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Stress and nerve growth factor Findings in animal models and humans

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Abstract

Stress is elicited by environmental, social or pathological conditions occurring during the life of animals and humans that determine changes in the nervous, endocrine and immune systems. In the present review, we present data supporting the hypothesis that stress-related events both in animal models and humans are characterized by modifications of endogenous nerve growth factor (NGF) synthesis and/or utilization. Stress inducing alteration in NGF synthesis and/or utilization appears to be more severe during neurogenesis and in early postnatal life. However, NGF endogenously released during stress may promote remodeling of damaged tissues following acute and/or chronic stressful events.

Keywords: NGF; Stress; Schizophrenia; Electroconvulsive treatment; Environmental changes; Neurotrophin; Behavior

1. Stress

Stress is triggered by numerous unexpected environmental stimuli occurring during life, such as aggressive behavior, fear, forced physical activity, sudden environmental changes, social isolation or pathological situations (Denenberg et al., 1964; Greenough and Volkmar, 1973; Hilakivi-Clarke et al., 1991; McEwen and Sapolsky 1995; Mohammed et al., 1990, 1993; Weiner, 1989). Considerable evidence published in the last decades has focused on a constellation of neurochemical, biochemical and molecular effects caused by stress in the central nervous system (CNS) and in the endocrine and immune systems (Ben-Eliyahu et al., 1991; Eichelmann, 1992; Jiang et al., 1990; Levine et al., 1967; Nisipeanu and Korczyn, 1993; Santucci et al., 2000; Smith, 1996; Ueyama et al., 1997; Walsh et al., 1973). Neurohormones, cytokines and catecholamines have been considered as mediators of stress-induced immune and endocrine-related alterations, as well as in relation to the expression and severity of neuroimmunological and immunological disorders. Recent findings indicate that circulating and brain nerve growth factor (NGF) levels undergo significant variations after exposure to stressful events (Alleva et al., 1993; Aloe et al., 1986, 1990; Lakshmanan, 1987). We have shown that intermale aggressive behavior induced in mice by social isolation causes alteration in the NGF levels in the bloodstream (Aloe et al., 1990; Maestripieri et al., 1990) and in the CNS (Aloe et al., 1986, 1990, 1994b). We have also provided evidence that anxiety-like behavior induced by fear, alcohol consumption, heroin withdrawal and neuropsychiatric-like disorders is also characterized by an altered basal NGF level in the bloodstream (Aloe et al., 1997b; Bersani et al., 1999; Fiore et al., 1999, 2000, 2001), suggesting a possible NGF implication in the physiopathological response to stress and stress-related events. NGF is also implicated in the activation of the hypothalamic–pituitary–adrenal (HPA) axis (Otten et al., 1979; Scaccianoce et al., 1993; Snider and Johnson, 1989), representing a link between neuroendocrine and immune elements, that translates environmental messages, such as a stressful condition, into physiopathological responses. Chronic stress, depression and glucocorticoids seem to be key factors that lead to loss of brain neurons and reduced size of the hippocampus (Gould et al., 1990; Lane et al., 1997; Meaney et al., 1988).

The aim of this review is to present these and other emerging studies supporting the hypothesis that stress-

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related events both in animal models and humans are characterized by dysregulation of endogenous NGF synthesis and/or utilization. Because stress is known to affect the constitutive presence of hormones and cytokines, i.e., compounds known to play a regulatory role in NGF synthesis, a brief outline of these interrelated aspects will also be discussed.

