Rassegne

Nerve growth factor in the psychiatric brain

Il fattore di crescita nervosa nelle patologie cerebrali psichiatriche

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SUMMARY. The nerve growth factor (NGF) belongs to a family of proteins named neurotrophins, consisting of NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5 and NT-6. NGF regulates a large number of physiological mechanisms that result in neurotrophic, metabotrophic and/or immunotrophic effects. Neurodegenerative diseases, including Alzheimer disease, psychiatric disorders (e.g. depression and schizophrenia) and brain parasitic infection have in common the effect of changing the brain levels of neurotrophins, in particular NGF. The contribution of both NGF and its receptor TrkA in such events and the recent promising results of NGF based therapies are here presented and discussed.

KEY WORDS: NGF, Alzheimer disease, depression, brain, parasite, alcohol, neurodegeneration.

RIASSUNTO. Il fattore di crescita nervosa (NGF) appartiene a una famiglia di proteine chiamate neurotrofine, costituita dall'NGF, il fattore neurotrofico di derivazione cerebrale (BDNF), la neurotrofina-3 (NT-3), NT-4/5 e NT-6. L'NGF regola un gran numero di meccanismi fisiologici che provocano effetti neurotrofici, metabotrofici e/o immunotrofici. Le malattie neurodegenerative, tra cui la malattia di Alzheimer, il danno indotto dall'alcol, i disturbi psichiatrici (per es., depressione e schizofrenia) e l'infezione parassitaria cerebrale hanno in comune l'effetto di modificare i livelli cerebrali di neurotrofine, in particolare l'NGF. Vengono qui presentati e discussi il contributo dell'NGF e del suo recettore TrkA in tali eventi e i recenti promettenti risultati delle terapie basate sull'NGF.

PAROLE CHIAVE: NGF, malattia di Alzheimer, depression, cervello, parassita, alcol, neurodegenerazione.

INTRODUCTION

Nerve growth factor (NGF), firstly isolated in 1956, is a neuropeptide regulating the survival and proliferation of selected neurons[1] in central and peripheral nervous system. Actually, NGF and its comparative molecules collectively known as neurotrophins are well documented mediators of multiple biological events in health and disease[2-4], varying their effects from that neurotrophic[5,6] through immunotrophic[7,8] to metabotrophic[9,10]. Thus, NGF is implicated in the pathogenesis of a large spectrum of neuronal diseases (Alzheimer's and other neurodegenerative diseases) and non-neuronal disorders (atherosclerosis, obesity, type 2 diabetes mellitus and other cardiometabolic disorders)[8,10-14]. Particularly in the brain, NGF plays a key role in several diseases leading to cell death and/or neurodegeneration during development or aging[15-21]. NGF is synthesized as a 130 kD precursor (proNGF) that is a complex of three proteins: α-NGF, β-NGF and β-NGF the latter acting as a serine protease that cuts the subunit releasing the 26 kD mature NGF; this latter form is biologically active as a multifunctional signaling molecule[8,22,23]. NGF binds two types of receptors: the low-affinity NGF receptor p75 (LNGFR/p75^{NTR}) and the tropomyosin-related kinase A (TrkA)[22,24]. TrkA receptor binding produces the homodimerization of the receptor and the autophosphorylation of the tyrosine residue of the cyto-

plasmic tail. The site of the TrkA phosphorylation is a docking site for the Shc adaptor protein that is in turn phosphorylated beginning several intracellular pathways involved in cell survival[22,25]. One of these involves the activation of the serine/threonine kinase Akt that develops, by the recruitment on TrkA receptor complex, the growth factor receptor bound protein 2 (Grb2) and of another docking protein, the Grb2-associated Binder1 (GAB1). This structure activates phosphatidylinositol-3 kinase (Pl3K) that, in turn, activates Akt. Inhibiting or blocking the activity of Pl3K or Akt may elicit the death of sympathetic neurons in culture even after NGF administration; instead. when both kinases are constitutively expressed, neuronal cells can survive without NGF[26,27]. NGF is involved primarily in the growth, proliferation, and survival of sympathetic and sensory neurons undergoing apoptosis if NGF is missing[28-30].

