Iranian Journal of
Medical Hypotheses and Ideas

Original article

Open Access

The pleiotropism of nerve growth factor sensorial pathway: supplemental growth stimuli could be required during danger signalization like a surviving "proclaim"

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Received: 22 April 2008
Accepted: 28 June 2008
Published: 4 July 2008
Iran J Med Hypotheses Ideas, 2008, **2**:16

Abstract

Nerve growth factor (NGF) is the founder-member of neurotrophins family that provides growth and surviving effect not only for neuronal tissue but also for various non-neuronal cellular populations. It effectuates its physiologic or pathologic functions in sensorial neuronal system and some certain tissues through NGF-receptors such as tyrosinkinase A and p75, involving also transient receptor potential vanilloid 1, substance P and its receptor NK1 (members of NGF-pathways – NGFP). In different situations, such as stress-related or inflammatory pathologies (including allergy, asthma, depression, multiple chemical sensivity, stressful or dangerous events, etc), are reported elevated local and serologic concentrations of these mediators.

Reflecting on the pleiotropic effects of mentioned substances, it could be suggested that over-regulation of NGFP mediators is generally required during identification of somatic or psycho-emotional integrity threatening like a surviving proclaim. In this context, the identification of a danger may induce NGFP-mediated growth stimuli to assure better surviving possibilities for the organism, maybe as a compensatory effect. Experiments in knockout animals with regards to genes of NGFP mediators could be helpful for the verification of its role as leader of information in the mentioned processes. Some investigations in such animals have demonstrated their abnormal passivity to fight for vital demands, whereas the behavior of subjects with down-regulation of aforementioned factors is associated with sensory or cognitive disorders such as congenital insensivity for pain with anhidrosis, schizophrenia, diabetes, or self-mutilatory behaviors. The last mentioned facts manifest the inability to recognize the situation of bodily and mental integrity during the NGFP insufficiency, leading to the necessity for further pharmacologic investigations with regards to NGFP mediators in the related pathologies.

Keywords
Infliximab, NGF-pathway, pleiotropism, information, integrity's threatening, surviving proclaim

Introduction

Nerve growth factor (NGF) is the founder-member of neurotrophins family (1). This cornerstone of neurological science is a polypeptide, that represents a high level of genetic and immunologic homology in various species (1). Humane NGF is a dimmer of two identical subunits with 118 monoacids, associated with each-other due to a monovalent binding (1). The principal physiological functions of NGF are the growth and surviving induction not only for neuronal cells but also for a wide variety of non-neuronal cellular populations (1-7).

These functions are mediated due to activation of NGF-receptors such as tyrosinkinase A (TrkA) – the high affinity specific receptor, and panneurotrophin receptor p75 – the low affinity receptor (8-9). The activation of TrkA during physiological or pathological processes supports NGF functions, while the activation of p75 shows a functional complexity indicating that p75 can play a regulatory role in these processes (3,10-14). Apart from NGF receptors, in the functioning of sensory neuronal system are involved transient receptor potential vanilloid 1 (TRPV1), substance P (SP), and its receptor neurokinin receptor NK1 (15-22). This pathway can be called NGF sensory pathway (NGFP).

During last decades, many studies have demonstrated the local or serologic overregulation of NGF or NGFP mediators during diverse pathologies. Thus, SP and NK1 are involved in some psychoses such as depression, terrorizing, and affective psychoses (23,24). Thus, among depressive subjects it is reported a high concentration of SP in cerebrospinal liquid compared to normal or schizophrenic subjects (24,25). Similar findings are described in central nervous system among animals of the experimental models (26,27). Meanwhile, the exposition to stressful situations, such as first time parachute jumping, has been associated with high circulatory NGF concentration (17,28,29). Similar findings regarding NGFP mediators in serum and limbic brain areas are found in experimental animals exposed to different stressful situations, such as isolation or privation from indispensable living territories (23,24,30,31). A further pathology associated with NGFP overregulation is the multiple chemical sensitivity (MCS): This entity represents a clinical syndrome characterized by recidivant multiple unspecific complaints in different systemic organs, which can be developed as reactions to many chemicals unrelated to each-other such as tobacco smoke, solvents, perfumes, car exhausts, etc (32-35). During development of this pathology it is reported a high SP concentration in serum, associated with local neurosensorial inflammatory response or neuronal fiber proliferation in lungs (34-36).

