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Authors

Rodríguez De Fonseca, F
Gorriti, MA
Bilbao, A
et al.

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Role of the Endogenous Cannabinoid System as a Modulator of Dopamine Transmission: Implications for Parkinson's Disease and Schizophrenia

FERNANDO RODRÍGUEZ DE FONSECA^{a*}, MIGUEL A. GORRITI^a, AINHOA BILBAO^a,
LETICIA ESCUREDO^a, LUIS MIGUEL GARCÍA-SEGURA^b, DANIELE PIOMELLI^c and MIGUEL NAVARRO^a

^aDepartamento de Psicobiología, Facultad de Psicología, Universidad Complutense de Madrid, SPAIN, ^bInstituto Cajal, Consejo Superior de Investigaciones Científicas, Madrid and ^cDepartment of Pharmacology, University of California at Irvine, USA

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The endogenous cannabinoid system is a new signaling system composed by the central (CB₁) and the peripheral (CB₂) receptors, and several lipid transmitters including anandamide and 2-arachidonylglycerol. This system is the target of natural cannabinoids, the psychoactive constituents of *Cannabis sativa* preparations (marijuana, hashish). Acute and chronic cannabis exposure has been associated with subjective feelings of pleasure and relaxation, but also to the onset of psychiatric syndromes, a decrease of the efficacy of neuroleptics and alterations in the extrapyramidal system regulation of motor activity. These actions points to a tight association of the cannabinoid system with the brain dopaminergic circuits involved in addiction, the clinical manifestation of positive symptoms of schizophrenia and Parkinson's disease. The present work discuss anatomical, biochemical and pharmacological evidences supporting a role for the endogenous cannabinoid system in the modulation of dopaminergic transmission. Cannabinoid CB₁ receptors are present in dopamine projecting brain areas. In primates and certain rat strains it is also located in dopamine cells of the A8, A9 and A10 mesencephalic cell groups, as well as in hypothalamic dopaminergic neurons controlling prolactin secretion. CB₁ receptors co-localize with dopamine D₁/D₂ receptors in dopamine projecting fields. Manipulation of dopaminergic transmission is able of altere the syn-

thesis and release of anandamide as well as the expression of CB₁ receptors. Additionally, CB₁ receptors can switch its transduction mechanism to oppose to the ongoing dopamine signaling. Acute blockade of CB₁ receptor potentiates the facilitatory role of dopamine D₂ receptor agonists on movement. CB₁ stimulation results in sensitization to the motor effects of indirect dopaminergic agonists. The dynamics of these changes indicate that the cannabinoid system is an activity-dependent modulator of dopaminergic transmission, an hypothesis relevant for the design of new therapeutic strategies for dopamine-related diseases such as the psychosis and Parkinson's disease.

INTRODUCTION

The endocannabinoid system in the brain is configured by the central cannabinoid receptor, CB₁ (Devane *et al.*, 1988), and the endogenous ligands anandamide (Devane *et al.*, 1992) and 2-arachidonyl glycerol (Mechoulam *et al.*, 1995; Stella *et al.*, 1997). Acute and chronic effects of *Cannabis sativa* derivatives on central nervous system

* Correspondence should be addressed to: Dr. Fernando Rodríguez de Fonseca and Dr. Miguel Navarro. Departamento de Psicobiología, Facultad de Psicología. Universidad Complutense de Madrid. Campus de Somosaguas, Madrid 28223. Phone 34-1-3943082, Fax 34-1-3943189, E-mail pspsc10@sis.ucm.es

