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Endogenous cannabinoid signaling and psychomotor disorders[☆]

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Abstract

The effects of cannabinoids on motor behaviors and cognitive functions are well documented. The discovery of the CB1 cannabinoid receptor and the mapping of its distribution in the central nervous system have provided a rationale to elucidate the molecular and cellular mechanisms of cannabinoid actions. The identification of naturally occurring ligands for these receptors, anandamide and 2-arachidonylglycerol, has prompted a large research effort aimed at investigating the physiological role of the endogenous cannabinoid system, as well as its potential use as a target for novel therapeutic interventions. This mini-review discusses the participation of the endogenous cannabinoid system in the regulation of motor behaviors, pointing out its possible involvement in the pathophysiology of psychomotor disorders. © 2000 Elsevier Science Inc. All rights reserved.

Keywords: Anandamide; 2-Arachidonylglycerol; Cannabinoid receptors; Basal ganglia; Motor disorders

1. Introduction

Diseases affecting the control of movement have analog patterns in cognitive disorders. Motor impairment and/or execution of complex behavioral sequences often accompany psychotic symptoms, as in the case of obsessive-compulsive disorders. Such an occurrence likely reflects the anatomical overlapping of brain areas serving both motor and cognitive functions [1].

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Cannabimimetic drugs represent an interesting tool to investigate psychomotor behaviors, because of their documented ability to influence both motor and cognitive performances (for review see [2]). Indeed, cannabinoid administration is accompanied by profound effects on motor behaviors [3,4], as well as by attenuation of *d*-amphetamine-induced hyperactivity and stereotypy [5,6]. In addition, cannabinoid substances produce a large spectrum of psychotropic effects in humans, ranging from euphoria, short-term memory impairment, altered perception of space and time, and dream states [4]. Similarities between certain cognitive impairments occurring in psychoses and the pharmacological effects of Δ^9 -tetrahydrocannabinol, the active principle in marijuana and hashish, have also been documented [7,8].

The discovery of the brain cannabinoid receptor, CB1, and the mapping of its neuroanatomical distribution, have greatly improved our understanding of the effects of cannabimimetic drugs on psychomotor functions. CB1 receptors are most concentrated in areas of the central nervous system (CNS) that are critical for the regulation and processing of motor functions, cognition, and motivation [9–11]. In keeping with this distribution, disruption of the CB1 receptor gene has been shown to severely impair movement control and to result in a functional reorganization of the basal ganglia [12,13].

The pharmacological properties of cannabis-derived drugs have prompted clinical evaluations of marijuana use in motor disturbances, such as spasticity, tremor, and dystonias (for review see [14]). At the same time, the discovery of naturally occurring ligands of cannabinoid receptors, and the identification of their pathways of biosynthesis and inactivation, have opened a new research field aimed at investigating the physiological role of these molecules in health and disease, as well as their possible use as a new target for therapeutic interventions.

The purpose of this mini-review is to draw together these studies, pointing out to the potential involvement of the endogenous cannabinoid system in psychomotor disorders.

2. The endogenous cannabinoid system

The cloning of the CB1 cannabinoid receptor [15] and the mapping of its distribution in the brain (see for review [16]) has impelled the search for the corresponding naturally occurring ligands within the brain. Two endogenous cannabimimetic substances have been identified so far, arachidonylethanolamide (anandamide) [17,18] and 2-arachidonylglycerol (2-AG) [19–21]. Unlike neurotransmitters that are released from synaptic terminals via vesicle secretion, both anandamide and 2-AG are thought to be produced upon demand through stimulus-dependent cleavage of two distinct phospholipid precursors present in neuronal membranes (for review see [22]). Anandamide, but not 2-AG, is released extracellularly by neural activity evoked by localized pulses of high K^+ [23], and it is thought to act near its sites of production as a local neuromodulator. Whether 2-AG is produced *in vivo* under physiological circumstances and/or it exits neurons in other regions of the CNS, has not been determined yet.

