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Review

The endocannabinoid system: a physiological perspective on its role in psychomotor control

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Abstract

The discovery of cannabinoid receptors has led to the identification of two natural activators for these receptors, anandamide and 2-arachidonoylglycerol, and to the elucidation of their biochemical pathways of formation and inactivation. Although the physiological significance of the endogenous cannabinoid system is still poorly understood, important information is becoming available on the possible functional roles of this system in the basal ganglia, a forebrain region that is involved in the control of sensorimotor and motivational aspects of behavior. These discoveries — which are going to enrich the way in which we look at basal ganglia functions — are summarized in this mini-review. The role of the endocannabinoids as modulators of psychomotor behaviors and the potential therapeutic perspectives deriving from the pharmacological manipulation of the endogenous cannabinoid system are also discussed.

Keywords: Cannabinoid receptors; Anandamide; 2-Arachidonoylglycerol; Dopamine; Basal ganglia; Psychosis

1. The endogenous cannabinoid system

The recreational and medicinal properties of cannabis-derived preparations have been known for centuries. The pharmacological actions of cannabis have been ascribed to its major constituent, Δ^9-tetrahydrocannabinol, which binds with high affinity to specific cannabinoid receptors, named CB1 and CB2 (Matsuda et al., 1990; Munro et al., 1993). Both receptors belong to the superfamily of G protein-coupled membrane receptors, inhibit adenylate cyclase and *N*- and *Q*-type calcium channel activity (Mackie and Hille, 1992; Howlett, 1995; Pan et al., 1996) and stimulate potassium channel conductance (Henry and Chavkin, 1995; Mackie et al., 1995). Despite these similarities, substantial differences in the primary structures of these receptors (45% overall homology) as well as in their anatomical distribution have been reported (for a review, see Pertwee, 1997). Although expressed throughout the body,

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CB1 receptors are particularly abundant in the central nervous system (CNS), where they mediate the psychotropic effects of cannabimimetic drugs (Fride and Mechoulam, 1993; Smith et al., 1994). By contrast, CB2 receptors have been primarily found in immune cells, suggesting a possible contribution of this receptor subtype to cannabinoid-mediated modulation of the immune response (Klein et al., 1998).

Just as the finding of opiod receptors led in the 1970s to the discovery of a series of morphine-like chemicals in the brain — the enkephalins and the endorphins —the identification of cannabinoid receptors has prompted a vast search for their naturally occurring ligands. As a result, two endogenous substances displaying cannabinoid-like effects have been identified (endocannabinoids), arachidonoylethanolamide (anandamide) (Devane et al., 1992; Di Marzo et al., 1994) and 2-arachidonoylglycerol (2-AG) (Mechoulam et al., 1995; Sugiura et al., 1995; Stella et al., 1997). Unlike classic neurotransmitters, anandamide and 2-AG are not stored into synaptic vesicles, but are produced upon demand through the cleavage of two

