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Brain-derived neurotrophic factor correlates with functional and cognitive impairment in non-disabled older individuals

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ABSTRACT

We used a complete battery of geriatric and psychometric tests to evaluate whether plasma-borne brain-derived neurotrophic factor (BDNF), a master molecule in neuroplasticity, is associated with the severity of functional and cognitive impairment in non-disabled older individuals. There was a significant positive correlation between BDNF plasma concentrations and the Barthel index, a measurement of the ability of individuals to perform the activities of daily living ($p = 0.03$) and the concentration subcategory measured with the mini mental state examination (MMSE) test ($p = 0.01$). Furthermore, plasma BDNF inversely and significantly correlated with the blood eosinophil count ($p = 0.01$), the total cholesterol concentration ($p = 0.04$), and high-density lipoprotein cholesterol ($p = 0.04$). However, BDNF did not correlate with any other socio-demographic or clinical characteristics, other analytical parameters measured in the blood, or any other geriatric assessment scales. Our results suggest that BDNF may play a role in the pathophysiology of functional impairment in the elderly and in some aspects of cognitive function. However, more studies are needed to understand the relationship between circulating BDNF and functional impairment to determine if BDNF represents a candidate biomarker for this type of cognitive impairment.

1. Introduction

Brain-derived neurotrophic factor (BDNF) is a protein encoded by the BDNF gene which belongs to the neurotrophin family. It is produced inside the brain by different cell types and can be transported outside the brain through the blood–brain barrier (Iughetti et al., 2011; Mowla et al., 2001; Pan et al., 1998). BDNF has a protective effect on neuronal differentiation and growth during development and in neuronal survival and maintenance in adulthood (Henderson, 1996; Tapia-Arancibia et al., 2004), and is considered to be a master molecular mediator of brain plasticity (Arancio and Chao, 2007; Schinder and Poo, 2000; Tanaka et al., 2008). Several clinical studies have shown alterations in blood BDNF concentration in patients with neuropsychiatric disorders such as major depression (Karege et al., 2002; Shimizu et al., 2003), schizophrenia (Toyooka et al., 2002), and Alzheimer disease (Peng et al., 2005; Tapia-Arancibia et al., 2008). In addition, numerous physiological and environmental factors can increase the expression of BDNF, i.e. learning (Jones et al., 2006), living in an enriched environment (Brown et al., 2003), physical exercise (Van Praag et al., 1999), food restriction (Lee et al., 2002; Seroogy et al., 2002), long-term antidepressant drug treatment (De Foubert et al., 2004), and estrogen exposure (Matsuki et al., 2014). In contrast, stress (Givalois et al., 2001; Jacobsen and Mork, 2006), weight gain (Lommatzsch et al., 2005), and peripheral hormones such as glucocorticoids (Parque et al., 2015) downregulate its expression, and BDNF plasma concentrations also naturally decrease with age (Lommatzsch et al., 2005; Tapia-Arancibia et al., 2008). Moreover, Krabbe et al. (2009) showed that decreased plasma BDNF differentially increases the risk of mortality in women depending on their functional status, education, morbidity, and low-grade inflammation (but independently of age), further suggesting the involvement of this neurotrophin in the disease networks and multi-morbidity associated with the elderly. Recently, Coelho et al. (2013) suggested that circulating BDNF could somehow be linked to the phenotype of frailty in old age. Frailty has been defined as a multidimensional geriatric syndrome characterized by a decline in physiological reserves which results in increased vulnerability and a reduced ability to cope with stress factors (Fried et al., 2001). It is a common syndrome in older adults with a prevalence of frailty at around 11% (Collard et al., 2012) and prefrailty at around 40–50% (Fernández-Garrido et al., 2014) in community-dwelling adults aged 65 years or over.

Because BDNF can cross the blood–brain barrier in both directions, and given its crucial role in brain function and that several reports show that blood concentrations of BDNF decrease during aging, we hypothesized that reduced BDNF concentrations in blood might correlate

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with the severity of cognitive and functional impairment in older individuals.

The aging process in older individuals is very heterogeneous, but several aspects of aging-related impairments are linked to changes in different physiological systems. It is possible that the reduction in the BDNF concentration in blood is associated with some specific aspects of aging and does not necessarily reflect a general impairment in functional and cognitive functions. Therefore in this study we aimed to separately analyze the associations, if any, between blood BDNF concentrations and several other parameters related to functional and cognitive impairment, frailty, and neuropsychiatric symptoms in older individuals, which are included in the complete geriatric assessment.

Frailty was measured according to the five criteria proposed by Fried: involuntary weight loss, low energy or exhaustion, slow mobility, muscle weakness, and low physical activity (Fried et al., 2001). The Barthel index was used as a tool to quantify functional impairment, and geriatric and psychological assessments were performed using a scale validated for older individuals: the Tinetti gait and balance index to determine the risk of falls, the Norton scale for pressure-ulcer risk, the mini-mental score examination test (MMSE) to assess cognitive impairment, and the Yesavage scale for geriatric depression. Moreover, we also explored the relationship between these tests and blood analytical parameters in order to find any alterations related to the concentration of BDNF.

