InBrain Pharma

Personalized brain medicine

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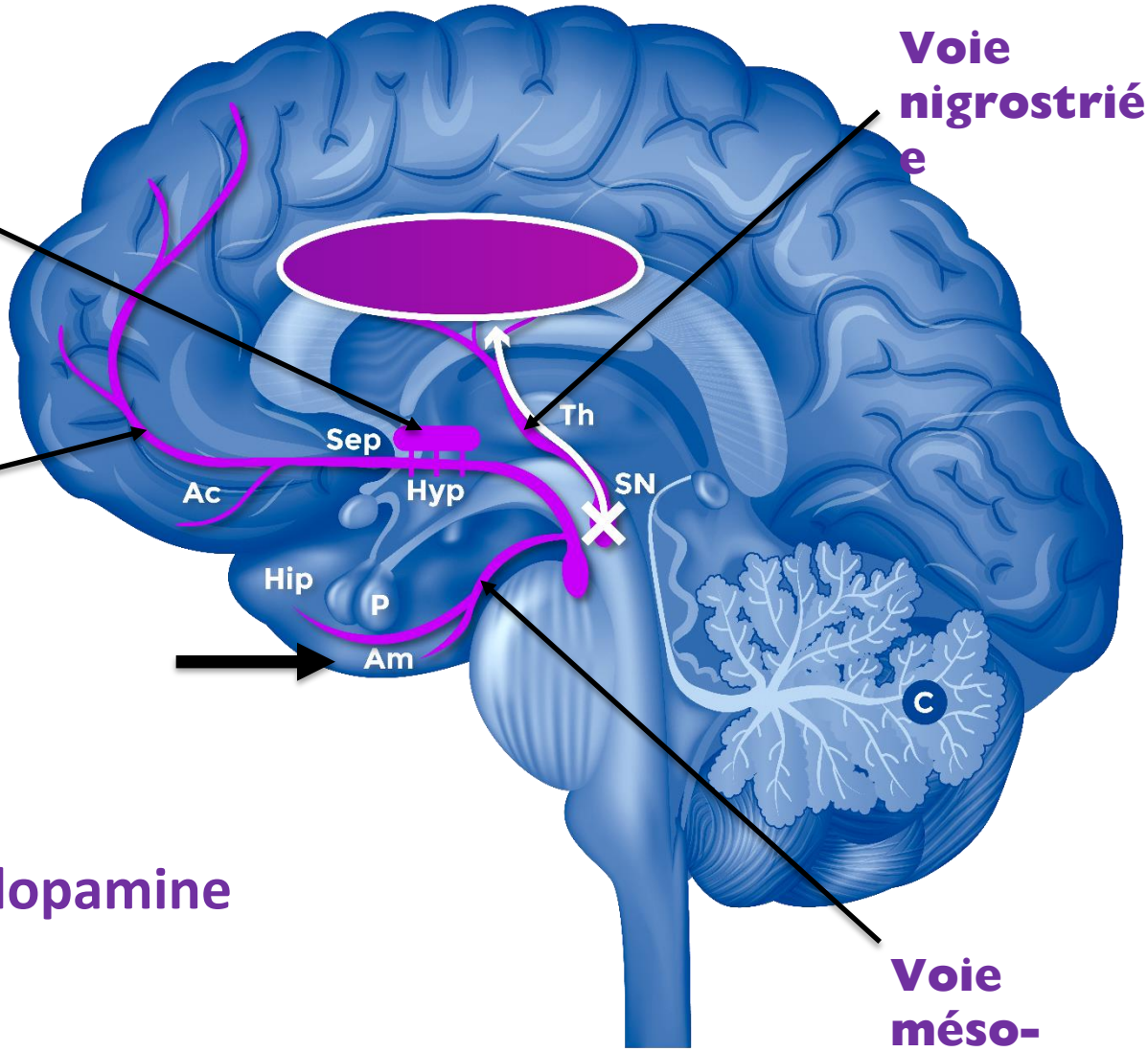
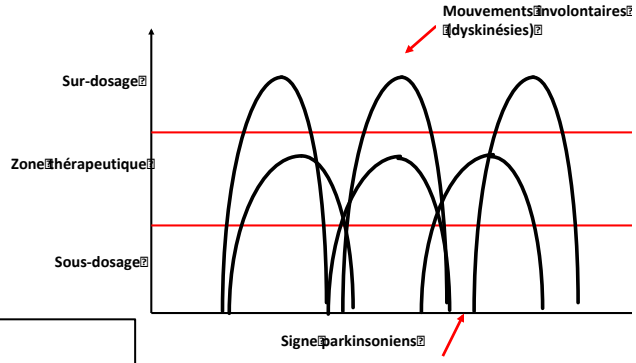
Parkinson'Disease

