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The role of Nogo-A in axonal plasticity, regrowth and repair

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Abstract Axonal damage leads to permanent deficits in the adult central nervous system (CNS) not only because of the weak intrinsic ability of adult neurons to activate their growth program but importantly also because of the presence of specific growth inhibitors in the CNS tissue and the environment of the damaged axons. The well-studied myelin-derived protein Nogo-A is involved in various cellular and molecular events contributing to the failure of CNS axons to regrow and reconnect after transection. Recent studies have shown that, by acting in a negative way on the cytoskeleton and on the growth program of axotomized neurons, Nogo-A exerts fast and chronic inhibitory effects on neurite outgrowth. On the other hand, the blockade of Nogo-A results in a marked enhancement of compensatory and regenerative axonal extension *in vivo*; this enhancement is often paralleled by significant functional recovery, for example, of locomotion or skilled forelimb reaching after spinal cord or stroke lesions in rats and monkeys. Surprisingly, the blockade of Nogo-A or its receptor NgR in the hippocampus has recently been demonstrated to enhance long-term potentiation. A role of Nogo-A in synaptic plasticity/stability might therefore represent an additional, new and

important aspect of CNS circuit remodeling. Function-blocking anti-Nogo-A antibodies are currently being tested in a clinical trial for improved outcome after spinal cord injury.

Keywords Axonal damage · Nogo-A · Nogo-A receptor · Inhibition · Function-blocking antibodies · Long-term potentiation · Remodeling

Nogo-A protein expression in the intact and injured central nervous system

Nogo-A is a transmembrane protein of about 1200 amino acids (aa) including a C-terminal 200-aa reticulon (RTN) domain (Chen et al. 2000; GrandPre et al. 2000). It has been purified from mammalian central nervous system (CNS) myelin and is one of the most potent neurite growth inhibitors in CNS myelin and tissue (Spillmann et al. 1998). Nogo-A is mainly expressed by oligodendrocytes in the adult CNS (Huber et al. 2002; Wang et al. 2002b). The high endogenous expression of Nogo-A by oligodendrocytes shows little increase around a spinal cord injury site (Huber et al. 2002). Before myelin formation, Nogo-A is strongly expressed by developing and immature neurons and neuronal Nogo-A persists at a high level in plastic CNS regions such as the cortex, the hippocampus and dorsal root ganglia (Huber et al. 2002; Peng et al. 2011). The presence of Nogo-A in plastic areas of the adult CNS appears paradoxical and suggests additional functions unrelated to axonal plasticity. Nevertheless, after axonal severing in the optic nerve, we have observed an up-regulation of Nogo-A that is most striking in a subpopulation of retinal ganglion cells with larger soma sizes (Pernet et al. 2011). In the pyramidal neurons and interneurons of the cortex, increased Nogo-A levels have been seen in stroke perilesional areas (Cheatwood

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et al. 2008). The functions of Nogo-A under these conditions of neuronal damage are not known.

Nogo-A neutralization or knock-out or Nogo receptor suppression enhances axonal growth after injury

The functional deficits after spinal cord injury depend on the location and severity of the damage. In the case of an incomplete spinal cord lesion, a spontaneous remodeling of intraspinal circuits, e.g., by the formation of detour pathways, contributes to the recovery of hindlimb function (Bareyre et al. 2004). Under more severe lesion conditions in which recovery is not observed, the intrathecal infusion of function-blocking anti-Nogo-A antibodies significantly improves sensory-motor functions and stimulates axonal sprouting from damaged and intact fibers (Thallmair et al. 1998; Raineteau et al. 2001; Liebscher et al. 2005; Freund et al. 2006, 2009; Gonzenbach et al. 2012). Long-range axonal regeneration and increased compensatory growth of intact fibers have been observed after the application of various anti-Nogo-A antibodies. A delay in the delivery of these antibodies by 1 week but not 2 weeks, is efficient to increase corticospinal tract axon regeneration over several millimeters after dorsal thoracic spinal cord lesion (Gonzenbach and Schwab 2008). Consistent with this, hindlimb function is improved when antibody infusion begins no later than 1 week after injury. In contrast, in a rat stroke model, skilled forelimb movements recover, even when anti-Nogo-A treatment is started as late as 9 weeks after ischemic brain damage (Tsai et al. 2011). Importantly, similar anatomical and behavioral results have been obtained with reagents blocking the Nogo receptor NgR1 (Li and Strittmatter 2003; Lee et al. 2004; Wang et al. 2006, 2011), the NgR-associated protein Lingo-1 (Ji et al. 2006), or the downstream signaling components RhoA (Dergham et al. 2002; Fournier et al. 2003; Lord-Fontaine et al. 2008) or ROCK (Fournier et al. 2003; Duffy et al. 2009). All these findings not only establish a strong proof-of-principle for the clinical use of Nogo-A immunotherapy in different CNS injury types but also raise interesting questions about the normal physiological role played by Nogo-A in the complex CNS of higher vertebrates.

