Deprenyl and Desmethylselegiline Protect Mesencephalic Neurons from Toxicity Induced by Glutathione Depletion

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ABSTRACT

Oxidative stress is thought to play an important role in the pathogenesis of Parkinson's disease (PD). Glutathione (GSH), a major cellular antioxidant, is decreased in the substantia nigra pars compacta of PD patients. The aim of the present study was to investigate whether deprenyl and its desmethyl metabolite, putative neuroprotective agents in the treatment of PD, could protect cultured rat mesencephalic neurons from cell death caused by GSH depletion due to treatment with L-buthionine-(S,R)-sulfoximine (BSO). BSO (10 μM) caused extensive cell death after 48 hr, as demonstrated by disruption of cellular integrity and release of lactate dehydrogenase into the culture medium. Both deprenyl and desmethylselegiline, at concentrations of 5 and 50 μM, significantly protected dopaminergic neurons from toxicity without preventing the BSO-induced loss in GSH. Protection was not associated with monoamine oxidase type B inhibition in that pargyline, a potent MAO inhibitor, was ineffective and pretreatment with pargyline did not prevent the protective effects of deprenyl. Protection was not associated with inhibition of dopamine uptake by deprenyl because the dopamine uptake inhibitor mazindol did not diminish BSO toxicity. The antioxidant ascorbic acid (200 μM) also protected against BSO-induced cell death, suggesting that oxidative events were involved. This study demonstrates that deprenyl and its desmethyl metabolite can diminish cell death associated with GSH depletion.

GSH is an essential tripeptide found in all animal cells. It provides reducing equivalents that are needed to maintain thiols of proteins and antioxidants (Meister, 1991) and to remove hydroperoxides, thereby protecting cells against oxidative damage (Cohen, 1983). A reduction in the major cellular antioxidant GSH has been detected in the SNc of patients with PD (Sian et al., 1994). Furthermore, a similar reduction in GSH has been found in the SNc of cases with incidental Lewy body disease (Dexter et al., 1994), who are thought to have a preclinical form of PD. These findings suggest that a reduction in GSH, with the consequent development of oxidative stress, may be a critical factor in the pathogenesis of PD. Experimentally, levels of GSH can be reduced by inhibiting the enzyme γ-glutamylcysteine synthetase by BSO (Griffith and Meister, 1979). Reduction in GSH levels by BSO has been shown to increase the sensitivity of neurons to toxicity caused by impaired energy metabolism (Zeevalk et al., 1997), 6-OHDA (Pileblad et al., 1989), MPTP and MPP⁺ (Wüllner et al., 1996; Bhave et al., 1996).

R-(−)-Deprenyl (selegiline), a relatively selective inhibitor of MAO-B at doses of 10 mg/day, is used in the treatment of PD as a putative neuroprotective agent. It has been shown to delay the emergence of disability and the progression of signs and symptoms in the early phase of the disease (Myllylä et al., 1992; Olanow et al., 1995; Tetrad and Langston, 1989). The Parkinson Study Group, 1989, 1993). Although there is some debate as to whether the benefits associated with deprenyl treatment in PD are due to putative neuroprotection or to the symptomatic effects of the drug (Olanow and Calne, 1992; Schulzer et al., 1992), there is clear evidence from laboratory studies that deprenyl provides a neuroprotective effect. Deprenyl has been shown to protect DA neurons in vitro against the toxicity of MPP⁺ (Koutsilieri et al., 1996; Mytilineou and Cohen, 1985) and NMDA excitotoxicity (Mytilineou et al., 1997a). Deprenyl has also been shown to protect against toxicity due to 6-OHDA (Knoll, 1978; Salonen et al., 1996), the noradrenergic toxin DSP-4 (Finnegan et al., 1990) and the cholinergic toxin AF64A (Bronzetti et al., 1992). Furthermore, deprenyl has been reported to enhance

ABBREVIATIONS: BSO, L-buthionine-(S,R)-sulfoximine; DA, dopamine; DMS, R-(−)-desmethylselegiline; GSH, reduced glutathione; 6-OHDA, 6-hydroxydopamine; LDH, lactate dehydrogenase; MAO, monoamine oxidase; NMDA, N-methyl-D-aspartate; PD, Parkinson’s disease; TH, tyrosine hydroxylase; MEM, minimal essential medium; PBS, phosphate-buffered saline; SOD, superoxide dismutase; SNc, substantia nigra pars compacta.

