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CASE REPORT

Low-dose niacin supplementation modulates GPR109A, niacin index and ameliorates Parkinson's disease symptoms without side effects

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Key Clinical Message

A 65-year-old male, Parkinson's disease patient, was evaluated for GPR109A expression, niacin index, UPDRS scale, handwriting test, and quality of sleep with and without niacin treatment. The evaluation was repeated 3 months after niacin was stopped. Niacin modulated the abovementioned parameters and showed the overall improvement without side effects.

Keywords

GPR109A, inflammation, niacin, Parkinson's disease.

Introduction

Inflammation is thought to be a critical feature in Parkinson's disease (PD) pathology [1]. GPR109A is an anti-inflammatory G-protein receptor that is present in human macrophages and neutrophils at higher levels of expression than in other organs and tissues [2]. Its anti-inflammatory role is well-established in in-vivo and in-vitro studies [3–5]. We are the first to find upregulation of GPR109A receptor expression in the blood samples and substantia nigra in PD [6]. The physiological ligand of GPR109A is beta-hydroxy butyrate (BHB). In addition, another compound, niacin (aka vitamin B3 or nicotinic acid), also acts on GPR109A as its agonist in suppressing inflammation. The aromatic amino acid decarboxylase inhibitor carbidopa (typically prescribed as a part of carbidopa/levodopa) was shown to deplete niacin levels in the body in PD patients [7]. Niacin supplementation to restore or increase its level may potentially enhance the anti-inflammatory mechanisms of GPR109A. A chanced discovery of improvements in motor symptoms and physical function was observed in a PD patient who was prescribed niacin to treat his hypercholesterolemia [8]. His blood cholesterol improved, but the dosing was too high (1 g) and produced unacceptable nightmares and skin reactions in the patient.

Case History

A 65-year-old man with PD underwent 45 days of daily 250 mg niacin supplementation (qd). He was diagnosed with idiopathic PD in 2007. He is on carbidopa/levodopa since November 2007. He indicated no family history, previous head injuries, nor chronic exposure to neurotoxins from organic solvents, pesticides, fungicides, and herbicides. His Hoehn and Yahr (H&Y) score was rated at 2.5 with bradykinesia being more prominent than rigidity and tremor. His disease progression, though still relatively early, suggested a postural instability/gait difficulty (PIGD) phenotype. He was evaluated 2–3 h following the first morning dose of carbidopa/levodopa 25/100 mg (q4 h) both at baseline and after 45 days of niacin supplementation and after 90 days of niacin abstention.

Improvements in motor, cognitive, and sleep measures were observed following the intervention: The patients'

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Unified Parkinson's Disease Rating Scale (UPDRS) Motor Score (section 3) (24–19.5 points, −19% change), UPDRS bradykinesia (7.5–6.5, −13%), Trail Making Test Part A (47–35 sec, −25%), Part B (94–60 sec, −36%), PDQ8 quality of life questionnaire (20–10 points, −50%), PD Sleep Scale questionnaire (65–82 points, 27%), Rapid eye movement electroencephalography (REM EEG) night sleep (18–81 min, 350%), deep sleep (4–15 min, 275%), and overall sleep efficiency (27–71%, 161%). His walking speed (over 20 feet/6.1 m) before the niacin treatment was relatively normal (1.1 m/sec) and did not change appreciably after 45 days (1.2 m/sec).

Overall, the patient tolerated the niacin schedule well and reported no side effects. Hepatic function tests (data not shown) after niacin treatment remained normal.

In the course of the niacin regimen, his GPR109A expression in white blood cells steadily reduced to normal levels comparable to that of his spouse (Fig. 1A). Both BHB levels in the plasma and NAD-NADP ratio in red blood cells were also normalized in the patient with niacin therapy (Fig. 1B). Niacin depletion represented by NAD-NADP ratio (niacin index) is considered mild compared to that in pellagra. His fine visuomotor coordination as reflected by the area encompassing the intersecting pentagon drawings taken from the Mini–Mental State Examination evaluation was 3× larger, from 11 to 34 cm^2 (Fig. 1C).

After 3 months of niacin abstention, the niacin index (NAD/NADP ratio) was down and BHB levels went up. UPDRS section 3 went back up to 24.5 points and his sleep efficiency dropped down to 16%. The PD patient's fine visuomotor coordination (intersecting pentagons) was also reduced in size (Fig. 1C).

