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Circulating Glial-derived neurotrophic factor is reduced in late-life depression

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\textbf{Abstract}

\textbf{Background:} The Glial Cell-line derived neurotrophic factor (GDNF) is part of the TGF-\(\beta\) superfamily and is abundantly expressed in the central nervous system. Changes in GDNF homeostasis have been reported in affective disorders.

\textbf{Aim:} To assess serum GDNF concentration in elderly subjects with late-life depression, before antidepressant treatment, as compared to healthy elderly controls.

\textbf{Methods:} Thirty-four elderly subjects with major depression and 37 age and gender-matched healthy elderly controls were included in this study. Diagnosis of major depression was ascertained by the SCID interview for DSM-IV and the severity of depressive symptoms was assessed by the Hamilton Depression Rating Scale (HDRS-21). Serum GDNF concentration were determined by sandwich ELISA.

\textbf{Results:} Patients with major depression showed a significant reduction in GDNF levels as compared to healthy elderly controls (\(p < 0.001\)). Also, GDNF level was negatively correlated with HDRS-21 scores (\(r = -0.343, p = 0.003\)).

\textbf{Discussion:} Our data provide evidence that GDNF may be a state marker of depressive episode in older adults. Changes in the homeostatic control of GDNF production may be a target to development of new antidepressant strategies.

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1. Introduction

Several lines of evidence suggest a widespread abnormality in neurotrophic cascades in age-related neuropsychiatric disorders, such as Alzheimer’s disease and late-life depression (Teixeira et al., 2010). Most data derive from studies assessing circulating levels of BDNF and NGF, showing a significant reduction of circulating neurotrophins in these patients which correlates with the stage of cognitive impairment and the severity of depressive symptoms (Forlenza et al., 2010a, b; Yu et al., 2008; Diniz et al., 2010a). Also, these cascades can be a target for therapeutical interventions as many drugs currently used to treat these disorders increase the concentration of these factors (de Sousa et al., 2011; Brunoni et al., 2008; Leyhe et al., 2008). In addition, other conditions, such as cerebrovascular changes and the senescence process itself, may have a significant impact on neurotrophic cascades homeostasis (Tapia-Arancibia et al., 2008; Lee et al., 2006; Alleva and Francia, 2009).

The Glial Cell-line derived neurotrophic factor (GDNF) is part of the Transforming Growth Factor \(\beta\) (TGF-\(\beta\)) superfamily and is abundantly expressed in the CNS (Airaksinen and Saarma, 2002). It exerts its effects by the activation of GDNF-receptor \(\alpha\) (GFR\(\alpha\)) and the “Rearranged during Transfection” Protooncogene (RET) receptor (Airaksinen and Saarma, 2002). In the adult CNS, it plays a major role in the protection of catecholaminergic, dopaminergic and cholinergic neurons (Pascual et al., 2008), as well as, axonal regeneration after injury (Straten et al., 2002).

Changes in GDNF homeostasis have been reported in patients with affective disorders. Reduced mRNA expression in leukocytes as well as reduced GDNF levels in serum have been reported in patients with major depression and bipolar disorder (Otsuki et al., 2008; Zhang et al., 2008, 2010). However, increased GDNF circulating levels have also been reported in patients during manic and depressive episodes in bipolar patients (Barbosa et al., 2011; Rosa et al., 2006), and in patients with unipolar depression in brain tissue (Michel et al., 2008). In addition, one study reported significantly lower peripheral GDNF levels in euthymic adult patients with previous history of unipolar depressive disorder and bipolar disorder (Takebayashi et al., 2006).
However, few studies addressed the role of GDNF in late-life depressive disorder. A recent study assessed peripheral GDNF levels in elderly subjects with major depression (Wang et al., 2011). In this work, GDNF serum levels were significantly increased in elderly subjects with late-onset depression (LOD) as compared to gender and age-matched healthy subjects. Given the paucity of data on peripheral GDNF levels in late-life depression and the contradictory findings in the literature, our aim is to compare serum GDNF levels in elderly subjects with late-life depression vs. age and gender-matched controls. Specific clinical characteristics of the late-life depression may influence the pattern of neurobiological changes observed in these patients. These include, for instance, the association between cerebrovascular disease and late age of onset of the first depressive episode (Alexopoulos et al., 1997), the increase of pro-inflammatory status in elderly patients with non-late onset recurrent depression (Diniz et al., 2010b,c), or the higher GSK3B enzymatic activity in patients with more severe depressive episode and cognitive impairment (Diniz et al., 2011). Therefore, we further addressed whether changes on serum GDNF levels is associated to the severity of depressive symptoms and cognitive impairment, the age of onset of late-life depression and history of previous depressive episode.