functioning are mediated through the action of THC, its main psychoactive constituent (Gaoni and Mechoulam, 1964) on specific brain CB₁ cannabinoid receptors. The potential adverse effects of *Cannabis* consumption may include, among others, anxiety-like disorders (Halikas *et al.*, 1985; Rodríguez de Fonseca *et al.*, 1997), increased risk for the onset of psychotic syndromes (Andréasson *et al.*, 1987; Nuñez-Domínguez and Gurpegui-Fernández, 1997) and a decrease of the therapeutic effectiveness of neuroleptics (Knudsen and Vilmar, 1984). The psychopathological features associated to acute and chronic *Cannabis* exposure points to a tight connection between the endogenous dopamine transmission systems (dopamine-releasing and dopamine receptor-expressing neurons) and the endogenous cannabinoid system. Dopamine neurons, mainly those from the nigrostriatal and the mesocorticolimbic pathways, have been considered relevant for the process of reward and stress signals, drug addiction, and the positive symptoms of schizophrenia (Grace, 1991; Le Moal and Simon, 1991).

There is a growing literature confirming the above proposed contribution of the endogenous cannabinoid system in dopamine-related diseases such as addiction (Gardner and Vorel, 1998; Navarro *et al.*, 1998), stress (Rodríguez de Fonseca *et al.*, 1997), psychoses (Andréasson *et al.*, 1987; Knudsen and Vilmar, 1984; Nuñez-Domínguez and Gurpegui-Fernández, 1997) or extrapyramidal disorders such as Parkinson's disease or dystonias (Clifford, 1983; Glass *et al.*, 1997; Rodríguez de Fonseca *et al.*, 1994b and 1998). However, in order to understand that contribution to dopamine-related neuropsychiatric conditions we need to solve one of the striking challenges in the cannabinoid field: the explanation of the physiological role of a system densely present in dopamine-projecting brain areas, with a highly preserved neurobiological properties throughout the evolution, but with a low tonic activity as revealed by functional antagonism studies (Howlett, 1995; Gueu-

det *et al.*, 1995; Navarro *et al.*, 1997). In the present work we will briefly discuss the biochemical, anatomical and behavioral components of the interaction between dopamine and endocannabinoid systems. We will propose a model under which explore the potential relevance of these interactions for the understanding and treatment of neurodegenerative disorders such as Parkinson's disease, and psychiatric syndromes such as schizophrenia.

NEURONATOMICAL ANALYSIS OF THE PRESENCE OF CANNABINOID RECEPTORS IN BRAIN DOPAMINE CIRCUITS

Cannabinoid CB₁ receptors are distributed in the mammalian brain at a higher levels than any other known G-protein-coupled receptor (Herkenham *et al.*, 1990; Mailleux and Vanderhaeghen, 1992; Matsuda *et al.*, 1990 and 1993; Tsou *et al.*, 1998). They are expressed in areas of the central nervous system that contribute to the control of movement (caudate-putamen, globus pallidum, entopeduncular nucleus, substantia nigra and cerebellum), memory and cognition (hippocampal formation, cingulate cortex), processing of emotions and motivational responses (amygdalar complex, nucleus accumbens, olfactory cortex), pain perception (central gray matter, dorsal horn of spinal medulla), and neuroendocrine integration (paraventricular, arcuate, supraoptic and ventromedial hypothalamic nuclei). (Mailleux and Vanderhaeghen, 1992; Matsuda *et al.*, 1993). The analysis of this distribution reveals that the pharmacological profile described for CB₁ agonists (Dewey, 1986; Howlett, 1995) matches with the anatomical distribution of both CB₁-agonist binding sites and CB₁ mRNA. Interestingly, cannabinoid receptor antagonist SR141716A (Rinaldi-Carmona *et al.*, 1994) has been used to confirm this specific neuroanatomical profile, and has revealed the existence of an endogenous cannabinoid tone in the hippocampus, substantia nigra and limbic sys-

