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AGING-RELATED OXIDATIVE STRESS: POSITIVE EFFECT OF MEMORY TRAINING

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Abstract—The cognitive impairment characterizing the phenotype of older adults has been related to the efficiency of the antioxidant system. This study aimed at investigating the effect of memory training (MT) on memory, global cognitive functioning, and the oxidant and antioxidant capacity of plasma. We recruited 52 healthy subjects aged over 60. Twenty-nine subjects were submitted to 6-months of MT (Experimental Group, EG), and 23 were used as a Control Group (CG). Global cognitive functioning was assessed by the Mini-Mental State Examination (MMSE) and Short- and Long-Term Memory (STM and LTM, respectively) by the Rey Auditory Verbal Learning Test (RAVLT) at baseline (T0) and after 6-months (T1). Meanwhile, Reactive Oxygen Metabolites derivative compounds (d-ROMs), Biological Antioxidant Potential (BAP), and their ratio were evaluated on plasma. Results showed that the MMSE and RAVLT scores improved in EG at T1. At the same time, the d-ROMs levels significantly decreased, while the BAP and BAP/d-ROMs ratio showed an opposite trend. In both groups, the MMSE and LTM scores were negatively associated with d-ROMs levels, and positively correlated with BAP levels and the BAP/d-ROMs ratio. When we considered the Δvalue (Δvariable = variable post-MT *minus* variable pre-MT) in EG, the ΔMMSE and ΔLTM scores were negatively associated to Δd-ROMs, and positively to ΔBAP and ΔBAP/dROM. In conclusion, our results suggest that MT improves memory and global cognitive functioning. These processes were significantly associated to increase in resistance against oxidative stress at the plasma level in healthy older adults.

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Key words: aging, memory training, short-term memory, long-term memory, cognitive functioning, oxidative stress.

INTRODUCTION

Aging is associated with a cognitive decline, which affects several aspects of cognitive functioning, as well as memory, language, executive functions, and the speed of information processing. This impairment may worsen or improve depending on several factors, including active aging (Brooks Wilson, 2013; Martin et al., 2013), which permits an increase of opportunities for global health, participation and safety, while cognitive inactivity has been associated with a higher risk of age-related cognitive decline (Erickson et al., 2012; Tyndall et al., 2013).

Many studies have focused on the relevant role of the relation between cognitive skills and active aging (Gates and Valenzuela, 2010). It is well known that mental training positively influences many aspects of cognitive performance in healthy older adults, and the protocols devised to training on core cognitive processes resulted the most effective in reinforce cognition. It is indeed paralleled by improvement in other cognitive functions, even fluid intelligence, and allows moving the acquired skills from training to other contexts (Jaeggi et al., 2008; Sternberg, 2008). Nevertheless, studies on animals showed that task based on memory induced better learning in mice under novel training conditions in the future (Light et al., 2010), and if practiced during lifespan protects animals from typical age-related cognitive decline (Matzel et al., 2011). Several data suggest that this process has a positive impact on neuronal survival after training in central cerebral region, mainly in the hippocampus (Nokia et al., 2012; Shors et al., 2012). Therefore, the tasks focused to improve memory, represent a valid tool to ameliorate the day-to-day lives of the training participants.

The role of oxidative stress as one component affecting the progression of aging was first stated by Harman (1956). In general, the aging process is associated with a higher oxidative stress level, most probably caused by the reduced expression or deficiency in the activity of endogenous antioxidants (Ji 2001; Miles et al., 2004). Oxidative stress is defined as the imbalance between oxidants and antioxidants in favor of oxidant activity that potentially leads to tissue damage (Polidori et al., 2000; Franceschelli et al., 2014). The brain tissue is sensitive to oxidative balance and previous studies have reported that oxidative injury plays a key role in the pathogenesis of numerous neurodegenerative diseases (Chung et al., 2005; Connell et al., 2013; Hensley and Harris-White, 2015). This highlights oxidative stress as a likely process involved in the initiation and progression of cognitive decline. It has indeed been shown that

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cognitive impairment is strictly related to oxidative stress, and an efficient antioxidant system may preserve the cognitive function in older adults (Akbaraly et al., 2007; Rodrigues Siqueira et al., 2005).

Age-related memory and cognitive decline has been associated with a decrease in brain and plasma antioxidant levels and an increase in oxidative stress levels (Akbaraly et al., 2007; Rinaldi et al., 2003; Torres et al., 2011). Hence, plasma is an effective tool to measure oxidative stress levels in pathological and healthy subjects.

