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BRAIN RESEARCH

Research Report

Sub-chronical exposure to diphenyl diselenide enhances acquisition and retention of spatial memory in rats

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ABSTRACT

The present study was conducted to evaluate the effects of exposure to diphenyl diselenide [$(PhSe)_2$] on cognitive performance and glutamatergic parameters in normal Wistar rats. Animals were subcutaneously exposed to $(PhSe)_2$ acutely (G1) and sub-chronically for 4 weeks (G20) at the dose of 5.0 mg/kg or 8 weeks (G40) at the dose of 2.5 mg/kg and evaluated for behavioral and neurochemical analyses. In the water-maze, a significant increase in the number of crossing in the platform local was observed in the probe trial for both groups exposed to $(PhSe)_2$ (G20 and G40). In the T-maze, the latency to reach the extremity of the arm in the trial 2 was lower in both groups exposed to $(PhSe)_2$ (G20 or G40) when compared to the respective control groups. In the open-field test, no significant differences in the number of crossing and rearing were observed among groups. Furthermore, the basal [^{3}H]glutamate release by synaptosomes from whole brain of rats was significantly decreased in the G40 when compared to the control group. These findings suggest that sub-chronic exposure to $(PhSe)_2$ improved the performance of Wistar rats in the water-maze, a test that evaluates cognitive functions.

1. Introduction

Selenium is known to be an essential biological trace element for mammalian species (Ewan, 1976). Selenium in blood is taken up by erythrocytes and is distributed to the tissues via selenium binding proteins (Brtkova and Brtko, 1996). It has been established that the selenium atom is present as a selenocysteine residue in the active site of glutathione peroxidase (GPx) (Forstrom et al., 1978), thioredoxin reductase (Holmgren, 1985) and 5′-deiodinase (Behne and Kyriakopoulos, 1990). The redox activity of selenium has fundamental importance to the catalytic activity of these enzymes.

In vitro studies have suggested that organoselenium compounds can be considered potential antioxidant compounds (Parnham and Graf, 1991; Meotti et al., 2004). Of particular importance, the antioxidant activity of various organoselenium compounds seems to be related, at least in part, to their GPx-like activity (for review see Mugesh et al., 2001; Nogueira et al., 2004). Diphenyl diselenide [$(PhSe)_2$], an organoselenium compound widely used as intermediary in organic synthesis (Zeni et al., 2001), has been shown to exhibit in vitro (Rossato et al., 2002; Ghisleni et al., 2003) and in vivo (Burger et al., 2004) antioxidant activity in models of neurodegeneration. In addition, the antioxidant activity could explain some protective effects of $(PhSe)_2$ on other oxidative models of tissue damage (Santos et al., 2005; Borges et al., 2006; Barbosa et al., 2006).

The role of oxidative stress in the pathogenesis of diseases, such as Alzheimer's disease, has received considerable

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Abbreviations: Diphenyl diselenide: $(PhSe)_2$

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attention (Christen, 2000). One hypothesis suggests that, in Alzheimer's disease neuropathology, reactive oxygen species play a central role in the progression of the disease and on specific neuronal degeneration (Lethem and Orrel, 1997). Thus, several investigators have focused on the potential contribution of antioxidants in preventing these diseases (Mendelsohn et al., 1998; Iauner, 2000). Free radicals damage has also been implicated in processes related to aging and selective cell damage, both of which may contribute to cognitive impairment (Berr et al., 1998). Information regarding the benefits of antioxidant use as a way to delay the physiological decline in cognitive function associated with aging in human is of importance, particularly if one considers that the elderly population is increasing.

Recently, Rosa et al. (2003) have reported that acute $(PhSe)_2$ administration enhances cognitive performance of mice in an object recognition paradigm. In contrast, intra-hipocampal injections of ebselen, a complex organoselenium compound with neuroprotective activities, caused a marked impairment in inhibitory avoidance task in rats (Porciúncula et al., 2002). Therefore, the modulation of memory by organochalcogens has not been fully explored. Furthermore, data about the potential effect of $(PhSe)_2$ on cognitive tests other than the object recognition task is not available in the literature.