Another pathway of NGF mediated neuronal survival involves the mitogen-activated protein kinase (MAPK). This pathway leads to the activation of the membrane-associated G protein Ras that phosphorylates the serine/threonine kinase Raf. This phosphorylation activates the MAPK cascade regulating transcription[25]. Both pathways give rise to phosphorylation of the cyclic AMP response element binding protein (CREB), a transcription factor that translocates into the nucleus controlling the expression of anti-apoptotic genes. NGF plays also a delicate role in the fine regulation of learning and memory abilities during development, adult life and aging by influencing synaptic plasticity, tissue growth and attrition in crucial areas of the limbic system[4,31-35]. The present review amplifies and updates findings for the contribution of NGF in the pathogenesis and therapy of neuropsychiatric disorders, in which cognitive and memory disorders are prevalent[36-38] (Figure 1).

BRAIN PLASTICITY, BEHAVIOR AND NGF

Growth factors regulating the pathways involved in normal brain development have a significant role in the pathophysiology of mental disorders including those with a neurodevelopmental origin. Significant changes in growth factors' levels were observed in patients and in animal models where altered levels of these proteins were found to induce psychiatric behavior[34,39-46]. During the embryonic and postnatal stages, psychophysical stressors altering the environment can modify the standard brain development opening the way in the adulthood to psychopathologies such as depression, alcohol abuse and drug dependence, schizophrenia, anomalous social behavior[47-52], conditions that will require in adulthood, very important and expensive psychosocial behavioral to improve the life and abilities of patients with several mental disorders[53-55]. Neurotrophins, together with hypothalamic-pituitary-adrenal (HPA) axis, play a pivotal role in controlling brain plasticity and behavior, particularly in crucial periods during ontogenesis, when forming brain is extremely sensitive to external stimulations[56]. In rat models, stress during pregnancy increases fetal and maternal plasma corticosterone causing hypothalamic-pituitary-adrenal (HPA) axis dysregulation and a prolonged elevation of plasma glucocorticoids in response to stressing events[49,50]. Neurotransmitter activity and synaptic development are altered by increased activity of corticosterone and corticotrophin-releasing hormone (CRH) in the developing brain eliciting behavioral disturbances in adulthood. Indeed, rats exposed to gestational stress develop depressive-like behaviors and hyper-anxiety combined with the amygdala increase in CRH activity[49,50]. Quite interestingly, changes in the HPA axis de-

