



The promise of neuroprotective agents in Parkinson's disease

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Parkinson's disease (PD) is characterized by loss of dopamine neurons in the substantia nigra of the brain. Since there are limited treatment options for PD, neuroprotective agents are currently being tested as a means to slow disease progression. Agents targeting oxidative stress, mitochondrial dysfunction, and inflammation are prime candidates for neuroprotection. This review identifies Rasagiline, Minocycline, and creatine, as the most promising neuroprotective agents for PD, and they are all currently in phase III trials. Other agents possessing protective characteristics in delaying PD include stimulants, vitamins, supplements, and other drugs. Additionally, combination therapies also show benefits in slowing PD progression. The identification of neuroprotective agents for PD provides us with therapeutic opportunities for modifying the course of disease progression and, perhaps, reducing the risk of onset when preclinical biomarkers become available.

Keywords: neuroprotection, neurodegeneration, Parkinson's disease

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder that results from the death of neuronal cells containing dopamine (DA) in the midbrain. Usually at the time of clinical diagnosis the patient has already lost 60% or more of the neurons in the substantia nigra pars compacta (SNpc). PD affects approximately 3% of the population over the age of 65. Most cases of PD are idiopathic and current evidence suggests that environmental factors along with a genetic susceptibility are the major causes (Lang and Lozano, 1998). Genetic forms of PD exist, but they represent less than 5% of the cases (Langston, 1998). Oxidative stress, mitochondrial dysfunction, and inflammation play key roles in the development of PD (Michel et al., 2002; Jenner, 2003). Because a large proportion of the baby boomers are reaching the typical age of onset for PD, there have been increased efforts to search for neuroprotective agents that will prevent the irreversible loss of neurons. In this review we summarize the current evidence that neuroprotective agents may be useful for preventing or slowing the development of PD.

CAFFEINE AND NICOTINE ARE PROMISING NEUROPROTECTIVE STIMULANTS FOR PARKINSON'S DISEASE

Most epidemiological studies support a protective benefit of drinking caffeinated beverages (Ross et al., 2000; Ascherio et al., 2001; Saaksjarvi et al., 2008), although one study showed no benefit (Xu et al., 2006). Animal studies in general also indicate that caffeine is neuroprotective. Chronic caffeine administration in mice provided protection against dopaminergic neuron toxicity from exposure to a combination of paraquat and maneb (van den Pol, 1986; Kachroo et al., 2010). In addition, acute and chronic

treatment of mice with caffeine reduced the effect of acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Chen et al., 2001) and 6-hydroxydopamine (6-OHDA) treatment on striatal DA loss (Joghataie et al., 2004). Motor dysfunctions were attenuated and DA levels increased after caffeine treatment in MPTP- and 6-OHDA-treated animals (Joghataie et al., 2004; Aguiar et al., 2006). In addition, caffeine treatment partially restored noradrenaline, DA, 3,4 dihydroxyphenylacetic acid, homovanillic acid, and their metabolites in 6-OHDA-lesioned rats (Aguiar et al., 2006). Although serotonin levels decreased, levels of its metabolite, 5-hydroxyindoleacetic acid, were unchanged. In treatment, the time frame of caffeine's beneficial effects is extended by its metabolites theophylline and paraxanthine, which also exert protective effects (Xu et al., 2010). An additional benefit of caffeine is that tolerance does not develop with long-term exposure (Xu et al., 2002).

The effect of estrogen on caffeine's neuroprotective capabilities is significant. Results from epidemiological studies showed improvement in male Parkinson's patients only (Ascherio et al., 2001; Costa et al., 2010). Interestingly, in post-menopausal women, caffeine consumption is also linked to a reduced risk of PD, but only among those who were not taking hormone-replacement therapy (Ascherio et al., 2003). In a follow up case-controlled study the relationships between gender, caffeine intake, estrogen, and the risk of PD were examined by investigating single nucleotide polymorphisms (SNPs) in the caffeine metabolizing genes [the cytochrome P450 (CYP) gene CYP1A2 and *N*-acetyltransferase 2 (NAT2)] and estrogen receptors (ESR1 and ESR2). A significant increased risk of PD was observed in women who had the CYP1A2 polymorphism, whereas NAT2, ESR1, and ESR2 had marginal effects on PD risk (Palacios et al., 2010). In another study, estrogen and caffeine were administered to both male and female

MPTP-treated mice, which prevented neuroprotection in all of the animals (Xu et al., 2006). Thus, the beneficial effects of caffeine may be limited to men and post-menopausal women who are not receiving hormone-replacement therapy.

Complimentary genetic and pharmacological data from rodent studies indicate that one mechanism by which caffeine reduces dopaminergic toxicity is through antagonism of adenosine A_{2A} receptors (see review Prediger, 2010). In contrast, the indirect pathway of the basal ganglia contributes to the progression of PD via glutamatergic neuron overstimulation through adenosine A_{2A} receptors (Bove et al., 2005b). Caffeine also activates PI3K/Akt signaling and thus reduces apoptosis (Nakaso et al., 2008).

Nicotine is comparable to caffeine with regards to lowering the risk of developing PD (Simon et al., 2009). In a Chinese epidemiological study, there was a significant reduced rate of PD in individuals who drank coffee and smoked cigarettes, which was dose-dependent (Tan et al., 2003). Toxicant responsive enzymes, including CYP1A1, CYP2E1, and glutathione S-transferase (GST) enzymes GST-ya, GST-yc, GSTA4-4, and vesicular monoamine transporter-2 play critical roles in modulating the protective effects of nicotine and caffeine in MPTP-treated animals (Singh et al., 2008). Interestingly, decaffeinated coffee and nicotine-free tobacco were neuroprotective in a *Drosophila* model of PD, but, the neuroprotection depended on the cytoprotective transcription factor nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) and cafestol (an activator) (Trinh et al., 2010). This suggests that coffee and tobacco containing Nrf2-activating compounds account for the decreased risk of PD.

Nicotine without caffeine, has also shown beneficial effects in reducing the risk of PD in epidemiological studies and animal studies (reviewed in Quick, 2004). Animals receiving nicotine at low doses (0.1 mg/kg s.c) *in vitro* showed reduce DA depletion resulting from MPTP and 6-OHDA treatments (Ferber et al., 1998; Costa et al., 2001). A large dosage of nicotine (0.4 mg/kg s.c), however, enhanced dopamine loss *in vivo* (Ferber et al., 1998). Additionally, nicotine attenuated motor deficits and nigrostriatal neurodegeneration produced by chronic administration of rotenone in mice. In 6-OHDA-lesioned rats, subchronic nicotine (0.4 mg/kg) and apomorphine treatment reduced parkinsonian contralateral rotations (Meshul et al., 2002). Chronic nicotine treatment in MPTP-treated primates restored and maintained dopaminergic function and prevented cell loss in the SNpc (Quik et al., 2006). In addition, simple exposure to tobacco smoke prior to MPTP treatment reduced the loss of striatal DA in mice (Carr and Rowell, 1990). Additionally, in humans, acute nicotine treatment can improve impaired controlled semantic processing in PD patients (Holmes et al., 2011). To date, nicotine is still in Phase II trials focusing on optimizing dosage and increasing sample size.

