Life Sciences 192 (2018) 115–127

Contents lists available at ScienceDirect

Life Sciences

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

Regulation of noradrenergic and serotonergic systems by cannabinoids: relevance to cannabinoid-induced effects

Aitziber Mendiguren*, Erik Aostri, Joseba Pineda

Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), E-48940 Leioa, Bizkaia, Spain

ARTICLE INFO

Keywords:
Locus coeruleus
Dorsal raphe nucleus
Noradrenaline
Serotonin
Cannabinoid
CB_1 receptor
Firing

ABSTRACT

The cannabinoid system is composed of Gi/o protein-coupled cannabinoid type 1 receptor (CB_1) and cannabinoid type 2 (CB_2) receptor and endogenous compounds. The CB_1 receptor is widely distributed in the central nervous system (CNS) and it is involved in the regulation of common physiological functions. At the neuronal level, the CB_1 receptor is mainly placed at GABAergic and glutamatergic axon terminals, where it modulates excitatory and inhibitory synapses. To date, the involvement of CB_2 receptor in the regulation of neurotransmission in the CNS has not been clearly shown.

The majority of noradrenergic (NA) cells in mammalian tissues are located in the locus coeruleus (LC) while serotonergic (5-HT) cells are mainly distributed in the raphe nuclei including the dorsal raphe nucleus (DRN). In the CNS, NA and 5-HT systems play a crucial role in the control of pain, mood, arousal, sleep-wake cycle, learning/memory, anxiety, and rewarding behaviour. This review summarizes the electrophysiological, neurochemical and behavioural evidences for modulation of the NA/5-HT systems by cannabinoids and the CB_1 receptor. Cannabinoids regulate the neuronal activity of NA and 5-HT cells and the release of NA and 5-HT by direct and indirect mechanisms. The interaction between cannabinoid and NA/5-HT systems may underlie several behavioural changes induced by cannabis such as anxiolytic and antidepressant effects or side effects (*e.g.* disruption of attention). Further research is needed to better understand different aspects of NA and 5-HT systems regulation by cannabinoids, which would be relevant for their use in therapeutics.

1. Introduction

Cannabinoids elicit their effect mainly through activation of Gi/o protein-coupled cannabinoid (CB) receptors; the cannabinoid type 1 (CB_1) receptor, which is mainly expressed in the central nervous system (CNS) and the cannabinoid type 2 (CB_2) receptor primarily located in the immune system [106]. In the rat brain, the CB_1 receptor is widely distributed in the basal ganglia, cerebral cortex (CC), cerebellum, olfactory bulb and hippocampus (HC) while it is less abundant in the hypothalamus (HT), spinal cord and brainstem, including the locus coeruleus (LC) and the dorsal raphe nucleus (DRN) [51,52]. Immunocytochemical and electron microscopic studies have shown that the CB_1 receptor is mainly located at GABAergic and glutamatergic axon terminals in the CNS, whereas low labelling is present at somatodendritic sites [52,127]. Thus, one of the main functions attributed to the endocannabinoid system in the brain is to modulate the excitatory and inhibitory synapses [56], which has been related to CB_1 receptor. Yet, the role of the CB_2 receptor in the regulation of CNS neurotransmission has not been widely studied.

The cannabinoid system is involved in the regulation of common physiological processes such as nociception, control of motor activity, emesis, learning/memory, emotional behaviour, cardiovascular and feeding/reward responses [65]. Therefore, over the last years, this system has been proposed as an interesting therapeutic target for the treatment of nausea and vomiting, obesity, chronic pain and neurodegenerative diseases [2,133]. However, activation of this system produces several side effects that have restrained the therapeutic value of cannabinoids. Among others, they alter attention, emotional state or cognitive function [68,53,72]. CB receptors are endogenously activated by N-arachidonoylethalonamine (anandamide) and 2-arachidonoylglycerol (2-AG) and then inactivated through a membrane transporter facilitated reuptake and degraded by an intracellular fatty acid amide hydrolase (FAAH) (anandamide) or monoglyceride lipase (MAGL) (2-AG) [56].

The majority of noradrenergic (NA) cells in mammalian tissues are located in the LC, which is involved in the regulation of numerous functions such as arousal, emotional state and pain (Table 1). It has been shown that the LC could filter irrelevant stimuli from specific tasks

* Corresponding author at: Department of Pharmacology, Faculty of Medicine and Nursing, University of the Basque Country (UPV/EHU), B. Sarriena s/n, E-48940 Leioa, Bizkaia, Spain.
E-mail address: aitziber.mendiguren@ehu.eus (A. Mendiguren).

https://doi.org/10.1016/j.lfs.2017.11.029
Received 11 July 2017; Received in revised form 29 October 2017; Accepted 16 November 2017
Available online 21 November 2017
0024-3205/

Table 1
Localization, projections and functions of the locus coeruleus and the dorsal raphe nucleus.