Function-blocking antibodies directed against Nogo-A have been extensively used by our group and have allowed us to develop a potential therapy to treat human CNS injuries and diseases. In vivo experiments in rats and in monkeys represent essential preclinical tests to validate the efficiency and safety of Nogo-A antibody administration. In non-human primates, the dexterity of the paralyzed arm and hand after a cervical hemisection is almost completely restored by the intrathecal delivery of a Nogo-A-specific antibody (Freund et al. 2006, 2009). Fine motor movement recovery is associated with a large amount of corticospinal axon sprouting past

the lesion site and innervation of the lower cervical cord segments. The concept of therapeutic antibody administration in the CNS was first tested in clinical trials targeting Nogo-A; the anti-human Nogo-A antibody ATI355 produced in collaboration with Novartis Pharma (Basel) has recently been established as being safe for patients with spinal cord injuries in a Phase I clinical trial (<http://clinicaltrials.gov/ct2/show/NCT00406016>) with 52 acutely injured, severe para- and tetraplegic patients (Abel et al. 2011). A placebo-controlled Phase II clinical trial is currently in preparation. In another CNS disease, amyotrophic lateral sclerosis (ALS), the ectopic expression of Nogo-A at the neuromuscular junction is an early sign of the disease and is thought to cause synapse destabilization and thereby motor control loss (Dupuis et al. 2002; Jokic et al. 2005, 2006). As has been proposed for spinal cord injury, GlaxoSmithKline (GSK) has developed a humanized anti-Nogo-A antibody (GSK1223249) to prevent Nogo-A-induced synaptic destabilization and motoneuron degeneration in ALS (<http://clinicaltrials.gov/ct2/show/NCT00875446>). Preliminary results of a Phase I clinical trial have recently been presented (Pradat et al. 2011). Intravenous injections of GSK1223249 appear to be well tolerated by the 76 patients enrolled in the trial. A larger Phase II international trial is scheduled for 2012 to assess the therapeutic benefits of GSK1223249 on ALS symptoms.

Molecular mechanisms mediating Nogo-A-induced axonal growth inhibition

Cell surface Nogo-A

Cytoskeleton regulation

Two principal domains of Nogo-A have been shown to exert inhibitory effects on neurite outgrowth: the Nogo-66 sequence in the C-terminal RTN region and a 160-aa fragment called Nogo-A delta20 in the Nogo-A-specific region (Oertle et al. 2003b). A clear mechanism has been elucidated for Nogo-66-mediated growth inhibition; a receptor complex composed of the Nogo-66 receptor NgR1, a glycosyl-phosphatidylinositol-linked leucine-rich repeat protein (Fournier et al. 2001) and the NgR1-associated proteins Lingo (Mi et al. 2004) and p75 (Wang et al. 2002a) or Troy (Shao et al. 2005) is stimulated by Nogo-66 leading to the intracellular activation of the RhoA/ROCK/cofilin pathway that prevents actin cytoskeleton polymerization in the growth cone and thereby blocks neurite extension (Nash et al. 2009; Fig. 1). Consistent with this, in Nogo-A knock-out (KO) mice, growth cone motility is increased compared with wild-types (Montani et al. 2009). Surprisingly, the same receptor complex and downstream mechanisms seem also to be involved in the growth inhibitory effects of other myelin-associated proteins, such as