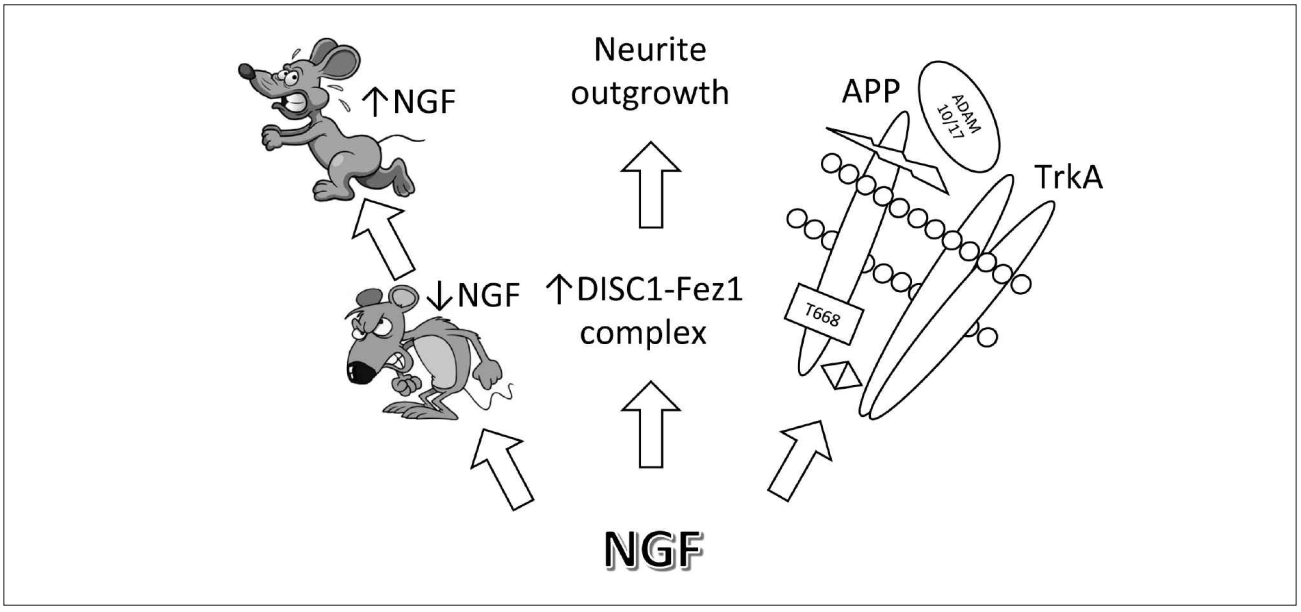

Figure 1 (From left) NGF regulates social behavior in male mice; NGF stimulation upregulates DISC1-Fez1 complex promoting neurite outgrowth; NGF stimulation elicits APP/TrkA binding favoring the non amyloidogenic pathway.

scribed in prenatally stressed mammals were also described in humans with endogenous major depression[57-59]. Significantly, it has been proven that ectopic expression of Brain Derived Neurotrophic Factor (BDNF) *in vivo* increases CRH, whereas reduced expression of BDNF, or its receptor TrkB, decreases CRH expression and normal HPA functions[60]. Also during early postnatal life, nervous system development is sensitive to stressing events, and this contributes to inter-individual differences in vulnerability to psychopathologies. During the postnatal development of CNS, the neural network undergoes deep rearrangements[61,62] and is particularly susceptible to external stimuli. In this period, NGF and BDNF regulates brain plasticity for a better adaptation to the environment[8,63]. For example, mice grown in a nest with caregiving mother show better social behaviors and skills if compared to mice raised in standard laboratory conditions. These socially enriched mice show higher levels of NGF and BDNF in the hippocampus and hypothalamus[64,65]. In the mouse, NGF is secreted and produced also by the submaxillary salivary glands[66,67]. Neurobehavioral studies have demonstrated that aggressive behavior in adult male CD-1 mice induces a remarkable release of NGF from salivary glands into the bloodstream. These findings demonstrated a link between the NGF serum concentration and the achieved status in the fighting were subordination almost double serum levels of NGF compared to dominant mice[68-70]. Other works have assessed the correlation between increased NGF levels and subordinate behavior[6,71]. In male mice, NGF chronic administration decreased aggressive behavior[70]. NGF release was also activated by psychosocial stress that depends on interspecific interactions while physical stressors may produce less evident effects[64,65]. Intermale aggressive behavior increases the synthesis of NGF in the hypothalamus[72] likely because the NGF levels depends on psychological stimuli associated with anxiety, fear, hormones and neurotransmitters release to integrate the neuroendocrine response and the behavior in order to confirm the physiological homeostasis[6,8,73].

ALCOHOL-INDUCED BRAIN CHANGES AND NGF

Numerous human studies have shown that binge or chronic alcohol consumption as well as alcohol drinking during gestation or lactation are a central inducing-cause of brain alterations[74] including mental retardation in adults, adolescents and children[75-84]. As for the alcohol consumption during pregnancy, the plethora of consequences in children induced by alcohol are described as Fetal Alcohol Spectrum Disorders[85-88]. It has been clearly shown that chronic or binge alcohol consumption as well as alcohol exposure during fetal development may significantly impair neurotrophic factors production in the brain also affecting the expression of their receptors[89-96]. NGF is probably the most important neurotrophin involved in ethanol-induced toxicity. Many brain studies have disclosed that NGF and its receptors are altered during prenatal/acute/chronic alcohol abuse[97-102]. In particular, as previously revealed[97] alcohol inhibits the expression of endogenous extracellular signal-regulated kinase (ERK) and the phosphatidylinositol-3-kinase (PI3K)[103-105]. Furthermore, data evidenced several epigenetic roles of NGF and BDNF in regulating the serum levels of interleukin-6 (IL-6), of tumor necrosis factor-α (TNF-α) and the symptomatology of alcohol dependence[106-108]. In particular, it has been shown an elevation in NGF and IL-6 serum levels following alcohol consumption as well as an association between BDNF, TNF-α serum levels and the history of alcohol abuse, suggesting that changes in the methylation of neurotrophins genes may contribute to the development of alcohol dependence by affecting relevant downstream signalling cascades[97,108].

