Involvement of enkephalins and delta-opioid receptors in the expression of levodopa-induced dyskinesia in a model of hemiparkinsonian rat

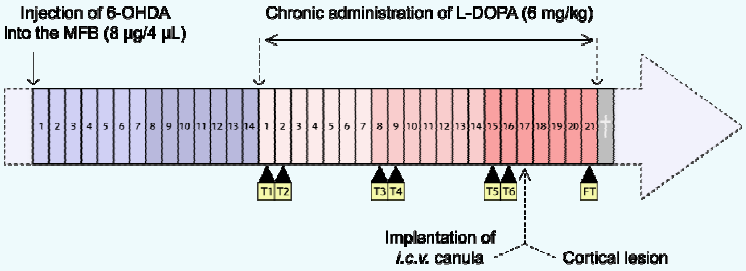
F. Billet, J. Costentin & N. Dourmap

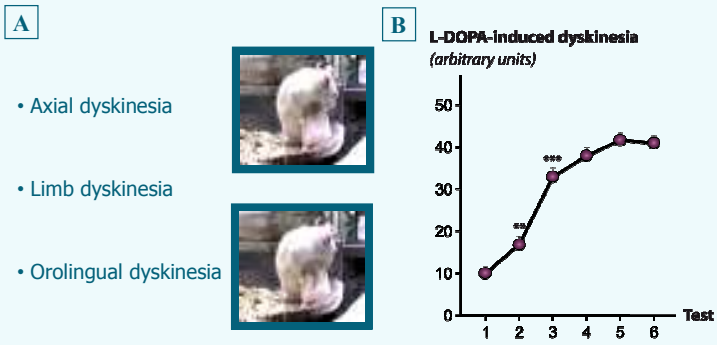
Fabrice-Billet@orange.fr

www.striatum.fr

Unité de Neuropsychopharmacologie Expérimentale - CNRS FRE 2735 - IFRMP 23
Faculté de Médecine et de Pharmacie - 22 Bd Gambetta, 76183 Rouen Cedex
Tel: 02.35.14.86.02 - Fax: 02.35.14.86.03 - E-mail: nathalie.dourmap@univ-rouen.fr

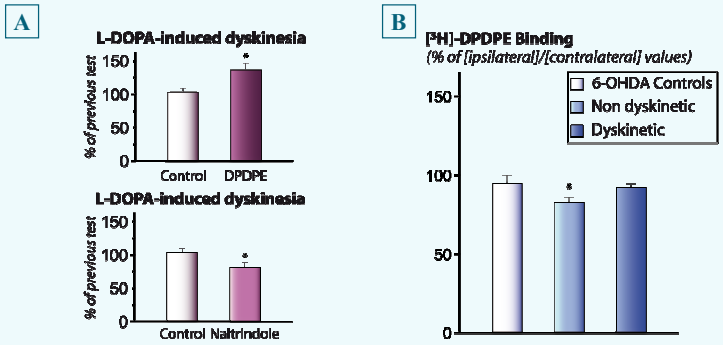
L-DOPA-induced dyskinesia is a major complication of the pharmacotherapy commonly used in Parkinson's disease. Numerous hypotheses have been suggested for these motor complications but alterations focusing on dopamine and glutamate are favoured. Interestingly, our previous experiments performed in rats (Billet *et al.*, 2004; Billet *et al.*, 2007) indicate that δ-opioid receptors located on corticostriatal terminals modulate the release of these two neurotransmitters in the striatum, which is thought as key structure in the control of psychomotor behaviours. The present study was therefore performed to test the involvement of δ-opioid receptors, and more precisely of those located on corticostriatal neurons, in dyskinesia induced by L-DOPA in hemiparkinsonian rats.

