

Review Article

OPEN ACCESS

Neurotrophic Peptides: Potential Drugs for Treatment of Amyotrophic Lateral Sclerosis and Alzheimer's disease

Jessica Ciesler, Youssef Sari*

University of Toledo, College of Pharmacy and Pharmaceutical Sciences, Department of Pharmacology, Toledo, OH 43614, USA

Corresponding Author & Address:

Youssef Sari*

University of Toledo, College of Pharmacy and Pharmaceutical Sciences, Department of Pharmacology, Health Science Campus, 3000 Arlington Avenue, HEB282G, Toledo, OH 43614, USA; Email: youssef.sari@utoledo.edu; Tel: 419-383-1507 (Office)

Published: 8th April, 2013

Accepted: 8th April, 2013

Received: 7th February, 2013

Open Journal of Neuroscience, 2013, 3-2

© Sari et al, licensee Ross Science Publishers

ROSS Open Access articles will be distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided that the original work will always be cited properly.

Keywords: Amyotrophic Lateral Sclerosis, Alzheimer's disease, ADNF-9, NAP, Colivelin

ABSTRACT

Neurodegenerative diseases are characterized by the progressive loss of neurons and glial cells in the central nervous system correlated to their symptoms. Among these neurodegenerative diseases are Alzheimer's disease (AD) and amyotrophic lateral sclerosis (ALS). Neurodegeneration is mostly restricted to specific neuronal populations: cholinergic neurons in AD and motoneurons in ALS. The demonstration that the onset and progression of neurodegenerative diseases in models of transgenic mice, in particular, is delayed or improved by the application of neurotrophic factors and derived peptides from neurotrophic factors has emphasized their importance in neurorestoration. A range of neurotrophic factors and growth peptide factors derived from activity-dependent neurotrophic factor/activity-dependent neuroprotective protein has been suggested to restore neuronal function, improve behavioral deficits and prolong the survival in animal models. In this review article, we focus on the role of trophic peptides in the improvement of AD and ALS. An understanding of the molecular pathways involved with trophic peptides in these neurodegenerative diseases may shed light on potential therapies.

INTRODUCTION

Neurodegenerative diseases are difficult to treat and are frequently incurable due to the complicated nature of the underlying mechanisms of neuronal cell death. Neurodegenerative diseases including Alzheimer's disease (AD) and Amyotrophic lateral sclerosis (ALS) result in a debilitating loss of memory and motor function, respectively. Although the mechanisms of action in neurodegenerative diseases are unclear, the potential underlying mechanisms can be divided into two categories. The first, unique to each neurodegenerative disease, is a trigger that

initiates activation of cell death machinery. The second, which is thought to be universal among neurodegenerative diseases, is a directorial process to complete death of neurons [For review, see ref. [1]].

ALS is suggested to be related to a loss of motor neurons, progressively impairing the voluntary motor neuron system and resulting in motor paralysis. This is suggested to be caused by mutation of the superoxide dismutase-1 (SOD1) gene, causing motoneuronal death [2]. Alternatively, neuronal loss in AD results in memory deficit. A widely accepted theory for the

mechanism of AD is that A β is the primary factor for its neurotoxic effect [3-7].

Although there are currently no effective drugs for the treatment of neurodegenerative diseases, potential therapeutic targets for symptomatic treatments of neurodegenerative diseases may include neuroprotective factors, encompassing neurotrophins and neuroprotective peptides [8-10]. A deficit in the presence of endogenous neurotrophic factors may play a key role in the attenuation of the progression of neurodegenerative diseases [For review, see ref. [11]]. The types of neuroprotection demonstrated by neurotrophic factors include the prevention of oxidative stress that induces apoptosis, promotion of cell survival, and possible cell growth. Neurotrophic factors may improve cellular function and increase neuronal metabolism, which can even lead to restoration of synaptic connections by growth of new axons. Neurotrophic factors are categorized by their activity in preventing neuronal cell death [For review, see ref. [11]].

We focus in this review on NAP (NAPVSIPQ) peptide derived from activity neuroprotective protein and ADNF-9 peptide derived from activity-dependent neurotrophic factor (ADNF). Both NAP and ADNF-9 display activity in the femtomolar range, enhancing cell survival and outgrowth of dendrites in the form of D-acid analogues such as D-NAP and D-ADNF-9 [12, 13]. ADNF-9 and NAP peptides share functional and structural similarities, originally intended for use against β -amyloid peptides for reduction of toxicity and increased protection of neurons [14]. A novel hybrid peptide called colivelin was synthesized by the addition of ADNF-9 to the N-terminus of a humanin derivative. Colivelin has potential neuroprotective effect in some neurodegenerative diseases such as AD [15]. We discuss in this review article the two most prevalent neurodegenerative diseases: ALS and AD, including the mechanisms, current treatments, and implications of trophic peptides in treating neurodegenerative diseases.

OVERVIEW OF NEURODEGENERATIVE DISEASES: ALS AND AD

Alzheimer's disease

The most common neurodegenerative

disease is AD, regularly known for its characteristic devastating memory and cognitive deficits. Neuronal cell death in the cortical area of the brain is believed to be related to the irreversible progression of dementia and cognitive disorders. The exact mechanism of action leading to AD is unknown, but there is a widely accepted theory regarding amyloid- β 's (A β s) as the primary factor for its neurotoxic effect in AD pathology. *In vivo* experiments have shown that cell death may result from extreme concentrations of toxic A β s [15-20]. Studies in both mice and human AD patients demonstrated that aggregation of the β -amyloid peptide has been found to form oligomers along the microtubules of neuroprocesses in the AD brain [14]. There also have been studies indicating that toxic A β concentrations of 1-25 μ M or higher are the cause of neuronal cell death *in vitro*, supporting the A β cascade theory [2]. An *in vitro* study suggested that A β -related cell death is mediated by A β receptors as well as severe potential death-mediating receptors for toxic A β [2].