Nicotine is an alkaloid that is the predominant ingredient found in cigarettes. It has a high rate of absorption and diffuses quickly through the bloodstream and across the blood-brain barrier (BBB). Nicotine reduces the oxidative stress that is associated with the progression of PD by scavenging free radicals produced by monoamine oxidase-B (MAO-B), which metabolizes DA (Fowler et al., 1996; Iida et al., 1999). In addition, nicotine is capable of augmenting neurotrophic factors and cholinergic receptor expression (Ferrea and Winterer, 2009). Nicotine pretreatment attenuated

the loss of dopaminergic cells in MPTP-induced mesencephalic neurons (Quik and Jeyarasasingam, 2000). Neuroprotection was blocked by a nicotine receptor antagonist suggesting the effect was mediated by nicotinic acetylcholine receptors (nAChR; Quik and Jeyarasasingam, 2000). These results suggest that the neuroprotective mechanism of nicotine may be directly or indirectly connected to the nAChR up-regulation in cerebral cortical blood flow (Linville et al., 1993). Moreover, it indicates that nAChR agonists could be beneficial in slowing the progression of PD (Maggio et al., 1997). Recently it has been suggested that stimulating nAChRs or PI3K/Akt/PKB signaling could suppress dopaminergic cell death induced by rotenone (Takeuchi et al., 2009). In similar studies, nicotine induced fibroblast growth factor (FGF-2) and the brain-derived neurotrophic factor (BDNF) in the striatum (Maggio et al., 1997). Neuroprotection of DA neurons by nicotine is primarily gated by cytoplasmic Ca²⁺ through a mechanism involving α -bungarotoxin-sensitive (α 7) nAChRs and secondarily through T-type voltage-gated calcium channels (Toulorge et al., 2011).

URATE AND URIC ACID HAVE MODERATE NEUROPROTECTIVE PROPERTIES

Uric acid (UA) is a natural antioxidant that can reduce oxidative stress by acting as a scavenger of free radicals and an iron chelator (Ames et al., 1981; Davies et al., 1986; Yu et al., 1998; Hink et al., 2002). Urate suppresses oxyradical accumulation (Yu et al., 1998), inhibits cytotoxic activity of lactoperoxidase (Everse and Coates, 2004), and protects against DA-induced apoptosis (Jones et al., 2000). UA has been found to suppress oxidative stress and prevent dopaminergic cell death in animals (Duan et al., 2002). In addition, slower rates of clinical progression were observed in untreated early stage PD patients who have higher plasma, serum, and cerebrospinal fluid (CSF) concentrations of UA (Schwarzschild et al., 2008; Ascherio et al., 2009). In contrast, lower levels of urate were present in CSF (Tohgi et al., 1993) and post-mortem in the SNpc of patients with PD (Church and Ward, 1994). In a population-based cohort study of 4,695 participants aged 55 years and older, higher serum levels of UA were associated with a significantly decreased risk of PD (de Lau et al., 2005). Urate therapy reduced the risk of PD in a dose-dependent manner (de Lau et al., 2005; Schwarzschild et al., 2008). Additionally in a prospective study of subjects with early stage PD there was a 49% reduction in the progression of the disease with high urate intake (Schwarzschild et al., 2008).

Like caffeine, urate (Alonso et al., 2007) and UA (Alonso et al., 2007; Schwarzschild et al., 2008; Andreadou et al., 2009) show a gender-specific bias with a greater benefit observed in male PD patients. Epidemiological studies however contradict these results and show no gender specificity (de Lau et al., 2005; Annanmaki et al., 2007; Chen et al., 2009).

Life style choices play an important role in PD progression. Exercise, for example, decreases PD, possibly by increasing serum UA levels and decreasing excretion of UA (Schlesinger and Schlesinger, 2008). Additionally, individuals who eat diets that increase plasma urate levels have a reduced risk of PD. Dietary changes expected to increase plasma urate levels like dairy protein (but not milk) (Choi et al., 2005) and vitamin C contribute to reducing the risk of PD in men (Gao et al., 2008). These studies also

suggest that a PD patient's diet should include adequate sources of purines, such as meat and seafood, which results in higher concentrations of UA (Annamaki et al., 2007). Diets that result in lower UA levels could accelerate disease progression (Annamaki et al., 2007). One must keep in mind however that a high concentration of UA in the blood serum increases the risk of gout and high alcohol and fructose consumption compounds this risk (Choi et al., 2004). Therefore, even if PD patients choose to modify their diet for potential neuroprotective effects, the physician must carefully monitor them for other at risk chronic diseases (Gao et al., 2008).

VITAMIN D, BETA-CAROTENE AND RIBOFLAVIN ARE CANDIDATES FOR NEUROPROTECTIVE AGENTS

Vitamin E (α -tocopherol) is a lipid-soluble antioxidant that can inhibit iron accumulation, suppress microglial activation, scavenge oxygen radicals, and prohibits the peroxidation of membrane lipids (Tappel, 1962; Burton et al., 1983; Cheeseman et al., 1988; Chow, 1991; Lan and Jiang, 1997; Li et al., 2001). Vitamin E also induces interleukin-1 α and tumor necrosis factor (TNF)- α and suppresses p38 MAPK and NF κ B activation (Li et al., 2001). Vitamin E is regulated by α -tocopherol transfer protein (TTP) in the liver and brain (Kaempf-Rotzoll et al., 2003). Studies have demonstrated that lack of TTP causes a systemic deficiency of vitamin E in humans and mice (Traber and Sies, 1996; Yokota et al., 2001), which can lead to enhanced oxidative stress in the brain (Yokota et al., 2001). However, vitamin E is also believed to reduce oxidative stress caused by iron accumulation in the brain (Lan and Jiang, 1997). Vitamin E deficiency increases MPTP toxicity in mice (Odunze et al., 1990). Vitamin E supplementation, however, had a protective effect on DA neurons in the SNpc (Roghani and Behzadi, 2001) and reduced DA loss (Lan and Jiang, 1997). Pretreatment with vitamin E was shown to reduce lipid peroxidation levels (Lan and Jiang, 1997), but depletion of striatal DA was not attenuated by pretreatment (Gong et al., 1991; Chi et al., 1992). Other studies have shown that vitamin E has no protective effects against DA-induced toxicity in PC12 cells (Offen et al., 1996) and only partial protection in MPTP-treated rodents (Perry et al., 1987). In addition, a genetic vitamin E deficiency did not affect MPTP susceptibility in mice (Ren et al., 2006). So either the protective effects of vitamin E is dependent on the mechanism by which PD is induced or high acute dose of vitamin E have different neuroprotective effects than chronic low doses (Fariss and Zhang, 2003; Ricciarelli et al., 2007).

There are no differences in the amount of vitamin E in the cerebellum (Dexter et al., 1992) or CSF (Molina et al., 1997) between PD patients and healthy individuals. Clinical trials also show no neuroprotective benefit of taking vitamin E (Fernandez-Calle et al., 1992; LeWitt, 1994; Morens et al., 1996). A meta-analysis however showed a protective effect of both moderate intake (0.67–0.98) and high intake (0.78, 0.57–1.06) of vitamin E (Etminan et al., 2005). Thus, choosing foods that are vitamin E-rich may be neuroprotective (Perlmutter, 1988; Zhang et al., 2002). The risk of PD was significantly lower in men than in women with high intake of vitamin E from food (Zhang et al., 2002).