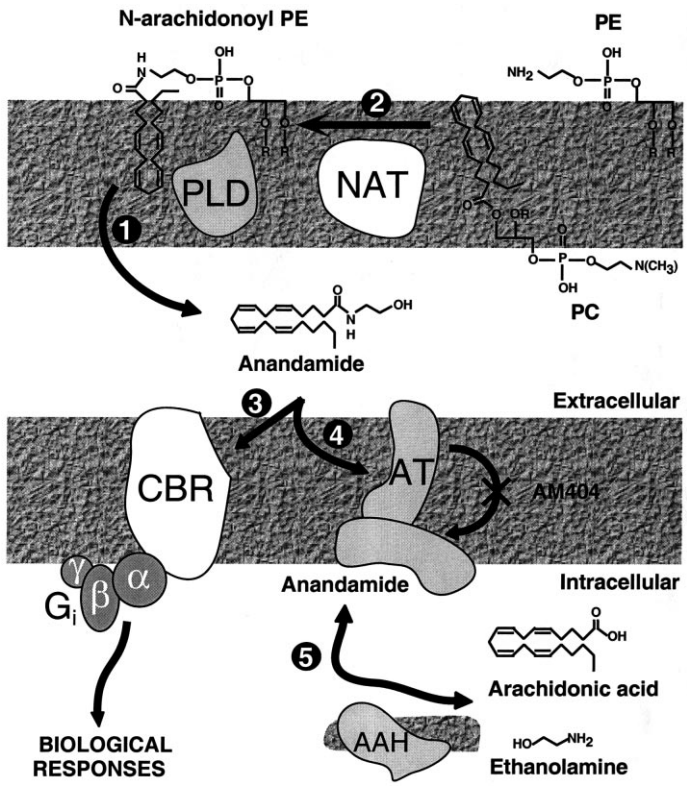

Fig. 1. Anandamide can be generated by hydrolysis of *N*-arachidonoyl phosphatidylethanolamine (*N*-arachidonoyl PE), catalyzed by phospholipase D (PLD) **(1)**. An *N*-acyl transferase activity (NAT) **(2)** mediates the synthesis of new *N*-arachidonoyl PE by detaching an arachidonate moiety from the *sn*-1 position of other phospholipids — such as phosphatidylcholine (PC) — and by transferring it to the primary amino group of PE. The NAT/PLD pathway described here gives also rise to a family of saturated and monounsaturated acylethanolamides, such as palmitoylethanolamide and oleylethanolamide (Schmid et al., 1996). Although these molecules do not activate cannabinoid receptors, they exert a variety of pharmacological effects, including anti-inflammation (Mazzari et al., 1996) and analgesia (Calignano et al., 1998). Newly formed anandamide is released into the extracellular space, where it can activate G protein-coupled cannabinoid receptors (CBR) **(3)**. Anandamide can be inactivated by a carrier-mediated transport (AT) **(4)**, which can be inhibited by AM404. Once inside the cells, anandamide is hydrolyzed into arachidonic acid and ethanolamine by a membrane-bound anandamide amidohydrolase (AAH) **(5)**. In vitro, AAH may also act in reverse, catalyzing the formation of anandamide from arachidonic acid and ethanolamine. R: fatty acid group.

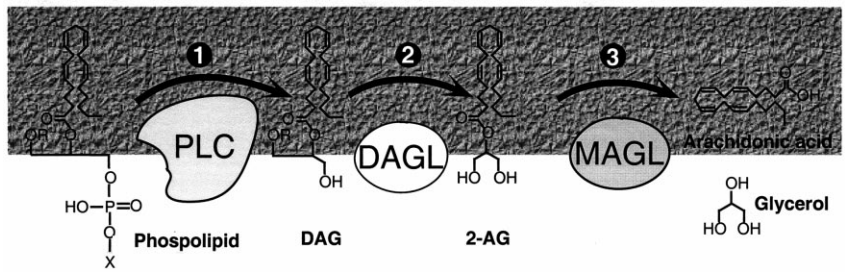

Fig. 2. Hypothetical mechanism of formation and inactivation of 2-arachidonoylglycerol (2-AG). Phospholipid hydrolysis by phospholipase C (PLC) produces 1,2 diacylglycerol (DAG) **(1)** which in turn, may be cleaved by a DAG lipase (DAGL) of unknown structure to yield 2-AG **(2)**. 2-AG may be taken up by cells through the same transport system as anandamide (not shown in Figure). Intracellular 2-AG may be hydrolyzed to arachidonic acid and glycerol by anandamide amidohydrolase (not shown) or by an uncharacterized esterase such as monoacylglycerol lipase (MAGL) **(3)**. Alternitively, 2-AG may be produced for the hydrolysis of phospholipids catalyzed by phospholipase A_1 (PLA_1), which forms lysophospholipids, followed by lysophospholipase C (lyso-PLC) (data not shown). Although the PLC/DAG lipase pathway may be predominant in cortical neurons (Stella et al., 1997), a role for the PLA_1/lyso-PLC pathway cannot be excluded (Piomelli et al., 1998).

