Data and hypotheses on the role of nerve growth factor and other neurotrophins in psychiatric disorders

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Summary Nerve growth factor (NGF) was discovered and characterized for its role on the growth, differentiation and maintenance of specific neurons of the peripheral nervous system. Subsequent studies revealed that NGF is synthesized and released within the central nervous system and exerts a trophic and functional role on basal forebrain cholinergic neurons; it is involved in a protective role following brain insults induced by an epileptic status, seizure, as well as surgical and chemical lesions.

More recently our collaborative studies provided evidence that NGF is implicated in neurobehavioral response including cerebral alterations associated with psychiatric disorders. In this brief review, ongoing and emerging data are presented and discussed. © 2000 Harcourt Publishers Ltd

INTRODUCTION

The submerged areas of the Nerve Growth Factor iceberg loom very large

Rita Levi-Montalcini, 1987 (1)

Nerve growth factor (NGF) is the best characterized member of the neurotrophin family. Originally, NGF was thought to be critical for the survival of sympathetic and some sensory and central cholinergic neurons. However, it is now clear that NGF also functions outside the nervous system, particularly within the neuroendocrine and immune systems (2).

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Neurotrophins are polypeptides that can affect cell survival and activity in the central nervous system (CNS). For instance, neurotrophins can block neuronal cell death in lesioned animals and increase the expression of cholinergic and dopaminergic neuronal phenotypes, thereby indicating a possible therapeutic potential in degenerative diseases. The family includes nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), Neurotrophin-3 (NT-3), Neurotrophin-4/5 (NT-4/5), and Neurotrophin-6 (NT-6). Neurotrophins can be produced within the CNS with regional differences in distribution and can also enter the CNS by retrograde axonal transport (3).

These molecules interact with two different types of receptors on the surface of neurones. One type, the high-affinity neurotrophin receptors, belong to the Trk family of tyrosine kinase receptors (TrkA, TrkB and TrkC) which bind to specific neurotrophins. The other type of neurotrophin receptor, p75, is a transmembrane glycoprotein lacking a tyrosine domain and binds with low affinity to
all neurotrophins. TrkA, first identified as the product of the human trk proto-oncogene, acts as a functional high-affinity NGF receptor. TrkA is a 140 kDa transmembrane glycoprotein whose tyrosine kinase activation is stimulated upon NGF binding. TrkA activation results in the phosphorylation and activation of several signalling proteins thus initiating a process that leads to the survival, differentiation, and functional maintenance of selected populations of neurons (4).

**Early discovery and outline of the review**

The discovery of the NGF represents a corner stone in neurosciences as it has provided the possibility of understanding the subtle mechanisms regulating differentiation of nervous cells, growth and direction of axons, synthesis and release of neurotransmitters and some controversial aspects of embryogenesis. Moreover, the discovery of NGF has promoted the identification and isolation of other neurotrophins which are active on different specific cell systems (for details see refs 5,6).

NGF was discovered at the beginning of the 1950s (7–10) as a completion of studies in experimental embryology (1). NGF was found in mouse tumors such as sarcoma 180 and 37 (8,11) and later in snake venom (12) and in male mouse salivary glands (1,13). NGF is known to be produced by a great variety of cells, not only of the CNS and the peripheral nervous system (PNS) (1,14), but also in cells belonging to the immune and endocrine system (2). In the CNS the greatest quantity of NGF is produced in the cortex, the hippocampus and in the pituitary gland, but significant quantities are also produced in other areas of the CNS, including the spinal cord. NGF has also been produced for a few years in a recombinant way and is usefully employed in preclinical and clinical studies, particularly in peripheral and central neuropathies (15,16).

**The family of neurotrophins**

Growth factors represent a heterogeneous group of polypeptides that regulate a series of cell functions such as differentiation, growth and trophism of specific cell phenotypes (17). Neurotrophic factors, or neurotrophins, are a class of growth factors whose action is performed particularly on cells belonging to the CNS and the PNS. The main factors which belong to the family of neurotrophins, besides NGF are BDNF, NT-3, NT-4/5, NT-6 and others, such as ciliary neurotrophic factor (CNTF) (18). NGF and NT-4/5 have a high affinity for receptor Trk-A, while BDNF has a high affinity for TrkB; NT-3, instead, binds TrkA, TrkB and TrkC and it has a high affinity for the latter (4).

