REVIEW

Function of Nogo-A/Nogo-A Receptor in Alzheimer's Disease

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SUMMARY

Nogo-A is a protein inhibiting axonal regeneration, which is considered a major obstacle to nerve regeneration after injury in mammals. Rapid progress has been achieved in new physiopathological function of Nogo-A in Alzheimer's disease in the past decade. Recent research shows that through binding to Nogo-A receptor, Nogo-A plays an important role in Alzheimer's disease (AD) pathogenesis. Particularly, Nogo-A/Nogo-A receptors modulate the generation of amyloid β -protein ($A\beta$), which is thought to be a major cause of AD. This review describes the recent development of Nogo-A, Nogo-A receptor, and downstream signaling involved in AD and pharmacological basis of therapeutic drugs. We concluded the Nogo-A/Nogo-A receptor provide new insight into potential mechanisms and promising therapy strategies in AD.

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Introduction

Alzheimer's disease (AD) is a prevalent neurodegenerative disease that progressively impairs the memory and cognition of patients [1] and is particularly common in the elderly. The main pathological changes are senile plaques (SP) caused by accumulation of $A\beta$ and neurofibrillary tangles formed by hyperphosphorylated tau [2]. Until now, the causes of AD have not been completely clear. Age is a major contributing factor due to the fact that the prevalence of AD in patients above 65 grows exponentially. According to studies on patients with familial AD, there are three genes that are mutated in these patients, namely amyloid β -protein precursor (APP), presenilin 1 (PS1), and presenilin 2 (PS2) [3]. However, patients with familial AD only account for a small number of cases, the majority of patients with AD arise from sporadic onset [4], neither have family history or a Mendelian distribution, nor are related to the diversity of the apolipoprotein E (ApoE4) gene [5]. Mutation in the APP and PS genes leads to excessive $A\beta$ generation, whereas changes in the ApoE4 gene results in altered clearance and transport of

$A\beta$, which may contribute to amyloid plaque deposition and accelerate the progression of AD [6].

Although research on AD pathogenesis has made substantial progress, the exact etiology is not well understood. To date, there are many hypotheses to explain the pathogenesis of AD, including the amyloid, tau hyperphosphorylation, oxidative stress and excitotoxicity, and inflammation hypotheses, of which the amyloid hypothesis is the most accepted. The 40-residue $A\beta$ peptide ($A\beta_{40}$) and 42-residue $A\beta$ peptide ($A\beta_{42}$) are the two major forms of $A\beta$ monomers. The highly amyloidogenic $A\beta_{42}$ is more prone to aggregate and more neurotoxic than the shorter $A\beta$ species. They are generated from cleavage of APP by β -secretase and γ -secretase. In light of the amyloid hypothesis, overproduction and accumulation of $A\beta$ trigger the onset and accelerate the development of AD [7].

Despite the substantial progress on studying AD pathogenesis, an effective treatment to delay the onset and progression of AD has not been developed. There is an urgent need to research the pathogenesis of AD and identify a novel target for drug intervention. Recent studies suggest that the Nogo-A/Nogo-A receptor

plays an essential role in the progression of AD, affecting neurodegeneration as well as A β metabolism. Consequently, interventions directed at this target may not only promote neuroregeneration and restore the neural network, but may also reduce the generation of A β , playing dual roles in treating AD. This review will summarize recent advances in Nogo-A/Nogo-A receptor research in AD and aim at providing new ideas for AD pathogenesis and drug intervention.

Discovery of Nogo-A/Nogo-A Receptor

Nogo-A is a myelin protein with a molecular mass of 256 KDa, composed of 1192 amino acids, and is encoded by the Nogo gene. Nogo-A was found to inhibit neurite outgrowth in dorsal root ganglion cells [7,8], PC12 cells [7], and cerebellar granule cells [9], which is considered a major obstacle to nerve regeneration after injury in adult mammalian CNS. Later it was discovered that Nogo-A belonged to a larger reticulon protein family (RTN). To distinguish it from the other three types of RTNs [10], Nogo is also called RTN 4 and Nogo-A is called RTN4A, respectively. Nogo-A has a short C-terminal tail, an extracellular N-terminus, and two transmembrane domains. Fragment analyses and binding studies showed that Nogo-A contains more than one growth inhibiting domain, and two principal domains of Nogo-A have been shown to induce growth cone collapse and exert inhibitory effects on neurite outgrowth: the Nogo-66 loop (1055–1120 amino acid residues, located between two hydrophobic domains) and Nogo-A- Δ 20 (544–725 amino acid residues, part of “Amino-Nogo”) [11,12].

Fournie et al. [13] first discovered the existence of the Nogo-66 receptor (NgR), which specifically bound to Nogo-66 domain. Afterward several homologous NgRs were consecutively found and the one binding to Nogo-66 was renamed NgR1, a glycosphosphatidylinositol-anchored protein (GPI) with a plurality of leucine-rich repeat (LRR) structures. In addition to Nogo-66, two other myelin-associated inhibitors (MAIs), myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp) [14], can bind to NgR1 and limit axon regeneration and sprouting in the injured brain. Moreover, a novel receptor for Nogo-66, paired immunoglobulin-like receptor B (PirB), was recently discovered, and it plays a role similar to NgR1 [15].

To transduce intracellular signals, NgR1 forms a receptor complex including the membrane proteins p75 neurotrophin receptor (p75NTR) and/or a TNF receptor family member TROY, the LRR-protein LINGO-1 and converge on the activation of RhoA, leading to growth inhibition via the rho-associated coiled coil-containing protein kinase (ROCK) [16]. Activation of the RhoA/ROCK pathway results in actin depolymerization via the regulation of LIM kinase (LIMK) and cofilin, increased actomyosin contraction via regulation of the myosin light chain II (MLC II) and disassembled microtubule via the collapsin response mediator protein 2 (CRMP2) [16]. Furthermore, the combination of Nogo-66 and receptor inhibits the activation of phosphorylated protein kinase B (PKB) and glycogen synthase kinase 3 β (GSK3 β) [17,18]. The CRMP-4 is a major target of GSK-3 β in controlling cytoskeleton dynamics and has the ability to complex with RhoA [19,20]. Other signaling components of Nogo-A include protein kinase C (PKC) and epidermal growth factor receptor (EGFR), whereby

pharmacological blockade of PKC α/β and EGFR was shown to decrease Nogo-66 and myelin-mediated growth inhibition [21,22].

