Intranasal nerve growth factor for prevention and recovery of the outcomes of traumatic brain injury

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Abstract

Traumatic brain injury is one of the main causes of mortality and disability worldwide. Traumatic brain injury is characterized by a primary injury directly induced by the impact, which progresses into a secondary injury that leads to cellular and metabolic damages, starting in the first few hours and days after primary mechanical injury. To date, traumatic brain injury is not targetable by therapies aimed at preventing and/or limiting the outcomes of secondary damage but only by palliative therapies. Nerve growth factor is a neurotrophin targeting neuronal and non-neuronal cells, potentially useful in preventing/limiting the outcomes of secondary damage in traumatic brain injury. This potential has further increased in the last two decades since the possibility of reaching neurotrophin targets in the brain through its intranasal delivery has been exploited. Indeed, molecules intranasally delivered to the brain parenchyma may easily bypass the blood-brain barrier and reach their therapeutic targets in the brain, with favorable kinetics, dynamics, and safety profile.

In the first part of this review, we aimed to report the traumatic brain injury-induced dysfunctional mechanisms that may benefit from nerve growth factor treatment. In the second part, we then exploited the experimental evidence relating to the action of nerve growth factor (both in vitro and in vivo, after administration routes other than intranasal) on some of these mechanisms. In the last part of the work, we, therefore, discussed the few manuscripts that analyze the effects of treatment with nerve growth factor, intranasally delivered to the brain parenchyma, on the outcomes of traumatic brain injury.

Key Words: intranasal delivery; nerve growth factor; pharmacology; traumatic brain injury

Introduction

Traumatic brain injury (TBI) is sudden damage to the brain resulting from external mechanical force, such as impact, severe acceleration/deceleration, and blunt force. The global highest incidence rates of TBI between 1990 and 2006 were in Central Europe, Eastern Europe, and Central Asia. Incidence, prevalence, and years of life lived with disability estimate for every cause of injury by age, sex, and location for 1990–2016 are available through the tool at http://ghdx.healthdata.org/gbd-results-tool. To date, there are no pharmaceutical therapies aimed at treating the multiple outcomes of TBI. Only palliative care are available that, according to the definition of the World Health Organization (https://www.who.int/health-topics/palliative-care), improves the quality of life of patients, facing the problem associated with life-threatening illness, through the prevention and relief of suffering by employing early identification, assessment and treatment of pain and physical, psychosocial and spiritual problems.

Nerve growth factor (NGF) is a neurotrophic peptide primarily discovered for its ability in regulating the growth and survival of peripheral sensory, sympathetic, and central cholinergic neurons. Fifty years of studies have then shown that NGF also targets non-neuronal cell populations in the central nervous system (CNS), modulating their behavior. This NGF peculiarity has laid the foundation for a broad line of pre-clinical and clinical studies aimed to investigate its pharmacological potential for the treatment of neurodegenerative and neurotraumatic diseases (Manni et al., 2021). This potential has further increased in the last two decades since it has been demonstrated the possibility of reaching neurotrophin targets in the brain through its intranasal delivery, which allows bypassing the blood-brain barrier and ensures rapid and extensive spreading of the drug through the brain parenchyma (Manni et al., 2021).

This review summarized the current knowledge about specific molecular mechanisms that are dysregulated in TBI and may be targeted and modulated by NGF treatment, highlighting the possible role that intranasal NGF could play in the prevention and/or recovery of acute and chronic TBI outcomes.

Search Strategy

The articles included in this review were retrieved by an electronic search of the PubMed database, up to 2021, for literature describing the role of NGF on TBI. Dozens of search sessions were conducted, using the phrases “traumatic brain injury” and/or “nerve growth factor” combined with one or more of following keywords (principal among others): neuroinflammation, microglia, astrocyte, beta-amyloid, tau, mitochondria, oxidative stress, excitotoxicity, energy metabolism, protein aggregation, protein misfolding, intranasal delivery, intracerebroventricular, intra-parenchyma, therapeutic target. Articles were included if they were deemed to contribute to the understanding of the link between TBI and NGF and the therapeutic potential of the latter in counteracting or overcoming the disabling outcomes of TBI.

