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BDNF interferes with a treatment neutralizing Nogo-A in adult macaques subjected to incomplete spinal cord injury (SCI)

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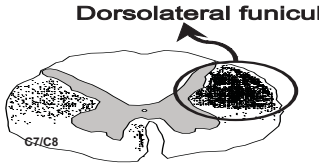
INTRODUCTION

Neutralizing the neurite growth inhibiting molecule Nogo-A promotes both regeneration and functional recovery in rodents and monkeys with a SCI. However, the rostro-caudal extent covered by regenerating corticospinal (CS) fibers remains limited and the soma of axotomized CS neurons shrinks as in untreated animals. A different line of studies has shown that neurotrophic factors such as BDNF (brain-derived neurotrophic factor) may induce neurite growth and prevent atrophy of axotomized neurons.

To investigate whether the effects obtained by neutralizing Nogo-A can be strengthened by BDNF, the recovery of lesioned monkeys was investigated using a manual dexterity task which primarily relies on the integrity of the CS system. The effects of the treatment on the soma of CS neurons and on the amount of sprouting at the C3 level were also evaluated.

RESULTS

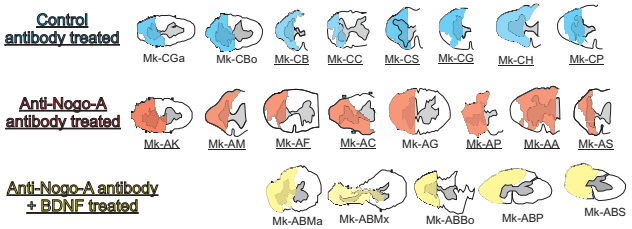
1) Where do CS axons travel along the spinal cord ?



(Schmidlin, E. et al., 2005)

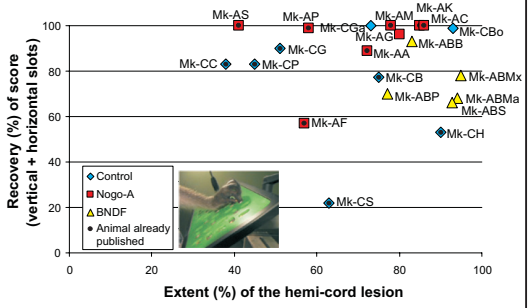
After a BDA injection in MI, stained CS fibers are mainly located in the contralateral dorsolateral funiculus.

2) What is the impact of the lesion on the CS tract ?



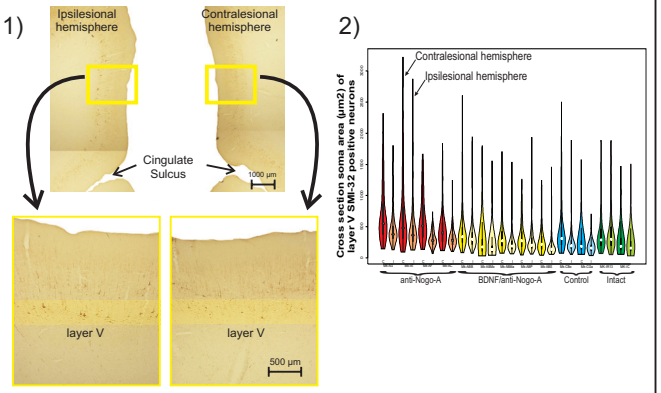
In most animals, the dorsolateral funiculus was completely transected by the cervical cord lesion.

3) Does treatment improve functional recovery?



As reported earlier, the animals treated with the anti-Nogo-A antibody showed improved levels of functional recovery when compared to animals treated with a control antibody.
In the animals treated with the combination BDNF + the anti-Nogo-A antibody, the level of functional recovery was similar to that observed in control antibody treated monkeys.

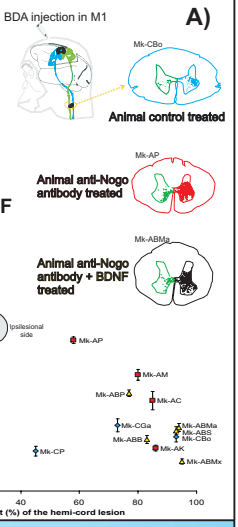
4) Does the presence of BDNF hinder the shrinkage of CS neurons?



1) As in control and in anti-Nogo-A treated animals, the SMI-32 staining revealed inter-hemispheric differences between the pyramidal neurons of cortical layer V in animals that received BNDF.
2) The presence of BDNF does not hinder the shrinkage of layer V pyramidal neurons in motor cortex.

5) Does the treatment favor sprouting at C3 level?

The normalized number of CS fibers in the ipsilesional ventral grey matter is not increased by combining BDNF with the anti-Nogo-A antibody.



METHODS

Lesion

A unilateral cervical spinal cord lesion was performed at C7-C8 level on 3 groups of monkeys:
- controls (using a control antibody; n=8)
- anti-Nogo-A (using an antibody neutralizing Nogo-A; n=9)
- BDNF/anti-Nogo-A (using BDNF with an antibody neutralizing Nogo-A; n=5)

Anatomical assessment

1) Biotinylated dextran amine (BDA) was injected into the motor cortex and the number of CS fibres was counted rostrally to the lesion at C3 level.
2) SMI-32 staining was used in M1 in order to measure the number and cross-sectional area of pyramidal neurons in the layer V.

Behavioural assessment

Functional recovery was investigated using a modified version of the Brinkman-task, which measures hand and finger dexterity.

CONCLUSION

Our data suggest that the association between BDNF and the anti-Nogo-A antibody reduces the positive impact of the antibody neutralizing Nogo-A alone. In fact, the animals treated with the combination of BDNF and of the anti-Nogo-A antibody present a level of functional recovery comparable to animals treated with a control antibody. Furthermore, anatomical analysis suggests that sprouting of CS fibers at the cervical (C3) level is comparable to that observed in control antibody treated monkeys, in line with the behavioural data. The shrinkage of layer V pyramidal neurons of motor cortex is not reduced by the presence of BDNF.