Vitamin C or ascorbate, is highly concentrated in the CNS, and is associated primarily with the activity of glutamatergic neurons, which makes it a good candidate for a neuroprotector or a neuromodulator (Grunewald, 1993). Vitamin C is decreased in

vascular parkinsonisms (Paraskevas et al., 2003). Results from a pilot study in which high doses of vitamin E and C were given to participants showed a decrease in PD progression in early stage patients (Fahn, 1992). Yet, other studies have shown few beneficial effects of vitamin C alone and some have shown an increase risk of PD (Scheider et al., 1997; Zhang et al., 2002; Etminan et al., 2005). In a case-controlled study of people who consumed diets rich in vitamin C, there was a 40% risk reduction of PD than those consuming small amounts (Perlmutter, 1988). Because of the conflicting data, there is currently not enough data to support vitamin C as neuroprotective for PD.

Calcitriols are a group of fat-soluble secosteroids that include vitamin D and its derivatives D₂, D₃, D₄, and D₅ (Garcion et al., 2002). D₃ is obtained through the skin during sun exposure and can be ingested (Eyles et al., 2003). Vitamin D deficiency is prevalent in PD patients (Sato et al., 1997). Vitamin D receptors (VDR) in the brain are found primarily in dopaminergic neurons in the SNpc (Eyles et al., 2005) and VDR mRNA expression in the blood is a useful risk marker for identifying PD patients (Scherzer et al., 2007). Vitamin D has anti-inflammatory properties, it can regulate expression of glial cell line-derived neurotrophic factor (GDNF), and regulates calcium (Ca²⁺) homeostasis (Evans, 1988; Naveilhan et al., 1996; Garcion et al., 2002; Smith et al., 2006; Chan et al., 2009; Butler et al., 2011). A disruption of Ca²⁺ homeostasis accelerates SNpc dopaminergic neuron loss (Butler et al., 2011). In contrast, GDNF stimulation can alleviate PD symptoms in both primate and PD patients (Gash et al., 1996; Kordower et al., 2000; Gill et al., 2003). Vitamin D was also shown to be beneficial in 6-OHDA-treated animals and in cell cultures (Wang et al., 2001; Smith et al., 2006). In addition, vitamin D increased neuromuscular function in parkinsonian rodents (Holick, 2007). In contrast to these findings, one case-controlled human study found an increased risk of PD with high consumption of vitamin D (Anderson et al., 1999). Together these findings suggest that dietary intake of vitamin D in moderate amounts may be effective in protecting individuals from PD progression although further studies are needed (Holick, 2007).

Serum levels of vitamin A are similar between, PD patients and controls suggesting that levels of vitamin A are unrelated to the risk of PD (Fernandez-Calle et al., 1992, 1993; Jimenez-Jimenez et al., 1993; Etminan et al., 2005). An epidemiological study, however, found that there was a decrease in the risk of PD in individuals who consumed foods containing carotenoids and beta-carotene (Perlmutter, 1988). Vitamin A's precursor beta-carotene, may offer neuroprotective effects by preventing lipid peroxidation (Glover, 1960; Kartha and Krishnamurthy, 1977). A recent study showed that pretreatment with beta-carotene partially protected against MPTP-induced neurotoxicity in mice (Perry et al., 1985; Yong et al., 1986), although the same was not true of primates (Perry et al., 1987).

Riboflavin, vitamin B-2, is a water-soluble vitamin present predominantly in dairy products (Powers, 2003). Its biologically active forms are flavin adenine dinucleotide and flavin mononucleotide, which are electron carriers that participate in a wide range of redox reactions (Huennekens, 1956; Merrill et al., 1981). Riboflavin plays an active role in energy production and affects iron accumulation (Sirivech et al., 1977; Powers et al., 1983; Powers, 1987). The mechanism of action of riboflavin in the brain remains unknown,

but may involve glutathione depletion, cumulative mitochondrial DNA mutations, disturbed mitochondrial protein complexes, and abnormal iron metabolism (Di Monte, 1991; Jenner et al., 1992; Logroscino et al., 1997). Riboflavin may also effect glutathione production (Perlmutter, 1988). The amount of riboflavin is lower in PD patients compared to healthy and disease controls, suggesting that taking riboflavin supplements may be beneficial (Coimbra and Junqueira, 2003). Intake of riboflavin, compared to other B-vitamins was shown to reduce the risk of PD (Murakami et al., 2010). In fact, the risk of PD was reduced 51% by users obtaining a high consumption (Perlmutter, 1988) and daily doses of riboflavin for 6 months showed improved motor capacity of PD patients in 3 months (Coimbra and Junqueira, 2003). These promising results indicate that additional longitudinal studies are needed to determine the long-term effects of chronic administration of riboflavin supplements.

AMONG THE SUPPLEMENTS CREATINE SHOWS THE MOST PROMISE AS A NEUROPROTECTIVE AGENT

Coenzyme Q10 (CoQ10), also known as ubiquinone, is a promising agent for neuroprotection in PD and other neurodegenerative diseases because of its role in the mitochondrial electron transport chain (METC) and as an antioxidant (Beal and Shults, 2003). CoQ10 serves as an electron acceptor in complex I and II of the METC. CoQ10 is protective by inhibiting SIN-1-induced apoptosis (Sharma et al., 2004), suppressing intra-mitochondrial and intra-nuclear biosynthesis of 8-OH-2dG, inhibiting translocation of caspase-3, attenuating α -synuclein expression, and blocking intra-mitochondrial accumulation of metal ions (Ebadi et al., 2004).

Animal studies have shown that rotenone-induced parkinsonism reduced CoQ10 concentrations in plasma and the striatum with a corresponding decrease in striatal levels of DA, mitochondrial complex I activity and ATP levels, as well as significant increase in B-cell lymphoma 2 (Bcl-2) expression (Abdin and Hamouda, 2008). Administration of CoQ10 protected the nigrostriatal dopaminergic neurons in MPTP-treated mice (Shults et al., 1999). In addition, a diet containing CoQ10 (1,600 mg/kg/day, 2 months) or CoQ10 supplementation diminished neural tissue damage (Clerehugh et al., 2008). CoQ10 was also effective in preventing DA depletion, loss of tyrosine hydroxylase neurons and formation of α -synuclein inclusions in the SNpc in mice (Clerehugh et al., 2008).