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neuronal survival in animals after MPTP (Tatton and Greenwood, 1991), facial nerve axotomy (Salo and Tatton, 1992) and ischemia (Knollema et al., 1995; Sivenius et al., 1994). The mode of action of deprenyl in providing neuroprotection or neuronal rescue is unclear. Benefits do not necessarily depend on MAO inhibition because in some experiments they can be attained with doses that do not inhibit MAO-B and other MAO inhibitors do not show similar protective effects (Mytilineou et al., 1997a; Tatton and Chalmers-Redman, 1996). It has recently been shown that deprenyl-induced neuroprotection is associated with up-regulation of antiapoptotic and antioxidant molecules (Carrillo et al., 1994a; Tatton et al., 1994).

Deprenyl is metabolized in humans and experimental animals to DMS and R-(−)-methamphetamine by the P450 enzyme system (Barrett et al., 1996; Heinonen et al., 1994; Yoshida et al., 1986). Recent studies have shown that DMS is present in the plasma for up to 24 hr after a single oral administration (10 mg/kg) to humans (Heinonen et al., 1997). DMS has been shown to exert protection similar to that of deprenyl against excitotoxicity in mesencephalic cultures (Mytilineou et al., 1997b) and against trophic support withdrawal in PC12 cells (Tatton and Chalmers-Redman, 1996).

In the present study, we evaluated the effect of deprenyl on GSH levels in mesencephalic cultures and its capacity to protect against cell degeneration caused by reduction in GSH by BSO. We demonstrate that deprenyl induces a dose-dependent increase in GSH in mesencephalic cultures. Furthermore, we show that depletion of GSH by BSO is accompanied by cell death, which can be attenuated by treatment with deprenyl through a mechanism that does not depend on restoration of GSH levels. Similar protection is obtained with the deprenyl metabolite DMS.

Methods

Materials. Pregnant rats were purchased from Taconic Farms (Germantown, NY). MEM was obtained from Gibco (Grand Island, NY), horse serum was from Gemini (Calabasas, CA) and NU serum was from Becton Dickinson (Bedford, MA). Antibodies to TH were obtained from Eunice Tech International (Ridgefield Park, NJ), and the Vectastain ABC Kit was from Vector Laboratories (Burlingame, CA). Deprenyl and DMS were gifts from Somerset Pharmaceuticals (Tampa, FL). Other chemicals were from Sigma Chemical (St. Louis, MO).

Cell culture. Mesencephalic cultures were prepared from rat embryos on gestational day 14 as described previously (Mytilineou et al., 1993). Dissociated cells were plated onto poly-l-ornithine (0.1 mg/ml)-coated dishes (35 mm in diameter; Falcon) at a density of 10⁵ cells/cm². The feeding medium consisted of MEM with 30 mM glucose, 2 mM glutamine, 10% horse serum and 10% NU serum (which contains 25% fetal calf serum and other additions).

Treatment of cultures. On day 5 in vitro, the entire 1.5 ml of feeding medium was removed and replaced with 1.5 ml of MEM containing only 5% NU serum (to avoid high blanks in the LDH assay) and BSO (10 μM) with or without deprenyl. The treatment was repeated after 24 hr. The same protocol was followed in testing all other compounds used in the study.

LDH assay. A modification of the method by Bergmeyer et al. (1963) was used to determine LDH activity in the culture medium and the cells. Culture medium was collected, centrifuged to remove debris and frozen at −80°C until assay. Cells were collected in 1.0 ml of 50 mM potassium phosphate buffer, pH 7.2, sonicated in the cold for 10 sec and frozen at −80°C. Then, 100 μl of supernatant and 100 μl of NADH (1.2 mg/ml H₂O stock) were added to 800 μl of buffer, and the samples were vortex-mixed. Next, 250-μl aliquots (triplicates) were placed into 96-well plates at room temperature, and reaction was initiated by the addition of 25 μl of sodium pyruvate (0.35 mg/ml H₂O stock). The rate or disappearance of NADH was measured at 340 nm on a plate reader (Spectramax, Molecular Devices Corporation, Sunnyvale, CA).

