# Stress, anxiety and schizophrenia and neurotrophic factors: the pioneer studies with nerve growth factor

## *Stress, schizofrenia e fattori neurotrofici: gli studi pionieristici con il nerve growth factor*

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**SUMMARY.** The aim of this review is to highlight past and ongoing studies on neurotrophin (NT) role, in particular focusing on nerve growth factor (NGF), on behavioral response to stress, agonistic and emotional behavior, anxiety, and schizophrenia. One of the first evidences of NGF involvement in behavioral response to a social challenge was published in 1986. In male mice, agonistic encounters caused a massive NGF release into the bloodstream and in the hypothalamus. Subsequent studies revealed that this NGF release was not strictly linked to agonistic behavior, but to mice hierarchical status, with subordinates having higher NGF levels than dominants. This observation led to the hypothesis and later to the demonstration that NGF release is associated to anxiety-related behaviors. Later studies provided evidence for the involvement of NTs, including NGF, in the development of neuropsychiatric disorders. Interestingly, pharmacological treatment can reduce the effects of the maldevelopment and neuropathology due to NT imbalance during early periods of life crucial for development. Further understanding of the core pathophysiological mechanism for neurodegenerative and psychiatric disorders will eventually provide tools for amelioration of symptoms of those psychiatric disorders characterized by an NT imbalance.

**KEY WORDS:** neurotrophins, NGF, stress, anxiety, psychiatric disorders, schizophrenia, antipsychotic drugs.

**RIASSUNTO.** L'obiettivo di questa rassegna è quello di presentare gli studi passati e ancora in corso sul ruolo delle neurotrofine (NT), con particolare riguardo per il fattore di crescita nervoso (NGF), sulla risposta comportamentale allo stress, sul comportamento agonistico ed emozionale, sull'ansia e la schizofrenia. Una delle prime evidenze dell'implicazione del NGF nella risposta comportamentale a una sfida sociale è stata pubblicata nel 1986. Nei topi maschi, episodi di aggressività causavano un rilascio consistente di NGF nel sangue e nell'ipotalamo. Studi successivi hanno dimostrato che questo innalzamento del NGF non era strettamente correlato al comportamento agonistico, ma allo stato gerarchico dei topi, con i topi subordinati con livelli di NGF più alti rispetto ai dominanti. Questa osservazione portò all'ipotesi e successivamente alla dimostrazione che il rilascio di NGF era associato ai comportamenti ansia-correlati. Studi eseguiti successivamente hanno fornito l'evidenza dell'implicazione delle NT, incluso il NGF, nello sviluppo dei disturbi neuropsichiatrici. Appare molto interessante il fatto che il trattamento farmacologico può ridurre gli effetti del *maldevelopment* e dei quadri neuropatologici dovuti allo squilibrio delle NT durante le fasi precoci della vita, cruciali per lo sviluppo. Inoltre, la comprensione del meccanismo patologico *core* per i disturbi neurodegenerativi e psichiatrici potrà eventualmente fornire gli strumenti per migliorare i sintomi di quei disturbi psichiatrici caratterizzati da uno squilibrio delle NT.

**PAROLE CHIAVE:** neurotrofine, NGF, stress, ansia, disturbi psichiatrici, schizofrenia, antipsicotici.

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## INTRODUCTION

Among neurotrophins (NTs), nerve growth factor (NGF) was the first to be identified and the best characterized member of neuroprotective molecules, collectively called neurotrophins. Besides NGF, the main factors belonging to the NT family are: brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), neurotrophin-4/5 (NT-4/5), neurotrophin-6 (NT-6) and others, such as ciliary neurotrophic factor (CNTF) (1). These polypeptides can affect cell survival and activity in central nervous system (CNS). In particular, NGF is thought to play its role for survival of sympathetic and some sensory and central cholinergic neurons (2). Additionally, this molecule acts outside of the nervous system, particularly within neuroendocrine and immune system.

### *NGF, stress and anxiety-related behavior*

First evidence of a link between NGF and behavior was the observation that in male mice, following agonistic episodes, NGF is released into the bloodstream from salivary glands and that its circulating levels are highly correlated with the number of agonistic episodes (3). NGF release appears to be specifically induced by agonistic encounters, which are considered a classical model of psychosocial stress in male mice (4). Remarkably, NGF circulating levels reflect not only the number of aggressive episode, but also animal hierarchical status. In pairs of fighting mice, thus, subordinates have larger NGF circulating levels relative to dominants (5). These observations were first evidence of a direct link between psychosocial stress and NGF circulating levels in an animal model.