2. NGF

NGF is the first discovered and best characterized member of a family of neurotrophic factors collectively called neurotrophins, which include brain-derived neurotrophic factor (BDNF) and neurotrophins 3 and 5 (NT-3, NT-5) (Barde, 1990). The term NGF was introduced to describe a growing effect on the developing sensory and sympathetic neurons of birds and mammals (Levi-Montalcini, 1987; Levi-Montalcini and Angeletti, 1966, 1968; Levi-Montalcini et al., 1990; Thoenen et al., 1987). High concentrations of NGF are present in the CNS where they are known to play a crucial role in growth, plasticity (Snider and Johnson, 1989; Spillantini et al., 1989; Thoenen and Barde, 1980; Thoenen et al., 1987) and normal function of brain neurons as well as in a variety of CNS disorders (Drago et al., 1994; Thoenen et al., 1987), including those associated with cognitive function deficits (Calamandrei and Alleva, 1995; Calzà et al., 1997; Fischer et al., 1987). Thus, NGF influences the development and functioning of the forebrain cholinergic neurons, which are involved in learning and cognitive processes (Levi-Montalcini, 1987; Neeper et al., 1995) and participate in the neuroregulation and fine-tuning of behavior during aging (Chen et al., 1995; Fatranskà et al., 1987; Fischer et al., 1987; Thoenen et al., 1987). The biological effects of NGF on target cells are mediated by two different receptors: TrkA receptor, which is a classical tyrosine kinase receptor activated in response to neurotrophin binding, and the p75 receptor, a member of the superfamily of TNF receptor-related molecules. p75 binds all the neurotrophins, displays extracellular and transmembrane domains, and lacks cytoplasmatic kinase domain for signal transductions, while TrkA receptor displays intracellular, transmembrane and extracellular domains, and transduces neurotrophin signaling through autophosphorylation by increasing tyrosine phosphorylation of cellular protein (Barde, 1990; Barbacid, 1993).

The largest known amounts of NGF are produced by the salivary glands (SGs) of adult male mice, which, even more than 40 years after the discovery of NGF, still represent the largest and best available NGF source. Smaller concentrations of NGF can be found in snake venom, guinea pig prostate, the seminal fluid of guinea pigs and bulls, and human skin (Aloe et al., 1994a; Levi-Montalcini, 1987; Levi-Montalcini and Angeletti, 1968). Physiologically significant quantities of NGF are synthesized and released also by a variety of nonneuronal and neuronal cells in birds and mammals. Changes in NGF levels have been observed during neuroendocrine dysregulation, in autoimmune and allergic diseases, neonatal stimulation (Pham et al., 1997) and following neurological insults (Levi-Montalcini et al., 1990; Alleva et al., 1993; Aloe et al., 1994a; Drago et al., 1994).

NGF is an important trophic factor for sympathetic neurons and is implicated in the responsiveness of immune competent cells (Aloe et al., 1994a, 1997a). There is evidence that NGF acts as an autocrine/paracrine factor in the development and regulation of immune cells and that it is produced by mast cells, eosinophils, and T and B lymphocytes, all of which express functional NGF receptors. NGF also promotes proliferation and differentiation of T and B lymphocytes and acts as a survival factor for memory B lymphocytes (Aloe et al., 2001a,b; Torcia et al., 1996).

Within the brain, NGF has been found in cortical association areas as the entorhinal cortex and its expression undergoes significant changes following chemical or surgical insults (Burgos et al., 1995; Drago et al., 1994; Fiore et al., 1999, 2000, 2001; Tsong-Hai et al., 1996). The entorhinal cortex and the hippocampus are associational areas that play a key role in the integration of behavioral outputs. Human studies on the entorhinal cortex and hippocampus also revealed that changes in these brain areas are associated with neuropsychiatric-like disorders (Bersani et al., 1999; Freedman et al., 1992; Gold and Weinberger, 1995; Kleinman et al., 1988) and recent studies have suggested that neurotrophic factors may be also implicated in neurodevelopmental disorders (Drago et al., 1994).

3. NGF and hormones

Biochemical, pharmacological and structural studies have revealed that NGF is synthesized in the granular convoluted tubules of the mouse male SG soon after puberty and that the female SG produces less NGF than the males (Levi-Montalcini, 1987; Levi-Montalcini and Angeletti, 1968). Exogenous administration of testosterone to young or adult females enhances the synthesis of NGF in the SG, whereas castration in males drastically reduces the SG NGF levels (Levi-Montalcini and Angeletti, 1968). Moreover, males and females respond differentially to NGF and/or NGF antibodies, which further suggests an involvement of male hormones in the NGF effect (Lane et al., 1997). There is also consistent evidence that in the CNS, NGF is hormonally regulated. Studies carried out in developing and adult rats showed that the amount of NGF produced and/or stored in the hippocampus decreases following adrenalectomy and is enhanced by exogenous administration of corticosteroids (Aloe, 1989; Lindholm et al., 1992; Tirassa et al., 1997). The hormonal effect is dose-dependent, since high dosages can also cause NGF down-regulation. Likewise, thyroid or thymic hormones seem to be implicated in the regulation of NGF synthesis, both within and outside the CNS. Indeed, we and others have provided evi-