Apart from Nogo-66, Nogo-A- Δ 20 is another extracellular domain in the N-terminal region of Nogo-A (Amino-Nogo), which regulates axonal regeneration [11]. Although Hu and Strittmatter [23] revealed that some integrins, such as α_v and α_5 , are sensitive to Nogo-A and are involved in the inhibition of axonal outgrowth mediated by Amino-Nogo, its mechanism had been unclear until very recently. Kember et al. [24] discovered that the sphingosine 1-phosphate receptor 2 (S1PR2) had been identified as a specific receptor and signal transducer for the Nogo-A- Δ 20. The S1PR2 is one kind of G-protein-coupled receptor, which contains 7-transmembrane domain and belongs to the subfamily of S1PR. The S1PR family is thought to be activated by the low-molecular-weight lipid ligand sphingosine 1-phosphate (S1P), which exerts diverse receptor-specific effects on various cell types including regulation of apoptosis, cell motility, and cytoskeleton dynamics [25]. Nogo-A- Δ 20 binding to S1PR2 activates the G-protein G-13, the leukemia-associated Rho guanine exchange factor (RhoGEF) LARG and RhoA, which induce the inhibition of neurite growth or fibroblast spreading [24]. On the other hand, Nogo-A- Δ 20 could upregulate the expression levels of the RhoA and downregulate the levels of phosphor-cyclic AMP response element-binding (p-CREB) in dorsal root ganglion cells [26]. It has been identified that Akt acts as a novel signaling component of the amino-Nogo pathway and the activation of Akt blocks the inhibitory effects of amino-Nogo [27].

Nogo-A plays a pivotal role in the prevention of axonal regeneration after central nervous system (CNS) injury in mammals, which has been extensively studied in the field of spinal cord trauma, ischemic stroke, optic nerve injury, and models of multiple sclerosis [12]. The interaction of Nogo-A with its different receptors (NgR1, S1PR2, and PirB) restricts plasticity and neurite growth via the activation of different signaling pathways [28]. Additionally, recent studies have suggested that Nogo-A signaling plays novel important roles in the repression of synaptic plasticity in mature neuronal networks of the CNS, which extend our understanding of Nogo-A's function far beyond its well-studied role as axonal-growth inhibitor [29–32]. Here, this review will describe recent developments in the study of Nogo-A/Nogo-A receptor and signaling in AD and the pharmacological basis of therapeutic drugs.

The Distribution of Nogo-A and Nogo-A Receptor in AD Brain

The distributions of Nogo-A and NgR1 have been reported using *in situ* hybridization in the rat CNS. Nogo-A is abundantly expressed in both neurons and oligodendrocytes throughout the central nervous system, particularly with high levels of Nogo-A expression in the olfactory bulb, pyramidal cells and interneurons in the hippocampus, spinal motor neurons, and dorsal root ganglion cells [33,34]. In contrast, NgR1 mRNA expression is very restricted and has been found to be expressed in the neocortex, hippocampus, and amygdala in human brain [33].

The PirB is expressed in a variety of hematopoietic cells, which include B cells, mast cells, macrophages, granulocytes, and den-

driftic cells [35]. Recent studies have demonstrated that PirB is also expressed in regions of the CNS, including the cerebral cortex, hippocampus, cerebellum, and olfactory bulb but not in the adult spinal cord [36]. PirB is expressed at low or undetectable levels, although its expression may be more prominent during neural development or after ischemia [37]. In addition, PirB expression in the hippocampus and cortex significantly increased following treatment with lipopolysaccharide, which is a strong inducer of innate immunity and chronic inflammation in CNS [38].

The S1PR2 express widely in immune, nervous, metabolic, cardiovascular, musculoskeletal, and renal systems and the bioactive S1PR2 involved in cell proliferation, angiogenesis, inflammation, and malignant transformation [25]. Situ hybridization revealed exclusive S1PR2 expression in the hippocampal pyramidal/granular neurons of wild-type mice. The immunohistochemistry/microarray analyses identified enhanced gliosis in the whole hippocampus and neighboring neocortex in seizure-prone S1P2^{-/-} mice [39].

Gil *et al.* [40] provided evidence that Nogo-A is overexpressed by hippocampal neurons and is associated with A β deposits in SP as determined by immunohistochemistry in patients with AD. The ratio of NgR1-immunopositive neurons to the total number of neurons is significantly higher in the CA1 and CA2 subfields of the human AD hippocampus than that in normal aging hippocampus [41]. Furthermore, Park and Strittmatter [42] reported that the distribution of Nogo and NgR1 differs in the brain sections of patients with AD. Specifically, NgR1 centralizes in the neuron cell body and a fraction of NgR1 protein is also concentrated in amyloid plaques in the normal aging group, whereas Nogo-A shifts to the neuronal perikarya in all of AD cases. The distribution of other two receptors PirB and S1PR2 in patient with AD remains unclear.

Role of Nogo-A in AD

In the past decade, research has shown that Nogo-A plays an essential role in neurodegeneration. It was first discovered that there were four members in the reticulon family, including RTN1, RTN2, RTN3, and RTN4-B, all of which were binding partners of the beta-site APP cleaving enzyme 1 (BACE1 or β -secretase) [43]. In addition, an increase in the expression of any reticulon protein substantially reduces the production of A β in HEK-293 cells, while lowering the expression of RTN3 by RNA interference increases the secretion of A β [44]. It has been shown that RTNs interact with BACE1 and negatively modulate its processing of APP at the β -secretase site and overexpression of RTN3 in neurons has reduced amyloid deposition and RTN3 deficiency facilitates amyloid deposition [45–47]. Besides, Transgenic mice overexpressing RTN3 are accumulated in a distinct population of dystrophic neurites [48] and the presence of dystrophic neurites impairs cognition in AD brain.

RTN3 appears to regulate the formation of both amyloid deposition via negative modulation of BACE1 activity and dystrophic neurites via the formation of RTN3 aggregates [49]. Blocking abnormal RTN3 aggregation is therefore a promising therapeutic strategy for enhancing cognitive function of patients with AD.