distinct membrane phospholipid precursors (for a review, see Piomelli et al., 2000) (Fig. 1). This reaction appears to be initiated by activation of neurotransmitter receptors, as indicated by the enhanced outflow of anandamide in rat striatum following stimulation of dopamine D2-family receptors (Giuffrida et al., 1999). Similarly, application of cholinergic agonists has been shown to increase 2-AG production in the rat aorta (Mechoulam et al., 1998). After its release, anandamide is inactivated by carrier-mediated transport into cells (Beltramo et al., 1997; Hillard et al., 1997; Piomelli et al., 1999) followed by intracellular hydrolysis, catalyzed by a rather nonselective amidohydrolase enzyme (Deutsch and Chin, 1993; Désarnaud et al., 1995; Ueda et al., 1995; Cravatt et al., 1996) (Fig. 1). 2-AG, which may be taken up by cells through the same transport system as anandamide (Piomelli et al., 1999; Beltramo and Piomelli, 2000), is hydrolyzed intracellularly into glycerol and arachidonic acid by enzyme systems that include anandamide amidohydrolase (Goparaju et al., 1998) and an uncharacterized monoacylglycerol lipase (Stella et al., 1997; Goparaju et al., 1998, 1999) (Fig. 2). In intact astrocytoma cells, however, the contribution of anandamide amidohydrolase to anandamide hydrolysis appears to be minor, as indicated by the ineffectiveness of amidohydrolase inhibitors to prevent 2-AG metabolism (Beltramo and Piomelli, 2000).

The discovery of natural agonists at cannabinoid receptors and the identification of their biochemical pathways of formation and inactivation have spurred new interest on the physiological roles of these molecules throughout the body. These efforts have led to the identification of a possible regulatory function of the endocannabinoid system in the processing and execution of motor behaviors.

2. Cannabinoid actions and psychomotor control

The ability of cannabimimetic drugs to influence motor and cognitive performances is well documented (for a review, see Rodríguez de Fonseca et al., 1998). Indeed, cannabinoid administration in animals is accompanied by profound effects on motor behaviors (Hollister, 1986; Pertwee, 1997), which include catalepsy, decreased motor activity and attenuation of *d*-amphetamine-induced hyperactivity and stereotypy (Pryor et al., 1978; Gorriti et al., 1999). In humans, marijuana intoxication causes impaired performances in tests requiring fine psychomotor control (for example, tracking of a moving point on a screen with a stylus, or driving performance at flight simulators) (for a review, see Iversen, 2000). Moreover, cannabinoid substances produce a large spectrum of psychotropic effects, including

euphoria, working memory deficits and altered perception of space and time (Hall and Solowij, 1998). The psychomotor effects of cannabimimetic drugs are consistent with the anatomical distribution of CB1 receptors, which are highly expressed in areas of the CNS that play a key role in the regulation and planning of motor actions, such as the basal ganglia, cerebellum and neocortex (Herkenham et al., 1991a; Matsuda et al., 1993; Tsou et al., 1998). In keeping with this distribution, the inactivation of the CB1 receptor gene by homologous recombination produced a phenotype characterized by severe motor impairment and functional reorganization of the basal ganglia (Zimmer et al., 1999), a forebrain region involved in the sensorimotor and motivational aspects of behavior (Graybiel, 1995). Furthermore, in vivo microdialysis studies carried out in the rat striatum have shown the presence of extracellular levels of anandamide, which are modulated by activation of dopamine D2-family receptors (Giuffrida et al., 1999) (Fig. 3). These observations not only indicate that anandamide represents a primary component of the network of neurochemicals in the striatum, but also suggest a possible cross-talk between the endocannabinoid system and other neurotransmitters regulating basal ganglia functions. Although conclusive evidence for such interactions is still lacking, neuroanatomical studies have shown that striatal CB1 receptors are mainly localized in GABA-ergic medium-spiny neurons (Herkenham et al., 1991b; Mailleux and Vanderhaeghen, 1992) and are co-expressed with μ-opioid receptors (Navarro et al., 1998). Moreover, it is known that exogenous administration of cannabinoids can inhibit the stimulation-evoked release of striatal neurotransmitters, such as γ-aminobutyric acid (GABA) (Szabo et al., 1998) and regulates proenkephalin mRNA levels in the striatum (Mailleux and Vanderhaeghen, 1994).