SCHIZOPHRENIA AND NGF

Data from human and animal models suggest a function of neurotrophins also in the vulnerability to stress-related neuropsychosis[109,110]. Increasing literature evidences demon-

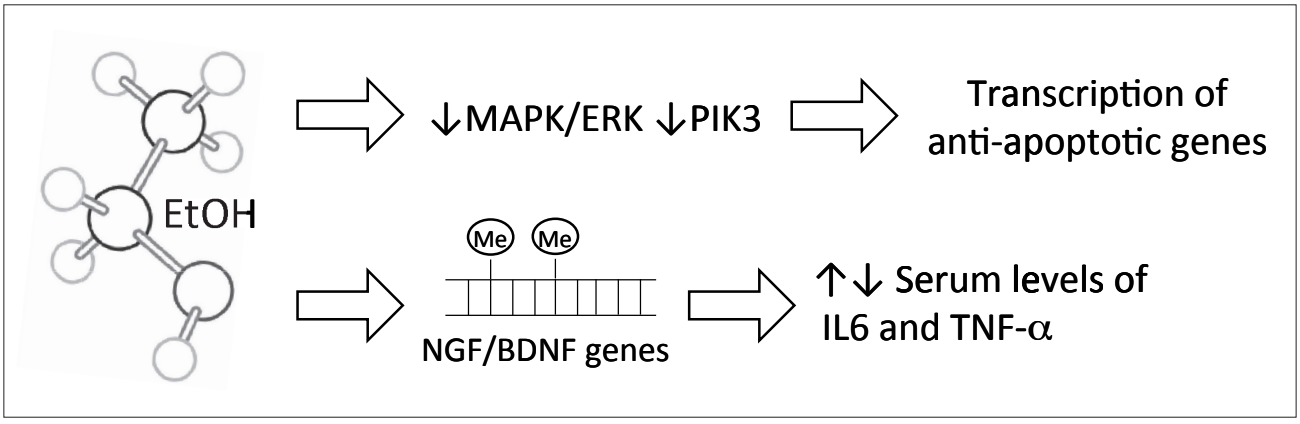

Figure 2 Alcohol alters brain levels of NGF and its receptors and impair MAPK/ERK and PIK3 pathways that control the expression of anti-apoptotic genes; EtOH alters methylation pathway of NGF and BDNF genes, that, in turn regulate serum levels of IL6 and TNF-alpha.

strate that in psychopathological conditions the constitutive levels of neurotrophins are disrupted in both brain and plasma. In schizophrenics without neuroleptic therapy, NGF plasma levels are lower if compared to healthy subjects[40]. Haloperidol administration in human and mice drastically depletes NGF plasma levels[111] inducing sedation. By contrast, the atypical antipsychotics olanzapine, clozapine, and risperidone induced higher levels of plasmatic NGF compared to non-medicated first-episode psychotic patients[112]. The crucial role played by NGF during cholinergic neurons development for regulating learning and memory could explain the vulnerability of the schizophrenic brain and the cognitive alterations observed in this disease; low levels of NGF may trigger consequent neurodevelopmental deficits. In schizophrenics, brain imaging studies evidenced modifications in selected brain areas such as prefrontal, temporal and anterior cingulum involved in affective-cognitive processes[113-116]. Furthermore, the post-mortem examination of schizophrenic brains disclosed a reduction of cell proliferation in the entorhinal cortex, prefrontal region and anterior cingulate that could elucidate the onset of the disease[40,114]. In animal models, behavioral deficits associated with schizophrenic symptoms[117] may be caused also by maternal exposure to risk factors such as alcohol drug abuse and obstetric complication[118] that inhibit entorhinal and cortical neurogenesis[56].

Schizophrenia is a multifactorial mental disorder elicited by social, genetic and developmental factors[119,120]. Disrupted-in-schizophrenia 1 (DISC1)[121,122] which is expressed by neurons of the hippocampus, cerebral cortex, cerebellum and olfactory bulb in the rat brain is known to have a role in this disease[123,124]. The coded protein binds other proteins including fasciculation and elongation protein zeta-1(Fez1), which is involved in axonal outgrowth. DISC1-Fez1 molecular complex colocalizes in the growth cone of neurite proposing a function in the extension process also confirmed by the fact that these proteins are expressed in early ontogenic stages. In PC12 cells, neurodifferentiation following NGF stimulation was observed a drastic increase in Fez1 evidencing that NGF regulates the neurite outgrowth and extension upregulating DISC1-Fez1 complex[125]. When DISC1 translocation prevents the complex being formed, neurite extension cannot occur leading to an immature brain development and supporting the hypothesis that schizophrenia is basically a neurodevelopmental disease[125].

