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Cannabinoid modulation of noradrenergic circuits: implications for psychiatric disorders

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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.

Keywords

Cannabinoid receptor type1; adrenergic receptor; nucleus accumbens; nucleus of the solitary tract; Sprague-Dawley

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

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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 (Johns, 2001; Degenhardt *et al.*, 2003; 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; Viveros *et al.*, 2005; Fernandez-Espejo *et al.*, 2009; Parolaro *et al.*, 2010). 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.

1. 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 & Gorzalka, 2005; Morrish *et al.*, 2009) and antagonists (Shearman *et al.*, 2003; Tzavara *et al.*, 2003; Griebel *et al.*, 2005) 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 (Haller *et al.*, 2004b; Degroot, 2008; Moreira & Lutz, 2008; Carvalho *et al.*, 2010b). 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 (Negrete *et al.*, 1986; Cleghorn *et al.*, 1991; Baigent *et al.*, 1995), 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; Southwick *et al.*, 1999; Nutt, 2002; Nutt, 2006; Itoi & Sugimoto, 2010). 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; Weinshenker & Schroeder, 2007; Itoi & Sugimoto, 2010). 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 (Southwick *et al.*, 1999; Sara, 2009). 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 & 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 & 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 & 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 & 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 (Meana *et al.*, 1992; De Paermentier *et al.*, 1997; Callado *et al.*, 1998), 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.

2. 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 (Peet, 1994; Bond *et al.*, 2008; 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 (Herkenham *et al.*, 1991; Mailleux & Vanderhaeghen, 1992; Matsuda *et al.*, 1993; Derbenev *et al.*, 2004; Jelsing *et al.*, 2008). 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 (Patel & Hillard, 2003; Oropeza *et al.*, 2005) 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; Himmi *et al.*, 1998; Mendiguren & Pineda, 2004; Mendiguren & Pineda, 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.

2.1 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 (Herkenham *et al.*, 1991; Mailleux & Vanderhaeghen, 1992; Matsuda *et al.*, 1993; Derbenev *et al.*, 2004; Jelsing *et al.*, 2008). Some studies using dual immunohistochemical detection of dopamine-β-hydroxylase (or tyrosine hydroxylase, TH) and CB1r have shown that some of the CB1r-positive neurons in the LC (Scavone *et al.*, 2006; Scavone *et al.*, 2010) and NTS (Carvalho *et al.*, 2010a) are noradrenergic. Moreover, electron microscopic analysis revealed that most of CB1r found in the LC are distributed post-synaptically. The role of post-synaptic CB1r is not yet fully understood although reports of post-synaptic CB1r inhibiting cortical interneurons in an autocrine manner have been described (Bacci *et al.*, 2004). In Scavone's study (2010), most of post-synaptic CB1r were found in the cytoplasm, which may reflect newly synthesized receptor on its way to dendritic processes or axon terminals in target regions. It was also shown that CB1r localized to post-synaptic profiles received mostly asymmetric (excitatory) type synapses. One can speculate that upon activation by excitatory (glutamatergic) terminals, endocannabinoids are produced and released to act on post-synaptic CB1r, thus directly inhibiting transmission without altering glutamate transmission. CB1r was also detected within pre-synaptic profiles in the LC, where the synaptic specializations were more commonly of the symmetric (inhibitory) type. Symmetric (inhibitory) synapses are thought to be GABAergic, thus suggesting that cannabinoids can have a greater impact on GABAergic transmission as compared to glutamatergic transmission. It appears that cannabinoids in the LC may mediate different signal transduction pathways depending on the pre vs post-synaptic localization of CB1r.