2. Materials and methods

2.1. Design and study population

A cross-sectional study was conducted between 2013 and 2014 in older non-disabled individuals with a residential profile, who were institutionalized in one of the five long-stay centers for the elderly in the province of Valencia, Spain (GeroResidencias La Saleta, Valencia). Frailty was assessed using the Fried scale (Fried et al., 2001); we selected residents of either gender, aged 60 years or more, and with the ability to get up from a chair and walk six meters. Participants were excluded if they presented dementia, major psychiatric disease (schizophrenia, bipolar disorders, etc.), blindness, acute infections, or known cancer.

We measured frailty syndrome (using Fried criteria) in each participant. The functional, mental, and structural conditions of the participants were evaluated using the following validated geriatric assessment scales: the Barthel index, Lawton and Brody scale, MMSE, Yesavage scale, Tinetti Index, and Norton Index. We measured several hematological and biochemical parameters including blood plasma BDNF concentrations, as well as socio-demographic characteristics including the number of medications taken, and the type and number of any comorbidities.

2.2. Ethical considerations

According to the requirements of the Declaration of Helsinki, written consent was obtained from all of the selected subjects before beginning the study, after having informed them about the procedures involved and the purpose of the research. The whole study protocol was approved by the local ethical committee at the University of Valencia.

2.3. Measurement of frailty criteria

Frailty was measured according to the five Fried criteria (Fried et al., 2001), as previously reported by our group (Fernández-Garrido et al., 2014). Briefly the criteria were assessed as follows: 1) Unintentional body weight-loss (5% or 4.5 kg or more in the last year). 2) Self-reported chronic fatigue: they met the criteria if they answered "A few times", "Often", or "Most of the time" to the question "How often in the last week did you feel that everything you did was an effort?", included in the Center for Epidemiologic Studies depression scale (Radloff, 1977). 3) Low physical activity levels were measured using the Spanish adaptation of the Minnesota leisure-time physical activity questionnaire (Elosua et al., 1994, 2000; Ruiz-Comellas et al., 2012). 4) According to the standards of the short physical-performance battery (Guralnik et al., 1994), participants who walked 4.6 m in a longer time than the worst quintile of the gender and height-adjusted sample fulfilled the reduced walking-speed criterion. Our values were: men taller than 173 cm: ≥6 s, height <173 cm: ≥7 s; women taller than 159 cm: ≥ 6 s, height <159 cm: ≥ 7 s, 5) To measure muscle weakness, grip strength (Kg) was measured three times for each hand alternately with a hydraulic dynamometer (Jaymar) according to the standards of the Hispanic established-populations for epidemiological studies of the elderly (Ottenbacher et al., 2002). Participants were considered fragile if they met at least three criteria and prefrail if they met one or two. All measurements were performed by trained members of the Department of Nursing at the University of Valencia, using a questionnaire with detailed instructions.

2.4. Geriatric assessment

Functional status was evaluated using the Barthel index and Lawton and Brody scale. The Barthel index defines the ability to perform the basic activities of daily living (Mahoney and Barthel, 1965) and measures the level of independence in the following 10 items: feeding, bathing, dressing, grooming, defecating, urinating, toilet use, transfers (e.g. from armchair to bed), walking, and climbing stairs. The index has a score range 0–100, where 0 is total dependence and 100 corresponds to total independence. The ability to perform the instrumental activities of daily living was assessed using the Lawton and Brody scale (Lawton and Brody, 1969) which evaluates 8 items (ability to: use the telephone and transport systems, manage their own medications and money, and to do shopping, cooking, housekeeping, and laundry) and assigns them a value of 1 (independent) or 0 (dependent). The final score is the sum of all the response values. It ranges from 0 (full dependency) to 8 (total independence).

The MMSE test and Yesavage scale were used to assess the mental state of the participants. The MMSE test was used to detect cognitive impairment; it evaluates different items grouped into five sections: orientation, immediate memory, attention and calculation, delayed recall, and language and construction; it has a score range of 0–30 and the highest scores indicate better performance (Folstein et al., 1975). The Yesavage scale quantifies depressive symptoms in older adults; it consists of 15 items with a dichotomous response (yes or no) pattern. One point is given to each response suggestive of a depressive episode. An overall score of five or more indicates depression (Sheikh and Yesavage, 1986).

Finally the structural state was evaluated using the Norton index and Tinetti index. The Norton scale is used to measure the risk of developing pressure ulcers (Norton, 1987). It measures five items (general condition, mental state, activity, mobility, and incontinence) with a severity scale of 1 to 4; the lower the score, the higher the risk. Fall-risk was evaluated with the Tinetti index; it assesses balance and gait according to how the specific actions are implemented. The maximum score is 12 for gait and 16 for balance and the sum of both scores gives the risk of falls, which is high when the score is lower than 19 (Tinetti et al., 1986).

2.5. Brain-derived neurotrophic factor measurement and analytical parameters

Blood samples were obtained from each subject between 7:30 a.m. and 10 a.m. in the morning to avoid hormonal fluctuations and their potential influence on BDNF levels. Ten ml blood was collected was collected into two BD Vacutainer tubes containing EDTA. After extraction, the blood samples were allowed to stand for 15 min and were centrifuged at 1500 rpm for 10 min at room temperature. Subsequently the plasma supernatants were aliquoted and stored at −20 °C until analysis. After thawing, the samples were centrifuged at 1500 rpm for 10 min at