



NERVE GROWTH FACTOR IN BRAIN DISEASES

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The nerve growth factor (NGF) belongs to a family of proteins termed neurotrophins, consisting of NGF, brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5 and NT-6. Today, NGF is well recognized to mediate a large number of trophobiological actions resulting in neurotrophic, immunotrophic and/or metabotropic effects. The pathobiology of neurodegenerative diseases, including Alzheimer disease, psychiatric disorders (e.g. depression and schizophrenia) and brain parasitic infections have in common the effect of altering the brain levels of neurotrophins and in particular NGF. The involvement of NGF and its TrkA receptor in these pathologies and the recent promising results of NGF therapies are presented and discussed.

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INTRODUCTION

At the end of the nineteenth century, it was envisaged by Santiago Ramon y Cajal but has not been proven that life at the neuronal level requires trophic support. By a rare combination of scientific reasoning and intuition, the proof was obtained by Levi-Montalcini, Viktor Hamburger and Stanley Cohen in the early 1950's in the Washington University in St Louis, MO, United States, where the first cell growth factor, namely nerve growth factor (NGF), was discovered. This was embodied in a conceptual framework of the neurotrophic theory, which reveals a pivotal role of effector cells in the control of neuronal differentiation, survival and function *via* production of NGF. Today, NGF and its relative molecules collectively designated neurotrophins are well recognized as mediators of multiple biological phenomena in health and disease, ranging from the neurotrophic through immunotrophic to metabotropic effects. Consequently, NGF is implicated in the pathogenesis of a large spectrum of neuronal disorders (Alzheimer's and other neurodegenerative diseases) and nonneuronal disorders (atherosclerosis, obesity, type 2 diabetes mellitus and other cardiometabolic diseases).

The present review updates and enlarges evidences for the involvement of NGF in both pathogenesis and therapy of various brain diseases (Tabl. 1).

Table 1. *Potential role of nerve growth factor in the pathogenesis and therapy of brain diseases*

Neurological diseases

Alzheimer's disease, Mild cognitive impairment, Huntington's disease, Parkinson's disease,
Parasitic infections, Human immunodeficiency virus-associated dementia, Epilepsy, Down syndrome, Rett syndrome

Psychiatric diseases

Depression, Schizophrenia, Eating disorders (anorexia nervosa; bulimia nervosa), Autism,
Attention deficit and hyperactivity disorder (ADHD)

NERVE GROWTH FACTOR

Nerve growth factor (NGF), firstly isolated in 1951, is a neuropeptide that regulates the proliferation and survival of target neurons (1). Nerve growth factor plays a subtle role in several brain pathologies leading to brain cell death and/or neurodegeneration during development or during

aging (2–11). Nerve growth factor is synthesized as a 130 kD precursor (proNGF) that is a complex of three proteins: α -NGF, β -NGF and γ -NGF the latter acting as a serine protease that cuts the Beta subunit N terminal producing the 26 kD mature NGF that is biologically active as a multifunctional signaling molecule (12–14). Nerve growth factor is involved primarily in the growth, survival, and proliferation of sympathetic and sensory neurons that undergo apoptosis in its absence (15–18). It also plays a delicate role in the physiological regulation of other biological structures as the immune and the endocrine systems and the adipose tissue (14,19–23). Nerve growth factor binds two classes of receptors: the tropomyosin-related kinase A (TrkA), and the low-affinity NGF receptor p75 (LNGFR/p75^{NTR}) (12, 24, 25). TrkA receptor binding produces the homodimerization of the receptor and the autophosphorylation of the tyrosine residue of the cytoplasmic tail. This site of TrkA phosphorylation is a docking site for the Shc adaptor protein that is in turn phosphorylated starting several intracellular pathways involved in cell survival (12, 26). Among them, one involves the activation of the serine/threonine kinase Akt and develops with the recruitment on TrkA receptor complex of a second adaptor protein, the growth factor receptor bound protein 2 (Grb2) and another docking protein, the Grb2-associated Binder1 (GAB1). This complex activates phosphatidylinositol-3 kinase (PI3K), that activates Akt. Blocking the activity of PI3K or Akt provokes the death of sympathetic neurons in culture also in presence of NGF administration, while when both kinases are constitutively expressed neurons can survive without NGF (27,28).