Glutathione and protein assays. GSH was quantified with a modification of a standard recycling assay based on the reduction of 5,5-dithiobis-(2-nitrobenzoic acid) with glutathione reductase and NADPH (Tietze, 1969). The medium was first aspirated, and the cultures were rinsed three times with 1.5 ml of cold, sterile PBS. For experiments presented in table 1 and figure 4, the cells were collected on ice in PBS, pelleted by centrifugation at 700 × g for 15 min and sonicated for 10 sec (Vibra-Cell model V1A; Sonics and Materials, Danbury, CT) in 250 μl of 0.4 M perchloric acid, followed by recentrifugation at 18,000 × g for 15 min. For all other experiments, cells were collected directly in 0.4 M PCA. GSH assays were performed on the supernatant, and protein was quantified in the pellet. Protein content was measured according to the method of Lowry et al. (1951).

TH immunocytochemistry. Cultures were fixed in 4% paraformaldehyde in 0.1 M phosphate buffer, pH 7.4, for 30 min at room temperature, permeabilized by a 30-min treatment with 0.2% Triton X-100 and exposed to TH antibodies (1:1000 dilution) at 4°C overnight. They were then processed with the peroxidase-coupled avidin-biotin kit with 3,3’-diaminobenzidine as a chromogen. The number of dopaminergic neurons in cultures was determined by counting the number of cells positively immunostained for TH. Forty fields (1 × 1 mm) in two transverse strips across the diameter of the dish were counted using an inverted microscope (Nikon, Melville, NY) at 20× magnification; this represented 4% of total area of the culture dish.

Statistical assessment. For multiple comparisons, statistical analysis was carried out with analysis of variance followed by Tukey’s test. Significance between two groups was tested by independent two-tailed t test.

Results

We examined the effect of deprenyl on GSH levels in mesencephalic cultures. Treatment with deprenyl for 48 hr, beginning on day 5 in vitro, resulted in a dose-dependent increase in GSH (table 1). Deprenyl, at concentrations of 15 to 100 μM, provided a 16% to 32% increase in GSH over control levels.

Treatment of mesencephalic cultures with the GSH synthesis inhibitor BSO (10 μM) caused a time-dependent reduction of GSH to 40% of control levels at 24 hr and to 20% at 48 hr (fig. 1A). Cell survival, estimated by the release of the ubiquitous cytosolic enzyme LDH into the medium, was not affected at 24 hr despite a 60% reduction in GSH levels (fig. 1B). However, at 48 hr, the further loss of GSH was

<table>
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<th>Deprenyl</th>
<th>Glutathione Increase</th>
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<tr>
<td>Control</td>
<td>8.23 ± 0.26</td>
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<tr>
<td>5</td>
<td>8.59 ± 0.29</td>
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<tr>
<td>15</td>
<td>9.53 ± 0.36*</td>
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<td>50</td>
<td>9.86 ± 0.33*</td>
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<td>100</td>
<td>10.84 ± 0.16*</td>
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Cultures were treated with deprenyl for 48 hr, starting at day 5 in vitro. Data are mean ± S.E.M. (n = 30) from five experiments, except for 100 μM deprenyl (one experiment, n = 6). Significance was tested by ANOVA followed by Tukey’s test (t test for 100 μM deprenyl data).

* P < .05; ** P < .01 compared with control cultures.
accompanied by a 15-fold increase in the amount of LDH released into the culture medium, indicating loss of membrane integrity and cell death (fig. 1B). Cell death was also evident when the cultures were examined by phase contrast microscopy (see fig. 3, a and b).

Because the toxicity of BSO was prominent at 48 hr, this time point was used to test the effects of various drugs. Deprenyl at concentrations of 0.5, 5 and 50 μM provided a dose-dependent protection against BSO-induced cell death (fig. 2). With 0.5 μM deprenyl, the lowest concentration tested, the effect on LDH release was not significant, but at 5 and 50 μM, deprenyl significantly reduced LDH release caused by BSO (P < .001). With the highest deprenyl concentration (50 μM), LDH release induced by BSO was reduced by 82% compared with cultures treated with BSO alone (fig. 2A). To ensure that deprenyl did not directly influence LDH levels in the cultures, we measured cellular LDH activity at 48 hr after treatment with 50 μM deprenyl. There was no significant difference between control and deprenyl-treated cultures, indicating that the reductions in LDH seen in figure 2 result from protection against BSO toxicity. After BSO administration, the number of DA neurons, as determined by counting TH-positive cells, was reduced to 54% of control levels (fig. 2B). Deprenyl significantly attenuated the BSO-induced loss of DA neurons to 78% of control values at 5 μM (P < .01) and completely prevented cell loss at 50 μM (P < .001).