3. Cannabinoid signaling and dopamine

There is substantial evidence supporting a role for the cannabinoid system as a modulator of dopaminergic activity in the basal ganglia. Administration of exogenous cannabinoids was found to increase dopamine release in rat nucleus accumbens (Chen et al., 1990; Gessa et al., 1998; Gardner and Vorel, 1998) and to excite dopaminergic neurons in the ventral tegmental area and substantia nigra (French et al., 1997). However, other studies indicate that cannabinoids potentiate the behavioral effects of dopamine antagonists (neuroleptics) (Anderson et al., 1996) and reduce

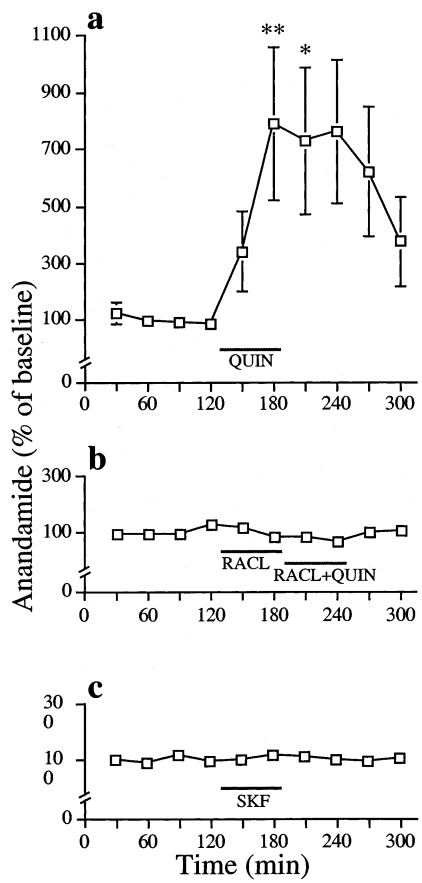

Fig. 3. Activation of D_2-like dopamine receptors evokes anandamide release in rat striatum. Effects on dialysate anandamide levels of intrastriatal administration of **(a)** quinpirole (QUIN, 10 μM), a D_2-like agonist; **(b)** raclopride (RACL, 20 μM), a D_2-like antagonist applied alone or with quinpirole; **(c)** SKF38393 (SKF, 10 μM), D_1-like agonist. Results are means ± SEM ($n = 6$ for each condition) of the amount of anandamide present in 30 min dialysate samples, expressed as percent of baseline values. One asterisk: $P < 0.05$; Two asterisks: $P < 0.001$ (ANOVA followed by Student–Newmann–Keuls multiple comparison test).

electrically evoked dopamine release from rat striatal slices (Cadogan et al., 1997). The possibility suggested by these results, that cannabinoids may regulate dopamine functions is supported by several biochemical and behavioral studies. In vivo experiments indicate that chronic treatment with dopamine D2-family receptor antagonists up-regulates CB1 receptor expression in the rat striatum (Mailleux and Vanderhaeghen, 1993). Further, injection of cannabinoid receptor agonists into the basal ganglia counteracts the motor responses of locally administered D2-receptor agonists (Sañudo-Peña et al., 1996, 1998; Sañudo-Peña and Walker, 1998). Even further, the hyperactivity associated with post-synaptic D2 receptor activation is accompanied by a dramatic increase of anandamide output in the striatum (Fig. 3) and is potentiated by the CB1 antagonist SR141716A (Giuffrida et al., 1999; Masserano et al., 1999). In keeping with these results, administration of the anandamide transport blocker, AM404 (Beltramo et al., 1997), has been shown to counteract several characteristic responses mediated by activation of post-synaptic D2-like receptors, such as apomorphine-induced yawning and quinpirole-induced motor activation (Beltramo et al., 2000). Taken together, these data point to a key role of the endogenous cannabinoid system in the regulation of psychomotor activity, and suggest that this system may offer a therapeutic target in pathologies involving a dysregulation of dopamine neurotransmission.