Another pathway of NGF mediated neuronal survival involves the mitogen-activated protein kinase (MAPK). This pathway leads to activation of the membrane-associated G protein Ras that phosphorylates the serine/threonine kinase Raf. This phosphorylation activates the MAPK cascade that regulates transcription (26). Both of these pathways give rise to phosphorylation of the cyclic AMP response element binding protein (CREB), a transcription factor that translocates into the nucleus, where controls the expression of antiapoptotic genes.

NGF and Alzheimer disease

Alzheimer disease (AD), the most common form of dementia in the old age, is characterized by early perturbations of synaptic proteins and synaptic functions with the generation of abnormal tau and amyloid proteins. After the release in

the intracellular space of these abnormal proteins begins the massive deposition of senile plaques (SP) of β -amyloid ($A\beta$) peptide and the aggregations of neurofibrillary tangles (NTF) that originate from hyperphosphorylated tau protein. As a consequence, during the progression of the disease, appears a serious and progressive memory deficit, a massive neuronal loss and a complete deterioration of the brain homeostasis (29–32). The basal forebrain cholinergic neurons innervate the hippocampus and the cerebral cortex, the regions that control memory and attention. These regions are more susceptible to the AD and the first to be involved (33–36).

In the pathophysiological mechanisms of AD, it turned out to be fundamental the protective role of neurotrophic factors, secreted proteins that control differentiation, plasticity, pruning and survival of forebrain cholinergic neurons (FBCN) of the hypothalamus, cortex and hippocampus. Indeed, the signaling of these peptides is seriously altered in the course of the disease (37). Among these neurotrophins the most studied for its role in the AD is NGF, a glycoprotein of three subunits α , β and γ that is produced as a precursor pro-NGF and is processed intracellularly to mature NGF by the subunit of the protein (37, 38).

Nerve growth factor signaling involves three types of receptors expressed in BFCN: the high-affinity tropomyosin-related kinase A (TrkA), the low-affinity neurotrophin receptor (p75^{NTR}) and sortilin. NGF binding to its receptor TrkA activates the pathway signaling of cell survival, while in the presence of lower levels of NGF and/or TrkA the precursor form of NGF (pro-NGF) binds to p75^{NTR} and to sortilin provoking an apoptotic signaling that brings to neurodegeneration (39–41).

Nerve growth factor release by cortical and hippocampal neurons is involved in the processing of amyloid precursor protein (APP) to generate the soluble APP that is neuroprotective and a strong inhibitor of the enzyme β -secretase 1 (BACE1) that controls APP amyloidogenic cleavage (42, 43). Recent studies in animal and cellular models have shown the protective role of NGF against AD induced neurodegeneration. Also, there is evidence that the perturbation of NGF signaling is one of the earliest events in AD onset (44). In a cellular model such as primary hippocampal neurons, the NGF deprivation generates an Alzheimer's like molecular syndrome with the development of $A\beta$ -amyloid plaques and aggregations of neurofibrillary tangles (45). Also, an antibody directed to NGF provokes similar phenotypic effects and neuronal deficits in the AD11 mouse model of AD (46).

The protective role of NGF observed in vivo and in vitro is exerted by the modulation of the processing of amyloid precursor protein (APP) (42, 43).

Nerve growth factor stimulation of primary cholinergic septal neurons promotes the binding of NGF receptor TrkA to APP. This binding blocks the APP phosphorylation at threonine 668 (T668) residue in the cytosolic tail of the protein. T668 phosphorylation is a post-translational modification of APP that induces APP cleavage by the enzyme BACE1, that controls the amyloidogenic pathway of maturation (42,43,46).

In AD development, where there is a deficit of NGF, amyloid generation increases and could affect the initial synaptic alteration observed in mild cognitive impairments and early AD. The newly generated amyloid inhibits the endocytosis of NGF/TrkA complex and this negative feedback loop marks the AD onset (29).