NGF is a dimeric protein in which each polypeptidic chain has a PM equal to 13250 Dalton. Positive AAs prevail and the NGF molecule is positively charged when measured at neutral pH. Each polypeptidic chain is stabilized by three sulfide bridges, as in other proteins with cell secretion such as insulin and antibodies. The aminoacid sequence of NGF resembles, in part, that of insulin, so, in the past, both proteins were considered to originate from the same ancestral gene (19) originating both the proinsulin and the NGF precursor.

The NGF was isolated and characterized by Varon and Shooter (20) and by Bocchini and Angeletti (21). They discovered that the NGF dimer was combined to two proteins α and β and it derived from a larger polypeptidic precursor called pro-NGF. Later studies using the X-ray crystallography revealed the tridimensional structure of NGF (1,22).

**EVIDENCE ON THE ROLE OF NGF IN THE CNS AND PNS**

There are considerable evidences that most of the tissues belonging to animal vertebrates contain and release very low quantities of NGF. For more than 35 years, NGF has been considered a very powerful and selective growth factor in sympathetic and sensory neurons and in cells deriving from the neuronal crest (1,23). However, more recent studies have demonstrated that NGF is also produced in the adult CNS, where receptive molecules are found (24). In animal models, the neurotrophin is mostly present in the frontal cortex, the hippocampus and the hypothalamus of rats and, in these areas, NGF synthesis is also regulated by stressful psychosocial events (see the following chapter). Furthermore, NGF exerts a trophic action on the cholinergic neurons of the basal forebrain, particularly at the level of the medial septum, the nucleus basalis of Meynert, the Broca’s diagonal band, and on the cerebellum cholinergic neurons. The trophic function exerted on the cholinergic neurons takes place both during development and in adulthood (25,26). The spectrum of action was once considered limited to a differentiation function related to specific central and peripheral neuronal classes, whereas today studies reveal that it is also extended to other kinds of non-neuronal cells. NGF is particularly involved in the functioning of the immunohematopoietic system (27) and in physiological situations caused by neuroendocrine changes (2,28,29). Recently, NGF has also been studied for its clinical application in peripheral neuropathies as induced by diabetes, leprosy, surgical traumas and in clinical trials on AIDS, as mentioned in a recent conference on NGF (30). This molecule was studied in the past and is still studied today in a preclinical and clinical context in relation to pathologies of the CNS as Alzheimer’s and Parkinson’s diseases (31,32). One of our clinical studies was recently published in the New England Journal of Medicine: for the first time the
NGF therapeutic role is demonstrated in eye pathology as a neurotrophic keratitic ulcer. The research was carried out with patients who were hospitalized at the Ophthalmology Division of the SS. Giovanni e Paolo Hospital in Venice and it highlighted that a topical application of NGF rapidly recovers the lesion. Fifteen months later, the follow-up demonstrated a complete restitutio ad integrum of the cornea with no local and/or systemic side effects (33).

NGF in mechanisms of seizure

In 1989, Gall and Isackson discovered a link between NGF and convulsion by demonstrating that in mouse there is an increase in mRNA for NGF after a limbic seizure (34). Other studies showed that chemicals such as phenylpentetetrazolium (35,36), kainic acid (37), bicuculline (38), NMDA (39), or quinolonic acid (40) given in the brain demonstrated an increase in NGF and its mRNA in various cerebral areas. The same phenomenon was observed in unilateral electrolytic lesions of the dentate gyrus of the hippocampus (34,41–45) and in the basolateral amygdala (45,46) with low (50–70 mA) or high (150 mA) intensity electroshock (47). These studies highlighted the increase in mRNA tissue levels for NGF within 30 min up to 24 h after the beginning of convulsions. The areas where the increase in the messenger can be identified are mainly represented by the granular cells of the dentate gyrus, then by the olfactory cortex and the neocortex, the pyriform cortex, the pyramidal layer of the parietal cortex, the CA1–CA3 regions of the amygdala, the granular layer of the hippocampus, the entorhinal cortex, most of the limbic areas, the cerebellum and the mid-brain, neurons from the II and III layer of neocortex. Finally, the presence of sprouting of muscarinic and cholinergic fibers is an interesting finding: it increases in the molecular layer of the dentate gyrus 1 week after an epileptic state, while antibodies directed against NGF reduce the cholinergic fiber branching but do not reduce the muscarinic ones (48). Convulsive activity is not supported by all neurotrophins in the same way since the mRNA expression for NT-3 is strongly reduced after a convulsion (45,48).

