Journal of the Neurological Sciences 347 (2014) 34–38

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

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

Review article

A novel treatment target for Parkinson's disease

Chandramohan Wakade *, Raymond Chong **

Department of Physical Therapy, Georgia Regents University, Augusta, GA, USA

ARTICLE INFO

Article history:
Received 28 February 2014
Received in revised form 19 September 2014
Accepted 14 October 2014
Available online 23 October 2014

Keywords:
GPR109A
HCAR2
HM74a
Inflammation
Niacin
Niacinamide

ABSTRACT

We hypothesize that GPR109A message and expression are up-regulated in individuals with Parkinson's disease (PD). GPR109A is a high-affinity niacin receptor. Niacin is a precursor for NAD–NADH which is needed for dopamine production. Thus, niacin supplementation may serve three purposes: reduce inflammation through GPR109A-related mechanisms, increase dopamine synthesis in the striatum through NADPH supply and increase NAD/NADH ratio to boost mitochondrial functions. GPR109A and its agonists are known to exert anti-inflammatory actions in the skin, gut and retina. However these roles are neither anticipated nor established in the CNS. For the first time here we propose the roles of GPR109A and its agonists including niacin in CNS pathology. Moreover we predict that the neuroprotective roles of either niacin or butyrates in CNS occur via GPR109A.

© 2014 Elsevier B.V. All rights reserved.

Contents

* Corresponding author. Tel.: +1 706 721 9058.
** Corresponding author. Tel.: +1 706 721 1489.
E-mail addresses: cwakade@gru.edu (C. Wakade), rchong@gru.edu (R. Chong).

http://dx.doi.org/10.1016/j.jns.2014.10.024
0022-510X/© 2014 Elsevier B.V. All rights reserved.

1. Introduction

1.1. Role of niacin in protecting against Parkinson's disease (PD)

The protective role of niacin (also known as nicotinic acid) in PD has been suggested in a small number of anecdotal reports. Two case–control studies found that those who consumed a niacin-rich diet had a decreased risk of developing the disease after correcting for occupational and environmental factors [1,2]. The average odds ratio among those who consumed niacin-rich food items was 0.3. A single-case report described an account of a man with PD who was initially given 500 mg of niacin daily to treat his high triglyceride level [3]. The treatment appeared to work and a higher dose of 1000 mg was subsequently attempted. Three months later, during a follow-up primary care visit, the patient's family reported an unexpected positive side-effect of the niacin treatment in the form of an increase in his physical functioning. They included the ability to rise from a chair (which he previously was unable to do without assistance) and walk faster (which he previously was very slow to execute due to freezing). These improvements were thought to be attributed to a noticeable decrease in his rigidity and bradykinesia, the classical symptoms of the disease.

Animal models of PD also appear to support the role of niacin as a potential neuroprotective agent. Niacinamide (also known as nicotinamide, the amide form of niacin) supplementation in rats not only accelerated recovery on the vibrissae–forelimb placing test compared to saline treatment but also improved performances in other behavioral and cognitive tests including the bilateral tactile adhesive removal test and the Morris water maze working memory task [4]. In another rat study, niacinamide infusion was found to protect against MPTP-induced substantia nigra compacta (SNc) cell loss and striatal dopamine (DA) depletion [5].

1.2. Depletion of niacin in Parkinson's disease

We hypothesize that individuals with Parkinson's disease will show low levels of niacin for at least two reasons. First, the levodopa medication that is commonly used to treat PD symptoms may deplete niacin levels by interfering with tryptophan breakdown. Intraperitoneal administration of L-dopa (100 and 200 mg/kg) in rat brains has been found to decrease tryptophan, tyrosine and serotonin to their lowest levels after one hour [6]. Second, tryptophan metabolism itself appears to be impaired in PD patients, as reported in individuals who were diagnosed but had not yet been treated with anti-PD drugs [7]. Individuals with PD therefore need to obtain niacin directly, either from niacin-rich food or as a vitamin supplement.

