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Editorial

Preliminary Preclinical and Clinical Data and the Therapeutic Prospects of Low-Dose BDNF in the Pediatric Field

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INTRODUCTION

Brain-Derived Neurotrophic Factor (BDNF) is a polypeptide with a pivotal role in maintaining neuroplasticity (intended as the brain's ability to modify its connections and functionality in response to experiences and learning) [1]. BDNF mainly promotes the survival, growth, and differentiation of both neurons and synapsis. BDNF shows neuroprotective effects, potentially preserving neurons from damage and degeneration. BDNF is implicated in mood regulation, and its dysregulation has been linked to depression and other mood disorders [2]. BDNF is also involved in the regulation of inflammatory response directly (*via* down-regulation of NF-kB [3] and, therefore, of the main steroid mediators of inflammation) and indirectly (*via* up-regulation of IL-10) [4], and in ROS modulation increasing the expression of genes encoding for scavenger enzyme systems such as Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) [5,6].

As a potential treatment tool, BDNF is considered a therapeutic target for various neurological and psychiatric disorders. Delivering BDNF to the brain remains a challenge [7]: The combination of stem cells and BDNF-releasing pharmaceutical forms is a promising approach in regenerative medicine, especially in the treatment of neurological diseases. Pharmacologically active BDNF can be orally delivered as low dose hydroalcoholic formulation (1 pg/ml), as assessed by both *vivo* and clinical studies [8-10]. low-dose BDNF is therapeutically applied following the guidelines of Low Dose Medicine (LDM) a medical approach born from the encounter between Molecular Biology with Psycho-Neuro-Endocrine-Immunology (P.N.E.I.) [11,12]. LDM refers, for what it concerns to the therapeutic aspects, to a modern form of nano-pharmacology for the delivery of low dose signaling molecules (cytokines, hormones, neuropeptides and growth factors). In LDM medications, the carrier effect is achieved through application of SKA technology (Sequential Kinetic Activation), a drug delivery system (codified and standardized by GUNA S.p.a, Milan, Italy), based on the principles of "release activity": the ability of a specific substance to release its activity in the aqueous milieu [13], which allows the nano-concentrations of signaling molecules [in their physiological working range: between 10^{-6} (microgram) for hormones [14] and 10^{-15} (femtogram) for the other messenger molecules [15] to be biologically active modulating P.N.E.I. auto-regulation mechanisms.

DESCRIPTION

In agreement with these premises, the scientific research on low dose BDNF shows that this signaling molecule is active on the Central Nervous System (CNS) promoting neuronal plasticity and cognitive performance and at the cardiovascular level regulating the contractile ability of cardiac muscle tissue.

Neuronal plasticity

The progressive loss of proliferative capacity and vitality of neurons and astrocytes (neuroplasticity) can be considered the cellular cause of age-related cognitive decline. Molinari, et al. conducted a basic research study, using *in vitro* and *in vivo* assays for the study of brain aging, to evaluate the biological activity of low-dose BDNF (10 fg/ml) as a pharmacological tool suitable for therapeutic purposes [8]. The primary aim of the study was to evaluate the effect of low-dose BDNF on some of the key parameters of "health" and the aging processes of the brain. Lower BDNF expression in the nervous system is directly correlated with the onset of cognitive deficits and increased sensitivity to stress. Briefly, the study was conducted using both *in vitro* and *in vivo* models: An *in vitro* intestinal barrier model (Caco-2 cell line), an *in vitro* Blood-Brain Barrier (BBB) model, and cultures of neurons and astrocytes were used to evaluate the ability of low-dose BDNF to overcome biological barriers and exert biological effects on two of the main cell lines of the CNS.

An animal model (wild-type mice aged 14 to 18 months) suitable for simulating brain aging was used to quantify the presence of BDNF in the cerebrospinal fluid following oral administration of BDNF. Analysis of the considerable amount of data obtained from the trials allowed the researchers to highlight several significant aspects:

- Low-dose BDNF can cross the Blood-Brain Barrier (BBB).
- Low-dose BDNF exerts a biological effect by increasing neuronal viability and the proliferative capacity of astrocytes.

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- Low-dose BDNF can reduce oxidative stress through the upregulation of Nrf2/ARE signaling pathway increasing SOD and GPx synthesis
- Low-dose BDNF maintains normal levels of Tau protein, thus preserving correct neuronal polarity, by downregulation of Tau protein kinase activity.
- Low-dose BDNF increases the levels of Apolipoprotein E2
- Low-dose BDNF can reach the brain within the first 24 hours from oral administration, reaching peak levels within 48 hours, and then remaining present in the brain for a considerable period after the end of treatment.

All the results obtained support the hypothesis that the treatment with low-dose BDNF can provide protection to the brain by slowing its degeneration.