All this research on animal models certifies the importance of NGF in the mechanisms of seizure. More evidence supports the hypothesis that mechanisms regulating humans and animal convulsions are the same. Indeed, epileptic patients exhibit a synaptic reorganization of muscarinic fibers similar to the one observed in animals subjected to kindling, which suggests that kindling and human epilepsy certainly share common mechanisms (49).

Based on such observations, we began to study whether the amount of NGF changes as a result of electroconvulsive therapy (ECT). ECT is a therapy inducing convulsions comparable to those observed in general epilepsy. We unexpectedly found that ECT and NGF exert some important analogous functions associated with convulsive mechanisms; both enhance synaptic sprouting, increase monoamine synthesis and turnover, induce neuroendocrine effects and regulate homeostasis (2,50). We studied the NGF plasma levels of schizophrenic and depressed patients who underwent ECT. We demonstrated a remarkable increase in the levels of this neurotrophin within 5–10 minutes from the convulsion and a return to basal levels 20 minutes later (51). The same result can be observed during the I, IV and VIII ECT (52). Moreover, we observed a meaningful increase in NGF levels before the beginning of the ECT session induced by the stress due to the ECT waiting (53).

THE ROLE OF NGF IS STRESS AND BEHAVIOR

NGF and stress

The first study on the possible role of NGF in behavioral functions goes back to 1986 when it was demonstrated that mouse aggressive behavior induced by 6–8 weeks of isolation caused an increase in NGF blood levels. The amount of NGF was directly correlated to the frequency of fighting episodes. NGF was released by mouse salivary glands within a few minutes after the fighting session and the protein remained in circulation for 3–4 h. The administration of NGF induced also an increase in adrenal gland volume which was more evident at a medullary level. Neither corticosteroids nor ACTH induced a NGF release in the blood (54). An increase in NGF and mRNA for NGF was observed at hypothalamic level, especially in the paraventricular nucleus (55). The increase was observed in specific zones and not in other brain areas such as the cortex, hippocampus, cerebellum or other peripheral organs. All together these studies demonstrate that NGF plays a key role in coping response associated with changes in neuroendocrine mechanisms as a result of stressful events (2).

Later studies on animal models demonstrated that anxiogenous situations, psychic stress and stressful environmental conditions such as delivery (28), produce an increase in NGF particularly in the hypothalamus (54–60). Other authors have recently confirmed and developed these results by showing that the platelet-derived growth factor (PDGF) increases in human blood as a consequence of psychic stress (61). Physical activity induces an increase in fibroblast growth factor (FGF-2) and its mRNA in the hippocampus (62), and potentiates mRNAs for BDNF and NGF in many adult rat brain areas (63). In addition, nerve growth factor-like activity was detected in equine peripheral blood after running exercise (64).
What seems very interesting in all these studies is that NGF release is strongly linked to aggressive behavior; in fact the serum of mice, who are continually subjected to frustrating and submissive episodes, contains higher levels of NGF compared with those present in dominant attacking animals (56,59). This finding strongly suggests that stressing situation, probably associated with anxiety, may play a role in the regulation of NGF synthesis and release (65).