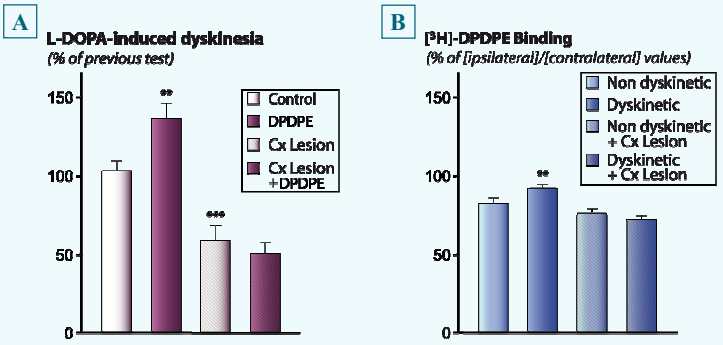




1. TIME COURSE OF EXPERIMENTATIONS. The first day, animals received an injection of 6-OHDA (8 µg in 4 µL) into the MFB (A/P: - 3.8 mm, M/L: - 1.5 mm, D/V: - 8.5 mm). Two weeks later, and for 21 days, animals were daily injected *i.p.* with a solution containing L-DOPA (6 mg/kg) and benserazide (15 mg/kg). Each of these 3 weeks, 2 consecutive tests were performed to evaluate the intensity of dyskinesia produced by L-DOPA (T1 to T6). The last day, a final test (FT) was performed to evaluate the effects of *i.c.v.* infused treatments. Four days before the final test, animals were submitted to a second surgery during which *i.c.v.* canula were implanted and cortical lesions were produced by thermo-coagulation of the ipsilateral cortex on 2 points (A/P: + 3.4 mm, M/L: - 3.0 mm, D/V: - 1.0 mm; A/P: + 0.5 mm, M/L: - 3.0 mm, D/V: - 0.8 mm).

2. EVALUATION AND DEVELOPMENT OF L-DOPA-INDUCED DYSKINESIA. (**A**) Twenty minutes after the injection of L-DOPA, each animal was observed (for 1 min, each 20 min) and 3 subtypes of abnormal and involuntary movements were evaluated: axial, limb and orolingual dyskinesia. A score ranging from 0 to 4 was assigned to each animal and for each subtype of dyskinesia depending on its severity. Only 50% of animals developed abnormal movements during the 3-week L-DOPA administration. (**B**) The graph shows the intensity of dyskinesia expressed by these animals. Means ± SEM of 48 rats are compared using 1 factor ANOVA with repeated measures followed by a Tukey's test. ** $P < 0.01$, *** $P < 0.001$ *vs.* previous test.





3. EFFECT OF DPDPE OR NALTRINDOLE ON L-DOPA-INDUCED DYSKINESIA AND EVALUATION OF STRIATAL δ-OPIOID RECEPTORS DENSITY. (**A**) The last day of the 3-week daily treatment with L-DOPA, animals expressing L-DOPA-induced dyskinesia were, 10 min before the final test (FT), submitted to the *i.c.v.* administration of DPDPE (10 µg in 5 µL) or naltrindole (10 µg in 5 µL). Data are expressed as percent of the score obtained by each animal at the previous test. Means ± SEM of 12 rats per group are compared using 1 factor ANOVA followed by a Tukey's test. * $P < 0.05$ *vs.* dyskinetic control animals. (**B**) Animals were killed the day after the final test (FT) and the density of δ-opioid receptors was evaluated on membrane suspensions prepared from their striata. Control animals were chronically injected with Ringer instead of L-DOPA. Data are expressed as percent of the ratio [specific binding in the ispilateral striatum]/[specific binding in the contralateral striatum]. Means ± SEM of 16 to 36 rats per group are compared using 1 factor ANOVA followed by a Tukey's test. * $P < 0.05$ *vs.* control animals.

4. INFLUENCE OF CORTICOSTRIATAL DEAFFERENTATION ON L-DOPA-INDUCED DYSKINESIA EVOKED BY DPDPE AND ON STRIATAL δ-OPIOID RECEPTORS DENSITY. Four days before the final test (FT), animals expressing L-DOPA-induced dyskinesia were submitted or not to the lesion of the ipsilateral cortex (Cx Lesion). The last day, DPDPE (10 µg in 5 µL) was *i.c.v.* injected 10 min before the final test (FT). Data are expressed as percent of the result obtained by each animal at the previous test. Means ± SEM of 12 rats per group are compared using 1 factor ANOVA followed by a Tukey's test. ** $P < 0.01$, *** $P < 0.001$ *vs.* control animals. (**B**) Animals were killed the day after the final test (FT) and the density of δ-opioid receptor was evaluated on membrane suspensions prepared from their striata. Data are expressed as percent of the ratio [specific binding in the ispilateral striatum]/[specific binding in the contralateral striatum]. Means ± SEM of 16 to 36 rats per group are compared using 1 factor ANOVA followed by a Tukey's test. ** $P < 0.01$ *vs.* control animals.

Endogenous enkephalins modulate the expression of L-DOPA-induced dyskinesia by stimulating δ-opioid receptors. Moreover, it appears that δ-opioid receptors located on terminals of corticostriatal neurons could be involved in the development of these dyskinesia.