Interestingly, the PFC and the Acb, two brain regions implicated in mood disorders and that receive noradrenergic afferents from the LC and NTS respectively, show a very different pattern of CB1r distribution with respect to noradrenergic terminals (Figure 1). In the PFC, CB1r can be found in noradrenergic terminals (approximately 30% of CB1r-positive fibers were noradrenergic) (Oropeza *et al.*, 2007) while in the Acb the percentage of co-localization of CB1r and DβH is very low (Carvalho *et al.*, 2010a). This may reflect a different consequence to the modulation of NE by endocannabinoids in these two brain regions. In line with this, the impact of systemic WIN 55,212-2 administration on AR expression differs between the PFC and Acb (Carvalho *et al.*, 2010a) (see below). CB1r

shows an interesting topographical distribution in the Acb, with higher expression of CB1r being found in the shell of the Acb at mid-rostral levels and higher CB1r expression in the core of the Acb at caudal levels (Carvalho *et al.*, 2010a). The heterogeneous distribution of CB1r throughout the Acb may reflect different effects of the endocannabinoid system on the modulation of behavioral output in the Acb. It is proposed that the subregions of the Acb (shell and core) can be further subdivided with respect to function (Zahm, 1999). For instance, anatomical and behavioral studies support a rostro-caudal gradient for appetitive versus aversive behaviors (Reynolds & Berridge, 2001; Reynolds & Berridge, 2002; Reynolds & Berridge, 2003). In line with this, the possibility exists that the influence of cannabinoids on Acb function are greater with respect to certain behaviors as compared to others, due to the heterogeneous distribution of CB1r in this limbic-motor region.

2.2 Effects of cannabinoids on noradrenergic transmission

Effects on LC activity—Several studies have reported cannabinoid-induced effects on LC neuronal activity. Namely, cannabinoid receptor agonists have been shown to increase LC spontaneous firing (Mendiguren & Pineda, 2004; Mendiguren & Pineda, 2006; Muntoni *et al.*, 2006). Patel and Hillard showed increased Fos labeling in noradrenergic neurons in the LC following systemic injection of CP55940 and WIN 55,212-2 (2003). In this study, it was also shown that both CB1r agonists increase Fos expression in dopaminergic neurons. However, the activation of dopaminergic neurons by cannabinoid receptor agonists is blocked by an α1-AR antagonist and by an α2-AR agonist, suggesting that CP55940 and WIN 55,212-2 may be activating dopaminergic neurons by first activating LC-NE neurons. In another study, Oropeza and colleagues (2005) showed that systemic WIN 55,212-2 induces Fos expression in noradrenergic neurons of the LC. This effect was blocked by the CB1r antagonist SR 141716A, suggesting a role for CB1r. Recordings from LC-NE neurons in anaesthetized rats have shown that systemic and central administration of cannabinoids, dose-dependently, increased the firing rate of the LC (Mendiguren & Pineda, 2006; Muntoni *et al.*, 2006). This effect was blocked by administration of the CB1r antagonist SR141716A. Interestingly, administration of SR141716A alone caused a significant reduction of LC spontaneous firing, suggesting that LC is under the control of an endogenous cannabinoid tone. This hypothesis is further supported by evidence showing that URB597, a selective inhibitor of fatty acid amide hydrolase (FAAH), the enzyme responsible for degradation of the endocannabinoid, anandamide, is able to enhance the spontaneous firing rate of LC-NE neurons (Gobbi *et al.*, 2005).

Cannabinoids have also been shown to inhibit KCL-evoked excitation of the LC (Mendiguren & Pineda, 2007), indicating that cannabinoids may have a protective role in the LC by preventing over-activation of neuronal activity. Hyper-activity of the LC has been proposed to alter behavioral flexibility and disable focused or selective attention (Aston-Jones *et al.*, 1999a; Aston-Jones *et al.*, 1999b; Aston-Jones *et al.*, 1999b; Usher *et al.*, 1999; Aston-Jones, 2002). On the other hand, the phasic firing of the LC is important for optimal performance on tasks that require focused attention. Thus, excess inhibitory actions of cannabinoids may lead to a decrease in the phasic activation of the LC, which could result in an overall disruption of attention in both animals and humans (Jentsch *et al.*, 1997; Solowij *et al.*, 2002; Arguello & Jentsch, 2004).