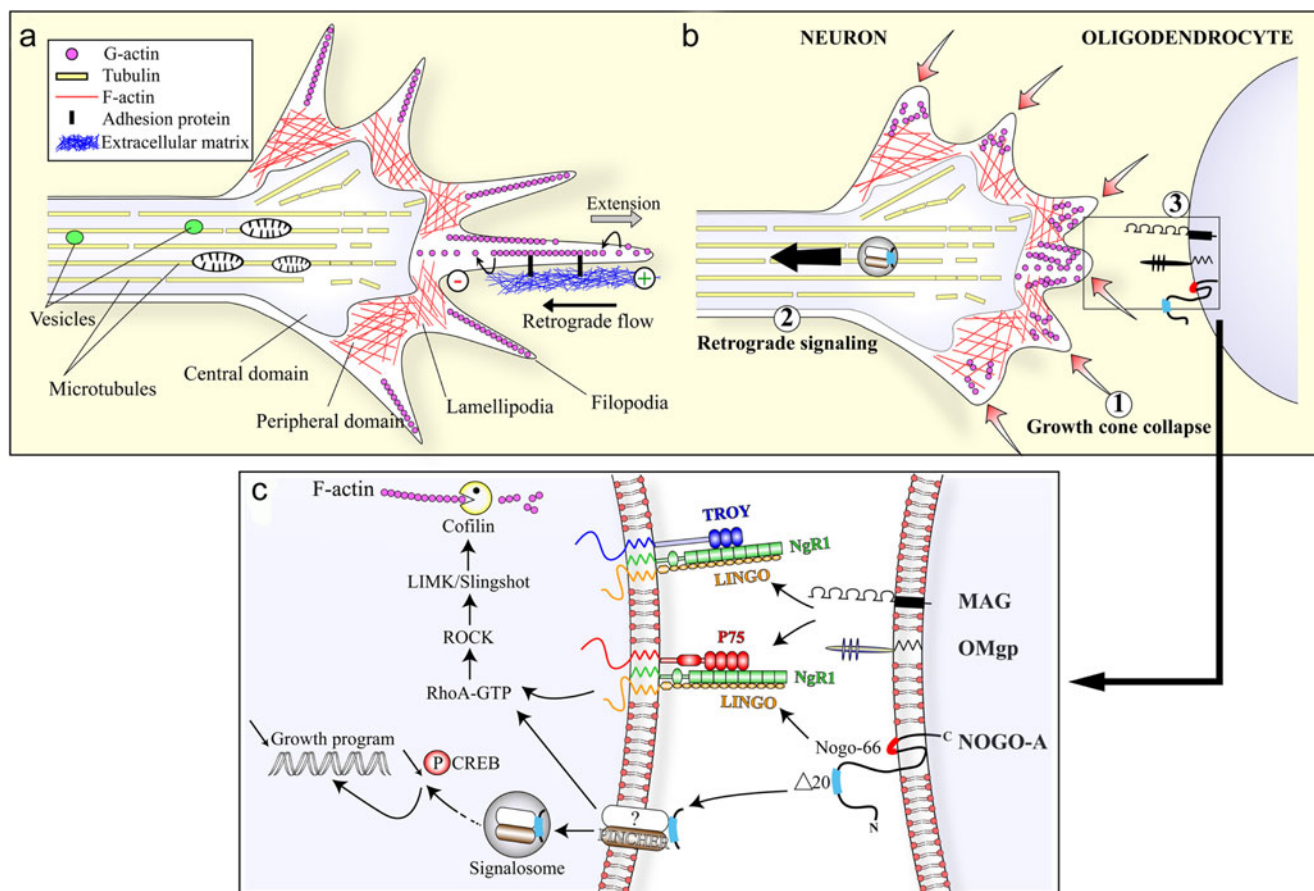


Fig. 1 Molecular mechanisms of Nogo-A-mediated axonal growth inhibition. **a** Organization of the growth cone. The growth cone is composed of a central domain containing the microtubules involved in the transport of organelles and of a peripheral domain in which actin filaments (*F-actin*) form a cytoskeleton meshwork in the lamellipodia and filopodia. The protrusion of the filopodia occurs at the plus end (+) of the actin filament and is required to allow the traction of the growth cone on the extracellular matrix. **b** Growth cone inhibition. The contact of filopodial extensions with myelin-associated inhibitors such as Nogo-A (1) triggers the quick collapse of F-actin in the growth cone (2). The retrograde signaling is thought to mediate the long-term effects of Nogo-A on the repression of the neuronal growth program (3). **c** Nogo-66 and other myelin inhibitors exhibited at the cell surface

of oligodendrocytes bind to and stimulate a common neuronal receptor complex. The transduction of the signal passes through the intracellular activation of the RhoA/ROCK pathway and involves the actin-severing enzyme cofilin, a main effector in the disassembly of the growth cone cytoskeleton. Alternatively, the Nogo-A delta20 region is internalized by an unknown receptor via a pincher-dependent mechanism. The uptake of Nogo-A delta20 leads to the activation of the RhoA/ROCK/cofilin cascade. In addition, the resulting molecular complex can also be retrogradely transported in signalosomes to the neuronal cell body in which it activates RhoA, negatively regulates phospho-CREB and thereby attenuates the neuronal growth program (abbreviations are explained in the text)

myelin-associated glycoprotein (MAG) and oligodendrocyte myelin glycoprotein (OMgp) (Wang et al. 2002a). One way in which myelin-associated inhibitors activate the small GTPase RhoA might be by the phosphorylation and inactivation of GSK3beta, thereby allowing CRMP4 and RhoA interaction (Alabed et al. 2010).