Molecular Mechanisms Involved in Primary and Secondary Traumatic Brain Injury

TBI is made up of two closely connected phases. Primary injury occurs at the moment of trauma and is directly induced by the force of the impact which mechanically destroys blood vessels and cellular membranes, produces axonal sharing, and may damage the blood-brain barrier and meninges. Secondary injury is the direct result of primary injury and leads to cellular and metabolic damages triggered in the first few hours and days by primary mechanical injury (Ng and Lee, 2019).

TBI excitotoxicity and neuroinflammation

The development of neuroinflammation is one of the main effects of secondary injury that encompasses the activation of two types of glial cells, microglia (Eyolfson et al., 2020) and astrocytes (Zhou et al., 2020). These cells possess the peculiar characteristic of playing a role in both reparative and neurodegenerative processes (Kwon and Koh, 2020). This characteristic is due to the potential to assume different phenotypes, in response to environmental stimuli and the animal’s ability to adapt to the evolution of the early response to injury (Kwon and Koh, 2020). In acute post-damage phases, rupture of...
membranes results in the release of damage-associated molecular patterns, priming the brain resident microglia (Simion et al., 2017). Microglia cells are the primary mediators of the brain’s innate immune response and react to TBI through inflammation (Selkoe and Trojanowski, 2011), which can switch from anti-inflammatory (M2-like to pro-inflammatory (M1-like) phenotype and vice-versa depending on the different pathophysiological conditions of the microenvironment. Under physiological conditions, microglia exist in a quiescent state with branching micropseudopods. Upon activation, microglial cells are activated and assume the pro-inflammatory phenotype, with amoeboid morphology (Eylöffson et al., 2020), which has the primary function to eradicating cellular and molecular debris. In addition to pro-inflammatory cytokines and chemokines (e.g., interleukin-1β), activated microglia also produce other neurotoxic products after an injury such as nitric oxide and superoxide free radicals that generate reactive oxygen species (ROS) and reactive nitrogen species (Mannix and Whalen, 2020). ROS are generated in neurodegenerative conditions, such as Alzheimer’s disease (AD) and Parkinson’s disease (PD), through the mitochondrial electron transport chain (MITEC), which is associated with damage-associated molecular pattern signaling, inflammation, and amyloid plaque deposition (Simpson and Oliver, 2020). Interestingly, in vitro, microglia play a pivotal role in the clearance of amyloid-beta (Aβ)-plaque, after TBI it is involved in Aβ-plaque deposition both directly, as the active microglia exhibit increased expression of y-secretase (Nadler et al., 2008), and indirectly, as the microglia-released pro-inflammatory cytokines can upregulate the downregulation of Aβ-synthesis and y-secretase activity, concomitant with increased production of Aβ (Liao et al., 2004). In healthy individuals, astrocytes accomplish many structural and support functions. They regulate the cerebral perfusion, maintain the brain blood flow (Marina et al., 2020), preserve the blood-brain barrier integrity (Kadyr et al., 2020), and regulate neurotransmitter homeostasis, uptaking and metabolizing synaptic neurotransmitters releasing transmitters during their presynaptic axons to neurons (Mahmoud et al., 2019). Astrocytes respond to TBI by a process commonly referred to as reactive astroglia, which involves their structural and functional activation, including hypertrophy, increased expression of the intermediate filaments (nestin, vimentin, and glial fibrillary acidic protein) (Zhou et al., 2020). In response to TBI, astrocytes not only proliferate but also increase their size and form an astrogial scar that is a protective physiological mechanism to prevent further damage to other brain regions (Mira et al., 2021). However, astrogial scar often exacerbates negative outcomes such as excitotoxicity and neuroinflammation (Zbeks et al., 2018). Following TBI, astrocytes are responsible for spontaneous seizure and neurodegeneration (Shandla et al., 2019). They strongly contribute to the extracellular accumulation of excitatory amino acids, both by increasing their release due to cell breakdown and intracellular calcium accumulation and by decreasing the glutamate reuptake, which was found downregulated in GABAergic cells from TBI patients and also in rodent and TBI animal models (Goodrich et al., 2013). Glutamate accumulation also interferes with the physiologic neural function, which relies on the constant orchestration and integration of excitatory and inhibitory potentials. In astrocytes, glutamate is converted to glutaamine and returned to its presynaptic cell or neighboring y-amino butanonic acid (GABA) interneuron for conversion back to glutamate and then to GABA, respectively (Guerriero et al., 2018). Following TBI, astrocytes participate in the synaptogenesis and synaptic plasticity. First, β-secretase removes the fragment of APP’s transmembrane domain, favoring the translocation of Aβ from the cellular membrane to the extracellular space. Aβ plaques enhance inflammation, oxidative stress, and the development of cerebral microvascular disease, also promoting the loss of microglial cells and the senescence of neural stem/progenitor cells by affecting forebrain and hippocampal neurogenesis and eliciting a senescence response in associated astrocytes (Johnson et al., 2010). Microglia play a central role in Aβ accumulation after TBI (Mannix and Whalen, 2012), contributing to the phagocytic clearance of Aβ but can also promote its formation through the activation of γ-secretase, boosted by the microglial secretion of inflammatory cytokines (Mannix and Whalen, 2012). Nerve Growth Factor for Traumatic Brain Injury Management