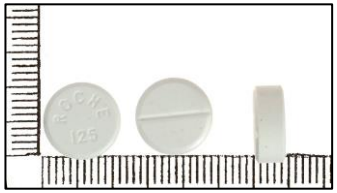


Continue need of dopamine

Parkinson’s disease evolution

LIFE QUALITY





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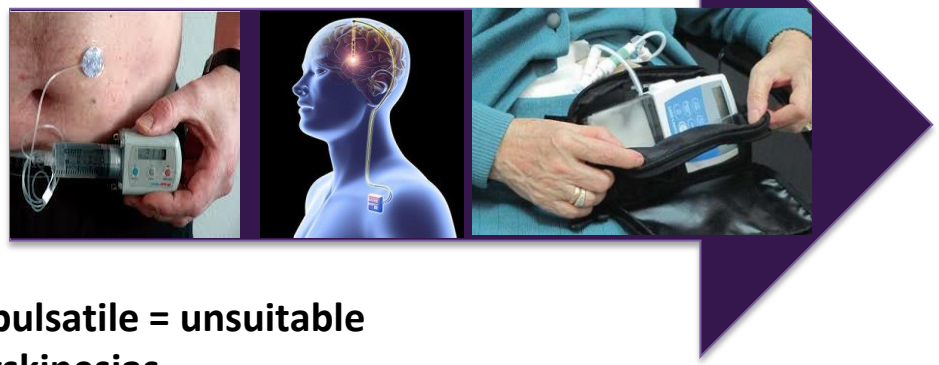
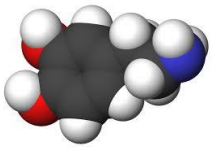


Oral treatment with dopamine precursor: L-dopa pulsatile = unsuitable and induces complications like fluctuations and dyskinesias

TIME

0 5 10 20

Dopamine solution directly delivered inside the brain for the treatment of Parkinson's disease

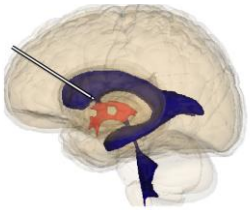


Natural molecule (Dopamine)