Alternatively, amyloid precursor protein (APP) has been suggested to play a major role in activation of a neuronal cell-death signaling cascade when TGF β 2 binds as a natural ligand for APP [21, 22]. Hashimoto and colleagues found TGF β 2 to also be down-regulated by administration of toxic A β . A β binds to the extracellular domain of APP in glial and neuronal cells, TGF β 2 paracrinally and autonomously signaling the APP mediated cells. β -amyloid accumulation has been suggested to occur prior to Tau hyperphosphorylation, suggesting a possible cause and effect between accumulation and hyperphosphorylation [14]. At the present time, the FDA has approved acetylcholinesterase inhibitors and NMDA-type glutamate receptor antagonists for the treatment of moderate to severe AD [For review, see ref. [23]]. Currently there are no FDA approved treatments for behavioral and psychotic symptoms exclusive to AD, but many medications are used "off-label". Semagacestat, a γ -secretase inhibitor, is currently being studied under two Phase III clinical trials for the treatment of AD [24]. Semagacestat is thought to lower levels of A β in the brain by blocking cleavage of membrane-bound β -amyloid precursor proteins via γ -secretase, as seen in studies using transgenic mice [25, 26]. In addition,

studies have been conducted to investigate the role of A β , tau proteins, and insulin on the onset and progression of AD [27-29]

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is another neurodegenerative disease affecting the motor neurons, brainstem, and spinal cord. ALS is more commonly known as Lou Gehrig's disease. Degeneration of motor neurons leads to characterized progressive loss of motor control, eventually leading to muscular dystrophy, motor paralysis, and death due to respiratory failure. Most cases of ALS are sporadic in occurrence, but about 10% of cases are familial [30]. Both forms share similar characteristics, and onset occurs typically in adulthood [31], although juvenile onset ALS has been reported as an autosomal recessive mutation in ALS2.

The initial trigger for onset of this multifactorial disorder is still unknown. However, several factors may lead to motor neuron degeneration, including mitochondrial dysfunction, oxidative stress, protein aggregation, protein misfolding, neuro-inflammation, cytoskeleton abnormalities, defective axonal transport, dysfunctional growth factor signaling, and excitotoxicity [30-32]. Mitochondrial abnormalities occur early in ALS pathogenesis; mutant SOD1 was found to be associated with mitochondria in the intermembrane space, possibly triggering apoptosis [33]. SOD inclusion formation may recruit proapoptotic BAX to mitochondria. A possible non-cell autonomous process characterized in ALS is inflammation, which appears in microglial and astroglial cells, resulting in mitochondrial damage and apoptosis [34-36]. Protein misfolding and aggregation mechanisms are still unclear, but protein inclusions have been found in human ALS, including ubiquitinated skein-like inclusion, bunina bodies, and hyaline inclusions rich in neurofilament proteins [37]. Alternatively, patients with mutant SOD1 have shown decreased levels of excitatory amino acid transporters (EAAT2), causing a decreased removal of glutamate from the synapse as well as increased glutamate in the cerebrospinal fluid [38, 39].

Based on studies performed in transgenic mice, mutations on the SOD1 gene lead to the familial form of ALS [2, 15]. In SOD1 transgenic

mice, evidence of dynein defects related to dynein-mediated axonal transport processes have been reported to be the earliest pathologies in ALS. Neurons are very sensitive to dynein dysfunction, as dynein is highly expressed in neurons; this may suggest the vulnerability of the motor neurons (For review, see ref.[30]). Mutations in the SOD1 gene are thought to lead to a toxic gain of function, as opposed to a loss of function found in other neurodegenerative diseases [40]. Other studies suggest that angiogenic activity plays a critical role in the development of ALS. Mutations in ALS patients may be associated with functional loss of angiogenic activity and null mutations in progranulin, an angiogenic protein [31].

Currently, riluzole is the only prescribed treatment for ALS, but it only provides moderate survival in patients. Riluzole was initially investigated as an antiseizure drug and was later found to have neuroprotective properties [41]. Among other drugs, ceftriaxone a β -lactam antibiotic known to upregulate glutamate transporter 1 (GLT1), or EAAT2, and dextramipexole are currently in Phase III clinical trials in ALS patients [42, 43].

ROLE OF NEUROTROPHIC DERIVED PEPTIDES IN ALS AND AD

NAP peptide derived from activity-dependent neuroprotective protein in ALS and AD

The parent protein, ADNP, is essential for brain development; it is found in the nuclei, cytoplasm, and occasionally along cytoplasmic microtubules [44, 45]. *In vitro* studies showed that recombinant ADNP was found to protect neurons against severe oxidative stress [46]. NAP mimics the neuroprotective activity of ADNP in its ability to cross the blood-brain barrier, interact with tubulin, enhance assembly of microtubules, and promote neuronal outgrowth [44, 47, 48]. The specific association of NAP with tubulin was detected by fluorescent NAD distribution at the cellular level in cells that express neuron-specific β III-tubulin as well as astrocyte tubulin, which does not express β III-tubulin [14, 44, 49]. It is demonstrated that NAP colocalizes with microtubules, which regulate Ca²⁺ signaling in neurons (Figure 1) [44, 50, 51]. NAP's association

with Ca^{2+} mobilization may contribute to neuronal survival. Changes in mitochondrial Ca^{2+} homeostasis were found to be correlated with life-death pathways of cells in microtubule formation [49]. Other studies suggest that NAP is regulated by polyADP-ribosylation (Figure 1) [50] or that NAP stimulates the MAPK/ERK and PI3-K/Akt pathways [52]. Pascual and colleagues found that

stimulation of MAPK/ERK and PI3-K/Akt leads to the phosphorylation of the transcription factor cAMP response element-binding protein (CREB), which produces neuronal outgrowth and differentiation (Figure 1). NAP protection and adaptation to enhance cognitive function can possibly be attributed to protection against apoptosis as a result of microtubule loss.

Figure 1.