The biological actions of anandamide are terminated by two subsequent reactions consisting of high-affinity transport into cells [24–26], followed by hydrolysis catalyzed by an amidohydrolase enzyme [27–30]. 2-AG is thought to be inactivated by cleavage into glycerol

and arachidonic acid. The enzyme activity involved in this reaction has not been clearly identified, though anandamide amidohydrolase and monoacylglycerol lipase have been suggested to play a role [21,31,32].

Other saturated and monounsaturated fatty acylethanolamides (AEs) are produced by activated neurons together with anandamide [18] (Stella and Piomelli, submitted). Although these lipids share a common biosynthetic mechanism with anandamide [33], they do not bind to cannabinoid receptors and they are not released extracellularly *in vivo* [23]. The possible physiological roles of these compounds are still largely unexplored. One exception is represented by palmitylethanolamide (PEA) which was shown to exert peripheral anti-inflammatory and antinociceptive effects, mediated through a putative CB2-like cannabinoid receptor [34,35].

3. Cannabinoid signaling in basal ganglia

The basal ganglia are a forebrain region playing a key role in sensorimotor and motivational aspects of behavior [1,36]. The high density of CB1 receptors in this area [37,38] indicates that cannabinoid substances may modulate essential aspects of basal ganglia physiology. The existence of an endogenous cannabinergic tone in the basal ganglia has been suggested by the finding that the CB1 receptor antagonist SR141716 was able to produce increased locomotion in mice and stereotypies in rats [39,40]. These findings have been recently confirmed by *in vivo* microdialysis studies, showing that membrane depolarization stimulates the outflow of anandamide from striatal neurons [23].

Functional interactions between endogenous cannabinoids and distinct neurotransmitter systems modulating basal ganglia functions have been also postulated. Neuroanatomical studies have shown that CB1 receptors are mainly located in the terminals of GABA-ergic medium-spiny neurons projecting from the striatum to the globus pallidum and substantia nigra [38,41]. Although direct evidence for an interaction between endogenous cannabinoids and GABA-ergic system is still lacking, it is known that exogenously administered cannabinoids can modulate GABA transmission, as suggested by their ability to inhibit GABA release from striatal and hippocampal nerve terminals [42,43] and potentiate GABA-induced catalepsy [44,45]. Coexpression of μ -opioid and CB1 receptors in striatal cells [46] indicates that opioids and endocannabinoids can also interact within the striatum. In keeping with this, chronic cannabinoid exposure regulates proenkephalin mRNA levels in the rat striatum [47].

Finally, a role for the cannabinoid system as a modulator of dopaminergic activity in basal ganglia is emerging. Activation of cannabinoid receptors was shown to cause significant reductions of the electrically evoked dopamine release from rat striatal slices [48], and to potentiate neuroleptic-induced catalepsy [49]. Moreover, injection of cannabinoid receptor agonists into the basal ganglia counteracts the motor responses of locally administered D2-receptor agonists [50–52]. Conversely, cannabinoid-mediated motor behaviors can be affected by dopamine manipulations. For example, chronic administration of dopamine D1 and D2 receptor agonists results in differential modulation of the locomotor effects of the cannabinoid agonist HU-210 [2], suggesting a possible cross-talk between dopaminergic and cannabinergic systems within the striatum. In this regard, the observation that anandamide

Fig. 1. A hypothetical model of the functional interaction between endocannabinoid and dopaminergic systems in dorsal striatum. Activation of dopamine D2-like receptors by dopamine may elicit the extracellular release of anandamide through a mechanism that remains undetermined. Anandamide, in turn, may counteract D2-mediated motor behaviors by engaging CB1 cannabinoid receptors [23].

