# Magnesium in Parkinson's disease: an update in clinical and basic aspects

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**Abstract**

**Magnesium (Mg) is essential for cell functions such as transport of calcium and potassium ions, and modulates signal transduction, energy metabolism, and cell proliferation. Several studies elucidated a reduced concentration of Mg in patients with Parkinson's disease (PD), and experimentally, severe loss of dopaminergic neurons exclusively in the substantia nigra in 1-year-old rats that had been subjected to continuously low Mg intake (one-fifth of the normal level) over generations. A study conducted by the authors revealed a significant and striking effect of Mg to prevent neurite and neuron pathology, and also to ameliorate neurite pathology in a rat Parkinson disease (PD) model involving culture of ventral mesencephalic-striatal cells with 1-methyl-4-phenylpyridinium ($MPP^+$). Mg is expected to prevent and ameriolate Parkinson's disease in cases where it would be able to cross into the brain in a suitable way.**

## Introduction

Parkinson's disease (PD) is a neurodegenerative disease occurring in middle-aged and aged humans characterized by clinical symptoms including tremor and rigidity (Parkinson, 1817). It has been reported that almost 90% of the patients are sporadic and 10% are familial. Sporadic PD shows neuropathological features involving the appearance of Lewy bodies (Lewy, 1912; Tretiakoff, 1919) and loss of neurons in the substantia nigra (Figures 1 and 2) and substantia innominata. After establishment of the disease as an entity, it was revealed that dopaminergic neurons in the vetral tegmental area, noradrenergic neurons in the locus coeruleus and motor vagal nucleus, serotonergic neurons in the dorsal raphe nucleus, and neurons in the sympathetic ganglia and visceral autonomic nervous system are involved in the disease with neuronal loss and presence of Lewy bodies (Jellinger, 1999). In the present manuscript, the authors review the role of magnesium (Mg) in the pathogenesis and pathomechanisms in clinical and basic aspects of PD.

## Mg in Parkinson's disease and related diseases

Uitti et al (1989) analyzed four brain regions (frontal cortex, caudate nucleus, substantia nigra and cerebellum) for concentrations of 24 metals (Ag, Al, As, B, Be, Ca, Cd, Co, Cr, Cu, Fe, K, Pb, Mg, Mn, Mo, Na, Ni, P, Se, Ti, V, W, Zn) by atomic absorption and atomic emission spectroscopy in brains of 9 patients with PD, 15 patients with other chronic neurological diseases and 12 subjects of controls. The results were that brains of PD and parkinsonism secondary to neurofibrillary tangle disease showed lower concentrations of Mg in the caudate nucleus and copper in the substantia nigra than control brains. Barbiloni et al (1999) performed in vivo phosphorus magnetic resonance spectroscopy on the occipital lobes of 13 patients with PD, 15 patients with multiple system atrophy and 16 age-matched healthy subjects. They reported that patients with PD showed significantly increased contents of inorganic phosphate (Pi), decreased cytosolic free [$Mg^{2+}$], and unchanged phosphocreatine and pH. Bocca et al (2006) examined concentrations of Ca, Cu, Fe, Mg, Si and Zn by inductively coupled plasma atomic emission spectrometry (ICP-AES) in blood, urine and cerebrospinal fluid (CSF) of 91 PD patients and 18 controls. They concluded that Mg concentration in CSF of PD patients decreased with the duration and severity of the disease.

It has been proposed that Mg deficiency is involved in the pathogenesis of parkinsonism-dementia complex (PDC) and amyotrophic lateral sclerosis (ALS) in the Chamorro population on

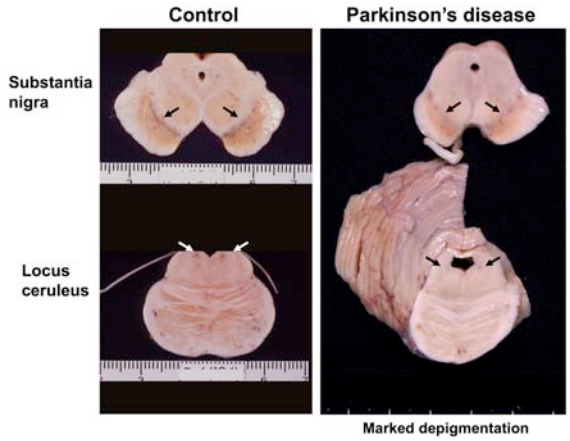


**Figure 1.** Midbrain and upper pons. The substantia nigra and locus coeruleus in the patient with Parkinson's disease show marked depigmentation as compared with those of controls.

