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Characterization of intracellular elevation of glutathione (GSH) with glutathione monoethyl ester and GSH in brain and neuronal cultures: Relevance to Parkinson's disease

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Abstract

Parkinson's disease (PD) is associated with loss of total glutathione (GSH) which may contribute to progressive cell death. Peripheral GSH administration has been used clinically with reported benefits. Despite this, there is little specific information to characterize its cellular uptake or clearance, brain elevation with peripheral delivery or neuroprotective efficacy in PD models. The current study was carried out to provide this information using in vitro and in vivo approaches. In rat mesencephalic culture, the monoethyl ester of GSH (GEE), but not GSH (1–10 mM, 24 h) produced a dose-dependent elevation in GSH. The half-life for clearance was 10.14 h and was not different in cells depleted of GSH prior to loading. Elevation of GSH with GEE protected neurons from oxidative stress with H_2O_2 or metabolic stress with the complex I and II inhibitors MPP^+ and malonate, respectively. To determine if peripheral administration of GEE could elevate brain GSH levels, rats were administered 0.1–50 mg/kg/day GEE via osmotic minipump either subcutaneously (sc) or via a cannula placed into the left cerebral ventricle (icv) for 28 days. Only central delivery of GEE resulted in significant elevations of brain GSH. Elevation of brain GSH by icv infusion of GEE was examined for its neuroprotective effects against chronic central delivery of MPP^+. Infusion of 0.142 mg/kg/day MPP^+ for 28 days caused a selective ipsilateral loss of striatal dopamine. Co-infusion of MPP^+ with 10 mg/kg/day GEE significantly protected against striatal dopamine loss. These findings show that the ethyl ester of GSH but not GSH per se can elevate intracellular GSH, that brain elevation of GSH requires central delivery of the ethyl ester and that this elevation provides neuroprotection against oxidative stress or chronic mitochondrial impairment.

Keywords: Oxidative stress; Glutathione ethyl ester; Neurodegeneration; Neuroprotection

Introduction

The underlying etiology of sporadic Parkinson's disease (PD) remains elusive, although much evidence implicates oxidative stress in the process. The substantia nigra (SN) from autopsied brain material has been shown to contain increased levels of protein carbonyls (Alam et al., 1997), malondialdehyde or 4-hydroxynonenol (Dexter et al., 1994a; Yoritaka et al., 1996) and 8-hydroxy-2-deoxyguanosine (Sanchez-Ramos et al., 1994), indicative of oxidative damage to proteins, lipids and DNA, respectively. One of the earliest biochemical derangements observed in the SN of patients with PD is loss of total glutathione levels (Perry and Yong, 1986; Jenner et al., 1992; Sian et al., 1994), without a corresponding increase in oxidized glutathione levels (Sian et al., 1994). This decrease is also observed in incidental Lewy body disease, a condition thought to presage PD (Jenner et al., 1992; Dexter et al., 1994b). Glutathione is a major antioxidant in the cell, and logically it would follow that the loss of intracellular GSH would contribute to the increase in free radical damage to cellular constituents. Thus, supplementation with antioxidants should be neuroprotective. Clinical studies, with vitamins E or C, however, have not supported this proposal (Fahn, 1992; Shoulson, 1998). More recent studies with co-enzyme Q10, have shown more promise (Shults et al., 2002), but it is unclear if protective benefits derive from its antioxidant properties or from other factors (Echtay et al., 2000, 2002; Papucci et al., 2003). In addition to direct removal of reactive oxygen species by GSH, a number of associated enzymes confer varied roles for

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