release can be induced by pharmacological activation of the D2 class of dopamine receptors in freely moving animals [23] suggests that endogenous cannabinoids may represent a primary component of the network of neurochemicals modulating striatal function. Further support to this hypothesis is provided by behavioral studies showing that the hyperactivity associated with post-synaptic D2 receptor activation [53,54] is markedly potentiated by the CB1 antagonist SR141716A [23]. Taken together, these data suggest that pharmacological blockade of cannabinoid receptors enhances quinpirole-induced motor activation by removing the inhibitory control exerted by the endogenously released anandamide. Furthermore, the lack of effect of SR141716A when given alone at the same dose used to potentiate quinpirole-induced motor activation [39,40], indicate that anandamide can reach a sufficient concentration to induce its behavioral effects only after stimulation of D2 receptors. Thus, the released anandamide may offset dopamine D2-induced facilitation of psychomotor activity (Fig. 1).

4. Cannabinoids and psychomotor disorders

Functional interactions between endogenous cannabinoids and dopaminergic system may have important therapeutic implications in pathologies that involve dysregulated dopamine neurotransmission, such as Parkinson's disease [55,56], Tourette syndrome [57,58], and schizophrenia [59,60]. On a speculative basis, the blockade of anandamide inactivation [24] and the consequent increase of endogenous levels of this lipid, may be beneficial in reducing hyperactivity and hyperkinesia associated with Huntington's disease, a pathology where a massive loss of CB1 receptor binding has been reported in the basal ganglia of postmortem

patients [61,62]. However, the potential therapeutic use of cannabinoids for the treatment of psychomotor disorders is not only matter of speculation. It has been shown that blockade of CB1 receptors may potentiate or prolong the effects of dopamine-based therapies currently used in Parkinson's disease [63,64] and use of Δ^9 -THC for the treatment of Tourette syndrome has been reported [65,66].

Increasing evidence suggests that schizophrenia may be associated with abnormalities in the function of the endogenous cannabinoid system. Clinical evidence indicates that cannabis consumption is significantly higher in schizophrenic patients than normal individuals [67] and chronic use of high doses of cannabinergic substances may precipitate schizophrenic symptoms in vulnerable patients [68,69]. Additional support for a role of cannabinoid signaling in schizophrenia comes from the observation that anandamide is markedly elevated in the cerebrospinal fluid (CSF) of schizophrenic individuals [8]. The non-cannabinoid acylethanolamide PEA is also increased in these patients. Although PEA is produced in the CNS through a biosynthetic mechanism similar to anandamide's [18], this lipid is not released *in vivo* as a consequence of D2-receptor stimulation. Therefore, further investigations are needed to clarify the physiological role of PEA in the CNS as well as its possible link to schizophrenia.

Drugs that block D2-like dopamine receptors have been extensively used to mitigate symptoms of psychoses and motor disorders. Given the linkage between D2-receptor activation and anandamide release, it is likely that the high CSF levels of this lipid may reflect homeostatic adaptations of the endogenous cannabinoid system to disturbances in dopamine neurotransmission occurring in schizophrenia [70–72]. Additional support for this possibility comes from the observation that chronic treatment with D2-family antagonists results in upregulated expression of CB1 receptor mRNA in striatum [73]. On the other hand, alterations in cannabinoid signaling may directly contribute to the manifestation of subgroups of symptoms in schizophrenic syndromes [7,8]. Further investigations in larger populations of patients and studies aimed at determining the neuronal origin of the AEs in CSF may help elucidate the possible participation of these lipids in the pathogenesis of schizophrenia.

5. Concluding remarks

The studies discussed in this review highlight the potential usefulness of the endogenous cannabinoid system as a target for novel therapeutic agents for the treatment of psychomotor disorders. Pathologies associated with dysfunction in dopamine transmission such as Parkinson's disease, Tourette syndrome, and schizophrenia are potential candidates to benefit from cannabinoid-based therapies. Yet, further basic research is necessary to improve our understanding of the role played by the endogenous cannabinoid system in these pathologies. Future efforts aimed at developing new drugs able to change the levels of endogenous cannabinoid ligands may result in more specific therapeutic interventions than those provided by direct-acting cannabimimetics.

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