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Influence of corticostriatal δ-opioid receptors on abnormal involuntary movements induced by L-DOPA in hemiparkinsonian rats

Fabrice Billet [1], Jean Costentin, Nathalie Dourmap *

Experimental Neuropsychopharmacology Laboratory (EA 4359), University and Hospital Institute of Biomedical Research, University of Rouen, IFR23, 76183 Rouen, France

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ABSTRACT

Chronic L-3,4-dihydroxyphenylalanine (L-DOPA) treatment of Parkinson's disease induces in time numerous side effects, such as abnormal involuntary movements called L-DOPA-induced dyskinesias (LIDs). An involvement of glutamate transmission, dopamine transmission and opioid transmission in striatal output pathways has been hypothesized for the induction of LIDs. Interestingly, our previous experiments indicated that some striatal δ-opioid receptors are located on terminals of glutamatergic corticostriatal neurons and that stimulation of these receptors modulates the release of glutamate and dopamine. The present study was performed to test the involvement of δ-opioid receptors, and more precisely of those located on corticostriatal neurons, in abnormal involuntary movements induced by L-DOPA in hemiparkinsonian rats. The effects of a selective agonist, [D-Pen^2, D-Pen^5]-enkephalin (DPDPE) and a selective antagonist (naltrindole) of δ-opioid receptors on LIDs were investigated in animals submitted or not to a corticostriatal deafferentation. Our results indicate that DPDPE and naltrindole respectively enhanced and reduced LIDs in animals in which the ipsilateral cortex was preserved intact. However, the lesion of the ipsilateral cortex prevented the stimulant effect of DPDPE on LIDs. The [^{3}H]-DPDPE binding to striatal membranes prepared from the whole striatum was also studied. A significant increase in density of δ-opioid receptors was found in the striatum of dyskinetic animals as compared to non-dyskinetic animals but this difference was abolished by the corticostriatal deafferentation. These results indicate that δ-opioid transmission modulates the expression of LIDs in rodents and suggest that the δ-opioid receptors involved in this effect are located on terminals of corticostriatal neurons.

Introduction

Parkinson's disease (PD) is one of the most frequent neurological disorders of the elderly. It is characterized by tremor, rigidity, akinesia and loss of postural reflexes. Although effective at early stages, the common treatment with the dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) induces in time numerous side effects in the majority of patients, such as abnormal involuntary movements (AIMs) called L-DOPA-induced dyskinesias (LIDs). As a matter of fact, it has been reported that LIDs are observed in up to 80% of patients 5 years after the initiation of L-DOPA therapy (Hurtig, 1997; Nutt, 2001). However, the appearance of these motor complications, their severity and their clinical course fluctuate extensively. In addition to this disparity, the treatment of LIDs is complicated even more by the existence of numerous hypotheses concerning the neurochemical alterations underlying their development.

Pulsatile stimulation of post-synaptic dopamine receptors coupled with the progressive loss of nigrostriatal neurons is commonly thought as the most important factor in the development of LIDs (Olanow et al., 2006). According to this hypothesis, LIDs can be prevented or reversed by long-acting dopaminergic agonists providing a more continuous stimulation of striatal dopamine receptors (Olanow, 2004; Steiger, 2008). However, constant dopaminergic stimulation is expensive and impractical for the routine treatment of a large number of patients. Furthermore, dopamine agonists may also produce adverse effects such as nausea, symptomatic orthostatic hypotension, dizziness, somnolence or hallucinations (Pahwa et al., 2006).

On the contrary to the "dopamine hypothesis", numerous studies performed in animal models support the view that drugs acting to inhibit glutamate transmission can ameliorate the motor complications associated with the L-DOPA therapy and therefore strongly implicate glutamate receptors in the pathogenesis of LIDs (for reviews, see Cenci

Abbreviations: AIMs, abnormal involuntary movements; DPDPE, [D-Pen^2, D-Pen^5]-enkephalin; EDTA, ethylenediaminetetraacetic acid; 6-OHDA, hydroxydopamine hydrochloride, HPLC, high performance liquid chromatography; L-DOPA, L-3,4-dihydroxyphenylalanine + benserazide; LID, L-DOPA-induced dyskinesia; MFB, medial forebrain bundle; NMDA, N-methyl-D-aspartate; PD, Parkinson's disease; A/P, anteroposterior coordinate; M/L, mediolateral coordinate; D/V, depth/vertical coordinate.