Reduced levels of CoQ10 are present in PD patients' plasma and platelets (Matsubara et al., 1991; Gotz et al., 2000) and in cortex (Hargreaves et al., 2008), which correlated with reduced activity of complex I and II/III (Shults et al., 1997, 1999). In addition, the percent of CoQ10 in its oxidized form is elevated in PD patients (Sohmiya et al., 2004). Chronic administration of CoQ10 in PD patients delays the progression of PD (Shults et al., 2002; Shults, 2003) with no adverse effects (Galpern and Cudkowicz, 2007). Additionally, CoQ10 supplements showed promising results in a small group of *de novo* PD patients during phase II clinical trials although no follow up study has been published (Shults et al., 2002). More recently, another human trial found inconclusive results from CoQ10 supplements in PD patients (Investigators, 2007). CoQ10 (2,400 mg/day) and vitamin E (1,200 IU/day)

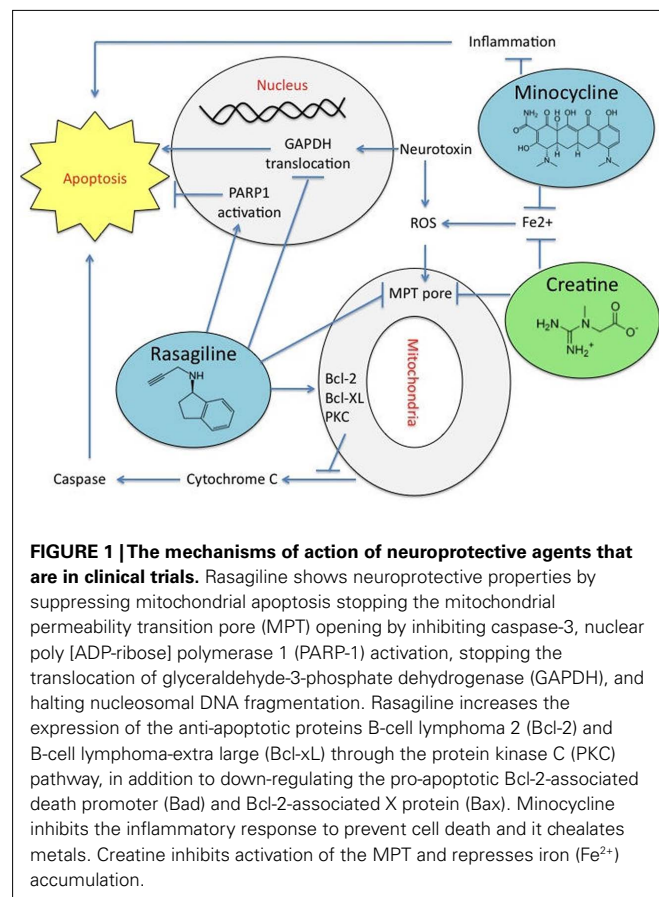
together initially was thought to be beneficial for PD patients (Shults et al., 2004), however, in Phase III trials it was deemed futile (NINDS¹).

Creatine is a guanidino compound found primarily in meat products and is produced endogenously by the liver, kidney, and pancreas (Tarnopolsky and Beal, 2001; Adhiketty and Beal, 2008). Creatine possesses antioxidant properties and can regulate intracellular calcium, suppress extracellular glutamate levels, and inhibit the opening of the mitochondrial permeability transition pore (MPT; **Figure 1**) (Xu et al., 1996; Lawler et al., 2002; Dedeoglu et al., 2003).

A combination of CoQ10 and creatine shows an additive neuroprotective effect in chronic MPTP-treated mice (Yang et al., 2009). Additionally, creatine has shown promising neuroprotective effects in combination with CoQ10 in PD patients (Yang et al., 2009). Alone, creatine protects against MPTP-induced DA depletion in the SNpc (Matthews et al., 1999). Interestingly, in a stage II clinical trial creatine showed a delay in the progression of PD by 50% compared to controls that received a placebo (Investigators, 2006). In a follow up study 18 months later, creatine continued to show efficacy as a neuroprotective agent (Investigators, 2008) and it is currently in Phase III trials (NET-PDLS²).

¹http://www.ninds.nih.gov/disorders/clinical_trials/CoQ10-Trial-Update.htm

²<http://clinicaltrials.gov/ct2/show/NCT00449865>



Omega-3 polyunsaturated fatty acids appear to be neuroprotective for several diseases (Bousquet et al., 2011) including a small study with PD patients (da Silva et al., 2008). Animal studies have shown that the omega-3 fatty acid docosahexaenoic acid (DHA) can replace the omega-6 fatty acids already present in the brains of mice that had been given supplements after MPTP treatment (Bousquet et al., 2008). DHA is an essential factor in growth and development in the brain (Horrocks and Yeo, 1999) and has anti-inflammatory capabilities due to its ability to inhibit cyclo-oxygenase-2 (COX-2) (Massaro et al., 2006). DHA (5–50 $\mu\text{g/ml}$) protected neurons against cytotoxicity, inhibited both nitrogen oxide (NO) production and Ca^{2+} influx, and increased the activities of antioxidant enzymes of glutathione peroxidase and glutathione reductase (Wang et al., 2003) in cell cultures. DHA does not alter the levels of glutathione (GSH) (Wang et al., 2003). Animal studies showed that DHA decreased apoptosis of dopaminergic cells after MPTP treatment (Ozsoy et al., 2011). Short-term administration of DHA (100 mg/kg) reduced 40% of the levodopa-induced dyskinesias in Parkinsonian primates (Samadi et al., 2006). DHA also preserved DA levels, tyrosine hydroxylase (TH)-positive neurons and nuclear receptor related-1 protein expression from MPTP-induced neurotoxicity in mice (Bousquet et al., 2008). Chronic administration of uridine and DHA increased the levels of neural phosphatides and proteins in synaptic membranes (Wurtman et al., 2006) and dendritic spines in rodents (Sakamoto et al., 2007). DHA and uridine administration also reduced parkinsonian related behaviors and elevated DA levels in 6-OHDA rats (Cansev et al., 2008). Human studies on the effects of DHA are now needed before recommendations may be made to PD patients.

DHA's proposed mechanisms of neuroprotection are linked to its anti-oxidative activity *in vivo* (Hashimoto et al., 2002; Yavin et al., 2002; Calon et al., 2004; Wu et al., 2004; Bazan, 2005), its ability to increase glutathione reductase activity (Hashimoto et al., 2002) and decrease the accumulation of oxidized proteins (Calon et al., 2004; Wu et al., 2004) and levels of lipid peroxide and reactive oxygen species (ROS) (Hashimoto et al., 2002, 2005). DHA also triggered inactivation of cell-signaling pathways leading to caspase activation (Calon et al., 2004, 2005) and hyperphosphorylation of tau (Green et al., 2007). In addition, DHA regulates the PI3K/Akt cascade (Akbar and Kim, 2002; Akbar et al., 2005; Kim, 2007). DHA has no association with beta-secretase or gamma-secretase complex, but it can down-regulate presenilin-1 *in vitro* and *in vivo* (Lim et al., 2005; Green et al., 2007). Other potential mechanisms of action of DHA include regulation of inflammation, gene transcription, and cell membrane properties (de Urquiza et al., 2000; Salem et al., 2001; Jump, 2002).

Melatonin has been associated with nigrostriatal protection, reduced auto-oxidation of L-3,4-dihydroxyphenylalanine, and has antioxidant properties (Fertl et al., 1993; Miller et al., 1996; Reiter et al., 1997; Khaldy et al., 2000; Rocchitta et al., 2006). Decreased levels of melatonin are present in PD patients compared to controls (Sandyk, 1990). Melatonin's free radical scavenging properties and its ability to easily pass the BBB suggest that it may be neuroprotective (Antolin et al., 2002; see review Mayo et al., 2005).

Animal studies have shown that melatonin can prevent cell death and damage induced by MPTP (Acuna-Castroviejo et al.,

1997), 6-OHDA (Kim et al., 1998), and iron (Maharaj et al., 2006a) in neurons and astrocytes (Martin et al., 2002). Melatonin blocked apoptosis and necrosis in 6-OHDA-treated undifferentiated and nerve growth factor (NGF)-differentiated PC12 cells (Mayo et al., 1998, 1999). Contrary to these results, striatal DA depletion and DA neuron loss increased after melatonin treatment of rotenone-induced Parkinsonism (Tapias et al., 2010). Melatonin given to PD patients improved the duration of sleep and reduced sleep disturbances (Dowling et al., 2005). There are no clinical studies to date that have investigated whether melatonin is neuroprotective for PD patients.