To check whether or not similar results can be obtained in humans we measured the NGF plasma levels in young parachute soldiers on their first jump. A blood sample was taken from soldiers who knew they were going to jump the following day and from soldiers who knew they were not going to jump. A second blood sample was taken from the parachute soldiers 20 min after the jump. The results confirmed that also in humans an anxious state can induce a remarkable increase in NGF in the bloodstream and that such increase precedes the release of classical stress hormones such as cortisol and ACTH (66).

These observations on humans confirm and extend findings obtained in animal models and demonstrate that NGF is involved in the activation of anxiety-related phenomena. They also confirm the results of earlier studies on animal models which showed that NGF release in bloodstream, as well as in the CNS, isn't correlated only to aggressive behavior but also to submission and anxiety conditions (56,67–69).

These observations and others directed our investigation towards the possible role of NGF in conditions of chronic ethanol intake in animal models. We were able to demonstrate that alcohol induces a strong decrease in NGF activity in mouse hippocampus and hypothalamus and an important decrease in the choline acetyltransferase enzyme in the septum, hippocampus, and striatum. These data support the hypothesis that NGF is implicated in alcohol related pathologies (70).

Implications of NGF in arousal-sedation situations

Animal models characterized by dominance-submission showed that aggressive behavior is also followed by high-hypothalamic levels of NGF (54). This brain area represents the most rostral part of the reticular formation and is involved in physiological and behavioral modifications that follow changes in the bodily homeostasis. Since behavioral arousal is probably associated with high NGF levels (53,66), we can hypothesize that sedative states are characterized by a central reduction of the levels of this neurotrophin.

In order to study and prove such a hypothesis, we investigated to see if substances that cause sedation and/or catalepsis in animal models were able to lower hypothalamic and plasma levels of NGF. Results of studies carried out with mice subjected to ethanol treatment in their adult stage (70) or haloperidol administration in their prenatal stage, elucidate the presence of a remarkable alteration of NGF levels (71,72). Soon after, we studied whether sedative doses of haloperidol induce a decrease in NGF plasma levels in humans as well. The administration of haloperidol, 2 mg in the morning between 8 and 10 a.m., led to a remarkable decrease in NGF plasma levels 2 hours after the administration of the neuroleptic (73).

These first studies performed on humans prove that neurotrophin levels, such as NGF, regulate functional modifications in the CNS, respond to drug administration and possibly modulate the phenotypic representation of psychiatric disorders.

NGF AND PSYCHIATRIC DISORDERS

The idea of studying NGF in psychiatric disorders originates from studies on animal models which provided evidence that this molecule plays an important role in the embryonic development of the CNS, in response to stress, in integrating neuroendocrine functions, in activating aggressive and defensive behavior, as well as in mechanisms present in kindling and degenerative diseases such as Alzheimer’s and Parkinson’s disease.

Therefore, in the present section we will particularly analyse the role of NGF in the area of depression and schizophrenia.

Hypothesis on the role of neurotrophins in depression

In the last decades, biological research on depression has developed the hypothesis that there is an alteration in the catecholaminergic and serotoninergic systems in the CNS at the origin of this type of illness, and a secondary involvement of other neurotransmitter systems (74). It was shown that some receptors are coupled to coupling factors or G proteins while others have an enzymatic activity which is inherent to their structure and is activated by the ligando. Phosphorylation of second messengers enhances the activity of distinct proteins which are able to regulate the functioning of the membrane channels or regulate the genic expression in the long term (75). The modification of genic expression seems to be mediated by the so called ‘transcription factors’ as CREB (CAMP response element) and SRE (serum response element), that, once phosphorylated, are able to bind to genic promoters with a following modification of the genic expression (76).

The therapeutic latency of antidepressive drugs (AD) might be explained by following the hypothesis that the increase in monoamines at synaptic level induces, through a sort of genic long term
modifications in the membrane concentration of such receptors. On the basis of such experimental checks, it is hypothesized that as well as modifying genic expression of monoaminergic receptors, AD drugs can also modify central levels of neurotrophins (77). Studies performed on animal models demonstrated that gross modifications induced by kindling enhance NGF and BDNF (44–46); the same reaction was observed in patients subjected to ECT (51,52). On the basis of these experimental data, we may hypothesize that the therapeutic improvement with ECT as observed in depressed patients who are non responder to a pharmacological therapy, may be associated with a significant release of neurotrophins, particularly NGF.