FIGURE 1 Neuroanatomical distribution of CB₁ receptors in the substantia nigra of the Wistar rat brain, as revealed by immunocytochemical double labelling and confocal microscopy. Red fluorescence corresponds to tyrosine hydroxylase (TH) immunopositive cells, whereas green fluorescence reveals the location of cannabinoid CB₁ receptors. Double labelling appears as a yellow/orange fluorescence. Details on the method have been previously described (Rodríguez de Fonseca *et al.*, 1999). **A.** Panoramic view of the substantia nigra pars compacta showing cells labelled only for TH (white arrow) or double-labelled for TH and CB₁ (yellow arrow). **B** and **C.** Higher magnification of the external border of the pars compacta, showing those cells and cells only labelled for CB₁ receptor (red arrow). **D.** Panoramic view of the substantia nigra showing TH-labelled dendrites from the pars compacta (white arrow) penetrating into the pars reticulata which express CB₁-receptor immunopositive terminals (white arrow) (See Color Plate I at the back of this issue)

tem which also correlates with the neuroanatomical distribution of CB₁ receptors (Gessa *et al.*, 1997; Gueudet *et al.*, 1995; Navarro *et al.*, 1997; Rodríguez de Fonseca *et al.*, 1997).

Although cannabinoid CB₁ receptors were formerly described in specific brain locations related to dopamine circuits, such as the basal ganglia, the extended amygdala and the limbic cortices, they seemed to be absent in brain dopaminergic neurons (Herkenham *et al.*, 1990; Matsuda *et al.*, 1993). However recent studies (Ong and Mackie, 1999; Rodríguez de Fonseca *et al.*, unpublished, see Figure 1) have revealed strain and species-specific differences in the distribution of CB₁ receptors in brain dopamine cells. We have found that in the Wistar rat, as opposed to the deeply studied Sprague-Dawley strain (Herkenham *et al.*, 1991; Matsuda *et al.*, 1993; Tsou *et al.*, 1998), dopaminergic cells express low to moderate amount of CB₁ receptors. Similar findings were reported in the primate brain, (Ong and Mackie, 1999), supporting the possibility of a direct action of CB₁ receptor agonists on dopamine neurons, as suggested in early electrophysiological studies using pharmacological antagonists of the CB₁ receptor (French *et al.*, 1997; Guedet *et al.*, 1995)

It is generally accepted is that CB₁ receptors co-localize with dopamine receptors in neurons of dopamine-projecting fields such as the basal ganglia and limbic cortex (Herkenham *et al.*, 1991; Mailleux and Vanderhaeghen, 1993). Both kind of receptors are mostly found in GABAergic projecting neurons, (although glutamatergic neurons expressing CB₁ receptors have been reported, including those from the cortex and the subthalamic nuclei, Rodríguez de Fonseca *et al.* 1998; Sañudo-Peña and Walker, 1997). In the basal ganglia circuitry, GABAergic medium-spiny striatal neurons that express CB₁ receptors, receive afferents from dopamine neurons of the substantia nigra pars compacta and show co-expression of dopamine D₁, D₂ and D₃ receptors (Surmeier *et al.*, 1996). Their axon ter-

minals innervating the globus-pallidum, substantia nigra pars reticulata and subthalamic nucleus contain high amounts of CB₁ receptors (Herkenham *et al.*, 1991). Figure 2 illustrates a typical image of functional cannabinoid CB₁ receptors in the mesencephalon of the rat, mapped by CB₁ agonist-stimulated GTPγS incorporation (Sim *et al.*, 1996). The dense activation of the substantia nigra, mainly the pars reticulata, indicates the potential relevance of the endogenous cannabinoid system in basal ganglia functioning.

FUNCTIONAL ASPECTS OF CANNABINOID-DOPAMINE INTERACTIONS

In the brain areas described above, relevant for most neuropsychiatric diseases, CB₁ stimulation might either directly modulate the activity of dopaminergic neurons or interfere with the transduction of dopamine signal at postsynaptic dopamine receptors co-localized with CB₁. The presence of CB₁ receptors in dopamine cells allow a direct regulation of dopaminergic activity (i.e. spontaneous and evoked firing, synthesis and release of dopamine, etc...) by the endogenous cannabinoid system.