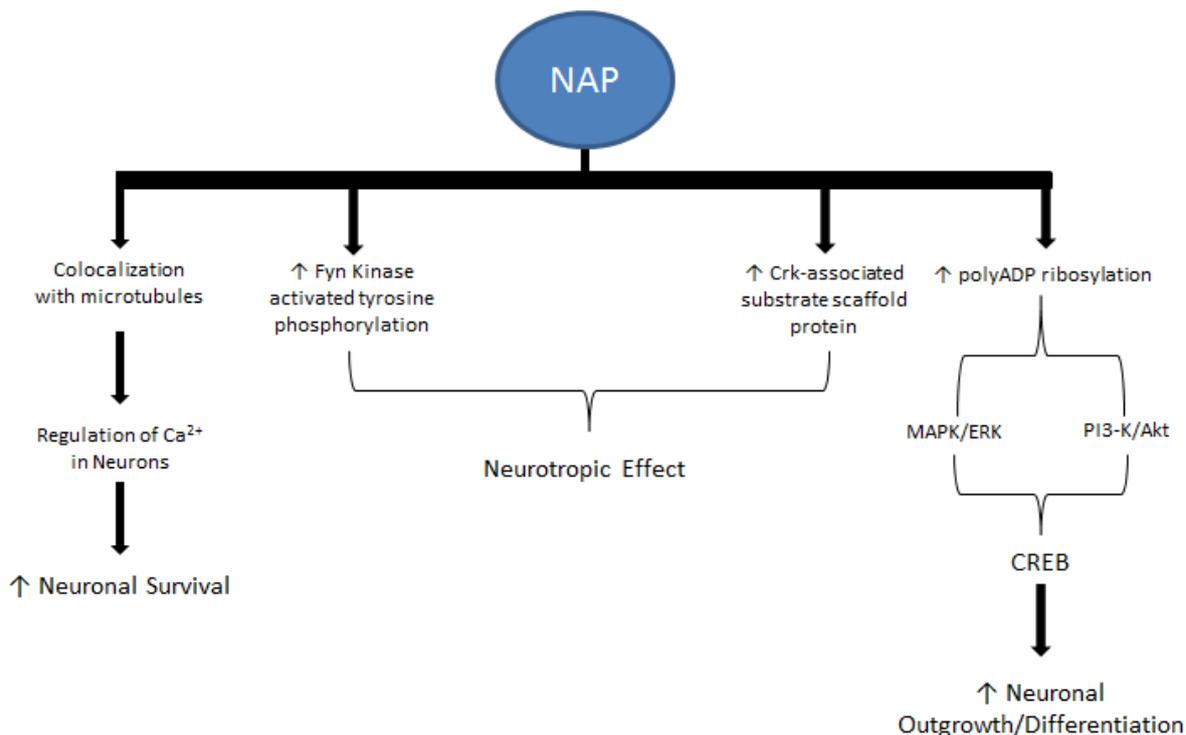


Figure 1. Diagram shows several pathways involving NAP neuroprotection. Among these pathways, NAP can co-localize with microtubules to regulate neuronal Ca^{2+} homeostasis to increase neuronal survival. The neuroprotective effect of NAP, mediated by increases in Fyn kinase, activated tyrosine phosphorylation and the level of Crk-associated substrate scaffold protein. Alternatively, increases in neuronal outgrowth and differentiation might be mediated through CREB involving MAPK/ERK and PI3-K/Akt pathways, which are activated by increased polyADP ribosylation.

Studies regarding a mouse model for AD have shown deregulation of ADNP expression in the hippocampus [53]. Tau mutants have decreased affinity to microtubules, leading to less protection and aggregation of tau. NAP's neurotrophic effect lies in the activation of Fyn Kinase activated tyrosine phosphorylation and Crk-associated substrate (Cas) scaffold protein (Figure 1) [14]. NAP treatment is also associated with chromatin remodeling and neurite outgrowth due to enhanced poly-ADP ribosylation, connected with ADNP signaling (Figure 1) [44, 48-50]. While protecting against neurotoxins, NAP

does not affect cell division [54]. In addition, studies have found that treatment with NAP in ADNP knockdown mice resulted in enhanced cognition and improved associated deficiencies [48]. Positive study results and clean toxicity reports have landed NAP in phase II clinical trials with a primary focus on AD-related cognitive impairment [14]. Studies are also being conducted to evaluate the effects of NAP in ALS models associated with cytoskeletal dysfunction. NAP extended life span in ALS mouse models when administered prior to disease onset, protecting against tauopathy [55].

Figure 2.

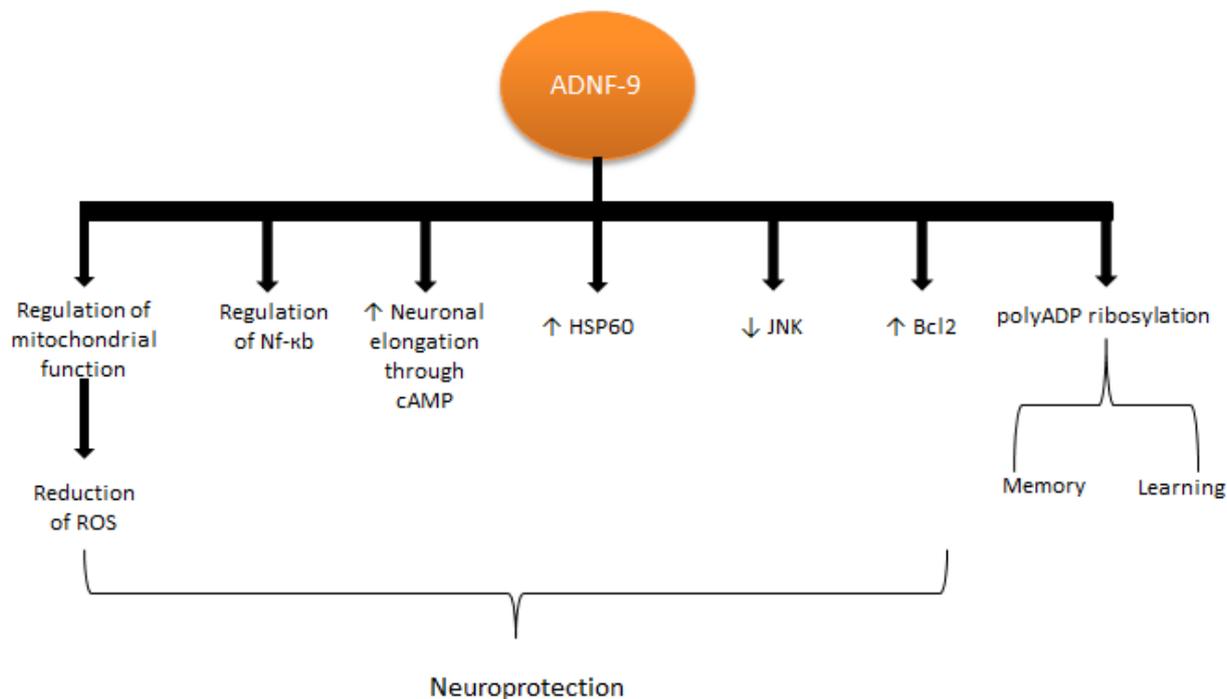


Figure 2. Diagram shows several pathways involving ADNF-9 neuroprotection. Among these pathways, ADNF-9 regulates mitochondrial function and NF- κ B, increases neuronal elongation, decreases HSP60, decreases JNK, and increases Bcl2. ADNF-9 ameliorates learning and memory through polyADP ribosylation.

