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Short communication

Brain-derived neurotrophic factor expression increases after enzyme replacement therapy in Gaucher disease

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ABSTRACT

Mutations in the *GBA* gene are related to an increased risk of developing neurodegenerative diseases. The exact molecular mechanisms involved in the interaction between *GBA* and α-synuclein, a protein that has been associated with several neurological diseases, remain unsolved. Brain-derived neurotrophic factor (BDNF) is a neurotrophin that is important for the normal development of the peripheral and central nervous system, and it plays a key role in neuronal survival and synaptic plasticity in the adult brain. A reduction in BDNF expression has been reported in patients with Parkinson's disease, Alzheimer's disease and dementia with Lewy bodies. We analyzed BDNF levels in the plasma of Gaucher Disease (GD) patients who were not being treated with enzyme replacement therapy (ERT) and then subsequently following ERT; we compared the levels to those of healthy controls. We demonstrated that BDNF levels were remarkably diminished in GD patients who were under no specific treatment and these levels increased following ERT. This is the first study that demonstrates a variation in the plasma levels of a neurotrophic factor in GD type 1 patients. Further studies are required to correlate BDNF level variations with the clinical findings and the response to therapy in GD patients. Low levels of BDNF are associated with neurodegenerative diseases; therefore, BDNF could provide a new therapeutic target for GD patients with neurological symptoms.

1. Introduction

Gaucher disease (GD, OMIM 230800) is one of the most prevalent lysosomal disorder, with an estimated worldwide incidence of 1 case per 57,000 live births (Meikle and Hopwood, 2003), although this rate can reach 1 in 850 among Ashkenazi Jews (Mistry et al., 2011).

GD is caused by mutations in both alleles of the *GBA* gene, which codes for lysosomal glucocerebrosidase (EC 3.2.1.45), an enzyme responsible for catalyzing the hydrolysis of glucocerebroside into glucose and ceramide (Beutler, 2006). Consequently, there is intracellular accumulation of the substrate in macrophages, particularly in the spleen, liver, bone marrow, and lungs. GD is therefore a multisystem disorder and exhibits phenotypic heterogeneity. Classically, GD is subdivided into three main forms (types I, II and III) defined by clinical characteristics, disease course, and ethnic prevalence. Nevertheless, there is a wide range of findings that overlap across the classical forms, which has led to a new assessment of GD as a continuous spectrum of disorders rather than a disease with three distinct subtypes (Beutler, 2006). Although the genetic changes and biochemical pathways that underlie GD have been well characterized, the mechanisms whereby the accumulation of glucocerebroside leads to clinical manifestations have yet to be fully determined (Jmoudiak and Futerman, 2005; Hughes and Pastores, 2010).

Mutations in the *GBA* gene have been associated with an increased risk of developing Parkinson's disease and dementia with Lewy body inclusions (Sidransky et al., 2009; Nalls et al., 2013). The exact molecular mechanisms involved in the interaction between *GBA* and α-synuclein, the main protein associated with these neurological diseases, remains unsolved.

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family, a group of neuronal growth factors including nerve growth factor (NGF), neutrotrophin-3 (NT-3) and neurotrophin-4 (NT-4) (Binder and Scharfman, 2004). These proteins are not only important for the normal development of the peripheral and central nervous system but they also play a key role in neuronal survival and synaptic plasticity in the adult brain (Arancio and Chao, 2007).

A reduction in BDNF expression has been reported in patients with Parkinson's disease, Alzheimer's disease and dementia with Lewy

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bodies (Murer et al., 2001; Imamura et al., 2005). Recently, increasing evidence suggests that alterations in the brain neurotrophic support and, in particular, in BDNF expression and signaling, might contribute to neurodegeneration (Balaratnasingam and Janca, 2012). Additionally, patients with mood disorders, such as major depression, present with decreased serum levels of BDNF, which increase following medication treatment (Lee and Kim, 2010; Bocchio-Chiavetto et al., 2010).

In this pilot study, we analyzed BDNF levels in the plasma of Brazilian adult type 1 GD patients during and after imiglucerase shortage which occurred in 2009–2010, and we showed the response of BDNF after the restart of enzyme replacement therapy.

2. Methodology

2.1. Study population

The study group was composed of 14 GD type 1 adult patients (7 males and 7 females, one splenectomized; median age = 35.7 years; median time of treatment pre-shortage = 5.8 years; median ERT dose pre-shortage = 25.7 UI/kg), 8 healthy controls (6 females and 2 males, median age = 37.1 years) and 5 male patients with Fabry disease on regular treatment (median age = 37.4 years).

We analyzed plasma samples from patients with a biochemical and molecular diagnosis of GD who were followed at the State Reference Center for Gaucher disease of Rio Grande do Sul, Brazil. Patients provided written informed consent for participation in the study, and clinical and biochemical data were obtained by chart review. The samples were obtained during the period of imiglucerase shortage (at least 4 months with no GD specific treatment) and after the shortage ended (at least 6 months on ERT). The control samples were obtained during routine blood work. All of the samples were collected, centrifuged in less than 1 h of collection and stored at −80 °C. The study was approved by the Hospital de Clínicas de Porto Alegre Research Ethics Committee.