Another receptor has recently been identified for Nogo-66, MAG and OMgp, called paired immunoglobulin-like receptor-B (PirB; Atwal et al. 2008). In primary neuron cultures, the blocking of PirB partially relieves the myelin-protein-induced inhibition of axonal outgrowth (Atwal et al. 2008). However, the genetic deletion of PirB alone fails to increase axonal growth in vivo after corticospinal tract transection (Nakamura et al. 2011), traumatic brain lesion (Omoto

et al. 2010), or optic nerve crush (Fujita et al. 2011). As for NgR1, the regenerative and behavioral outcomes observed after PirB ablation might depend on the lesioned tract (Cafferty and Strittmatter 2006) or on (yet unknown) co-receptors. More work will be necessary to specify the contribution of PirB to the molecular mechanisms underlying axonal regeneration failure in vivo.

The biochemical mechanisms triggered by the Nogo-A domain Nogo delta20 in neurons remain more elusive. The receptor(s) bound by Nogo delta20 has(have) not been identified as yet. However, purified Nogo delta20 has been shown to destabilize the cytoskeleton, as has been found for Nogo-66, in a RhoA-dependent manner (Niederost et al. 2002; Joset et al. 2010).

The neuronal growth program

The long-term effects of growth-promoting and growth-repressing molecules are often regulated at the gene expression level. Our group has recently demonstrated that growth cone collapse and RhoA activation require the Pincher-dependent internalization of Nogo-A delta20 in primary neurons. In addition to affecting the growth cone cytoskeleton assembly, Nogo-A-delta20-containing signalosomes are retrogradely transported to the cell body in which they activate RhoA, downregulate cAMP response element-binding protein (CREB) phosphorylation and repress the cellular growth program (Joset et al. 2010) (Fig. 1). Interestingly, a similar mechanism of retrograde signaling has previously been described for neurotrophic factors that exert opposite growth-promoting effects on axons and that activate neuronal plasticity (Shao et al. 2002). Strikingly, the group of Filbin has reported that neurotrophic factors can overcome myelin-associated protein-mediated growth inhibition by up-regulating cAMP and P-CREB, leading to the activation of arginase I expression, a rate-limiting enzyme for the synthesis of polyamines (Cai et al. 2002; Gao et al. 2004). The signaling of negative and positive regulators of axonal growth might therefore converge on the same intracellular transcription factors. However, additional molecules controlling the cellular growth program might be changed after Nogo-A action, such as the signal transducer and activator of transcription (Stat; Bareyre et al. 2002) or the Akt (protein kinase B)-mTOR (mammalian target of rapamycin) pathway. Recent observations suggest that Nogo-A decreases synaptic protein translation by antagonizing the mTOR activation required in long-term potentiation (LTP; Baldwin et al. 2011). The role of those molecules and pathways remains to be clarified in the CNS (Bareyre et al. 2011).

At first glance, the presence of two inhibitory active sites within the Nogo-A sequence seems intriguing. However, interaction of more than one active site of a signaling molecule with more than one subunit of a multi-subunit receptor complex is well known, e.g., for neurotrophic factors, Wnt, semaphorins, or netrin (Schwab 2010). The two domains of Nogo-A might differ such that they mediate plasticity and growth repression. For Nogo-A delta20, short- and long-term inhibitory mechanisms might operate at the cytoskeleton and gene expression level, whereas Nogo-66/ NgR1 has been proposed to induce acute growth cone collapse and neurite growth inhibition but not chronic outgrowth blockade (Chivatakarn et al. 2007). A bimodal functioning of Nogo-A via its two domains activating distinct receptors or subunits might therefore contribute to the acute and chronic impairment of axonal plasticity. This could have relevance for the design of repair strategies for the lesioned CNS.