The delivery of NGF in clinical studies has been pursued since 1980 for the treatment of diseases such as peripheral neuropathies or AD, to provide trophic support to damaged, NGF-responsive neurons of the peripheral and central nervous system (Aloe et al., 2012). Despite the relative failures
of these attempts, mainly related to the invasiveness of pharmacological delivery methods and the development of potentially harmful side effects, NGF has been studied, in more recent times, for its pharmacological potential, first of all in the field of neuroprotection (Eftimiadi et al., 2021), and then on the outcomes of neurotraumas (Manni et al., 2021). For the latter, the rationale for the development of NGF-based treatment protocols was founded on: the action of NGF on cellular targets in the CNS other than central cholinergic neurons (i.e. glial cells, immune cells, and the vascular endothelium) (Manni et al., 2021); preclinical and clinical evidence for a neuroprotective action of endogenous NGF after TBI (Da Silva Meirelles et al., 2017; Lin et al., 2021); the possibility of using delivery methods, namely intranasal inoculation, for targeting specific CNS structures, which guarantees low invasiveness associated with satisfactory safety profiles (Manni et al., 2021).

There is both preclinical and clinical evidence, which indicates how treatment with NGF can positively influence the evolution of clinical picture secondary to TBI (Manni et al., 2021). In recent years, the intranasal route of NGF administration has become increasingly important, so much so that it is currently the subject not only of preclinical studies but also of clinical trials in patients suffering from the outcomes of TBI (EudraCT N. 2019-002282-35, https://www.clinicaltrialsregister.eu/ctr-search/trial-2019-002282-35/IT; NCT01212679, https://www.clinicaltrials.gov/ct2/show/NCT01212679?term=intranasal+NGF&draw=2&rank=2) (Chiaretti et al., 2017). Table 1 summarizes all the manuscripts in which the effect of intranasally delivered NGF on the outcomes of TBI has been studied. This data highlights the in vivo in vitro cyclin D1-mediated cell cycle progression to the S phase (gray dotted lines). (C) NGF has a pro-angiogenic activity, stimulating the production and the release of VEGF. (D) Cell membrane TrkA challenge by NGF promotes upregulation of Bcl-2 and downregulation of caspase-3 limiting the mitochondria-mediated apoptosis (black solid lines). Furthermore, the challenge of TrkA receptors exposed to mitochondrial membrane negatively affects Ca2+ mitochondrial entry and ROS production/release. (E) NGF signaling limits tau hyper-phosphorylation, inhibiting aggregation in neurofilibrillary tangles (NFTs). Furthermore, NGF regulates the levels of APP phosphorylation, thus controlling APP/ TrkA binding, which in turn, by masking the β- and α-secretase cleavage sites, limits the formation of Aβ plaques. Black solid lines indicate direct action of the receptor challenge by NGF, gray dotted lines show pathways altered by the action of NGF. AB: Amyloid beta; APP: amyloid precursor protein; Bcl2: B-cell lymphoma 2; NFT: neurofilibrillary tangles; NGF: nerve growth factor; p75NTR: p75 neurotrophin receptor; ROS: reactive oxygen species; TLR4: Toll-like receptor-4; TrkA: tropomyosin receptor kinase A; VEGF: vascular-endothelial growth factor.