The NGFP overregulation is also reported in some immunological disorders. Thus, there are reported high concentrations of NGFP mediators originated from immune cells or sensory neurons in serum or bronchioalveolar lavage (BAL) during allergic processes (8,9,15,17,37). In this respect, a higher serological concentration with regards to NGF is found among different allergic subjects compared to control ones, while asthmatic patients have shown a higher NGF concentration even in comparison with patients suffering from allergic rhinitis or urticaria (17,38,39). In addition, the increase of NGF level in BAL and the bronchial hyperreactivity, induced during allergen-provocation in sensitized animals, was reduced after their treatment with anti-NGF antibodies (8,17,40). Increased levels with regards to NGF receptors are shown also in BAL and lungs in experimental asthma models, indicating that NGFP has a proinflammatory role (17). On the other hand, it is reported the recruitment of different leucocytes, which secrete or are affected by NGFP mediators during allergic inflammation (9,15,17,20,37,41-45).

High concentrations of NGFP mediators are shown also in diverse inflammatory or painful syndromes such as fibromyalgia, peripheral neuropathy, rheumatoid arthritis, migraine, or ulcerative colitis (24,46-50). Thus, during the pain perception or exposition to different noxious stimuli are involved such mediators as NGF, TRPV1, TrkA, NK1, SP or calcitonin gene-related peptide (CGRP), while for the surviving of the relative neurons NGF presence was found to be essential (24,51-56).

The hypothesis

NGFP mediators play a crucial role in the phys-pathology of different diseases. Thus, many studies have demonstrated that NGF and NGFP are associated with different functions. The main functions are on the first hand the induction of growth or survival rates for different cellular subpopulations, and on the other hand the induction of pathological symptoms during inflammatory or stress-associated pathologies. However, based on the international publishing sources such as PubMed, there is any information about the reasons and the meaning of this pleiotropism. In this respect, it could be supposed that pleiotropism of NGFP and the overregulation of NGF mediators during above-mentioned conditions may lead to the idea that supplemental growth stimuli during such pathologies could be required during danger signalization as a surviving "proclaim" or as a compensatory response. By this I mean that during local or systemic inflammation as well as during stress-related neuro-psychological pathologies the organism always has detected a real or unreal noxious factor, which should be affronted even

through the induction of supplemental survival stimuli. The importance of this hypothesis consists in the fact that the reduction of symptoms intensity due to therapeutical blockage of this pathway should be associated by an alerting system in order to avoid the decrease of growth and survival rates for various cellular subpopulations as well as the suppression of sensory and cognitive abilities. On the other hand, the substitutive treatment with NGFP compounds during pathologies that represents respective deficits may be associated not only with trophic improvement but also with improvement of sensory and cognitive capacities.