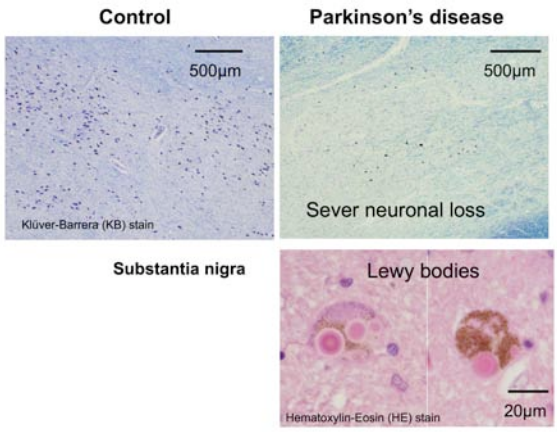


**Figure 2.** The substantia nigra of a patient with Parkinson's disease shows severe loss of neurons as compared with a control subject. Some remaining neurons represent Lewy bodies.

Guam, which is a member of the Mariana islands in the western Pacific Ocean, as well as in the Kii peninsula of Japan and in West New Guinea (Yase 1978, Garruto *et al,* 1984). PDC is a disease entity that was established by Hirano *et al,* (1961a, 1961b) that affects the neurons in the substantia nigra, brainstem, and temporal and frontal cortex. The disease is characterized by the presence of neurofibrillary tangles in the remaining neurons, and disease-specific granular hazy inclusions in the astrocytes (Oyanagi *et al,* 1997; Oyanagi, 2005), tau-positive fine granules in the cerebral white matter (Yamazaki *et al,* 2005), and widespread TDP-43-immunopositive inclusions (Hasegawa *et al,* 2007). Patients exhibit parkinsonism and dementia, and usually die within about 5 years from infectious diseases (Hirano *et al,* 1961a; 1961b; Chen and Chase, 1985). ALS is a motor neuron disease affecting the Betz cells in the cerebral cortex, and facial and hypoglossal nuclei in the brainstem and anterior horn cells in the spinal cord, and usually patients die of respiratory failure within 5 years after the onset.

## Possible pathomechanisms in Parkinson's disease

### *Mitochondrial damage and oxidative stress*

Increased expression of 4-hydroxy-2-nonenal (HNE) (Yoritaka *et al*, 1996), decreased activity of mitochondrial complex I and a decreased amount of alpha-ketoglutarate dehydrogenase complex (KGDHC) in the pigmented neurons of the substantia nigra (Hattori *et al*, 1991; Mizuno *et al*, 1994) have been reported in affected patients. In the substantia nigra, decreased activity of catalase and peroxidase (Ambani *et al*, 1975) and increased amounts of protein carbonyls, 8-hydroxy-2'-deoxyguanosine (8-OHdG)/8-hydroxy-guanine (8-OHG), 4-hydroxynonenal-lysine and malondialdehyde-lysine (MDAL) (Alam *et al*, 1997a,b; Zhang *et al*, 1999; Dalfo *et al*, 2005) have been reported.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) was the first human parkinsonian agent to be characterized. It is converted to 1-methyl-4-phenylpyridinium ($MPP^+$) by monoamine oxidase B in astrocytes. $MPP^+$ damages mitochondrial complex I of dopaminergic neurons after transfer by the dopamine transporter, and increased calcium permeability of the mitochondrial membrane induces free radicals (Smeyne *et al*, 2005). $MPP^+$ has been used to induce selective degeneration of dopaminergic neurons in an experimental model of PD (Nakamura *et al*, 2000). In addition, rotenone, 6-hydroxydopamine (6-OHDA), paraquat and annonacin have been used as noxious agents to create in vivo models of PD (Fornai *et al*, 2003; Champy *et al*, 2004; Bove *et al*, 2005) (Figure 3). Dopamine and dopamine quinones themselves are considered to be causes of oxidative stress. PINK1 (PTEN-induced putative kinase 1) maintains mitochondrial function, and the gene is causative in some familial PD (Valente *et al*, 2004).