Cognitive performance in pediatric age

Supino observed the action of low-dose BDNF on Specific Learning Disabilities (SLD) through an observational study [9] on young patients with a SLD diagnosis (reported discrepancy between the levels of academic performance due to learning disorders involving difficulty in concentration or attention, in language development, or in processing visual and auditory information). low-dose BDNF was associated with standard treatment (educational management and medical, behavioral and psychological therapy). Therapeutic overlapping with low-dose BDNF promoted an evident improvement (+50%) *vs.* the standard treatment group in test performance (WISC-IV-Wechsler Intelligence Scale for Children), and an increase in self-esteem. The considerable result obtained by administering Guna-BDNF on the performance of subjects with SLDs allowed these young patients to obtain better scholastic performance and a more effective inclusion in their peer groups, thereby sparing them detrimental feelings of inadequacy and isolation.

Cardiac contractile activity

The research group coordinated by Fioranelli, et al. conducted an experimental clinical study [10] aimed at evaluating the potential impact of low-dose BDNF on reducing episodes of Paroxysmal Atrial Fibrillation (PAF). Twenty-two patients (17 males and 5 females) with a confirmed diagnosis of PAF and no structural heart disease were enrolled. Each patient received low-dose BDNF in the morning, without altering their current treatments. During the 24-month study, the arrhythmic burden was assessed as well as the average monthly duration of PAF episodes. At the end of the study period, data from the 22 patients were analyzed. Arrhythmic burden, measured as the average monthly duration of PAF episodes, was significantly reduced after low-dose BDNF administration. Low-dose BDNF therapy has been shown to have a significant impact in reducing arrhythmic burden and atrial fibrillation recurrence, with high efficacy in patients over 70 years of age and without structural heart disease.

This selection of studies clearly demonstrates the concrete possibility of using low-dose BDNF for therapeutic purposes, exploiting its characteristic ability to modulate neuronal cellular function and, by extension, its potential to support neuronal plasticity. This latter aspect is crucial to hypothesizing the use of BDNF in pediatric age: neuronal plasticity, in fact, varies with age and is at its peak in pediatric age, when the brain is in full development.

Future prospective

BDNF is essential for proper brain formation during childhood and adolescence, influencing neuronal growth, the formation of new synapses, and brain plasticity [16]. In pediatrics, BDNF holds promising prospects for its potential influence on children's neurological development and health. As previously illustrated, studies suggest that BDNF is crucial for neurogenesis, neuronal survival, synaptic plasticity, and cognitive function. Based on existing literature and research on low-dose BDNF, its potential applications in pediatrics are conceivable in the following fields:

BDNF as an adjuvant in the treatment of SLD

In the context of Specific Learning Disabilities (SLD), neuroplasticity plays a crucial role in supporting intervention and compensation strategies [17]. An effective brain plasticity is pivotal for the modification of neural connections and functions to address the challenges posed by SLD, promoting the development of new skills and strategies. Some researchs suggest that lower BDNF levels may be associated with increased vulnerability to learning disabilities. However, the relationship between BDNF and learning disabilities is complex and still under study. It's still unclear whether decreased BDNF is a cause of learning disabilities or a consequence of learning disabilities [16]. The observational study promoted by Supino [9] highlights the effectiveness of low-dose BDNF to increase scholastic abilities resulting from an improvement in intellectual performances.

BDNF as an adjuvant in the treatment of Autism Spectrum Disorders (ASD)

In ASD, alterations in neuroplasticity are observed and are probably related to modifications of local or global connectivity, or changes in neuronal excitation and inhibition processes [18,19]. These alterations in plasticity can contribute to social and communication difficulties, repetitive and restrictive behaviors, and the variability in abilities and characteristics observed in people with Autism Spectrum Disorders. Preliminary studies indicate that BDNF levels may be altered in children with ASD [20], suggesting a possible role in pathogenesis and paving the way for potential targeted therapies based on low-dose BDNF administration.

BDNF as an adjuvant in the treatment of Attention Deficit Hyperactivity Disorder (ADHD)

Neuronal plasticity plays a crucial role in Attention Deficit Hyperactivity Disorder (ADHD) [21]. Specifically, brain plasticity can be harnessed to improve cognitive functions impaired in ADHD, such as attention, impulse control, and organization. The downregulation of BDNF signaling may be involved in the development of ADHD [22] and may be a factor to be considered in the search for more effective treatments. low-dose BDNF could be administered to support endogenous BDNF homeostasis.

In addition to these fields of application, which are elective based on the central role played by BDNF in their onset and progression, BDNF can also be indicated for the management of other manifestations of discomfort or pathologies which may affect the pediatric population [23]. Although depression and anxiety are more commonly studied in adults, research shows that low BDNF levels can affect the stress response and emotional stability in children, paving the way for potential interventions.

Research on BDNF as a pharmacological tool in pediatrics is ongoing, and further investigation is needed to fully understand its role and potential therapeutic applications. However, the availability of a pharmaceutical form of BDNF with proven efficacy and high compliance and safety profiles may constitute an essential factor for the setting up of clinical studies in the above-mentioned fields.

CONFLICT OF INTEREST

Prof. Sergio Bernasconi carries out consultancy activities for Guna S.p.a.

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