Discussion

Some of the observed improvements were based on subjective assessments, and the patient may have biased his responses due to lack of blinding. However, we also found improvements in the objective biochemical analyses and EEG night-sleep tests. We consider the anecdotal findings of the short-term therapeutic effect of low-dose niacin supplementation to be novel. We have shown that GPR109A is upregulated in the periphery and in the substantia nigra of PD patients [9]. This upregulation may indicate that PD is amenable to anti-inflammatory intervention with niacin. Although peripheral GPR109A levels in WBCs are not shown to be correlated with the GPR109A levels in the substantia nigra, we wanted to test the hypothesis that GPR109A agonist such as niacin will help reduce inflammation and thus ameliorate PD symptoms. Niacin is known to act via different mechanisms inside cells. Niacin acts via GPR109A related and nonrelated mechanisms. At a given time, it is hard to

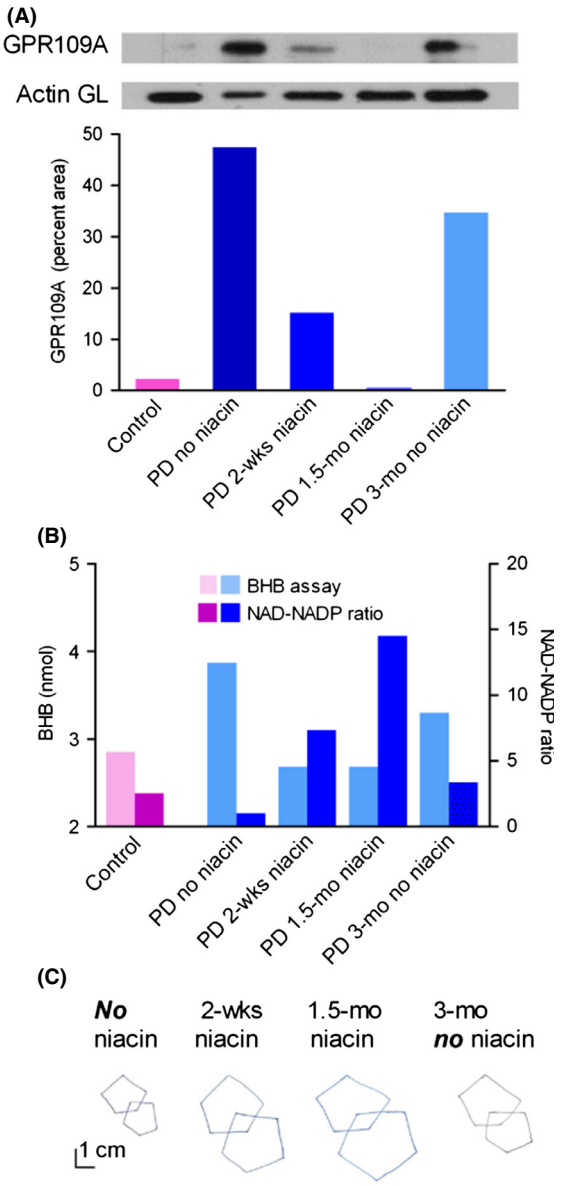

Figure 1. (A) The GPR109A western blot and densitometry: GPR109A expression levels shown in the WBCs of the Parkinson's disease (PD) patient and control (his spouse). Beta-actin was used as the housekeeping protein to ensure equal protein loading. GPR109A levels were studied at the baseline (PD no niacin), after 2 weeks of niacin treatment (PD 2-wks niacin), after 6 weeks of niacin treatment (PD 1.5-mo niacin), and after 3 months of a gap in the niacin treatment (PD 3-mo no niacin). (B) The beta hydroxyl butyrate (BHB) levels and NAD/NDAP ratio are shown at the baseline (PD no niacin), after 2 weeks of niacin treatment (PD 2-wks niacin), after 6 weeks of niacin treatment (PD 1.5-mo niacin), and a after a gap of 3 months in the niacin treatment thereafter (PD 3-mo no niacin). Control (spouse) levels were only drawn at the baseline. (C) The handwriting of the patient is demonstrated with the scale at the baseline (No niacin), 2 weeks after niacin treatment (2-wks niacin), 6 weeks of niacin treatment (1.5-mo niacin), and a gap of 3 months of niacin treatment (3-mo no niacin).

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predict which pathway is operating predominantly. In the presented case, 45 days of treatment with low-dose niacin was helpful in modulating the expression of GPR109A. Additionally, the UPDRS scores, sleep quality, and handwriting were improved. These benefits were abolished when niacin treatment was stopped for 3 months. A randomized controlled study is warranted to better understand whether niacin may indeed represent a novel treatment target in PD [9]. Additional observational studies are required for longer duration, with proper controls and double-blind studies to substantiate these findings.

Conclusion

Based on the presented case, GPR109A expression level could be a prognostic indicator of ongoing inflammation in PD and low-dose niacin may be beneficial over time hopefully with very few side effects. We truly believe that this work will be valuable for understanding the pathogenesis of PD and may lead to new therapeutic avenues.

Patient Consent

Patient consent was obtained according to the internal review board (IRB) guidelines at the Georgia Regents University.

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Conflict of Interest

None declared.

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