A subsequent study on emotional and physical stress carried out on young soldiers confirmed and extended to humans previous findings in mice (6). In this study blood samples were collected from Italian soldiers before and after parachute jumping in order to detect NGF variations in the bloodstream due to such a stressful event. Interestingly, not only were the NGF levels elevated due to psychological stress, but they also preceded the enhancement of cortisol and ACTH plasma levels, as a sort of early alert mechanism associated with a homeostatic adaptation. Similarly, another study on humans measuring oxytocin in pregnant and lactating women revealed that circulating NGF increase along with the *pre-* and *post-partum* oxytocin enhancement, whereas in the umbilical cord NGF levels remain at baseline level (7). Again, a possible interpretation of this outcome can be viewed in light of subjects' anxiety state. It is, indeed, worth stressing out that subjects perceiving the delivery approaching (the parturient women) had high NGF levels. On the other hand, it is not known whether during prenatal neurogenesis a variation of circulating NT can be influenced by changes in maternal hormonal *milieu*.

In the wake of the above-mentioned human studies, a study on alcoholic subjects yielded that chronic alcohol withdrawal, and not just the mere alcohol presence in the bloodstream, alters circulating NGF levels, indicating thus that events linked to alcohol withdrawal (such as anxiety, tremor, and hyper-excitability) are involved in NGF release into the bloodstream (8). Consistently, another human study revealed that high perceived stress and depression in caregivers are associated with elevated NGF blood levels (9). Therefore, NGF blood levels might provide an early marker of stress perception in both humans and other animals as a sort of "alerting" behavior at both cellular and organism levels. Indeed, besides trophic function, NGF seems to be involved in stress response and function of hypothalamic-pituitary-adrenocortical axis response (10), regulating hormonal and behavioral responses to both environmental and social challenging situations. The evidence that an "emotional response" induced by parachute jumping causes NGF enhancement preceding corticosteroid release (6) is consistent with this hypothesis.

In many animal species, including humans, a challenging situation can be represented by the acquisition/defense of a resource, such as territory, food and/or mating partner. Emanuele, et al. (11) reported that NGF levels (and not of other NTs) are significantly elevated in the early phase of romantic love, reporting a positive correlation between romantic love intensity and circulating NGF levels. Furthermore, these researchers followed up subjects in "acute love" that maintained the relationship and interestingly observed that NGF levels were restored to baselines after 12-24 months, i.e. during the phase of "chronic love". Overall this study provides further evidence for the role of NGF in human social chemistry.

The idea that anxiety status of experimental subjects could be a *file rouge* linking together changes in NGF levels in both humans and mice was the starting point for several and different projects focusing on mental disorders, such as alcohol/drug addiction, anxiety, depression, schizophrenia. It is worth pointing out that an altered defense mechanism is implicated in many of, if not all, the above-mentioned diseases. The notion of serum NGF should be considered as a state rather than a trait-dependent variable (12), particularly in considering early symptoms of cognitive disorders.

*NGF and psychiatric disorders*

The observation that neuronal loss or decreased neurogenesis occurs in brains of patients with a long history of depression (13) provides a connection between this syndrome and NTs. Consistently, in an animal model of depression, namely the Flinders Sensitive Line (FSL) rats, altered levels of both NGF and BDNF in several brain areas have been reported (14). Not only there is a relation between NGF and psychiatric disorders, but also a link between this molecule and drug treatment for such disorders. For instance, Iannitelli, et al. (15) reported that the therapeutic improvement with electroconvulsive therapy (ECT) in depressed patients is associated with a significant release of NTs, particularly NGF. Remarkably, in addition to an ECT direct effect on NGF levels, Bersani, et al. (16) reported a significant increase in NGF before the ECT session started (i.e., induced by the ECT waiting). Therefore, besides an enhancement of both synaptic sprouting and monoamine synthesis/turnover, NGF and ECT can promote neuroendocrine effects and regulate homeostasis (17).

