JAVMA

Dysmetabolism of the nerve growth factor pathway in the aging brain plays a pivotal role in cognitive decline

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Abstract

Nerve growth factor (NGF) is one of several neurotrophic proteins necessary for normal development and function of the mammalian nervous system. Nerve growth factor is necessary for normal brain cholinergic function, and reduced brain cholinergic activity is a hallmark pathological feature of human Alzheimer's disease (AD). In both aging humans and transgenic rodent models, disruption of the normal NGF metabolic pathway (NGF dysmetabolism) leads to brain neuronal damage, loss of synaptic plasticity, and cognitive decline. Nerve growth factor dysmetabolism in AD patients is a gradual process, beginning years prior to the development of mild cognitive impairment. In addition to changes in the levels of specific molecular regulators of the NGF pathway, there are changes in the proportions of the 2 major receptors for NGF and its precursor (proNGF) in the brain: the tropomyosin kinase A (TrkA) receptor and the p75 neurotrophin ($p75^{NTR}$) receptor. Nerve growth factor has high affinity for TrkA receptors, the stimulation of which has neuroprotective effects. The precursor of NGF has higher affinity than NGF for $p75^{NTR}$ receptors; stimulation of $p75^{NTR}$ receptors by proNGF has deleterious effects on neurons. With NGF dysmetabolism, the respective ratios of available NGF/proNGF and TrkA/$p75^{NTR}$ receptors are decreased, favoring neuronal damage. In rodent models genetically engineered to produce monoclonal antibodies against NGF, neuronal damage and cognitive decline occur, even when the antibodies are targeted specifically against peripheral (ie, not CNS) NGF. Because canine cognitive dysfunction is a naturally occurring model of human AD, NGF dysmetabolism may be relevant to aging dogs. This article will review details of NGF dysmetabolism and how this aberrant pathway contributes to cognitive decline.

Keywords: nerve growth factor (NGF), dysmetabolism, cognitive, dogs, Alzheimer's disease

The Importance of Nerve Growth Factor in Cognition and the Normal Nerve Growth Factor Metabolic Pathway

Progressive decline of brain cholinergic activity is a major pathological feature of Alzheimer's disease (AD). The primary source of cholinergic supply to vital brain regions (eg, cerebral cortex, hippocampus) are basal forebrain cholinergic neurons (BFCNs).[1–3] These neurons depend on a steady supply (primarily via retrograde axonal transport from BFCN target regions, chiefly the hippocampus and cerebral cortex) of nerve growth factor (NGF) for normal function and survival **(Figure 1)**; NGF is one of several neurotrophic proteins involved in both development and maintenance of the nervous system.[1–5] Nerve growth factor is normally produced and degraded via a pathway consisting of several key regulatory proteins **(Figure 2)**. Nerve growth factor (also referred to as mature NGF or mNGF) is released into the extracellular space as a precursor protein, called proNGF. This precursor protein is converted into NGF by plasmin, the latter of which is derived from plasminogen via the action of tissue plasminogen activator (tPA), which is inhibited by a protein called neuroserpin. Nerve growth factor is degraded by metalloproteinases (MMPs; primarily MMP3 and MMP9). Most MMPs are inhibited by tissue inhibitor of metalloproteinases 1. Normally, the checks and balances provided by this pathway ensure a predominance of NGF over its precursor protein, proNGF.[2,3,6]

There are 2 main cellular receptors for NGF: the tropomyosin kinase A (TrkA) receptor and the p75 neurotrophin ($p75^{NTR}$) receptor.[1–4,6] Nerve growth factor has a high level of affinity for the TrkA receptor; interaction of NGF with the TrkA receptor produces trophic and neuroprotective effects, supporting survival and normal functioning of BFCNs.[2–4,6] The $p75^{NTR}$ receptor has low affinity for binding of several neurotrophins, with highest affinity for proNGF; overall, stimulation of the $p75^{NTR}$ receptor produces deleterious effects (eg, neuronal apoptosis, stimulation of beta-amyloid [Aβ] production), particularly when bound to proNGF.[2–4,6–9] However, binding of NGF to

Received September 5, 2025
Accepted October 30, 2025
Published online December 5, 2025

doi.org/10.2460/javma.25.09.0578

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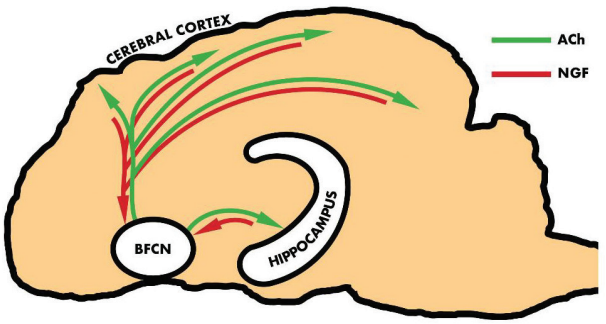


Figure 1—Schematic illustration demonstrating the interactions between basal forebrain cholinergic neurons (BFCNs) and the hippocampus and cerebral cortex. ACh = Acetylcholine. NGF = Nerve growth factor.

