Diphenyl diselenide-supplemented diet and swimming exercise enhance novel object recognition memory in old rats

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Abstract The benefits of exercise and the element selenium on mental health and cognitive performance are well documented. The purpose of the present study was to investigate whether the intake of a diet supplemented with diphenyl diselenide [(PhSe)₂] and the swimming exercise could enhance memory in old Wistar rats. Male Wistar rats (24 months) were fed daily with standard diet chow or standard chow supplemented with 1 ppm of (PhSe)₂ during 4 weeks. Animals were submitted to swimming training with a workload (3 % of body weight, 20 min/day for 4 weeks). After 4 weeks, the object recognition test (ORT) and the object location test (OLT) were performed. The results of this study demonstrated that intake of a supplemented diet with (PhSe)₂ and swimming exercise was effective in improving short-term and long-term memory as well as spatial learning, increasing the hippocampal levels of phosphorylated cAMP-response element-binding protein (CREB) in old rats. This study also provided evidence that (PhSe)₂-supplemented diet facilitated memory of old rats by modulating cAMP levels and stimulating CREB phosphorylation, without altering the levels of Akt.

Keywords Selenium · Organoselenium · Exercise · Memory · Age

Introduction

The benefits of exercise and physical fitness on mental health and cognitive performance are well documented (Chaddock et al. 2010; Colcombe and Kramer 2003; Colcombe et al. 2006; Cotman and Berchtold 2002; Cotman et al. 2007; Kramer and Erickson 2007; Vaynman and Gomez-Pinilla 2005). Recently, studies have been carried out in humans using noninvasive brain imaging techniques to investigate exercise-related changes in brain structure (Chaddock et al. 2010; Erickson et al. 2009, 2011). Some of the most compelling evidence of exercise-mediated brain changes has been found in the hippocampus, a brain structure involved with memory as well as stress regulation (Kim and Diamond 2002; Small et al. 2011). Persuasive evidence have indicated that physical activity acts as a protective factor in the incidence of dementia (Aarsland et al. 2010) and that regular aerobic exercise can reduce rates of cognitive decline in older adults (Hillman et al. 2008). Consistent with human research, rodent studies demonstrated that exercise facilitated acquisition and/or retention in various hippocampal-dependent tasks (Greenwood et al. 2007; Nichol et al. 2007; Radak et al. 2006; Schweitzer et al. 2006; van Praag et al. 2005; Vaynman et al. 2004) and elevated brain-derived neurotrophic factor (BDNF) and cAMP-response element-binding protein (CREB) levels

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(Molteni et al. 2002; Shen et al. 2001; Vaynman et al. 2007).

Selenium (Se) is a fundamental component of the living cells of a variety of organisms. It is found in a limited number of molecules and will interact only with few functional groups of biomolecules (thiol-thiolate groups) or with strong pro-oxidant peroxides (Arner 2009). Evidence has been found to suggest that the trace element Se may influence cognitive functions (Akbaraly et al. 2007; Smorgon et al. 2004). This way, our research group has investigated the pharmacological properties of organoselenium compounds in animal models (Nogueira and Rocha 2011; Nogueira et al. 2004). It has been reported that organoselenium compound diphenyl diselenide [(PhSe)₂] displays cognitive-enhancing properties in the object recognition test (ORT) (Rosa et al. 2003) and in the Y-maze and Morris water maze tests (Souza et al. 2010; Stangherlin et al. 2008) in rodents.

Based on the abovementioned, this study aimed to investigate whether the intake of a diet supplemented with diphenyl diselenide and the swimming exercise in old Wistar rats could enhance memory of these animals.

Materials and methods

Animals

Adult (4 months) and old (24 months) male Wistar rats were obtained from a local breeding colony and were housed in cages, with free access to food and water. They were kept in a separate air-conditioned (22±2 °C) room, on a 12-h light/12-h dark cycle, with lights on at 7:00 a.m. The animals were used according to the guidelines of the Committee on Care and Use of Experimental Animal Resources, the Federal University of Santa Maria, Brazil.

Drugs

Diphenyl diselenide [(PhSe)₂] was prepared and characterized in our laboratory by the method previously described (Paulmier 1986). Analysis of the ¹H NMR and ¹³C NMR spectra showed analytical and spectroscopic data in full agreement with its assigned structure. The chemical purity of (PhSe)₂ (99.9 %) was determined by GC/MS.

All other chemicals were obtained from analytical grade and standard commercial suppliers.