NGF AND MAJOR DEPRESSION DISORDER

Major depression disorder (MDD) is one of most common brain disorders that implicates depression, fatigue, a decrease in concentration, scarce interest in normal daily activities and suicidal intentions[126]. Several neurotrophins including NGF and BDNF are involved in MDD pathogenesis[127-129]. MDD patients display reduced serum NGF; the same diminution was observed in hippocampus mRNA and protein expression of NGF, BDNF and their receptors in post-mortem brain examination[130,131]. A chemical mediator of the NGF decrease is Interferon-gamma (IFN-γ), as was demonstrated in IFN-γ knockout mice models that develop a depressive-like behavior, increased immobility and parallel reduction of NGF levels[132,133].

The administration of NGF in rats reduces the expression of the cholinergic gene CHRNA5 and prokineticin receptor1 (PROKR1) mimicking the effects of fluoxetine and amitriptyline therapy. The improvement of the depression-like behavior is achieved by modulating the expression of several genes in the amygdala and hippocampus[134].

NGF AND ALZHEIMER DISEASE

Alzheimer disease (AD) is the most common type of dementia in the old age. AD is characterized by early alterations of synaptic proteins and synaptic functions with the formation of abnormal tau and amyloid proteins. After the discharge in the intracellular space of these abnormal proteins starts the massive deposition of senile plaques (SP) of the β-amyloid (Aβ) peptide and the aggregations of neurofibrillary tangles (NTF) originating from the hyperphosphorylated tau protein. According to the literature, during the progression of the disease, a serious and progressive memory deficit associated with a massive neuronal loss and a total deterioration of the brain homeostasis were observed[135-137]. The basal forebrain cholinergic neurons (BFCN) innervating the hippocampus and the cerebral cortex, brain areas controlling memory and attention are quite susceptible to the AD and the first to be involved[138,139].

In the pathophysiological mechanisms of AD, neurotrophic factors play a fundamental and protective role. Neurotrophins control plasticity, differentiation, pruning and survival of the BFCN and the signaling of these peptides is extremely altered in the course of the disorder[140]. NGF is most studied neurotrophin for its role in AD development[140,141].

NGF signaling in BFCN involves three types of receptors: the high-affinity tropomyosin-related kinase A (TrkA), the low-affinity $p75^{NTR}$ neurotrophin receptor ($p75^{NTR}$) and sortilin. NGF binding to its receptor TrkA activates the pathway signaling of cell survival, while in the presence of minor levels of NGF and/or TrkA the precursor form of NGF (pro-NGF) binds to the low-affinity p75 receptor and/or to sortilin determining an apoptotic signal leading to neurodegeneration[142,143].

Indeed, NGF release by cortical and hippocampal neurons is involved in the processing of amyloid precursor protein (APP) to produce the soluble and neuroprotective APP known also to be a strong inhibitor of the enzyme β-secretase 1 (BACE1) that regulates APP amyloidogenic cleavage[144]. Recent studies in cellular and animal models have demonstrated the protective role of NGF against AD induced neurodegeneration. Moreover, there is strong evidence that the changes in NGF signaling is one of the earliest events in AD beginning[145]. In a cellular model such as the primary hippocampal neurons, NGF removal generates an Alzheimer's like molecular condition with the development of Aβ-amyloid plaques and aggregations of neurofibrillary tangles[146]. Also, an antibody pointed to NGF induces similar phenotypic effects and neuronal deficits in the AD11 mouse model of AD[147]. The neuroprotective role of NGF observed *in vivo* and *in vitro* is exerted by the regulation of APP processing[144,148].

NGF stimulation of primary cholinergic septal neurons elicits the binding of TrkA receptor to APP. This binding

blocks the APP phosphorylation at the threonine 668 (T668) residue in the cytosolic tail of the protein. T668 phosphorylation is an APP post-translational modification inducing APP cleavage by the enzyme BACE1 that controls the amyloidogenic pathway of maturation[144].