2. Methods

2.1. Patients’ recruitment and assessment

Elderly subjects with evidence of current major depressive episode were recruited to this study (n = 34), being 16 with late-onset major depressive (LOD, first depressive episode after 65 years-old) and 18 with non-late onset depression (non-LOD, first depressive episode before 65 years-old). All patients are part of a cohort dedicated to the study of the neurobiology of late-life depression (Diniz et al., 2010b, 2010c). The diagnosis of major depressive disorder (first or recurrent episode) was made according to DSM-IV criteria (American Psychiatric Association, 2000) following the Structured Clinical Interview for DSM-IV disorders (SCID) (First et al., 2002). Patients were free of any antidepressant treatment for at least one month prior the initial clinical and laboratory assessments.

The severity of the depressive symptoms was evaluated by the scores on the 21-item Hamilton Depression Rating Scale (HDRS-21) (Hamilton, 1960). Cognitive assessment was carried out with the Cambridge Cognitive test (CAMCOG) (Roth et al., 1986; Nunes et al., 2008) and the Mini-mental state examination (MMSE) (Folstein et al., 1975).

Thirty-seven healthy elderly subjects, with no evidence of current psychiatric or cognitive disorders, were included in this study as a comparison group. They had no evidence of current axis I DSM-IV psychiatric diagnosis and HDRS-21 scores below 7. Among the subjects in the comparison group, 18 had history of a previous depressive episode and were on full remission, for at least 6 months (HDRS-21 < 7), at the time of clinical and laboratory assessment.

All patients and subjects in the comparison group comprise of subsample of elderly subjects enrolled in a prospective clinical study on cognitive aging (Diniz et al., 2008; Forelzena et al., 2010a, b). They underwent the same clinical, cognitive and psychiatric work-up as the depressed patients. The elderly subjects in the comparison group were age and gender-matched to the elderly depressed patients.

2.2. Sample collection and GDNF analysis

Five milliliters of blood were drawn from each subject by venipuncture at 8–10 a.m. before clinical assessment. Samples were immediately centrifuged 2 × at 3000 × g for 10 min, and serum was kept frozen at −70 °C until assayed.

Serum GDNF concentration was measured according to the procedure provided by the manufacturer using sandwich ELISA kits for GDNF (DuoSet, R&D Systems, Minneapolis, MN, USA). All samples were assayed in duplicate. The detection limits for these assays were 10 pg/mL. Concentration is expressed as pg/mL.

2.3. Statistical analysis

GDNF serum levels did not show a normal distribution in this sample (Kolmogorov–Smirnoff test, p = 0.005). We log-transformed the GDNF levels to normalize its distribution and to be able to carry out parametric statistical analyses. Student t test was carried out to assess mean differences of GDNF serum level and other continuous variables between depressed patients and controls. Chi-square with Fisher exact test analyses were carried out to assess differences in the frequency of dichotomous variables between depressed patients and controls. Pearson analyses were carried out to assess the correlation between GDNF levels and socio-demographic, severity of depressive symptoms and cognitive performance.

All statistical analyses were carried with the Software Package for Social Science v. 14.0 for Windows (SPSS, Chicago, IL).

