Neuritin, A Neurotrophic Factor in Nervous System Physiology

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Abstract: Neuritin (also known as candidate plasticity gene 15, cpg15) is an activity-induced glycosylphosphatidylinositol-anchored axonal protein and is mainly expressed in the brain. Neuritin mRNA expression is modulated by neurotrophic factors, synaptic activity, hormones, sensory experience, and electroconvulsive seizure therapy. Neuritin has several effects in the nervous system, such as promoting neurite outgrowth, modulating neurite outgrowth during neuronal differentiation, protecting motor neuron axons, promoting dendritic growth, shaping dendritic arbors of target neurons, regulating synaptic plasticity, stabilizing active synapses, promoting synaptic maturation and neuronal migration, promoting the development and maturation of visual cortical neurons, regulating apoptosis of proliferative neurons, and regenerating peripheral nerve and spinal axons. Neuritin is also implicated in cerebral ischemia, depression, and cognitive function in schizophrenia, and it upregulates transient outward K⁺ currents in neurons, suggesting that neuritin may be a potential therapeutic target in peripheral and central nervous system diseases. This review focuses on the expression, distribution, and physiological functions of neuritin in the nervous system.

Keywords: Antidepressant, cerebral ischemia, cognitive function, dendritic growth, nerve regeneration, neurite outgrowth, neuritin, synaptic plasticity.

INTRODUCTION

As a member of the “neurotrophic” family of neurotrophic factors, neuritin (also known as candidate plasticity gene 15, cpg15) is a neurotrophic factor located within the 6p24-p25 interval on chromosome 6. It was originally isolated in a screen for activity-regulated genes induced by kainate-stimulated seizure in the rat dentate gyrus [1] and, subsequently, in humans [2]. Neuritin is a small, highly conserved protein attached to the cell membrane through a glycosylphosphatidylinositol anchor and is sensitive to physiological stimuli such as light activation of the visual cortex [3]. With multiple roles in neurodevelopment and synaptic plasticity, neuritin is involved in the re-establishment of neuronal connectivity following traumatic damage to the central nervous system, which is under the control of several neurotrophic and neuroregenerative factors. Given that neuritin has now been shown to be involved in responses to both central and peripheral injuries and appears to be a common effector molecule for several neurotrophic and neurotherapeutic agents, understanding the neuritin pathway is an important goal for the clinical management of nervous system injuries.

This review examines studies of neuritin in vivo and in vitro since 1996 to provide a comprehensive report on the characteristics of neuritin. Progress in the study of neuritin is reported, with a particular emphasis on nervous system physiology and pathology, such as neurite outgrowth, dendritic growth, synaptic plasticity, nerve regeneration, cerebral ischemia, and depression.

Though there are many recent reviews on other neurotrophic factors [4, 5], a comprehensive review about neuritin has not been published. Here, we have reviewed the distribution, gene regulation, and effects of neuritin on diseases of the nervous system in vivo and in vitro.

DISTRIBUTION AND EXPRESSION PATTERNS

Neuritin mRNA and protein were first detected in the Xenopus spinal cord during development [6]. Neuritin is only expressed in retinal ganglion cells in the retina, and its protein is concentrated in axon tracts, including retinal axons [7]. Neuritin mRNA is also expressed in primary cultured Schwann cells [8] and shows the highest levels of expression in the brain [9] (Table 1).

Neuritin expression increases in the rat visual cortex during postnatal development, with a peak at postnatal day 28 that is coincident with eye opening. Dark rearing affects neuritin mRNA expression from the peak of the critical period into adulthood in the visual cortex, but not in the lateral geniculate nucleus or superior colliculus. Neuritin expression is lower in the visual cortex at postnatal day 28 in dark-reared rats than in controls. In dark-reared animals, neuritin mRNA levels remain constant and do not undergo the normal decrease with maturation [10]. Developmental expression of neuritin in the visual cortex of normal and monococular deprived rats changes in stages with vision [11, 12].