During the development of AD, NGF deficit is associated with an increased amyloid generation, initial synaptic alteration as observed in mild cognitive impairments and early AD. The newly generated amyloid inhibits the endocytosis of the NGF/TrkA complex and this negative feedback loop marks the AD beginning[135].

In rat models of aging, increased levels of pro-NGF and p75NTR in the hippocampus and prefrontal cortex are associated with a deficit in spatial learning and memory[149]. An elevation in pro-NGF levels was also discovered in mild cognitive impairment and AD patients and during the examination of postmortem AD brain[145]. The alteration of the NGF signaling is an early event during the progression of the AD as disclosed by studies on animal and cellular models[150]. In animal models, as aged rats, the blocking of NGF/TrkA signaling induces a serious deficit in cholinergic function[151,152]. In animal models of AD, the perturbation of NGF signaling leads to a general loss of central cholinergic activities[153]. The effect of the imbalance in NGF/TrkA signaling leads to a pathological APP processing[146]. In transgenic mice lacking APP/TrkA interaction, a severe degeneration of cholinergic neurons and cognitive deficits were described[154]. These studies support the hypothesis of the *neurotrophic model* of AD development. Indeed, the reduction of NGF level and the increase in pro-NGF would activate the synaptic failure and the abnormal amyloid and tau deposition creating a neurodegenerative cascade[27,155].

New pieces of evidence corroborate the relationship between NGF and APP processing based on a physical interaction between APP and NGF receptors[150]. The APP iuxtamembrane region containing the β and β-secretase cutting sites and matches the first 16 aa of A peptide is sufficient for the interaction with TrkA and the binding to p75NTR[156]. APP and TrkA proteins localize in the plasma membrane, endoplasmic reticulum (ER), Golgi and endocytic vesicles where the peptides form homodimers[150].

In primary septal neurons, NGF treatment elevates APP/TrkA complexes in ER and Golgi without increasing proteins level probably because NGF disrupts this association through the control of the APP phosphorylation[148,150]. NGF withdrawal induces a decrease in APP/TrkA complexes and the same pattern is observed with cell death inducers such as A peptide and rapamycin. Furthermore, NGF, supporting APP/TrkA complexes, inhibits the APP/APP homodimers that are more prone to amyloidogenic processing carried out by β- and γ-secretase[148,150].

The APP post-translational alterations are crucial for the physiological or amyloidogenic pathways[157]. The phosphorylation of the threonine residue 668 (T668) is related to amyloid production, synaptic deficits and apoptosis[158,159]. This phosphorylation inhibits APP/TrkA binding and elevates Aβ production in cholinergic neurons *in vivo* and *in vitro*. A recent finding has shown that NGF can reduce APP T668 level in cultured BFCN. It is also possible that the detachment of APP from TrkA is due to changes in the conformation of APP upon its phosphorylation[148].

In the physiological anti-amyloidogenic pathway, binding of NGF to TrkA elicits TrkA phosphorylation and TrkA docking of the signaling adaptor SH2 containing sequence C (ShcC). Activated ShcC blocks c-Jun N-terminal kinase (JNK), a ser/thr APP kinase, preventing the APP phosphorylation at threonine residue 668 (T668). Since TrkA can bind only APP molecules not phosphorylated at T668, the NGF decrease of APP p668 levels arouses ATP-TrkA binding, and the TrkA mediated trafficking of APP to the plasma membrane and Golgi apparatus and the preferential cleavage of APP by the neuronal b-secretases ADAM10-17. Contrariwise, the reduced availability of mature NGF and/or the reduced expression levels of TrkA result in pre-apoptotic signals that stimulate JNK, increase APP pT668 and disturb APP-TrkA interaction favoring the β-secretase 1 amyloidogenic pathway[148].

Beneficial role of NGF on cholinergic neurons is carried out downregulating T668 phosphorylation, stimulating APP/TrkA binding and trafficking the complex to subcellular compartments, as Golgi complex, that is depleted of the amyloidogenic enzyme like BACE1. Tau pathology is also implicated in non-Alzheimer disorder pathophysiology (suspected non-Alzheimer disease pathophysiology - SNAP). In AD, many studies have demonstrated a synergism between tangles and plaques, with abnormal tau that enhances Aβ toxicity and *vice-versa*[160,161].