Experimental design

Figure 1 illustrates the experimental design of this study. The animals were divided into one group of adult sedentary (animals that did not swim, adult control group) and four groups of old animals: old sedentary (animals that did not swim, control group), exercise (swimming-trained animals, exercise group), sedentary+(PhSe)₂ (animals that did not swim and were supplemented with 1 ppm (PhSe)₂ diet, (PhSe)₂ group), and exercise+(PhSe)₂ (swimming-trained animals and supplemented with 1 ppm (PhSe)₂ diet, exercise+(PhSe)₂ group). All protocol steps used in this study are described below.

Dietary supplementation

The animals were fed daily with standard diet chow or standard chow supplemented with 1 ppm of (PhSe)₂ during 4 weeks. The supplementation began after the period of adaptation to swimming training. The preparation and concentration of supplemented standard chow was based on a previous study (de Bem et al. 2009). The standard diet was pulverized with ethyl alcohol, whereas the supplemented diet was pulverized with (PhSe)₂ [1 mg of (PhSe)₂/100 g standard chow] dissolved in ethyl alcohol (1 mg/100 ml). The standard and supplemented diets were stored at room temperature for 3 h to evaporate the alcohol and then kept at 4 °C for no more than 1 week.

Exercise training protocol

Twenty-four-month-old rats were submitted to the pre-training session with duration of 20 min/day for 1 week (exercise and exercise+(PhSe)₂ groups). After adaptation, rats were submitted to a swimming training session with a workload (3 % of body weight, 20 min/day for 4 weeks) (Ravi Kiran et al. 2004). The swimming training was performed between 13:00 and 15:00 p.m. in water at a temperature of 32 °C±1. Rats from sedentary and sedentary+(PhSe)₂ groups were placed in the bottom of a separate tank with shallow water (5 cm) at 32 °C±1, without the workload (adaptation to the water). At the end of the exercise training, rats were towel-dried and returned to their respective cages.

Fig. 1 Experimental design of this study

Behavioral tests

Twenty-four hours after the last swimming training day, the animals were submitted to behavioral tests (Fig. 1).

Object recognition test

All animals were submitted to a habituation session where they were allowed to freely explore the open field for 5 min. No objects were placed in the box during the habituation trial (de Lima et al. 2005). Twenty-four hours after arena exploration, training was conducted by placing individual rats for 5 min in the field, in which two identical objects (objects 1A and 2A; duple Lego toys) were positioned in two adjacent corners, 9 cm from the walls. In a short-term memory (STM) test given 1.5 h after training, the rats explored the open field for 5 min in the presence of one familiar (A) and one novel (B) object. All objects presented similar textures, colors, and sizes, but distinctive shapes. The results were expressed as exploratory preference; a recognition index was calculated for each animal by the ratio $TB/(TA+TB) \times 100$ [TA=time spent exploring the familiar object A; TB=time spent exploring the novel object B]. Between trials, the objects were washed with 10 % ethanol solution. In a long-term memory (LTM) test given 24 h after training, the same rats explored the field for 5 min in the presence of familiar object A and a novel object C (Stangherlin et al. 2009).

Object location test

The apparatus used for this test was the same field used in the ORT as the LTM objects (object A and object C). The object location test (OLT), a hippocampal-dependent spatial memory task, was performed to

evaluate potential cognitive deficits resulting from aging. The period of acclimation was performed as in the ORT.

In the sample trial, objects A and C were placed in the apparatus as described in the ORT. After 5 min of the object exploration, the rats were returned to their home cages for a 4-h interval. Subsequently, in the test trial, object C was moved to a location that was diagonally opposite to object A, and the rat was left in the field for 5 min of exploration (De Rosa et al. 2005). The time spent exploring novel and familiar objects location was recorded. The exploration criterion and the results were expressed as in ORT.

Activity chamber

The spontaneous locomotor activity was evaluated in the activity chamber. The animals were pre-exposed to the chamber before testing, and activity was monitored under light and sound-attenuated conditions. Testing took place in a clear acrylic chamber (500×480×500 mm) equipped with 16 infrared sensors for the automatic recording of horizontal activity (Model EP149, Insight Instruments Ltda, São Paulo, Brazil). Each animal initially was placed in the center of the testing chamber and allowed to freely move while being tracked by an automated tracking system. The data (distance traveled and velocity) were collected and recorded during 5 min.

Western blot assay

After behavioral tests (Fig. 1), all animals were killed by decapitation, brains were collected, and hippocampus was separated.