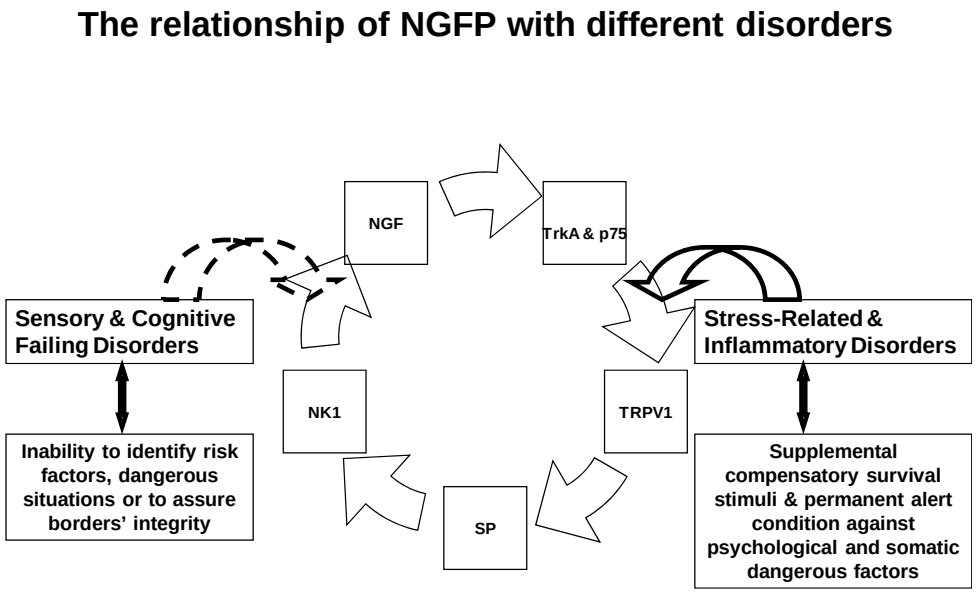

Figure 1. The relationship of NGFP with different disorders

The circle of arrows represents the steps of activation with respect to NGFP mediators. Stressfully situations or neuroimmunological disorders heats or overregulates this pathway. The agonistic direction of the respective arrow indicates this effect. In contrast, during sensory or cognitive failing disorders there is a downregulation or depletion of this pathway. This effect is indicated by the antagonistic direction of the respective arrow (with respect to NGFP).

Evaluation of the hypothesis and experimental data

Attention is paid in the last decades to the identification of structures that synthesize or release the complex of NGFP mediators. It seems that this complex embodies informative signalization structures, especially within sensorial centers such as spinal, jugular-nodose or trigeminal ganglia, as well as in hippocampus and other consciousness-associated constituent parts of limbic system (19,22,27,57-59). In addition, these mediators are described in peripheral tissues such as mucosa, inflammatory cells, or in peripheral neuronal fibers (2,15,17,19,48,60). In this context, the induction of neurokinins and stimulation of NGF-related receptors during inflammatory disorders could be explained with an identification of harmful stimuli for the local systems. In these circumstances the organism can react with an inflammatory response (including pathologic symptoms, such as pain, edema, erythema, etc). These responses should be considered a complex of protective mechanisms, which try to escape organism or affected tissue from the ungrateful situation (61). Furthermore, the induction of these neurokinins can induce again the neurotrophins' synthesis and release, leading therefore to the potentiation of survival rates for various cellular populations (62,63).

In fact, the biochemical messengers possess rather detectorial than meaning properties, because the information is produced due to consciousness, while neuronal fibers and mucosa alone are not conscious (59). However, if the patient cannot reflect about their situation, consequently he should not suffer this handicap (64,65). In this context, during the situations that are associated with increased NGFP expression (such as allergy, MCS, stressful vital events or depression), the affected

subjects can be informed about exposition to real or imaginary dangers, even if in the reality perceptions are only hypotheses about the environment (26,27,35,38,59,66). This opinion could be based on the fact that inflammatory disorders such as allergy and asthma are associated with noxious contact between antigen and organism, MCS with contact to various "harmful" substances, wounds with violation of bodily integrity, while depressive and anxious psychoses are associated with violation of mental and emotional integrity (because of persistent suffering or alerting), independently to the fact if the stimuli is real or not.

To estimate the hypothesis availability are necessary further detailed investigations. During these trials, the knockout (KO) animals with regards to offended genes should be experimentally exposed to the life danger or threatening events. Thus, the exposed animals to insufficient nutritive or territorial resources, to separation from parents, to stressful events or to inflammatory symptom-associated disorders should be observed in many aspects. Put succinctly, during these trials it should be studied their behavior, the neurological activity of brain centers that show NGPP synthesis or release (for example due to positron emission tomography), the expression of NGFP mediators in these neurological centers as well as in peripheral tissues, etc. The obtained data should be compared with data originated from wild-type animals. Furthermore, attention should be paid in the fact that experimental animals should be exposed also to various stressors or stressful situations in order to compare the response during the acute stress from the response during the chronic one. Apart from in vivo studies, some tissue cultures or slices from experimental wild-type, transgenic or KO animals can be exposed to noxious stimuli to show the expression dynamism with regards to NGFP mediators.