1.3. Niacin and dopamine production

Besides two enzymes being required for the formation of dopamine from L-tyrosine (L-tyrosine → L-dopa → dopamine), three coenzymes are also required. These are THFA (for L-tyrosine to L-dopa), pyridoxal phosphate (for L-dopa to dopamine), and NADH (for the formation of THFA and pyridoxal phosphate). They are made from vitamins via the following means:

1 folic acid → dihydrofolic acid → tetrahydrofolic acid
2 pyridoxine → pyridoxal → pyridoxal 5-phosphate (this requires zinc as a cofactor)
3 niacin → NMN → NAD → NADH (or NADP) → NADPH.

To increase tetrahydrofolate production, NADPH is required:

$$\text{dihydrofolate} + \text{NADPH} + \text{H}^{+} \xrightarrow{\text{dihydrofolate reductase}} \text{terahydrofolate} + \text{NADP}^{+}.$$

With reduced niacin levels in PD, less NAD, NADH and NADPH will form which further reduces striatal dopamine production. Instead of providing ready-made coenzymes to the system, it is plausible to provide the natural source for the coenzyme, which is niacin in this case.

1.4. Niacinamide

Like niacin, niacinamide also generates NAD–NADH and therefore is also critically involved in energy production. Unlike niacin however, we hypothesize that it does not stimulate the anti-inflammatory response since there is no evidence to our knowledge that it acts on GPR109A.

1.5. Ketogenic diet

There is compelling evidence on the neuroprotective role of ketogenic diet (KD) in various neurological disorders including epilepsy, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, stroke, TBI and mitochondrial disorders [8]. Although the mechanisms through which the KD works in these disorders are unclear, modulation of energy production is thought to be the central process. It is also plausible that the KD such as butyrates may have neuroprotective actions in reducing inflammation via the GPR109A receptor.

2. Hypothesis and theory

2.1. Inflammation in PD

The etiology of PD has gained widespread attribution to inflammatory processes [9,10]. For example, increased formation of neopterin and enhanced degradation of tryptophan suggest activated cell-mediated immune response in a subgroup of patients with advanced PD [11]. Although inflammation may initially be beneficial, its prolonged and uncontrolled presence is known to contribute toward the progression of brain damage. Neutrophils and macrophages cross the leaky blood–brain barrier and cytokines (interleukins, tumor necrosis factor, interferon gamma) secreted by them initiate the inflammatory cascade and secondary damage in the brain.

2.2. Anti-inflammatory role of GPR109A and its association with niacin

We hypothesize that niacin may play an important role in the neuroprotection against PD via the GPR109A pathway by either enhancing anti-inflammatory mechanisms associated with the condition or by increasing blood supply to hypoperfused areas in the brain. GPR109A (also known as niacin receptor 1 (NIACR1), hydroxycarboxylic acid receptor 2 (HCAR2), HM74a in humans and PUMA-G in mice) is a G protein-coupled high-affinity niacin receptor [12]. Beta-hydroxyl butyrate (beta-HB) is its physiological ligand [13]. GPR109A and its agonists are known for their anti-inflammatory roles in a variety of in-vivo and in-nitro experimental conditions cited below including the skin, gut and retina. However their anti-inflammatory roles have never been proposed nor established in the brain.

GPR109A agonists suppress lipopolysaccharide (LPS)-induced inflammation via NFkB pathway in the gut [14]. GPR109A is present in a variety of human tissues including the brain [15]. Immune cells express the highest levels of GPR109A protein in humans [15]. GPR109A was formerly considered as an orphan receptor but is now gaining recognition beyond its known role in adipocytes and macrophages. Butyrates (which also act on GPR109A) are known to inhibit inflammation through inhibiting NFκB in Crohn's disease [16]. These anti-inflammatory properties provide a rationale for assessing butyrates in the treatment of CD. Cytokines such as interferon gamma are known to stimulate GPR109A in murine marcophages, thereby substantiating their role in inflammation [17]. GPR109A agonists also supress lipopolysaccharide (LPS)-induced inflammation via NFkB pathway in the gut [18]. Butyrates are known to inhibit NFκB activation via GPR109A and increase IκB levels in-vitro in intestinal epithelial cell lines [19]. It has also been shown that GPR109A is involved in the

Download English Version:

https://daneshyari.com/en/article/8276471

Download Persian Version:

https://daneshyari.com/article/8276471

Daneshyari.com