Neuritin is distributed inside axons and on the axon surface and is trafficked to and from the axonal surface by membrane depolarization. An elliptic pHluorin-neuritin fusion protein was expressed in optic tectal explants and in retinal ganglion cells of intact Xenopus tadpoles to assess neuritin trafficking in vivo. Depolarization by KCl increased...
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**GENE REGULATION**

Neuritin promotes dendritic and axonal growth and neurite outgrowth of cultured hippocampal and cortical neurons, and it accelerates synaptic maturation in vivo. A multitude of stimuli alter neuritin mRNA expression in both physiologic and pathologic states (Fig. 1).

**Neurotrophic Factors and Hormones**

Testosterone is a neurotrophic factor for pelvic autonomic neurons. Serum testosterone levels decline in diabetic patients and in rats. Neuritin was downregulated in sensory neurons from streptozotocin-induced diabetic rats and upregulated by nerve growth factor (NGF) treatment [14], which has been suggested in the etiology of diabetic sensory neuropathy. Cavernosum and seminal vesicle weights declined in 10-wk and 12-wk diabetic rats, indicating a decrease in serum testosterone because these tissues are preserved by testosterone. Tyrosine hydroxylase (sympathetic)-positive neuron soma and nitric oxide synthase (parasympathetic)-positive areas decrease in pelvic ganglia from 10-wk diabetic rats, but neuritin mRNA levels remained stable in pelvic ganglia from 12-wk diabetic rats. Neuritin mRNA was upregulated by NGF in cultured sensory neurons and by testosterone in cultured pelvic ganglia neurons [15]. As neuritin has been linked to neurite outgrowth, regulation of neuritin is a potential target for the prevention or reversal of the degeneration of pelvic autonomic neurons in diabetes. Brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor also increased the neuronal levels of neuritin mRNA in vitro [16, 17].

Gonadal steroids significantly induced neuritin mRNA expression 2 d after motoneuron injury. Interestingly, regardless of steroid treatment, neuritin was initially downregulated following injury in the early postaxotomy stages [18]. Androgens upregulated neuritin mRNA expression both in vivo and in vitro [19, 20].

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**Table 1. Distribution, Expression Patterns and Function of Neuritin in Nervous System**

<table>
<thead>
<tr>
<th>Region</th>
<th>Distribution/expression</th>
<th>Function</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td>1. Brain</td>
<td>Expressed in sensory regions (the visual, auditory, and olfactory systems) and regionally higher in the dentate gyrus, followed by the hippocampus, cerebral cortex, and cerebellum</td>
<td>/</td>
<td>[9]</td>
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<tr>
<td>2. Neurons located in cortical layers 2/3 and 4</td>
<td>Primarily upregulated by visual stimulation and persists for at least 48 h</td>
<td>/</td>
<td>[3]</td>
</tr>
<tr>
<td>3. Visual cortex, lateral geniculate nucleus, and superior colliculus</td>
<td>Expression increases dependent on retinally driven action potentials after postnatal day 28 but independent of early expression.</td>
<td>/</td>
<td>[10]</td>
</tr>
<tr>
<td>4. Visual cortex of monocular deprived rats</td>
<td>Protein expression is lower and is upregulated in reverse suture rats (6, 12, 24, 48 h, and 1 wk)</td>
<td>promotes structural remodeling and synaptic maturation to affect development and maturation and to participate in visual developmental plasticity</td>
<td>[11]</td>
</tr>
<tr>
<td>5. Visual cortex of monocular deprived rats</td>
<td>Correlated with visual experience and age factor, and higher expression in the critical period (postnatal 21, 28, and 45 d) is influenced by monocular form deprived</td>
<td>promotes structural remodeling and synaptic maturation to affect development and maturation and to participate in visual developmental plasticity</td>
<td>[12]</td>
</tr>
<tr>
<td>6. Primary cultured Schwann cells</td>
<td>mRNA and protein are expressed and down-regulated under high-glucose concentration</td>
<td>apoptosis of Schwann cells because of down-regulation</td>
<td>[8]</td>
</tr>
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</table>
Synaptic activity induces neuritin mRNA expression, and its translated protein may affect neural function [21]. Transcriptional activation is a key link between neuronal activity and long-term synaptic plasticity. Neuritin is an immediately-early gene induced by Ca^{2+} influx through N-Methyl-D-aspartate receptors and L-type voltage-sensitive calcium channels. Neuritin expression requires convergent activation of the Ca^{2+}/calmodulin-dependent protein kinase and mitogen-activated protein kinase pathways. Although activation of protein kinase A is not required for activity-dependent expression, neuritin is induced by cAMP in active neurons. cAMP response element-binding protein binds the neuritin promoter in vivo and partially regulates its activity-dependent expression [22].