+

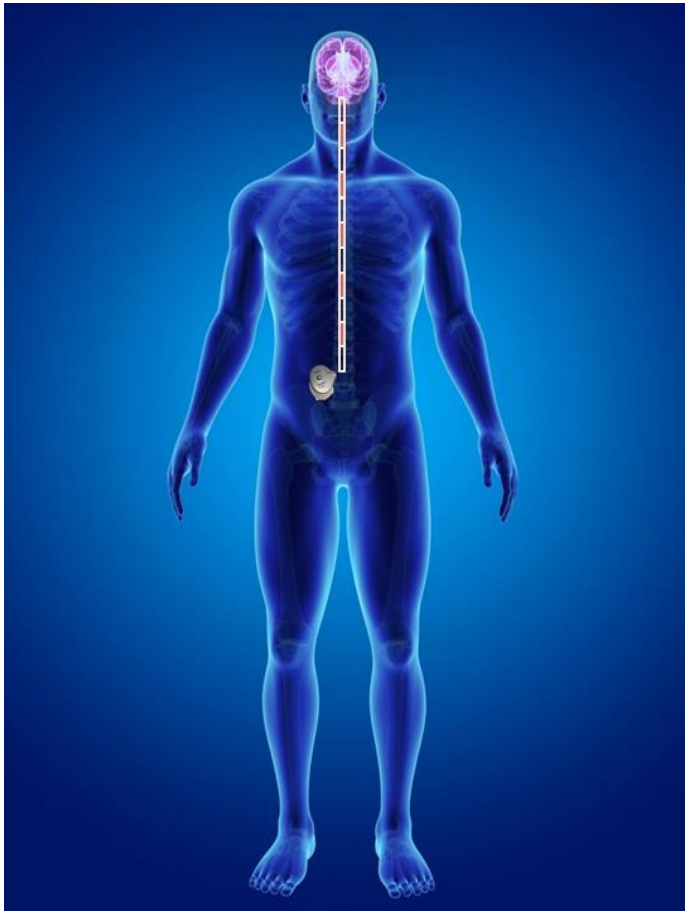
Commercial pump

+



known route of administration

=



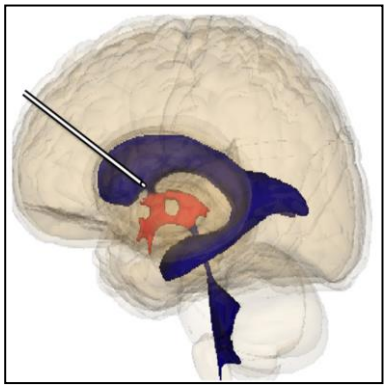
intra-ventricular administration of dopamine ?

Two case reports of patients in 1984 and 1989

→ Aim: avoid the toxic metabolites of L-dopa that may induce hallucinations and confusion by directly infuse dopamine

→ Continuous administration of hydrochloride of dopamine in aerobic conditions

intra-ventricular administration of dopamine



Proc. of the Colloquium on the Use of Embryonic Cell Transplantation for Correction of CNS Disorders, Chestnut Hill, MA, 1983
Appl. Neurophysiol. 47: 62–64 (1984)

Treatment of Severe Parkinson's Disease by Intraventricular Injection of Dopamine[1]

Nagagopal Venna, Thomas D. Sabin, Joe Idahosa Ordia, Vernon H. Mark, M.D.

Neurosurgical Unit, Boston City Hospital, Boston, Mass., USA

Key Words. Parkinson's disease · Intraventricular dopamine

This is a preliminary report of the treatment of a patient with severe Parkinson's disease (PD) by the injection of dopamine into the cerebral ventricles. The patient is a 65-year-old man with PD for 17 years, who was confined to bed and chair existence and had a moderate degree of dementia for 1 year. Treatment with Sinemet® and bromocriptine was severely limited because of an acute confusional state with hallucinations from even small doses of the drugs. Based on the hypothesis that the neuropsychiatric toxicity of Sinemet may be related to the breakdown products of *L*-dopa other than dopamine in the brain, and in view of the profound disability caused by PD, it was decided to use dopamine itself. Since dopamine does not cross the blood-brain barrier it was planed to inject it intraventricularly.

1st case in 1981 (Venna *et al.*, 1984)**:**

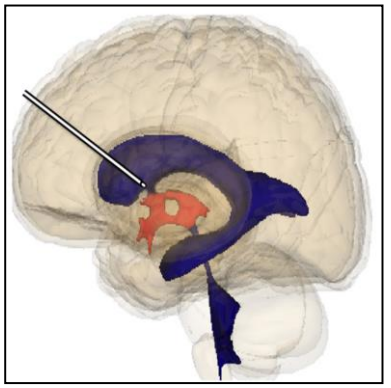
- Man of 65 years, 17 disease duration at a very advanced stage (H-Y: 4, severe axial disorders, dementia, hallucinations)
- Ommaya system with bilateral administration in the frontal horne