NGF can control the steady-state levels and the post-translational maturation of tau that is cleavage, ubiquitination, and phosphorylation[162,163]. NGF withdrawal brings to tau hyperphosphorylation and to abnormal cleavage of the N terminal fragment of the protein lacking the microtubule-binding domain. The same tau fragment was also observed in animal AD models with impaired NGF signaling[162,164].

NGF IN AUTISM SPECTRUM DISORDER

Autism Spectrum Disorder (ASD) includes deficits in social communication and repetitive behavioral patterns. Genetic perturbations play a critical role in ASD with hundreds of genes associated with it. However, such aberrations do not converge in a common molecular pathway. Genetic investigations and behavioral observations show the overlapping of ASD with other psychiatric diseases, such as bipolar disorder, schizophrenia, and Attention Deficit and Hyperactivity Disorder (ADHD)[165,166]. Investigating differential alternative splicing (DAS) in the blood of 2-4 years old boys with a diagnosis of ASD, it was disclosed significant DAS changes in several genes of NGF receptors and signaling if compared to controls[167]. In another study, Lu et al. showed several NGF single-nucleotide polymorphism associated with deficits in nonverbal communication, one of the main autistic trait[168].

NGF AND BRAIN PARASITOSIS

The role of NGF in parasitic disorders is not yet clearly recognized but some information emerged from investigations on *Trypanosoma cruzi* and *Schistosoma mansoni* brain neuroinflammation.

Chagas disease or American trypanosomiasis is a tropical parasitic disorder caused by the protist *Trypanosoma cruzi*

spread to humans and mammals by the insects "kissing bugs" of the subfamily Triatominae[169,170]. During the early phase of the disease, symptoms are not present or are mild with headache, fever and swollen lymph nodes. Only the 40% of people develop severe symptoms of the disorder after 30-40 years from the infection. Symptoms may include heart failure due to enlargement of heart ventricles, or enlarged esophagus or colon (megaesophagus or megacolon). This disease affects about 6,6 million people mostly in Central America and Mexico[171].

Trypanosoma cruzi releases the NGF mimetic neurotrophin called PDNF (parasite-derived neurotrophic factor), a membrane-bound neuraminidase/trans-sialidase that can bind TrkA but not $p75^{NTR}$[5,172]. Trypanosoma infection in the CNS is usually asymptomatic and neuronal examination has revealed some sort of neuroprotection and neurons preservation even near foci of inflammatory cells or parasite nest[173]. Neuroprotection and neuroregeneration were also discovered in animals with chronic or acute infection[174-177]. Signs of sprouting of sympathetic and parasympathetic nerve fibers were observed in the heart and colon with elevated levels of several neurotransmitters[178,179]. These findings have shown that *Tripanosoma cruzi* PDNF is a functional simulator of NGF that can bind TrkA, can produce TrkA autophosphorylation and can trigger Pl3K/Akt and MAPK-Erk1/2 signaling eliciting cell survival and neurite outgrowth. Quite interestingly, the inability of binding $p75^{NTR}$ inhibits the cell-death signaling pathway[180,181]. From and evolutionary and adaptive point of view, given the critical role of TrkA in neuronal maintenance, the parasitic invader utilizes TrkA to reduce tissue damage, to stimulate protective mechanisms and tissue repair maximizing host-parasite equilibrium in order to prolong parasitism. This mechanism could reveal a general and unexpected model of host-parasite interaction[180].

Neuroschistosomiasis refers to the *Schistosoma mansoni* infection of the central nervous system and depends basically on the presence of parasite eggs in the nervous tissue and on the host immune response. After eggs deposition, the mature embryo secretes and excretes antigenic and immunogenic mediators that start the granulomatous reaction[182,183]. A large number of eggs and granulomas in CNS areas disrupts adjacent tissues by the inflammatory reaction and the mass effect[182-186]. In mice infected that manifest granulomas in several CNS areas it was found an increase in NGF levels in the cortex, hypothalamus, and brain stem with paw hyperalgesia[187,188]. This murine model of chronic infection suggests that the neuropathological and sensory deficits observed in human infection are associated with abnormal NGF levels and/or activity in peripheral and central nervous systems caused by the local growth of granulomas[67,189-195].