Neuritin is upregulated in the hippocampus after both acute and chronic electroconvulsive seizure therapy. Neuritin is also upregulated in the granule cell layer and in CA1 pyramidal cells of the dentate gyrus upon chronic electroconvulsive seizure therapy. Neuritin mRNA is also enriched in the choroid plexus and regulated by electroconvulsive seizure therapy. Regulation of neuritin is involved in growth factor and angiogenic-endothelial signaling [23].

Regulation of gene transcription by neuronal activity is key to the translation of sensory experience into long term changes in synaptic structure and function. Whisker trimming experiments to modulate sensory experience in the barrel field of the somatosensory cortex showed that neuritin expression was depressed in barrels corresponding to trimmed whiskers and was enhanced in the spared D1 whisker of 4-wk-old mice. Changes in neuritin mRNA levels first appeared in layer 4, peaked 12 h after deprivation, and then declined rapidly. In layers 2/3, changes in neuritin expression appeared later, peaked at 24 h, and persisted for days. Induction of neuritin expression was diminished in both adolescent and adult cAMP-responsive element-binding protein knockout mice. Neuritin’s spatio-temporal expression pattern and its regulation by cAMP-responsive element-binding protein are consistent with a role in experience-dependent plasticity of cortical circuits [24]. HuD, a neuron-specific RNA binding protein, regulates neuritin expression via the 3′-untranslated region, which requires the presence of an AU-rich element [25].

EFFECTS ON NERVOUS SYSTEM

Many ligands that affect nervous system development are members of gene families that function together to coordinate the assembly of complex neural circuits. Accumulating evidence has indicated that neuritin mainly affects the nervous system in several animal and cellular models (Fig. 2). Because the neuritin receptor has not been identified, the physiological functions of neuritin through its receptor and the related intracellular signal transduction mechanisms remain unclear.

**Promoting Neurite Outgrowth**

Neural activity and neurotrophins induce synaptic remodeling, in part, by altering gene expression. Neuritin is expressed in postmitotic, differentiating neurons of the developing nervous system and in neuronal structures associated with plasticity in adults. Neuritin’s cDNA encodes a glycosylphosphatidylinositol-anchored protein that was identified by screening for hippocampal genes that are induced by neural activity. Neuritin mRNA is induced by neuronal activity and by BDNF and neurotrophin-3. Recombinant neuritin promotes neurite outgrowth and arborization in primary embryonic hippocampal and cortical cultures [2]. These results suggest that neuritin acts as a downstream effector of neurite outgrowth.

![Fig. (2). Effects of neuritin on nervous system physiology and pathology.](image)

Time-lapse two-photon imaging of single motor neuron axons labeled with green fluorescent protein combined with labeling of presynaptic vesicle clusters and postsynaptic acetylcholine receptors in Xenopus laevis tadpoles has been used to determine the dynamic rearrangement of individual axon branches and the time scale of synaptogenesis during motor axon arbor development in vivo. Motor neuron axon elaboration and synaptogenesis are concurrent and iterative. Neuritin is expressed during motor axon arbor development. Neuritin expression enhances the development of motor neuron axon arbors by promoting neuromuscular synaptogenesis and by increasing the addition of new axon branches [26].