- Slow titration from 40 µg to 16 mg
- Dose dependent (akinesia and rigidity) from 8 to 16 mg over 5 months

- Transient adverse events: arterial pressure increase, yawning, rhinorrhoea, facial flush transient during titration & hallucinations recurrence with high dose

- **Authors' conclusion : feasible, well tolerated, potential treatment for patients without dementia, but remaining challenge of dopamine oxidation**

intra-ventricular administration of dopamine



Intraventricular Infusion of Dopamine in Parkinson's Disease

M. K. Horne, FRACP, E. G. Butler, FRACP, B. S. Gilligan, FRACP, J. Wodak, FRACP, R. J. Stark, FRACP, and G. A. Brazenor, FRACS

A patient with severe end-stage Parkinson's disease and troublesome fluctuations in motor function was treated with a long-term intraventricular infusion of dopamine. There was modest improvement in speech and mentation and there was smoother control of motor symptoms that was superior to that achieved by conventional oral medications.

Horne MK, Butler EG, Gilligan BS, Wodak J, Stark RJ, Brazenor GA. Intraventricular infusion of dopamine in Parkinson's disease. Ann Neurol 1989;26:792–794

2nd case in 1987 (Horne *et al.*, 1989)

- Man of 53 years, 19 disease duration at a very advanced stage (H-Y: 3, very severe motor fluctuations, anarthria, painful dystonia, dementia, hallucinations)

- **Shiley Infusaid pump (Pfizer)** implanted the left frontal horn and connected to the pump in the pectoral region

- Slow titration from 2.5 to 45 mg
- Dose dependent (akinesia and rigidity) from 10 to 16 mg over 7 months

- Adverse events: confusion & hallucinations recurrence at 40 mg

- **Authors' conclusion : feasible, well tolerated, potential treatment for patients without dementia: improvement of motor fluctuation, gait dysarthria**

General conclusion :

→ **Potential treatment for a better motor control (fluctuation)**

→ **However two remaining challenges: dopamine oxidation & tachyphylaxia**

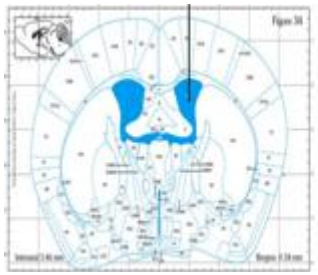
Our improvement: free oxygen dopamine

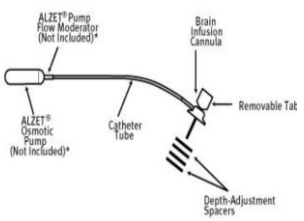
Summary of preclinical results

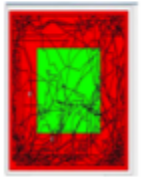
- anaerobic dopamine is no toxic in vitro and in vivo
- Restoration of motor skills (parkinsonian models of MPTP mice, 6-OH rats)
- Without dyskinesia and fluctuation unlike peripheral L-dopa
- Broad therapeutic index, excellent tolerance, no tachyphylaxis