In rat models of aging, elevated levels of pro-NGF and p75^{NTR} in hippocampus and prefrontal cortex are associated with a deficit in spatial recognition and memory (47). An increase in pro-NGF levels was also observed in mild cognitive impairment and AD patients and also in postmortem AD brain examination (44). The perturbation of NGF signaling is an early event during the progression of the AD as evidenced by the studies on animal and cellular models (30). In animal models of aged rats the blocking of NGF/TrkA signaling provokes a serious deficit of cholinergic function (48,49). In animal models of AD, the alteration of NGF signaling brings to a general loss of central cholinergic function (50). The effect of the imbalance in NGF/TrkA signaling is a pathological APP processing (45). In transgenic mice lacking the APP/TrkA interaction, it is observed a serious degeneration of cholinergic neurons and cognitive deficits (51). These studies seem to support the hypothesis of the *neurotrophic model* of AD development where the reduction of NGF level and the increase of pro-NGF would trigger the synaptic failure and the abnormal amyloid and tau deposition starting a neurodegenerative cascade (28,52).

New pieces of evidence prove that the relationship between NGF and APP processing relies on a physical interaction between APP and NGF receptors (30). The APP juxta-membrane region which contains the α and β -secretase cutting sites and matches the first 16 aa of $A\beta$ peptide is sufficient for the interaction with TrkA and the binding to p75^{NTR} (53). APP and TrkA proteins localize in the plasma membrane, endoplasmic reticulum (ER), Golgi and endocyt-

ic vesicles where the proteins form homodimers (30).

In primary septal neurons, NGF treatment increases APP/TrkA complexes in ER and Golgi without increasing the protein level probably because NGF affects the association through the control of APP phosphorylation (30, 43). NGF withdrawal induces a decrease of APP/TrkA complexes and the same pattern is observed with cell death inducers such as A β peptide, and rapamycin. Furthermore, NGF, favoring APP/TrkA complexes, disadvantages the APP/APP homodimers that are more prone to amyloidogenic processing carried out by β and γ -secretase (30, 43).

The APP post-translational modifications are critical for the physiological or amyloidogenic pathway (54). The phosphorylation of threonine residue 668 (T668) is connected to amyloid production, synaptic deficits and apoptosis (55, 56). This phosphorylation blocks APP/TrkA binding and increases A β 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 possible that the detachment of APP from TrkA is caused by a change in the conformation of APP upon this phosphorylation (43).

In the physiological anti-amyloidogenic pathway, binding of NGF to TrkA induces 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 reduction of APP p668 levels stimulates 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 α -secretases ADAM10-17. Conversely, reduced availability of mature NGF and/or reduced expression levels of TrkA result in pre-apoptotic signals that activate JNK, increase APP pT668 and disturb APP-TrkA interaction favoring the β -Secretase 1 amyloidogenic pathway (43).

Beneficial role of NGF on cholinergic neurons is carried out downregulating T668 phosphorylation, stimulating APP/TrkA binding and trafficking to subcellular compartments, as Golgi complex, that is depleted of the amyloidogenic enzyme like BACE1. Tau pathology is implicated in non-Alzheimer disease pathophysiology (suspected non-Alzheimer disease pathophysiology - SNAP). In AD many studies demonstrated a synergism between tangles and plaques, with abnormal tau that enhances A β toxicity and *vice-versa* (57, 58).

Nerve growth factor can regulate the steady-state levels and the posttranslational maturation of tau that is phosphorylation, cleavage, and ubiquitination (59, 60). NGF withdrawal brings to hyperphosphorylation of tau that is A β -dependent and to abnormal cleavage of the N terminal fragment of the protein that lacks the microtubule-binding domain. The same tau fragment was also observed in animal AD models with impaired NGF signaling (59, 61).

NGF and Schizophrenia

Growth factors that control pathways involved in normal brain development have an important role in the pathophysiology of mental illness that has also a neurodevelopmental origin. Significant alterations of their levels were observed in patients and also in animal models where altered levels of these proteins induce psychiatric behavior (62).