**Promoting Neuronal Survival and Neurite Growth**

Neuritin 2 is the only paralog of neuritin in the mouse and human genome. Both neuritin and neuritin 2 are expressed predominantly in the nervous system. Neuritin 2 expression increases by more than two-fold in response to kainate-induced seizures and increases nearly four-fold in the visual cortex in response to 24 h of light exposure following dark adaptation. Neuritin and neuritin 2 diverge in their spatial and temporal expression profiles. Neuritin 2 mRNA is most abundant in the retina and the olfactory bulb, as opposed to neuritin, which is most abundant in the cerebral cortex and the hippocampus. Neuritin is expressed in retinal ganglion cells, but neuritin 2 is expressed in bipolar cells. The onset of neuritin 2 expression is slower than that of neuritin. Neuritin 2 is glycosylphosphatidylinositol-anchored to the cell membrane and is released in a soluble, secreted form with lower efficiency compared to that of neuritin. Neuritin and neuritin 2 form homodimers and heterodimers with each other. Neuritin and neuritin 2 promoted neuronal survival
and neurite growth with the same efficacy in hippocampal explants and dissociated cultures [27]. These findings suggest that neuritin and neuritin 2 perform similar cellular functions but may play distinct roles in vivo through their cell-type- and tissue-specific transcriptional regulation. Additional research is needed to investigate the similarities and differences in the regulation of gene expression and the physiological functions for both membrane-bound and soluble proteins.

**Modulating Neurite Outgrowth During Neuronal Differentiation**

PC12 cells are a valuable model for unraveling the mechanism of action of neuritin on neurite outgrowth. PC12 cells treated with NGF for 5 d showed changes in genes regulating neural plasticity, cytoskeletal organization, and lipid metabolism, which included neuritin, the PDZ protein Mrt1, lipoprotein lipase, tropomodulin 1 and rhoB [28]. Neuritin mRNA was upregulated by NGF in PC12 cells hours before neurite outgrowth became appreciable. PC12 cells transfected with a plasmid expressing neuritin had a higher response to NGF, as shown by the levels of SMI312-positive phosphorylated neurofilament proteins (markers for axonal processes) and tyrosine hydroxylase, the percentage of cells bearing neurites and the average length of neurites. Neuritin knockdown decreased neurite outgrowth. Neuritin potenti-
ated the NGF-induced differentiation of PC12 cells but did not affect tyrosine kinase or epidermal growth factor receptor gene expression. S-methylsulfoxioure, a potent inhibitor of inducible nitric oxide synthases, partially inhibited NGF-mediated neuritin induction, which suggests that NGF regulates neuritin expression in PC12 cells via signaling pathways triggered by nitric oxide [29]. These results show that neuritin has a role in modulating neurite outgrowth during NGF-induced differentiation of PC12 cells.

**Protecting Motor Neuron Axon**

Deletion of the survival of motor neuron (SMN) 1 gene causes spinal muscular atrophy. HuD is a novel neuronal SMN-interacting partner. SMN and HuD form a complex in spinal motor axons, and both interact with neuritin mRNA in neurons. Neuritin is highly expressed in the developing ventral spinal cord and promotes motor axon branching and neuromuscular synapse formation, indicating a crucial role in the development of motor axons and neuromuscular junctions. Neuritin mRNA localizes into axonal processes. SMN deletion decreased neuritin mRNA levels in neurons, and neuritin overexpression partially rescued the SMN-deficient phenotype in zebrafish [30]. Thus, the interaction of SMN and HuD proteins with neuritin mRNA rescues motor neuron axonal defects.

