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Review Article

Niacin Metabolism and Parkinson's Disease

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Abstract

Epidemiological surveys suggest an important role for niacin in the causes of Parkinson's disease, in that niacin deficiency, the nutritional condition that causes pellagra, appears to protect against Parkinson's disease. Absorbed niacin is used in the synthesis of nicotinamide adenine dinucleotide (NAD) in the body, and in the metabolic process NAD releases nicotinamide by poly(ADP-ribosyl)ation, the activation of which has been reported to mediate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson's disease. Recently nicotinamide N-methyltransferase (EC2.1.1.1) activity has been discovered in the human brain, and the released nicotinamide may be methylated to 1-methylnicotinamide (MNA), via this enzyme, in the brain. A deficiency in mitochondrial NADH:ubiquinone oxidoreductase (complex I) activity is believed to be a critical factor in the development of Parkinson's disease. MNA has been found to destroy several subunits of cerebral complex I, leading to the suggestion that MNA is concerned in the pathogenesis of Parkinson's disease. Based on these findings, it is hypothesized that niacin is a causal substance in the development of Parkinson's disease through the following processes: NAD produced from niacin releases nicotinamide via poly(ADP-ribosyl)ation, activated by the hydroxyl radical. Released excess nicotinamide is methylated to MNA in the cytoplasm, and superoxides formed by MNA via complex I destroy complex I subunits directly, or indirectly via mitochondrial DNA damage. Hereditary or environmental factors may cause acceleration of this cycle, resulting in neuronal death.

Key words: nicotinamide N-methyltransferase, 1-methylnicotinamide, poly(ADP-ribosyl)ation, mitochondria, complex I

Introduction

Because procaryotes proliferate by cell division, aging of the individual cell does not occur. In eucaryotes, however, fatal aging occurs. Aging of the neuron begins immediately after its differentiation. The presence of mitochondria, especially their electron transport systems, makes possible an enormous energy supply in eucaryotic cells, and the coenzyme, nicotinamide adenine dinucleotide (NAD), may play an important role in their functioning (1). Contrarily, is it too reckless to attribute the cause of the fatal aging which occurs in eucaryotics cell to the existence of mitochondria and NAD?

In advanced countries, the prevalence of Parkinson's disease is so high that it is classified as one of the diseases of the aged. Any causal substance for Parkinson's disease will therefore be, not a special compound, but a common one, such as a food nutrient. A number of researchers have reported a relationship between niacin intake and Parkinson's disease. Some findings have indicated that niacin is neuroprotective (2, 3), whereas others have not supported it and niacin showed no clear relation with Parkinson's disease (4–6). NADH has been reported to relieve some of the symptoms of Parkinson's disease, but it did not influence the tissue content of dopamine in vivo experiment (7). Because in advanced countries, enough amounts of niacin are already commonly consumed, these case-control or follow-up studies might not offer any meaningful results regarding the relation between Parkinson's disease and niacin.

Neurotoxicity of niacin has not been reported by the epidemiological study yet, but other several epidemiological reports have indirectly indicated a contributory role for niacin in the pathogenesis of Parkinson's disease. Parkinson's disease is very low in Africa and China (8) where pellagra, caused by niacin deficiency, is a common complaint. Isoniazid, an anti-tubercular agent, relieves the symptoms of Parkinson's disease (9), but induces pellagra as a side effect. Parkinson's disease patients

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consume less than average alcohol (10), while heavy drinking is associated with pellagra. Consequently, the people who tend to suffer from niacin deficiency might tend not to suffer from Parkinson's disease. Because, in advanced countries, sufficient niacin to prevent pellagra is commonly consumed, my knowledge of niacin metabolism in the living body may provide evidence consistent with this hypothesis. In this paper the possible role of niacin in the pathogenesis of Parkinson's disease is investigated through a detailed discussion of niacin metabolism.

1. Background of the hypothesis: niacin, mitochondrial dysfunction and Parkinson's disease

Genetic inheritance does not play a significant role in idiopathic Parkinson's disease of advanced age (11) or may play a part of the pathogenesis suggested by the discoveries of the causative genes of familial Parkinson's disease, such as alpha-synuclein, parkin and DJ-1 (12). In the meantime, environmental chemical compounds have been suspected of causing Parkinson's disease since 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was discovered to cause Parkinson's disease artificially (13). It has been reported that the urinary excretion of 1-methylnicotinamide (MNA) is considerably raised and the excretion of its catabolic product, pyridone, is reduced in Parkinson's disease patients after nicotinamide administration (14). Nicotinamide methylation in the bodies of Parkinson's disease patients is accelerated. Human neurons express transporters, such as hOCT2, that translocate MNA from interstice to neuron (15). MNA or nicotinamide could be transported from blood to brain by specific transport mechanisms (16, 17), which may effect a specific phenomenon in the neuron.