Several experimental approaches have shown both possibilities (for review see Gardner and Vorel, 1998; Rodríguez de Fonseca *et al.*, 1998). Interaction between dopamine receptors and CB₁ receptors has a neurobiological support in the similar structure of both receptorial systems. These receptors belong to the family of G-protein coupled receptors for neurotransmitters (Matsuda *et al.*, 1990; Howlett, 1995). Both types of receptors are coupled to the same transduction systems, including the control of cAMP synthesis, and the regulation of Ca²⁺ and K⁺ channels (Hampson *et al.*, 1995; Howlett, 1995; Mackie and Hille, 1992).

FIGURE 2 Coronal autoradiography showing the stimulatory effects of the cannabinoid CB₁ receptor agonist WIN 55,212-2 on GTP γ -S incorporation in the mesencephalon of the rat brain. WIN 55,212-2 (5 μ M) produced a marked incorporation of GTP γ -S in the substantia nigra of the rat brain, which appear heavily labelled (SN, red color). Other areas specifically labelled were the ventral tegmental area (VTA), the periaqueductal graymatter (PAG) and the superficial layer of the superior colliculus (SC) (See Color Plate II at the back of this issue)

Dopamine-cannabinoid interactions in the nigrostriatal system

At the level of the different dopamine circuits, the role of the endogenous cannabinoid system seemed to be different. In the *nigrostriatal* pathway most of the effects observed after CB₁ receptor stimulation point to an indirect regulation of dopaminergic activity, through the action of CB₁ receptor expressing GABAergic neurons of the outflow nuclei of basal ganglia (Maneuf *et al.*, 1996, Navarro *et al.*, 1993b; Pertwee and Greentree, 1988). Striatal dopamine turnover was not

found to be affected after acute THC exposure neither in Sprague-Dawley (Rodríguez de Fonseca *et al.*, 1992) nor in Wistar rats (Navarro *et al.*, 1993b). However, acute systemic administration of cannabinoid receptor agonists were found to induce a small increase in the spontaneous activity of nigrostriatal dopaminergic neurons measured by either extracellular recordings (French *et al.*, 1997) or by in vivo voltammetry in the striatum (Ng Cheong *et al.*, 1988). The direct or indirect nature of these effects remains to be conclusively determined. However, a recent

study has partially clarified the links between the endogenous cannabinoid system and dopamine transmission. (Giuffrida *et al.*, 1999). In this study we have demonstrated by *in vivo* microdialysis that the extracellular levels of anandamide in the dorsal striatum are greatly increased after the activation of dopamine D₂ family of receptors (i.e. after quinpirole infused by reverse dialysis), but not after stimulation of dopamine D₁ receptors (i.e. after infusion with the D₁ agonist SKF 38393). The D₂-receptor evoked anandamide release may serve to limit the extent of behavioral activation induced by dopamine in the striatum. These findings are in agreement with other reports showing an increased behavioral response to the indirect dopamine receptor agonist amphetamine in animals chronically treated with the cannabinoid receptor agonist THC and displaying down-regulated CB₁ receptors (Gorriti *et al.*, 1999; Rodríguez de Fonseca *et al.*, 1994a). As shown in figure 3, the pretreatment with the CB₁ antagonist SR141716A potentiates the stimulation of motor behavior elicited by systemic administration of quinpirole. This effect was not observed when the facilitatory effect on movement was induced by a D₁ agonist (Figure 4). Other laboratories have described pharmacological interactions between dopamine D₂ receptor and cannabinoid CB₁ receptors which support this model. Thus, the group of J.M. Walker has shown that regional administration of D₂ family of agonists opposes the behavioral responses to the injection of CB₁ agonists (Sañudo-Peña *et al.*, 1996; Sañudo-Peña and Walker, 1998).