3. Results

Table 1 shows the socio-demographic and clinical characteristics of the study sample. Patients with late-life depression showed significantly lower scores on the MMSE and CAMCOG and had fewer years of formal education. We carried out analysis of covariance (ANCOVA) to control for the confounding effect of education on the cognitive performance. The scores on MMSE and CAMCOG remained significantly lower in the depressed patients as compared to elderly controls (MMSE, p = 0.001; CAMCOG, p < 0.001). The most common clinical comorbid conditions in depressed patients were high blood pressure (85%), dyslipidemia (62%), their frequencies were not significantly different from those in control group (high blood pressure, 78%, p = 0.6; dyslipidemia, 66%, p = 0.8).

GDNF serum level was significantly reduced in patients with late-life depression as compared to healthy elderly subjects (Table 2). The reduction in GDNF level remained statistically significant after controlling for the educational, cognitive performance and the severity of depressive symptoms (analysis of covariance, F = 11.35, d.f. = 1, p = 0.001).

GDNF level showed a weak negative correlation with HDRS-21 scores (r = −0.343, p = 0.003) in the whole sample. No

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Socio-demographic and clinical characteristics of the study sample.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>n</td>
</tr>
<tr>
<td>Comparison group (n = 37)</td>
<td>29/8</td>
</tr>
<tr>
<td>Late-life depression (n = 34)</td>
<td>25/9</td>
</tr>
<tr>
<td>67.8 ± 5.4</td>
<td>69.7 ± 4.5</td>
</tr>
<tr>
<td>Late-life depression (n = 34)</td>
<td>1.1 ± 1.8</td>
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<td>28.9 ± 1.4</td>
</tr>
<tr>
<td>Late-life depression (n = 34)</td>
<td>26.8 ± 2.4</td>
</tr>
</tbody>
</table>

W: woman; M: Men. HDRS-21: Hamilton Depression Rating Scale – 21 items; CAMCOG: Cambridge Cognitive test; MMSE: Mini-Mental State Examination.

Data values depicted as mean ± standard deviation.
significant correlation was found between GDNF level and CAM-COG or MMSE scores ($r = 0.21, p = 0.08$ and $r = 0.15, p = 0.2$, respectively) or age ($r = -0.06, p = 0.6$) (Fig. 1).

Age of onset of depressive disorder did not significantly influence GDNF levels (LOD, GDNF level $2.51 \pm 0.93$ vs. non-LOD, GDNF level $2.76 \pm 0.65$, $p = 0.36$). Similarly, previous history of major depressive episode in the comparison group did not influence GDNF levels (positive history, GDNF level $3.32 \pm 0.61$ vs. negative history, GDNF level $3.22 \pm 0.51$, $p = 0.8$).

As serum GDNF can be significantly reduced in patients with cognitive impairment and dementia (Straten et al., 2009), we stratified the patients with late-life depression according to the presence of significant cognitive impairment (CAMCOG scores $< 86$) (Nunes et al., 2008; Diniz et al., 2011). We found no significant differences in GDNF levels in patients with cognitive impairment (CAMCOG<$ 86$, $n = 17$, GDNF level $2.68 \pm 0.2$; CAMOCG$\geq 87$, $n = 17$, GDNF level $2.57 \pm 0.2; p = 0.7$).

### Table 2

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>GDNF serum level (pg/ml)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late-life depression ($n = 34$)</td>
<td>2.64 $\pm$ 0.79</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Comparison group ($n = 37$)</td>
<td>3.27 $\pm$ 0.56</td>
<td></td>
</tr>
</tbody>
</table>

GDNF serum level: log-transformed data.
Data values depicted as mean $\pm$ standard deviation.

In the present study, we found a significant reduction in GDNF serum levels in patients with late-life depression that was negatively correlated with the severity of depressive symptoms. Our findings were independent of patients’ age, educational level. Age of onset of depressive disorder and previous history of depressive episode did not influence GDNF levels in this sample. We also found no significant impact on GDNF levels after stratifying depressed patients according to the presence of cognitive impairment. Taken together, the present results suggest that decreased concentration of serum GDNF may be a state marker of current depressive episode in late-life. In addition, the reduction of peripheral GDNF observed in our study provide additional evidence that GDNF homeostasis may play an important role in the physiopathology of major depression in the elderly.