The protective effect of deprenyl was also apparent when cultures were examined by phase contrast microscopy (fig. 3; left). BSO-treated cultures showed an extensive loss of cells and neuronal processes (fig. 3b). Cotreatment with 50 μM deprenyl completely prevented these changes (fig. 3c) and rendered the cultures indistinguishable from controls (fig. 3a). Similar results were obtained in cultures labeled with antibodies to TH (fig. 3; right). In BSO-treated cultures, TH-positive neurons were markedly reduced in number, and many surviving cells were severely damaged in comparison with the controls (fig. 3, d and e). These changes were completely prevented by the addition of 50 μM deprenyl (fig. 3f).

To determine whether deprenyl protected from BSO toxicity by preventing the loss of GSH, we measured GSH levels in the cultures 24 hr after BSO treatment. We chose this time point because the cells remain relatively intact and GSH levels would not be further reduced in BSO-treated cultures by leakage from cells. GSH levels were reduced to 48% of controls in cultures treated with a combination of 10 μM BSO and 50 μM deprenyl compared with 38% in cultures treated with BSO alone (fig. 4A); BSO-treated cultures had a 15% reduction in protein levels as well (fig. 4B).

Fig. 2. Deprenyl protects from BSO-induced cell loss in mesencephalic cultures. Cultures were treated on the fifth day in vitro with 10 μM BSO in the absence or presence of deprenyl (0.5–50 μM). Cell viability was determined at 48 hr by measuring LDH released into the medium (A) and by counting neurons stained positively with TH antibodies (B). Data are mean ± S.E.M. expressed as percentage of control values (n = 24/group). Mean LDH values in controls varied between experiments from 0.16 ± 0.02 to 0.27 ± 0.03 units/dish. TH-positive neurons in control cultures varied from 235 ± 26 to 515 ± 51 cells/cm². ***P < .01, ***P < .001 compared with cultures treated with BSO alone; analysis of variance followed by Tukey’s test.
To examine whether the protective effect of deprenyl was related to the inhibition of MAO, we tested the effect of the potent MAO inhibitor pargyline (fig. 5). Pargyline (50 μM) failed to prevent BSO-induced LDH release. In this experiment, we also examined whether binding of deprenyl to MAO was necessary for its protective effect; we treated cultures with 50 μM pargyline for 18 hr and removed it before the beginning of treatment with BSO and deprenyl. Pargyline is an irreversible inhibitor of MAO, and 5 to 10 days are required for recovery of MAO activity after pargyline in the rat brain (Neff and Goridis, 1972). Furthermore, pretreatment of rats with deprenyl reduces 3H-pargyline binding in the brain by >80%, suggesting that the two inhibitors occupy the same binding sites (Gramsbergen et al., 1986). Our data showed that preexposure to 50 μM pargyline did not protect against BSO toxicity and did not prevent the protective effect of 50 μM deprenyl as determined by LDH release. In comparison with control cultures, LDH release was increased by 90% after BSO treatment, 968% after pargyline plus BSO, 427% after BSO plus deprenyl and 266% after pargyline plus BSO plus deprenyl.

Because deprenyl, and especially its R(-)-amphetamine metabolites, has been reported to inhibit uptake of DA (Fang and Yu, 1994), we investigated the effect of mazindol, a potent inhibitor of DA uptake (fig. 5). Mazindol (1 μM) did not have a neuroprotective effect in BSO-treated cultures, even though at this concentration it inhibited 3H]DA uptake more than the highest concentration of deprenyl (determined in separate experiments). [3H]DA uptake in the presence of 1 μM mazindol was decreased to 4.1 ± 0.3% of control compared with 19.9 ± 0.5% of control in the presence of 50 μM deprenyl.

We have previously shown that the deprenyl metabolite DMS is also neuroprotective against excitotoxic injury (Mytilineou et al., 1997b); hence, we examined the ability of DMS (0.5, 5 and 50 μM) to protect from cell death 48 hr after BSO treatment. Like deprenyl, DMS protected from BSO-induced LDH release at concentrations of 5 and 50 μM, whereas it had no significant effect at 0.5 μM (fig. 6).