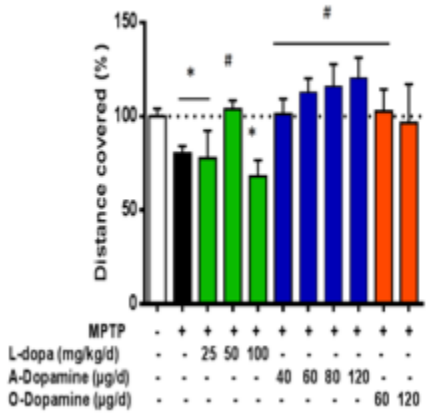
Details of preclinical results

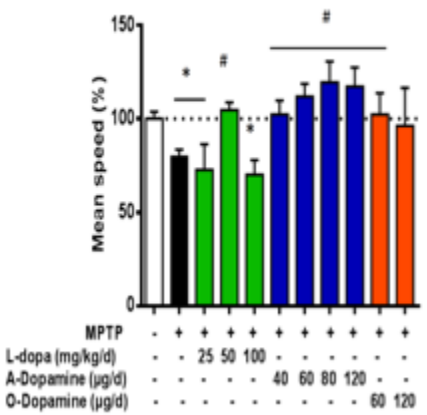
MPTP mouse









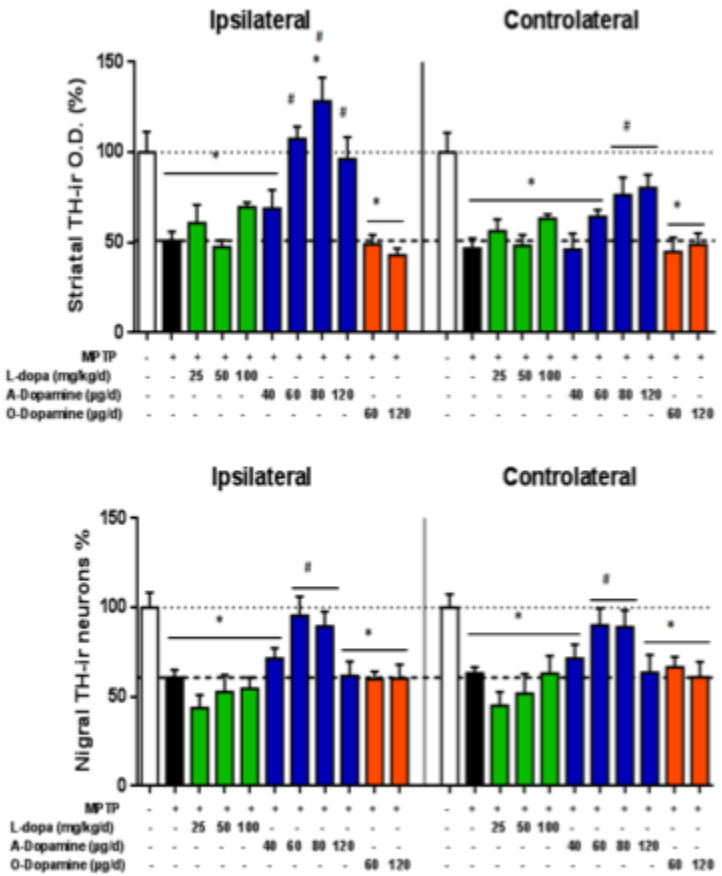


Complete functional recovery of motor handicap after 7 days of A-dopamine

(covered distance parcourue and mean speed (10 min)