**Enhancing Dendritic Growth**

Activity-dependent and activity-independent mechanisms work in concert to regulate neuronal growth, ensuring the formation of accurate synaptic connections. Neuritin functions as a cell-surface growth-promoting molecule in vivo. In *Xenopus laevis*, neuritin enhanced dendritic arbor growth in projection neurons, with no effect on interneurons. Neuritin modulated the growth of neighboring neurons by an intracel-

lular signaling mechanism through its glycosylphosphatidylinositol link [31]. Neuritin may represent a new class of activity-regulated, membrane-bound, growth-promoting proteins that permit exquisite spatial and temporal control of neuronal structure.

**Presynaptic Shaping of Dendritic Arbors of Target Neurons**

Neuritin is expressed in the cat visual system at high levels in the lateral geniculate nucleus, but at very low levels in its synaptic target, layer 4 of the visual cortex. Prenatally, when neuritin mRNA in the lateral geniculate nucleus is most abundant, expression is insensitive to action potential blockade by tetrodotoxin. Postnatally, neuritin emerges in the lateral geniculate nucleus coincident with the development of ocular dominance columns in the visual cortex. Neuritin can be detected in layers 2/3 and 5/6 of the visual cortex postnatally, and its expression in layers 2/3 is regulated by activity during known periods of activity-dependent plasticity for these layers [32]. The localization and regulation of neuritin expression in the visual system are consistent with a presynaptic role for neuritin in shaping dendritic arbors of target neurons during activity-dependent synaptic rearrangements, both in development and in adulthood.

**Mediating Synaptic Plasticity**

Neuritin, an effector gene, is a target for signal transduction pathways that mediate synaptic plasticity and therefore may take part in an activity-regulated transcriptional program that directs long-term changes in synaptic connections [22]. Treatment with cocaine or seizure induction increases the levels of HuR, HuD, and p-glycogen synthase kinase 3β protein, as well as neuronal mRNAs encoding neuritin protein in different regions of the brain and in dissociated neurons [33]. Post-transcriptional regulation of neuronal mRNAs, such as neuritin, by the RNA binding protein HuD mediates protein synthesis-dependent changes in synaptic plasticity [34].

**Stabilizing Active Synapses on Dendritic Spines**

Deletion of neuritin in mice delays the developmental maturation of axonal and dendritic arbors, as visualized by anterograde tracing and diolistic labeling, respectively. Synaptic maturation is also delayed, and many dendritic spines initially lack functional synaptic contacts. While circuits eventually develop, in vivo imaging revealed that spine maintenance is compromised in the adult, leading to a gradual attrition in spine numbers. Loss of neuritin also leads to poor learning. Neuritin knockout mice required more trials to learn, but memories were retained following learning [35]. These results imply that neuritin stabilizes active synapses on dendritic spines, resulting in selective spine and/or arbor stabilization and synaptic maturation, and that synapse stabilization mediated by neuritin is critical for efficient learning.

**Improving Synthetic Maturation**

Tectal cell expression of neuritin increases the elaboration of presynaptic retinal axons by decreasing the rate of branch retraction. Neuritin expression improves retinotectal synapse maturation by recruiting functional AMPA receptors
to synapses. Expression of truncated neuritin lacking its glycosylphosphatidylinositol anchor does not promote axon arbor growth and blocks synaptic maturation [36]. These findings demonstrate that neuritin coordinately increases the growth of pre- and postsynaptic structures and the number and strength of their synaptic contacts.

**Increasing Neuronal Migration**

Neuritin was highly expressed in a model of migrating neurons using immortalized mouse cells (GN11 cells), but not in a model of non-migrating mouse neurons (GT1-7 cells). GN11 cell migration was enhanced by overexpressed neuritin and decreased by silenced neuritin. The effects of neuritin on neuronal migration were confirmed ex vivo on rat cortical interneurons and acute embryonic brain slices. Neuritin level modulation affected GN11 cell morphology and was paralleled by neuritin-induced α-tubulin post-translational modifications, a well-recognized marker of microtubule stability [37]. These data show that neuritin increases the migration of neuronal cells, and its levels affect microtubule stability.