Effects on NTS activity—There is compelling evidence for complex actions of cannabinoids in the NTS. In the NTS not all neurons are sensitive to Δ9-THC or other cannabinoid-based analogs (Himmi *et al.*, 1996; Himmi *et al.*, 1998). About 50% of NTS neurons are responsive to cannabinoid-based analogs, a response apparently mediated by CB1r. Interestingly, a subset of NTS neurons exhibit increased activity following cannabinoid exposure, while others exhibit decreased neuronal activity. Moreover, both

WIN 55,212-2 and the antagonist rimonabant were able to increase Fos expression in the NTS, albeit in different subsets of neurons (Jelsing *et al.*, 2009). In a study focusing on cardiovascular function, a subset of NTS neurons with baroreceptive properties was found to increase discharge after application of endocannabinoid anandamide and the endocannabinoid uptake inhibitor AM404 (Seagard *et al.*, 2005), similarly to conditions in which there is an increase in blood pressure. The different responses to cannabinoid analogs observed in the NTS may be due to the fact that the NTS is a heterogeneous nucleus containing a large variety of neurotransmitters and neuropeptides. Catecholaminergic, serotonergic, dopaminergic, GABAergic and cholinergic neurons can be found within similar subregions of the NTS (Barraco *et al.*, 1992). Since most studies fail to identify the neurochemical properties of the neuronal population analyzed, it is hard to speculate regarding the functional implications of these findings. In any case, the different studies reveal that cannabinoids can strongly influence activity of NTS neurons. With respect to NTS noradrenergic neurons, it has been shown that noradrenergic neurons in the NTS are positive for CB1r (Carvalho *et al.*, 2010a), providing anatomical evidence for a potential action of cannabinoids on noradrenergic neurons. In addition, some Δ9-THC-sensitive neurons were depressed when clonidine, a α2-AR agonist, was co-administered, suggesting that these neurons are likely noradrenergic (Himmi *et al.*, 1996).

The effects of cannabinoids on NE release in target regions—Several studies have reported that systemic and local administration of cannabinoid analogs alters the release of NE in specific areas of the brain. Systemic administration of WIN 55,212-2 or Δ9-THC has been shown to increase the release of NE in the PFC and in the Acb (Jentsch *et al.*, 1997; Oropeza *et al.*, 2005; Page *et al.*, 2007). Jentsch and colleagues (1997) showed an increase in NE turnover in the PFC and Acb of rats after systemic injection of Δ9-THC. They also show that Δ9-THC increased dopamine turnover but only in the PFC; no effects were observed in serotonin turnover. Oropeza and colleagues (2005) report an increase of NE release in the PFC with concomitant Fos activation in noradrenergic neurons of the LC; importantly, this effect was blocked by SR 141716A, a CB1r antagonist. In another study, repeated administration of WIN 55,212-2 increased the release of NE in PFC with increased expression of TH in the LC (Page *et al.*, 2007). Consistent with this, rats administered Δ9-THC or WIN 55,212-2 exhibited an increased activity rate of TH and increased levels of NE turnover in the LC, hippocampus, cortex, hypothalamus and cerebellum (Moranta *et al.*, 2004). In addition, decreased synthesis of serotonin and dopamine were observed upon Δ9-THC or WIN 55,212-2 administration. Interestingly, an *in vitro* study, has shown that cannabinoids have the ability to inhibit the activity of monoamine oxidase (MAO), the enzyme responsible for the metabolism of monoamine neurotransmitters, such as NE and dopamine (Fisar, 2010), which could be another mechanism that results in increases in NE levels. In line with increased release of NE in the PFC and in the Acb, another study has reported alterations in the expression of ARs, as well as in the NE transporter (NET) (Reyes *et al.*, 2009). Reyes and colleagues have shown that acute administration of WIN 55,212-2 decreases NET expression in the PFC, which in addition to LC activation (Oropeza *et al.*, 2005), increased TH activity in the LC (Moranta *et al.*, 2004; Page *et al.*, 2007) and inhibition of MAO (Fisar, 2010) may account for the increased release of NE. Furthermore, repeated systemic administration of WIN 55,212-2 was shown to decrease the levels of β1-AR in the PFC (Reyes *et al.*, 2009). In contrast, abstinence from WIN 55,212-2 induced an upregulation of β1-AR, which could be interpreted as a rebound effect attributed to a return to basal levels following a period of abstinence. No changes were observed in α2A-AR levels. In the Acb, it has been shown that β1-AR expression was decreased with acute or repeated administration of WIN 55,212-2 (Carvalho *et al.*, 2010a). Additionally, α2A-AR was decreased but only after repeated administration; this effect persisted with abstinence from WIN 55,212-2 (Carvalho *et al.*, 2010a). The lower levels of β1-AR may represent an