Although organoselenium compounds have been proposed as potential neuroprotective drugs, they can also induce neurotoxic effects in rodents (Nogueira et al., 2003a). In fact, $(PhSe)_2$

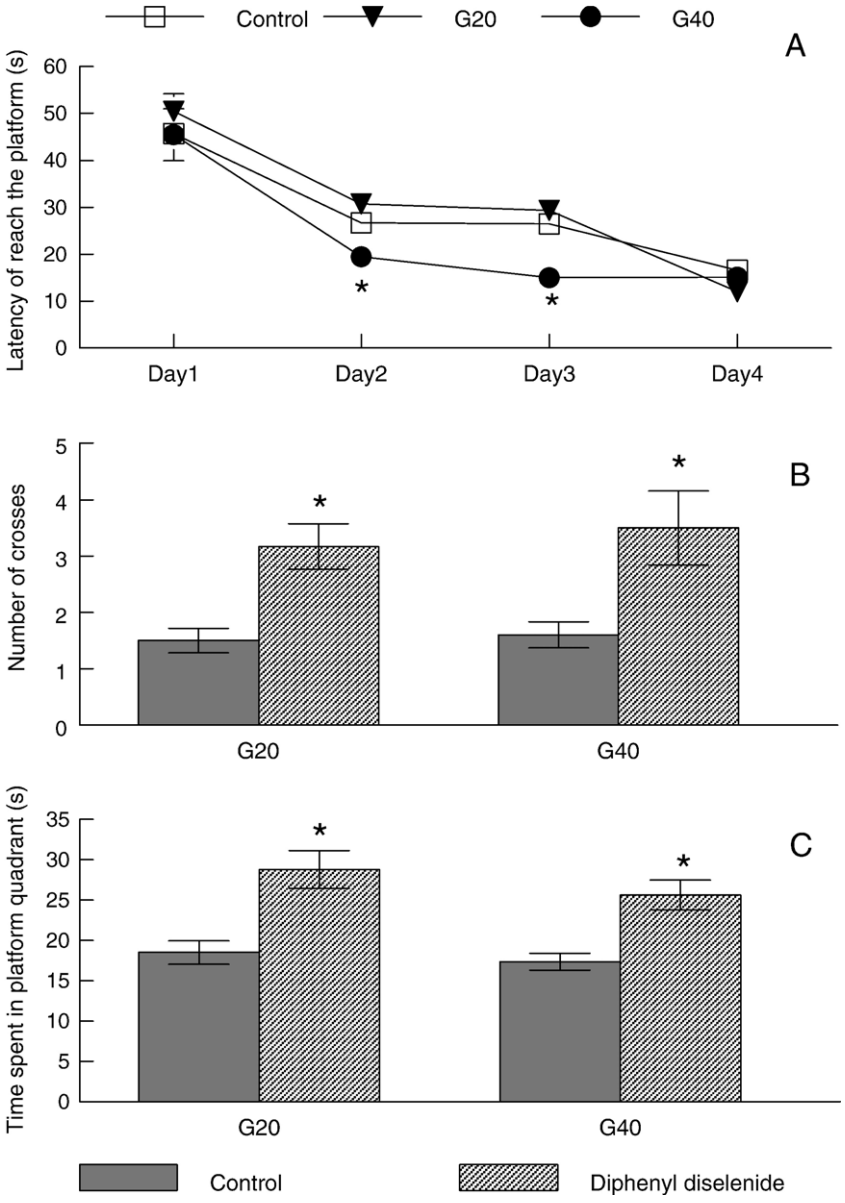

Fig. 1 – Effects of $(PhSe)_2$ on the water-maze test. Panel A — Latency (s) to reach the platform in the acquisition phase. The latencies were measured in four trial sessions for four days and were calculated as mean of total time spent in four trials of each day. Because the latencies of controls were similar in G20 and G40, the controls are represented in a same line. Panel B — Number of crossings over the former platform position, in the probe test. Panel C — Time spent (s) in platform quadrant (NW), in the probe trial. In all panels the data are reported as a mean ± S.E.M. *Denote $p < 0.05$ as compared to the control group. G20 (sub-chronical exposure with 20 doses of $(PhSe)_2$) and G40 (sub-chronical exposure with 40 doses of $(PhSe)_2$).