Reorganization of sensory afferents in the dorsal column nuclei following spinal cord hemisection in monkeys

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INTRODUCTION

The anti-Nogo-A antibody treatment has been shown to improve the functional recovery of hand dexterity and and to enhance corticospinal sprouting in non-human primate following spinal hemisection, making the peri-lesion territory permissive to axonal growth (*Freund et al., 2007; 2009*). In order to tentatively increase beneficial effects, brain-derived neurotrophic factor (BDNF) has been combined with anti-Nogo-A antibody treatment, for its stimulating effect on axonal growth.

The aim of the present study was to assess after a cervical hemisection (C7-C8) : 1)- effect on sensory afferents in the dorsal column nuclei (nucleus cuneatus and nucleus gracilis); 2)- effect on the tractus cuneatus and the tractus gracilis at C3 level; 3)- impact of the combined treatment (anti-Nogo-A antibody and BDNF).

CONCLUSION

These preliminary data show that:

1- Nucleus and tractus cuneatus were not affected by the lesion (in line with the cervical level of the lesion).

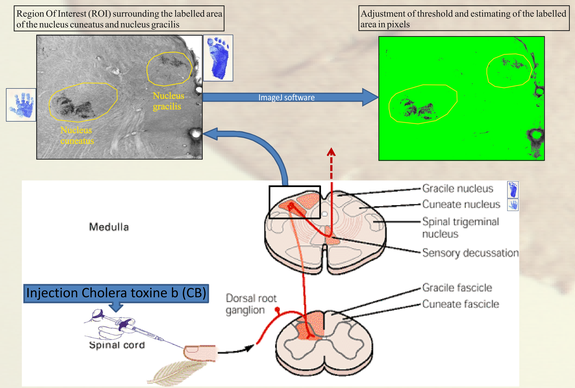
2- Lesion affected ipsilateral nucleus gracilis in its rostral portion and tractus gracilis.

3- There is no observable impact of the combined treatment on sensory afferents in the dorsal column nuclei.

METHODS

Experiments were conducted on eight adult monkeys (*Macaca fascicularis*) distributed in three groups: Intact (Mk-I); Control (Mk-C); combined anti-Nogo-A antibody and BDNF treated group (Mk-AB)

1. Hemisection of the spinal cord in the four lesioned monkeys at cervical segment C7-C8.
2. Four weeks intrathecal treatment with anti-Nogo-A antibody combined with BDNF in three monkeys (MK-ABP, MK-ABB and Mk-ABS) and control antibody in one monkey (MK-CBo). Treatment started immediately after the spinal hemisection.
3. Subcutaneous injection of *Cholera Toxin b* (CB) in the five fingers of both hands and in the five toes of both feet in all eight monkeys.
4. Sacrifice after at least one week of survival time after CB injections to allow transganglionic axonal transport (for reference see *Darian-Smith 2004*), by intracardial perfusion with a solution of paraformaldehyde under deep anaesthesia.
5. Brainstem were dissected and transversal frozen sections were cut at 50µm thickness.
6. Immunostaining of CB.
   Histochemical staining of Myelin with gold reaction.
7. Analysis of the labelled area for CB and myelin using ImageJ software.