With respect to these estimations, some significant data are reported in the previously published studies. Thus, the lack of NK1 receptor in KO mice or the use of its antagonists in guinea pigs was not associated with expected aggressiveness regarding territorial demands or with vocalizations of young animals after isolation from their mothers, indicating that NGFP could play a principal role in these processes (24,52,66-68). In contrast, the early maternal separation of wild-type animals induced NGF expression in both the dorsal and ventral hippocampus, associated with an increased ability to respond to subsequent stressors with compensatory mechanisms (57,66). Additionally, in experimental models there are some reports about alterations of lithium brain concentrations through neurotrophic factors in the hippocampus, frontal cortex, occipital cortex and striatum, suggesting that these factors play a role in depression as well as in the mechanism of lithium's action (69). These data indicate that SP and NK1 antagonists could be efficacious as antidepressants and anxiolytics (70-73). Similarly to aforementioned trials, experiments in guinea pigs treated with TrkA blocker or in p75-KO mice demonstrated also a reduction of inflammatory symptoms in models of bronchial asthma, manifesting their important role during immune processes (38,74).

Similarly to these experimental models, some pathological conditions among human subjects show alterations with respect to NGFP compounds. Thus, in schizophrenic subjects (who sometimes demonstrate self-mutilatory behavior) is described a low concentration of SP in liquor, while NGF serological level in such subjects was lower than in normal ones (23,24,75). Moreover, fetal brain tissue of schizophrenic mothers show reduced neuroproliferative ability because of downregulation of NGFP mediators (23,76). Similar to these reports, loss of neurons in specific brain regions, such as limbic system, and the downregulation of SP and NK1 in these regions are described in schizophrenic subjects (26,77,78). On the other hand, NGF show different ultradian variation among schizophrenics compared to healthy subjects, supporting the hypothesis of a certain role of NGF in schizophrenia (79). As expected, NGF levels were significantly higher in chronic schizophrenic patients, which were treated with antipsychotics (80).

An other clinical case associated with a downregulation of NGFP-mediators is the congenital insensitivity to pain with anhidrosis (CIPA): This is an autosomal recessive hereditary disorder, characterized by recurrent fever, anhidrosis (inability to sweat), the inability to react against noxious stimuli, self-mutilation behavior, and mental retardation (81,82). The anomalous pain is due to the absence of dorsal root ganglia that are responsible for pain sensation and absence of afferent neurons activated by tissue damaging stimuli (81,83). The responsible gene for CIPA is a TrkA defect of NGF signal transduction, leading to the failure of nociceptive and sympathetic neuronal surviving support (1,81-86). Experiments in TrkA or NGF mice with KO genotype may lead to CIPA phenotype (81,85,86). Self-mutilatory behavior and recidivant non-easy curable trauma during CIPA can result in critical complications often with fatal consequences (81,82,87). These reports indicate that such pathologies are clinical examples among humans, which could help us to conceive more profound ideas about the probably expected results originated from proposed experiments above.

Other similar pathologies to the aforementioned ones are the neuropathia-associated disorders. In this respect, it is reported that peripheral neurons express less SP, TRPV1, TrkA or CGRP during

diabetes mellitus than in normal subjects, associated by axon atrophy (88-90). The downregulation of mentioned mediators is a NGF-depended effect (88,90). In contrast to above-mentioned situations, the overexpression of NGF in glial cells and spinal ganglia during the experimental sciatic neuronal constriction has induced neuropathic pain (91). The undersensibility toward nociceptive stimuli or neuropathic symptoms during diabetes or leprosy are reported in case of p75 receptor lack or decrease of CGRP and tachykinin immunoreactivity, because the underregulation of p75 may lead to an equilibrating reduction of TrkA expression (90,92,93). Alternatively, the increased NGF level during reparative fibrotising is associated with a simultaneous increase of TrkA production in fibroblasts, while the prolongation of this stimuli may induce the production of p75, indicating that p75 has a regulatory growth function during these processes (94-96). Interestingly, the NGF and insulin treatment both increased paw withdrawal to mechanical stimulation in experimental diabetic mice (60). Similarly to this report, in Alzheimer's disease there is a role for NGF in the pathogenesis and treatment of this disease, since a recent clinical trial has shown benefit from its exogenous application (46,58).

