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

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

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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 deter- mining 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 age6standard deviation: 6067 years) and 15 healthy controls (56.4 6 13 years). For demographics and clinical characteristics of the participants, see Supplementary File 1. The controls were healthy individuals who had a nor- mal 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 (Comit□e de Protection des Per- sonnes Ouest VI) and registered on ClinicalTrials.gov (iden- tifier NCT01353183). Written informed consent was obtained from each patient and from each healthy volunteer before the endoscopic procedure. Two gastrointestinal biop- sies 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, Hoerdt, 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 results[3] and dem- onstrate that gastrointestinal inflammation occurs in PD patients. They support a growing body of research that sug- gests the participation of a neuroinflammatory process in PD pathogenesis, involving not only the central nervous sys- tem 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 expla- nation for these effects is that ibuprofen-induced COX-2 inhibition may mitigate the progression of neurodegenera- tion through diminishing the production of toxic-free radi- cals 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.

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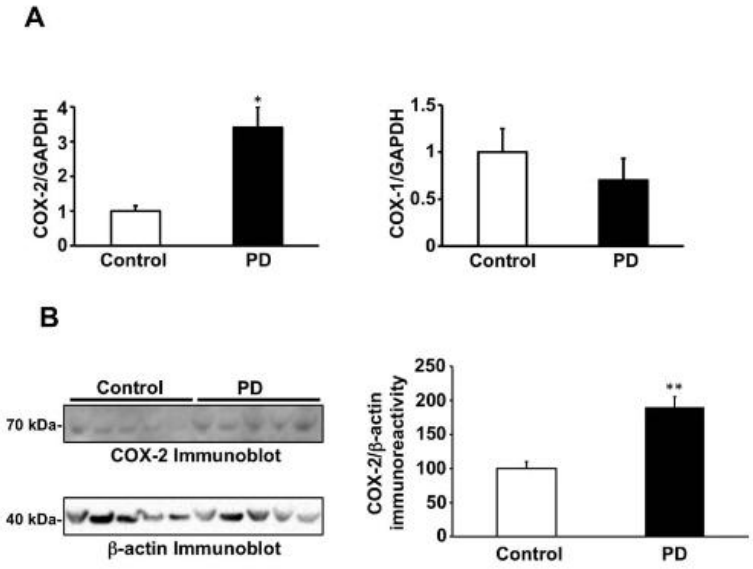

FIG. 1. Expression of cyclooxygenase-2 (COX-2) in colonic biopsies from PD patients and controls. Total RNA and proteins were isolated from colonic biopsies (2 pooled-biopsies per participant) of 13 PD patients and 15 controls. (**A**) The mRNA expression levels of COX-2 and COX-1 were determined by 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 ± standard error of the mean. Patients versus control, $^{*}P<.05$, $^{**}P<.01$, nonparametric Mann–Whitney test. GAPDH, Glyceraldehyde 3-phosphate dehydrogenase.