Taken together these observations led to the idea that antidepressant treatments exert their beneficial action by regulating synthesis and/or release of NTs (18), although there is no evidence for a defect in NTs or their receptors to cause directly a human disease affecting nervous system (19). Indeed, antidepressants generally restore normal levels of NT expression in the brain (13). For instance, lithium, the classical drug used against bipolar depression, increases NGF concentrations in hippocampus and other brain regions (20). Likewise, haloperidol can reduce NGF levels in psychotic patients (21). Besides NGF, another NT, BDNF, injected into the brain has antidepressant-like effects and it can lead to recovery of behavioral deficits in the forced swim test in an animal model of depression, namely the learned helplessness (22).

*Animal model of schizophrenia*

Epidemiological studies indicate that gestational and postnatal alterations in brain neurogenesis may increase the risk of developing behavioral and/or neuropathological deficits leading to schizophrenia during early and late post-natal life (23). This neurodevelopmental disorder is characterized by behavioral impairments in cognitive and social performances, disruption of brain cytoarchitectural and neural plasticity in limbic system, particularly in entorhinal cortex (EC) and hippocampus (24). There is also evidence that brain injury due to maternal starvation, infection, and anoxic birth can lead later in life to behavioral and brain structural deficits resembling those observed in schizophrenia (25-27). Neurotrophic factors are signaling molecules that are able to influence survival, differentiation, maintenance and connectivity of developing and adult brain nerve cells, including those that are severely damaged and, thus, underlying schizophrenic-related behaviors (28).

The observations that NGF and BDNF play a crucial role during primary development of cholinergic neurons underlying learning and memory regulation (29-31) and that NGF blood levels in schizophrenic patients are lower compared to healthy controls (32) suggested a link between memory impairments and NT distribution in schizophrenic patients (33). Several animal models resemble some steps of human schizophrenia pathogenesis due to maldevelopment occurring early in life, namely asphyxia and drug-induced models. Using the former model, it has been observed that reduced BDNF levels in striatum of $N_2$-exposed rats couple with the risk of developing some symptoms of schizophrenia, such as social withdrawal, neophobia and stereotypy (34). Consistently, similar behavioral effects in a trans-generational drug-induced model for schizophrenia have been reported (35,36). Rats exposed to MAM during prenatal life (particularly at gestational day 12) showed impairments in learning and memory and in nociception associated to altered NGF levels in EC. Furthermore, prenatal MAM-exposure induces abnormalities in limbic system resembling some morphological and behavioral findings observed in human schizophrenia. In subsequent years, we reported changes at behavioral, cellular, biochemical and molecular levels in limbic system of adult prenatally MAM-exposed rats (28,37). Our findings suggested that dysregulation of synthesis and secretion of NTs, such as NGF and BDNF, is involved in brain and behavioral alterations (28,37). Furthermore, using the MAM model we investigated the effects of two antipsychotics, namely Clozapine and Haloperidol, on NGF and BDNF levels in both brain and bloodstream (38). Clozapine and haloperidol administration during adolescence affected both NGF and BDNF levels in both brain and bloodstream of prenatally MAM-exposed rats. Thus, this observation provided further evidence that the MAM model can be a useful tool to investigate biochemical and molecular mechanisms involved in the behavioral effects of antipsychotic drugs.

The new generation of antipsychotics such as risperidone and olanzapine compared to the first generation, such as haloperidol and chlorpromazine, have neuroprotective effects in both human patients and animal models (39). Animal studies suggest that such effects are probably mediated through an enhanced

expression of NTs, particularly NGF and BDNF. Thus, changes of NGF plasma concentrations in response to treatment with antipsychotics may, indeed, have a significant role in restoring brain structure and function.

*Treatment of psychiatric disorders with NGF*

The idea of studying the NGF role in psychiatric disorders originates from findings on animal models indicating that this molecule plays a crucial role in CNS development, in stress response, in integrating neuroendocrine functions, in activating agonistic behavior, as well as in mechanisms at the basis of kindling and neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. The first human studies provided evidence that NTs, particularly NGF, regulate CNS functional changes, respond to drug administration and possibly modulate the phenotypic representation of psychiatric disorders (21). Therefore, molecules known to regulate neuronal plasticity in learning and memory have been proved to be also involved in the actions of drugs used against depression and bipolar disorders. As a consequence, NGF was studied in the past and is still being studied today in preclinical and clinical contexts in relation to development and treatment of CNS pathologies (40,41). The hypothesis underlying the NT use as therapeutics assumes that these diseases result in decreased NT availability in affected brain neurons, and decreased NT receptor number on affected neurons. The exogenous NT administration can compensate such deficits. Under these conditions, the hypothesis is that NT administration would provide symptomatic treatment for the disease state rather than a cure for these nervous system disorders.