dence that tyroxine administration increases the levels of NGF not only in the SG, but also in other endocrine glands as well as in the CNS (Aloe et al., 1994a; Calamandrei et al., 1996). Studies published over the last few years indicate that glucocorticoids released during chronic stress cause cell atrophy and/or cell death in the hippocampus, while antidepressant treatment increases brain neurogenesis. The interaction between NGF and hormones has been reported in different areas and conditions. This hypothesis is further supported by findings showing that circulating NGF levels are modified in physiological conditions characterized by neuroendocrine changes, such as pregnancy or child birth (Luppi et al., 1993). NGF stimulates the HPA axis by enhancing the secretion of ACTH and glucocorticoids (Otten et al., 1979; Scaccianoce et al., 1993; Smith, 1996; Snider and Johnson, 1989).

4. NGF and cytokines

Cytokines are produced not only by cells of the immune system, but also by cells localized within the CNS. They are generally associated with immune and inflammatory responses and participate in a variety of immunological and neuroimmunological disorders. There is also evidence showing that cytokines are involved in promoting repair of damaged brain and spinal cord neurons. For example, cytokines such as tumor necrosis factor (TNF-α) and some interleukins (IL-1, IL-6) can be produced in the brain as a result of neurodegenerative disorders, trauma, ischemia, infection, inflammation and in response to stress (Aloe et al., 1998; Lindholm et al., 1987). Whether these effects on damaged nerve cells are direct or mediated by neurotrophic factors is not clear. Results of studies carried out in our laboratory in recent years suggest that TNF-α, IL-1 and IL-6 exert their effect through the stimulation of NGF. Indeed, in vitro studies have demonstrated that IL-1 and TNF-α are strong promoters of NGF synthesis (Lindholm et al., 1987, 1992). We found that in transgenic mice overexpressing TNF-α, TNF-α is associated with the presence of endogenous NGF in the brain (Aloe et al., 1998). We have also shown that several autoimmune inflammatory disorders are characterized by altered coexpression of NGF and TNF-α (Aloe et al., 1997a, 1998). Synthesis and release of cytokines are affected by stressful events that can be associated with inflammatory responses and/or neuroimmunological and immunological disorders, including neoplasm (Aloe et al., 1997a; Ben-Eliyahu et al., 1991; Kogner et al., 1993; Riley, 1975). The available data are not fully consistent, since stress has been shown in some cases to potentiate immune function and to retard tumor growth, suggesting that different factors are implicated in the latter pathophysiological events. These observations seem to suggest that stress, under certain conditions and through the release of neurotrophic molecules, including NGF, positively influences neuronal circuits and microplasticity.

5. Stress and NGF

The observation that stress can produce significant alterations in circulating NGF levels raised the question as to whether prolonged exposure to high release of endogenous NGF and corticosteroids may elicit production of NGF antibodies. To address the question of whether chronic stressful conditions affect long-lasting neuroimmune interaction, we tested the effect of the endogenous released NGF on the immune responses. Using an NGF-deprived animal model (Johnson et al., 1993), we found that in a large number of subjects, chronic stress can induce the production of NGF antibodies as detected by both the inhibitory action of the mouse serum on rat sympathetic neurons in vitro and by the reduced adrenergic innervation of the iris (Aloe et al., 1995). Thus, under conditions of prolonged physiological stress, the adrenal steroids, acting in concert with excitatory amino acid neurotransmitters and depending on the extent and level of exposure, can cause reversible dendritic alterations or permanent neuronal loss, particularly in the aged brain (Black et al., 1990; Gould et al., 1990; Meaney et al., 1988). This observation suggests that a useful preclinical and clinical strategy might be to study individual differences in vulnerability to stress-induced effects in both animal and human populations, and to devise strategies that may help to protect the brain against long-term damage. Why only a relative small proportion of chronic stressed mice develop NGF antibodies is at present not known. However, such a wide intraspecific variability may tentatively be explained as different coping styles when repeatedly confronting an aggressive conspecific. It is also possible that this variability might be linked to the fact that winning or losing a social confrontation differentially affects endocrine and immune responses generating NGF antibodies. In addition, it has been reported that high levels of glucocorticoids or stress can induce atrophy on the dendritic branches of pyramidal neurons of the CA3 region of the rat hippocampus (Gould et al., 1990) and other studies carried out in rodents and in humans suggest that prolonged exposure to glucocorticoids might be associated with cognitive impairment and hippocampal neuronal loss (Meaney et al., 1988; McEwen and Sapolsky, 1995).