adaptive mechanism following increases in extracellular NE in the Acb after WIN 55,212-2 treatment. The decreased in α2A-AR expression only after repeated exposure to WIN 55,212-2 may reflect a secondary mechanism to increase NE release. Activation of α2A-AR is known to decrease cAMP production in the axon terminal, decreasing the release of vesicular NE (Wozniak *et al.*, 2000).

Interestingly, some reports have also shown that the CB1r antagonist, SR141716A, is capable of increasing NE release in the PFC (Tzavara *et al.*, 2003) and in the hypothalamus (Tzavara *et al.*, 2001), and the administration of SR141716A is accompanied by antidepressant effects in the forced swim test. However in another study, SR141716A alone did not trigger an effect in the levels of NE compared to vehicle treated animals; however, in this study, it was observed that SR141716A blocked the effects of WIN 55,212-2-induced NE release (Oropeza *et al.*, 2005). These contradictory effects can be explained in part by the different doses used in these studies. In the latter, SR141716A was used at 0.2mg/kg while in the former study the doses applied ranged from 1mg/kg to 10mg/kg. The findings from studies involving CB1r antagonism can also reflect the existence of a basal tone of endocannabinoids in these regions.

Based on the reported effects of cannabinoids on NE transmission, it is of great interest to understand the functional consequences of NE on cannabinoid-induced behaviors, namely aversion and anxiety.

3. Contribution of norepinephrine to cannabinoid-induced behaviors

Emerging studies have revealed an important role for NE in cognitive and limbic function. While, for many decades, the LC-NE system was seen as the main source of forebrain NE and was intensely investigated for its role in attention, memory and behavior, increased interest in the NTS has contributed to increasing the complexity of how this neuromodulator regulates forebrain targets. Several studies have reported the existence of direct ascending projections from the NTS to limbic areas such as the bed nucleus of the stria terminalis (BNST), central nucleus of the amygdala (Ricardo & Koh, 1978; Reyes & Van Bockstaele, 2006) or Acb (Delfs *et al.*, 1998) and these ascending projections have been shown to significantly impact motivated behaviors (Aston-Jones *et al.*, 1999a; Delfs *et al.*, 2000). Blockade of β-ARs is known to impair memory, decrease anxiety and increase depressive symptoms (Gottschalk *et al.*, 1974; Sternberg *et al.*, 1986; Patten, 1990) by targeting structures such as the hippocampus, PFC, amygdala or BNST (Delfs *et al.*, 2000; Aston-Jones, 2002; Tully & Bolshakov, 2010). Thus, the effects of NE are region specific and rely on highly intricate neurocircuitries within cortical and limbic systems. The next section details the impact of cannabinoids on selected NE circuits.