To date, a growing body of efforts is being devoted to the investigation on the NGF potential use as therapeutic, since the recent development of recombinant DNA technology for the production of large amounts of active human NGF (42). There are, though, pros and cons of NGF systemic administration to take into account. Beside promoting synaptic plasticity and preventing or reversing experimental neuropathies, NGF can elicit other responses. For instance, NGF can affect sympathetic nervous system (43,44), blood pressure (45), proliferation of neurogenic tumor cells, body weight gain (46), and nociception (hyperalgesia) (47). It is, thus, conceivable that further knowledge of NGF pharmacokinetic properties will address the choice of appropriate dose regimens to optimize its potential healing actions and hopefully reduce negative side effects (48).

Concerning other NTs, only recently, a number of studies linked a single nucleotide polymorphism in the BDNF gene with memory impairments, as well as altered susceptibility to neurodegenerative and/or psychiatric disorders, such as Alzheimer's (49) and Parkinson's diseases (50), depression (51), eating (52) and bipolar disorder (53). A common clinical symptom among these disorders is varying degrees of higher cognitive abilities. With the established role of BDNF in mediating processes related to learning and memory (54,55), this susceptibility to cognitive impairments may have broad roles in multiple disorders affecting nervous system functioning (19). As mentioned above, low BNDF levels were reported in both schizophrenic patients (32,56) and depressed patients (57,58). Recently low BDNF plasma levels have been indicated as biological marker of suicidal depression (59). Several studies reported antidepressant effects of exogenous BDNF administration into specific brain areas, particularly in the hippocampus (for a review, see reference 60). Similar effects in animal models of depression have been reported for other growth factors, such as NT-3 (61), insulin-like growth factor-I (IGF-I) (62), and vascular endothelial growth factor (VEGF) (63). Therefore, it is conceivable that drugs that selectively stimulate the NT synthesis and/or activate the NT signaling pathways could represent potential pharmacological tools in the treatment of depression- and schizophrenic-like disorders.

## THE EFFECT OF ANTIPSYCHOTIC DRUGS IS MEDIATED BY NEUROTROPHINS

Clozapine has been reported to increase NGF levels in both blood and EC, whereas BDNF levels in EC only (38). In the hippocampus, haloperidol enhances NGF levels, while in the striatum this drug elevates both the NGF and BDNF levels (39). Given that both of these NTs are markedly involved in promoting and maintaining brain neuron plasticity clozapine or haloperidol may produce their effects modulating NGF/BDNF synthesis and release. Furthermore, in prenatally MAM-exposed rats, clozapine and haloperidol influence both TrkA and TrkB expression. Particularly, in the hippocampus clozapine increases TrkB expression, whereas haloperidol elevates TrkA/TrkB expression in EC, which is known to be a highly vulnerable structure in schizophrenic brain (56,64-66). In human *post-mortem* schizophrenic brains, TrkB expression appears to be reduced either with or without neuroleptic treatment (67), while in living schizophrenic patients NGF and BDNF baselines undergo through significant changes (12,32,67,68). The second-generation of antipsychotics, olanzapine, quetiapine, and

clozapine enhance neurite outgrowth induced by NGF in PC12 cells (69). Chronic exposure to haloperidol, but not to the atypical antipsychotics risperidone or clozapine, alters choline acetyltransferase brain levels (65,70), an enzyme regulated by NGF (71). As already mentioned, in rat hippocampus and striatum, haloperidol administration decreased NGF or BDNF levels (39). Furthermore, a time-course study on haloperidol effects yielded elevated NGF values in hippocampus after 1 or 2 weeks of treatment (72). These findings led to the hypothesis that the MAM-exposed rat model represents a stool for investigating undesired side effects of antipsychotics and eventually neurotrophic-linked molecular events and mechanisms involved in "schizophrenia-like" diseases.