Moreover, Maslish *et al.* [50] reported, deleting Nogo-A ameliorated learning and memory deficits of APP transgenic mice and

decreased AD related pathology. It is hypothesized that the overexpression of Nogo-A and activation of NgR1 inhibit neurite outgrowth and alter neuronal metabolism, resulting in overproduction of A β ₄₂ [51].

Recently, studies show that Nogo-A could serve as an crucial negative regulator of synaptic plasticity and cognitive function [29,32]. Studies of long-term potentiation (LTP) in hippocampal slice demonstrated that administration of soluble Nogo-66 or OMgp altered synaptic plasticity, suppressing LTP and enhancing long-term depression (LTD) [12]. Acute neutralization of endogenous Nogo-A or NgR1 or knockdown of Nogo-A increased LTP *in vivo*. Interestingly, it has been suggested that synaptic activity is one of the most important factors that regulate A β levels, facilitates APP internalization and cleavage [6]. However, there is hardly researches to report the relationship between the novel roles of Nogo-A played in synaptic plasticity and the pathogenesis of AD. Thus, data support the view that Nogo-A triggers the onset and development of AD via influencing the metabolism of A β and probably restricting synaptic plasticity.

Role of Nogo-A Receptor in AD

NgR1 was the first Nogo-A receptor discovered with a signaling pathway that played an important role in inhibiting axon regeneration. The NgR-mediated response to myelin inhibitors is known to participate in restricting axonal and synaptic plasticity [52]. Thus, brain myelin proteins impede both physiological plasticity and the repair of pathological injury by a shared NgR mechanism. NgR1 might be involved in the pathological process of AD by affecting the metabolism of APP [42].

Park *et al.* [53] highlighted that overexpression of NgR decreased A β production in neuroblastoma culture. As their experiments in transfected cells showed, NgR1 interacted with APP in the domain of A β . Importantly, the binding capacity varied depend on the length of A β , and they demonstrated that the central 15–28 aa of A β associated with specific surface-accessible patches on the leucine-rich repeat concave side of the solenoid structure of NgR, different from binding zone of Nogo-66.

To explore whether the interaction between NgR and A β had physiological functions, researchers conducted *in vivo* experiments on mice. Previously, researchers [54] found that mice lacking NgR1 showed increased A β accumulation in the hippocampal dentate gyrus and cerebral cortex. Cerebroventricular administration of NgR (310) ecto-Fc reduces levels of A β in the brain of APP swe/PSEN-1 Δ E9 mice, and there is a negative correlation between the level of A β , NgR1, and dystrophic neurites. They also found that subcutaneous injection of NgR (310) ecto-Fc reduced brain A β deposition in APP swe/PSEN-1 Δ E9 transgenic mice and improved short-term memory. NgR1 functions as a peripheral sink for A β , contributing to the clearance of peripheral A β , resulting in decreased accumulation in the brain and improved in transgenic mice. The possibility of side effects is also reduced due to the fact that NgR1 cannot cross the blood brain barrier (BBB). Therefore, it is likely that the peripheral association of NgR (310) ecto-Fc with central A β residues provides an effective therapeutic approach for AD.

Zhou *et al.* [55] proposed that a family of proteins named Nogo receptor proteins (NgR1 to NgR3) regulated production of A β via

interaction with APP. Further mapping of the interacting domain indicates that a small region adjacent to the BACE1 cleavage site of APP mediates the interaction of APP with NgR. These results suggested that increased interaction between Nogo receptor and APP reduces surface expression of APP and favors processing of APP by BACE1.

In addition to these myelin-associated inhibitors (MAIs), other ligands for NgR1 have been discovered. For instance, B-lymphocyte stimulator (BlyS) is a negative regulator of neuronal functions. NgR1 is identified as a high-affinity receptor for BlyS, which inhibits dorsal root ganglion outgrowth *in vitro* [56]. It has been found [57] that cartilage acidic protein-1b as an endogenous NgR antagonist that competes with Nogo for binding to NgR1 and highlights the complex regulation of Nogo-A and NgR1 function *in vivo*. The study shows that NgR1 and NgR3, but not NgR2 also bind chondroitin sulfate proteoglycans (CSPGs) using double and triple KO mice of NgR1, NgR2, and NgR3 [58]. Another ligand is the leucine-rich glioma inactivated protein (LGI), which competitively binds to NgR1 and Nogo-66 [59]. Disintegrin and metalloproteinase domain-containing protein 22 (ADAM22) serves as a receptor for LGI, binds to NgR1, and forms a stable complex [60], playing a role in synaptic maturation and dendrite formation. Additional research suggested that downregulation of LGI3 clearly inhibited A β uptake by cultured rat astrocytes and LGI3 is involved in A β uptake by astrocytes through endocytosis [61].

In 2008, researchers identified another receptor for the three mentioned myelin-associated inhibitors (MAIs), paired immunoglobulin-like receptor B (PirB), which is structurally unrelated to the NgRs but is able to bind to and mediate the growth inhibitory effects of Nogo-A, MAG, and OMgp [15]. In studies of the activation of the PirB pathway in axon outgrowth inhibition, Taylor et al. [62] reported that the scaffold protein Plenty of SH3s (POSH) could limit axon growth through a Shroom3-ROCK-myosin signaling pathway. Dickson et al. [63] found that POSH, which is an intracellular signal transducer, in association with Shroom3 and the mixed lineage kinase (LZK), relays axon outgrowth inhibition downstream of Nogo-66 and PirB. It has been suggested that a POSH-dependent mechanism operates to inhibit axon outgrowth in different types of CNS neurons. To confirm the function of PirB, Omoto et al. [64] performed experiments on PirB gene-knockout mice and found that the number of sprouting fibers within either the corticospinal or corticorubral tract was not enhanced in PirB-knockout mice, suggesting that blocking the function of PirB is not sufficient to promote axonal regeneration or functional recovery after cortical injury. However, evidence for a role of PirB in spinal cord regeneration is sparse *in vivo* [65]. Recently, Kim et al. [66] demonstrated that murine PirB and its human homology leukocyte immunoglobulin-like receptor B2 (LilrB2), which is present in human brain, are receptors for A β oligomers with nanomolar affinity. Compared to A β monomer, A β oligomers have a higher binding affinity for PirB. It has also been reported that the deleterious effect of A β oligomers on hippocampal long-term potentiation required PirB in a transgenic model of AD. PirB contributes to not only to memory deficits in adult mice, but also to loss of synaptic plasticity in the juvenile visual cortex. These results imply that LilrB2 is responsible for human AD neuropathology and blocking the interaction between A β oligomers and LilrB2 may be a potential strategy for AD therapy.