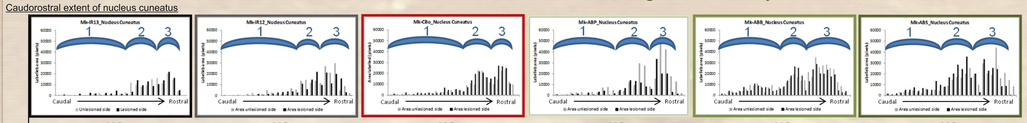


RESULTS

CB: nucleus cuneatus

Intact | Control | Anti-Nogo-A antibody combined with BDNF

Caudorostral extent of nucleus cuneatus

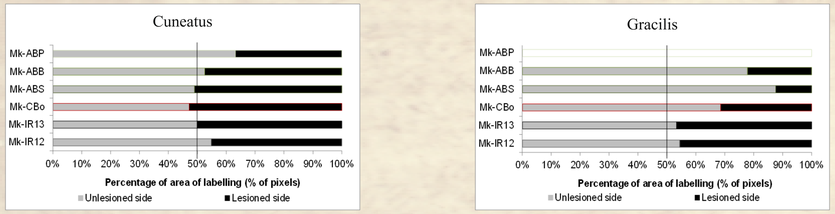


NS | NS | NS | NS | NS

Statistical comparison for paired values along caudorostral extent of nucleus

Sum of differences between unlesioned side and lesioned side for the 3 zones

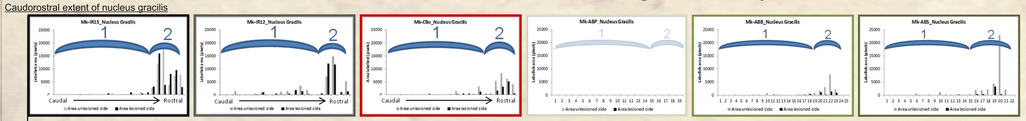
Representation in percentage of the labelling area for each side reference total amount of labelling on both sides



CB: nucleus gracilis

Intact | Control | Anti-Nogo-A antibody combined with BDNF

Caudorostral extent of nucleus gracilis

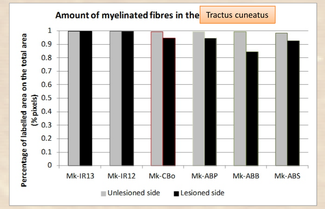


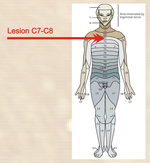
NS | NS | p=0.03 | p=0.005 | p<0.001

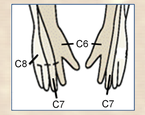
Statistical comparison for paired values along caudorostral extent of nucleus gracilis

Sum of differences between unlesioned side and lesioned side for the 2 zones

Myelin





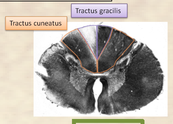


Dermatome: sensory projection of the different part of the skin on the spinal cord.

Exemple of myelin labelling at C3 level in spinal cord.

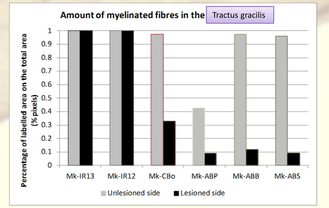
Mk-ABP

Monkey lesioned on both sides of the tractus gracilis



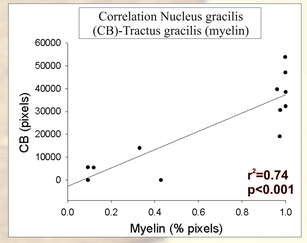
Mk-ABB

Exemple representing the lesion localization area in the tractus gracilis.

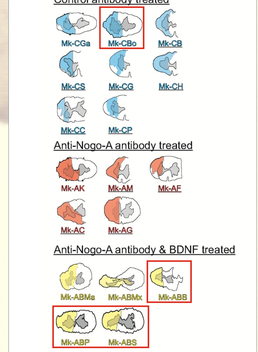


PROSPECT

Results obtained for the nucleus and tractus gracilis showed a significant correlation between the amount of myelinated fibres in the tractus and the area of labelled projections by sensory ascending pathways of the dorsal column in the nucleus. In light of this result we would include all others monkeys previously analysed for spinal cord lesion in order to compare anti-Nogo-A antibody treated group with the combined anti-Nogo-A antibody and BDNF treated group and the Control antibody group. For all these monkeys, we would like to analyze the proportion of myelinated fibres in the dorsal colmun pathway and assess the possible beneficial effect of our treatments on the sensory pathways.



Anatomical reconstruction of the lesion territory



Monkeys included in CB and Myelin analyses

Monkeys included in spinal cord hemisection study assessing motor pathway and could be included in the myelin analysis.

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