The antioxidant GSH, which is involved in iron metabolism and plays an ancillary role in thiol–redox control, is depleted in the SNpc of PD patients (Perry et al., 1982; Riederer et al., 1989; Pearce et al., 1997). When GSH was depleted *in vitro* and *in vivo*, there was oxidative damage of complex I proteins (Chinta and Andersen, 2006; Chinta et al., 2007; Kumar et al., 2011), defects in basal ganglia formed (Sian et al., 1994), and the ubiquitin–proteasome system functioned poorly (Martin and Teismann, 2009), but the electron transport chain complex was unaffected (Heales et al., 2011). Collectively these studies suggest that GSH may facilitate cascading events leading to oxidative stress (Bharath et al., 2002; Garrido et al., 2011).

Animal studies have also shown that excessive or reduced GSH levels can initiate degeneration of DA neurons (Garrido et al., 2011). However, chronically decreased GSH concentrations in the brain did not directly correlate to a reduction in the viability of DA neurons in the SNpc, nor decrease the number of striatal DA terminals, but does make neurons more susceptible to neurotoxins (Schulz et al., 2000). Treatment with MPTP in GSH peroxidase-deficient mice resulted in depletion of DA (Klivenyi et al., 2000). In nigral TH immune responsive cells similar results were seen with a greater reduction of DA neurons when lower levels of GSH were present prior to toxin administration (Pileblad et al., 1989; Seaton et al., 1996; Wullner et al., 1996). These studies suggest that the concentration of GSH is key to its neuroprotective capabilities. It has been hypothesized that enhancement of GSH synthesis or inhibition of its degradation may result in a decrease in disease progression (Schulz et al., 2000).

Phytic acid (IP6) is a naturally occurring iron chelator in food that acts by altering cell-signaling pathways and the activity or expression of antioxidant enzymes (Shamsuddin et al., 1997; Xu et al., 2011). IP6 is capable of inhibiting MPTP, 6-OHDA, and iron toxicity in cell culture (Xu et al., 2008, 2011). IP6 increases cell survival in MPTP-treated cells and repressed caspase-3 activity and DNA fragmentation (Xu et al., 2008). IP6 also suppressed hydroxyl radical formation after 1-methyl-4-phenylpyridinium (MPP+) treatment in rats (Obata, 2003). Further animal and human studies are needed to test IP6's antioxidant's properties.

SEVERAL COMMONLY PRESCRIBED DRUGS ARE EMERGING AS THERAPEUTIC AGENTS FOR PD

Common household drugs such as aspirin and Ibuprofen protect against neuro-inflammation, which can lead to neurodegeneration in the brain (Hirsch and Hunot, 2009). The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been shown to lower the risk of PD in epidemiological studies (Chen et al., 2003; Ton et al.,

2006; Wahner et al., 2007; Gao et al., 2011) and protect against neuronal death, ROS/peroxidation, and dopaminergic neurotoxicity by inhibiting cyclo-oxygenase enzymes in animals (Bilodeau et al., 1995; Kaufmann et al., 1997; Aubin et al., 1998; Saini et al., 1998; Casper et al., 2000; Sairam et al., 2003). Pretreatment with NSAIDs is neuroprotective in MPTP and 6-OHDA-treated animals and *in vitro* (Esposito et al., 2007). In humans there was a reduction in PD risk observed in individuals who use Ibuprofen, but no reduction was found in individuals who use NSAIDs or Acetaminophen (Chen et al., 2005; Ton et al., 2006; Driver et al., 2011; Gao et al., 2011). A case-controlled study also concluded that NSAIDs and aspirin show no association with altering the risk of PD (Becker et al., 2011). In some studies there was a reported increased risk of PD observed in individual who use aspirin (Bower et al., 2006; Hernan et al., 2006). In contrast, other studies showed that aspirin was protective and functioned by ROS scavenging *in vivo* (Di Matteo et al., 2006; Maharaj et al., 2006b). Ibuprofen protects DA neurons against glutamate toxicity and decreases MPTP toxicity *in vitro* (Casper et al., 2000; Morioka et al., 2004; Carrasco et al., 2005). A meta-analysis determined that regular use of Ibuprofen also reduced the risk of developing PD in humans by 40% (Samii et al., 2009; Gao et al., 2011). The results from these studies together suggest that Ibuprofen and aspirin may be neuroprotective.

The dihydropyridine L-type calcium channel blocker Isradipine has been reported to reduce hypoxia-induced activation of Ca^{2+} -dependent xanthine oxidases, monoamine oxidases, cytosolic phospholipase A₂, and cyclo-oxygenases (COX-2) along with a decrease in free radical generation and cytochrome-c release (Barhwal et al., 2009). Increased expression of calpain, caspase-3, (Barhwal et al., 2009), and glutamate-induced neurotoxicity (Pizzi et al., 1991) was also inhibited by Isradipine.

The use of L-type Ca^{2+} channel antagonists protects SNpc DA neurons in MPTP-treated animals (Kupsch et al., 1995, 1996; Chan et al., 2007), but the same was not true of 6-OHDA-treated animals (Sautter et al., 1997). This discrepancy may be the result of the different mechanisms by which the two toxins act on mitochondria (Bove et al., 2005a). Currently very few studies specifically address Isradipine's neuroprotective capabilities, however a dose-dependent effect was observed in 6-OHDA-treated animals (Ilijic et al., 2011). In a pilot study in which PD patients were treated with Isradipine no negative side effects were noted thus paving the way for further clinical testing (Simuni et al., 2010).

Because a mutation in the DJ-1 protein causes early onset of autosomal PD (Bonifati et al., 2003; Ibanez et al., 2003) and lower levels of DJ-1 are associated with PD, it is thought that drugs that up-regulate DJ-1 may slow disease progression by moderating oxidative stress and protein aggregation (Zhou et al., 2011). DJ-1 acts through multiple pathways, and works in parallel with PINK1/parkin (Zhou et al., 2011). Phenylbutyrate, a chaperone molecule and histone deacetylase inhibitor, increased DJ-1 expression in DA cell cultures, rescued cells from oxidative stress, and reduced α -synuclein aggregation (Zhou et al., 2011). In MPTP-treated animals, phenylbutyrate protected DA neurons in the SNpc and increase DJ-1 expression (Gardian et al., 2004; Zhou et al., 2011). Long-term administration of phenylbutyrate reduced deterioration in motor and cognitive

functions in mice (Zhou et al., 2011). Similar results were seen with 4-phenylbutyrate in rotenone-treated mice (Inden et al., 2007).

Type 2 diabetes has been correlated with an increase risk of PD and a high prevalence of insulin resistance has been found in PD patients, suggesting that the two chronic diseases may share similar dysregulated pathways that play a role in cell death and dysfunction (Arvanitakis et al., 2004; Jeerakathil et al., 2007). Possible shared pathways may be related to insulin regulation, suggesting that diabetes drugs may possess neuroprotective effects (Holst et al., 2011). Glucagon-like peptide-1 (GLP-1) is commonly used to treat type 2 diabetes. GLP-1 also acts as a growth factor in the brain, and can induce neurite outgrowth and protect against oxidative injury in cultured neuronal cells (Perry et al., 2007). The anti-apoptotic actions of GLP-1 is thought to be related to the activation of the transcription factor cAMP response element-binding protein by phosphorylation (Perry et al., 2002; Li et al., 2009). Previous studies have also claimed that PDA, PI3K, and MAPK may be involved in the mechanism of action of GLP-1, in addition to MAPK-independent signaling and growth factor-dependent Ser/Thr kinase AktPKB (Lazaroff et al., 1995; During et al., 2003; Perry and Greig, 2005).