In addition to the NgR1 and PirB, a crucial Nogo-A receptor was discovered recently. Kempf et al. [24] firstly reported that the S1PR2 was recognized as a high-affinity receptor for Nogo-A- Δ 20 and Nogo-A- Δ 20 bounding to S1PR2 extracellular domain loops2 and loops3, which is distinct from the proposed S1P binding pocket. It has been suggested that Nogo-A- Δ 20 domain of Nogo-A binds to S1PR2 and activates the signal transduction through the G-protein G13, RhoGEF LARG and RhoA. Deleting or blocking S1PR2 counteracts Nogo-A- Δ 20 and myelin-mediated inhibition of neurite outgrowth and cell spreading, similar to previous results obtained by blocking Nogo-A.

Alzheimer's disease is considered as a wide loss of synapses and deficits in spatial memory. The S1PR2 could be identified as an important regulator of synaptic stabilization in the adult CNS. The potential maintains high during the LTP when the S1PR2 had been pharmacologically blocked [24]. Vitolo et al. [67] revealed that A β treatment of cultured hippocampal neurons leads to inhibition of LTP via inactivation of cAMP/PKA/CREB-signaling pathway. The previous studies suggested that Nogo-A- Δ 20 could induce a decreased levels of p-CREB, which may aggravate the inhibition of LTP induced by A β [26].

It had been found that the migration of neural progenitor cells toward areas of brain infarction is significantly enhanced when S1PR2 blocked using a specific inhibitor JTE013 [68]. S1PR2 remarkably expresses in the hippocampus and augments extensive gliosis in this area through the study of S1PR2^{-/-} mice. These mice were also susceptible to lethal seizures and displayed impaired spatial working memory in the eight-arm radial maze test and increased anxiety in the elevated plus maze test [39].

It has been well known that the NgR1 and PirB could combine with A β . It could be hypothesized that another Nogo-A receptor S1PR2 binds to A β . However, there is no study on the correlation between S1PR2 and A β .

Downstream Signaling of Nogo-A Receptor and AD

As we know, Nogo-A exerts the inhibition effect of neuron regeneration and plasticity by binding to three different Nogo-A receptors (NgR1, S1PR2, and PirB) via different signaling pathway [12,28]. But the RhoA/ROCK pathway is the common signaling pathway, and the activation of the RhoA/ROCK pathway results in a destabilization of the cytoskeleton affecting microtubules via CRMP2 and actin fibers via MLCII and Cofilin [16]. Several reports have highlighted findings that RhoA/ROCK pathways are involved in the progression of AD.

The Rho-ROCK pathway considered a key regulator of action cytoskeleton remodeling and dendritic spine maintenance [69]. Rho-ROCK pathway was also involved in AD by playing different roles including regulation of APP metabolism, inhibition of neuron regeneration, decreased level of phosphorylated tau and inactivation of glycogen synthase kinase 3 β [69–72].

Rho-ROCK may be involved in the metabolism of APP, which affects the generation of A β . Several reports have shown that a subset of nonsteroidal antiinflammatory drugs (NSAIDs) could decrease the levels of A β both *in vitro* and *in vivo* [73,74]. But the mechanism of lowering A β production is controversial. Although the first study has demonstrated that NSAIDs directly modulates

the γ -secretase activity [75], another study suggested that NSAIDs reduce $A\beta$ production because of inhibiting the RhoA/ROCK pathway [76]. Recently, Fasudil as a Rho kinase inhibitor was shown to have beneficial effects on cognitive impairment and neuronal toxicity induced by $A\beta$ [77].

Statins are also reported to reduce levels of $A\beta$ by inhibiting the Rho-ROCK pathway *in vitro* and *in vivo* [78]. Inhibition of Rho-ROCK results in activation of α -secretase cleavage or the enhancement of APP lysosomal degradation, both of which lead to the reduction of $A\beta$ production [79–81]. It has been found that ROCK inhibitor Y-27632 promotes neuron regeneration and reduces $A\beta$ in cortical neurons [51]. However, the exact mechanisms of how ROCK regulates APP processing are not well understood. Lane et al. [82] reported that ROCK formed complexes with the Vps10-domain protein and sortilin-related receptor (SorL1). Both ROCK inhibition and ROCK knockdown enhanced generation of both soluble APP and $A\beta$. Additionally, activation of PKC resulted in increased shedding of the ectodomains of both APP and SorL1, and this was paralleled by an apparent increase in the level of the phosphorylated form of SorL1. These results highlighted the potential importance of SorL1 in elucidating the regulation of APP metabolism through ROCK and PKC.

With regard to the mechanism by which $A\beta$ limits axon generation of SH-SY5Y cells, Kubo [72] reported that inactivation of collapsin response mediator protein-2 (CRMP-2) via ROCK-induced phosphorylation results in neurite outgrowth inhibition. Chacon et al. [83] found that inactivation of RhoA-GTPase and activation of protein tyrosine phosphatase 1B (PTP1B) protect cultured hippocampal neurons against the noxious effects of $A\beta$. Heredia et al. [84] indicated that $A\beta$ degeneration requires the activation of LIMK1 and the rearrangement of actin cytoskeleton. In addition, high levels of p-LIMK1 were found in AD brain. Hamano [71] suggested that pitavastatin reduces total and phosphorylated tau levels in a cellular model of tauopathy via the inactivation of Rho/ROCK in primary neuronal cultures.

Recently, Qin et al. [85] supported that silent information regulator of transcription 1 (SIRT1) was involved in the cleavage of APP through the regulation of ROCK expression. Afterward, it was also demonstrated that $A\beta_{25-35}$ -suppressed SIRT1 activity was significantly reversed by resveratrol via the ROCK downregulation. These results clearly revealed that resveratrol protected PC12 cells from $A\beta$ -induced cell apoptosis through regulation of SIRT1 and ROCK [86].