4. Cannabinoids and psychomotor disorders

The potential therapeutic use of cannabinoids for the treatment of psychomotor disorders is not only a matter of speculation. Indeed, pre-clinical studies have shown that blockade of CB1 receptors may be beneficial in the management of dyskinesias resulting from prolonged dopamine-based therapies in Parkinson's disease (Maneuf et al., 1997; Brotchie, 1998). Furthermore, oral administration of Δ^9-THC has been reported to alleviate tics and compulsive behaviors in patients affected by Tourette syndrome (Müller-Vahl et al., 1998, 1999).

Certain similarities between cannabis intoxication and some psychotic symptoms have focussed the attention of psychiatrists on the possible involvement of cannabinoids in the pathogenesis of schizophrenia (for a review, see Thomas, 1993). Heavy cannabis use may precipitate a toxic psychosis in individuals with a previous history of psychotic illness (Negrete et al., 1986; Andréasson et al., 1987; Linszen et al., 1994). This observation has led to propose a 'cannabinoid hypothesis of schizophrenia', which postulates that the psychotic symptoms of this disease result from a over-activity of the endogenous cannabinoid system (Emrich et al., 1997). In accordance with this theory, clinical trials of the CB1 receptor antagonist SR141716A, as a novel antipsychotic, are currently under way. However, down-regulation of CB1 cannabinoid receptors resulting from exposure to high levels of cannabinoid drugs may dampen the ability of the endogenous cannabinoid system to counteract dopamine actions, thus contributing to the manifestation of psychotic symptoms. This possibility is supported by the observation that chronic treatment with D2-family antagonists results in up-regulated expression of CB1 receptor mRNA in striatum (Mailleux and Vanderhaeghen, 1993), and by the finding that the behavioral responses induced by *d*-amphetamine — a screening test for antipsychotic drugs — are blocked by Δ^9-THC administration in non-habituated animals, but are potentiated in animals made tolerant to cannabinoids (Gorriti et al., 1999). In this context, the elevated levels of anandamide found in the cerebrospinal fluid of schizophrenic patients (Leweke et al., 1999) might result from a homeostatic adjustment of the endogenous cannabinoid system to a functional hyperdopaminergia, rather than being a direct cause of psychosis. Likewise, the propensity of schizophrenic patients to consume more cannabis than normal individuals (Dixon et al., 1991; Kovasznay et al., 1997) might be interpreted as a misguided attempt to 'self-medicate' the symptoms caused by a dysregulation of dopamine neurotransmission. Further investigations aimed at measuring CB1 receptor expression and determining the neuronal origin of the anandamide in CSF in a larger sample of

patients may help elucidate the possible contribution of the endocannabinoid system to the pathogenesis of schizophrenia.

5. Concluding remarks

The studies discussed in this review highlight the role played by the endocannabinoids in the modulation of psychomotor behaviors. The notion that these compounds are an important component of the neurotransmitter network regulating basal ganglia function is supported by experimental and clinical evidence. The existence of a cross-talk between the endocannabinoid and dopaminergic systems suggest the possibility to devise new strategies for the pharmacological manipulation of dopamine dysregulation, and may lead to novel cannabinoid-based therapies for the treatment of neuropsychiatric pathologies such as Parkinson disease, attention deficit hyperactivity disorders (ADHD) and schizophrenia.

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