During the embryonic and postnatal stages, psychophysical stress altering the environment can modify the normal development of the brain opening the way in the adulthood to psychopathologies such as hyper-anxiety, anomalous social behavior, alcohol abuse and drug dependence, schizophrenia, and depression (63–67). In the rat, gestational stress increases maternal and fetal plasma corticosterone with dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and a prolonged elevation of plasma glucocorticoids in response to stress events (64, 65). Synaptic development and neurotransmitter activity are modified by increased activity of corticosterone and corticotrophin-releasing hormone (CRH) in developing brain causing behavioral dysfunctions in adulthood. For example, rats exposed to intrauterine stress develop depressive-like behaviors and hyper-anxiety coupled with the increase of CRH activity in the amygdala (64,65). Interestingly, abnormalities in the HPA axis described in prenatally stressed animals were also reported in humans with endogenous depression (68–70). Also during early postnatal life, the development of the nervous system is sensitive to stress events, and this contributes to inter-individual differences in vulnerability to psychopathology. In the postnatal development of CNS, the neural network undergoes deep rearrangements (71, 72) and is particularly sensitive to external stimuli. In this phase, the role of NGF and BDNF is to modulate brain plasticity to better adapt to the environment. As an example, mice grown in a nest with caregiving mothers display better social interaction and skills compared to mice bred in standard laboratory conditions. The socially enriched mice present also higher levels of NGF and BDNF

in hippocampus and hypothalamus (73, 74). In the mouse, NGF is produced and secreted by the submaxillary salivary glands (75, 76). Neurobehavioral studies have shown that intraspecific fighting in adult male mice provoked a remarkable release of NGF from salivary glands into the bloodstream. These observations demonstrated a correlation between the serum concentration of NGF and the status achieved in the fighting where the subordinate mice showed double serum levels of NGF compared to dominant mice (77–79). Other studies have confirmed the association between increased NGF levels and subordinate behavior (80, 81). In male mice, the chronic administration of NGF reduced aggressive behavior (79). NGF release was activated by psychosocial stress that depends on interspecific interactions while physical stressors have less pronounced effects (73, 74). Intermale aggressive behavior increases the synthesis of NGF in the hypothalamus (82) probably because the NGF levels respond to psychological stimuli connected to fear and anxiety and interplay with hormones and neurotransmitters to integrate the neuroendocrine response and the behavior to ensure the physiological homeostasis (2, 14, 81). Data from humans and animal models suggest a role of neurotrophins also in vulnerability to stress-related neuropsychosis (83, 84). Growing literature evidences showed that in psychopathological disease the constitutive levels of neurotrophins are altered in both brain and plasma. In schizophrenic patients, without neuroleptic therapy, the plasma levels of NGF are lower compared to healthy controls (85). Administration of the antipsychotic drug haloperidol in human and mice drastically reduces the plasma levels of NGF (86) inducing sedation. In contrast, the atypical antipsychotics risperidone, clozapine, and olanzapine showed higher levels of plasmatic NGF compared to never-medicated first-episode psychotic patients (87). The critical role of NGF during the development of cholinergic neurons that control learning and memory could explain the vulnerability of schizophrenic brain and the cognitive deficits observed in this disease because the low levels of NGF trigger a consequent neurodevelopmental deficit (14, 88). In schizophrenic patients, brain imaging studies showed alteration in brain areas such as prefrontal, temporal and anterior cingulum known to be involved in affective-cognitive integration (89). Also, the schizophrenic brain post-mortem examination showed a reduction of cell proliferation in the entorhinal cortex, anterior cingulate and prefrontal region that could explain the origin of the disease (85, 89). In animal models, behavioral deficits that correlate to schizophrenic

symptoms (90) develop also by maternal exposure to risk factors such as ethanol and drug abuse that inhibit entorhinal and cortical neurogenesis (91).

Schizophrenia is a multifactorial mental disease triggered by social, genetic and developmental factors (92). Among the genes that have been observed to be involved in this disease one is *Disrupted-in-schizophrenia 1* (DISC1) (93,94) which is expressed by neurons of the cerebral cortex, hippocampus, olfactory bulb and cerebellum in rat brain (95–97). The protein binds other proteins including fasciculation and elongation protein zeta-1(Fez1), involved in axonal outgrowth. DISC1-Fez1 molecular complex colocalizes in the growth cone of neurite suggesting a role in the process of extension also confirmed by the fact that these proteins are expressed in early ontogenic stages. Studying the neurodifferentiation of PC12 cells stimulated with NGF was observed a drastic increase of Fez1 suggesting that NGF controls the neurite extension and outgrowth upregulating DISC1-Fez1 complex (92). When the DISC1 translocation prevents the complex being formed, neurite extension cannot happen and the brain development remains immature, supporting the hypothesis that schizophrenia is essentially a neurodevelopmental disease (92).