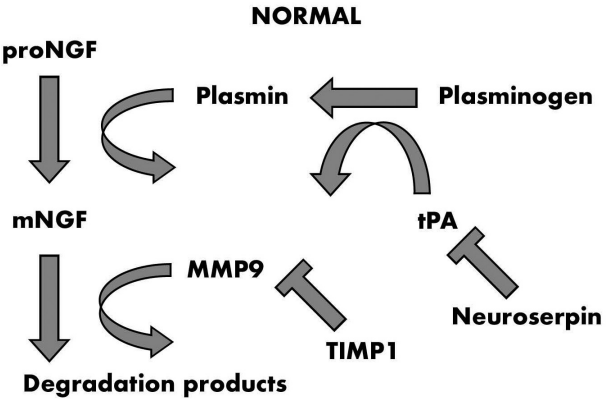


Figure 2—The normal NGF metabolic pathway. MMP9 = Matrix metalloprotease 9. mNGF = Mature NGF. proNGF = Precursor to NGF. TIMP1 = Tissue inhibitor of metalloproteases 1. tPA = Tissue plasminogen activator. (From Pentz R, Iulita MF, Ducatenzeiler A, Bennett DA, Cuello AC. The human brain NGF metabolic pathway is impaired in the pre-clinical and clinical continuum of Alzheimer's disease. *Mol Psychiatry*. 2021;26[10]:6023–6037. Redrawn with permission.)

the p75^{NTR} receptor will lead to neurotrophic effects when there is interaction between the TrkA receptor and p75^{NTR} receptor. In the healthy brain, there is a preponderance of NGF (vs proNGF) and adequate TrkA receptors to allow interaction between these receptors and the p75^{NTR} receptors.[2–4,6–9]

The Roles of TrkA/p75^{NTR} Receptor Imbalance and NGF Dysmetabolism in Cognitive Decline

It has been demonstrated that TrkA receptors are diminished in human AD brains, whereas p75^{NTR} receptors remain normal or are increased. This imbalance allows for less trophic effects (mediated primarily through TrkA receptors) and more deleterious effects on neurons (mediated primarily through p75^{NTR} receptors).[4,6,10] In addition to the low TrkA/p75^{NTR} ratio in the AD brain, several aberrations of the NGF metabolic pathway have been identified **(Figure 3)**.[2,3,6] The precise mechanisms by which these changes occur are not completely understood, but progressive accumulation of Aβ and neuroinflammation are

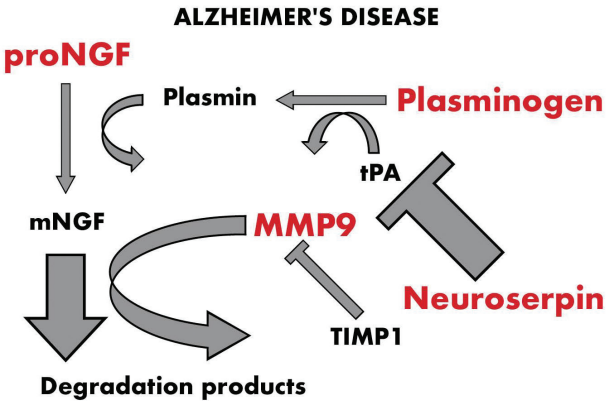


Figure 3—The abnormal (dysmetabolic) NGF metabolic pathway. (From Pentz R, Iulita MF, Ducatenzeiler A, Bennett DA, Cuello AC. The human brain NGF metabolic pathway is impaired in the pre-clinical and clinical continuum of Alzheimer's disease. *Mol Psychiatry*. 2021;26[10]:6023–6037. Redrawn with permission.)

thought to be involved.[3,6] The 2 main features of NGF dysmetabolism are impaired conversion of proNGF to NGF and increased degradation of NGF.[2,3,6] The preponderance of proNGF interacting with p75^{NTR} receptors in this altered pathway has deleterious effects, including stimulating further production of toxic Aβ accumulation in the brain.[2,3,6–12] In addition to high proNGF and low NGF levels, specific abnormalities identified in NGF dysmetabolism include increased levels of MMPs, neuroserpin, and plasminogen and decreased levels of plasmin, tPA, and tissue inhibitor of metalloproteinases 1.[2,3,6] A study[6] that analyzed donated postmortem brain tissue samples from people with varying levels of brain Aβ deposition and no cognitive impairment, mild cognitive impairment, and AD derived a timeline detailing the progression of NGF dysmetabolism **(Figure 4)**.