## CONCLUDING REMARKS

In our review we highlighted the recent and ongoing studies on NTs role, particularly NGF, in psychiatric diseases. It is often difficult to extrapolate animal data to human outcomes, but findings obtained through animal studies can lead to interesting working hypothesis in the clinic. The idea of using NT administration to treat neurological diseases is based on the assumption of symptomatic treatment of impaired neurons. It has become evident that appropriate delivery of sufficient NT quantities to target neurons is a major obstacle, besides large side effects, such as epileptic activity. Development of small molecules, that can readily cross the blood-brain barrier to activate NT receptors, could represent an additional tool in understanding whether NTs, including NGF, may have a therapeutic potentiality. Indeed, Chao, et al. (19) recently hypothesize that the road of receptor activation should be actively pursued with pharmacological studies utilizing peptides and other small molecules that might serve as NT agonists or antagonists. It is conceivable that such an alternative road could provide further understanding to identify novel pathophysiological mechanisms involved in the development of neurodegenerative and psychiatric disorders.

## REFERENCES


1. Barde YA: The nerve growth factor family. Progress in Growth Factor Research, 1990, 2, 237-248.
2. Aloe L, Alleva E, De Simone R: Changes of NGF level in mouse hypothalamus following intermale aggressive behaviour: biological and immunohistochemical evidence. Behavioural Brain Research, 1990, 39, 53-61.
3. Aloe, Alleva, Böhm, Levi-Montalcini: Aggressive behavior induces release of nerve growth factor from mouse salivary gland into the bloodstream. Proceedings of the National Academy of Sciences of the USA, 1986, 83, 6184-6187.
4. Axelrod J, Reisine TD: Stress hormones: their interaction and regulation. Science, 1984, 224, 452-459.
5. Maestripieri D, De Simone R, Aloe L, Alleva E: Social status and nerve growth factor serum levels after agonistic encounters in mice. Physiology & Behavior, 1990, 47, 161-164.
6. Aloe L, Bracci-Laudiero L, Alleva E, Lambiase A, Micera A, Tirassa P: Emotional stress induced by parachute jumping enhances blood NGF levels and the distribution of NGF receptors in lymphocytes. Proceedings of the National Academy of Sciences of the USA, 1994, 91, 10440-10444.
7. Luppi P, Levi-Montalcini R, Bracci-Laudiero L, Bertolini A, Arletti R, Tavernari D, et al.: NGF is released into plasma during human pregnancy: an oxytocin-mediated response? Neuroreport, 1993, 4, 1063-1065.
8. Aloe L, Tuveri MA, Guerra G, Pinna L, Tirassa P, Micera A, et al.: Changes in human plasma nerve growth factor level after chronic alcohol consumption and withdrawal. Alcoholism, Clinical and Experimental Research, 1996, 20, 462-465.
9. Hadjiconstantinou M, McGuire L, Duchemin AM, Laskowski B, Kiecolt-Glaser J, Glaser R: Changes in plasma nerve growth factor levels in older adults associated with chronic stress. Journal of Neuroimmunology, 2001, 116, 102-106.
10. Levi-Montalcini R, Skaper SD, Dal Toso R, Petrelli L, Leon A: Nerve growth factor: from neurotrophin to neurokine. Trends in Neurosciences, 1996, 19, 514-520.
11. Emanuele E, Politi P, Bianchi M, Minoretti P, Bertona M, Geroldi D: Raised plasma nerve growth factor levels associated with early-stage romantic love. Psychoneuroendocrinology, 2006, 31, 288-294.
12. Jockers-Scherübl MC, Rentzsch J, Danker-Hopfe H, Radzei N, Schürer F, Bahri S, et al.: Adequate antipsychotic treatment normalizes serum nerve growth factor concentrations in schizophrenia with and without cannabis or additional substance abuse. Neuroscience Letters, 2006, 400, 262-26.
13. Duman RS, Heninger GR, Nestler EJ: A molecular and cellular theory of depression. Archives of General Psychiatry, 1997, 54, 597-606.
14. Angelucci F, Aloe L, Vasquez PJ, Mathé AA: Mapping the differences in the brain concentration of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF) in an animal model of depression. Neuroreport, 2000, 11, 1369-1373.
15. Iannitelli A, Aloe L, Bersani G, Maselli P, Angelucci F, Bracci-Laudiero L, et al.: Seizure-induced serum NGF levels increase after ECT in psychiatric patients: a first pilot study in man. Behavioural Pharmacology, 1995, 6, 93-94.
16. Bersani G, Iannitelli A, Fiore M, Angelucci F, Aloe L: Data and hypotheses on the role of nerve growth factor and other neurotrophins in psychiatric disorders. Medical hypotheses, 2000, 55, 199-207.
17. Fink M: Neuroendocrinology and ECT: a review of recent developments. Comprehensive Psychiatry, 1980, 21, 450-459.
18. Duman RS, Malberg J, Thome J: Neural plasticity to stress and antidepressant treatment. Biological Psychiatry, 1999, 46, 1181-1191.
19. Chao MV, Rajagopal R, Lee FS: Neurotrophin signalling in health and disease. Clinical Science (London), 2006, 110, 167-173.
20. Hellweg R, Lang UE, Nagel M, Baumgartner A: Subchronic treatment with lithium increases nerve growth factor content in distinct brain regions of adult rats. Molecular Psychiatry, 2002, 7, 604-608.

