

Cyclooxygenase 2 is upregulated in the gastrointestinal tract in Parkinson's disease

Camille Pochard, Laurène Leclair-Visonneau, Emmanuel Coron, Michel Neunlist, Malvyne Rolli-Derkinderen, Pascal Derkinderen

► **To cite this version:**

Camille Pochard, Laurène Leclair-Visonneau, Emmanuel Coron, Michel Neunlist, Malvyne Rolli-Derkinderen, et al.. Cyclooxygenase 2 is upregulated in the gastrointestinal tract in Parkinson's disease. *Movement Disorders*, Wiley, 2018, 33 (3), pp.493-494. 10.1002/mds.27237 . hal-03153579

HAL Id: hal-03153579

<https://hal-cnrs.archives-ouvertes.fr/hal-03153579>

Submitted on 8 Mar 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Cyclooxygenase 2 Is Upregulated in the Gastrointestinal Tract in Parkinson's Disease

Camille Pochard, MSc,^{1,2,3}
Laurène Leclair-Visonneau, MD,^{1,2,4}
Emmanuel Coron, MD, PhD,^{1,2,3,4}
Michel Neunlist, PhD,^{1,2,3}
Malvyne Rolli-Derkinderen, PhD,^{1,2,3}
Pascal Derkinderen, MD, PhD^{1,2,4,5*}

¹Inserm U1235, Nantes, France ²University Nantes, Nantes, France

³CHU Nantes, Institut des Maladies de l'Appareil Digestif, Nantes, France

⁴Inserm, Centre d'investigation clinique, Nantes, France

⁵CHU Nantes, Department of Neurology, Nantes, France

*Corresponding author: Dr. Pascal Derkinderen, Inserm U1235, 1 rue Gaston Veil, 44035 Nantes, France; derkinderenp@yahoo.fr; pascal.derkinderen@chu-nantes.fr

Since its discovery in the early 1990s, cyclooxygenase-2 (COX-2) has emerged as a major player in inflammatory reactions in neurodegenerative disorders and especially in Parkinson's disease (PD). COX-2 is upregulated in dopaminergic neurons of the substantia nigra in both PD patients and experimental parkinsonism.¹ Furthermore, nonsteroidal anti-inflammatory drugs that inhibit COX-2 activity protect against dopamine degeneration in animal models of PD.² It is now well established that PD is not only a neurodegenerative condition of the central nervous system but also a disorder of the gastrointestinal tract. In line with these observations, we have recently shown that similarly to the brain, the main proinflammatory cytokines were upregulated in the colon of PD patients.³ In the current study, we propose to extend these results by determining if COX-2 is also upregulated in the gastrointestinal tract in PD.

A total of 28 individuals participated in this study: 13 PD patients (mean age 67 years) and 15 healthy controls (56.4 ± 13 years). For demographics and clinical characteristics of the participants, see Supplementary File 1. The controls were healthy individuals who had a normal colonoscopy for colorectal cancer screening. Controls and PD patients were excluded if they suffered from irritable bowel syndrome, and none of the patients or controls received any corticosteroid and/or nonsteroidal anti-inflammatory treatment 6 months prior to enrollment. The study protocol was approved by the local Committee on Ethics and Human Research (Comité de Protection des Personnes Ouest VI) and registered on ClinicalTrials.gov (identifier NCT01353183). Written informed consent was obtained from each patient and from each healthy volunteer before the endoscopic procedure. Two gastrointestinal biopsies per participant were taken at the junction between the sigmoid and descending colon during the course of a recto-sigmoidoscopy for the PD patients and colonoscopy for the controls. Total RNA and protein were isolated from the 2-pooled biopsies using the NucleoSpin Triprep Kit (Macherey-Nagel, Hoerd, France). RT-PCR and Western Blot analyses were performed as previously described.^{3,4} For primers and antibody details, see Supplementary File 2. A significant 3.4-fold increase in the expression levels of COX-2 mRNA was observed in biopsies from the PD patients when compared with the controls (Fig. 1A). In contrast, no significant change in the expression level of COX-1 was observed (P5.20; Fig. 1A). The results were confirmed at the protein level (Fig. 1B).