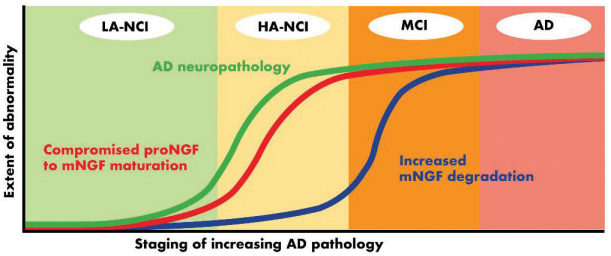


Figure 4—Timeline of NGF dysmetabolism in people with progressive brain beta-amyloid deposition. AD = Alzheimer's disease. HA-NCI = High amyloid—no cognitive impairment. LA-NCI = Low amyloid—NCI. MCI = Mild cognitive impairment. (From Pentz R, Iulita MF, Ducatenzeiler A, Bennett DA, Cuello AC. The human brain NGF metabolic pathway is impaired in the pre-clinical and clinical continuum of Alzheimer's disease. *Mol Psychiatry*. 2021;26[10]:6023–6037. Redrawn with permission.)

This study demonstrated that NGF dysmetabolism occurs in advance of any obvious cognitive decline; it also showed that impaired conversion of proNGF to NGF occurs early in the disease process, with accelerated NGF degradation occurring in later stages of the disease.[6]

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Transgenic Mouse Models Support the Role of NGF in Cognitive Decline

The creation of a genetically modified mouse strain (AD11) that produces monoclonal antibodies against NGF provided the means to prove a causal relationship between disruption of NGF activity and development of degenerative brain disease analogous to human AD. Once AD11 mice reach adulthood, they produce enough anti-NGF antibody to inhibit NGF's action; subsequently, neurodegenerative brain changes characteristic of human AD develop (eg, deposition of Aβ and tau proteins, neuronal loss, loss of BFCN cholinergic activity). In addition to these structural changes, affected mice display evidence of cognitive decline.[13] Because the monoclonal antibody produced by AD11 mice has a high affinity for NGF (not proNGF), it was hypothesized that blocking NGF in this mouse model would lead to preferential proNGF/p75^{NTR} signaling, with resultant deleterious effects, such as Aβ deposition.[13,14] Support for this hypothesis comes from another transgenic mouse model (AD12), in which anti-NGF antibody mice were crossed with mice whose genes for coding the p75^{NTR} receptor were excised; in this model, no deposition of Aβ was observed, suggesting a direct role of proNGF/p75^{NTR} interaction in the accumulation of toxic Aβ in the brain.[15] To investigate the effect of diminished TrkA signaling, a transgenic mouse model that produced anti-TrkA receptor antibodies was created; Aβ deposition and loss of BFCN cholinergic activity developed in the brains of these mice. They also exhibited cognitive decline in spatial learning (maze test) and object recognition (nonspatial short- and long-term visual memory, discerning objects that are new vs familiar).[15]

In the AD11 transgenic mouse model, both cells in the CNS and nearly all nonlymphoid peripheral tissues produce monoclonal antibodies against NGF. To ascertain what, if any, effects may occur if only peripheral NGF blockade were to occur, another transgenic mouse model (AD10) was created in which anti-NGF monoclonal antibodies were produced in the periphery only (via splenic lymphocytes, no CNS production). In this model, anti-NGF antibodies caused disruption of the blood-brain barrier by means of damaging the sympathetic nervous system at the level of the cranial cervical ganglia; subsequently, anti-NGF antibodies entered the brain and produced an AD-like scenario nearly identical to that observed in the AD11 strain **(Figure 5)**.[16] Damaging the sympathetic nervous system by blocking NGF has been shown to result in disruption of the blood-brain barrier in other rodent studies.[17,18]