ADNF-9 peptide derived from activity-dependent neurotrophic factor in AD and ALS

ADNF is a glial neurotrophic protein factor and, along with ADNP, it is released in response to vasoactive intestinal peptide (VIP) that protects neurons from tetrodotoxin-induced cell death by electrical blockade as well as related insults from AD and ALS. ADNF is suggested to be essential for neuronal survival and embryonic growth regulated by VIP [56-61]. ADNF-9 derived from ADNF, also known as SAL (SALLRSIPA), is the active core of its parent compound and mimics its neuroprotective activity [56, 57]. In AD, ADNF-9 has been found to protect against A β , apolipoprotein E deficiencies, and oxidative insults, as well as enhancing synapse formation [56, 62-64]. It is noteworthy that ADNF-9 showed a greater prevention of cell death associated with stress than did other ADNF derived peptides such as ADNF-14, which also protects against cell death [56] and provides neuroprotection against AD-related toxicity [57, 65]. ADNF-9 protects against A β peptide and oxidative stress through regulation of mitochondrial function, reduction of accumulating reactive oxygen species, and regulation of the Nf-

kb transcription factor (Figure 2) [62, 66]. Moreover, ADNF-9 also promotes axonal elongation through cAMP-dependent mechanisms and increases chaperonin expression of heat shock protein 60, which leads to neuroprotection against A β insult (Figure 2) [66-68]. *In vitro* studies using both hippocampal and cortical neurons demonstrated that ADNF-9 stimulates synapse formation [69]. ADNF-9 was also shown to have an effect on memory and learning in association with polyADP ribosylation catalyzed by poly(ADP-ribose)polymerase-1 (Figure 2) [50]. Other possible mechanisms of neuroprotection include the Bcl2 mitochondrial intrinsic signaling pathway, which regulates cell survival and apoptosis [70] and the extrinsic JNK signaling pathway [71]. The all D-amino acid analogue of ADNF-9 was found to protect against A β tau hyperphosphorylation, in early events, *in vitro* and *in vivo*, with regards to neuroprotection and maintenance of neuronal organization [72]. ADNF-9 was tested in *in vitro* and *in vivo* ALS models [58]. This study demonstrated that ADNF-9 suppressed SOD-1-mediated cell death. The neuroprotective effect of ADNF-9 involves CaMKIV

and tyrosine kinase signaling pathways. Neuroprotection is thought to occur as a result of CaMKIV and tyrosine kinase involvement when ADFN is administered intracerebroventricularly. Although prolonged survival of the ALS mouse model was marginal, it did provide insight into a possible treatment for ALS.

Colivelin, hybrid synthetic peptide of ADFN-9 and Humanin, in AD and ALS

Neuroprotective peptide colivelin was created by adding ADFN-9 to the N-terminus of the humanin peptide [2, 73]. Humanin was identified as an endogenous neuroprotective peptide, which is suggested to protect against AD-related toxicity and cytotoxicity as a result of various stimuli [1, 74]. Moreover, studies have

shown that humanin suppresses neurotoxicity through extracellular cell surface receptors, which induce cytoprotective signals [74, 75]. It is suggested that humanin interacts with the Bcl-2 family of proapoptotic proteins, blocking their action in the cytosol (Figure 3) [74, 76, 77]. Although the mechanisms of action of colivelin in neuroprotection are unclear, two independent prosurvival signals have been suggested: a humanin mediated STAT3 pathway and ADFN-9 mediated Ca²⁺/calmodulin-dependent protein kinase IV pathway (Figure 3) [73]. It is noteworthy that ADFN-9 is active in the femtomolar concentration range, but activity is lost by about 10 nM, whereas humanin analogue AGA(C8R)HNG17 is active starting at 10 pM [56-58, 73].

Figure 3.