21. Aloe L, Iannitelli A, Bersani G, Alleva E, Angelucci F, Maselli P, et al.: Haloperidol administration in humans lowers plasma nerve growth factor level: evidence that sedation induces opposite effects to arousal. Neuropsychobiology, 1997, 36, 65-68.
22. Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM: Antidepressant-like effect of brain-derived neurotrophic factor (BDNF). Pharmacology, Biochemistry and Behavior, 1997, 56, 131-137.
23. Rapoport JL, Addington AM, Frangou S, Psych MR: The neurodevelopmental model of schizophrenia: update 2005. Molecular Psychiatry, 2005, 10, 434-449.
24. Weinberger D: Cell biology of the hippocampal formation in schizophrenia. Biological Psychiatry, 1999, 45, 395-402.
25. Decker MJ, Rye DB: Neonatal intermittent hypoxia impairs dopamine signaling and executive functioning. Sleep & Breathing, 2002, 6, 205.
26. Hulshoff Pol HE, Hoek HW, Susser E, Brown AS, Dingemans A, Schnack HG, et al.: Prenatal exposure to famine and brain morphology in schizophrenia. American Journal of Psychiatry, 2000, 157, 1170-1172.
27. Sperner-Unterweger B: Immunological aetiology of major psichiatric disorders: evidence and therapeutic implications. Drugs, 2005, 65, 1493-1520.
28. Fiore M, Korf J, Antonelli A, Talamini L, Aloe L: Long-lasting effects of prenatal MAM treatment on water maze performance in rats: associations with altered brain development and neurotrophin levels. Neurotoxicology and Teratology, 2002, 24, 179-191.
29. Mobley WC, Rutkowski JL, Tennekoon GI, Gemski J, Buchanan K, Johnston MV: Nerve growth factor increases choline acetyltransferase activity in developing basal forebrain neurons. Brain Research, 1986, 387, 53-62.
30. Spillantini MG, Aloe L, Alleva E, De Simone R, Goedert M, Levi-Montalcini R: Nerve growth factor mRNA and protein increase in hypothalamus in a mouse model of aggression. Proceedings of the National Academy of Sciences of the USA, 1989, 86, 8555-8559.
31. Yuen EC, Mobley WC: Therapeutic potential of neurotrophic factors for neurological disorders. Annals of Neurology, 1996, 40, 346-354.
32. Bersani G, Iannitelli A, Maselli P, Pancheri P, Aloe L, Angelucci F, et al.: Low nerve growth factor plasma levels in schizophrenic patients: a preliminary study. Schizophrenia Research, 1999, 37, 201-203.
33. Aloe L, Iannitelli A, Angelucci F, Bersani G, Fiore M: Studies in animal models and humans suggesting a role of nerve growth factor in schizophrenia-like disorders. Behavioural Pharmacology, 2000, 11, 235-242.
34. Laviola G, Adriani W, Rea M, Aloe L, Alleva E: Social withdrawal, neophobia, and stereotyped behavior in developing rats exposed to neonatal asphyxia. Psychopharmacology, 2004, 175, 196-205.
35. Talamini LM, Koch T, Ter Horst GJ, Korf J: Methylazoxymethanol acetate-induced abnormalities in the entorhinal cortex of the rat; parallels with morphological findings in schizophrenia. Brain Research, 1998, 789, 293-306.
36. Fiore M, Talamini L, Angelucci F, Koch T, Aloe L, Korf J: Prenatal methylazoxymethanol acetate alters behavior and brain NGF levels in young rats: a possible correlation with the development of schizophrenia-like deficits. Neuropharmacology, 1999, 38, 857-869.
37. Di Fausto V, Fiore M, Aloe L: Exposure in fetus of methylazoxymethanol in the rat alters brain neurotrophins' levels and brain cells' proliferation. Neurotoxicology and Teratology, 2007, 29, 273-281.