* Corresponding author. Fax: +33 235 14 86 03.
E-mail address: nathalie.dourmap@univ-rouen.fr (N. Dourmap).
[1] Present address: Myelin Maintenance & Peripheral Neuropathies Laboratory (EA 6309), University of Limoges, FR 3503 GEIST, 87025 Limoges, France.

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and Konradi, 2010; Sgambato-Faure and Cenci, 2012). Furthermore, amantadine, which is thought to mainly act as an antagonist of NMDA receptors, is clinically considered as an effective treatment of LIDs (da Silva-Junior et al., 2005; Del Dotto et al., 2001; Pahwa et al., 2006). However, the duration of amantadine benefit is relatively brief (Thomas et al., 2004) and amantadine administration also induces adverse effects such as confusion, worsening of hallucinations, oedema or livedo reticularis (Crosby et al., 2003; Hayes et al., 2006; Sladden et al., 2003).

Numerous other neurochemical and molecular factors have been proposed from animal models and/or PD patients as potentially responsible for LIDs, including for instance GABA receptors (Calon and Di Paolo, 2002; Calon et al., 1999), adenosine A_{2A} receptors (Calon et al., 2004; Chase et al., 2003; Kase et al., 2003) and neuropeptides (Cenci et al., 1998; Fritschi et al., 2003; Henry and Brotchie, 1996). Among the latter, a particular interest was devoted to opioid peptides whose precursors, as proenkephalin or prodynorphin, or respective mARNs, appear overexpressed in the dopamine-depleted striatum, in animal models of LIDs and/or in postmortem brain tissue studied from PD patients treated with L-DOPA (Aubert et al., 2007; Brotchie et al., 1998; Carta et al., 2008; Hanrieder et al., 2011; Henry and Brotchie, 1996; Henry et al., 2003; Nisbet et al., 1995), suggesting that upregulation in the activity of inhibitory indirect striatopallidal enkephalinergic or direct striatonigral dynorphinergic pathways occurred after repeated D1 receptor stimulation (Carta et al., 2008). Furthermore, increased opioid transmission has been shown by positron emission tomography in PD patients affected by LIDs (Piccini et al., 1997) and a positive correlation has been demonstrated in primates between LIDs and activation of opioid receptors in the striatum (Chen et al., 2005), which is thought as a key structure in the control of psychomotor behaviors. Interestingly, our previous experiments performed in normal rats (Billet et al., 2004, 2007) indicated that some striatal δ-opioid receptors are located on terminals of glutamatergic corticostriatal neurons and that the stimulation of these receptors modulates the release of glutamate and, as a consequence, the release of dopamine, two neurotransmitters on which focus the main hypotheses of LIDs. However, although naltrindole, an antagonist of δ-opioid receptors, has been shown to reduce LIDs in primates (Henry et al., 2001), the involvement of striatal δ-opioid receptors in LIDs remains controversial since alterations in striatal δ-opioid radioligand binding were observed between non-dyskinetic and dyskinetic rats (Johansson et al., 2001) but not in primates (Hallett and Brotchie, 2007).

The present study was performed to test the involvement of δ-opioid receptors, and more precisely of those located on corticostriatal neurons, in abnormal involuntary movements induced by L-DOPA in hemiparkinsonian rats. For this purpose, we attempted to determine the effects of δ-opioid receptors on LIDs expressed by these animals, using an agonist, [D-Pen^2, D-Pen^5]-enkephalin (DPDPE) and an antagonist (naltrindole) of these receptors. In addition, we assessed the ability of DPDPE to reproduce its effect in hemiparkinsonian rats treated with L-DOPA and submitted to an ipsilateral thermic lesion of the cortical region overlapping the dopamine-depleted striatum, in order to destroy corticostriatal afferents. In both experiments, we measured the [^{3}H]-DPDPE binding to striatal membranes prepared from the intact and the dopamine-depleted striatum.