**Regulating Apoptosis of Proliferative Neurons**

Endogenous neuritin is essential for the survival of undifferentiated cortical progenitors in vitro and in vivo. Neuritin overexpression in vitro expanded the progenitor pool by preventing apoptosis, leading to an enlarged, indented cortical plate and cellular heterotopias within the ventricular zone, similar to the phenotypes of mutant mice with supernumerary forebrain progenitors [9]. Neuritin expressed during mammalian forebrain morphogenesis may help balance the neuronal number by countering apoptosis in specific neuroblast subpopulations, thus influencing final brain size and shape.

**Stimulating Peripheral Nerve Regeneration**

Axonal regeneration is defective in diabetic neuropathy, which contributes to the loss of axons in the extremities and neuronal dysfunction. A population of small diameter neurons in the dorsal root ganglia expressed neuritin, which was transported along the sciatic nerve in vivo. NGF upregulated neuritin expression in sensory neurons in vitro through the activation of mitogen-activated protein kinase or phosphatidylinositol-3 kinase. Neuritin silencing inhibited NGF-mediated neurite outgrowth. Neuritin levels were reduced in both the dorsal root ganglia and sciatic nerve of diabetic rats, and these deficits were reversed by NGF treatment [14]. In the facial motor nucleus of the rat facial nerve crush axotomy model, electrical stimulation of the proximal nerve stump and testosterone propionate administration had differential effects on the expression of candidate genes, including BDNF and neuritin [38].

Neuritin mRNA is expressed in the basal condition of immortalized motor neurons and was selectively upregulated by androgens in NSC34/mouse androgen receptor cells. Neuritin silencing inhibited the androgenic effect on neurite outgrowth [19]. After crush injury to the facial nerve in Syrian hamsters, androgen treatment enhanced axonal regeneration rates and upregulated neuritin mRNA three-fold at 2 d post-injury, which was prevented by simultaneous treatment with flutamide, an androgen receptor blocker. The androgen dihydrotestosterone upregulated neuritin mRNA expression by approximately one-fold in motoneuron/neuroblastoma cells transfected with androgen receptors, but not in cells lacking androgen receptors [20]. These data show that neuritin is under the control of androgens and indicate that neuritin is an important effector of androgen in enhancing peripheral nerve regeneration following injury.

**Promoting Axonal Regeneration After Spinal Cord Injury**

Functional recovery after spinal cord injury may result, in part, from axon outgrowth and related plasticity through coordinated changes at the molecular level. The identified cluster includes neuritin, attractin, microtubule-associated protein 1a, and myelin oligodendrocyte protein genes. The cluster mRNAs were depressed in both ventral and dorsal horn neurons within 24 h after spinal cord injury, followed by strong re-induction during the next 2 wk, which paralleled functional recovery. The mRNA and protein expression of the gene cluster was also evaluated in spinal cord tissue and in single neurons and was shown to play a role in axonal plasticity. The cluster members acted synergistically to drive neurite outgrowth in primary dorsal root ganglion cells [39].

According to the Basso, Beattie and Bresnahan locomotor scale, neuritin and His proteins increased the score of rats over time after operation (3, 7, 14, and 28 d). Neuritin increased the score more significantly than His protein from 14 d, but both scores were lower than that of sham-operated rats at different time points after the operation. The injured spinal tissue exhibited normal morphology after operation in sham-operated rats. From 7 d after operation, neuritin-treated rats had more deeply stained Nissl bodies, less physaliferous cells, and more nerve synapses than His protein-treated rats. In the spinal cord beginning at 7 d after operation, neuritin and His protein increased neurofilament 200 and 43KD growth-associated protein expression more than that of the sham-operated rats at each time point, with neuritin exhibiting more significant effects than the His protein [40]. These findings show that the local application of exogenous neuritin can promote axonal regeneration and recovery of the locomotor function of hindlimbs after acute spinal cord injury in rats.

