anatomical studies using autoradiography have identified moderate CB1r binding and CB1r mRNA in the principal noradrenergic nuclei, the LC and NTS (Derbenev et al., 2004; Herkenham et al., 1991; Jelsing et al., 2008; Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993). Characterization of CB1r distribution in the LC showed that CB1r is localized to somato-dendritic profiles as well as within axon terminals and neurochemical characterization of LC neurons showed that some of the CB1r-positive neurons are noradrenergic (Scavone et al., 2010). The existence of CB1r in the LC and NTS suggests that cannabinoids may modulate noradrenergic activity. In fact, administration of cannabinoid-like agents has been shown to increase Fos expression in LC noradrenergic neurons (Oropeza et al., 2005; Patel and Hillard, 2003) and in NTS neurons (Jelsing et al., 2009). Moreover, cannabinoid-like agents are also able to modulate LC and NTS firing (Himmi et al., 1996, 1998; Mendiguren and Pineda, 2004, 2006; Muntoni et al., 2006) suggesting that CB1r in the LC and NTS are functionally active. These anatomical and physiological studies reveal a potential mechanism by which cannabinoids exert their effects on mood, cognition and arousal. Moreover, cannabinoids have been shown to increase NE release in the prefrontal cortex (PFC, Oropeza et al., 2005). Interestingly, activation of α2-AR in the hypothalamus leads to the production of endocannabinoids (Kuzmiski et al., 2009) and CB1r and β2-AR have been shown to physically interact in vitro (Hudson et al., 2010), contributing to the notion that the two systems interact.

3.1. Anatomical localization of CB1r in noradrenergic circuits

With respect to the noradrenergic system, autoradiographic binding studies have shown the existence of a moderate density of CB1r protein and mRNA in the LC and NTS (Derbenev et al., 2004; Herkenham et al., 1991; Jelsing et al., 2008; Mailleux and Vanderhaeghen, 1992; Matsuda et al., 1993). Some studies using dual immunohistochemical detection of dopamine-β-hydroxylase (or tyrosine hydroxylase, TH) and CB1r