Huesa et al. [87] found a prominent RhoA mislocalization in patients with AD and in the Tg2576 mouse model. RhoA immunostaining decreased in the neuropil and markedly increased in the neurons of patients with AD, and decreased in synapses and increased in dystrophic neurite of Tg2576 mice. R-Flurbiprofen (belong to NSAID) lowered the level of $A\beta$ and improved learning and memory deficits in a transgenic animal model of AD [88]. Musilli et al. [89] showed the Rho-GTPase activator cytotoxic necrotizing factor 1 (CNF1) reduced locomotor hyperactivity in 4-month-old TgCRND8 mice and reversed the cognitive impairment compared to wild-type animals. The reporter has shown that peripheral administration of the ROCK inhibitor hydroxyfasudil improves spatial learning and working memory in the rodent model, which suggests the potential value of ROCK inhibitor for the promotion of cognition in humans [70].

As discussed, inhibition of ROCK can promote spatial learning and working memory and regulate the metabolism of $A\beta$, which suggests that ROCK appears to be a good target for AD therapy.

Another downstream signaling molecule of Nogo-A/Nogo-A receptor is PKC. A growing body of recent studies illustrates that protein kinase C (PKC) signaling pathways are causally concerned about the pathology of AD [90]. PKC plays crucial roles in synaptic plasticity and short memory. PKC can be activated by a variety of signaling systems, of which the calcium concentration is one of the key factors that mediate the activation of PKC, triggering short-term synaptic plasticity. DAG activates PKC with the coordination of Ca^{2+} and then causes cascade reactions by protein kinases C [91]. Once the calcium overload, it significantly increased the expression of calcium/calmodulin-dependent protein kinase II- α . As a result, PKC system is overactivated and inevitably damage neurons. PKC α and PKC β , two Ca^{2+} dependent PKC isoforms, are necessary for posttetanic potential (PTP), a form of plasticity responsible for underlining short-term memory. Fioravante et al. [92] discovered that disruption of the PKC β C2 domain binding to Ca^{2+} specifically prevents PTP, suggesting that the increase of Ca^{2+} evoked by tetanic stimulation leads PKC β to produce PTP. Thus, the shortage of PKC is hypothesized to be a reason for short-term memory deficits of AD.

On the other hand, PKC regulates $A\beta$ production and clearance [93]. PKC is involved in the processing of the APP, subsequently leading to the abnormal production and accumulation of $A\beta$ by the sequential actions of β -secretase and γ -secretase, which is deemed to be detrimental in the onset and development of AD [94]. According to Yang et al. [95] research on SK-N-SH and PC12 cells, DAG stimulated the release of α -secretase form of soluble APP (sAPP α) in the nonamyloidogenic way. However, the increase of sAPP α secretion by deprenyl was blocked by the mitogen-activated protein kinase (MAPK) inhibitor U0126 and PD98059 and PKC inhibitor GF109203X, indicating that deprenyl activates PKC and leads sAPP α to release. Other studies also show that blockade of PKC ϵ activation decreased phorbol ester-induced secretion of sAPP α [96]. Since sAPP α was generated by nonamyloidogenic pathway, it can be hypothesized that the activation of PKC leads APP to metabolize mainly through nonamyloidogenic pathway and causally reduces its metabolism via β -secretase pathway, which may indirectly decrease the secretion of $A\beta$. Therefore, PKC activators are regarded as a potent strategy in AD therapy.

Concluding Remarks

In summary, the Nogo-A/Nogo-A receptor plays an important role in AD pathology, and its effects and intrinsic mechanisms are thought to be related to the several key aspects. First, the Nogo-A/Nogo-A receptor and the downstream Rho-ROCK pathway inhibits axon outgrowth and synapse remodeling, becoming an obstacle to neuronal regeneration and blocking the recovery of damaged neural networks in AD. Second, it influences the metabolism of APP. Nogo-A and downstream signaling to ROCK contribute to the generation of $A\beta$, which may be a precipitating factor of neuronal degeneration and accelerate the onset of AD. In contrast, NgR could function by reducing $A\beta$ production. The newly discovered protein S1PR2 is a novel receptor for Nogo-A which also

activates ROCK and mediates neuronal plasticity. Another newly discovered protein PirB is also a novel receptor for Nogo-A that interacts with A β and mediates its neurotoxicity. As discussed, the effect of Nogo-A and the Nogo-A receptor signal system on the pathogenesis of AD is relatively complicated. Whether it promotes or delays the progress of AD depends on the expression and state of various proteins and the interaction of the different signaling pathways. Further study is necessary to clarify the exact effects and in-depth mechanisms of the Nogo-A/Nogo-A receptor on AD pathogenesis. New strategies targeted at key proteins of Nogo-A/Nogo-A receptor signaling have emerged as potential interventions in the progression of AD and bring new hope for AD therapy.