To determine whether BSO-induced cell death was associated with oxidative damage resulting from GSH depletion, we examined the effect of the antioxidant ascorbic acid. Ascorbic acid (200 μM) significantly reduced LDH release caused by BSO treatment (fig. 7). In this set of experiments, deprenyl (50 μM) almost completely prevented the BSO-induced release of LDH. The combination of deprenyl and ascorbic acid further reduced the levels of LDH, although this effect was not significant. As with deprenyl, ascorbic acid did not prevent the reduction in GSH caused by BSO. In cultures treated with BSO for 24 hr, GSH levels were 36.7 ± 2.7% of control compared with 42.1 ± 1.5% of control with the BSO and ascorbic acid combination.

**Discussion**

Inhibition of GSH synthesis by BSO has been described as a model for oxidative injury (Mårtensson et al., 1991). The cytotoxic effect of reduced GSH levels may be due to a failure to adequately clear hydrogen peroxide with resultant oxidant stress (Meister, 1991). Mitochondria depend on GSH and GSH peroxidase to detoxify hydrogen peroxide produced con-
Depletion of GSH is associated with destruction of mitochondria (Jain et al., 1991) and a decrease in the number of mitochondria in the brain, liver and lungs of newborn rats (Mårtensson and Meister, 1991).

We show that treatment of mesencephalic cultures for 24 hr with the inhibitor of GSH synthesis BSO (10 μM) caused ~60% reduction in GSH levels without apparent cell death. Continuous during the course of oxidative phosphorylation. Depletion of GSH is associated with destruction of mitochondria (Jain et al., 1991) and a decrease in the number of mitochondria in the brain, liver and lungs of newborn rats (Mårtensson and Meister, 1991).

This observation is in agreement with the study of Zeevallk et al. (1997) showing no loss of DA neurons in mesencephalic cultures when GSH levels were decreased by 68%. However, when GSH levels were reduced to 20% of controls by a second 24-hr treatment with BSO, we observed extensive cell loss and breakdown of cellular integrity by phase contrast microscopy. Cell death was also documented by increased LDH release into the culture medium and by a reduction in the number of neurons stained positively with TH antibodies. The need for an extensive reduction in GSH levels before loss of cell viability could be explained by preferential preservation of the GSH pool within mitochondria, which is known to be affected only after cytosolic GSH levels have been severely exhausted (Meister, 1991).

In our study, deprenyl protected against BSO-induced neuronal death in a dose-dependent manner. There was no significant protection at 0.5 μM. At 5 μM, deprenyl reduced the BSO-induced LDH release by 37% and the loss of TH-positive neurons by 24%. At 50 μM, deprenyl reduced LDH release by 92% and completely prevented the loss of DA neurons. The deprenyl concentrations needed for protection from BSO toxicity are similar to those reported to increase the survival of DA neurons in culture (Roy and Bedard, 1993) and to protect from excitotoxic injury (Mytilineou et al., 1997a). Although it is probably unlikely that these concentrations are reached in human brain after a 10 mg/kg oral dose, the understanding of the mechanism by which deprenyl prevents BSO-induced cell death in the cultures could lead to the design of more active or better tolerated compounds. On the other hand, Tatton et al. (1994) reported neuronal rescue effects of deprenyl at nanomolar concentrations. The reason for the differences in the effective deprenyl concentrations is not known, but it could be due to the nature of the toxic event and the mechanism by which protection is generated. The metabolite of deprenyl, DMS, was also effective in protecting against BSO toxicity, with a potency similar to that of deprenyl. This observation is in keeping with our recent finding that DMS protects against NMDA receptor-mediated cell death (Mytilineou et al., 1997b).

It is interesting to speculate on the mechanism responsible for the capacity of deprenyl to provide neuroprotection in the BSO-treated mesencephalic cultures. Deprenyl was initially used in the treatment of PD based on its ability to inhibit MAO-B and thereby limit hydrogen peroxide production from MAO-B-mediated oxidation of DA. However, a number of studies now suggest that deprenyl-induced neuroprotection is not dependent on MAO-B inhibition (Tatton and Chalmers-Redman, 1996; Mytilineou et al., 1997a). Because DMS protected to a comparable degree as deprenyl in our study and is a substantially less potent inhibitor of MAO than deprenyl (Borbe et al., 1990), it is not likely that neuroprotection in this model is dependent on inhibition on MAO-B. The failure of pargyline to protect against BSO toxicity further supports the notion that deprenyl neuroprotection is independent of its capacity to inhibit MAO-B. This observation may have clinical significance because MAO inhibition limits the dose of deprenyl that can be safely employed and restricts the opportunity to use high doses in PD patients in an attempt to obtain meaningful neuroprotection.

