Karolinska Institutet

**Institutionen för Neurovetenskap**

# On Nogo Receptors,

# plasticity and lasting memories

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# ABSTRACT

The central nervous system has very limited ability to repair itself after injury but has been shown to exhibit remarkable experience-driven structural plasticity at the synaptic level. These changes correlate strongly with behavioral performance and are thought to underlie learning and memory. MAG, OMgp and Nogo are a group of neurite growth inhibitors present in CNS myelin and exerting effects by binding to a common receptor, NgR1. Because Nogo is also expressed by neurons and NgR1 is exclusively expressed in neurons and downregulated by activity, NgR1 may regulate plasticity. For local synaptic plasticity to occur one requirement could be that NgR1 signaling decreases. In fact, NgR1 is rapidly downregulated in key areas associated with plasticity such as hippocampus in a variety of different models of neuronal activity. When NgR1 is knocked out, mice show increased plasticity and continue to demonstrate ocular dominance shift plasticity in the visual cortex into adulthood.

The aim of this thesis was to further investigate how the Nogo-system is regulated and to evaluate how it may influence memory formation. It is confirmed that increased neuronal activation (using Kainic acid) causes rapid downregulation of NgR1 and a more detailed time course of this effect is presented. The NgR1 downregulation might be further potentiated through an increase of the endogenous NgR1 antagonist LOTUS in the dentate gyrus. In contrast to NgR1, both NgR2 and NgR3 were mostly upregulated following kainic acid injection. As the spectrum of known ligands for the different NgRs differ, this could result in a change in responsiveness to different inhibitor types and might favor increased local plasticity while keeping plasticity at the level of non-terminal axons and main dendrites in check.

We created a mouse with inducible overexpression of NgR1 in forebrain neurons (MemoFlex) to test the hypothesis that reduced NgR1 levels are important for memory formation. We found that while NgR1 overexpression does not impair 24 h memory and day to day learning, it significantly impairs formation of lasting memories as shown in both the Morris water maze and a passive avoidance test. By turning the NgR1 transgene off (by doxycycline) at different time points, we were able to demonstrate that NgR1 downregulation-dependent memory consolidation occurs during the first 7-9 days after a memory-forming event. MemoFlex mice exhibited increased sensitization to amphetamine (that could be normalized by turning off the transgene), as if they were unable to "learn" and hence cope with amphetamine injections lasting for as long as a week. When retested after 110 days MemoFlex mice showed a significant reduction of "sensitization memory" compared to their performance at the end of the sensitization period. Control mice tended to increase sensitization during the withdrawal period. Mice lacking NgR1 did not differ from control mice with respect to a week-long amphetamine sensitization. Analysis of spine density and subtypes in the cingulate gyrus and the shell of nucleus accumbens indicated that NgR1 overexpression has significant effects on spine dynamics.

NgRs have also been shown to affect the deposition and formation of Aβ-plaques in mouse models of Alzheimer's disease. To test if NgR1 overexpression would affect plaque deposition we crossed MemoFlex mice with plaque-forming APPswe/PSEN1 mice. While we could not see any significant change in plaque formation in APPswe/PSEN1 mice with NgR1 overexpression, they were significantly impaired in the Morris water maze. The fact that performance was significantly decreased while plaque formation was unaffected could result from impairment of compensatory synaptic plasticity that otherwise occur in plaque-forming mice.

Taken together, these studies suggest a role for the Nogo-system, and in particular NgR1, for the formation of lasting memories.

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