Exendin-4 (Ex-4), an analog of GLP-1, protected DA neurons from degeneration, preserved DA levels, and improved motor function in rodents (Li et al., 2009) by inhibiting microglial activation and matrix metalloproteinase-3 expression (Kim et al., 2009). Ex-4 has also been shown to protect ventral mesencephalic dopaminergic cells in culture, reverse nigral lesions, and protect against 6-OHDA toxicity (Harkavyi et al., 2008; Li et al., 2009). Ex-4 receptors also show neuroprotection by mediating and increasing neurogenesis in the subventricular zone in rodents (Bertilsson et al., 2008). In addition to Ex-4, other analogs of GLP-1 offer promising neuroprotective effects (see review Harkavyi and Whitton, 2010). One of these, Liraglutide, has been shown to be neuroprotective in an Alzheimer's disease model (McClean et al., 2010, 2011).

RASAGILINE AND MINOCYCLINE ARE CURRENTLY IN CLINICAL TRIALS AS NEUROPROTECTIVE AGENTS FOR PD

Rasagiline is a selective and potent propargylamine MAO-B inhibitor (Tatton et al., 2003), that reduces MPTP and 6-OHDA toxicity in PC12 and SH-SY5Y cells, (Maruyama et al., 2000) and is neuroprotective *in vivo* (Heikkila et al., 1985; Huang et al., 1999; Speiser et al., 1999; Sagi et al., 2001; Youdim et al., 2001a). Pretreatment with Rasagiline prevents nigrostriatal damage induced by MPTP in primates (Kupsch et al., 2001; Sagi et al., 2001). Chronic administration of Rasagiline increased DA neuron survival in lesioned SNpc and improved motor impairments (Blandini et al., 2004). Rasagiline also increased the expression of the neurotrophins BDNF, GDNF, and NGF (Murer et al., 2001). In humans, Rasagiline reduced the long-term progression and symptoms in PD (Hauser et al., 2009; Olanow et al., 2009). In a promising recent study, Rasagiline delayed the need for antiparkinsonian drugs and patients had lower scores on the PD rating scale in a Phase III study (Rascol et al., 2011).

Rasagiline suppresses mitochondrial apoptosis by inhibiting caspase-3 and nuclear poly [ADP-ribose] polymerase 1

Table 1 | Neuroprotective agents in PD models.

| Neuroprotective agents | Cell culture and animal studies | | Human and epidemiological studies | |
|------------------------|--|--|---|--|
| | Study | Results | Study | Results |
| Caffeine | A (van den Pol, 1986; Kachroo et al., 2010) | Decreased dopaminergic neuron toxicity in MPTP | E (Ross et al., 2000; Ascherio et al., 2001)*, (Saaksjarvi et al., 2008; Costa et al., 2010)* | Caffeinated beverages decreased the risk of PD |
| | A (Chen et al., 2001; Joghataie et al., 2004; Aguiar et al., 2006) | Decreased DA loss and restored DA levels in MPTP and 6-OHDA | E (Xu et al., 2006) | Caffeinated beverages have no effect on PD risk |
| | A (Joghataie et al., 2004; Aguiar et al., 2006) | Decreased motor dysfunctions in 6-OHDA | H (Ascherio et al., 2003) | A decrease in PD risk among women consuming caffeine and not taking hormone-replacement therapy |
| | A (Xu et al., 2002, 2010) | Caffeine increased metabolites associated with prevention of DA loss | | |
| | A (Xu et al., 2006) | Estrogen and caffeine prevented neuroprotection | | |
| Caffeine + nicotine | A (Trinh et al., 2010) | Decaffeinated coffee and nicotine-free tobacco were neuroprotective in <i>Drosophila</i> | E (Tan et al., 2003) | Caffeine and nicotine combined reduced the rate of PD |
| Nicotine | A (Ferber et al., 1998; Costa et al., 2001) | Nicotine reduced DA depletion resulting from MPTP and 6-OHDA | E (Quick, 2004; Simon et al., 2009) | Nicotine lowered the risk of developing PD |
| | A (Meshul et al., 2002) | Nicotine minimized parkinsonian contralateral rotations in 6-OHDA | | |
| | A (Quik et al., 2006) | Non-human primates maintained dopaminergic function and cell loss in the SNpc was prevented with nicotine administration | | |
| | A (Carr and Rowell, 1990)* | Tobacco smoke prior to MPTP treatment reduced the loss of striatal DA in mice | | |
| Urate and UA | A/C (Jones et al., 2000; Duan et al., 2002) | UA protects against DA-induced apoptosis | E (de Lau et al., 2005; Alonso et al., 2007; Annanmaki et al., 2007; Chen et al., 2009)*, (Schwarzschild et al., 2008)*, (Andreadou et al., 2009)* H (Ascherio et al., 2009) | Decreased risk of PD with UA and urate |
| | | | H (de Lau et al., 2005; Schwarzschild et al., 2008) | Slower rates of clinical progression of PD were seen with UA intake Serum UA correlates with a decreased risk of PD |
| Vitamin E | A (Oduze et al., 1990) | Vitamin E deficiency increases MPTP toxicity | E (Zhang et al., 2002; Etminan et al., 2005)* | Protection from PD with moderate vitamin E intake |
| | A (Lan and Jiang, 1997; Roghani and Behzadi, 2001) | Vitamin E supplementation protected DA neurons in the SNpc and reduced DA loss | H (Fernandez-Calle et al., 1992; LeWitt, 1994; Morens et al., 1996) | Clinical trials also show no neuroprotective benefit of taking vitamin E |
| | A (Gong et al., 1991; Chi et al., 1992) | Striatal DA was not attenuated by pretreatment of vitamin E | | |
| | C (Offen et al., 1996) | Vitamin E has no protective effects against DA-induced toxicity in PC12 cells | | |
| | A (Perry et al., 1987) | Vitamin E partially protected DA neurons in MPTP rodents | | |

(Continued)