38. Fiore M, Di Fausto V, Iannitelli A, Aloe L: Clozapine or haloperidol in rats prenatally exposed to methylazoxymethanol, a compound inducing entorhinal-hippocampal deficits, alter brain and blood neurotrophins' concentrations. Annali dell'Istituto Superiore di Sanità, 2008, 44, 167-177.
39. Pillai A, Terry AV Jr, Mahadik SP: Differential effects of long-term treatment with typical and atypical antipsychotics on NGF and BDNF levels in rat striatum and hippocampus. Schizophrenia Research, 2006, 82, 95-106.
40. Hefti F: Development of effective therapy for Alzheimer's disease based on neurotrophic factors. Neurobiology of Aging, 1994, 15, S193-S194.
41. Olson L, Backman L, Ebendal T, Eriksdotter-Jonhagen M: Role of growth factors in degeneration and regeneration in the central nervous system; clinical experiences with NGF in Parkinson's and Alzheimer's diseases. Journal of Neurology, 1994, 242, S12-S15.
42. Schmelzer CH, Burton LE, Chan WP, Martin E, Gorman C, Canova-Davis E, et al.: Biochemical characterization of recombinant human nerve growth factor. Journal of Neurochemistry, 1992, 59, 1675-1683.
43. Ueyama T, Hano T, Hamada M, Nishio I, Masuyama Y: New role of nerve growth factor: an inhibitory neuromodulator of adrenergic transmission. Brain Research, 1991, 20, 559, 293-296.
44. Zettler C, Head RJ, Rush RA: Chronic nerve growth factor treatment of normotensive rats. Brain Research, 1991, 538, 251-262.
45. Yan Q, Settle SL, Wilkins MR: Hypotension induced by intravascular administration of nerve growth factor in the rat. Clinical Science (London), 1991, 80, 565-569.
46. Yaeger MJ, Koestner A, Marushige K, Marushige Y: The use of nerve growth factor as a reverse transforming agent for the treatment of neurogenic tumors: in vivo results. Acta Neuropathologica, 1992, 83, 624-629.
47. Lewin GR, Ritter AM, Mendell LM: Nerve growth factor-induced hyperalgesia in the neonatal and adult rat. The Journal of Neuroscience, 1993, 13, 2136-2148.
48. Tria MA, Fusco M, Vantini G, Mariot R: Pharmacokinetics of nerve growth factor (NGF) following different routes of administration to adult rats. Exp Neurol, 1994, 127, 178-183.
49. Ventriglia M, Bocchio Chiavetto L, Benussi L, Binetti G, Zanetti O, Riva MA, et al.: Association between the BDNF 196 A/G polymorphism and sporadic Alzheimer's disease. Molecular Psychiatry, 2002, 7, 136-137.
50. Momose Y, Murata M, Kobayashi K, Tachikawa M, Nakabayashi Y, Kanazawa I, et al.: Association studies of multiple candidate genes for Parkinson's disease using single nucleotide polymorphisms. Annals of Neurology, 2002, 51, 133-136.
51. Sen S, Nesse RM, Stoltenberg SF, Li S, Gleiberman L, Chakravarti A, et al.: A BDNF coding variant is associated with the NEO personality inventory domain neuroticism, a risk factor for depression. Neuropsychopharmacology, 2003, 28, 397-401.
52. Ribasés M, Gratacós M, Armengol L, de Cid R, Badía A, Jiménez L, et al.: Met66 in the brain-derived neurotrophic factor (BDNF) precursor is associated with anorexia nervosa restrictive type. Molecular Psychiatry, 2003, 8, 745-751.
53. Sklar P, Gabriel SB, McInnis MG, Bennett P, Lim YM, Tsan G, et al.: Family-based association study of 76 candidate genes in bipolar disorder: BDNF is a potential risk locus. Brain-derived neutrophic factor. Molecular Psychiatry, 2002, 7, 579-593.
54. Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T: Hippocampal long-term potentiation is impaired in mice lacking brain-derived neurotrophic factor. Proceedings of the National Academy of Sciences of the USA, 1995, 92, 8856-8860.