References

- Babri S, Mohaddes G, Feizi I, et al. Effect of troxerutin on synaptic plasticity of hippocampal dentate gyrus neurons in a beta-amyloid model of Alzheimer's disease: An electrophysiological study. *Eur J Pharmacol* 2014;**732**:19–25.
- Giannopoulos PF, Joshi YB, Pratico D. Novel lipid signaling pathways in Alzheimer's disease pathogenesis. *Biochem Pharmacol* 2014;**88**:560–564.
- Selkoe DJ. Preventing Alzheimer's disease. *Science* 2012;**337**:1488–1492.
- El KN, Zaid N, Zaid Y, et al. Novel presenilin mutations within Moroccan patients with early-onset Alzheimer's disease. *Neuroscience* 2014;**269**:215–222.
- Ungar L, Altmann A, Greicius MD. Apolipoprotein E, gender, and Alzheimer's disease: An overlooked, but potent and promising interaction. *Brain Imaging Behav* 2014;**8**:262–273.
- Cheng X, Wu J, Geng M, et al. The role of synaptic activity in the regulation of amyloid beta levels in Alzheimer's disease. *Neurobiol Aging* 2014;**35**:1217–1232.
- Ma T, Klann E. Amyloid beta: Linking synaptic plasticity failure to memory disruption in Alzheimer's disease. *J Neurochem* 2012;**120**(Suppl 1):140–148.
- Chen MS, Huber AB, van der Haar ME, et al. Nogo-A is a myelin-associated neurite outgrowth inhibitor and an antigen for monoclonal antibody IN-1. *Nature* 2000;**403**:434–439.
- Niederost B, Oertle T, Fritsche J, et al. Nogo-A and myelin-associated glycoprotein mediate neurite growth inhibition by antagonistic regulation of RhoA and Rac1. *J Neurosci* 2002;**22**:10368–10376.
- Yan R, Shi Q, Hu X, et al. Reticulon proteins: Emerging players in neurodegenerative diseases. *Cell Mol Life Sci* 2006;**63**:877–889.
- Oertle T, van der Haar ME, Bandtlow CE, et al. Nogo-A inhibits neurite outgrowth and cell spreading with three discrete regions. *J Neurosci* 2003;**23**:5393–5406.
- Schwab ME, Strittmatter SM. Nogo limits neural plasticity and recovery from injury. *Curr Opin Neurobiol* 2014;**27**:53–60.
- Fournier AE, GrandPre T, Strittmatter SM. Identification of a receptor mediating Nogo-66 inhibition of axonal regeneration. *Nature* 2001;**409**:341–346.
- McDonald CL, Bandtlow C, Reindl M. Targeting the Nogo receptor complex in diseases of the central nervous system. *Curr Med Chem* 2011;**18**:234–244.
- Atwal JK, Pinkston-Gosse J, Syken J, et al. PirB is a functional receptor for Myelin inhibitors of Axonal regeneration. *Science* 2008;**322**:967–970.
- Kempf A, Schwab ME. Nogo-A represses anatomical and synaptic plasticity in the central nervous system. *Physiology* 2013;**28**:151–163.
- Shen JY, Yi XX, Xiong NX, et al. GSK-3 β activation mediates Nogo-66-induced inhibition of neurite outgrowth in N2a cells. *Neurosci Lett* 2011;**505**:165–170.
- Wang H, Shen J, Xiong N, et al. Protein kinase B is involved in Nogo-66 inhibiting neurite outgrowth in PC12 cells. *NeuroReport* 2011;**22**:733–738.
- Alabed YZ, Pool M, Ong Tone S, et al. GSK3 β regulates myelin-dependent axon outgrowth inhibition through CRMP4. *J Neurosci* 2010;**30**:5635–5643.
- Alabed YZ, Pool M, Tone SO, et al. Identification of CRMP4 as a convergent regulator of Axon outgrowth inhibition. *J Neurosci* 2007;**27**:1702–1711.
- Sivasankaran R, Pei J, Wang KC, et al. PKC mediates inhibitory effects of myelin and chondroitin sulfate proteoglycans on axonal regeneration. *Nat Neurosci* 2004;**7**:261–268.
- Koprivica V, Cho KS, Park JB, et al. EGFR activation mediates inhibition of axon regeneration by myelin and chondroitin sulfate proteoglycans. *Science* 2005;**310**:106–110.
- Hu FH, Strittmatter SM. The N-terminal domain of Nogo-A inhibits cell adhesion and axonal outgrowth by an integrin-specific mechanism. *J Neurosci* 2008;**28**:1262–1269.
- Kempf A, Tews B, Arzt ME, et al. The sphingolipid receptor S1PR2 is a receptor for Nogo-A repressing synaptic plasticity. *PLoS Biol* 2014;**12**:e1001763.
- Adada M, Canals D, Hannun YA, et al. Sphingosine-1-phosphate receptor 2. *FEBS J* 2013;**280**:6354–6366.
- Joset A, Dodd DA, Halegoua S, et al. Pincher-generated Nogo-A endosomes mediate growth cone collapse and retrograde signaling. *J Cell Biol* 2010;**188**:271–285.
- Deng K, Gao Y, Cao Z, et al. Overcoming amino-Nogo-induced inhibition of cell spreading and neurite outgrowth by 12-O-tetradecanoylphorbol-13-acetate-type tumor promoters. *J Biol Chem* 2010;**285**:6425–6433.
- Zagrebelsky M, Korte M. Maintaining stable memory engrams: New roles for Nogo-A in the CNS. *Neuroscience* 2014. doi:10.1016/j.neuroscience.2014.08.030.
- Delekate A, Zagrebelsky M, Kramer S, et al. Nogo-A restricts synaptic plasticity in the adult hippocampus on a fast time scale. *Proc Natl Acad Sci USA* 2011;**108**:2569–2574.
- Lee H, Raiker SJ, Venkatesh K, et al. Synaptic function for the Nogo-66 receptor NgR1: Regulation of dendritic spine morphology and activity-dependent synaptic strength. *J Neurosci* 2008;**28**:2753–2765.
- Raiker SJ, Lee H, Baldwin KT, et al. Oligodendrocyte-myelin glycoprotein and Nogo negatively regulate activity-dependent synaptic plasticity. *J Neurosci* 2010;**30**:12432–12445.
- Tews B, Schonig K, Arzt ME, et al. Synthetic microRNA-mediated downregulation of Nogo-A in transgenic rats reveals its role as regulator of synaptic plasticity and cognitive function. *Proc Natl Acad Sci USA* 2013;**110**:6583–6588.
- Hasegawa T, Ohno K, Sano M, et al. The differential expression patterns of messenger RNAs encoding Nogo-A and Nogo-receptor in the rat central nervous system. *Brain Res Mol Brain Res* 2005;**133**:119–130.
- Schwab ME. Functions of Nogo proteins and their receptors in the nervous system. *Nat Rev Neurosci* 2010;**11**:799–811.
- Lebbink RJ, de Ruiter T, Verbrugge A, et al. The mouse homologue of the leukocyte-associated Ig-like receptor-1 is an inhibitory receptor that recruits Src homology region 2-containing protein tyrosine phosphatase (SHP)-2, but not SHP-1. *J Immunol* 2004;**172**:5535–5543.
- Gou Z, Mi Y, Jiang F, et al. PirB is a novel potential therapeutic target for enhancing axonal regeneration and synaptic plasticity following CNS injury in mammals. *J Drug Target* 2014;**22**:365–371.
- Gou X, Zhang Q, Xu N, et al. Spatio-temporal expression of paired immunoglobulin-like receptor-B in the adult mouse brain after focal cerebral ischaemia. *Brain Inj* 2013;**27**:1311–1315.
- Deng XH, Ai WM, Lei DL, et al. Lipopolysaccharide induces paired immunoglobulin-like receptor B (PirB) expression, synaptic alteration, and learning-memory deficit in rats. *Neuroscience* 2012;**209**:161–170.
- Akahoshi N, Ishizaki Y, Yasuda H, et al. Frequent spontaneous seizures followed by spatial working memory/anxiety deficits in mice lacking sphingosine 1-phosphate receptor 2. *Epilepsy Behav* 2011;**22**:659–665.
- Gil V, Nicolas O, Mingorance A, et al. Nogo-A expression in the human hippocampus in normal aging and in Alzheimer disease. *J Neuropathol Exp Neurol* 2006;**65**:433–444.
- Zhu HY, Guo HF, Hou HL, et al. Increased expression of the Nogo receptor in the hippocampus and its relation to the neuropathology in Alzheimer's disease. *Hum Pathol* 2007;**38**:426–434.
- Park JH, Strittmatter SM. Nogo receptor interacts with brain APP and Abeta to reduce pathologic changes in Alzheimer's transgenic mice. *Curr Alzheimer Res* 2007;**4**:568–570.
- He WX, Lu YF, Qahwash I, et al. Reticulon family members modulate BACE1 activity and amyloid-beta peptide generation. *Nat Med* 2004;**10**:959–965.
- Murayama KS, Kametani F, Saito S, et al. Reticulons RTN3 and RTN4-B/C interact with BACE1 and inhibit its ability to produce amyloid beta-protein. *Eur J Neurosci* 2006;**24**:1237–1244.
- He W, Shi Q, Hu X, et al. The membrane topology of RTN3 and its effect on binding of RTN3 to BACE1. *J Biol Chem* 2007;**282**:29144–29151.