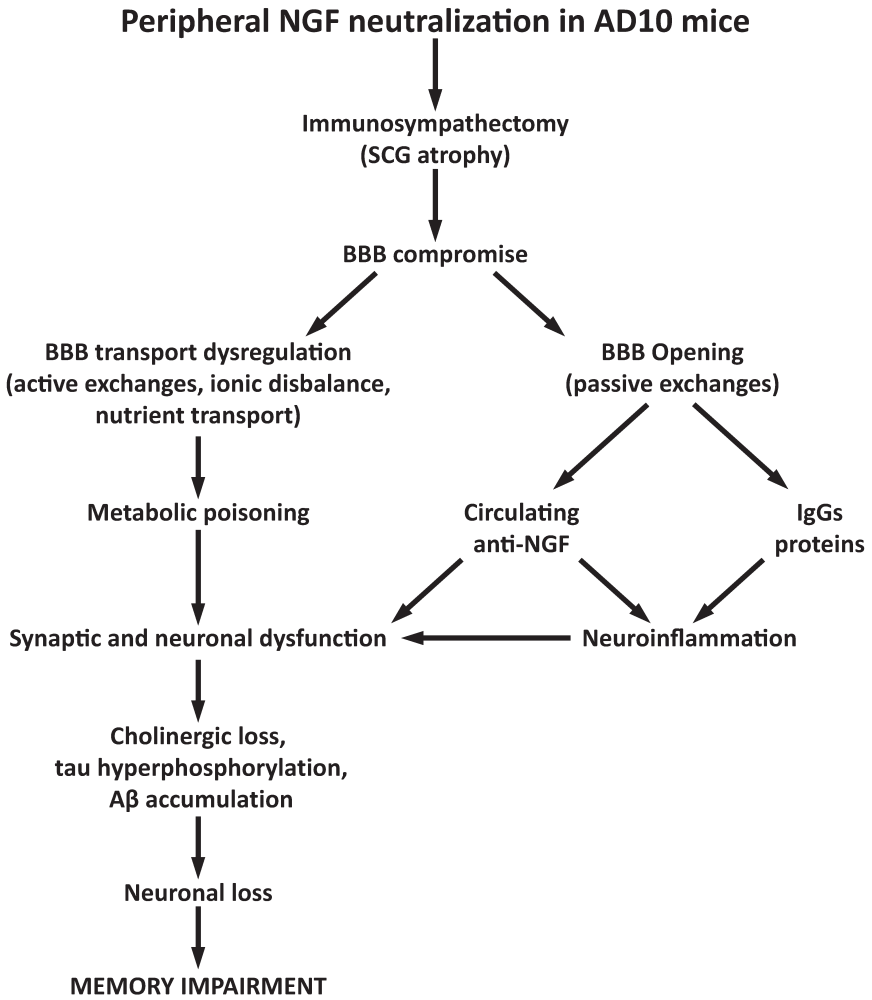


Figure 5—Schematic showing events leading to AD-like degeneration in AD10 mice. Aβ = Beta amyloid. BBB = Blood-brain barrier. IgG = Immunoglobulin G. SCG = Superior (cranial) cervical ganglia. (From Capsoni S, Tiveron C, Amato G, Vignone D, Cattaneo A. Peripheral neutralization of nerve growth factor induces immunosympathectomy and central neurodegeneration in transgenic mice. *J Alzheimers Dis*. 2010;20[2]:527–546. Redrawn with permission.)

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Potential Clinical Relevance of NGF Dysmetabolism in Canine Cognitive Dysfunction

Canine cognitive dysfunction (CCD) is the dog version of human AD and is very prevalent in the senior dog population.[19] Unlike transgenic mouse models of AD, CCD is a naturally occurring model of human AD, sharing many clinical, molecular, and pathological features.[19,20] Although NGF dysmetabolism has not been extensively studied in CCD patients, there is evidence that NGF-associated loss of BFCNs occurs in aging canines.[21] In addition, there is substantial evidence that the neurotrophins (including NGF) and their metabolic pathways are evolutionarily conserved across vertebrate species.[22–24] It is likely that NGF metabolism (and dysmetabolism) in aging dogs is similar to that described for human patients with AD and rodent AD models. To our knowledge, this similarity has not been directly investigated; however, a recent study[25] reviewed diagnostic and therapeutic strategies for CCD and highlighted the potential similarities for diagnostic biomarkers and reviewed treatment options. However, it did not comment on the role of NGF dysmetabolism in disease progression or therapeutics.[25] Our previous research in this area investigated transcranial photobiomodulation in cognitive-impaired dogs and showed potential benefit, but it was not without limitations, among which was the lack of comment on NGF dysmetabolism.[26] The aging dog population may provide avenues for further research into this aspect of dementia, including further diagnostic and therapeutic options.

Acknowledgments

None reported.

Disclosures

Dr. Brunke is a member of the *JAVMA* Scientific Review Board and was not involved in the editorial evaluation of or decision to accept this article for publication.

No AI-assisted technologies were used in the composition of this manuscript.

Funding

The authors have nothing to disclose.

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