Although the triggering of anandamide release seems to be dependent on D₂ receptor stimulation, the dopamine D₁ receptors plays also an important role in these cannabinoid-dopamine interaction. Thus, a previous report (Mailleux and Vanderhaeghen, 1993) demonstrated that the chronic blockade of D₁ receptors, which induce a compensatory hyperactivity in nigrostriatal dopaminergic cells, dramatically upregulated the expression of the CB₁

receptor mRNA in the dorsal striatum. Additional behavioural studies showed that CB₁ agonists blocked rotational behaviour induced by dopamine D₁ receptor agonists (Anderson *et al.*, 1995) whereas repeated stimulation of dopamine D₁ receptors (Rodríguez de Fonseca *et al.*, 1994) resulted in a potentiation of cannabinoid agonist-induced catalepsy and akinesia. These data suggest the existence of differences in the interactions between dopaminergic and cannabinoid systems regarding the different receptors involved. A current working hypothesis on the interaction between cannabinoid and dopamine receptors in the striatum is depicted in figure 5.

Whether these pharmacological effects are selective for the dorsal striatum or appear in other brain areas remains to be determined. Regional differences on the role of CB₁ receptors in controlling basal ganglia activity at mesencephalic sites have been proposed because of the dense presence of cannabinoid receptors in the substantia nigra (Glass *et al.*, 1997a). Thus, it has been found that cannabinoids activate substantia nigra pars reticulata neurons, probably by inhibiting GABA release from striatonigral projections through the stimulation of presynaptic CB₁ receptors (Tersigni and Rosemberg, 1996). This blockade of GABA release may be responsible for the *in vivo* observed increased activity of nigrostriatal dopamine neurons after acute cannabinoid exposure since they are under the influence of the striatonigral pathway (French *et al.*, 1997; Gueudet *et al.*, 1995; Ng Cheong *et al.*, 1988). An additional indirect source of regulatory inputs to the substantia nigra comes from the striatum through the subthalamic nucleus, whose activity may be modulated by CB₁ stimulation (Sañudo-Peña and Walker, 1997). On the other hand, cannabinoid receptors in the striatum seem to be negatively coupled to K⁺-stimulated (Navarro *et al.*, 1993) or electrically-evoked (Cadogan *et al.*, 1997) dopamine release, as revealed by *in vitro* studies. A balance between the activity of converging influences to the substantia nigra and local regulatory activi-

FIGURE 3 Effects of pretreatment with the cannabinoid CB₁ receptor antagonist SR141716A (1 mg/kg, i.p. 30 min. prior to second drug administration) on the acute effects of the dopamine D₂ receptor agonist quinpirole (0.025, 0.25 and 1 mg/kg, s.c.) on motor activity in male Wistar rats. Data were collected at different times after the injection of quinpirole (5, 60 or 120 min) to reveal the characteristic time and dose-dependent biphasic components of dopamine D₂ receptor agonists on motor behavior: an initial early inhibitory component derived of the stimulation of presynaptic D₂ receptors, and a late stimulatory component derived of the activation of postsynaptic receptors. Data were expressed as total time spent in absolute quietness (immobility, upper panels) or the number of crossings scored in a standard open field test (crossings, lower panels). Blockade of CB₁ receptors with SR141716A potentiates quinpirole-induced alterations on behavior, supporting for a role of the endogenous cannabinoid system in regulating dopamine facilitation of motor behavior. * $P < 0.05$ vehicle versus SR141716A-treated animals, # $P < 0.05$ versus vehicle-treated (0 dose) animals of the same pretreatment, Newman-Keuls

ties will then establish the nature of the actions of CB₁ agonists on the dopamine release in the striatum. Pharmacological manipulations of the acute sensitivity to cannabinoids by concurrent administration of GABAA and GABAB receptor acting drugs (Pertwee and Greentree, 1988; Romero *et al.*, 1995) support the involvement of GABA neurons in the mediation of cannabinoid

effects. This contribution can also be deduced from the finding of CB₁ receptor agonist-induced changes in striatal dopamine receptors (Navarro *et al.*, 1993b; Rodríguez de Fonseca *et al.*, 1992) or by the profound alterations in neuropeptide gene expression found in striatal GABAergic cells of CB₁ receptor-knockout mice (Steiner *et al.*, 1999).