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Conflict of Interest

The authors declare no conflict of interest.

46. Wataru A, Akiko O, Kazumi M, et al. Reduction of β -amyloid accumulation by reticulon 3 in transgenic mice. *Curr Alzheimer Res* 2013;**10**:135–142.
47. Shi Q, Ge Y, Sharoar MG, et al. Impact of RTN3 deficiency on expression of BACE1 and amyloid deposition. *J Neurosci* 2014;**34**:13954–13962.
48. Hui XY, Shi Q, Zhou XD, et al. Transgenic mice overexpressing reticulon 3 develop neuritic abnormalities. *EMBO J* 2007;**26**:2755–2767.
49. Prior M, Shi Q, Hu X, et al. RTN/Nogo in forming Alzheimer's neuritic plaques. *Neurosci Biobehav Rev* 2010;**34**:1201–1206.
50. Maslah E, Xie F, Dayan S, et al. Genetic deletion of Nogo/Rtn4 ameliorates behavioral and neuropathological outcomes in amyloid precursor protein transgenic mice. *Neuroscience* 2010;**169**:488–494.
51. Xiao F, Lin LF, Cheng X, et al. Nogo-66 receptor activation inhibits neurite outgrowth and increases (beta)-amyloid protein secretion of cortical neurons. *Mol Med Rep* 2012;**5**:619–624.
52. McGee AW, Yang YP, Fischer QS, et al. Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. *Science* 2005;**309**:2222–2226.
53. Park JH, Gimbel DA, GrandPre T, et al. Alzheimer precursor protein interaction with the Nogo-66 receptor reduces amyloid-beta plaque deposition. *J Neurosci* 2006;**26**:1386–1395.
54. Park JH, Widi GA, Gimbel DA, et al. Subcutaneous Nogo receptor removes brain amyloid-beta and improves spatial memory in Alzheimer's transgenic mice. *J Neurosci* 2006;**26**:13279–13286.
55. Zhou XD, He XY, He WX, et al. Interaction between amyloid precursor protein and Nogo receptors regulates amyloid deposition. *FASEB J* 2011;**25**:3146–3156.
56. Zhang L, Zheng SS, Wu HT, et al. Identification of BLYS (B Lymphocyte Stimulator), a non-myelin-associated protein, as a functional ligand for Nogo-66 receptor. *J Neurosci* 2009;**29**:6348–6352.
57. Sato Y, Iketani M, Kurihara Y, et al. Cartilage acidic protein-1B (LOTUS), an endogenous Nogo receptor antagonist for axon tract formation. *Science* 2011;**333**:769–773.
58. Dickendesher TL, Baldwin KT, Mironova YA, et al. NgR1 and NgR3 are receptors for chondroitin sulfate proteoglycans. *Nat Neurosci* 2012;**15**:703–712.
59. Thomas R, Favell K, Morante-Redolat J, et al. LGI1 Is a Nogo receptor 1 ligand that antagonizes myelin-based growth inhibition. *J Neurosci* 2010;**30**:6607–6612.
60. Fukata Y, Adesnik H, Iwanaga T, et al. Epilepsy-related ligand/receptor complex LGI1 and ADAM22 regulate synaptic transmission. *Science* 2006;**313**:1792–1795.
61. Okabayashi S, Kimura N. Leucine-rich glioma inactivated 3 is involved in amyloid beta peptide uptake by astrocytes and endocytosis itself. *NeuroReport* 2008;**19**:1175–1179.
62. Taylor J, Chung KH, Figueroa C, et al. The scaffold protein POSH regulates axon outgrowth. *Mol Biol Cell* 2008;**19**:5181–5192.
63. Dickson HM, Zurawski J, Zhang H, et al. POSH is an intracellular signal transducer for the axon outgrowth inhibitor Nogo66. *J Neurosci* 2010;**30**:13319–13325.
64. Omoto S, Ueno M, Mochio S, et al. Genetic deletion of paired immunoglobulin-like receptor B does not promote axonal plasticity or functional recovery after traumatic brain injury. *J Neurosci* 2010;**30**:13045–13052.
65. Borrie SC, Baeumer BE, Bandtlow CE. The Nogo-66 receptor family in the intact and diseased CNS. *Cell Tissue Res* 2012;**349**:105–117.
66. Kim T, Vidal GS, Djuricic M, et al. Human LILRB2 is a beta-amyloid receptor and Its Murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. *Science* 2013;**341**:1399–1404.
67. Vitolo OV, Sant'Angelo A, Costanzo V, et al. Amyloid beta -peptide inhibition of the PKA/CREB pathway and long-term potentiation: Reversibility by drugs that enhance cAMP signaling. *Proc Natl Acad Sci USA* 2002;**99**:13217–13221.
68. Kimura A, Ohmori T, Kashiwakura Y, et al. Antagonism of sphingosine 1-phosphate receptor-2 enhances migration of neural progenitor cells toward an area of brain. *Stroke* 2008;**39**:3411–3417.
69. Bolognin S, Lorenzetto E, Diana G, et al. The potential role of rho GTPases in Alzheimer's disease pathogenesis. *Mol Neurobiol* 2014;**50**:406–422.
70. Huentelman MJ, Stephan DA, Talboom J, et al. Peripheral delivery of a ROCK inhibitor improves learning and working memory. *Behav Neurosci* 2009;**123**:218–223.
71. Tadanori H, Yenb SH, Tania G, et al. Pitavastatin decreases tau levels via the inactivation of Rho/ROCK. *Neurobiol Aging* 2012;**33**:2306–2320.
