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Research Report

The effects of acute and chronic administration of phosphatidylserine on cell proliferation and survival in the dentate gyrus of adult and middle-aged rats

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ABSTRACT

Phosphatidylserine (PS) is an acidic phospholipid that is widely used as an alternative and/or complementary treatment of cognitive impairments. We hypothesize that these changes may be attributable, at least in part, to alterations in hippocampal neurogenesis. The aim of the present study was to investigate the effects of acute and chronic PS administration on hippocampal cell proliferation and survival in adult (5 months old) and middle-aged (12 months old) male Wistar rats. PS was injected daily (50 mg/kg, i.p.) during 7 days (acute experiment) or 21 days (chronic experiment). To label newly generated cells, rats received a single BrdU injection (200 mg/kg, i.p.) one day before PS treatment. The object recognition test was performed, and the rats were perfused. The brains were removed and processed with immunohistochemistry techniques for Ki-67 (cell proliferation) and BrdU (cell survival). The acute and chronic regimens were unable to promote cognitive improvement in either age group in the object recognition test. The analysis of cell proliferation showed a significant increase in the number of Ki-67-positive cells after acute and chronic PS administration in both age groups. The analysis of cell survival showed that acute and chronic PS administration increased the number of BrdU-positive cells only in adult animals.

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1. Introduction

Phosphatidylserine (PS) is an acidicphospholipid that is widely used as an alternative and/or complementary treatment of cognitive impairment resulting from aging process or neurodegenerative disorders (e.g., Alzheimer's). PS is a natural component of the brain cortex and represents the major phospholipid of brain synaptic membranes (Breckenridge et al., 1972). It plays an important role in the functioning of neuron membranes, such as signal transduction, secretory vesicle release, and cell-to-cell communication (Nishizuka, 1984; Blokland et al., 1999). The accumulation of PS in synaptic membranes can also modify the metabolism of glucose (Bruni et al., 1976), catecholamines (Toffano et al., 1976) and acetylcholinesterase (Mantovani et al., 1976). These structural and functional changes may be correlated with the cognitive improvement generally observed after treatment with PS in both animals and humans.

Scopolamine-induced cognitive impairments were reversed by PS treatment in rats (Zanotti et al., 1986; Vaisman and Pelled, 2009) and mice (Claro et al., 1999, 2006). Similar results were observed in rats with cognitive deficits induced by reserpine (Alves et al., 2000). PS administration in middle-aged rats improved their performance in memory and learning tests, such as passive and active avoidance (Drago et al., 1981; Zanotti et al., 1989) and the Morris water maze (Nunzi et al., 1992).

Crook et al. (1991) administered PS or placebo in 149 patients with age-associated cognitive deficits for 12 weeks. At the end of this period, patients presented significantly better performance in memory and learning tests when compared to the control group. The clinical analysis of the subgroups showed that patients with the worst memory deficits were more responsive to PS treatment. In another study, elderly patients with cognitive deficits showed a significant improvement in performance in memory and learning tests after treatment with PS for 15 weeks when compared to the respective control group (Vakhapova et al., 2011).

We hypothesize that the cognitive improvements observed after PS administration may be attributable, at least in part, to alterations in the production of new brain cells (neurogenesis) in the hippocampus. Although there are no data in the literature showing the effects of PS treatment on hippocampal neurogenesis, some evidence suggests this important correlation. Structural changes in neuronal membranes promoted by the accumulation of PS can directly stimulate neurogenesis by inhibiting apoptosis (Kim and Hamilton, 2000; Kim et al., 2000),and increasing cell proliferation (He et al., 2009) and survival (Guo et al., 2007; Kim et al., 2012). These changes can also improve the receptors' efficiency or promote the release of neurotransmitters associated with stimulation of hippocampal neurogenesis, such as serotonin, dopamine, and acetylcholine (Casamenti et al., 1979; Heron et al., 1980; Chalon et al., 1998; Park et al., 2012). The function of adult hippocampal neurogenesis has been strongly linked to learning and memory (Gould et al., 1999; Shors et al., 2001) and its disruption has been hypothesized to be important in the development and maintenance of several human psychopathologies (Jacobs et al., 2000; Malberg et al., 2000).

The aim of the present study was to investigate the effects of acute and chronic PS administration on episodic memory, and hippocampal cell proliferation and survival in adult and middle-aged rats.

2. Results

2.1. Object recognition test

The object recognition test aims to assess short- and long-term episodic memory. The index of memory retention is represented by the percentage of time the animal spends interacting with a new object rather than a familiar one.

Acute and chronic regimens were unable to promote cognitive improvement in either age group. No significant differences in memory retention were observed after acute PS administration in the short-term memory test (adult, $t_5=0.563$, $P>0.05$; middle-aged, $t_5=1.145$, $P>0.05$) and long-term memory test (adult, $t_5=0.127$, $P>0.05$; middle-aged, $t_5=0.352$, $P>0.05$) (Fig. 1). Chronic PS administration presented similar results in the short-term memory test (adult, $t_5=0.6718$, $P>0.05$; middle-aged, $t_5=1.299$, $P>0.05$) and the long-term memory test (adult, $t_5=1.973$, $P>0.05$; middle-aged, $t_5=0.672$, $P>0.05$) (Fig. 2).

2.2. Cell proliferation

The effect of acute and chronic PS administration on cell proliferation was assessed by quantitative analysis of the number of Ki-67-positive cells in the dentate gyrus of adult and middle-aged rats.

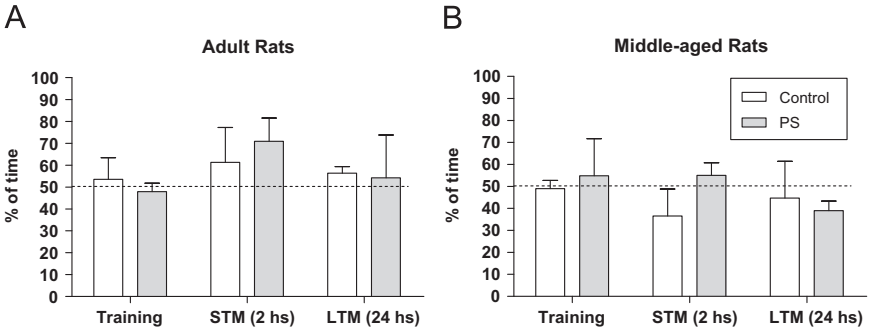

Fig. 1 – Effects of acute PS administration on memory retention in the object recognition test. (A) Adult animals; (B) middle-aged animals. ($n=5$). Values correspond to the percentage (%) of time exploring the new object ± SE. No statistically significant differences (two-way ANOVA) were detected.