Laloux et al., 2017

MPTP mouse

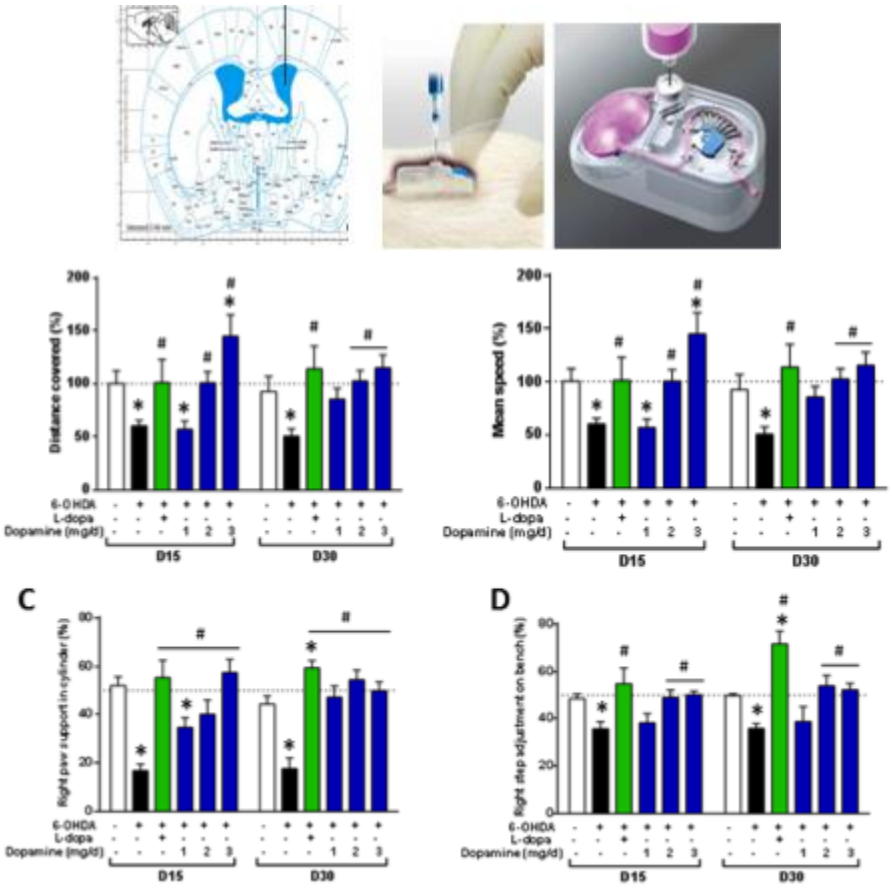


No deleterious effect but a neuroprotective effect of A-dopamine after 7 days

No beneficial effect with L-dopa and a deleterious effect with O-dopamine

Laloux et al., 2017

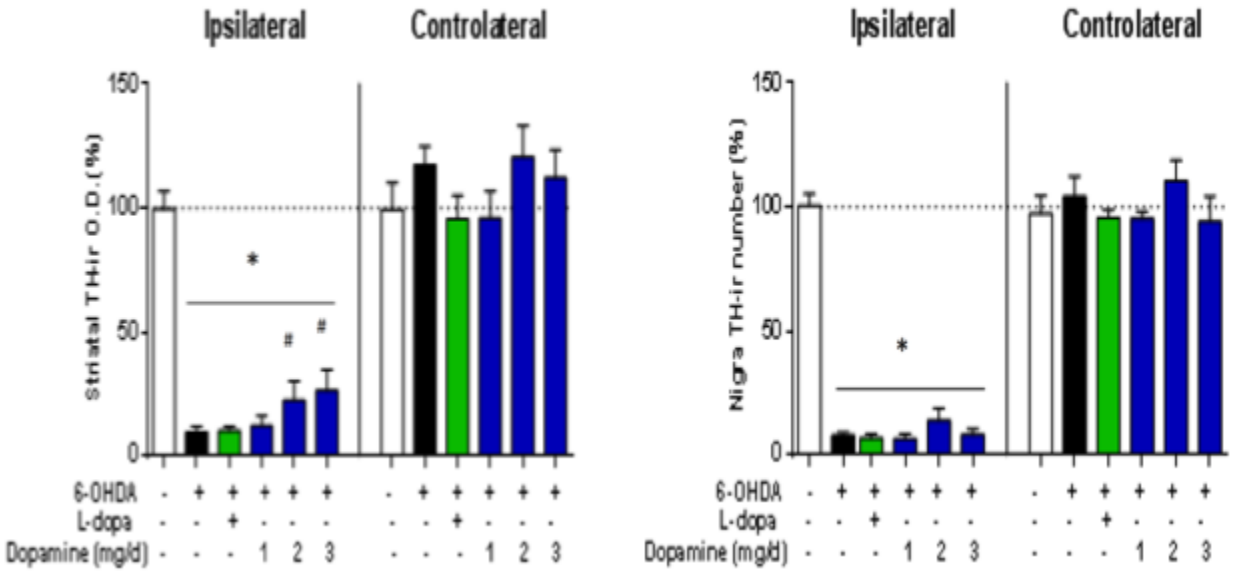
Rat 6-OHDA



Functional recovery of motor handicap without tachyphylaxia after 30 days

(Distance covered and mean speed in actimetry arena, right paw support in the cylinder test and right step adjustment in the stepping test) Laloux et al., 2017