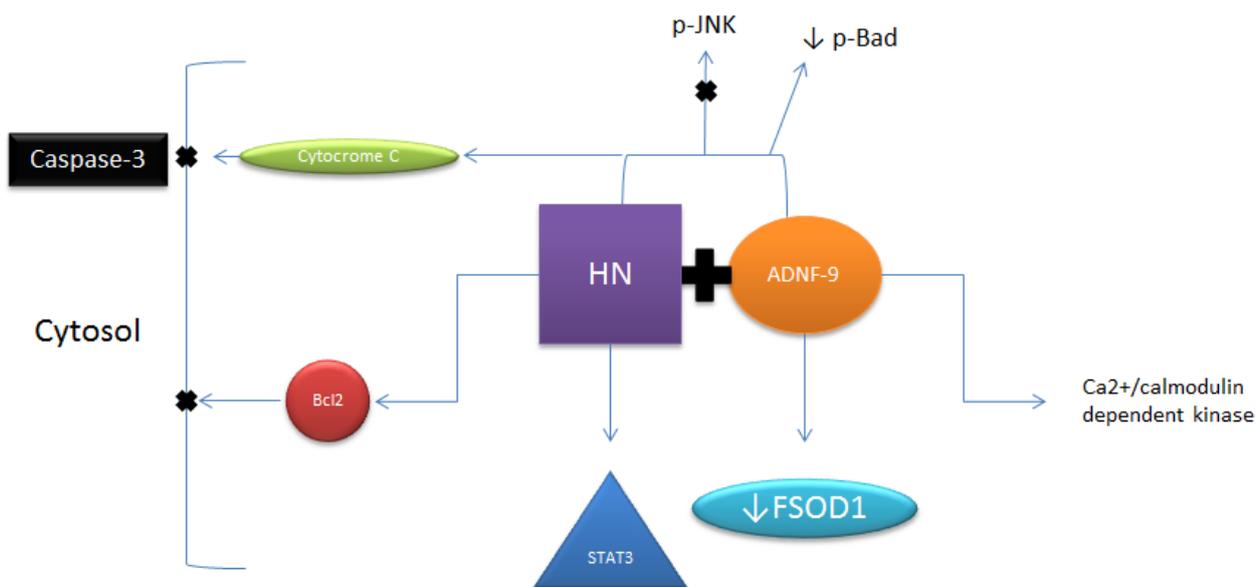


Figure 3. Diagram shows pathways involved in colivelin neuroprotection. Colivelin neuroprotection is mediated through Bcl2, cytochrome c and caspase-3 pathways. In addition, colivelin neuroprotection may involve STAT3, JNK and Bad pathways. It is suggested that ADFN-9 fragment of colivelin involves Ca²⁺/calmodulin dependent kinase.

Colivelin is active in the femtomolar range and does not lose activity at higher concentrations [73]. Humanin was found to provide neuroprotection against AD-related insults such as Aβ neurotoxicity [75]. The JAK2/STAT3 signaling pathway showed importance in colivelin neuroprotection against AD-related memory loss [78-80]. An *in vivo* study found that colivelin has more potent neuroprotective effects than humanin and ADFN-9 have when tested against

Aβ neurotoxicity [73].

Although, ADFN-9 was found to suppress the FSOD1 ALS-related gene [58], colivelin was found to be more neuroprotective than ADFN-9 in this model. Colivelin neuroprotection was associated with motor performance improvement but not increased lifespan in the ALS mouse model of SOD1 [58]. Moreover, another study showed that colivelin improved motor performance and

increased lifespan when compared to FSOD1, in addition to suppressing motoneuronal death [15].

CONCLUSION

The roles of neurotrophic factors and peptides are coming into focus for the treatment of neurodegenerative diseases such as AD and ALS. We discussed the potential application of neurotrophic peptides derived from ADNF and ADNP on the attenuation of the progression of ALS and AD. It is noteworthy that NAP is in Phase II clinical trials for the treatment of AD. ADNF-9 shows potential therapeutic effects in animal models of ALS. In addition, the hybrid peptide, colivelin, has been shown to be effective in animal

REFERENCES

- [1] Chiba T, Nishimoto I, Aiso S, Matsuoka M. Neuroprotection against neurodegenerative diseases: development of a novel hybrid neuroprotective peptide Colivelin. *Mol Neurobiol*. **2007**; 35: 55-84.
- [2] Matsuoka M, Hashimoto Y, Aiso S, Nishimoto I. Humanin and colivelin: neuronal-death-suppressing peptides for Alzheimer's disease and amyotrophic lateral sclerosis. *CNS Drug Rev*. **2006**; 12: 113-22.
- [3] Glenner GG, Wong CW. Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun*. **1984**; 120: 885-90.
- [4] Kang J, Lemaire HG, Unterbeck A, Salbaum JM, Masters CL, Grzeschik KH, Multhaup G, Beyreuther K, Müller-Hill B. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor. *Nature*. **1987**; 325: 733-6.
- [5] Goate A, Chartier-Harlin MC, Mullan M, Brown J, Crawford F, Fidani L, Giuffra L, Haynes A, Irving N, James L, et al. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. *Nature*. **1991**; 349: 704-6.
- [6] Kawasumi M, Hashimoto Y, Chiba T, Kanekura K, Yamagishi Y, Ishizaka M, Tajima H, Niikura T, Nishimoto I. Molecular mechanisms for neuronal cell death by Alzheimer's amyloid precursor protein-relevant insults. *Neurosignals*. **2002**; 11: 236-50.
- [7] Kawasumi M, Chiba T, Yamada M, Miyamae-Kaneko M, Matsuoka M, Nakahara J, Tomita T, Iwatsubo T, Kato S, Aiso S, Nishimoto I, Kouyama K. Targeted introduction of V642I mutation in amyloid precursor protein gene causes functional abnormality resembling early stage of Alzheimer's disease in aged mice. *Eur J Neurosci*. **2004**; 19: 2826-38.
- [8] Lu B, Pang PT, Woo NH. The yin and yang of neurotrophin action. *Nat Rev Neurosci*. **2005**; 6: 603-14.
- [9] Hefti F, Mash DC. Localization of nerve growth factor receptors in the normal human brain and in Alzheimer's disease. *Neurobiol Aging*. **1989**; 10: 75-87.
- [10] Chao MV, Rajagopal R, Lee FS. Neurotrophin signalling in health and disease. *Clin Sci (Lond)*. **2006**; 110: 167-73.
- [11] Sari Y. Potential drugs and methods for preventing or delaying the progression of Huntington's disease. *Recent Pat CNS Drug Discov*. **2011**; 6: 80-90.
- [12] Gozes I, Divinski I, Piltzer I. NAP and D-SAL: neuroprotection against the beta amyloid peptide (1-42). *BMC Neurosci*. **2008**; 9 Suppl 3: S3.
- [13] Lagrèze WA, Pielen A, Steingart R, Schlunck G, Hofmann HD, Gozes I, Kirsch M. The peptides ADNF-9 and NAP increase survival and neurite outgrowth of rat retinal ganglion cells in vitro. *Invest Ophthalmol Vis Sci*. **2005**; 46: 933-8.
- [14] Gozes I. NAP (davunetide) provides functional and structural neuroprotection. *Curr Pharm Des*. **2011**; 17: 1040-4.
- [15] Chiba T, Yamada M, Sasabe J, Terashita K, Aiso S, Matsuoka M, Nishimoto I. Colivelin prolongs survival of an ALS model mouse. *Biochem Biophys Res Commun*. **2006**; 343: 793-8.
- [16] Zhao B, Chrest FJ, Horton WE Jr, Sisodia SS, Kusiak JW. Expression of mutant amyloid precursor proteins induces apoptosis in PC12 cells. *J Neurosci Res*. **1997**; 47: 253-63.
- [17] Sudo H, Hashimoto Y, Niikura T, Shao Z, Yasukawa T, Ito Y, Yamada M, Hata M, Hiraki T, Kawasumi

models of ALS. In contrast to neurotrophic factors, these trophic peptides have the ability to cross the blood-brain barrier for efficacy. Ample evidence suggests that these trophic peptides have potential for the treatment of ALS and AD.