Several evaluation tests have been created to measure oxidative balance with the help of an additional evaluation of the ROS production and antioxidant system efficiency on plasma. Above all, the Reactive Oxygen Metabolites derivative compounds (d-ROMs) test is now indicated as the gold standard method to evaluate global oxidative status and has been validated applying electron spin resonance (ESR). This test provides a measure of the whole oxidant capacity of plasma (Alberti et al., 2000; Vassalle et al., 2006). The BAP (Biological Antioxidant Potential) test is used to measure the plasma biological antioxidant potential. It represents the ability of the plasma sample to reduce ferric ions to ferrous ions and this is possible due to the main element of plasma defense to oxidation (vitamin C, vitamin E, uric acid, bilirubin and so on) (Benzie and Strain, 1996; Dohi et al., 2005; Hetyey et al., 2007).

To our knowledge, there were not studies that have investigated the possible effect of memory training (MT) on parameters previously associated to aging phenotype at systemic level (e.g. redox balance, inflammation).

Considering the above mentioned in aggregate, we hypothesize that MT intervention could improve memory but also affect global degree of cognitive activities. At the same time, we investigated whether MT could affect other aspects of aging phenotype in modulating antioxidant capacity in healthy older adults.

EXPERIMENTAL PROCEDURES

Participants

Participants of the study were fifty-two healthy elderly volunteers (24 female, age range 60–80 years of age) recruited by word of mouth and pamphlets.

Anyone reaching the ‘‘exclusion criteria” adapted from the SENIEUR protocol for demographic suitability was excluded from the study (Ligthart et al., 1984). The exclusion criteria included factors thought to influence the relationship between the cognitive function and oxidative stress such as the presence of dementia, chronic inflammation, smoking, alcohol and Body Mass Index (BMI). Volunteers were invited to a preliminary screening session based on a full medical history and examination, anthropometric measurements, assessment of dietary habits, tobacco and alcohol consumption, and screening for cognitive impairment using the Mini-Mental State Examination (MMSE) (Folstein et al., 1975); while for short- and long-term memory the Rey Auditory Verbal Learning Test (RAVLT) was used (Lezak, 1995).

Further details; subjects with BMI <20 and >33 k/m^2 were excluded. Subjects with unusual dietary habits (e.g. vegetarians) were also excluded. Blood and urine tests, such as SGOT, SGPT, hemoglobin, hematocrit, serum electrolytes, blood urea, creatinine, albumin, total alkaline phosphatase, cholesterol (HDL, HDL-LDL ratio), and triglycerides needed to be within the normal range and their physical status needed to also be normal. Serology tests for the HIV and hepatitis C viruses needed to be negative. All the subjects underwent the same laboratory blood tests to assess the inflammatory status: erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were measured as nonspecific markers for inflammation and were utilized as exclusion criteria (Gabay and Kushner, 1999; Ablij and Meinders, 2002; Biasucci et al., 2004; Pesce et al., 2014). Habitual smokers were excluded because this factor has already been significantly marked as a strong pro-oxidant (Naga Sirisha and Manohar, 2013). The participants were invited not to consume >30 g/d for men and >20 g/d for women of alcohol beginning one week before the sample collection, in order to avoid any effects on the systemic oxidative state (Benson and Scholey, 2014).

Subjects having current infections, allergies, or a present and past history of autoimmune disorders, and those on current medication (including herbal remedies or vitamins) such as anti-inflammatory, antiviral agents or immunosuppressive medication that might directly or indirectly affect the systemic oxidant state were excluded.

The procedures of the study were described to all participants in detail, and a reflection time of at least 24 h was given before obtaining the written informed consent. Participants not having the capacity to consent to research participation were excluded. The non-Italian-speaking participants were excluded from the study because the inclusion of these participants would have meant not to be able to use standardized assessment techniques.

A total of 92 consecutive subjects (45 female) were invited to participate in the study. Ten subjects (4 female) were excluded as they were smokers, 3 male subjects were excluded because they had elevated ESR values, one female subject for an elevated CRP value. Eight male and 10 female were excluded as they are on medication. In the end, 60 consecutive subjects (65% of all subjects approached) were included in the study. After having signed the informed consent, the subjects were grouped through blocked randomization with gender stratified randomization. So, 30 subjects were assigned to the experimental group (EG) (15 female) and thirty to the control group (CG) (15 female) before the cognitive screening assessment. During the study, one female from EG, one male and 2 female from CG declined. One male and three females were excluded from CG. In the end, 52 subjects (56% of all subjects approached) completed the study.

The study was conducted according to the principles expressed in the Declaration of Helsinki and subsequent revisions and was approved by the local Ethics Committee.

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