Mitochondrial dysfunction has been implicated in the pathogenesis of several neurodegenerative diseases, including Parkinson's disease (18, 19), and the accumulation of deletions and point mutations in the mitochondrial genome has been a focus of attention (20, 21). Several researchers have reported that a deficiency of NADH: ubiquinone oxidoreductase (complex I) in the mitochondria plays a role in the pathogenesis of Parkinson's disease (22–24). The 30-, 25- and 24-kDa subunits of complex I were decreased in the striata of patients who died of Parkinson's disease (25). More than half of mitochondrially encoded polypeptides form part of the complex I, and mitochondiral polymorphisms are expected to reduce the risk of Parkinson's disease (26). Several researchers have measured respiratory enzyme activities or mitochondrial DNA (mDNA) in the muscle or platelets of Parkinson's disease patients to evaluate whether this change is specific to dopaminergic neurons or is the phenotypically relevant consequence of a widespread failure of the mitochondrial oxidative phosphorylation system (27, 28). They found no difference between Parkinson's disease and control groups. The acceleration of complex I subunit deficiency should therefore occur only in the brain of Parkinson's disease patients, and this specific mechanism of the neurons aroused my interest.

2. Metabolism of NAD with poly(ADP-ribosyl)ation

Most nicotinic acid exists in animals and plants in the form of nicotinamide, but it is absorbed in the intestines in the form of nicotinic acid, following deamination. It is used in the synthesis of NAD in the human body, and subsequently, in the metabolic process, NAD releases nicotinamide by poly(ADP-ribosyl)ation. This is methylated in the liver and is excreted into the urine as MNA.

DNA damage activates a nuclear enzyme poly(ADP-ribose) synthetase that facilitates DNA repair, and this enzyme activity can provide an early index of DNA damage following neurotoxic insults (29). Excessive activation of this enzyme can, however, deplete tissue stores of NAD, leading to cell death with the depletion of ATP (30). Poly(ADP-ribose) synthetase inhibitors and poly(ADP-ribose) synthetase gene deletion induced dramatic neuroprotection in experimental animals (31). Nitric oxide (via hydroxyl radical) stimulates auto-ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase (32–34). Several researchers have attempted to attenuate free radical mediated cerebral damage by inhibition of poly(ADP-ribose) synthetase (35, 36) or by supplementation of niacin (37). Poly(ADP-ribose) synthetase activation mediates MPTP neurotoxicity (38), and its inhibitors protect against MPTP-induced depletion of striatal dopamine (39) or brain NAD and ATP (40). But this is to pay attention to only one consequence of ADP-ribosylation. Poly(ADP-ribosyl)ation also results in the release from NAD of nicotinamide, which is methylated to MNA in the body. My interest has been in this other consequence of ADP-ribosylation.

3. Nicotinamide methylation in the brain

The occurrence of nicotinamide N-methyltransferase (NAMT) activity in the mammalian brain has been disputed. Shibata (41) reported NAMT activity in the rat brain and liver of 0 (not detected) and 0.282 nmol/mg·h, respectively, and Sano et al. (42), of 0 (not detected) and 5.19 nmol/mg·h, respectively. Both used high performance liquid chromatography with fluorescence detection. Seifert et al. (43), however, reported NAMT activity in the rat brain and liver of 0.4 and 18.6 nmol/mg·h, respectively, using thin-layer chromatography with radioisotope. Early attempts to detect NAMT activity used thin-layer chromatography with radioisotope or high performance liquid chromatography with fluorescence detection. Specificity and sensitivity using these earlier methods were much lower than with our method of gas chromatographic-mass spectrometric analysis in a selected ion monitoring mode. Using gas chromatographic-mass spectrometric analysis in a selected ion monitoring system, the NAMT activities of rat brain and liver were assayed at 0.30 nmol/mg·h and 0.51 nmol/mg·h, respectively (44).

Recently several researchers have reported about the NAMT protein in human brain in relation to the etiology of Parkinson's disease. The relative level of NAMT protein in the lumber cerebrospinal fluid in Parkinson's disease patients was higher than that in control (45). Expression of NAMT in the parkinsonian cerebella was higher than in the control group (46). From these results the excess NAMT in the central

nervous system might be implicated in the Parkinson's disease pathogenesis.

4. Neurotoxicity of MNA via damage to complex I

Neurotoxicity of MNA was reported using cultured neuroblastoma cells (47), but was not followed up, apart from our research investigating the mechanism of neurotoxicity of MNA. MNA injection in the rat substantia nigra pars compacta significantly decreased dopamine content in the striatum (44). MNA is able to destroy several of the subunits of cerebral complex I, especially 30-kDa protein (48). This subunit is a transmembranous (mitochondrial inner membrane) and iron-sulfur protein which is sensitive to lipid peroxidation (49). NADH oxidation and lipid peroxidation by MNA via rat brain submitochondrial particles (SMP), under conditions of pH ranging from pH 6.0 to 10.0, were verified. The pH optimum for NADH oxidation was 9.0 and the pH optimum for peroxidation by MNA of the lipid composing SMP was also 9.0. The lipid peroxidation in this assay was suppressed by superoxide dismutase (44). Using the paraquat model, it was demonstrated that the lipid peroxidation was caused by the hydroxyl radical which was formed from the superoxide radical (48).