FIGURE 4 Lack of effects of pretreatment with the cannabinoid CB₁ receptor antagonist SR141716A (1 mg/kg, i.p. 30 min. prior to second drug administration) on the acute facilitatory effects of the dopamine D₁ receptor agonist SKF 38393 (5 mg/kg, s.c.) on motor activity in male Wistar rats. Data were expressed as total time spent in absolute quietness (immobility, upper panels). They were collected at different times (5, 30, 60 or 120 min) after the injection of the D₁ agonist. * $P < 0.05$ versus saline-treated animals, Newman-Keuls

Dopamine-cannabinoid interaction in the mesocorticolimbic circuits

The *mesocorticolimbic* dopaminergic system has been found to be more sensitive than the nigrostriatal pathway to the acute administration of cannabinoids (Gardner and Vorel, 1998). First descriptions of THC actions in the brain pointed to an stimulation of mesocorticolimbic dopaminergic activity (Chen *et al.*, 1990). Direct extracellular recordings showed that systemic

administration of CB₁ agonists increased the activity of ventral tegmental area dopaminergic neurons (French *et al.*, 1997), associated to an increased dopamine release in the mesolimbic targets (Chen *et al.*, 1990; Gardner *et al.*, 1988; Gardner and Vorel 1998). However, whether this effect is produced by direct stimulation of CB₁ receptors present in dopaminergic cells or by transynaptic stimulation remains to be conclusively determined. In this respect, further research is required to establish a role for

dopamine D₂ and D₁ receptors on the response of mesocorticolimbic dopaminergic cells to acute cannabinoid exposure. On the other hand, blockade of CB₁ receptors with SR 141716A does not affect ventral tegmental area activity (Gueudet *et al.*, 1995), whereas μ -opioid receptor antagonists (naloxone, naloxonazine) block the increased dopamine release induced by CB₁ agonists administration, acting probably both at the ventral tegmental area neurons (Tanda *et al.*, 1997) and at their projecting terminals in the nucleus accumbens (Chen *et al.*, 1990; Gardner and Vorel, 1998). An interesting additional hypothesis is the possible glucocorticoid dependence of CB₁ agonists-induced mesolimbic activation. Cannabinoids are chemical stressors which activate the pituitary adrenal axis by stimulating ACTH release (Martín-Calderón *et al.*, 1998). They also induce anxiety-like responses (Rodríguez de Fonseca *et al.*, 1997). Acute stress is associated with a rapid activation of mesolimbic circuitry that can be mediated by glucocorticoid receptors present in mesolimbic dopaminergic neurons (Piazza *et al.*, 1996). Whether cannabinoid-induced activation of mesolimbic activity depends on the activation of pituitary-adrenal axis remains to be conclusively determined, but its demonstration may help support clinical observations on the role of *Cannabis* consumption as a vulnerability factor for the onset of psychosis or drug addiction (Andreasson *et al.*, 1987; Rodríguez de Fonseca *et al.*, 1997).

CANNABINOID-DOPAMINE INTERACTIONS AND DOPAMINE-RELATED DISEASES: WHAT IS NEXT?

As described above, endogenous cannabinoids are local mediators released to regulate information processing within the main relays of the basal ganglia nuclei. The suggested constitutive activity of the CB₁ receptor and its potential bidirectional coupling to the adenylate cyclase

suggest that this regulatory function affects processes of opposed nature within the striatum, indicating a potential role for this system as an homeostatic set-point mechanism (Glass and Felder, 1997b; Maneuf and Brotchie, 1997; Rodríguez de Fonseca *et al.*, 1998). The induction of a functional blockade of neurotransmitter uptake processes derived from CB₁ stimulation can affect to neurotransmitters of opposed nature, such as glutamate and GABA, supporting again this buffering role for the endogenous cannabinoid signalling within striatum (Maneuf *et al.*, 1996). Much work is needed in order to identify the potential regional variabilities in these mechanisms, as well as the pathological conditions on which a clear contribution of the endogenous cannabinoid system may enhance our knowledge of neurological disorders.