NGF and neuroinflammation

The first possible benefit deriving from the delivery of NGF to the brain for the therapy of TBI entails the reduction of neuroinflammation. NGF itself is an anti-inflammatory molecule, capable of modulating the synthesis of inflammation mediators and the phenotype of immune cells, during chronic inflammation in the peripheral field (Minnone et al., 2017). In the central nervous system, it partakes in the regulation of the metabolism and function of astrocytes and microglia, both cell populations being involved in the generation and perpetuation of inflammation (Colombo and Farina, 2016; Kwon and Koh, 2020). NGF regulates the phenotypes and functions of astrocytes and microglia (Pöyhönen et al., 2019). In vitro studies have shown that NGF stops the cell cycle of astrocytes in the G1 phase and initiates the activation of cyclin-dependent kinases (Cragnolini et al., 2012), an effect that limits the phenomenon of astrogliosis and the formation of the glial scar.

Intranasal administration of NGF in patients with TBI outcomes induces a significant increase in energy metabolism, as demonstrated by the increased uptake of the fluorodeoxyglucose tracer shown in the PET-CT scans (Chiaretti et al., 2017). Thus, an effect of NGF in the regulation of the metabolic interplay between astrocytes and neurons, dysregulated after TBI (Carpenter et al., 2015), should not be excluded, even if not yet directly demonstrated. Furthermore, the prevalent expression of the p75NTR, but not of TrkA was demonstrated in the primary culture of astrocytes (Cragnolini et al., 2012). Exogenous NGF could therefore compete with endogenous proNGF for the activation of this receptor on astrocytes, positively modulating astrocytic activation of this receptor on astrocytes, positively modulating astrocytic functions related to neuroreparative processes (Pöyhönen et al., 2019).

Additionally, NGF directs microglia toward a neuroprotective phenotype (Rizzi et al., 2018). Its regulation of the inflammatory response of primary mouse microglia was obtained via the activation of the high-affinity receptor TrkA (Fodeianaki et al., 2019). In this in vitro model, NGF downregulates LPS-induced production of pro-inflammatory cytokines and nitric oxide, inhibits TLR4-mediated activation of the NF-κB pathway (gray dotted lines), thereby downregulating the release of proinflammatory cytokines. (B) NGF-mediated activation of p75NTR interferes with astrocyte proliferation by blocking (black solid lines) cyclin D1-mediated cell cycle progression to the S phase (gray dotted lines). (C) NGF has a pro-angiogenic activity, stimulating the production and the release of VEGF. (D) Cell membrane TrkA challenge by NGF promotes upregulation of Bcl-2 and downregulation of caspase-3 limiting the mitochondria-mediated apoptosis (black solid lines). Furthermore, the challenge of TrkA receptors exposed to mitochondrial membrane negatively affects Ca2+ mitochondrial entry and ROS production/release. (E) NGF signaling limits tau hyper-phosphorylation, inhibiting aggregation in neurofilibrillary tangles (NFTs). Furthermore, NGF regulates the levels of APP phosphorylation, thus controlling APP/TrkA binding, which in turn, by masking the β- and α-secretase cleavage sites, limits the formation of Aβ plaques. Black solid lines indicate direct action of the receptor challenge by NGF, gray dotted lines show pathways altered by the action of NGF. AB: Amyloid beta; APP: amyloid precursor protein; Bcl2: B-cell lymphoma 2; NFT: neurofilibrillary tangles; NGF: nerve growth factor; p75NTR: p75 neurotrophin receptor; ROS: reactive oxygen species; TLR4: Toll-like receptor-4; TrkA: tropomyosin receptor kinase A; VEGF: vascular-endothelial growth factor.