The current findings extend our prior results³ and demonstrate that gastrointestinal inflammation occurs in PD patients. They support a growing body of research that suggests the participation of a neuroinflammatory process in PD pathogenesis, involving not only the central nervous system but also the peripheral autonomic networks along the so-called gut-brain axis.⁵ In large prospective studies, the use of ibuprofen, a potent COX-2 inhibitor, was associated with a lower risk of future PD.⁶ The most common explanation for these effects is that ibuprofen-induced COX-2 inhibition may mitigate the progression of neurodegeneration through diminishing the production of toxic free radicals in the brain.² Our results may suggest that the possible protective effects of ibuprofen in PD are not limited to the central nervous system but also involve the gastrointestinal tract.

Acknowledgments: This work was supported by a grant from France Parkinson. Work in Michel Neunlist's lab is supported by Comité d'Entente et de Coordination des Associations de Parkinsoniens, Association des Parkinsoniens de Loire Atlantique, Fédération française des groupements parkinsoniens, and Parkinsoniens de Vendée.

References

1. Teismann P, Tieu K, Choi D-K, et al. Cyclooxygenase-2 is instrumental in Parkinson's disease neurodegeneration. *Proc Natl Acad Sci USA* 2003;100:5473-5478.
2. Hirsch EC, Vyas S, Hunot S. Neuroinflammation in Parkinson's disease. *Parkinsonism Relat Disord* 2012;18(suppl 1): S210-S212.
3. Devos D, Lebouvier T, Lardeux B, et al. Colonic inflammation in Parkinson's disease. *Neurobiol Dis* 2013;50:42-48.
4. Clairembault T, Kamphuis W, Leclair-Visonneau L, et al. Enteric GFAP expression and phosphorylation in Parkinson's disease. *J Neurochem* 2014;130:805-815.
5. Houser MC, Tansey MG. The gut-brain axis: is intestinal inflammation a silent driver of Parkinson's disease pathogenesis? *NPJ Parkinson Dis* 2017;3:3.
6. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol* 2016;15: 1257-1272.

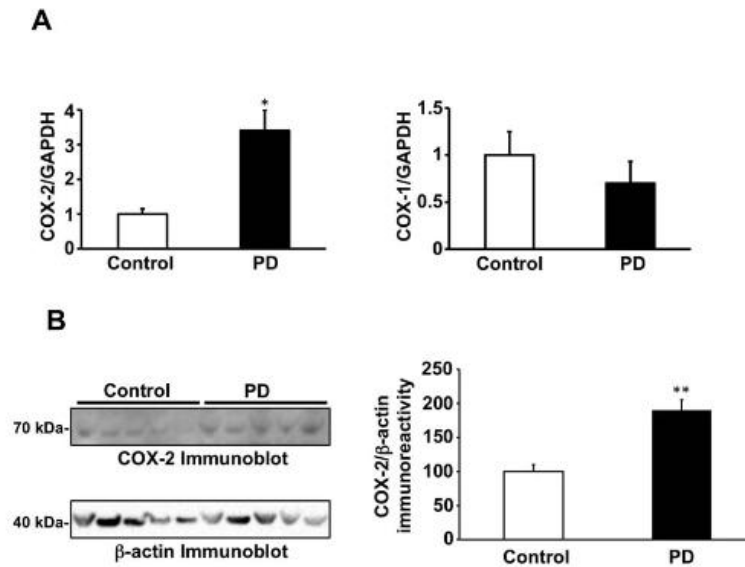


FIG. 1. Expression of cyclooxygenase-2 (COX-2) in colonic biopsies from PD patients and controls. Total RNA and proteins were isolated from colonic biopsies (2 pooled-biopsies per participant) of 13 PD patients and 15 controls. **(A)** The mRNA expression levels of COX-2 and COX-1 were determined by real-time PCR. A significant increase in the expression levels of COX-2, but not of COX-1, was observed in colonic biopsies from PD patients when compared with controls. **(B)** Protein extracts were subjected to immunoblot analysis using antibodies against COX-2 and β -actin. The optical densities of COX-2 immunoreactive band was measured, normalized to the optical densities of β -actin in the same samples, and expressed as percentages of controls. Data correspond to mean \pm standard error of the mean. Patients versus control, * $P < .05$, ** $P < .01$, nonparametric Mann-Whitney test. GAPDH, Glyceraldehyde 3-phosphate dehydrogenase.