72. Petratos S, Li QX, George AJ, et al. The beta-amyloid protein of Alzheimer's disease increases neuronal CRMP-2 phosphorylation by a Rho-GTP mechanism. *Brain* 2008;**131**:90–108.
73. Eriksen JL, Sagi SA, Smith TE, et al. NSAIDs and enantiomers of flurbiprofen target γ -secretase and lower A β 42 in vivo. *J Clin Invest* 2003;**112**:440–449.
74. Abdul-Hay SO, Luo J, Ashghodm RT, et al. NO-flurbiprofen reduces amyloid-beta, is neuroprotective in cell culture, and enhances cognition in response to cholinergic blockade. *J Neurochem* 2009;**111**:766–776.
75. Weggen S, Eriksen JL, Sagi SA, et al. Evidence that nonsteroidal anti-inflammatory drugs decrease amyloid 42 production by direct modulation of β -Secretase activity. *J Biol Chem* 2003;**278**:31831–31837.
76. Zhou Y. Nonsteroidal anti-inflammatory drugs can lower amyloidogenic A 42 by inhibiting rho. *Science* 2003;**302**:1215–1217.
77. Song Y, Chen X, Wang LY, et al. Rho kinase inhibitor Fasudil protects against β -Amyloid-induced hippocampal neurodegeneration in rats. *CNS Neurosci Ther* 2013;**19**:603–610.
78. Fassbender K, Simons M, Bergmann C, et al. Simvastatin strongly reduces levels of Alzheimer's disease beta -amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. *Proc Natl Acad Sci USA* 2001;**98**:5856–5861.
79. Parvathy S, Ehrlich M, Pedrini S, et al. Atorvastatin-induced activation of Alzheimer's alpha secretase is resistant to standard inhibitors of protein phosphorylation-regulated ectodomain shedding. *J Neurochem* 2004;**90**:1005–1010.
80. Pedrini S, Carter TL, Prendergast G, et al. Modulation of statin-activated shedding of Alzheimer APP ectodomain by ROCK. *PLoS Med* 2005;**2**:e18.
81. Ostrowski SM, Wilkinson BL, Golde TE, et al. Statins reduce amyloid-beta production through inhibition of protein isoprenylation. *J Biol Chem* 2007;**282**:26832–26844.
82. Lane RF, Gatson JW, Small SA, et al. Protein kinase C and rho activated coiled coil protein kinase 2 (ROCK2) modulate Alzheimer's APP metabolism and phosphorylation of the Vps10-domain protein, SorL1. *Mol Neurodegener* 2010;**5**:62.
83. Chacon PJ, Garcia MR, Rodriguez TA. Inhibition of RhoA GTPase and the subsequent activation of PTP1B protects cultured hippocampal neurons against amyloid beta toxicity. *Mol Neurodegener* 2011;**6**:14.
84. Heredia L, Helguera P, de Olmos S, et al. Phosphorylation of actin-depolymerizing factor/cofilin by LIM-kinase mediates amyloid beta-induced degeneration: A potential mechanism of neuronal dystrophy in Alzheimer's disease. *J Neurosci* 2006;**26**:6533–6542.
85. Qin W, Yang T, Ho L, et al. Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. *J Biol Chem* 2006;**281**:21745–21754.
86. Feng XW, Zhu DX, Gao Q, et al. Resveratrol inhibits b-Amyloid-induced neuronal apoptosis through regulation of SIRT1-ROCK1 signaling pathway. *PLoS One* 2013;**8**:e59888.
87. Huesa G, Baltrons MA, Gomez-Ramos P, et al. Altered distribution of RhoA in Alzheimer's disease and AbetaPP overexpressing mice. *J Alzheimers Dis* 2010;**19**:37–56.
88. Kukar T, Prescott S, Eriksen JL, et al. Chronic administration of R-flurbiprofen attenuates learning impairments in transgenic amyloid precursor protein mice. *BMC Neurosci* 2007;**8**:54.
89. Musilli M, Nicolai V, Borrelli S, et al. Behavioral effects of Rho GTPase modulation in a model of Alzheimer's disease. *Behav Brain Res* 2013;**237**:223–229.
90. Alkon DL, Sun MK, Nelson TJ. PKC signaling deficits: A mechanistic hypothesis for the origins of Alzheimer's disease. *Trends Pharmacol Sci* 2007;**28**:51–60.
91. Ekinci FJ, Shea TB. Free PKC catalytic subunits (PKM) phosphorylate tau via a pathway distinct from that utilized by intact PKC. *Brain Res* 1999;**850**:207–216.
92. Fioravante D, Chu YX, de Jong APH, et al. Protein kinase C is a calcium sensor for presynaptic short-term plasticity. *Elife* 2014;**3**. doi: 10.7554/eLife.03011.
93. Olariu A, Yamada K, Nabeshima T. Amyloid pathology and protein kinase C (PKQ): Possible therapeutic effects of PKC activators. *J Pharmacol Sci* 2005;**97**:1–5.
94. Shi J, Dong YZ, Cui MZ, et al. Lysophosphatidic acid induces increased BACE1 expression and A beta formation. *BBA-Mol Basis Dis* 2013;**1832**:29–38.
95. Yang HQ, Ba MW, Ren RJ, et al. Mitogen activated protein kinase and protein kinase C activation mediate promotion of sAPP alpha secretion by deprenyl. *Neurochem Int* 2007;**50**:74–82.
96. Yeon SW, Jung MW, Ha MJ, et al. Blockade of PKC epsilon activation attenuates phorbol ester-induced increase of alpha-secretase-derived secreted form of amyloid precursor protein. *Biochem Biophys Res Commun* 2001;**280**:782–787.