55. Desai NS, Rutherford LC, Turrigiano GG: BDNF regulates the intrinsic excitability of cortical neurons. Learn Mem, 1999, 6, 284-291.
56. Parikh V, Evans DR, Khan MM, Mahadik SP: Nerve growth factor in never-medicated first-episode psychotic and medicated chronic schizophrenic patients: possible implications for treatment outcome. Schiz Res, 2003, 60, 117-123.
57. Karege F, Perret G, Bondolfi G, Schwald M, Bertschy G, Aubry JM: Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res, 2002, 109, 143-148.
58. Toyooka K, Asama K, Watanabe Y, Muratake T, Takahashi M, Someya T, et al.: Decreased levels of brain-derived neurotrophic factor in serum of chronic schizophrenic patients. Psychiatry Res, 2002, 110, 249-257.
59. Kim YK, Lee HP, Won SD, Park EY, Lee HY, Lee BH, et al.: Low plasma BDNF is associated with suicidal behavior in major depression. Prog Neuropsychopharmacol Biological Psychiatry, 2007, 31, 78-85.
60. Duman RS, Monteggia LM: A neurotrophic model for stress-related mood disorders. Biological Psychiatry, 2006, 59, 1116-1127.
61. Shirayama Y, Chen AC, Nakagawa S, Russell DS, Duman RS: Brain-derived neurotrophic factor produces antidepressant effects in behavioral models of depression. The Journal of Neuroscience, 2002, 22, 3251-3261.
62. Hoshaw BA, Malberg JE, Lucki I: Central administration of IGF-I and BDNF leads to long-lasting antidepressant-like effects. Brain Research, 2005, 1037, 204-208.
63. Warner-Schmidt JL, Duman RS: VEGF is an essential mediator of the neurogenic and behavioral actions of antidepressants. Proceedings of the National Academy of Sciences of the USA, 2007, 104, 4647-4652.
64. Linden AM, Vaisanen J, Lakso M, Nawa H, Wong G, Castren E: Expression of neurotrophins BDNF and NT-3, and their receptors in rat brain after administration of antipsychotic and psychotrophic agents. Journal of Molecular Neuroscience , 2000, 14, 27-37.
65. Parikh V, Khan MM, Terry A, Mahadik SP: Differential effects of typical and atypical antipsychotics on nerve growth factor and choline acetyltransferase expression in the cortex and nucleus basalis of rats. J Psych Res, 2004, 38, 521-529.
66. Angelucci F, Mathe AA, Aloe L: Brain-derived neurotrophic factor and tyrosine kinase receptor TrkB in rat brain are significantly altered following haloperidone and risperidone administration. Journal of Neuroscience Research, 2000, 60, 783-794.
67. Takahashi M, Shirakawa O, Toyooka K, Kitamura N, Hashimoto T, Maeda K, et al.: Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. Molecular Psychiatry, 2000, 5, 293-300.
68. Tan YL, Zhou DF, Cao LY, Zou YZ, Zhang XY: Decreased BDNF in serum of patients with chronic schizophrenia on long-term treatment with antipsychotics. Neuroscience Letters, 2005, 382, 27-32.
69. Lu XH, Dwyer DS: Second-generation antipsychotic drugs, olanzapine, quetiapine, and clozapine enhance neurite outgrowth in PC12 cells via PI3K/AKT, ERK, and pertussis toxin-sensitive pathways. Journal of Molecular Neuroscience , 2005, 27, 43-64.
70. Angelucci F, Aloe L, Iannitelli A, Gruber SH, Mathe AA: Effect of chronic olanzapine treatment on nerve growth factor and brain-derived neurotrophic factor in the rat brain. European Neuropsychopharmacology, 2005, 15, 311-317.
71. Levi-Montalcini R: The nerve growth factor 35 years later. Science, 1987, 237, 1154-1162.
72. Terry AV, Jr Parikh V, Gearhart DA, Pillai A, Hohnadel E, Warner S, et al.: Time-dependent effects of haloperidol and ziprasidone on nerve growth factor, cholinergic neurons, and spatial learning in rats. The Journal of Pharmacology and Experimental Therapeutics, 2006, 318, 709-724.