2.2. BDNF plasma assay

BDNF levels were determined using the MILLIPLEX® MAP system (HNDG3MAG-36K, Millipore Corporation, Billerica, Massachusetts) according to the manufacturer's protocol. The samples were analyzed in duplicate, and when the difference between the reads was less than 10%, the mean was used. When the difference was greater than 10%, the sample was not included in the analysis. BDNF levels were estimated using a 5-parameter polynomial curve. Values are expressed in pg/mL.

2.3. Statistical analysis

The null hypothesis considered in the study was the absence of a difference in the BDNF concentration among the groups studied. The values were compared using nonparametric tests as Wilcoxon signed rank test since the distribution was not normal. When comparing BDNF values during imiglucerase shortage and after the restart of ERT a related sample test was used. All the analyses were made with the software IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY). The statistical significance value was $p < 0.05$.

3. Results

Fig. 1 shows the median BDNF plasma levels of healthy controls (2019.5 pg/mL; minimum = 36, maximum = 5325, interquartile range = 4039.5), GD patients not receiving ERT (138.5 pg/mL; minimum = 51, maximum = 238, interquartile range = 92) and GD patients receiving ERT (395 pg/mL; minimum = 107, maximum = 1533, interquartile range = 248). The comparison among patients not receiving ERT, healthy controls and patients receiving ERT was significant ($p < 0.001$ and $p < 0.002$, respectively).

The BDNF levels in the plasma of five patients with Fabry disease receiving regular treatment (data not shown in figures) did not differ from controls (mean BDNF = 977 pg/mL; minimum = 415, maximum = 2301, interquartile range = 818.5; p value = 0.2).

4. Discussion

The typical classification of GD into three clinical phenotypes is being reassessed following the neurological findings in type 1 GD patients (Cherin et al., 2010) and the relationship between carriers of *GBA* mutations and the development of Parkinson's disease and dementia with Lewy bodies (Goker-Alpan et al., 2004; Ziegler et al., 2007; Tsuang et al., 2012). Studies in the brains of mouse models of neuronopathic GD detected the intracellular accumulation of glycosphingolipids, glucosylceramide and psychosine, leading to neurodegeneration (Farfel-Becker et al., 2014). Additionally, it has been reported that deficiencies of neurotrophic factors, including BDNF, result in massive cell death and neurodegeneration in the central nervous system of GD mouse models (Kim et al., 2006), however no patient studies to date have evaluated these neurotrophic factors.

We analyzed BDNF levels in the plasma of GD patients not receiving ERT and following ERT and compared these levels to healthy controls. We demonstrated that BDNF levels are remarkably diminished in GD patients receiving no specific treatment and increased by greater than 3 times following 6 months of ERT but yet different from healthy subjects. We also analyzed plasma samples from patients with Fabry disease since this is a lysosomal disorder with prominent neurological features. There were no differences between BDNF levels of treated patients with Fabry disease and healthy subjects, unlike the findings in patients with Gaucher disease.

The possibility of trafficking across the blood–brain barrier remains open; however, evidence suggests that the levels of BDNF in the blood reflect the levels in the central nervous system. This is noted particularly in studies related to major depression (Bocchio-Chiavetto et al., 2010; Castren and Rantamaki, 2010). Additionally, correlations were observed between serum BDNF levels and cerebral cortex integrity (Lang et al., 2007) and cognitive function (Gunstad et al., 2008) in healthy adults. No patients in this study presented with neurological impairment, parkinsonism, cognitive decline or major depression. However, we did not detect changes in the scores on the quality of life questionnaires because the time frame of this study spanned only a few months, and it is well established that ERT improves the health-related quality of life of GD patients following several years of treatment (Hayes et al., 1998; Masek et al., 1999; Oliveira et al., 2013).

Based on these results, we hypothesize that BDNF plays a neurochemical role leading to an improvement of the mental health of patients with GD disease.

BDNF is a potent inhibitor of apoptosis-mediated cell death and neurotoxin-induced degeneration of dopaminergic neurons, and there are some studies suggesting that it may be used in the development of neuroprotective therapies, especially for Parkinson's disease (Scalzo et al., 2010), and further translated to new therapeutic options for GD patients with neurological symptoms.

5. Conclusion

This is the first study that demonstrates a variation in the plasma levels of a neurotrophic factor in GD type 1 patients. Further studies are required to associate BDNF level variations with the clinical findings and the response to therapy in GD patients. A follow up of these levels through time is necessary to verify whether this increase is dose and/or time dependent. Because low levels of BDNF are related to neurodegenerative diseases, BDNF could be a new therapeutic target for GD patients with neurological symptoms.