6-OHDA rat

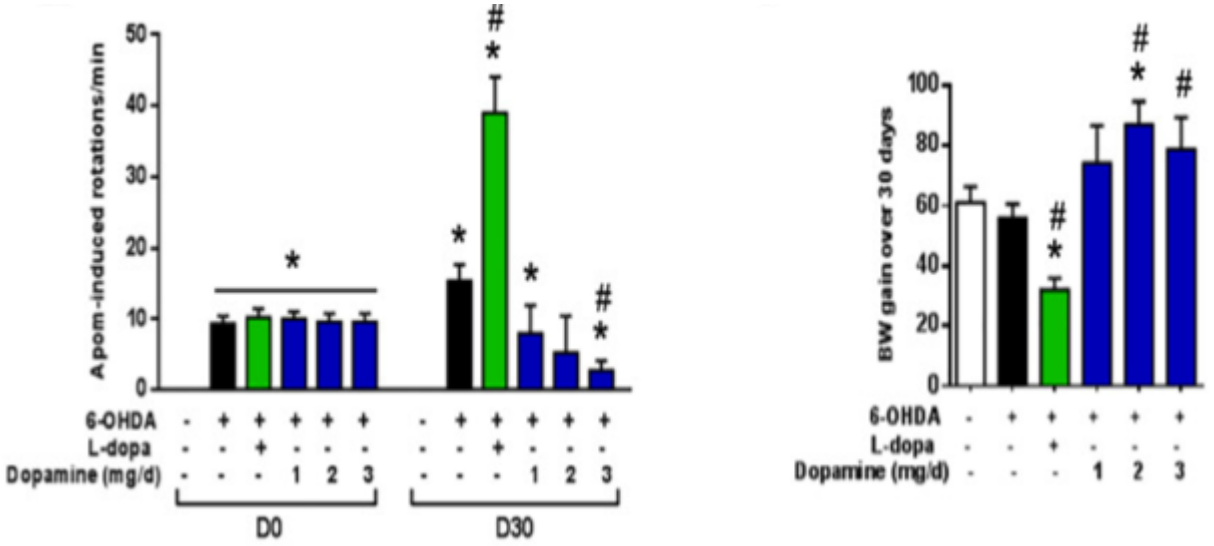


No deleterious effect of A-dopamine after 30 days (SN & striatum)

Post mortem analysis of brain and peripheral organs was without particularity

Laloux et al., 2017

6-OHDA rat



No abnormal behaviour sensitization induced by apomorphine
After 30 days of A-dopamine

Conversely, abnormal behaviour sensitization induced by L-Dopa
Weight loss under L-dopa

Laloux et al., 2017

Our improvement: free oxygen dopamine

Patent WO2015/173258

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Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Continuous cerebroventricular administration of dopamine: A new treatment for severe dyskinesia in Parkinson's disease?

C. Laloux [a], F. Gouel [a], C. Lachaud [a], K. Timmerman [a], B. Do Van [a], A. Jonneaux [a], M. Petrault [a], G. Garcon [c], N. Rouaix [b], C. Moreau [a,f], R. Bordet [a], J.A. Duce [d,e,1], J.C. Devedjian [a,1], D. Devos [a,g,*,1]

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Editorial

Intracerebroventricular dopamine for Parkinson's disease

David Devos, Devedjian J.C. and Moreau C.

« When I treated this patient with this strategy in 1989, it worked perfectly but we did not know the rhythm of dopamine and we were afraid of its oxidation ... Now everything is ready for a "game changing strategy" »

Malcolm Horne, Former Director of the Florey Institute
(4th Institute of Neuroscience in the world)

Goal

Clinical trial at Lille in 2020

Thank you for your attention

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eurasanté
Entreprendre et Réussir

CHU LILLE

Université de Lille

Inserm
Institut national de la santé et de la recherche médicale