Samples of hippocampus were homogenized in 10 mM Tris-HCl, 1 mM EDTA, pH 7.4, and centrifuged

(9,800×g at 4 °C for 5 min) to concentrate the proteins. The pellet was reconstituted in a buffer solution (10 mM Tris-HCl, pH 7.6, 5 mM MgCl₂, 1.5 mM KAc, 1 % NP-40, and protein inhibitor cocktail) (Sigma-Aldrich Co., St. Louis, Missouri, USA) and incubated for 30 min on ice followed by 10 min on ultrasonic bath, and then centrifuged (3,900×g for 10 min, at 4 °C). Hippocampal extracts were diluted to a final protein concentration 2 µg/ml in SDS-PAGE buffer. The samples (50 µg of protein) and pre-stained molecular weight standards (Sigma-Aldrich Co., St. Louis, Missouri, USA) were separated on 12 % resolving with 4 % concentrating SDS-polyacrylamide electrophoresis gels. Proteins were transferred to PVDF membrane using Transfer-Blot® Turbo™ Transfer System (1.0 mA; 0.5 h). After blocking with 5 % BSA solution, the blots were incubated overnight at 4 °C with rabbit anti-Akt (serine/threonine protein kinase) and rabbit anti-phospho-Akt (Ser 473) (1:500, Santa Cruz Biotechnology, Santa Cruz, CA, USA), rabbit anti-CREB (cAMP-response element-binding protein), and rabbit anti-phospho-CREB (Ser 133) (1:200, Santa Cruz Biotechnology, Santa Cruz, CA, USA). Rabbit anti-β-actins (1:200, Santa Cruz Biotechnology, Santa Cruz, CA, USA) were stained as an additional control of the protein loading. After primary antibodies incubation, membranes were washed and incubated with secondary antibodies conjugated with horseradish peroxidase (Bio-Rad Laboratories, Hercules, CA, USA) for 1 h at room temperature and developed with chemiluminescence kit (Amersham, São Paulo/Brazil). Optical density (OD) of the Western blotting bands was quantified using Image J (NIH, Bethesda, MD, USA) software for Windows. Each value was derived from the ratio between arbitrary units obtained by the protein band and the respective α-actin band. The results were showed by percentage of control of quantification of the phosphorylated ratio, OD of the phosphorylated band/OD of the total band.

Protein determination

The protein concentration was determined based on a previously described method (Bradford 1976), using bovine serum albumin (1 mg/ml) as a standard.

Statistical analysis

All experimental results are expressed as means±standard error medium (SEM). Statistical analysis was

performed using a one-way ANOVA followed by the Newman-Keul's test for post hoc comparison when appropriate. A value of $P<0.05$ was considered to be significant.

Results

There was no significant difference among adult control and old groups in the total time exploring both objects during training (data not shown).

Short-term memory

Statistical analysis revealed that percentage of preference for the new object was reduced in the old control group. One-way ANOVA [$F_{(4,20)}=13.94, P<0.0001$] showed that exercise or (PhSe)₂-supplemented diet increased the percentage preference of old rats when compared to old control rats. The association of swimming exercise and (PhSe)₂-supplemented diet enhanced the percentage of preference to new object in old rats when compared to all groups (Fig. 2a).

Long-term memory

One-way analysis showed the effect of age in the LTM. Old control rats had lower percentage of preference for the new object than adult control rats (Fig. 2b).

The one-way analysis [$F_{(4,20)}=10.73, P<0.0001$] of percentage preference in the LTM revealed that the association of swimming exercise and (PhSe)₂-supplemented diet or (PhSe)₂-supplemented diet enhanced this parameter of memory in old rats. The percentage of preference was better in the swimming exercise and (PhSe)₂-supplemented diet group than in the adult control group. The swimming exercise did not ameliorate the performance in the LTM (Fig. 2b).

Object location test

All situations, swimming exercise or (PhSe)₂-supplemented diet or their association, were effective to improve the percentage of preference in the OLT in old rats (Fig. 2c). The swimming exercise and the association of exercise and (PhSe)₂-supplemented diet increased the percentage of preference of old rats in the OLT when compared to adult control rats [$F_{(4,19)}=7.5, P=0.0008$] (Fig. 2c).