Table 1 | Traumatic brain injury and intranasal nerve growth factor

| Citations | Species/age | Trauma | IN-NGF treatment | Effects |
|-----------|-------------|--------|------------------|--------|
| Tian et al., 2012 | Adult rat | Modified Fenney’s weight-drop model | 50 mg/die starting 6 h post-TBI for 14 d | Decreased TBI-induced AD deposits | Improved functional impairment Reduced risk of developing AD Decreased TBI-increased aquaporin-4 content and brain edema Reduced apoptosis by up-regulation of Bcl-2 and down-regulation of caspase-3 Attenuated TBI-induced Tau hyperphosphorylation Decreased IL-1β secretion No effects on functional motor recovery after TBI Improved functional PET/CT, SPECT/CT and MRI Enhanced voluntary movements, facial mimicry, phonation, attention and verbal comprehension, ability to cry, cough reflex, oral motility, feeding capacity, and bowel and urinary functions |
| Lv et al., 2013 | Adult rat | Modified Fenney’s weight-drop model | 5 mg/die starting 6 h post-TBI for 12, 24 and 72 h | Decreased TBI-induced AD deposits | Improved functional impairment Reduced risk of developing AD Decreased TBI-increased aquaporin-4 content and brain edema Reduced apoptosis by up-regulation of Bcl-2 and down-regulation of caspase-3 Attenuated TBI-induced Tau hyperphosphorylation Decreased IL-1β secretion No effects on functional motor recovery after TBI Improved functional PET/CT, SPECT/CT and MRI Enhanced voluntary movements, facial mimicry, phonation, attention and verbal comprehension, ability to cry, cough reflex, oral motility, feeding capacity, and bowel and urinary functions |
| Lv et al., 2014 | Adult rat | Modified Fenney’s weight-drop model | 5 mg/die for 3 d before TBI | Decreased TBI-induced AD deposits | Improved functional impairment Reduced risk of developing AD Decreased TBI-increased aquaporin-4 content and brain edema Reduced apoptosis by up-regulation of Bcl-2 and down-regulation of caspase-3 Attenuated TBI-induced Tau hyperphosphorylation Decreased IL-1β secretion No effects on functional motor recovery after TBI Improved functional PET/CT, SPECT/CT and MRI Enhanced voluntary movements, facial mimicry, phonation, attention and verbal comprehension, ability to cry, cough reflex, oral motility, feeding capacity, and bowel and urinary functions |
| Young et al., 2015 | Adult rat | Controlled Cortical Impact | Cardiac arrest following a severe TBI secondary to a car accident | Decreased TBI-induced AD deposits | Improved functional impairment Reduced risk of developing AD Decreased TBI-increased aquaporin-4 content and brain edema Reduced apoptosis by up-regulation of Bcl-2 and down-regulation of caspase-3 Attenuated TBI-induced Tau hyperphosphorylation Decreased IL-1β secretion No effects on functional motor recovery after TBI Improved functional PET/CT, SPECT/CT and MRI Enhanced voluntary movements, facial mimicry, phonation, attention and verbal comprehension, ability to cry, cough reflex, oral motility, feeding capacity, and bowel and urinary functions |
| Chiaretti et al., 2017 | Human (4 yr old) | Cardiac arrest following a severe TBI secondary to a car accident | 4 cycles of 100 mg/kg with 1-mon inter-treatment interval through a mucosal atomiser device, 6 mon after TBI | Decreased TBI-induced AD deposits | Improved functional impairment Reduced risk of developing AD Decreased TBI-increased aquaporin-4 content and brain edema Reduced apoptosis by up-regulation of Bcl-2 and down-regulation of caspase-3 Attenuated TBI-induced Tau hyperphosphorylation Decreased IL-1β secretion No effects on functional motor recovery after TBI Improved functional PET/CT, SPECT/CT and MRI Enhanced voluntary movements, facial mimicry, phonation, attention and verbal comprehension, ability to cry, cough reflex, oral motility, feeding capacity, and bowel and urinary functions |
NGF and protein aggregation