ACKNOWLEDGMENTS

We would like to thank the National Institutes of Health-NIAA for their continuous support (R21AA017735; R21AA016115). We would also like to thank Charisse Montgomery for editing this review article.

CONFLICT OF INTEREST

None

- M, Kouyama K, Nishimoto I. Secreted Abeta does not mediate neurotoxicity by antibody-stimulated amyloid precursor protein. *Biochem Biophys Res Commun.* **2001**; 282: 548-56.
- [18] Hashimoto Y, Kaneko Y, Tsukamoto E, Frankowski H, Kouyama K, Kita Y, Niikura T, Aiso S, Bredesen DE, Matsuoka M, Nishimoto I. Molecular characterization of neurohybrid cell death induced by Alzheimer's amyloid-beta peptides via p75NTR/PLAIDD. *J Neurochem.* **2004**; 90: 549-58.
- [19] Hashimoto Y, Niikura T, Tajima H, Yasukawa T, Sudo H, Ito Y, Kita Y, Kawasumi M, Kouyama K, Doyu M, Sobue G, Koide T, Tsuji S, Lang J, Kurokawa K, Nishimoto I. A rescue factor abolishing neuronal cell death by a wide spectrum of familial Alzheimer's disease genes and Abeta. *Proc Natl Acad Sci U S A.* **2001**; 98: 6336-41.
- [20] Giovanni A, Wirtz-Brugger F, Keramaris E, Slack R, Park DS. Involvement of cell cycle elements, cyclin-dependent kinases, pRb, and E2F x DP, in B-amyloid-induced neuronal death. *J Biol Chem.* **1999**; 274: 19011-6.
- [21] Hashimoto Y, Chiba T, Yamada M, Nawa M, Kanekura K, Suzuki H, Terashita K, Aiso S, Nishimoto I, Matsuoka M. Transforming growth factor beta2 is a neuronal death-inducing ligand for amyloid-beta precursor protein. *Mol Cell Biol.* **2005**; 25: 9304-17.
- [22] Hashimoto Y, Nawa M, Chiba T, Aiso S, Nishimoto I, Matsuoka M. Transforming growth factor beta2 autocrinally mediates neuronal cell death induced by amyloid-beta. *J Neurosci Res.* **2006**; 83: 1039-47.
- [23] Cummings JL. Alzheimer's disease. *N Engl J Med.* **2004**; 351: 56-67.
- [24] Hopkins CR. ACS Chemical Neuroscience Molecule Spotlight on Semagacestat (LY450139). *ACS Chem Neurosci.* **2010**; 1: 533-4.
- [25] Cleary JP, Walsh DM, Hofmeister JJ, Shankar GM, Kuskowski MA, Selkoe DJ, Ashe KH. Natural oligomers of the amyloid-beta protein specifically disrupt cognitive function. *Nat Neurosci.* **2005**; 8: 79-84.
- [26] Elvang AB, Volbracht C, Pedersen LØ, Jensen KG, Karlsson JJ, Larsen SA, Mørk A, Stensbøl TB, Bastlund JF. Differential effects of gamma-secretase and BACE1 inhibition on brain Abeta levels in vitro and in vivo. *J Neurochem.* **2009**; 110: 1377-87.
- [27] Karczewska-Kupczewska M, Lelental N, Adamska A, Nikořajuk A, Kowalska I, Górska M, Zimmermann R, Kornhuber J, Strączkowski M, Lewczuk P. The influence of insulin infusion on the metabolism of amyloid beta peptides in plasma. *Alzheimers Dement.* **2012**.
- [28] Zhang Y, Zhou B, Deng B, Zhang F, Wu J, Wang Y, Le Y, Zhai Q. Amyloid-beta Induces Hepatic Insulin Resistance in vivo via JAK2. *Diabetes.* **2013**; 62: 1159-66.
- [29] Tomi M, Zhao Y, Thamotharan S, Shin BC, Devaskar SU. Early life nutrient restriction impairs blood-brain metabolic profile and neurobehavior predisposing to Alzheimer's disease with aging. *Brain Res.* **2013**; 1495: 61-75.
- [30] Soo KY, Farg M, Atkin JD. Molecular motor proteins and amyotrophic lateral sclerosis. *Int J Mol Sci.* **2011**; 12: 9057-82.
- [31] Padhi AK, Kumar H, Vasaiakar SV, Jayaram B, Gomes J. Mechanisms of loss of functions of human angiogenin variants implicated in amyotrophic lateral sclerosis. *PLoS One.* **2012**; 7: e32479.
- [32] Rosen DR, Siddique T, Patterson D, Figlewicz DA, Sapp P, Hentati A, Donaldson D, Goto J, O'Regan JP, Deng HX, et al. Mutations in Cu/Zn superoxide dismutase gene are associated with familial amyotrophic lateral sclerosis. *Nature.* **1993**; 362: 59-62.
- [33] Okado-Matsumoto A, Fridovich I. Amyotrophic lateral sclerosis: a proposed mechanism. *Proc Natl Acad Sci U S A.* **2002**; 99: 9010-4.
- [34] Van Den Bosch L, Robberecht W. Crosstalk between astrocytes and motor neurons: what is the message? *Exp Neurol.* **2008**; 211: 1-6.
- [35] Neusch C, Bähr M, Schneider-Gold C. Glia cells in amyotrophic lateral sclerosis: new clues to understanding an old disease? *Muscle Nerve.* **2007**; 35: 712-24.
- [36] Henkel JS, Beers DR, Siklós L, Appel SH. The chemokine MCP-1 and the dendritic and myeloid cells it attracts are increased in the mSOD1 mouse model of ALS. *Mol Cell Neurosci.* **2006**; 31: 427-37.
- [37] Wood JD, Beaujeux TP, Shaw PJ. Protein aggregation in motor neurone disorders. *Neuropathol Appl Neurobiol.* **2003**; 29: 529-45.
- [38] Rothstein JD, Van Kammen M, Levey AI, Martin LJ, Kuncl RW. Selective loss of glial glutamate transporter GLT-1 in amyotrophic lateral sclerosis. *Ann Neurol.* **1995**; 38: 73-84.
- [39] Spreux-Varoquaux O, Bensimon G, Lacomblez L, Salachas F, Pradat PF, Le Forestier N, Marouan A, Dib M, Meininger V. Glutamate levels in cerebrospinal fluid in amyotrophic lateral sclerosis: a reappraisal using a new HPLC method with coulometric detection in a large cohort of patients. *J Neurol Sci.* **2002**; 193: 73-8.
- [40] Shaw PJ. Molecular and cellular pathways of neurodegeneration in motor neurone disease. *J Neurol Neurosurg Psychiatry.* **2005**; 76: 1046-57.
- [41] Bellingham MC. A review of the neural mechanisms of action and clinical efficiency of riluzole in treating amyotrophic lateral sclerosis: what have we learned in the last decade? *CNS Neurosci Ther.* **2011**; 17: 4-31.