	Locus coeruleus	Dorsal raphe nucleus
Localization	Lateral border of the fourth ventricle.[a]	The ventromedial part of the PAG.[g,h]
Main afferences	Glutamatergic input from the lateral PGi.[a,b] GABAergic input from the PrH.[a,b]	RN, LC, VTA, SN, PFC, LHb, PAG, HT.[g,i]
Efferences	Cerebellum, thalamus, HT, PFC (the main efferent), HC, spinal cord and brainstem.[a]	CC, HT, CPu, SN, NAcc, VTA, amygdala and HC.[g,h]
Excitatory regulation	NA neurons: NMDA type and non-NMDA type, especially AMPA receptors under control condition.[b,c,d]	5-HT neurons: NMDA type receptors (glutamatergic regulation from the DRN and PAG).[h,j]
Inhibitory regulation	NA neurons: α_2-adrenoceptors, $GABA_A$ receptors and μ-opioid receptors.[b,c,e,f]	5-HT neurons: $GABA_A$, $GABA_B$ receptors (GABA regulation from DRN and PAG) and 5-HT_{1A} receptors.[h,k,l]
Functions	Sleep-wake cycle, arousal, cognition/memory, pain, cardiovascular/respiratory control and rewarding behaviour.[a]	Pain, mood, sexual and rewarding behaviour, feeding, motor activity, emesis, body temperature, learning/memory, sleep-wake cycle, anxiety, arousal and aggressiveness.[m,n]

α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), γ-Aminobutyric acid (GABA), caudate-putamen (CPu), cerebral cortex (CC), dorsal raphe nucleus (DRN), hippocampus (HC), 5-hydroxytryptamine (5-HT), hypothalamus (HT), lateral habenula (LHb), locus coeruleus (LC), *N*-methyl-D-aspartate (NMDA), noradrenaline (NA), nucleus accumbens (NAcc), paragigantocellular nucleus (PGi), periaqueductal gray (PAG), prefrontal cortex (PFC), prepositus hypoglossi (PrH), raphe nucleus (RN), substantia nigra (SN), ventral tegmental area (VTA).

[a] Samuels & Szabadi, 2008 [115].
[b] Williams et al., 1991 [134].
[c] Cherubini et al., 1988 [25].
[d] Ennis et al., 1992 [34].
[e] Arima et al., 1998 [4].
[f] Medrano et al., 2017 [82].
[g] Baumgarten & Grozdanovic, 1997 [13].
[h] Piñeyro & Blier, 1999 [107].
[i] Dorocic et al., 2014 [29].
[j] Jolas & Aghajanian, 1997 [55].
[k] Aghajanian & Lakoski, 1984 [1].
[l] Bonvento et al., 1992 [16].
[m] Berger et al., 2009 [14].
[n] Luo et al., 2016 [69].

to focus attention on a precise action. Thus, this nucleus fires in tonic or phasic modes during task performance. Slow and regular (tonic mode) pace is associated with poor performance and weak attentiveness while discharge in burst (phasic mode), when glutamatergic afferents are active, is linked to good task performance and focused attention [7]. With regard to the emotional state, chronic hyperactivity of the LC induces some depressive symptoms [123], while long-term administration of certain antidepressant drugs decreases spontaneous LC activity [124]. Finally, LC nucleus plays a role in the descending pathway of pain transmission since activation of the nucleus induces antinociception and reduces the response of the dorsal horn neurons to noxious stimuli [67].

The DRN is the principal source of forebrain serotonin (5-HT) in the CNS and it plays a crucial role in the control of anxiety, mood and pain [14,69] (Table 1). Stimulation of DRN/5-HT neurons elicits anxiolytic and antidepressant effects in behavioural tests [107,79,137]. In contrast, inhibition of the neuronal activity and the subsequent reduction of 5-HT release in DRN projections could result in depressive states [107,137]. Finally, as LC nucleus, stimulation of DRN produces antinociceptive effects while lesions of DRN inhibit the effect of analgesic drugs [137].

In summary, both DRN-5-HT and LC-NA systems regulate different functions that could be altered by cannabinoid administration. Therefore, reviewing the functional interactions between the monoaminergic and cannabinoid systems would be of impact to understand some of the therapeutic (*i.e.*, anxiolytic, antidepressant, antinociceptive effects) or side (*i.e.*, disruption of attention) effects of cannabinoids. This review integrates the morphological evidences for the different components of the cannabinoid system located on the LC and DRN, along with the findings about the effects of cannabinoids on the firing activity and the synthesis/release of NA/5-HT neurons and its consequences in the cannabinoid-induced behavioural effects.

2. Modulation of the noradrenergic system by cannabinoids: contribution to cannabinoid-induced effects

2.1. Localization of cannabinoid receptors in the locus coeruleus

In the CNS of rodents, CB_1 receptor is mainly located at axon terminals rather than on cell bodies [52,56,62,127]. Herkenham and colleagues showed a low to moderate CB_1 receptor binding in the rat LC by quantitative autoradiography *in vitro* [51]. Later on, sparse mRNA labelling and CB_1-receptor like immunoreactivity was detected in the proximity of the LC [78,127]. However, a more detailed analysis of the distribution of CB_1 receptor in the LC was published by Scavone and colleagues [118]. They showed that CB_1 receptors are mainly expressed at somatodendritic sites (~66%) of LC/NA cells, whereas a minor percentage is located at axon terminals (~22%) and glial processes (~12%). Most of cannabinoid CB_1 positive axon profiles form inhibitory synapses (~71%) while the minority represented excitatory synapses (~25%). At the cell level, CB_1 receptor is mainly present at cytoplasmic site (~59%) although expression at the cell membrane (41%) was also reported. To date the functional role of cytoplasmic CB_1 receptors in the LC and in other brain regions has not been well characterized. Thus, although some data for the involvement of mitochondrial CB_1 receptors in memory regulation have been recently published in the HC [50], CB_1 receptors located on LC cell bodies would probably represent newly synthesized receptors moving towards dendrites or axon terminals. Taken together, evidences demonstrate the presence of CB_1 receptors both at postsynaptic site on NA neurons and at presynaptic site, probably on GABAergic/glutamatergic axon terminals projecting to LC neurons. Additionally, in the frontal cortex (FC), the main projection area of the LC, the CB_1 receptor has been shown to be present at NA axon terminals [20,100,102,103].