6. NGF in arousal–sedation conditions

Repeated experiences of defeat and submission significantly enhance the level of NGF compared with the dominant, attacking male mouse (Maestripieri et al., 1990). The increased amount of NGF values in subordinate mice does not correlate with either the number of attacks received or the defensive reactions opposed to them, suggesting that other stimuli, e.g., of a psychological nature, are implicated in the mechanisms triggering the NGF release (Maestripieri et al., 1990). The results of these studies lead to the hypothesis that fear and anxiety-like conditions might be

associated with activation of NGF-releasing or NGF target cells. To gain more information about the correlation between NGF and anxiety-like behavior, we measured the circulating NGF levels in parachutists experiencing stress induced by their first jumping performance (Fig. 1). The results of these studies showed that the plasma concentration of NGF in soldiers who experienced parachute jumping for the first time increased above the baseline levels of soldiers who were not selected for jumping (Aloe et al., 1994c). These observations revealed that the increase in NGF levels preceded the increase in plasma cortisol and adrenocorticotropic hormone, while no changes in the baseline levels of circulating IL-1 or TNF-α were found. This suggests that the increased levels of NGF, occurring in the absence of inflammation, were not related to changes in these cytokines. The circulating NGF released following stress induced by parachute jumping is biologically active, since it can influence NGF receptor expression in peripheral lymphocytes (Aloe et al., 1994c). The fact that the increase in NGF levels precedes the increase in cortisol and ACTH release supports the hypothesis that NGF might be involved in some alert mechanisms associated with homeostatic adaptation (Levi-Montalcini et al., 1990).

The influence of anxiety-like behavior on circulating NGF levels has also been observed in subjects experiencing alcohol or heroin withdrawal (Aloe et al., 1996). Consistent with the observations on laboratory animals, we found that anxiety-like behavior induced by alcohol or heroin abstinence can lead to an upregulation of plasma NGF levels and, as observed in rodents, also lead to changes in NGF in the CNS (Aloe et al., 1996) (Fig. 2). Following these observations, we wondered whether an antianxiogenic condition would lower the constitutive level of circulating NGF. We thus investigated the effect of pharmacological compounds that are effective in producing sedation. Administration of haloperidol, a neuroleptic drug which induces sedation and is used clinically to treat psychiatric disorders, decreases NGF levels in the brain and blood of adult male mice (Alleva et al., 1996). Haloperidol administration in neuroleptic-free schizophrenic patients was found to reduce the basal NGF plasma levels (Aloe et al., 1997b). These observations strengthen the hypothesis that NGF may play a functional role in stress-coping responses. Whether the low NGF levels after haloperidol administration are due to a reduced synthesis and/or release of NGF or to an enhanced uptake in the NGF-responsive cells needs to be verified. Nonetheless, emerging evidence seems to indicate that haloperidol affects the metabolic rate of numerous cell types by interfering negatively with the activity of NGF-producing cells or NGF-receptive cells. Interestingly, the recent observation showing that treatment with haloperidol impairs dendritic spines in the striatum of adult rats (Kelley et al., 1997) and the study demonstrating the crucial role of NGF on nerve cell and synaptic plasticity (Burgos et al., 1995) suggest that NGF may be implicated in this haloperidol-impaired dendritic deficit.