Table 1 | Continued

| Neuroprotective agents | Cell culture and animal studies | | Human and epidemiological studies | |
|------------------------|---|---|---|--|
| | Study | Results | Study | Results |
| Vitamin E + vitamin C | | | H (Fahn, 1992) | Both vitamins combined decreased PD progression in early stage patients |
| Vitamin C | | | H (Scheider et al., 1997; Zhang et al., 2002; Etminan et al., 2005) | Few beneficial effects are seen with vitamin C and even an increased risk of PD |
| | | | H (Perlmutter, 1988) | Vitamin C intake reduced the risk of PD by 40% |
| Vitamin D | C (Butler et al., 2011) | Disruption of Vitamin D's Ca ²⁺ homeostasis properties accelerated SNpc dopaminergic neuron loss | E (Anderson et al., 1999) | An increased risk of PD is associated with high consumption of vitamin D |
| | H/A (Gash et al., 1996; Kordower et al., 2000), (Gill et al., 2003) | GDNF stimulation by Vitamin D can alleviate PD symptoms in primates and PD patients | | |
| | C/A (Wang et al., 2001; Smith et al., 2006) | Vitamin D produced beneficial effects against PD characteristics | | |
| | A (Holick, 2007) | Vitamin D increased neuromuscular function in parkinsonian rodents | | |
| Beta-carotene | (Perry et al., 1985, 1987; Yong et al., 1986) | Beta-carotene protected against MPTP neurotoxicity in mice, but not primates | E (Perlmutter, 1988) | A decrease in the risk of PD was seen with high B-carotene intake |
| Riboflavin | | | E (Perlmutter, 1988; Murakami et al., 2010) | Reduced risk of PD, with high riboflavin intake by 51% |
| | | | E (Coimbra and Junqueira, 2003) | Riboflavin supplementation improved motor capacity of PD patients |
| CoQ10 | A (Shults et al., 1999) | CoQ10 protected nigrostriatal dopaminergic neurons in MPTP | H (Shults et al., 2002; Shults, 2003; Galpern and Cudkowicz, 2007) | Chronic administration of CoQ10 delayed progression of PD in patients with no adverse effects in Phase II |
| | A (Cleren et al., 2008) | CoQ10 supplementation diminished neural tissue damage and prevented DA depletion in SNpc | Investigators (2007) | Inconclusive results of CoQ10 supplement showing neuroprotection in PD patients |
| CoQ10 + vitamin E | | | H (Shults et al., 2004) | Combination showed beneficial for PD patients, however, Phase III trials deemed it futile (NINDS, see text footnote 1) |
| Creatine | A (Matthews et al., 1999) | Creatine protected against MPTP-induced DA depletion in the SNpc | Investigators (2006) | Creatine delayed the progression of PD by 50% |
| | | | Investigators (2008) | Creatine showed efficacy as a neuroprotective agent in PD and is currently in Phase III trials (NET-PDLS, see text footnote 2) |
| CoQ10 + creatine | A/H (Yang et al., 2009) | Combination showed a neuroprotective effect in chronic MPTP and humans | | |

(Continued)

Table 1 | Continued

| Neuroprotective agents | Cell culture and animal studies | | Human and epidemiological studies | |
|-----------------------------|--|---|--|---|
| | Study | Results | Study | Results |
| DHA | A (Bousquet et al., 2008) | DHA supplements replaced omega-6 fatty acids after MPTP | | |
| | C (Wang et al., 2003) | Neurons were protected against cytotoxicity with DHA intake | | |
| | A (Ozsoy et al., 2011) | DHA decreased apoptosis of dopaminergic cells in MPTP | | |
| | A (Samadi et al., 2006) | DHA reduced 40% of the levodopa-induced dyskinesias in Parkinsonian primates | | |
| | A (Bousquet et al., 2008) | DHA preserved DA levels from MPTP-induced neurotoxicity in mice | | |
| DHA + uridine | A (Wurtman et al., 2006; Sakamoto et al., 2007) | This combination increased levels of neural phosphatides, proteins in synaptic membranes, and dendritic spines in rodents | | |
| | A (Cansev et al., 2008) | DHA and uridine administration also reduced parkinsonian related behaviors and elevated DA levels in 6-OHDA rats | | |
| Melatonin | A (Acuna-Castroviejo et al., 1997; Kim et al., 1998; Maharaj et al., 2006a) | Neuronal cell death damage induced by MPTP, 6-OHDA, and iron was protected with Melatonin administration | H (Dowling et al., 2005) | Melatonin improved duration of sleep and reduced sleep disturbances in PD patients |
| | A (Mayo et al., 1998, 1999) | Melatonin blocked apoptosis and necrosis in 6-OHDA and PC12 cells | | |
| | A (Tapias et al., 2010) | Striatal DA depletion and DA neuron loss increased after melatonin treatment of rotenone-induced Parkinsonism | | |
| GSH | A (Garrido et al., 2011) | Excessive or reduced GSH levels initiated degeneration of DA neurons | | |
| | C (Schulz et al., 2000) | Decreased GSH increased neuron susceptibility to neurotoxins, but did not correlate to DA viability or striatal terminals | | |
| | A (Klivenyi et al., 2000) | Depletion of DA was seen after MPTP treatment in GSH peroxidase-deficient mice | | |
| | A (Pileblad et al., 1989; Seaton et al., 1996; Wullner et al., 1996) | Low levels of GSH reduced DA neurons after toxin administration | | |
| IP6 | A/C (Xu et al., 2008, 2011) | IP6 inhibited MPTP, 6-OHDA, and iron toxicity in cell culture | | |
| | A (Xu et al., 2008) | IP6 increased cell survival in MPTP | | |
| | A (Obata, 2003) | IP6 suppressed hydroxyl radical formation after MPP+ treatment in rats | | |
| NSAID (ibuprofen + aspirin) | A/C (Bilodeau et al., 1995; Kaufmann et al., 1997; Aubin et al., 1998; Saini et al., 1998; Casper et al., 2000; Sairam et al., 2003) | NSAID's protected against neuronal death and dopaminergic neurotoxicity | E (Chen et al., 2003; Ton et al., 2006; Wahner et al., 2007; Gao et al., 2011) | NSAID's lowered the risk of PD |
| | | | E (Chen et al., 2005; Ton et al., 2006; Driver et al., 2011; Gao et al., 2011) | A reduction in PD risk was observed with Ibuprofen, but not NSAIDs or Acetaminophen |

(Continued)

Table 1 | Continued

| Neuroprotective agents | Cell culture and animal studies | | Human and epidemiological studies | |
|------------------------|--|--|---|---|
| | Study | Results | Study | Results |
| | A/C (Esposito et al., 2007) | NSAIDs showed neuroprotection in MPTP, 6-OHDA, and <i>in vitro</i> | E (Becker et al., 2011) | NSAID's and aspirin showed no association with altering the risk of PD |
| | A (Casper et al., 2000; Morioka et al., 2004, Carrasco et al., 2005) | Ibuprofen protected DA neurons against glutamate toxicity and decreased MPTP toxicity | E (Bower et al., 2006; Hernan et al., 2006) E (Samii et al., 2009; Gao et al., 2011) | Increased risk of PD shown with moderate aspirin intake Ibuprofen reduced the risk of developing PD in humans by 40% |
| Isradipine | A (Ilijic et al., 2011) | Isradipine showed neuroprotection against 6-OHDA | H (Simuni et al., 2010) | Isradipine was deemed futile for human trials |
| Phenylbutyrate | C (Gardian et al., 2004; Zhou et al., 2011) A (Zhou et al., 2011) | Phenylbutyrate protected DA neurons in the SNpc Reduced deterioration in motor and cognitive function in mice | | |
| Ex-4 | A (Li et al., 2009) | Protected DA neuron degeneration, preserved DA levels, and improved motor function in rodents | | |
| | A/C (Harkavyi et al., 2008; Li et al., 2009) | Ex-4 protected ventral mesencephalic dopaminergic cells in culture, reverse nigral lesions, and protected against 6-OHDA toxicity | | |
| Rasagiline | C.; (Heikkila et al., 1985; Huang et al., 1999; Speiser et al., 1999; Maruyama et al., 2000; Sagi et al., 2001; Youdim et al., 2001a) A (Kupsch et al., 2001; Sagi et al., 2001). | Reduces MPTP and 6-OHDA toxicity in PC12 and SH-SY5Y cells Rasagiline prevented nigrostriatal damage induced by MPTP in primates | H (Hauser et al., 2009; Olanow et al., 2009) | Rasagiline reduced the long-term progression and symptoms in PD |
| | A (Blandini et al., 2004) | Rasagiline increased DA neuron survival in lesioned SNpc and improved motor impairments | H (Rascol et al., 2011) | Rasagiline in a Phase III delayed the need for antiparkinsonian drugs and patients had lower scores on the Parkinson's disease rating scale |
| | C (Murer et al., 2001) | Rasagiline increased expression of neurotrophins | | |
| Minocycline | A/C (Du et al., 2001). | Minocycline blocked MPTP-induced degeneration of DA neurons in the SNpc~ preventing loss of striatal DA and its metabolites. Minocycline treatment also inhibited MPP+ mediated inducible NO synthase expression <i>in vivo</i> and blocked NO-induced neurotoxicity <i>in vitro</i> | H (Investigators, 2006) | Minocycline was deemed effective in Phase II slowing the progression of PD in patients. An 18-month follow up study showed no safety concerns with its use (Investigators, 2008), leading to Phase III trials |