Fig. 2 Effect of (PhSe)₂-supplemented diet (1 ppm for 4 weeks) and swimming exercise on the short-term memory (STM) (a) and long-term memory (LTM) (b) of adult control and old rats in the object recognition test. Object recognition test was carried out 48 h after the last training exercise. Recognition memory test was performed after 1.5 and 24 h of training for the STM and LTM, respectively. Object location test (c) was performed after 4 h of training for LTM. Values are expressed as the mean $\pm$ SEM ($n=4-6$ rats/group). Data were analyzed by one-way ANOVA followed by the Newman-Keul's test for post hoc comparison when appropriate. * $P<0.05$ as compared to adult control rats; ^a $P<0.05$ as compared to old control rats; # $P<0.05$ as compared to (PhSe)₂-treated rats; ^b $P<0.05$ as compared to exercised rats

Activity chamber

The one-way analysis showed the effect of age in traveled distance [$F_{(4,23)}=7.12$, $P=0.007$], velocity [$F_{(4,21)}=7.18$, $P=0.008$], crossings [$F_{(4,22)}=6.68$, $P=0.0011$], and [$F_{(4,21)}=39.00$, $P<0.0001$]. Swimming exercise, (PhSe)₂-supplemented diet, or their association was not effective in enhancing distance, velocity, and the number of crossings reduced in old rats. The number of rearings of old rats was increased in all situations (swimming exercise or (PhSe)₂-supplemented diet or their association) (Table 1).

CREB and Akt

Figure 3a illustrates pCREB/CREB ratio in the hippocampus in rats. One-way analysis of pCREB/CREB ratio [$F_{(4,11)}=10.87$; $P=0.0008$] revealed the effect of age. pCREB/CREB ratio was lower in old control rats than in adult control rats. Swimming exercise, (PhSe)₂-supplemented diet, or their association were effective in increasing pCREB/CREB ratio in old rats. One-way ANOVA showed that exercise and (PhSe)₂-supplemented diet increased the percentage preference of old rats when compared to adult control rats.

Table 1 Effect of (PhSe)₂-supplemented diet (1 ppm for 4 weeks) and swimming exercise on the locomotor behavior of adult control and old rats

	Distance (m)	Velocity (mm/s)	Crossings	Rearings
Adult control	21.39±2.94	77.45±11.14	46.71±4.32	24.67±1.25
Control	8.48±2.61*	32.72±8.88*	23.0±3.39*	4.4±0.40*
(PhSe) ₂	7.08±1.27*	25.86±4.91*	25.0±2.28*	11.0±1.7 ^a
Exercise	8.51±1.30*	34.75±5.12*	34.4±3.57*	18.4±1.5 ^{a#}
Exercise+(PhSe) ₂	10.74±2.02*	36.14±6.21*	27.0±5.14*	13.80±0.91* ^{ab}

Values are expressed as the mean±SEM ($n=5-6$ rats/group). Data were analyzed by one-way ANOVA followed by the Newman-Keul's test for post hoc comparison when appropriate.

* $P<0.05$ as compared to adult control rats; ^a $P<0.05$ as compared to old control rats; ^b $P<0.05$ as compared to exercised rats; [#] $P<0.05$ as compared to (PhSe)₂-treated rats

The ratio of pAkt/Akt in the hippocampus of rats is shown in Fig. 3b. The effect of age was not observed in the ratio of pAkt/Akt. One-way analysis revealed that swimming exercise increased pAkt/Akt ratio in old rats. (PhSe)₂-Supplemented diet suppressed the effect of swimming exercise in pAkt/Akt ratio. Exercise increased the pAkt/Akt ratio in old rats when compared to adult control rats [$F_{(4,11)}=4.61$, $P=0.0198$].

Discussion

The present study showed that intake of a supplemented diet with (PhSe)₂ and swimming exercise was effective in improving short-term and long-term memory as well as spatial learning, increasing the hippocampal levels of pCREB in old rats.

Experimental data support the idea that (PhSe)₂ (Rosa et al. 2003; Stangherlin et al. 2008) and exercise (Cotman and Engesser-Cesar 2002; van Praag 2009) improve cognitive function and learning and enhance acquisition and retention of spatial memory in rodents. The association of swimming exercise with (PhSe)₂-supplemented diet restored cognitive deficits impaired by age, enhancing short-term, long-term, and spatial memories. The effects of exercise and (PhSe)₂-supplemented diet on memory were accompanied by an increase in p-CREB/CREB ratio, which were higher than that of found in the adult control group. Reinforcing our results on p-CREB/CREB ratio, a decrease in p-CREB levels has been associated with age-induced memory impairment (Brightwell et al. 2007; Morris and Gold 2012) and deterioration of hippocampal plasticity (Wei et al. 2012). This result allows us to propose that

swimming exercise and (PhSe)₂-supplemented diet improved memory and increased hippocampal p-CREB levels, without altering the levels of p-Akt. It is important to note that (PhSe)₂-supplemented diet blocked the effect of swimming exercise in increasing the phosphorylation of Akt. This is an intricate effect of (PhSe)₂-supplemented diet which deserves further investigation.