7. NGF and stress-related events in humans

Following up the observations on stress responses and neurotrophin release in animal models and in humans, our studies were extended to human behavioral deficits. It was hypothesized that aggressive behavior and stress induced by maternal separation or delivery causing significant alteration of basal NGF levels (Aloe et al., 1986, 1994c; Cirulli et al., 1998; Luppi et al., 1993; Manni et al., 1998) or causing changes in neurotrophic factor during a critical developmental stage of brain neurogenesis can lead to schizophrenia-like behavior in adulthood (Beckmann and Jakob,

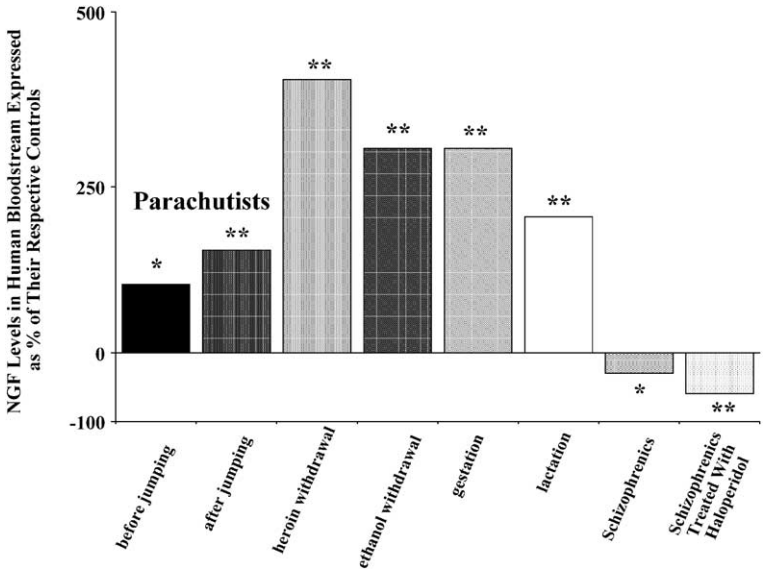

Fig. 1. Schematic picture showing the changes in NGF levels in humans following some stressing situations (**$P<.01$, *$P<.05$).

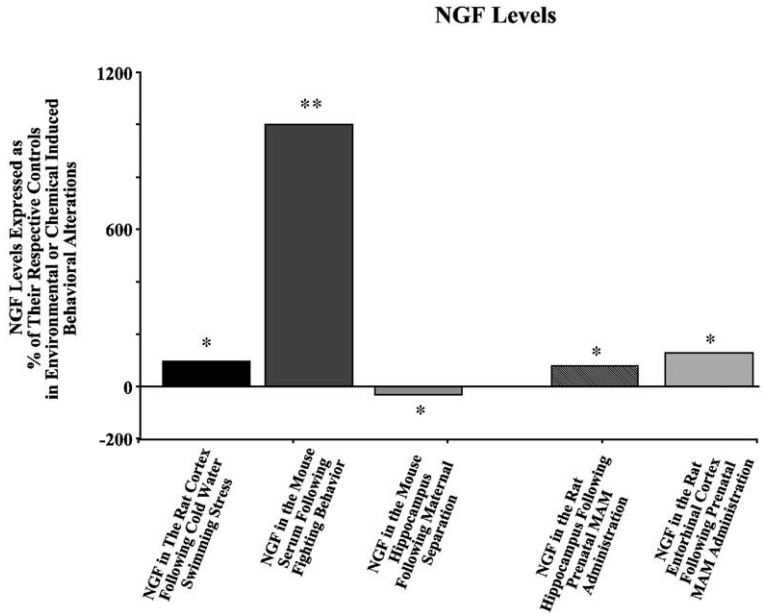

Fig. 2. Schematic picture showing the changes in NGF levels in animal models following some stressing situations ($**P<.01$, $*P<.05$).