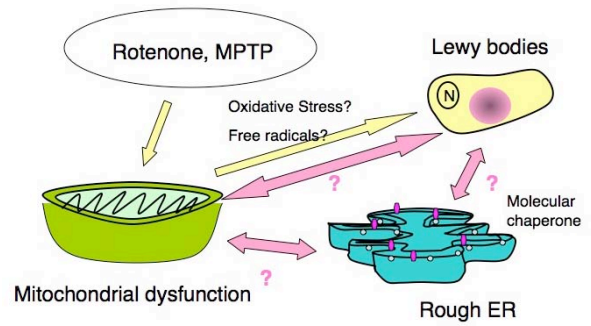


**Figure 3.** Possible relationship between mitochondria, rough ER and Lewy body formation.

***Unfolded protein retention and endplasmic reticulum stress***

Alpha-synuclein was found as a main component of the Lewy bodies and the gene was found to be a causative gene of a rare autosomal dominant PD (Polymeropoulos *et al,* 1997). It has been reported that multiplication of the gene was to be the cause of the disease (Singleton *et al*, 2003). It has been suggested that aggregates of alpha-synuclein cause potentiation of oxidative stress, possibly with interaction with iron. Synuclein was considered to be degraded in the proteasome. Knock-out of the 26S proteasome in the dopaminergic neurons induced "pale bodies" which is reported to be a prodrome of the Lewy bodies (Bedford *et al,* 2008).

Parkin and UCHL-1 are considered essential for ubiquitination of the unfolded proteins, and the gene mutations were found in some familial PD. It is considered that an oxidative stress may lead a combination of Parkin and DJ-1, and the combination suffocates unfolded protein degradation (Kitada *et al*, 1998; Bonifati *et al,* 2003). Mg has also been reported to inhibit spontaneous and iron-induced aggregation of alpha-synuclein (Golts *et al,* 2002) (Figure 4).

**Low Mg and Parkinson's disease model**

In the course of investigations into the pathogenesis of the PDC, the present authors performed an experiment in which rats were exposed to restricted intake of Ca and/or Mg over two generations. This resulted in severe loss of dopaminergic neurons exclusively in the substantia nigra in 1-year-old rats that had been subjected to continuously low Mg intake

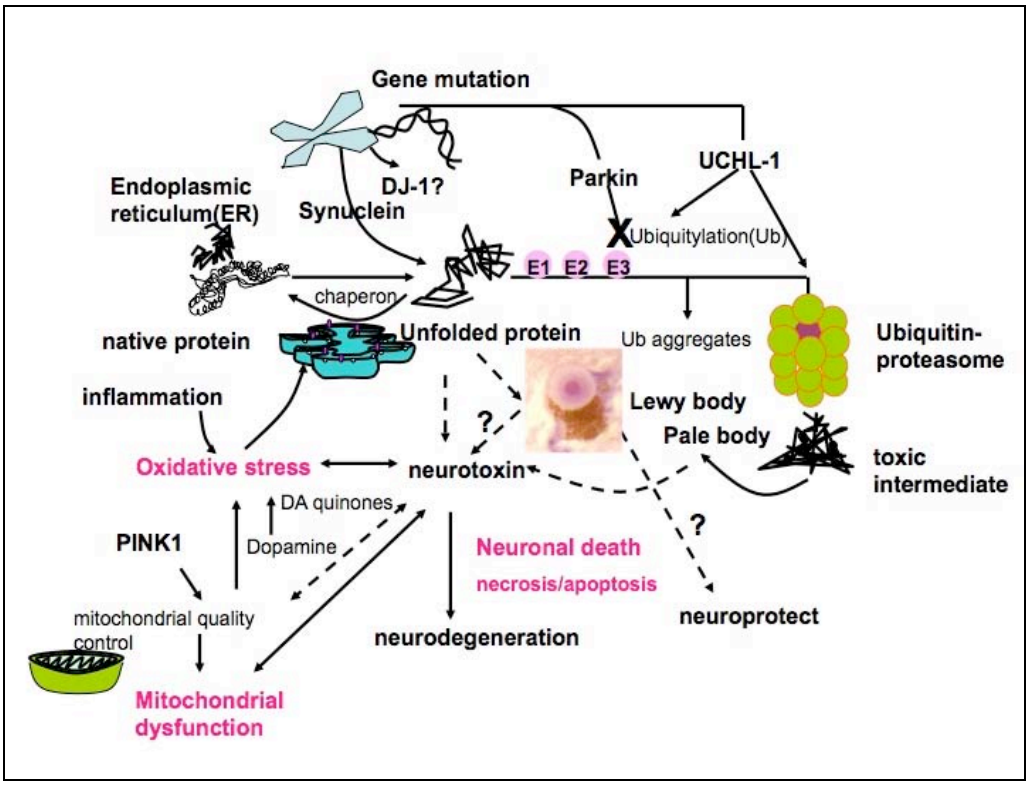


**Figure 4**. Scheme of possible pathomechanisms of dopaminergic neuron death in Parkinson's disease.

(one-fifth of the normal level) over generations (Oyanagi *et al*, 2006). This finding suggested a deep concern of low Mg intake over several generations to the pathogenesis of degeneration of the substantia nigra in humans.