Normal aging process does not seem to be associated with significant changes on GDNF expression or on its downstream signaling system (Alladi et al., 2010; Dass et al., 2006). However, animal models of accelerated aging found a significant reduction in brain GDNF expression leading to reduced neuronal viability. We found no significant correlation between age and GDNF levels. This finding was also observed in previous studies (Wang et al., 2011). However, the reduction of GDNF in depressed patients may be secondary to processes that lead to accelerated brain aging, such as heightened pro-inflammatory status, that are also observed in patients with late-life depression (Diniz et al., 2010d; Francheschi et al., 2000; Cunningham et al., 2009).

Recent evidence showed that stress-related conditions increase DNA methylation and histone modifications in the promoter region of GDNF gene in animal models of depression (Uchida et al., 2011). These epigenetic changes of GDNF gene determined significant decrement in GDNF mRNA expression, which was rapidly reversed by antidepressant treatment. Pre-clinical and clinical studies have demonstrated that effective antidepressant treatment is associated with significant increase in GDNF levels, despite negative findings have also been reported (Zhang et al., 2009; Hisaoka et al., 2001, 2011; Chen et al., 2001; Hisaoka et al., 2011; Golan et al., 2011). Thus, changes in GDNF levels may be a surrogate marker of anti-depressant response and a target for the development of new antidepressant strategies.

GDNF has a very complex regulation and exerts multiple functions in the peripheral and central nervous system. Contradictory findings have been reported in the literature, with some studies reporting decreased GDNF levels (Straten et al., 2009; Otsuki et al., 2008), but others report increased GDNF levels in affective disorders (Barbosa et al., 2011; Rosa et al., 2006; Michel et al., 2008; Wang et al., 2011). Given that GDNF has an important role in the survival and maintenance of monoaminergic neurons, it is tempting to hypothesize that the reduction of GDNF levels may have a close relationship to the abnormal regulation of the serotonergic system, as the significant reduction of post and pre-synaptic serotonin receptors observed in patients with late-life depression (Sheline et al., 2004; Meltzer et al., 2004). Such changes were correlated to the severity of depressive symptoms (Meltzer et al., 2004). In this context, the negative weak correlation between GDNF levels and depressive symptomatology may further suggest a relationship between abnormalities in the GDNF levels and a dysregulation of the serotonergic system in late-life depression. However, no study has directly evaluated the relationship of GDNF and serotonin system changes and, thus, it is necessary additional studies to address these hypotheses.

Our results are in contradiction with another recent study that evaluated peripheral GDNF levels in unmedicated patients with late-life major depression (Wang et al., 2011). This study found a significant increase in serum GDNF levels that correlated with cognitive performance. Despite the similar study design, the latter study was carried out in a population with a different ethnic ground (i.e. chinese population) what may help to explain in part the different results between the two studies. Additional studies with larger samples and including subjects from other ethnic backgrounds are necessary to confirm these findings.

In conclusion, we found a significant reduction in GDNF serum level that was negatively correlated with depressive symptoms of patients with late-life depression. Our data provide further support to the evidence of widespread change in neurotrophic cascades in affective disorders, including late-life depression. Given the
controversial findings regarding changes in the circulating levels of GDNF in patients with affective disorders, additional studies are of utmost importance to clarify the role of this neurotrophic factor in these disorders.

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Conflict of interest

The authors do not have any conflict of interest to report regarding this manuscript.

Authors role

Breno S. Diniz: study design, statistical analysis, writing of the first draft of the manuscript, final revision of manuscript. Antonio L. Teixeira: study design, labortatorial analysis, final revision of manuscript. Aline S. Miranda and Leda L. Talib: labortatorial analysis. Wagner F. Gattaz: study design and final revision of the manuscript. Orestes V. Forlenza: study design and final revision of the manuscript.

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