Discussion

NGF and its related mediators are involved in a wide variety of physiological or phys-pathological events as mentioned above. Apart from the induction of growth or surviving rates with respect to sensory neurological or non-neurological cellular populations, it is reported the overregulation of these compounds in these tissues during stress-related or inflammatory diseases (1). In effect, the relationship of neuronal factors and human endocrine and inflammatory responses has been thoroughly investigated in these years. Thus, the nervous system, through vagus nerve, can inhibit significantly and rapidly the release of macrophage tumor necrosis factor (TNF) and attenuate systemic inflammatory responses (97). This effect, called the cholinergic anti-inflammatory pathway, is an example that could expand our understanding of how the nervous system modulates immune responses (97,98). Generally, it is assumed that overproduction of cytokines can cause the clinical manifestations of disease, but recently, inflammation is considered on the same time a local, protective response to invasion or injury (98-100). Additionally, Watkins and Maier illustrated that inflammatory-induced pathological pain is not simply a strict neuronal phenomenon, but it is a component of immune response and is modulated by peripheral immune cells and spinal cord glia cells (101). With respect to this interaction, Joachim et al. have demonstrated that neutralization of NGF activity abrogates stress-induced effects on the percentage of SP+ sensory neurons in skin-innervating dorsal root ganglia (DRG) as well as on the dermal sensory nerve fibers (102). In other words, high stress perception results in an intense cross talk between the skin and skin-innervating DRG, which increases the likelihood of NGF-dependent neurogenic skin inflammation by enhancing sensory skin innervation (102). With respect to the inflammation of bronchial airways, there is reported a local concentration increase of NGFP compounds in the autochthonous and immigrated cellular populations, associated by the enhancement of their survival rates (except for epithelial cells, which show a damage) (103,104). The epithelial denudation of bronchi could be explained by the fact that, despite increased synthesis of NGF in the epithelial cells during airway inflammation, there is an absence of NGF receptors in this cellular population (in comparison with other autochthonous/immigrated cells of respiratory airways) (104).

Reflecting on the aforementioned facts, an important raising question might be: Why NGFP has exactly such different properties? What associates the surviving or growth stimulation with signalization (perception) of stressors? Firstly, the pleiotropic effects can increase the frequency of a gene even if it causes substantial effects on life span in the wild (105,106). In addition, mediators of NGFP are indispensable for the mammalian organism, and vice versa the organism is vital necessity for NGFP, because they cannot exist outside such organisms (1,46,58). On the other hand, mentioning that our existence can be meaningful due to concepts of being, understanding and speech, it could be assumed that being informed (understanding) has a key-role for our existence (107,108). In other words, the human being (or every mammalian) has organs not to exercise their functions per se, rather because these beings have inner specific qualities, which permit them to exist only organized in organs and systems. Thus, the human being does not have a stomach to digest: rather it is a digesting being (109). Likewise, the human being does not have sensorial systems to inform per se: he can survive only by being informed about the environment!

In this framework, many philosophers, biologists or psychologists have concluded that a specie could survive better and better, if they seize more and more precisely the relations in its environment, or if it could distinguish faster and more precisely the prey and the enemy (59). In this respect, the perception is orientation on environmental characteristics for vital and survival purposes, including the social life (59). A false exaggerated stressor (danger) signalization may

lead to a situation, in which a decent social life is non-conductible (such as during depression). Alternatively, the life is even in permanent danger during the situation of information's lack (such as during CIPA). Thus, the information is a vital power. Without this power (in this case represented by NGFP, but in interaction also with other pathways), the control over our body and our life is impossible, or in some situations the surviving too (81). In this context, it seems that the experience of danger (threatening) signals could be associated with an induction of supplemental vital and survival stimuli, independently to which organ, cellular population or system is threatened or involved. So, the stimulation of these surviving mechanisms may be an additional compensatory impulse for the organism.

Conclusion

NGFP is a vital instrument for mammalian organism and one of indispensable mechanisms of the information that seems to be required especially during the identification of a real or unreal danger providing also supplemental growth stimuli and therefore, better surviving possibilities. With respect to NGF, Levi-Montalcini has declared during her speech "NGF – 35 years later" that the submerged areas of NGF-iceberg loom very large (1). Nowadays, it is over more than a half century since NGF discovery, and her remark remains still actual. It could be not excluded that the forthcoming 50 years will not be enough to demonstrate the true identity card of NGFP, which may help us to use it for pharmacological purposes. During the last 15-20 years a modest intensified work is done with the intention of viewing through the depth of the ocean in which NGF-iceberg floats, but actually it could not be imagined how it seems the darkness of it in the depth and what it hides behind. Probably the success of a novel finding is condemned to be also measured with additional arisen questions. This fact should not be a shame, but probably the essential importance of human existence.

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