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UCM707, an inhibitor of the anandamide uptake, behaves as a symptom control agent in models of Huntington's disease and multiple sclerosis, but fails to delay/arrest the progression of different motor-related disorders

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Abstract To date, UCM707, (5Z,8Z,11Z,14Z)-*N*-(3-furylmethyl)eicosa-5,8,11,14-tetraenamide, has the highest potency and selectivity in vitro and in vivo as inhibitor of the endocannabinoid uptake. This may enable this compound to potentiate endocannabinoid transmission, with minimal side effects, in the treatment of several neurological disorders. In the present study, we examined whether the treatment with UCM707 produced beneficial effects, as other cannabinoid-related compounds have already shown, to alleviate motor deterioration or to delay/arrest neurodegeneration, in several models of neurological diseases such as Huntington's disease (HD), Parkinson's disease (PD) and multiple sclerosis (MS). UCM707 exhibited a notable anti-hyperkinetic activity in a rat model of HD generated by bilateral intrastriatal application of 3-nitropropionic acid. This effect was possibly associated with an amelioration of GABA and glutamate deficits induced by the toxin in the globus pallidus and the substantia nigra, respectively. However, UCM707 did not protect against the death of GABAergic neurons that occurs in rats with striatal atrophy generated by unilateral application of malonate, another animal model of HD, which is more useful to test neuroprotective strategies.

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In addition, UCM707 did not provide neuroprotection in rats with unilateral lesions of the nigrostriatal dopaminergic neurons caused by 6-hydroxydopamine, a rat model of PD. This was possibly due to the fact that UCM707 is devoid of anti-oxidant properties since another uptake inhibitor, AM404, that has these properties acted as a protective agent. Lastly, UCM707 was also unable to inhibit the development of the neurological impairment of rats with experimental autoimmune encephalomyelitis (EAE), an acute model of MS. However, UCM707, like other endocannabinoid uptake inhibitors reported previously, significantly reduced spasticity of the hindlimbs in a chronic relapsing EAE mice, a chronic model of MS. In summary, UCM707 might be a promising compound in HD to alleviate motor symptoms, which represents an important goal considering the current lack of efficient pharmacological treatments in this basal ganglia disorder. However, the compound was unable to delay neurodegeneration in this disorder and also in PD. In addition, UCM707 did not produce any neurological recovery from inflammatory attack in an EAE rat model of MS, although it retained the classic anti-spastic action shown by other uptake inhibitors in the EAE mouse model of this disease.

1. Introduction

Within the present interest in the endocannabinoid signaling system as a possible target for the treatment of several neurological disorders, special attention has been paid to the mechanism of endocannabinoid uptake (for a recent review, see McFarland and Barker, 2004). This mechanism is part of the process of termination of the biological activity of these endogenous compounds (Giuffrida et al., 2001). There are therapeutic possibilities offered by compounds, such as *N*-(4-hydroxyphenyl)-arachidonamide (AM404; for details, see Khanolkar et al., 1996; Beltramo et al., 1997), *N*-(4-hydroxy-2-methylphenyl)-arachidonamide (VDM11; for details, see De Petrocellis et al., 2000), or (*S*)-*N*-oleoyl-(1′-hydroxybenzyl)-2′-ethanolamine (OMDM2; for details, see Ortar et al., 2003) that block this process. These compounds, termed "indirect agonists," act by potentiating the action of endogenous ligands, and hence, they may be used in diseases where an increase in endocannabinoid transmission has been postulated to be of therapeutic value (Giuffrida et al., 2001; Pertwee, 2002). The use of these compounds may make possible to minimize the unwanted effects produced by the "direct activation" of cannabinoid CB_1 receptors with classical cannabinoids, through the control of endocannabinoid levels in a concentration range that avoids psychoactive side effects (Felder and Glass, 1998). However, some of these compounds, such as the case of AM404, may also behave as agonists of vanilloid TRPV1 receptors (Zygmunt et al., 2000) and, then, exhibit direct effects by itself (González et al., 1999; Beltramo et al., 2000).

We have recently designed and synthesized a series of arachidonic acid derivatives (López-Rodriguez et al., 2001, 2003a) that exhibit a high potency and selectivity in vitro as inhibitors of the endocannabinoid uptake, with negligible affinity for cannabinoid, CB_1 and CB_2, and vanilloid TRPV1 receptors, and the fatty acid amide hydrolase (FAAH) enzyme that hydrolyses endocannabinoids. One of these compounds, (5Z,8Z,11Z,14Z)-*N*-(3-furylmethyl)eicosa-5,8,11,14-tetraenamide, so-called UCM707, is the most potent and selective endocannabinoid uptake inhibitor described to date (López-Rodriguez et al., 2001, 2003a,b). In vivo, this compound does not produce any relevant cannabimimetic effects, such as hypomotility and antinociception (de Lago et al., 2002). However, it exhibited an interesting capability to enhance the hypokinetic and antinociceptive actions of subeffective doses of anandamide (de Lago et al., 2002). This may allow UCM707 to be used in several neurological disorders, where an elevation of the endocannabinoid tone has been postulated to have therapeutic benefits. Among these disorders, we can include Huntington's disease (HD), a genetic motor disorder characterized by striatal atrophy and hyperkinetic symptoms (see Cattaneo et al., 2001, for review). In HD, the elevation of the endocannabinoid tone has been reported to be antihyperkinetic and transiently correct the neurochemical deficits, although the concomitant activation of the vanilloid TRPV1 receptors seems to be necessary (Lastres-Becker et al., 2002, 2003a). UCM707 may also be useful to delay/arrest the progress of neurodegeneration in HD and Parkinson's disease (PD). PD is another neurodegenerative motor disorder which originates from the death of nigrostriatal dopaminergic neurons and causes a motor deterioration characterized by bradykinesia, rigidity and tremor (see Blandini et al., 2000, for review). This hypothesis is based on two observations: (i) that plant-derived, synthetic or endogenous cannabinoid agonists have been reported to be neuroprotective in acute or chronic neurodegeneration (see Fernández-Ruiz et al., 2005, for a recent review), and (ii) that production of endocannabinoids and even induction of specific cannabinoid receptor subtypes seem to be associated with the progression of neurodegeneration, presumably as a part of an endogenous protective response (see Fernández-Ruiz et al., 2005, for a recent review). Finally, UCM707 might provide symptom control in multiple sclerosis (MS), a neurological disease of autoimmune origin. MS is characterized by the occurrence of several neurological signs, such as paralytic attack and the development of residual paresis, including the development of spasticity, tremor, ataxia and pain (see Baker and Pryce, 2003, for review). In this disease, both direct or indirect (i.e., inhibitors of endocannabinoid inactivation) agonists of cannabinoid receptors have shown therapeutic benefits by alleviating specific signs (Baker et al., 2000, 2001) or by reducing the general neurological impairment from the inflammatory attack (Lyman et al., 1989; Wirguin et al.,