NGF and Major Depression Disorder

Major depression disorder (MDD) is the most common of brain disorders and involves depression, scarce interest in normal daily activities, fatigue, a decrease in concentration, suicidal intentions (98). Several neurotrophins including NGF and BDNF are involved in MDD pathogenesis (99, 100). Major depression disorder patients present reduced serum NGF, and the same reduction was observed in hippocampus mRNA and protein expression of NGF, BDNF and their receptors in post-mortem examination (101, 102). The chemical mediator of NGF reduction is interferon-gamma (IFN- γ), as was observed in IFN- γ knockout mice models that develop a depressive-like behavior, an increased immobility and a parallel reduction of NGF levels (103, 104).

The administration of NGF in rats decreases the expression of cholinergic gene CHRNA5 and prokineticin receptor1 (PROKR1) miming the effects of fluoxetine and amitriptyline therapy. The improvement of the depression-like behavior is realized by modifying the expression of several genes of amygdala and hippocampus (105).

NGF in Autism Spectrum Disorder

Autism Spectrum Disorder (ASD) involves deficits in social

communication and repetitive pattern of behavior. Genetic aberrations play a crucial role in developing ASD with hundreds of genes associated with it, which however do not show to converge in a common molecular pathway. Genetic studies and behavioral observations demonstrate the overlapping of ASD with other psychiatric disorders, such as schizophrenia, bipolar disorder, and Attention Deficit and Hyperactivity Disorder (ADHD) (106, 107). In a study of differential alternative splicing (DAS) in the blood of 2-4 years old boys with a diagnosis of ASD, there were significant DAS differences in several genes of NGF receptors and signaling compared to controls (108). Another study of Lu *et al* showed several SNP NGF associated with deficits in nonverbal communication that is one of the autistic trait (109).

NGF and Alcohol-Induced Mental Retardation

Several human evidences have shown that chronic or binge alcohol consumption as well as alcohol exposure during development are a main inducing-cause of brain changes (110) and mental retardation in both adults and children (88, 111–119). As for the gestational alcohol consumption, the plethora of effects in children induced by ethanol are described as Fetal Alcohol Spectrum Disorders (120–123). It has also been clearly demonstrated that chronic or binge alcohol consumption as well as alcohol exposure during development may impair brain neurotrophic factors production and the expression of their receptors (124–132). NGF is one of the most important neurotrophins involved in ethanol-induced toxicity. Indeed, NGF and their receptors are known to be altered in the brain during prenatal/acute/chronic alcohol consumption (133–138). In particular, as previously indicated (133) alcohol inhibits the expression of endogenous extracellular signal-regulated kinase (ERK) and the phosphatidylinositol-3-kinase (PI3K) (139–141). In addition, data disclosed several epigenetic rules of NGF and BDNF, the serum levels of interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) and the symptomatology of alcohol dependence (142, 143). In particular, it has been shown an increase 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 consumption, suggesting that changes in the methylation of neurotrophins genes may contribute to the development of alcohol dependence by affecting relevant downstream signalling cascades (133, 143).

NGF and Brain Parasitosis

The role of NGF in parasitic disease is not yet clear estab-

lished but some clues have emerged from the study on *Trypanosoma cruzi* and *Schistosoma mansoni* neuroinflammation of the brain.

Chagas disease or American trypanosomiasis is a tropical parasitic disease caused by the protist *Trypanosoma cruzi* spread to humans and mammals by the insects “kissing bugs” of the subfamily *Triatominae* (144, 145). During the early stage, symptoms are not present or are mild with fever, headache, swollen lymph nodes. Only 40% of people develop severe symptoms of the disease after 30-40 years from the infection that include heart failure due to enlargement of heart ventricles, or enlarged esophagus or colon (megaesophagus or megacolon). This disease affects 6,6 million people mostly in Central America and Mexico (146).