- [42] Rothstein JD, Patel S, Regan MR, Haenggeli C, Huang YH, Bergles DE, Jin L, Dykes Hoberg M, Vidensky S, Chung DS, Toan SV, Bruijn LI, Su ZZ, Gupta P, Fisher PB. Beta-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression. *Nature*. **2005**; 433: 73-7.
- [43] Gibson SB, Bromberg MB. Amyotrophic lateral sclerosis: drug therapy from the bench to the bedside. *Semin Neurol*. **2012**; 32: 173-8.
- [44] Divinski I, Mittelman L, Gozes I. A femtomolar acting octapeptide interacts with tubulin and protects astrocytes against zinc intoxication. *J Biol Chem*. **2004**; 279: 28531-8.
- [45] Pinhasov A, Mandel S, Torchinsky A, Giladi E, Pittel Z, Goldsweig AM, Servoss SJ, Brenneman DE, Gozes I. Activity-dependent neuroprotective protein: a novel gene essential for brain formation. *Brain Res Dev Brain Res*. **2003**; 144: 83-90.
- [46] Steingart RA, Gozes I. Recombinant activity-dependent neuroprotective protein protects cells against oxidative stress. *Mol Cell Endocrinol*. **2006**; 252: 148-53.
- [47] Gozes I, Zaltzman R, Hauser J, Brenneman DE, Shohami E, Hill JM. The expression of activity-dependent neuroprotective protein (ADNP) is regulated by brain damage and treatment of mice with the ADNP derived peptide, NAP, reduces the severity of traumatic head injury. *Curr Alzheimer Res*. **2005**; 2: 149-53.
- [48] Vulih-Shultzman I, Pinhasov A, Mandel S, Grigoriadis N, Touloumi O, Pittel Z, Gozes I. Activity-dependent neuroprotective protein snippet NAP reduces tau hyperphosphorylation and enhances learning in a novel transgenic mouse model. *J Pharmacol Exp Ther*. **2007**; 323: 438-49.
- [49] Divinski I, Holtser-Cochav M, Vulih-Schultzman I, Steingart RA, Gozes I. Peptide neuroprotection through specific interaction with brain tubulin. *J Neurochem*. **2006**; 98: 973-84.
- [50] Visochek L, Steingart RA, Vulih-Shultzman I, Klein R, Priel E, Gozes I, Cohen-Armon M. PolyADP-ribosylation is involved in neurotrophic activity. *J Neurosci*. **2005**; 25: 7420-8.
- [51] Mironov SL, Ivannikov MV, Johansson M. [Ca²⁺]_i signaling between mitochondria and endoplasmic reticulum in neurons is regulated by microtubules. From mitochondrial permeability transition pore to Ca²⁺-induced Ca²⁺ release. *J Biol Chem*. **2005**; 280: 715-21.
- [52] Pascual M, Guerri C. The peptide NAP promotes neuronal growth and differentiation through extracellular signal-regulated protein kinase and Akt pathways, and protects neurons co-cultured with astrocytes damaged by ethanol. *J Neurochem*. **2007**; 103: 557-68.
- [53] Fernandez-Montesinos R, Torres M, Baglietto-Vargas D, Gutierrez A, Gozes I, Vitorica J, Pozo D. Activity-dependent neuroprotective protein (ADNP) expression in the amyloid precursor protein/presenilin 1 mouse model of Alzheimer's disease. *J Mol Neurosci*. **2010**; 41: 114-20.
- [54] Gozes I, Divinsky I, Pilzer I, Fridkin M, Brenneman DE, Spier AD. From vasoactive intestinal peptide (VIP) through activity-dependent neuroprotective protein (ADNP) to NAP: a view of neuroprotection and cell division. *J Mol Neurosci*. **2003**; 20: 315-22.
- [55] Jouroukhin Y, Ostritsky R, Gozes I. D-NAP prophylactic treatment in the SOD mutant mouse model of amyotrophic lateral sclerosis: review of discovery and treatment of tauopathy. *J Mol Neurosci*. **2012**; 48: 597-602.
- [56] Brenneman DE, Gozes I. A femtomolar-acting neuroprotective peptide. *J Clin Invest*. **1996**; 97: 2299-307.
- [57] Brenneman DE, Hauser J, Neale E, Rubinraut S, Fridkin M, Davidson A, Gozes I. Activity-dependent neurotrophic factor: structure-activity relationships of femtomolar-acting peptides. *J Pharmacol Exp Ther*. **1998**; 285: 619-27.
- [58] Chiba T, Hashimoto Y, Tajima H, Yamada M, Kato R, Niikura T, Terashita K, Schulman H, Aiso S, Kita Y, Matsuoka M, Nishimoto I. Neuroprotective effect of activity-dependent neurotrophic factor against toxicity from familial amyotrophic lateral sclerosis-linked mutant SOD1 in vitro and in vivo. *J Neurosci Res*. **2004**; 78: 542-52.
- [59] Gozes I, Brenneman DE. A new concept in the pharmacology of neuroprotection. *J Mol Neurosci*. **2000**; 14: 61-8.
- [60] Furman S, Steingart RA, Mandel S, Hauser JM, Brenneman DE, Gozes I. Subcellular localization and secretion of activity-dependent neuroprotective protein in astrocytes. *Neuron Glia Biol*. **2004**; 1: 193-9.
- [61] Hill JM, Glazner GW, Lee SJ, Gozes I, Gressens P, Brenneman DE. Vasoactive intestinal peptide regulates embryonic growth through the action of activity-dependent neurotrophic factor. *Ann N Y Acad Sci*. **1999**; 897: 92-100.
- [62] Glazner GW, Boland A, Dresse AE, Brenneman DE, Gozes I, Mattson MP. Activity-dependent neurotrophic factor peptide (ADNF9) protects neurons against oxidative stress-induced death. *J Neurochem*. **1999**; 73: 2341-7.
- [63] Blondel O, Collin C, McCarran WJ, Zhu S, Zamostiano R, Gozes I, Brenneman DE, McKay RD. A glia-derived signal regulating neuronal differentiation. *J Neurosci*. **2000**; 20: 8012-20.
- [64] Bassan M, Zamostiano R, Davidson A, Pinhasov A, Giladi E, Perl O, Bassan H, Blat C, Gibney G, Glazner G, Brenneman DE, Gozes I. Complete sequence of a novel protein containing a