NGF-based therapy

The neuroprotective action of NGF in animal models of neurodegenerative disease justified the beginning of clinical trials of NGF therapy in humans for several brain diseases including AD, schizophrenia[196,197].

Encouraging results were disclosed in the basal forebrain for individuals with implanted connective cells engineered to synthesize and secrete NGF. In these studies, enhanced cell size and new neural fibers were observed. Furthermore, cells showing signs of pathology and protein clumps inside the cell body maintained a healthy size, activated prosurvival signaling and manifested stress resistance[198]. To potentiate the NGF expression, modified viruses containing the NGF gene were directly injected in the basal forebrain[198,199]. The protective role of NGF and its progressive decrease in AD is the rationale of the NGF therapy in which the administration of exogenous NGF could counteract the basal forebrain neurodegeneration[200]. First promising results were obtained in rodents where intracerebral NGF infusion was neuroprotective for cholinergic neuronal cells. Also in AD models like APP/PSI transgenic mouse, the less invasive treatment as ocular or nasal NGF administration decreased beta-amyloid deposition[201]. In AD patients, NGF phase I gene therapy has shown axonal sprouting without side effects[201].

Abnormalities in NGF levels or signaling and the resulting impairments in neuroplasticity and cognitive abilities were also observed in psychiatric disorders such as bipolar disorders, schizophrenia, alcohol use disorders, major depression and autism. In schizophrenic patients treated with atypical antipsychotic drugs, NGF levels increased leading to a reduction of negative symptoms[152,202]. In bipolar disorders, NGF decreases during the parossistic state but may be rescued by lithium administration by potentiating NGF concentration in the frontal cortex, hippocampus, and amygdala[203,204]. In children with Rett syndrome, a disorder causing a delay in development and cognitive abilities resembling autism, therapies with NGF-like activity drugs may improve motor and cortical functions by also potentiating social interactions[205].

NGF AS CLINICAL BIOMARKER OF PROGNOSIS AND DIAGNOSIS OF PSYCHIATRIC DISORDERS

Variations in the serum NGF concentrations have been associated with the pathogenesis and clinical symptoms of several psychiatric disruptions, such as: anxiety disease, mood disorders, schizophrenia, Alzheimer and others. Indeed, fluctuations in the serum levels of NGF and other growth factors are usually connected to the clinical severity and progression of mental illnesses[46]. Several experimental evidences clearly demonstrate that the serum analysis as biomarkers of neurotrophins, including NGF, could be quite useful to early disclose the onset of several psychiatric disorders[46]. The working hypothesis was based on the fact that the combined investigation of different neurotrophins could be utilized to establish whether or not such neuropeptides as biomarkers of psychiatric disorders or biomarkers of some cognitive, emotional and social deficits[46]. Available data in the literature[19,206,207] clearly stress the point that neurotrophins and other growth factors are *i)* involved in the pathophysiology of psychiatric pathologies with neurodevelopmental origin; *ii)* in animal models selected changes in the serum presence of neurotrophins and other growth factors may elicit psychiatric-like behaviors; *iii)* people affected by neuropsychiatric disorders may display significant modifications in certain neurotrophins and/or other growth factors; *iv)* disruptions in the blood levels of neurotrophins and/or other growth factors may be associated with the severity of the brain disease, changes in the behavior, poor social abilities, and cognitive performance decline. In particular, peripheral changes in

neurotrophins as NGF and/or BDNF resulted connected with functional impairments in cognitive and emotional processing whereas peripheral modifications in other growth factors as EGF, VEGF and FGF demonstrated subtle roles of these biomarkers in motor processing[46]. However, as suggested by different researchers, at the present time do not exist specific and reliable biomarkers for each psychiatric disorder, but a combined screening of biomarkers appears the only alternative to improve the early diagnosis and clinical follow-up of psychiatric individuals[46].

CONCLUSIONS

Many years of research have recognized the important trophic and homeostatic role of NGF that exerts its modulatory functions on endocrine, nervous, adipose and immune system activities. Future studies, through an extended knowledge of the molecular mechanisms of action of this small and versatile peptide, will help to develop effective brain therapeutic strategies for many clinical sectors including those involving neurodegeneration, neuroinflammation and neuroadipocrinology[2,20,23,180,181].

Conflicts of interests: authors do declare no conflicts of interest.

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