Moreover, the results on the object recognition test demonstrated that association of swimming exercise with (PhSe)₂-supplemented diet had additive effects only in short-term memory of old rats. Mechanisms to support the additive effects of swimming exercise with (PhSe)₂-supplemented diet may involve the cAMP/protein kinase A pathway and/or the mitogen activated protein pathway as well as hippocampal neurogenesis, reduction of oxidative stress, and increased brain-derived neurotrophic factor levels (Aguilar et al. 2011; Altarejos and Montminy 2011; Cotman and Engesser-Cesar 2002; Kim et al. 2013; Kwon et al. 2013; Leite et al. 2014; Nogueira et al. 2001; Serezani et al. 2008; Suzuki et al. 2011; van Praag 2009). In any case, the question that remains open is how (PhSe)₂ and swimming exercise interacts at a molecular level to enhance memory in old rats.

Experimental evidence has indicated that (PhSe)₂ crosses the blood-brain barrier and increases the selenium levels in the brain (Maciel et al. 2003; Nogueira et al. 2004; Prigol et al. 2009). With agreement with Stangherlin et al. (2008), who demonstrated that (PhSe)₂ enhances memory in adult rats, (PhSe)₂-supplemented diet was effective in restoring cognitive deficits caused by age in short-term and long-term memory as well as in spatial learning. Our previous study demonstrated that (PhSe)₂ increases the basal adenylate cyclase

Fig. 3 Effect of (PhSe)₂-supplemented diet (1 ppm for 4 weeks) and swimming exercise on pCREB/CREB ratio (a) and pAkt/Akt ratio (b) in the hippocampus of adult control and old male rats. Values are expressed as the mean±SEM (*n*=3–4 rats/group). Data were analyzed by one-way ANOVA followed by the Newman-Keul's test for post hoc comparison when appropriate. *P<0.05 as compared to adult control rats; ^a*P*<0.05 as compared to old control rats; ^b*P*<0.05 as compared to exercised rats. Representative qualitative Western blotting analysis at the top of the figure, graphic shows representative quantification of the proteins immunocontent normalized to β-actin protein

activity, indicating a direct effect on adenylate cyclase (Nogueira et al. 2001). It is well known that cAMP is an important second messenger that modulates a variety of physiological and pathophysiological manifestations (Serezani et al. 2008). In addition, it has been reported that cAMP stimulates CREB phosphorylation (Altarejos and Montminy 2011). Therefore, we can assume that (PhSe)₂-supplemented diet facilitated memory of old rats by modulating cAMP levels and stimulating CREB phosphorylation, without altering the levels of Akt.

The physical exercise is an effective, inexpensive, and low-risk strategy for maximizing brain health in later life (Larson 2010). It is known that regular aerobic

exercise increases capillary growth and dendritic connections in the hippocampus and results in improved cognitive functions (Cotman and Engesser-Cesar 2002), learning, and memory in old rats (van Praag 2009). In the present study, the swimming exercise program markedly improved age-related spatial learning corroborating previous studies in which exercise leads to improvements in hippocampal-dependent tasks such as spatial reference memory (Van der Borght et al. 2007; van Praag et al. 1999a, b). The swimming exercise also enhanced short-term memory in old rats. Moreover, the beneficial effects of exercise in memory were accompanied by the hippocampal activation of Akt and CREB signaling. The effects of exercise on p-CREB/CREB

and p-Akt/Akt are well reported in the literature (Aguiar et al. 2011; Chen and Russo-Neustadt 2009; Kim et al. 2013; Kwon et al. 2013; Suijo et al. 2013). The strong evidence linking CREB activity to neuronal plasticity and memory formation (Silva et al. 1998) suggests a direct effect of BDNF on exercise-induced improvements in learning and memory via CREB signaling (Shen et al. 2001; Suzuki et al. 2011; Vaynman et al. 2004) and Akt activation in the hippocampus of rodents (Aguiar et al. 2010; Chae and Kim 2009; Chen and Russo-Neustadt 2005, 2009).

Age-related locomotor declines were demonstrated in the present study. In fact, control old rats showed alterations in the distance traveled, velocity, crossings, and rearings. The association of (PhSe)₂-supplemented diet with swimming exercise or treatments isolated was not effective in improving the locomotor behaviors, excepting for the number of rearings, which were increased by all situations.

In conclusion, the results of the present study demonstrated that the association of (PhSe)₂-supplemented diet with swimming exercise enhanced novel object recognition memory in old rats. The enhancer effect of (PhSe)₂-supplemented diet and swimming exercise on memory was attributed to an increase in the levels of p-CREB.

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Conflict of interest The authors declare no conflict of interests in the present study.

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