- femtomolar-activity-dependent neuroprotective peptide. *J Neurochem.* **1999**; 72: 1283-93.
- [65] Gozes I, Bassan M, Zamostiano R, Pinhasov A, Davidson A, Giladi E, Perl O, Glazner GW, Brenneman DE. A novel signaling molecule for neuropeptide action: activity-dependent neuroprotective protein. *Ann N Y Acad Sci.* **1999**; 897: 125-35.
- [66] Glazner GW, Camandola S, Mattson MP. Nuclear factor-kappaB mediates the cell survival-promoting action of activity-dependent neurotrophic factor peptide-9. *J Neurochem.* **2000**; 75: 101-8.
- [67] White DM, Walker S, Brenneman DE, Gozes I. CREB contributes to the increased neurite outgrowth of sensory neurons induced by vasoactive intestinal polypeptide and activity-dependent neurotrophic factor. *Brain Res.* **2000**; 868: 31-8.
- [68] Zamostiano R, Pinhasov A, Bassan M, Perl O, Steingart RA, Atlas R, Brenneman DE, Gozes I. A femtomolar-acting neuroprotective peptide induces increased levels of heat shock protein 60 in rat cortical neurons: a potential neuroprotective mechanism. *Neurosci Lett.* **1999**; 264: 9-12.
- [69] Smith-Swintosky VL, Gozes I, Brenneman DE, D'Andrea MR, Plata-Salaman CR. Activity-dependent neurotrophic factor-9 and NAP promote neurite outgrowth in rat hippocampal and cortical cultures. *J Mol Neurosci.* **2005**; 25: 225-38.
- [70] Cory S, Adams JM. The Bcl2 family: regulators of the cellular life-or-death switch. *Nat Rev Cancer.* **2002**; 2: 647-56.
- [71] Sari Y, Weedman JM, Ge S. Activity-dependent neurotrophic factor-derived peptide prevents alcohol-induced apoptosis, in part, through Bcl2 and c-Jun N-terminal kinase signaling pathways in fetal brain of C57BL/6 mouse. *Neuroscience.* **2012**; 202: 465-73.
- [72] Shiryayev N, Pikman R, Giladi E, Gozes I. Protection against tauopathy by the drug candidates NAP (davunetide) and D-SAL: biochemical, cellular and behavioral aspects. *Curr Pharm Des.* **2011**; 17: 2603-12.
- [73] Chiba T, Yamada M, Hashimoto Y, Sato M, Sasabe J, Kita Y, Terashita K, Aiso S, Nishimoto I, Matsuoka M. Development of a femtomolar-acting humanin derivative named colivelin by attaching activity-dependent neurotrophic factor to its N terminus: characterization of colivelin-mediated neuroprotection against Alzheimer's disease-relevant insults in vitro and in vivo. *J Neurosci.* **2005**; 25: 10252-61.
- [74] Luciano F, Zhai D, Zhu X, Bailly-Maitre B, Ricci JE, Satterthwait AC, Reed JC. Cytoprotective peptide humanin binds and inhibits proapoptotic Bcl-2/Bax family protein BimEL. *J Biol Chem.* **2005**; 280: 15825-35.
- [75] Hashimoto Y, Niikura T, Ito Y, Sudo H, Hata M, Arakawa E, Abe Y, Kita Y, Nishimoto I. Detailed characterization of neuroprotection by a rescue factor humanin against various Alzheimer's disease-relevant insults. *J Neurosci.* **2001**; 21: 9235-45.
- [76] Zhai D, Luciano F, Zhu X, Guo B, Satterthwait AC, Reed JC. Humanin binds and nullifies Bid activity by blocking its activation of Bax and Bak. *J Biol Chem.* **2005**; 280: 15815-24.
- [77] Guo B, Zhai D, Cabezas E, Welsh K, Nouraini S, Satterthwait AC, Reed JC. Humanin peptide suppresses apoptosis by interfering with Bax activation. *Nature.* **2003**; 423: 456-61.
- [78] Chiba T, Yamada M, Sasabe J, Terashita K, Shimoda M, Matsuoka M, Aiso S. Amyloid-beta causes memory impairment by disturbing the JAK2/STAT3 axis in hippocampal neurons. *Mol Psychiatry.* **2009**; 14: 206-22.
- [79] Chiba T, Yamada M, Aiso S. Targeting the JAK2/STAT3 axis in Alzheimer's disease. *Expert Opin Ther Targets.* **2009**; 13: 1155-67.
- [80] Yamada M, Chiba T, Sasabe J, Terashita K, Aiso S, Matsuoka M. Nasal Colivelin treatment ameliorates memory impairment related to Alzheimer's disease. *Neuropsychopharmacology.* **2008**; 33: 2020-32.



Publish with **ROSS Science Publishers** and every scientist can easily read your work for free!

Your research papers will be:

- available for free to the entire scientific community
- peer reviewed and published immediately after acceptance
- cited in renowned open repositories upon indexation of the journal
- owned by yourself — author keeps the copyright