## Therapeutic possibility by Mg for Parkinson's disease

### *As a blocker of the glutamatergic NMDA receptor*

Mg controls cytochrome *c* release in mitochondria (Eskes *et al*, 1998), and decreases the activity of N-methyl-D-aspartate (NMDA) receptors in excitotoxicity (Mayer *et al*, 1984). Mg treatment has also been shown to decrease cerebral infarct volume in rats in vivo (Lyden *et al*, 2000). The mechanism responsible for the neuroprotective effect of Mg has been considered to be reduced presynaptic release of the neurotransmitter glutamate (Lin *et al*, 2002), and blockade of the glutamatergic NMDA receptor (Nowak *et al*, 1984)(Figure 5). A relationship between decreased Mg concentration in serum and migraine has been reported in humans, and it has been suggested that migraine might be caused by hypersensitivity of the NMDA receptor to glutamic acid and certain other neuro-excitatory amino acids due to Mg depletion (Cojocaru *et al*, 2006). A decrease of cytosolic free Mg in the occipital lobe of PD patients has also been demonstrated by phosphorus magnetic response spectroscopy (Barbiroli *et al*, 1999).

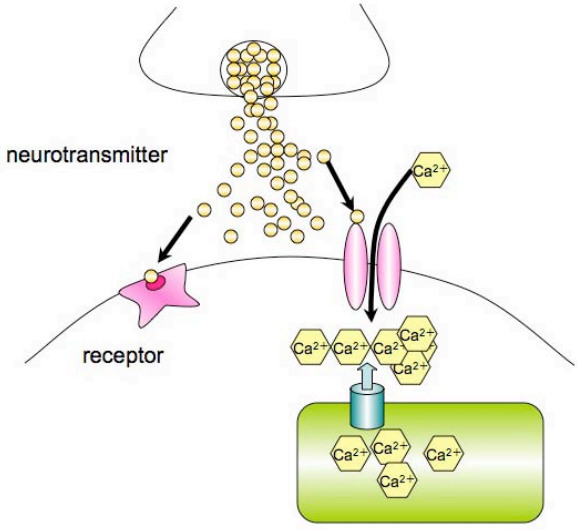


**Figure 5.** Metallic elements and neuron conduction.

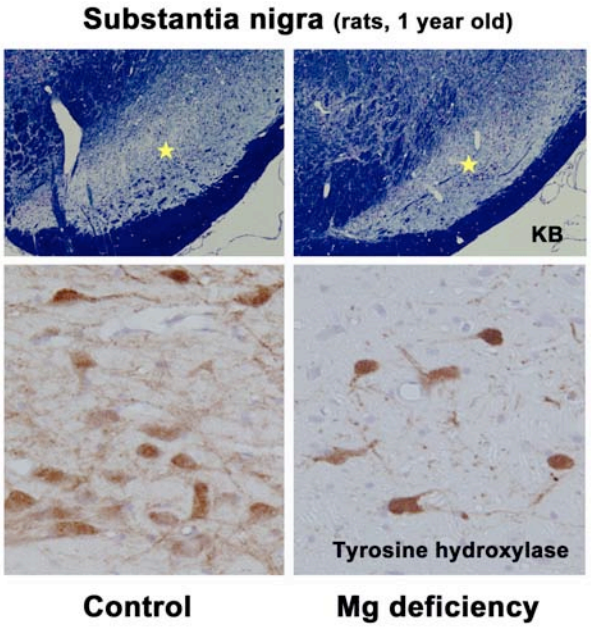


**Figure 6.** Severe atrophy and selective loss of dopaminergic neurons in the substantia nigra in rats with low Mg over generations (Oyanagi K, *et al*, 2006).

### *As an inhibiter of oxidative stress*

The present authors conducted a study to clarify the effects of Mg administration in a rat PD model involving culture of ventral mesencephalic-striatal cells with 1-methyl-4-phenylpyridinium ($MPP^+$), based on recent evidence for significant loss of dopaminergic neurons exclusively in the substantia nigra of 1-year-old rats after exposure to low Mg intake over generations (Oyanagi *et al*, 2006) (Figure 6). The results indicated that Mg might protect dopaminergic neurons in the substantia nigra from degeneration. The concentration of Mg in the culture medium varied from 0.8 mM, corresponding to the control condition, to 4.0 mM. Effects were estimated by counting the number of surviving dopaminergic neurons immunopositive for tyrosine hydroxylase and measuring the length of dopaminergic neurites. An increase in the concentration of Mg to 1.2 mM significantly inhibited the toxicity of $MPP^+$, and a concentration of 4.0 mM completely prevented any decrease in the number of dopaminergic neurons. The length of dopaminergic neurites was significantly preserved in the presence of Mg at 1.2 and 4.0 mM. An increase in the concentration of Mg to 1.2 and 4.0 mM led to a significant amelioration in the length of dopaminergic neurites after $MPP^+$ toxicity (Figure 7).