A further mechanism through which the acute and chronic outcomes of TBI can benefit from treatment with NGF pertains to the action of neurophins on tau pathology and metabolism (Li et al., 2016). The human brain has not only neurons, but also astrocytes, microglia, and oligodendrocytes that express Ngfr and TrkA, and -syn. NGF, damping pro-inflammatory cytokine production by microglia in the injured brain, is effective in reducing Aβ accumulation and cytotoxic effects by promoting its clearance by microglia (Capsoni et al., 2017). Further, a crosstalk between APP and TrkA pathways demonstrated, which may route APP metabolism toward a non-amyloidogenic fate. TrkA receptor binding to APP relies on a 20 amino acids long portion of APP, located in the juxtamembrane/extracellular domain and comprised between β- and α-secretase cleavage sites (Canu et al., 2017a, b). Thus, this occurs in the plasma membrane, endoplasmic reticulum (ER), Golgi, and endocytic vesicles where NGF controls the level of APP/TrkA association, by regulating the phosphorylation state of APP (Canu et al., 2017a, b; Figure 1). The higher concentration in the brain may shift the balance between amyloidogenic and non-amyloidogenic metabolism of APP toward the latter, as has been already described in a mouse model of AD (Cattaneo and Capsoni, 2019).

On the other hand, both endogenous and exogenous NGFs have been proven effective in regulating tau metabolism and post-translational modifications. Exogenous NGF regulates tau turnover in PC12 cells (Sadot et al., 1996) and its deprivation induces hp-tau (a prodromal of its aggregation in neurofibillary tangle) in the same in vitro model (Nuydens et al., 1997). Pharmacological stimulation of endogenous NGF or exogenous NGF delivery was effective in reducing tau phosphorylation in the brain of animal models of AD (Congdon and Sigurdsson, 2018). Interestingly, the relationship between proNGF and NGF in the nervous system plays a central role in the regulation of tau metabolism (Bedogni et al., 2003). hp-tau in vitro and in vivo, along with the upregulating effect of NGF on the expression of glycogen synthase kinase-3β (Shen et al., 2018). The increased production of proNGF by reactive astrocytes after trauma in the nervous system has been demonstrated (Sheng et al., 2020). Moreover, the interaction between proNGF and p75NTR participates in the development of the secondary brain damage after trauma (Sebastiani et al., 2015), while counteracting the activation of p75NTR or blocking proNGF provides neuroprotection and neurorestoration as a tool for therapeutic intervention on mouse models of AD (Montroll et al., 2020). Thus, it is conceivable that the exogenous delivery of NGF in TBI may shift the proNGF/NGF balance in favor of the mature form of NGF, attenuating, among others, the effects of proNGF on hp-tau.