Emerging hypothesis on the role of NGF in schizophrenia

Schizophrenia between ‘permissive’ and ‘diathesis-stress’ hypothesis

In recent years, complex as well as contradictory results from experimental research have suggested the hypothesis that factors which are active during the ontogenesis of the CNS may play a crucial role in the ethiopathogenesis of schizophrenia or, at least, in the liability to the illness. Such factors which are strongly heterogeneous are likely to be active in the pre- and peri-natal period. They contribute, in different ways, according to their nature and to the period of activation, to an anomalous development of brain organization, wavering between a condition of higher vulnerability, or higher risk of developing schizophrenia in adulthood (78).

At present, our knowledge on schizophrenia provides evidence that this disease has a multi-factor genesis, which is a result of a combination of a genetic liability and environmental factors. Both play an important and complementary role in the different phases of development and appear as an alteration in neurodevelopment (79).

Experimental checks on post mortem tissues and in vivo studies reveal a maldevelopment of the cortex in schizophrenic patients which could result in temporal-limbic and prefrontal impairments (80,81). Because of their neuropathological characteristics, such cortical changes lead us to suppose a presence of early alterations going back to the initial phases of CNS development. Brain imaging studies (TC, RMN, PET, SPECT) gave us the opportunity to carefully examine brain alterations and hypothesize a closer relationship between altered development and schizophrenic symptomatology. Such anomalies are in the medial and lateral temporal lobe (82), and in the cerebellum and encephalic midline (corpus callosum and septum pellucidum) (83). The prevailing hypotheses on the ethiopathogenesis of schizophrenia indicate that there is some interaction between genetic and environmental factors (84).

The first hypothesis, defined as being ‘non additive’ or ‘permissive’, indicates that both genetic factors and early environmental factors, such as obstetric complications in the course of pregnancy or during delivery, may separately induce abnormalities during brain development. In general, English researchers support such a hypothesis that accounts for the presence of ‘familiar’ and ‘sporadic’ forms of schizophrenia, which can be different from an epidemiological and pathogenetic point of view, although not necessarily from a psychopathological perspective; of course distinct pathogenetic contributions may coexist (85).

The second hypothesis, called ‘additive’ or ‘diathesis-stress’ asserts that non-genetic events or factors may only contribute to increase the risk of developing the illness which is mainly linked to a genetic liability; genetic factors could lead to an overt illness or severe personality disorders (86).

NGF neurodevelopmental alterations and liability to schizophrenia in adulthood

A great number of evidences published over the last few years suggest that the onset of schizophrenia in adulthood may be the consequence of early alterations in neurodevelopment, which are defined as neurodevelopmental encephalopathy by some authors (87,88). According to such hypothesis schizophrenia may be considered as a general disorder of brain maturation and organization that appears phenotypically before the appearance of classical symptoms in many patients. Possible risk factors (with exclusion of genetic predisposition which will be discussed in the following chapter) could be active in pregnancy and during the delivery (viral infections, nutritional disorders, alcohol or other drugs intake, obstetric complications) or in the early stages of life as familiar and environmental stressful events (81,87–93).

A possible role played by NGF in early alterations of the weak schizophrenic brain is also supported by the critical role played by such neurotrophin during the primary development of cholinergic neurons which are implicated in memory and learning processes (94–97). Alterations at this level induced by early events could create those cognitive deficits similar to the ones we observe in schizophrenic patients (98). Brain imaging studies in schizophrenics show the presence of alterations exactly in those areas (prefrontal, temporal, and anterior cingolus) that are implicated in cognitive-affective integration (99). On the basis of these observations, we assessed blood levels of NGF in schizophrenic patients who demonstrated a lower amount of NGF compared with healthy controls (100).
Possible role of neurotrophins in studies on the genetics of schizophrenia

There is general agreement about the fact that an alteration in neurodevelopment may be at the origin of schizophrenia; however, the heterogeneous clinical manifestations of schizophrenia in combination with the alterations in neurodevelopment have not yet been deeply studied. In recent years, the theory of an alteration in neurodevelopment as characterized by a cell migration disorder and by a neuronal and glial disconnection focused attention on the possible role played by specific neurotrophic factors, mainly NGF, BDNF, NT-3, NT4/5, NT-6.