(Continued)

Table 1 | Continued

| Neuroprotective agents | Cell culture and animal studies | | Human and epidemiological studies | |
|-------------------------|--|--|-----------------------------------|--|
| | Study | Results | Study | Results |
| A/C (Yang et al., 2003) | A (Faust et al., 2009; Radad et al., 2010) | DA neuroprotection by Minocycline was seen in a <i>Drosophila</i> model of PD and after rotenone toxicity in rodents | | |
| | A (Quintero et al., 2006). | Reduced the number of apomorphine-induced rotations in 6-OHDA-lesioned rats | | |
| | A (Diguët et al., 2004) | Minocycline exacerbated MPTP damage to DA neurons <i>in vitro</i> and <i>in vivo</i> | | |
| Minocycline + creatine | | | H (NET-PD, 2006) | Reduced progression in PD patients in Phase II |

C, cell culture; A, animal; H, human; and E, epidemiological. Studies showing gender specificity, where males show favorable results are denoted (*).

(PARP-1) activation, translocation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH), the opening of the MPT and DNA fragmentation (Figure 1; Youdim and Weinstock, 2001; Youdim et al., 2001b, 2003; Akao et al., 2002a; Bar Am et al., 2004; Bar-Am et al., 2004; Weinreb et al., 2004). Rasagiline also increases the expression of the anti-apoptotic proteins Bcl-2 and B-cell lymphoma-extra large (Bcl-XL) through the PKC pathway, in addition to down-regulating the pro-apoptotic Bcl-2-associated death promoter (Bad) and Bcl-2-associated X protein (BAX) (Youdim et al., 2001a, 2003; Akao et al., 2002b; Yogev-Falach et al., 2003; Bar Am et al., 2004; Bar-Am et al., 2004; Weinreb et al., 2004).

Minocycline is a semi-synthetic second-generation tetracycline that exerts anti-inflammatory and antioxidant effects (Ryan and Ashley, 1998; Ryan et al., 1998; Faust et al., 2009). Minocycline works by inhibiting the activation of microglia and attenuating the p38 MAPK cascade which reduces inflammatory cytokine synthesis (Figure 1; Yrjanheikki et al., 1998; Tikka et al., 2001; Wu et al., 2002). It is thought that Minocycline's neuroprotective properties may result from inhibition of NO-mediated neurotoxicity (Du et al., 2001). Additionally, Minocycline may be able to chelate metal ions.

In rodents, Minocycline blocked MPTP-induced degeneration of DA neurons in the SNpc, preventing loss of striatal DA, and its metabolites (Du et al., 2001). Minocycline treatment also inhibited MPP⁺ mediated inducible NO synthase expression *in vivo* and potently blocked NO-induced neurotoxicity *in vitro* (Du et al., 2001). Potent DA neuroprotection by Minocycline was also observed in a *Drosophila* model of PD (Faust et al., 2009) and after chronic rotenone toxicity in rodents (Radad et al., 2010). In addition, Minocycline administration reduced the number of apomorphine-induced rotations in 6-OHDA-lesioned rats,

reduced TH-positive cell loss and increased the size and fiber density of the remaining nigral cells (Quintero et al., 2006).

Although Minocycline inhibits microglial activation (Wu et al., 2002), other studies have shown it to significantly exacerbate MPTP-induced damage to DA neurons *in vitro* and *in vivo* (Yang et al., 2003). Similarly, Minocycline treatment of monkeys and mice produced more severe and rapid parkinsonism, behavior deficits, and greater loss of nerve endings (Diguët et al., 2004). Lack of neuroprotection was shown to be due to the inability of Minocycline to abolish the activation of TNF- α and its receptors, thereby failing to modulate TNF signaling after MPTP administration (Sriram et al., 2006). Minocycline administration in TNF- α knockout MPTP-treated mice increased leakage of the BBB, but these animals did not exhibit a greater loss of neurons (Zhao et al., 2007). In a phase II clinical trial, Minocycline was deemed effective in slowing the progression of PD in patients (Investigators, 2006) and an 18-month follow up study showed no safety concerns, thus paving the way to a phase III trial (Investigators, 2008). Additionally, neuroprotective effects of Minocycline combined with creatine demonstrate additive benefits in reducing PD progression in patients, and is currently in clinical trials (NET-PD, 2006).

CONCLUDING REMARKS

Some neuroprotective agents show promising results for slowing the progression of PD and these are summarized in Table 1. In general, these agents reduce oxidative stress, mitochondrial dysfunction, protein aggregation, inflammation, excitotoxicity, cell death, iron accumulation, or stimulate neurotrophic factors. In an earlier review, caffeine, CoQ10, creatine, Minocycline, and Rasagiline were identified as the top candidates for preventing neurodegenerative diseases (Ravina et al., 2003). However, current

research suggests that Minocycline, creatine, and Rasagiline are the most promising agents for neuroprotection in PD and all three are now in Phase III trials. In addition, a combination of Minocycline and creatine is in Phase III trials and CoQ10 and creatine is in Phase II. Other promising neuroprotective agents for PD include nicotine, caffeine, Ibuprofen, and DHA since they show strong neuroprotection. More moderate protective effects are observed with melatonin, vitamin D, and UA. In contrast, vitamin E, vitamin C, NSAIDs, aspirin, GSH, and CoQ10 alone show limited and/or inconsistent results for slowing disease progression. Of the remaining agents, IP6, riboflavin, beta-carotene, Liraglutide, Ex-4, Phenylbutyrate, and Isradipine show promising results in reducing the risk of PD, but further studies are needed to determine if they are neuroprotective in humans. Additionally, caffeine and UA may be promising, but only in male PD patients. These sex-specific

effects are a reminder that it is important to assess each PD patient's response to neuroprotective agents clinically since other unidentified variables, such as single nucleotide polymorphisms (SNPs) and hormones, may also affect an individual's response. Further research addressing the mechanism of the sex differences and how SNPs play a role in the response to neuroprotective agents is needed to optimize a therapeutic approach for treating PD.

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