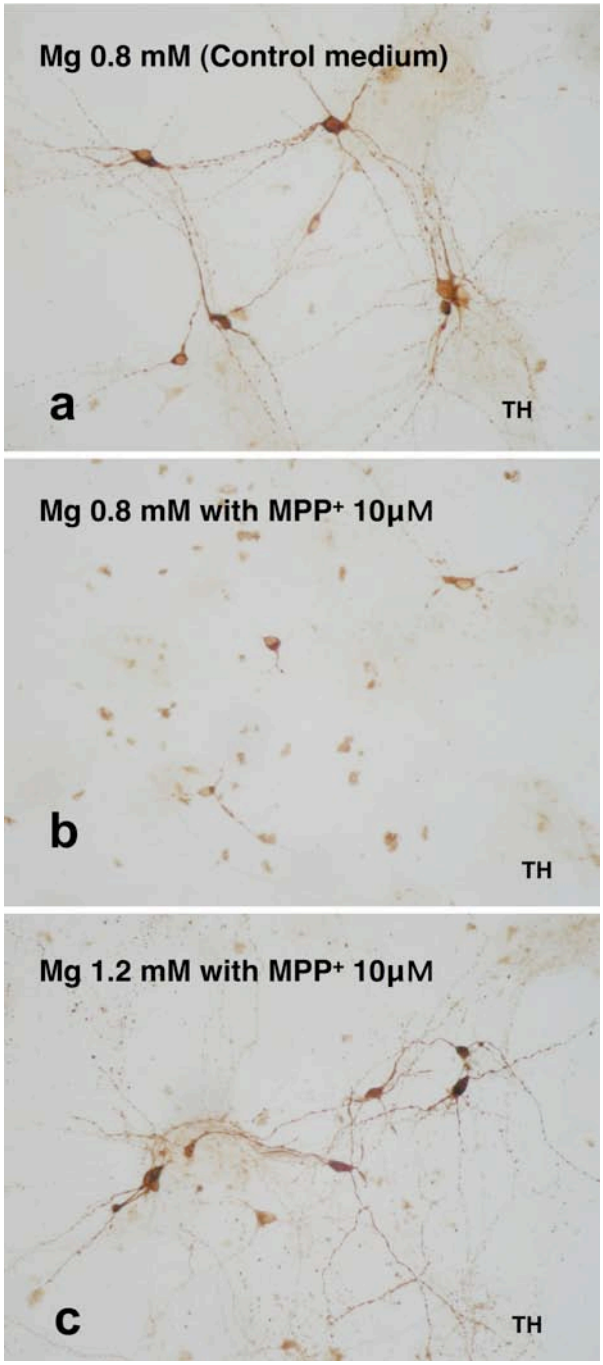


**Figure 7.** Prevention of $MPP^+$ toxicity by Mg in a Parkinson model (Hashimoto *et al*, 2008). **a:** normal condition of cultured nigral dopaminergic neurons. **b:** severe loss of dopaminergic neurons and the neuritis after $MPP^+$ administration. **c:** An increase in the concentration of Mg to 1.2 mM significantly inhibited the toxicity of $MPP^+$.

This was the first report to document a significant and striking effect of Mg for prevention of neurite and neuron pathology, and also amelioration of neurite pathology in a PD model. In addition, an increase in the Mg concentration to 1.2, 2.0, and 4.0 mM did not induce any degenerative features in the cultured dopaminergic cells, suggesting that a Mg concentration of up to 4.0 mM in the extracellular space might not induce any neuron degeneration in humans. Mg oxide per os has often been used as a laxative for patients with PD, but is reportedly not absorbed in the bowels, thus not affecting the serum concentration of Mg (Sakimura *et al*, 1998). Recent studies by the authors using mice also established that no significant alteration was found in the CSF of B6 mice injected intraperitoneally with Mg, even though the serum Mg concentration was significantly increased (Sun *et al, 2009*). Further research is necessary to find Mg compounds that can easily be absorbed in the bowels and pass through the blood-brain barrier, like Mg-L-threonate (Slutsky *et al*, 2010) and besides, via transporters that can carry Mg through the bowel mucosa, blood-brain barrier and plasma membrane of neurons.

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