The hypothesis of an alteration in neurodevelopment at the basis of the pathogenesis of schizophrenia has also been supported by molecular studies and, in more recent years, by studies on the genetics of neurotrophins. The evaluation of genetic factors in the ethiopathogenesis of schizophrenia is based on family, twin and adoption studies, but the results are not yet conclusive (101).

The results of studies on neuropathology and brain imaging support the presence of alterations in distinct brain areas, such as reduction of volume, reduction of neuronal density and changes in neuronal spatial organization (102). This framework is not associated with signs of degeneration, gliosis or inflammation, and the mechanisms that regulate these alterations are not yet understood. Nevertheless, we may suppose that alterations in schizophrenia involve cell growth, neuronal migration and their structures capable of making connections. When the structures that represent important nodes in the association network between frontal cortex and subcortical structure are damaged, synaptic alterations take place and will significantly influence superior cortical functions in adulthood (99). Alterations in structural and functional development of brain areas may be a consequence of an old genetic liability that is displayed in adulthood as a consequence of environmental events.

Growth factors mainly studied in schizophrenia are NGF, NT-3, BDNF and CNTF, because they play an important and mutual role in the early phases of development. Among them, NT-3 plays an important role because it is present in the immature regions of the CNS, in those areas where the proliferation, differentiation and migration of neuronal precursors have origin. Moreover, mRNA levels for NT-3 in the hippocampus of newborn animals are much higher than those of other neurotrophins in different brain regions (103). These data suggest that NT-3 gene may be considered one of the possible factors which contribute to the dysgenetic picture observed in schizophrenia. Recent studies have demonstrated a significant presence of the A3 allele (which is localized in the promoter region of the gene for the NT-3) in schizophrenic patients if compared with healthy controls. Genotype A3 was more frequent in schizophrenic patients in the homozygotic variant as well as in the heterozygotic variant and the risk of developing schizophrenia was equal to 2.4 in subjects where such polymorphism was present (104). The following year, the authors of the study continued their research, demonstrating a high frequency of homo- and heterozygosis for the Glu-63 allele instead of Gly-63 in the AP-1 region of the gene for NT-3. This alteration was found in a selected sample of schizophrenic patients who presented severe schizophrenic symptoms due to early alterations during development (105).

The results of the studies on CNTF confirm previous results regarding other neurotrophins; namely that neurotrophin alterations may be associated with the development of a liability to various psychiatric disorders mediated by an alteration of neuronal development that appears in adulthood combined to environmental events (106). Other studies showed that BDNF is involved in the embryogenesis of schizophrenia. Fetal brain tissues coming from mothers with schizophrenia displayed reduced neuroproliferative capabilities (107,108).

CONCLUSION

This brief review highlighted the studies on the role of neurotrophins, particularly NGF, in psychiatric diseases. These results were further analyzed in animal models and revealed that changes in NGF synthesis and/or release, and most likely in NGF receptor distribution on target-cells, also participate in CNS maldevelopment (109). The studies suggest that both, blood NGF and brain NGF play a role in the pathogenesis of schizophrenia. We have been trying to develop and identify a ‘model’ which offers the possibility of studying a few aspects linked to neuronal alteration in some areas of the CNS. By administrating drugs during specific points of fetal life, adult rodents showed behavioral and neuroanatomical changes due to deficits in entorhinal cortex development (110). Ongoing and emerging studies indicate that this particular cortical deficit, which is considered by some researchers to be specific of some psychiatric related disorders (111), is characterized by neurological alterations associated with impairments in NGF synthesis and/or utilization.

Many studies are still in course in order to verify and deepen the role of NGF in these animal models as well as in schizophrenia-related human pathologies.

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