Less is known about the relationship between NGF and -syn in TBI. The gene expression and protein production of the rat homolog of human -syn is up-regulated after transection of PC12 cells (Carito et al., 2012), a possible mechanism for NGF participation in presynaptic plasticity. An indirect relationship between normal NGF production in the brain and -syn metabolism is suggested by the evidence that NGF gene expression, as well as NGF-TrkA signaling, are reduced in diseases, such as Parkinson’s disease and dementia with Lewy bodies, characterized by the neurotoxic accumulation of -syn aggregates (Tong et al., 2009). However, to the best of our knowledge, a direct relationship between NGF/NGF-signaling deficiency and the pathological aggregation of -syn has not yet been demonstrated.

NGF and energy metabolism

NGF regulates several mitochondrial functions, thus it can positively affect the mitochondrial dysfunction generated by TBI (Simmons et al., 2020). NGF receptors are expressed in the mitochondrial compartment and TrkA activation protects isolated mitochondria of rat brain cortex from mitochondrial peroxidation by tert-butylhydroperoxide (T-BHP) induced by [Ca2+] (Carito et al., 2012). Moreover, NGF activates glutathione redox cycling and suppresses mitochondrial ROS production in cultured neurons (Kirkland et al., 2007). Continuous infusion of NGF in a rat model of TBI stimulates the activity of antioxidant enzymes in brain tissues, attenuating the neuronal damage induced by oxygen-free radicals, reducing the severe overload of [Ca2+], and stabilizing its homeostasis (Zhou et al., 2003; Figure 1). NGF also protects against neuronal death caused by mitocin C-treatment, regulating the gene expression of the transcriptional coactivator PGC-1α, a modulator of mitochondrial-related gene expression (Chen et al., 2012). Furthermore, a disruption of the AMPK response element-binding protein activity, such as that described in rat brain after TBI (Atkins et al., 2015), decreases the expression of a subset of mitochondrial genes and down-regulate mitochondrial respiration (Lee et al., 2005). Improving NGF-signalling induces, in turn, the phosphorylation of AMPK response element-binding protein (Sofroniew et al., 2001) with a subsequent decrease in the intracellular content of ROS and increased expression of the mitochondrial binding protein (Sofroniew et al., 2001) with a subsequent decrease in the mitochondrial response to trauma (Lv et al., 2014). In all of these studies, NGF is administered in a proximate way (Canu before or after) the trauma. The clinical data reported up to now (Chiaretti et al., 2017) are instead obtained by treating a stabilized and chronic picture, several months after the trauma. The study in question highlights how IN-NGF can improve parameters of perfusion, metabolism and brain function. The mechanisms by which IN-NGF, even after the chronicization of brain damage and the development of severe disabilities, is it however desirable that future NGF-based pharmacology for TBI will be developed as a tool for intensive care units, where the neuroprotective potential of NGF can be exploited to avoid the spread of injury from trauma and the consequent development of severe disabilities. The clinical data published so far show how IN-NGF can restore brain perfusion, as well as regulate the metabolic activity of brain cells, which was blunted following trauma (Chiaretti et al., 2017). Despite these promising data, mere metabolic reactivation may not be sufficient for the recovery of the connectivity and therefore the functions of the circuits involved in the damage. It is, therefore, necessary to explore the existing association between the use of NGF and therapies aimed at activating circuits that connect specific cortical areas with their sub-cortical counterparts (among others the cortical-striatal-thalamic-cortical loop), to avoid or recover the loss of motor and/or cognitive functions. Currently, stimulation through electrical currents (transcranial direct current stimulation) or magnetic currents (transcranial magnetic stimulation) appear to be promising, capable of modifying and/or stimulating the recovery of connectivity between the cortex and specific subcortical areas (among others the cortical-striatal-thalamic-cortical loop), to avoid or recover the loss of motor and/or cognitive functions. Currently, stimulation through electrical currents (transcranial direct current stimulation) or magnetic currents (transcranial magnetic stimulation) appear to be promising, capable of modifying and/or stimulating the recovery of connectivity between the cortex and specific subcortical areas (among others the cortical-striatal-thalamic-cortical loop), to avoid or recover the loss of motor and/or cognitive functions.
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