**Increasing Neuron Regeneration After Traumatic Brain Injury**

In rats with traumatic brain injury, neuritin-positive neurons were present in coronal sections of the frontal lobe at d 1, reached the highest level around d 14, and maintained elevated levels through d 21. Neuritin protein and mRNA levels increased in a similar temporal pattern. However, sham rats had undetectable levels of neuritin [41]. Increased neuritin expression in the frontal cortex implies that neuritin may be involved in regenerative and reparative processes following traumatic brain injury.

**Improving Cerebral Ischemia**

Immediate early genes represent the first wave of gene expression following ischemia and are induced extensively in the cerebral cortex and hippocampus of the ischemic
brain. BDNF and neuritin belong to a subgroup of immediate early genes implicated in synaptic plasticity that are known as effector immediate early genes. During the first 24 h of reperfusion following a 2 h occlusion of the middle cerebral artery, neuritin was persistently activated in the frontal cingulate cortex. In the dentate gyrus, neuritin was activated at 0-6 h and BDNF was activated at 0-9 h of reperfusion [42]. These data suggest a rapid and long term activation of immediate early gene effectors in distinct brain areas following ischemic injury in rat. Effector gene activation may be a part of long term synaptic responses of ischemic brain tissue. In a rat model of transient global ischemia, selectively blocking NR2A, but not NR2B, containing N-Methyl-D-aspartate receptors inhibited ischemia-induced phosphorylation of cAMP response element-binding protein and the subsequent upregulation of the cAMP response element-binding target genes such as neuritin and BDNF [43]. Neuritin expression in the mouse hippocampus was upregulated at 1-2 wk after transient global ischemia. In the dentate gyrus, the number of neuritin- and bromodeoxyuridine-positive cells increases concurrently after injury. During re-establishment of the neuronal network following glutamate-induced injury of primary hippocampal neurons in culture, neuritin was mainly located at the ends and turn-off regions of growth cones and in vesicles. Depletion of soluble neuritin protein secreted from the hippocampal cells in the culture media reduced neurite outgrowth and neuron-neuron connectivity [44]. These results imply that neuritin may function as a new factor required for re-establishment of the neuronal network after injury, providing a new strategy to enhance endogenous neurogenesis after ischemic brain injury.

Adipose-derived stem cells are labeled by DAPI before transplantation. DAPI-positive cells are observed around the cerebral infarcted area in adipose-derived stem cell-treated rats. In the ischemic regions of adipose-derived stem cell-treated rats, there were upregulated expression of neuritin and neurofilament 200 and downregulated expression of glial fibrillary acidic protein in middle cerebral artery-occluded rats at 7 d, 14 d, and 28 d [45]. These findings suggest that the transplantation of adipose-derived stem cells can induce the regeneration and repair of neuronal axons in rat brain after cerebral ischemia, partly by inhibiting the expression of glial fibrillary acidic protein and enhancing the expression of neuritin and neurofilament 200 in the brain.

Modifying Cognitive Function in Schizophrenia

A functional deficiency of glial growth factors including neuritin is among the distal causes in the genotype-phenotype chain that may result in the development of schizophrenia [46]. Neuritin has been linked to a subtype of schizophrenia that is characterized by pervasive cognitive deficits. After correction for multiple testing, linear regression analysis, but not logistic regression analyses, yielded a significant association for polymorphisms rs1475157 and rs9405890 with current IQ scores in schizophrenia patients. The rs1475157/rs9405890 haplotypes revealed a highly significant association with the abstraction component of current (“fluid”) intelligence and with percentage loss of IQ points between premorbid and current intelligence [47]. The association between variations in neuritin and schizophrenia suggests a role for neuritin as a modifier of cognitive function in schizophrenia, with implications for future research into the impact of the environment on the development and maintenance of “fluid” intelligence.