3.1 Cannabinoid-induced aversion

Cannabinoid agents have been shown to produce both preference and aversion in the place conditioning paradigm. Murray and Bevins (Murray & Bevins, 2010) recently considered the variability in behaviors associated with cannabinoid receptor agonist exposure and found that the most consistent factor impacting behavioral outcome was the dose of the cannabinoid receptor agent used. Low doses have a tendency to induce preference while high doses have a tendency to induce aversion. Place conditioning is a classical conditioning paradigm in which animals learn to associate the effect of a drug (or other discrete treatment) with particular environmental (contextual) cues. Place conditioning can identify both conditioned place preference and conditioned place aversion, and thus it can be used to study both rewarding and aversive effects of drugs (Bardo & Bevins, 2000; Carlezon, 2003). Place conditioning is useful in probing neural circuits involved in reward and aversion. For example, microinjection of amphetamine into the Acb produces conditioned place

preference, whereas microinjection of amphetamine into the area postrema produces a conditioned taste aversion (Carr & White, 1983; Carr & White, 1986). Other studies have shown that microinjection of μ opioid receptor agonists into the ventral tegmental area produces conditioned place preference, whereas microinjection of kappa opioid receptor into the ventral tegmental area, Acb, medial PFC or lateral hypothalamus produces conditioned place aversion (Shippenberg & Elmer, 1998). Hence, place conditioning studies enable parsing out the neural circuits involved in drug reward and aversion and identifying which drugs induce reward or aversion depending on the region and receptor subtypes being activated. Accordingly, monoaminergic transmission in several limbic structures (e.g. amygdala, PFC, bed nucleus of the stria terminalis and Acb) has been reported to be important for the expression of aversive behaviors (Aston-Jones *et al.*, 1999a; Delfs *et al.*, 2000; Ventura *et al.*, 2007; Kerfoot *et al.*, 2008).

The neural circuitry involved in mediating cannabinoid-induced aversion was recently elucidated (Figure 2) (Carvalho *et al.*, 2010b; Carvalho & Van Bockstaele, 2011). Both the Acb and bed nucleus of the stria terminalis receive direct noradrenergic projections from the NTS (Delfs *et al.*, 1998; Forray *et al.*, 2000; Forray & Gysling, 2004). Activation of the NTS has been shown to occur when conditioned taste aversion acquisition and expression occur (Sakai & Yamamoto, 1997; Swank, 2000). Although these studies did not provide any neurochemical characterization of the activated neurons, the possibility exists that some of the activated neurons are noradrenergic considering that the highest neuronal activation was seen in the caudal and intermediate NTS. The localization of CB1r to noradrenergic neurons in the NTS (Carvalho *et al.*, 2010a) and the ability of WIN 55,212-2 to induce NTS activation (Jelsing *et al.*, 2009) underlie the hypothesis that WIN 55,212-2 induces aversion by increasing NE release in target regions. Our results show that NE in the Acb, but not the BNST, is critical for WIN 55,212-2-induced aversion, as decreasing NE signaling in the Acb, either by immunotoxin depletion of noradrenergic fibers (Carvalho *et al.*, 2010b) or by blockade of β1-ARs (Carvalho & Van Bockstaele, 2011), impaired its expression. In addition, it is known that blockade of β1-AR reduces the excitability of accumbal neurons which may trigger aversion (Kombian *et al.*, 2006; Carlezon & Thomas, 2009). Interestingly, blockade of β1-AR did not impair lithium chloride-induced aversion (Carvalho & Van Bockstaele, 2011), suggesting that noradrenergic transmission may be specific to aversion to cannabinoid-based agents. Moreover, the lack of effect of in lithium chloride-induced aversion suggests that the β1-AR blocker did not impact learning.

Noradrenergic transmission in the bed nucleus of the stria terminalis has been implicated in the signaling of aversion in opiate withdrawal (Delfs *et al.*, 2000; Cecchi *et al.*, 2007) and visceral pain (Deyama *et al.*, 2009; Minami, 2009). However, our results seem to suggest that NE in the bed nucleus of the stria terminalis is not critical for WIN 55,212-2-induced aversion (Carvalho *et al.*, 2010b). While technical limitations should be taken into consideration, as the noradrenergic depletion achieved may have not been sufficient to remove all noradrenergic inputs, the possibility that NE in bed nucleus of the stria terminalis is not required for the expression of WIN 55,212-2 aversion is also plausible.