Deprenyl may provide neuroprotection by an antioxidant effect. The finding that ascorbic acid protects mesencephalic cells against the toxicity of BSO suggests that cell damage is
mediated by oxidative stress. We demonstrate that deprenyl causes a dose-dependent rise in GSH in otherwise untreated mesencephalic cultures. However, deprenyl does not prevent the loss of GSH due to inhibition of GSH synthesis by BSO. At 24 hr after BSO administration, GSH levels were reduced by 62% in control cultures and by 52% in cultures treated with deprenyl. This small difference is likely due to leakage of GSH from damaged cell membranes in cultures treated with BSO alone; cell damage is indicated by a 15% reduction of protein in this group (see fig. 4). Nevertheless, it is possible that a small attenuation in GSH depletion by deprenyl may prevent cell death if GSH preservation occurs in the mitochondrial compartment.

Deprenyl has been shown to enhance the activity of antioxidant enzymes such as SOD and catalase (Carrillo et al., 1994a, 1994b, 1994c; Thifault et al., 1995). Furthermore, Kushleika et al. (1996) reported recently that both forms (Cu, Zn- and Mn-) of SOD were increased in lymphocytes of deprenyl-treated parkinsonian patients. An antioxidant effect due to enhancement of SOD and catalase, even in the presence of GSH depletion, may account for the protective effect of deprenyl. There also are reports that deprenyl is a free radical scavenger (Thomas et al., 1997; Wu et al., 1993).

However, other propargyl MAO inhibitors, such as pargyline and clorgyline, inhibit free radical formation to a greater degree than deprenyl (Chiueh et al., 1994). Because pargyline does not protect against BSO-induced cell death, it seems unlikely that a direct antioxidant effect of deprenyl could explain the neuroprotection observed in our study.

Deprenyl has been reported to inhibit the uptake of DA (Zailla et al., 1986) and noradrenaline (Knoll and Magyar, 1972). Furthermore, the high concentration of the R(-)-amphetamine metabolites of deprenyl are potent uptake inhibitors and have been suggested to play a role in the protective effects of deprenyl against MPTP, 6-OHDA and DSP-4 toxicity in vivo (Ahola et al., 1993; Haapalina et al., 1997; Sziraki et al., 1994). However, inhibition of DA uptake does not seem to explain the neuroprotective effect of deprenyl against BSO-induced cell death, because mazindol, a potent uptake inhibitor, did not have protective effects.

It is also possible that deprenyl acts through an antia apoptotic mechanism. Recent studies have shown that deprenyl-induced protection of PC12 cells withdrawn from trophic support is associated with new protein synthesis, preservation of the mitochondrial membrane potential and up-regulation of the antiapoptotic molecules bcl-2 and bcl-XL (Tatton et al., 1994; Tatton and Chalmers-Redman, 1996). In this regard, it is noteworthy that bcl-2 has been shown to prevent BSO-induced cell death (Zhong et al., 1993).

The BSO model of neurodegeneration may be particularly relevant to PD in which there is evidence of decreased GSH (Sian et al., 1994; Riederer et al., 1989) and oxidative damage in the SNc (Jenner and Olanow, 1996). Furthermore, GSH levels are low in the SNc in incidental Lewy body disease, a condition thought to represent preclinical PD (Dexter et al., 1994).

The ability of deprenyl to protect cultured dopaminergic neurons from cell death associated with GSH reduction could be relevant to PD in which deprenyl may have a neuroprotective effect. Because the benefits we have observed with deprenyl in this study are dose dependent, it is possible that higher doses of deprenyl will provide more meaningful neuroprotection PD. However, doses of deprenyl of >10 mg/day are associated with nonselective MAO inhibition and the risk of a fatal "toxic effect" (Sunderland et al., 1985). Because we find comparable protective effects with DMS and DMS has a lower potential to inhibit MAO, it is possible that this agent may be better tolerated in PD patients and offer a greater possibility to provide neuroprotection.

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References


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