Trypanosoma cruzi produces the NGF mimetic neurotrophin called parasite-derived neurotrophic factor (PDNF), a membrane-bound neuraminidase/trans-sialidase that can bind TrkA but not p75^{NTR} (147, 148).

Trypanosoma infection of CNS is usually asymptomatic and neuronal examination has shown neuroprotection and neurons preservation also near foci of inflammatory cells or parasite nest (149). Neuroprotection and neuroregeneration were also observed in animals with acute or chronic infection (150–153). Signs of sprouting of sympathetic and parasympathetic nerve fibers were observed in heart and colon with increased levels of neurotransmitters (154, 155). These data have shown that PDNF is a functional mimic of NGF that can bind TrkA in an NGF inhibitible manner, can induce TrkA autophosphorylation and can trigger PI3K/Akt and MAPK-Erk1/2 signaling that promotes cell survival and neurite outgrowth. The inability of binding p75^{NTR} inhibits the cell-death signaling pathway (156, 157). Given the critical role of TrkA in neuronal maintenance, the parasitic invader utilizes this receptor to reduce tissue damage, to stimulate protective mechanisms and tissue repair maximizing host-parasite equilibrium in order to prolong parasitism. This mechanism could reflect a general and unexpected model of host-parasite interaction (156).

Neuroschistosomiasis (NS) 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 granulomatosis reaction. A large number of eggs and granulomas in CNS regions damage the adjacent tissues by the inflammatory reaction and the mass ef-

fect (158–162). In infected mice that manifest granulomas in several CNS regions it is observed an increase in NGF levels in the cortex, hypothalamus, and brain stem with paw hyperalgesia (163,164). 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 system caused by the local formation of granulomas (75,165–171).

NGF-based Therapy

The protective effect of NGF in animal models of neurodegenerative disease has led to clinical trials of NGF therapy in humans for several brain diseases including AD, schizophrenia (172,173) and hopefully for other brain pathologies.

Encouraging results were observed in patients' basal forebrain in which were implanted connective cells engineered to synthesize and secrete NGF. In these experiments were observed enhanced cell size and new formation of neural fibers. Also, the cell showing signs of pathology and protein clumps inside the cell body maintained a healthy size, activated prosurvival signaling and manifested stress resistance. To prolong the expression of NGF, modified viruses that contain the NGF gene were directly injected in the basal forebrain (174, 175). The protective role of NGF and its progressive decrease in AD is the rationale of NGF therapy in which the administration of exogenous NGF could antagonize the basal forebrain neurodegeneration. The first promising results were obtained in rodents where intracerebral NGF delivery was neuroprotective for cholinergic neurons. Also in AD models like APP/PSI transgenic mouse, the less invasive ocular or nasal administration of NGF reduces beta-amyloid deposition (176). In AD patients NGF gene therapy in phase I has shown axonal sprouting without side effects (176).

Anomalies in the levels of NGF or NGF signaling and the resulting impairment of neuroplasticity and cognitive functions were also observed in psychiatric disorders such as schizophrenia, depression, bipolar disorders, alcohol use disorders and autism. In schizophrenic patients in therapy with atypical antipsychotic drugs, NGF levels increase leading to a reduction of negative symptoms (49, 177). In bipolar disorders, NGF decreases during the manic state and is rescued by lithium administration that increases the NGF concentration in the frontal cortex, hippocampus, and amygdala (178). In children with Rett syndrome, a condition that causes a delay in development and cognitive disability resembling autism, therapies with NGF-like activity drugs improve motor and

cortical functions and increase social interactions (179).

CONCLUSIONS

Many years of research have well documented the important trophic and homeostatic role of NGF that exerts its modulatory activities on nervous, endocrine, adipose and immune system functions. Future researches, through a greater knowledge of the mechanism of action of this small and versatile peptide, will help to develop updated brain therapeutic strategies for many clinical areas including those involving neuroinflammation, neurodegeneration and neuroendocrinology (2, 20, 23, 180, 181).

CONFLICT OF INTEREST STATEMENT

The authors certify that they have no affiliations with or involvement in any organization with any financial interest in the subject matter discussed in this review article.

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