Intracellular and endoplasmic-reticulum-associated Nogo-A

Role in survival and axonal regeneration

On the basis of its 200-aa C-terminus, Nogo-A belongs to the RTN protein family, which is composed of four members (RTN1, RTN2, RTN3, RTN4) present in eukaryotes (Oertle et al. 2003a). Some structural and enzyme regulatory functions have been described for RTNs; they can influence the curvature of the endoplasmic reticulum (ER) and appear as structural regulators for the subcompartment “tubular ER” (Voeltz et al. 2006). RTNs can also interact with the anti-apoptotic intracellular proteins Bcl-2 or Bcl-XL and have therefore been claimed to play a role in cell death regulation (Tagami et al. 2000; Wan et al. 2007).

In ischemia and after oxidative stress, Nogo-A might act as a neuroprotective molecule. After middle cerebral artery occlusion, Nogo-A KO or the acute but not the delayed blockade of Nogo-A with antibodies decreases neuronal survival (Kilic et al. 2010). More recently, Nogo-A delta20 transfection in cortical neurons has been shown to protect against hydrogen-peroxide-induced cell death *in vitro*, supposedly by interacting with the enzyme peroxiredoxin 2, which scavenges reactive oxygen species (Mi et al. 2012).

Nogo-A has been observed to increase in the cell body of injured neurons suggesting that it exerts cell-autonomous effects on cell death and/or growth mechanisms (Cheatwood et al. 2008; Pernet et al. 2011). ER stress is thought to play a role in many degenerative diseases such as ALS (Atkin et al. 2006; Saxena et al. 2009), Alzheimer’s disease, or Parkinson’s disease (Doyle et al. 2011). As an RTN protein, the expression of which can change in compromised neurons, Nogo-A is suspected of influencing ER stress activation. After optic nerve injury, we have observed that Nogo-A is up-regulated in neurons together with other ER-stress-associated markers such as the pro-apoptotic transcription factor CHOP (Pernet et al. 2011). However, we have been unable to detect a change in CHOP expression or in the frequency of apoptosis when injury-induced Nogo-A is silenced selectively in neurons or fully deleted genetically. Our results are consistent with previous *in vitro* data showing that Nogo-A over-expression does not enhance the level of CHOP or that of the chaperon protein Bip (Yang et al. 2009). Therefore, the axon lesion-induced up-regulation of Nogo-A in neurons does not seem to be an important regulator of apoptosis *in vivo*.

Interaction of neuronal Nogo-A with β -secretase (BACE1)

The production of β -amyloid deposits is a hallmark of Alzheimer’s disease. Interestingly, the group of Yan has found *in vitro* that all RTN members including Nogo are able to bind and to inhibit the β -amyloid-converting enzyme 1 (BACE1), which transforms the amyloid precursor protein

(APP) into aggregating β -amyloid (He et al. 2004). In vivo, however, the physiological role of RTNs in this context is less clear. The over-expression of RTN3 in transgenic mice reduces the production of β -amyloid in the hippocampus but concomitantly causes the formation of RTN3 aggregates in dystrophic neurites (Shi et al. 2009b). The excess of RTN might compete with APP to bind BACE1, thereby sequestering BACE1 in the ER and prevent its enzymatic activity on APP (Shi et al. 2009b). However, we do not know whether RTNs and in particular Nogo-A, serve as substrates for BACE1 and can be secreted, for example, as bioactive fragments into the extracellular space. In addition, the experimental over-expression of RTN3 might not faithfully reproduce pathophysiological conditions such as those encountered in aging brains (Shi et al. 2009a). Much remains to be learnt at present on the possible roles of Nogo and RTN proteins in the regulation of intracellular enzymes such as BACE1 or of processes such as ER function or cell survival.

The re-formation of functional circuits after traumatic CNS lesions

Function-blocking antibodies against Nogo-A, NgR1-blocking peptides, antibodies against Lingo-1, or pharmacological blockers of the signal transducers RhoA and ROCK have been applied in various laboratories in spinal cord injury and stroke models in rats, in mice and, in some instances, also in monkeys. Enhancement of behavioral recovery in a variety of sensory-motor tests and enhanced sprouting and long-distance regeneration of lesioned and spared axons have been found (Zorner and Schwab 2010). Importantly, a high degree of similarity is present despite using different ways to interrupt Nogo-A signaling. Similar but overall weaker and variable results have been obtained in Nogo KO mice in spinal cord injury studies (Kim et al. 2003; Simonen et al. 2003; Zheng et al. 2003; Dimou et al. 2006; Cafferty et al. 2010; Lee et al. 2010).