3.2 Cannabinoid-induced anxiety

Cannabinoids have been shown to induce anxiolytic and anxiogenic effects using the elevated plus maze (EPM) or the elevated zero maze (EZM). The EZM is a modification of the well-established EPM. Both EPM and EZM are based on the natural conflict of rodents to explore a novel environment and their innate aversion to open, elevated and brightly lit spaces. As a consequence of the aversive properties of the open arms, subjects spend a greater amount of time on the closed arms and the proportion of total exploration in the open arms provides a measure of anxiety, such that increases in percent time spent on the open arms is considered to be indicative of anxiolytic drug action (Handley & Mithani, 1984;

Pellow & File, 1986). Conversely, decreases in percent time spent on open arms reflect an anxiogenic effect of the drug.

The differential results on anxiety following exposure to cannabinoid agents may be due to some of the following variables: prior drug use, dose used, basal anxiety levels and regional endocannabinoid basal tone (Degroot, 2008). Generally, the anxiogenic properties of cannabinoid agents occur more frequently in drug-naïve subjects and in novel/stressful environments (Haller *et al.*, 2004a; Viveros *et al.*, 2005; Degroot, 2008). This suggests that basal endocannabinoid tone is important in the response to exogenous cannabinoids. It has been shown that increases in endocannabinoid levels in specific brain areas are important for coping with anxiety-provoking stimuli (Marsicano *et al.*, 2002). In this scenario, endocannabinoids are thought to work to restore homeostasis. While under particular physiological situations, this increase in endocannabinoids may be restricted to specific brain regions, such as the amygdala (Marsicano *et al.*, 2002), in cases where exogenous/systemic cannabinoids are administered, the diverse nature of cannabinoid receptor activation may trigger an anxiogenic effect. Although, decreased NE tone in the Acb was able to reverse WIN 55,212-2-induced aversion, it was not sufficient to block WIN 55,212-2-induced anxiety (Carvalho *et al.*, 2010b). Decreasing NE tone in the BNST also failed to prevent WIN 55,212-2-induced aversion. These results suggest that WIN 55,212-2-induced anxiety is not mediated by NE input to the Acb or the BNST. These findings are not surprising as the Acb has not been implicated in the development of anxiety-like behaviors. On the other hand, the results obtained from NE depletion from the BNST are quite fascinating. The BNST is seen as an important nucleus for the expression of anxiety (Davis, 1998; Walker *et al.*, 2003; Davis, 2006) and is one of the richest areas in NE in the CNS (Forray & Gysling, 2004). Although NE in the BNST has been shown to mediate anxiety to certain stressors, it does not mediate anxiety in response to all types of stressors (Cecchi *et al.*, 2002). Considering this, it has been proposed that NE effects on anxiety are stimuli-specific. Moreover, other neurotransmitters have also been implicated in signaling anxiety in the bed nucleus of the stria terminalis, such as corticotropin releasing factor (Smith & Aston-Jones, 2008). It has been suggested that anxiogenic effects of endocannabinoids can be mediated by transient receptor potential vanilloid type-1 (TRPV1) activation (Campos & Guimaraes, 2009; Micale *et al.*, 2009) as anandamide but not 2- arachidonyl glycerol (2-AG) is a TRPV1 agonist (Zygmunt *et al.*, 1999). It is not clear whether WIN 55,212-2 has the ability to direct modulate TRPV1. WIN 55,212-2 has been shown to inhibit TRPV1 in trigeminal ganglion neurons (Patwardhan *et al.*, 2006; Wang *et al.*, 2011) but the role of TRPV1 in WIN 55,212-2-induced anxiety is not yet clear. Taken all together, the results suggest that WIN 55,212-2-induced anxiety is independent of noradrenergic transmission in the Acb and the bed nucleus of the stria terminalis.

