

Behavioral recovery from cervical hemi-section in monkeys is enhanced by anti-Nogo-A treatment

T. Wannier^{1,2*}; E. Schmidlin¹; P. Freund¹; J. Bloch³; A. Mir⁴; M.E. Schwab²; E.M. Rouiller¹

1. Medicine, Univ Fribourg, Fribourg, Switzerland 2. Neuromorphol, Univ Zurich, Zurich, Switzerland 3. Neurosurg, Univ Lausanne, Lausanne, Switzerland 4. Inst Biomed Res, Novartis, Basel, Switzerland

Contact: thierry.wannier@unifr.ch



Introduction:

Adult rodents subjected to a subtotal spinal cord lesion and receiving an antibody neutralizing the neurite growth inhibitor Nogo-A reach better functional recovery than animals receiving a control antibody.

The goal of the present study was to investigate whether applying an antibody neutralizing Nogo-A also leads to improved functional recovery in adult macaques subjected to a spinal cord lesion, corresponding to a cervical hemi-section.

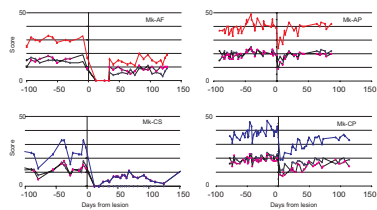
① Immediately after the lesion, the side homolateral to the lesion was impaired in all monkeys. The animals tended to keep their arm flexed at the elbow and their hindlimb extended. They were clumsy when using their hands and fingers.

Over a period of a few weeks, the behavioural capacity recovered progressively and the animals regained most of their locomotor abilities (walking, jumping, brachiation).

The dexterity also improved but reached various levels depending on the precise lesion location, lesion extent and on the treatment.

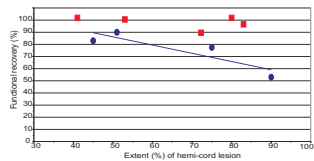
② Task: "Modified Brinkman board test" in which the monkey grasps food pellet out of small holes.

Tested on: 6 anti-Nogo-A treated animals and 6 control antibody treated animals.



Score: nb. of food pellets retrieved within first 30 sec.

■ vertical
◆ horizontal



Anti-Nogo-A treated monkeys recover faster and completely irrespective of their lesion extent

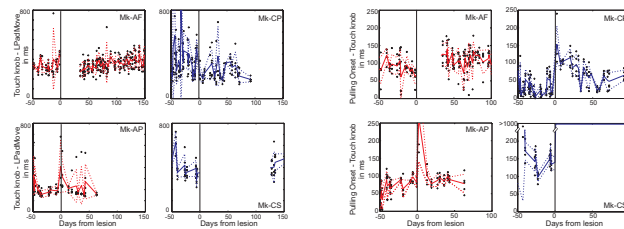
Materials and Methods:

Macaque monkeys were trained to perform a variety of motor task, to assess mainly manual dexterity. Then, the monkeys were subjected to a cervical hemi-section at C7/C8 level. A subgroup of monkeys were treated over a period of 4 weeks with Nogo-A antibodies, delivered intrathecally near the lesion using an osmotic pump. The other group of monkeys received a control antibody.

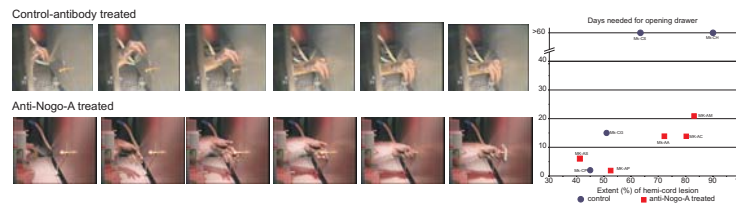
Due to the considerable variability of the lesion size, experimental conditions and behavioral tests performed, the data were analyzed by comparing four matched pairs of monkeys for these parameters, each pair comprising one treated and one control monkey.

③ Task: "Natural reach and grasp drawer task" in which the monkey reaches for a drawer, opens it and picks out a reward placed inside.

Tested on 6 anti-Nogo-A treated animals and 4 control antibody treated animals.



- the pulling phase, that requires a controlled grip force using the fingers, was most affected and recovered more slowly in the control animals.
- the reaching phase was little affected in control and anti-Nogo-A treated animals.



Two of the control animals never regained the capacity to perform the task correctly. All anti-Nogo-A treated animals recovered and performed the task correctly post-lesion.

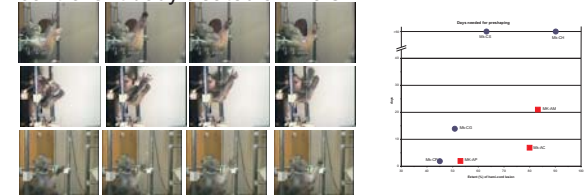
Support Contributed By: Swiss National Science Foundation (NCCR "Neural plasticity and repair") and Novartis Pharma
Conflict of Interest: Work supported by Novartis Pharma

Conclusion:

In adult macaques subjected to a hemi-section of the spinal cord, behavioral recovery is enhanced by applying an antibody neutralizing Nogo-A on the site of the lesion.

No signs of allodynia were detected.

④ Task: "Ballistic arm movement test" in which the monkey catches for a thrown food reward
Tested on: 7 anti-Nogo-A treated animals and 5 control antibody treated animals.



- All anti-Nogo-A treated animals shaped their hand normally, while two control animals remained unable to fully open the hand.
- The anti-Nogo-A treated animals recovered more rapidly.

⑤ Task: "Hindlimb grasp test" in which the monkey picks a food reward with the toes.
Tested on: 4 anti-Nogo-A animals and 2 control antibody treated animals



All animals extended their foot to reach the reward, but remained unable to grasp it.

⑥ During the whole post-lesion period of behavioural assessment, the animals did not lose weight, maintained normal social interactions with their mates (including grooming), remained cooperative with the experimenters and accepted to be manipulated without showing signs of discomfort.

These data suggest that the anti-Nogo-A treatment did not induce allodynia or other pain related states.