A defined succession of events probably controls the formation of functional reconnections in the damaged brain and spinal cord. A time window (1 week in the rat) seems to exist during which Nogo-A immunotherapy is efficient at activating spinal cord axon regeneration (Gonzenbach et al. 2012); the treatment with Nogo-A antibody has only weak behavioral and anatomical effects when delayed by 2 weeks after the injury compared with the acute or 1-week-delayed administration. The neuronal growth response occurring spontaneously after an axonal injury might condition the effects of Nogo-A neutralization on axonal regrowth. In the visual system, an intervention window has been defined in the growth-promoting inflammation paradigm; intra-ocular inflammation can only elicit axonal regeneration when the treatment is delivered 3 days before or after optic

nerve crush injury but not after 7 days (Yin et al. 2003). The time-course of growth-associated-molecule expression has revealed that, soon after axon transection, neurons attempt but fail to regenerate. Thus, the neutralization of Nogo-A might also facilitate the growth of neurons early after injury. The mechanisms of guidance of regenerating axons in the adult CNS and the molecular determinants of target recognition have not been studied so far. We do not know whether sprouts and regenerating axons reconnect to their original targets in the spinal cord or brain, or whether synapse formation occurs randomly. Finally, mechanisms of stabilization and pruning of connections and synapses, probably driven by activity and use, might lead to the formation of new functional circuits.

Nogo-A is a negative regulator of synaptic plasticity

The expression of Nogo-A in neurons or in glial cells might also control the formation and stability of synaptic contacts after a lesion. Most of our knowledge on the effects of Nogo-A on synaptogenesis and synaptic transmission is derived from a few developmental studies and from electrophysiological investigations in the hippocampus. By contrast, little is known as to the way in which Nogo-A blockade promotes functional synapses in the adult damaged CNS. Oligodendrocyte-expressed Nogo-A also acts as a growth-restricting factor in the developing brain; in the visual cortex, the end of the activity-driven plastic phase of synapse sprouting, pruning and stabilization (“critical period”) coincides with the myelination of layers IV–VI and the expression of Nogo-A. Nogo restricts the plasticity of the ocular dominance columns in the adult visual cortex in an NgR1-dependent manner, as shown by Nogo-KO and NgR1-KO mice analyses. Nogo/NgR1 signaling might therefore be a contributor to the end of the plastic so-called “critical period” (McGee et al. 2005).

In the adult hippocampus in which synaptic plasticity remains elevated throughout life, Nogo-A is highly expressed in pre- and postsynaptic neurons including CA3 and CA1 pyramidal cells (Lee et al. 2008). The addition of function-blocking anti-Nogo-A antibodies or Nogo-A KO induces marked changes in the complexity of the basal and apical dendritic arbors of CA1 and CA3 neurons and leads to massive sprouting of the CA3 axons (Zagrebelsky et al. 2010). The proportion of immature spines is also higher in the CA3 neurons. The dendritic and spine phenotypes can be reproduced by silencing NgR1 expression. Nogo-A thus appears here again as a stabilizer of synapses, the suppression of which leads to growth and higher plasticity in axons and dendrites. Electrophysiological recordings in acute hippocampal slices have revealed that the inactivation of Nogo-A or NgR1 with function-blocking antibodies or KOs increases LTP (Raiker et al. 2010; Delekate et al. 2011). Whether both neuronal and

glial Nogo-A influence synapse remodeling and LTP is not known.

Concluding remarks

Nogo-A appears to be a major inhibitor of axonal regeneration; it induces the quick destabilization of the actin cytoskeleton and, on a longer time scale, represses growth gene expression. Many studies have reported that the neutralization of Nogo-A or Nogo-A receptor elements restores plasticity, improves axonal growth and enhances behavioral recovery after injury with no obvious side-effects. The high significance of these results has prompted to test the effects of function-blocking Nogo-A antibodies in patients with spinal cord injuries. Clinical trials are currently ongoing. In contrast, the physiological role of Nogo-A has been less-well studied. In the intact CNS, Nogo-A might contribute to stabilizing axonal connectivity (Park et al. 2010; Schwab 2010). Compelling evidence indicates that Nogo-A also modulates synaptic contacts and negatively influences LTP in the hippocampus. Thus, the physiological function of Nogo-A in the healthy brain might be to prevent abnormal sprouting and to regulate the dynamics of the synaptic cytoskeleton during learning processes. Future research will help us to understand the way that neuronal and glial Nogo-A regulates nerve fiber growth and connectivity and the fine tuning of synaptic plasticity in the developing and adult CNS.

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