Conclusion

Growing evidence suggests an interaction between the cannabinoid and noradrenergic systems that has significant functional and behavioral implications. Importantly, cannabinoids can modulate noradrenergic transmission in both noradrenergic nuclei and target regions. This modulation seems to be circuit specific and may depend on the basal status of cannabinoid and NE levels. In addition, NE seems to be important for particular cannabinoid-induced behaviors. However, many questions remain regarding cannabinoid-adrenergic interactions in disease. It is clear that the noradrenergic system plays a role in certain psychiatric disorders. It is tempting to speculate that, under certain conditions, drugs targeting the endocannabinoid system may provide an effective tool to modulate and reverse impairments in noradrenergic transmission. However, numerous safety issues persist with cannabinoid-based agents that may preclude their widespread utility. The question also arises as to whether prevention of side effects induced by cannabinoid-based agents may

involve a combination of cannabinoid-based agents and modulators of the noradrenergic system.

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List of Abbreviations (in alphabetical order)

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

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Highlights

- Growing evidence suggests an interaction between the cannabinoid and noradrenergic systems that has significant functional and behavioral implications.
- The functional consequences of cannabinoid-based ligands on noradrenergic transmission impact conditioned place aversion and anxiety.
- Cannabinoid-based ligands can modulate noradrenergic transmission in both noradrenergic nuclei and target regions.
- Modulation of noradrenergic pathways is circuit specific and may depend on the basal status of brain norepinephrine levels.

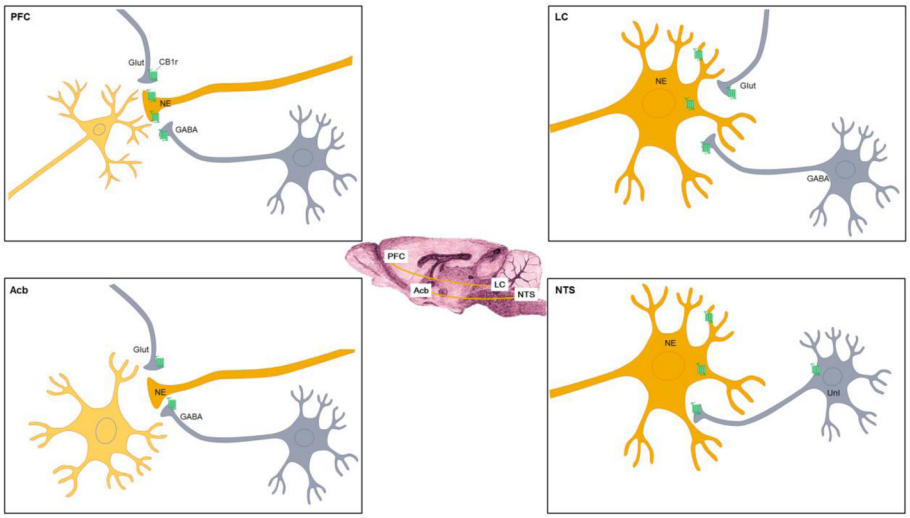

Figure 1.

The distribution of CB1r (indicated by green receptor) in noradrenergic circuitry. The LC is the sole source of NE to the PFC while the Acb primarily receives NE from the NTS (depicted in saggital section schematic at center of figure). In the LC, CB1r has been found both pre and post-synaptically. When post-synaptic, CB1r are localized to somatodendritic processes receiving both symmetric (putative GABAergic) and asymmetric (putative glutamatergic) synapses. In addition, CB1r are localized to axon terminals that are either inhibitory (GABA-containing terminals) or excitatory (glutamate-containing terminals) in the LC. In the PFC, NE terminals exhibit immunolabeling for CB1r, while in the Acb NE terminals are seldom immunoreactive for CB1r. Localization of CB1r on glutamatergic and GABAergic axon terminals in both the PFC and Acb have been well described. In the Acb, CB1r is found in terminals forming both symmetric and asymmetric type synapses. In the NTS, CB1r has been localized to NE neurons as well as to neurons whose phenotype has yet to be defined (defined as unlabeled, unl).