Thus the superoxide anion formed by NADH:MNA oxidation-reduction reaction via complex I might be involved in the etiology of Parkinson's disease by means of direct destruction of complex I subunits, or by an indirect effect via mDNA destruction. Because the human complex I consists of at least 36 nuclear- and 7 mitochondrial-encoded subunits (50, 51), the effect of superoxides formed by MNA on mDNA mutations requires further examination and clarification.

5. Conclusions

NAMT activity in the brain may convert nicotinamide to MNA and by this means damage the nigro-neostriatal dopaminergic neurons. The superoxide anion formed by MNA via the mitochondria may be involved in the etiology of Parkinson's disease. Fig. 1 demonstrates my hypothesis of the process of MNA neurotoxicity. NAD produced from niacin releases nicotinamide via poly(ADP-ribosyl)ation, activated by the hydroxyl radical. Released excess nicotinamide is methylated to MNA in the cytoplasm, and superoxides formed by MNA via complex I destroy complex I subunits directly, or indirectly via mDNA damage. Hereditary or environmental factors may cause acceleration of this cycle, resulting in neuronal death. At the level of niacin deficiency there are few nicotinamide methylated to MNA in the living body. But now in advanced countries, enough amounts of niacin are already commonly consumed, and its intake by most people might be over the threshold value causing Parkinson's disease. Aging and hereditary factors should affect individual responses to Parkinson's disease.

6. Perspectives

This hypothesis may have important implications for Parkinson's disease prevention.

Because maize (*Zea mays*) contains niacytin, which humans cannot utilize as niacin, and because maize is also low in tryptophan but abundant in leucine, which inhibits quinolinate phosphoribosyl transferase, the key enzyme for converting from tryptophan to NAD, niacin deficiency is observed in peoples whose main energy source is maize (52). When various countries in the world are sorted hierarchically by their main energy source in food consumption, South Africa, Zimbabwe and

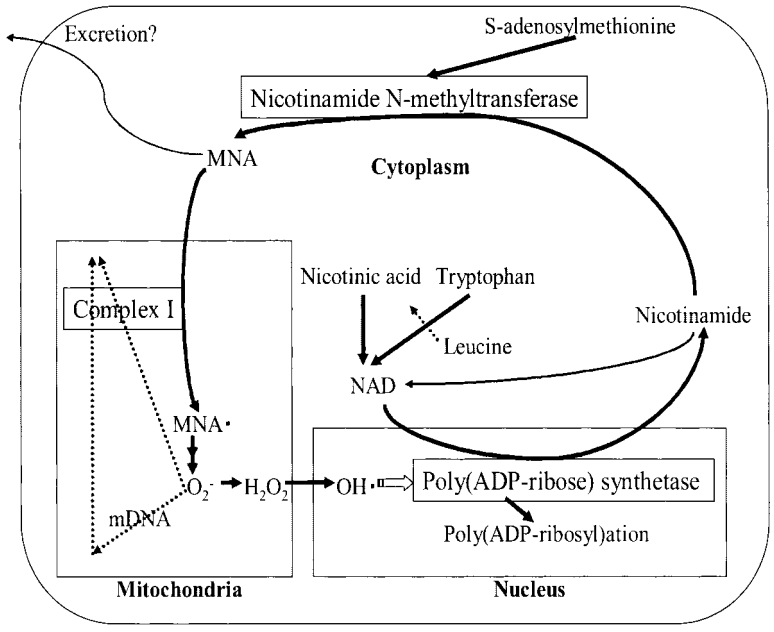

Fig. 1 Hypothesized process of MNA neurotoxicity. MNA, 1-methylnicotinamide; mDNA, mitochondrial DNA; NAD, nicotinamide adenine dinucleotide.

Japan are classified as a maize group (53). The prevalence or mortality rate of Parkinson's disease in these countries, South Africa (54), Zimbabwe (55) and Japan (56), is relatively low. In China, Keshan disease is prevalent in the maize production districts where selenium intake is very low. Niacin deficiency is also found in Keshan disease prevalent districts. Correlation coefficients for the prevalence of Parkinson's disease, maize yield, niacin intake, and selenium intake by province in China were analyzed (57), and a positive correlation was observed between selenium intake and niacin intake. A negative association was found between maize production and niacin intake and between maize production and prevalence of Parkinson's disease. Further, a retrospective study in Japan showed a preventive effect of maize on mortality from Parkinson's disease (58). These results suggest that maize, as a substitute for other grain crops, can be expected to prevent Parkinson's disease. Of course, the balance of nutrients is important to prevent pellagra.

Today, vitamins are ingested in excess in advanced countries, including Japan (59), while evidence for the long-term safety of their excessive intake is weak. In the light of the above argument, it may be necessary to revisit the recommended amount of niacin for daily consumption.

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