Materials and methods

Animals

The experiments were performed on male Sprague–Dawley rats (250–300 g, Charles River, Saint-Aubin-lès-Elbeuf, France). They were individually housed and maintained on a 12-h light/dark cycle, at a room temperature of 22 °C, under constant ventilation; they had access to food and water *ad libitum*. All animal manipulations were performed according to recommendations of the European Communities Council Directive of 24 November 1986 (86/609/EEC), particularly for "cerebral lesions produced by local injections of neurotoxins in the rat", "intracerebroventricular injections in the rat" and "cerebral lesions produced by thermo-coagulation in the rat" protocols that were approved by the Regional Ethical Committee (N/04-06-07/07, N/05-04-04/07 and N/17-04-04-19 respectively). All efforts were made to reduce the number of animals used in this study and to insure them optimal conditions of well-being, before, during and after each experiment.

Experimental design

The sequence of experimental manipulations and pharmacological treatments applied in the study is schematically described in Fig. 1. Experiments were performed from hemiparkinsonian rats obtained

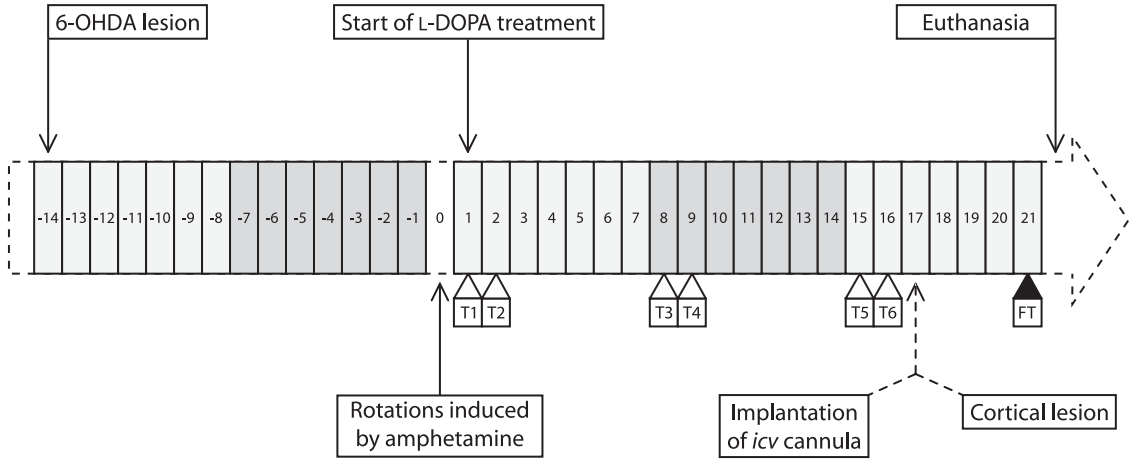

Fig. 1. Design of experiments. Two weeks before the L-DOPA treatment (D-14), the rats were submitted to unilateral injections of 6-OHDA into the MFB. Each of the 5 weeks of experiments is depicted within the arrow by an alternation of shaded areas. Numerals within the arrow denote the number of days from time 0, *i.e.* the day (D0) of rotational screening with amphetamine (2.5 mg/kg, *i.p.*). The daily treatment of animals with L-DOPA (6 mg/kg, combined with 15 mg/kg benserazide) started the next day (D1) for 21 days. The timing of behavioural testing sessions is shown below the arrow (T1 to T6). On the last day of the chronic L-DOPA administration, a final test (FT), was performed at D21 to evaluate the effects of *i.c.v.* infused treatments. Four days before the final test (D17), animals were submitted to a second surgery during which *i.c.v.* cannulas were implanted and cortical lesions were produced by thermo-coagulation of the ipsilateral cortex. The day after (D22), animals were euthanized by decapitation and their striata were removed to allow further experiments.