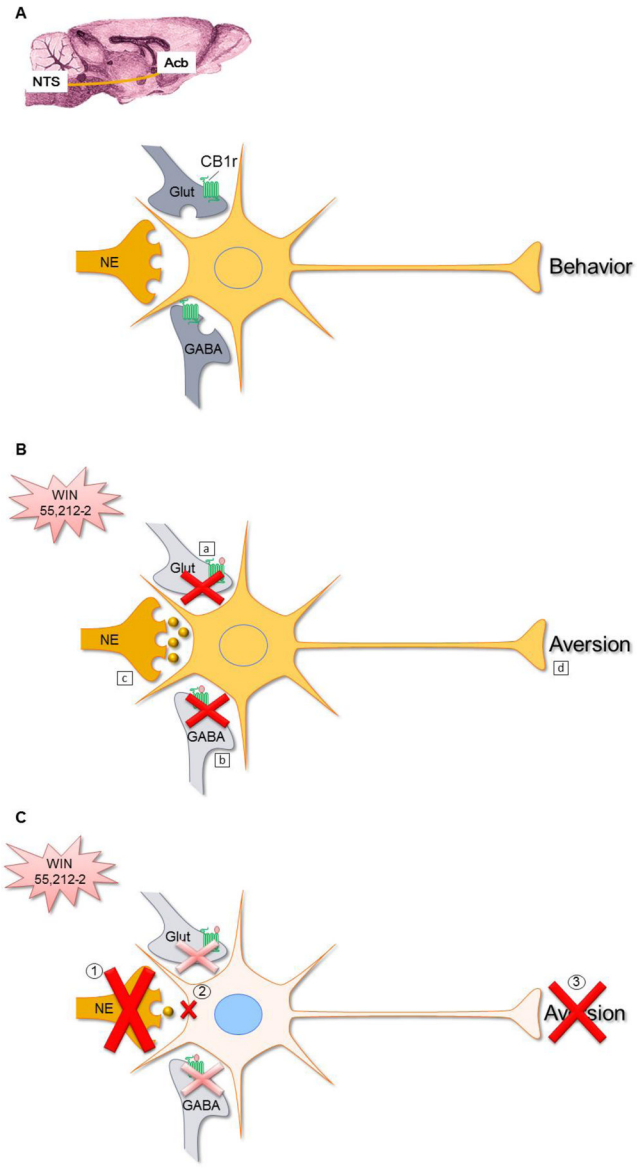

Figure 2. Schematic diagram summarizing proposed involvement of NE in neural circuitry underlying cannabinoid-induced aversion

A. Schematic diagram depicting glutamatergic (Glut), GABAergic (GABA) and noradrenergic (NE) innervation of Acb neurons. These neuromodulators are well known to regulate Acb activity and consequently behavior. CB1r (depicted in green) is primarily associated with GABA and Glut axon terminals in this region, and few NE terminals express CB1r.

B. In the presence of a cannabinoid receptor agonist (e.g. WIN 55,212-2), glutamate release is reduced (a, Robbe et al, 2001) together with a reduction in GABA (b, Manzoni and Bockaert, 2001). WIN 55,212-2 causes a concomitant increase in NE (c, Jentsch et al, 1997) that, in combination with a decrease in glutamate and GABA, induces activation of Acb neurons triggering aversion (d, Carlezon and Thomas, 2009).

C. Blocking NE transmission either by depleting NE (1) input or by blocking β1-adrenergic receptors (2), prevents the expression of WIN 55,212-2-induced aversion (3) (Carvalho et al, 2010; Carvalho and Van Bockstaele, 2011).