Treating Depression

Chronic unpredictable stress decreases neuritin expression in the hippocampus, and antidepressant treatment reverses the down-regulation of neuritin expression. Viral-mediated expression of neuritin in the hippocampus exhibited antidepressant actions and avoided the atrophy of dendrites and spines, as well as depressive and anxiety-like behaviors that are caused by chronic unpredictable stress. Neuritin knockdown increased depressive-like behaviors, similar to chronic unpredictable stress exposure. The ability of neuritin to increase neuroplasticity was verified using hippocampal-dependent learning tasks such as object recognition to discriminate a novel object from a familiar object during testing [48]. The results demonstrate a unique function of neuritin in models of stress and depression and a role for neuroplasticity in the response to antidepressant treatment and related behaviors. Developing strategies to target neuritin or related signaling pathways is a unique approach for improved antidepressant treatment.

A brief infusion of BDNF into the dentate gyrus of anesthetized adult rats triggered stable long-term potentiation at medial perforant path granule synapses that was transcription dependent and required upregulation of the immediate early gene Arc along with five other co-upregulated genes (neuritin, Narp, ADP-ribosylation factor-like protein-4, transforming growth factor-β-induced immediate early gene-1, and Carp) [49]. Chronic, but not acute, antidepressant treatment with fluoxetine resulted in upregulation of these BDNF/long-term potentiation-associated genes in the dentate gyrus, hippocampus proper, and prefrontal cortex. Neuritin mRNA expression increased at different levels in the prefrontal cortex, hippocampus proper, and dentate gyrus with a brain region-specific pattern [50]. These results link the chronic effects of antidepressant treatment to the molecular mechanisms underlying BDNF-induced synaptic plasticity. Using microarray analysis of the hippocampus after intracerebroventricular infusion, erythropoietin induced the expression of neurotrophic genes implicated in antidepressant action, such as BDNF, VGF (nonacronymic), and neuritin [51]. Furthermore, erythropoietin was sufficient to produce a robust antidepressant-like effect in novelty-induced hypophagia and forced swim tests in rodents.

Upregulating Transient Outward K⁺ Current in Neurons

Neuritin specifically increases the densities of transient outward K⁺ currents in rat cerebellar granule neurons, which are mediated by upregulated Kv4.2 expression, the main α-subunit of transient outward K⁺ currents. Exposure of cerebellar granule neurons to neuritin induced the phosphorylation of ERK, Akt and mammalian target of rapamycin (mTOR). Neuritin-induced transient outward K⁺ currents and increased expression of Kv4.2 were abrogated by ERK, Akt or mammalian target of rapamycin inhibitors, which were pharmacologically blocked by inhibitors to the insulin receptor, but not the insulin-like growth factor 1 receptor. Neuritin activated downstream signaling effectors of the insulin re-
ceptor in cerebellar granule neurons and HeLa cells [52], but the quality of commercially available recombinant neuritin has not been independently verified.

CONCLUSION

Neuritin is a new member of the neurotrophic factor family and is mainly expressed in the brain. Neuritin expression is modulated by several stimuli, such as neurotrophic factors and synaptic activity. Neuritin promotes neurite outgrowth, dendritic growth, neuronal migration, and the maturation of synapses in visual cortical neurons; regulates synaptic plasticity and apoptosis of proliferative neurons in peripheral nerves and in spinal axonal regeneration; improves recovery following cerebral ischemia; and is implicated in cognitive function in schizophrenia and depression. The specific receptor for neuritin has not been identified, making an understanding of the molecular and cellular dynamics and physiological actions of neuritin more challenging. Basic activity-related changes in the central nervous system are thought to depend on neuritin-mediated modification of synaptic transmission, especially in the hippocampus and neocortex. Pathologic levels of neuritin-dependent synaptic plasticity may contribute to cerebral ischemia and depression, whereas application of the trophic properties of neuritin may lead to novel therapeutic options in neurodegenerative diseases and perhaps even in neuropsychiatric disorders.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

NGF = Nerve growth factor
BDNF = Brain-derived neurotrophic factor
SMN = Survival of motor neuron

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