1994; Fiore et al., 1999). Indeed, a variety of emerging studies on postmortem human brain and on animal models seem to suggest that entorhinal cortex maldevelopment may be a prominent cause of schizophrenia-like deficits in adult life (Akil and Lewis, 1997). Studies carried out in our laboratory in collaboration with the Dipartimento di Psichiatria dell'Universita' di Roma showed that schizophrenic patients had decreased NGF levels in the bloodstream (Aloe et al., 1997b) compared to healthy subjects. Although the ethiopathogenesis of schizophrenia is known to be associated with a variety of genetic and epigenetic factors, there is emerging evidence to indicate that deficits in neurotrophic factors during a critical developmental period of neurogenesis may contribute to the developmental deficits leading to this human disorder (Aloe et al., 1997b; Bersani et al., 1999; Freedman et al., 1992; Kleinman et al., 1988). The hypothesis that neurotrophins, including NGF, might be implicated in the neurodevelopmental deficits of schizophrenia is supported by other recent studies showing that NT-3 gene polymorphism is associated with this disorder (Nanko et al., 1994) and by the fact that embryonic hippocampal tissue derived from schizophrenic women and transplanted into rat hosts displayed profound abnormalities in survival and growth compared to control tissue (Freedman et al., 1992). Other evidence supporting the hypothesis of a NGF role in schizophrenia-like behavior comes from recent observations that brain neurotrophin distribution in adult rodents is severely affected by electroconvulsive treatment (ECT), lithium administration or, as emerged by studies published in collaboration with the Department of Biological Psychiatry of Groningen University on entorhinal cortex maldevelopment (Angelucci et al., 2000a,b; Fiore et al., 1999, 2000, 2001). Furthermore, the observations that chronic treatment with haloperidol and risperidone alters the NGF and BDNF levels in restricted rat brain regions as well as the expression of high-affinity NGF receptors (Angelucci et al., 2000a,b) point to a potential role of neurotrophins in neuromaldevelopment. Interestingly, data recently published by our group indicate that significant changes in NGF and BDNF concentrations were also found in the frontal cortex, occipital cortex and hypothalamus of "depressed" Flinders-Sensitive Line rats compared to Flinders-Resistant Line control rats and these changes in neurotrophin expression were more marked in females than in males (Angelucci et al., 2000a).

8. Concluding remarks

There is now considerable experimental evidence to demonstrate that stress and stress-related events, via a complex network of multidirectional signals involving the nervous, endocrine and immune systems, can influence the production of important biological mediators, including neurotrophins. It is known, for example, that exposure to acute or chronic stress, regardless of age (Hadjiconstantinou et al., 2001; Mohammed et al., 1993), can lead to significant alteration of circulating and brain NGF and BDNF levels. It has also been shown that the NGF released during stress in young and adult subjects influences the basal activity of nerve, immune and endocrine cells (Levi-Montalcini et al., 1990) expressing NGF receptors and responding to the action of NGF. The alteration in NGF synthesis and/or utilization as a result of stressful events seems to be pathophysiologically more relevant during neurogenesis and in early postnatal life. Indeed, impairments of NGF

synthesis and/or utilization during a critical brain developmental phase may affect synaptic plasticity and lead to long-lasting behavioral and neuropathological deficits in adult life. Stress induced by fear or maternal separation in animal models is associated with a significant alteration of brain and circulating NGF levels and behavioral deficits in adult life (Cirulli et al., 1998; Kalin, 1993; Manni et al., 1998; Meaney et al., 1988). Since allergic reaction and asthma are characterized by an elevated presence of plasma NGF (Bonini et al., 1996), the question as to whether maternal separation, allergy and NGF are physiologically linked remains open.

Because the released NGF in response to stress is biologically active, one question raised by our findings is whether stress and release of NGF during or immediately following stress trigger or exacerbate immunological, neuroimmunological and endocrine disorders. The observation, that NGF has been shown to play a role in promoting tissue repair of damaged nerve cells (Eichelmann, 1992) and to have an antiinflammatory action (Aloe et al., 1997a) and healing properties in the case of cutaneous ulcers (Bernabei et al., 1999; Lambiase et al., 1998), seems to indicate that the NGF endogenously released during stress possibly participates in promoting cell repair and the remodeling of damaged tissues due to acute and or chronic stressful events. Based on our recent collaborative studies, it seems that NGF represents an important neurotrophic factor for the development of the entorhinal cortex that can co-occur with neuronal maldevelopment of this portion of the limbic system, which is implicated in schizophrenic-like deficits. The aim of our ongoing and future studies is to address these questions and to produce evidence to support or challenge this hypothesis.

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