The research findings discussed in this manuscript suggest that the endogenous cannabinoid system may serve as a target for the development of new strategies for the treatment of dopamine-related diseases, such as motor syndromes. Among those movement disorders, Parkinson's Disease and neuroleptic-induced dyskinesias and dystonias are firmly clinical entities that may be benefitted from therapy based on the endogenous cannabinoid system, together with Gilles de la Tourette syndrome and Huntington's chorea (Rodríguez de Fonseca *et al.*, 1998). As a potential practical utility of the model we can propose cannabinoid agonist for reducing unwanted effects of L-DOPA or dopaminergic agonists in Parkinson's disease or neuroleptic associated tardive dyskinesias, as well as a cannabinoid antagonist for reducing the effective dose of L-DOPA or dopamine agonists needed to alleviate akinesia (Maneuf *et al.*, 1997; Rodríguez de Fonseca *et al.*, 1998).

Besides motor disorders several neuropsychiatric conditions could also benefit from the availability of new compounds acting at the cannabinoid receptors, such as new and selective antagonists. That goal can also be addressed by designing drugs which may interfere with new

FIGURE 5 A proposed model for the interactions between dopaminergic transmission and the endogenous cannabinoid system in the dorsal striatum. Dopamine released from axon terminals of substantia nigra pars compacta neurons facilitates motor behavior through the activation of both dopamine D_2 and D_1 receptors located in medium-spiny GABAergic neurons of the dorsal striatum. Simultaneously, activation of dopamine D_2 receptors triggers the release of anandamide from a plasmalemma precursor, which in turn limited the activatory effects of dopamine by stimulating CB_1 receptors. Although depicted as a postsynaptic mechanism, anandamide could be originated through the activation of presynaptic D_2 receptors, and eventually may act at presynaptic CB_1 receptors

molecular mechanisms involved in cannabinoid transmission, such as the recently described anandamide transporter (Beltramo *et al.*, 1997). This latest target has open multiple possibilities for the treatment of dopamine-related diseases. A cardinal example could be the acute symptoms of schizophrenia, which are currently attributed, among other mechanisms, to an

hyperdopaminergic state. As depicted in figure 5, anandamide can act as a local mediator regulating dopamine activity. If anandamide release is also triggered in cortical areas upon dopamine D_2 receptor activation, as described in the dorsal striatum (Giuffrida *et al.*, 1999), an enhancement of anandamide levels through the pharmacological blockade of anandamide uptake or hydroly-

sis may act as a neuroleptic through its inhibitory action on dopamine receptor-evoked responses. In support of this hypothesis, preliminary reports have described the presence of elevated levels of anandamide in the cerebrospinal fluid of schizophrenia patients (Leweke *et al.*, 1999). An additional advantage of such therapeutic approach derives from the fact that anandamide is a partial agonist: the uptake blocker-induced rise in synaptic anandamide may not produce the unwanted side effects, including catalepsy, acute stress-like reactions or the fort receptor desensitization that characterize the action of full CB₁ receptor agonists (Dewey, 1986; Howlett, 1995).

The buffering effects of cannabinoids on synaptic transmission processes points to a neuroprotectant role for drugs aimed to potentiate cannabinoid transmission. Although glucocorticoid-dependent neuronal loss in the hippocampus has been found in rats after chronic treatment with THC (Landfield *et al.*, 1988) neuroprotective actions derived of cannabinoid CB₁ receptor stimulation have been described both *in vivo* and *in vitro* (Nagayama *et al.*, 1999). These findings indicate that a rational use of drugs aimed to the cannabinoid CB₁ receptor may protect neurons from different types of injuries derived of overstimulation of glutamate or dopamine release in central synapses.

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