Decreased Brain-Derived Neurotrophic Factor Serum Concentrations in Chronic Post-Stroke Subjects

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Background: Brain-derived neurotrophic factor (BDNF) plays a critical role in sensorimotor recovery after a stroke. However, few studies have assessed the circulating BDNF levels in post-stroke humans to understand its changes. This study was conducted to measure BDNF serum concentrations in subjects with chronic hemiparesis, as well as to correlate serum concentrations with age, post-stroke time, total score of Stroke Specific Quality of Life Scale (SS-QOL), mobility subscale score, and motor function of SS-QOL. *Methods:* Seventeen chronic post-stroke subjects matched by age and gender with healthy controls took part in the study. Personal data (age, hemiparesis side, and post-stroke time) were collected, and a physical examination (weight, height, body mass index) and SS-QOL assessment were carried out. On the same day, after the initial evaluation, venous blood samples were collected from the chronic post-stroke subjects and the healthy subjects. The BDNF serum concentrations were measured blindly by enzyme-linked immunosorbent assay. *Results:* Subjects with chronic hemiparesis presented a decrease in BDNF serum compared with healthy subjects ($P < .01$). There was no correlation between BDNF serum levels with post-stroke time, age or quality of life, mobility, and the upper extremity motor function ($P > .05$). BDNF concentrations are related to structural and functional recovery after stroke; thus, this reduction is important to understand the rehabilitation process more clearly. However, more studies are needed considering the genetic variations and other tools to assess motor impairment and functional independence. *Conclusion:* Chronic post-stroke subjects presented a decrease in BDNF serum concentrations, without a correlation with post-stroke time, age, and quality of life. **Key Words:** Brain-derived neurotrophic factor—stroke—neuronal plasticity—rehabilitation.

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Introduction

Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family that mediates neuronal proliferation, survival, and differentiation in both the central and the peripheral nervous systems.[1-3] BDNF is also involved in long-term potentiation, learning, memory formation, and recovery from brain injury.[3-5] Neurons and peripheral cells (endothelial cells, leukocytes, platelets, and muscle cells) secrete BDNF,[6-8] which can cross the blood–brain barrier.[9] However, this neurotrophin is mainly activity-dependent and synthesized by the glutamate neurons in various parts of the human brain, including the hippocampus, amygdala, and striatum.[10-12]

BDNF production and secretion may be influenced by factors such as age, gender, weight, height,[6] and circadian rhythm.[13] Furthermore, the BDNF levels are altered in various diseases, such as Alzheimer's disease,[14,15] Parkinson's disease,[16,17] multiple sclerosis, and depression.[18] Patients with Alzheimer's disease, Parkinson's disease, and depression showed a decrease in BDNF levels, whereas patients with multiple sclerosis showed an increase in BDNF levels. In relation to stroke, alterations in BDNF levels were observed by previous studies.[19-21] However, according to Rodier and coworkers,[22] few studies assessed the circulating BDNF levels in post-stroke humans without intervention and with the control group (CG) to understand the changes in BDNF concentrations after stroke.[23-25]

According to a study carried out on animals with brain ischemia, an increase in BDNF concentration occurred in injured and neighboring regions 24 hours after injury, and this increase was sustained up to 7 days post lesion in the motor cortex and was reduced at 28 days.[19] Furthermore, these authors observed that the time period of the increase of this central BDNF expression took place in parallel with bilateral motor deficits in the skill of reaching,[19] indicating that there is some relationship between BDNF concentrations and motor recovery.

Many studies have provided important information related to the BDNF expression in brain structures (local expression),[19-21] but it is unclear whether systemic concentrations of BDNF are altered after a stroke. Studies that investigated the expression of BDNF locally or systemically were conducted mainly on animals. Bejot and coworkers[20] described a BDNF increment in the brain tissue after 4 hours and 24 hours from brain injury in rats, but no changes in both plasma and BDNF serum concentrations were detected 4 hours, 24 hours, and 8 days post injury. Furthermore, brain concentrations after a stroke were not correlated with plasma concentrations or stroke severity. However, a positive correlation between plasmatic BDNF and stroke severity 4 hours after embolization was observed. Thus, these authors demonstrated that the severity of stroke is associated with plasma BDNF concentration in the acute stage, but the circulating BDNF levels do not reflect the brain BDNF level after stroke.

In humans,[23] plasmatic BDNF levels in the acute phase of stroke (4 days post stroke) are unchanged, even in the presence of significant blood–brain barrier dysfunction at day 2 and day 3 after a stroke. The authors reported that, according to studies conducted with animals, perhaps the increase in plasma BDNF concentrations occurred only during the first hours after stroke. Another study verified that during an acute phase, stroke patients presented higher serum BDNF than healthy subjects, whereas patients who had depression presented lower BDNF levels compared with patients with depression.[25] However, another study conducted with humans found that subjects who had depression 3-6 months after a stroke presented a reduction in BDNF serum compared with healthy subjects.[24]

There are many studies conducted on animals or humans in the acute and chronic post-stroke phase. These studies verified BDNF levels,[19-21] the effect of the polymorphism on motor recovery,[26-28] and the effect of some intervention on BDNF levels.[22,29-31] Although some studies consider the effect of other conditions, such as depression, in BDNF levels post stroke, to the best of our knowledge there are no data in the literature that address the serum BDNF levels in humans at the chronic post-stroke phase in a general way. Considering that this neurotrophin presents a critical role in sensorimotor recovery after stroke, the objective of this study was to measure BDNF serum concentrations in subjects with chronic hemiparesis, as well as to correlate serum concentrations with age, post-stroke time, and the total mobility and upper extremity function scores of the Stroke Specific Quality of Life Scale (SS-QOL). Thus, the hypothesis was that subjects with chronic hemiparesis would have lower BDNF serum concentrations than did healthy controls, and this decrease would be positively correlated with the SS-QOL score and negatively correlated with age and post-stroke time.

Materials and Methods

The cross-sectional study was approved by the Ethics Committee for Human Research at the Federal University of São Carlos (report # 112.551/2012), which is in agreement with resolution 196/96 from the National Health Council. The sample size was calculated using BDNF serum concentrations from five subjects with chronic hemiparesis and five healthy control subjects using the GPower 3.1 software (University of Kiel, Germany).[32] The average concentrations were 591.12 pg/mL (±286.13) and 969.66 pg/mL (±329.75), respectively. A power of .95 and alpha of .05 were considered for the calculation, requiring a total sample size of 10.

Subjects

Thirty-four male subjects (17 patients with stroke and 17 healthy individuals) selected from the local community were enrolled after giving written informed consent.