

Intrathecal treatment with anti-Nogo-A antibody improves functional recovery in adult rats after stroke

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Abstract Stroke often results in devastating neurological disabilities with no specific treatment available to improve functional recovery. Neurite growth inhibitory proteins such as Nogo-A play a critical role in impeding regain of function after stroke. We have reported that treatment with anti-Nogo-A antibody using the intracerebroventricular route resulted in improvement of function and neuroplasticity

in adult or aged rats after stroke. This present study tested a more clinically accessible route for applying anti-Nogo-A antibodies, the intrathecal route. Anti-Nogo-A or control antibody was administered intrathecally at lower lumbar levels 1 week after middle cerebral artery occlusion in adult rats. Our results show that anti-Nogo-A antibody delivered by this intrathecal route for 2 weeks penetrated into brain parenchyma and bound to myelin-enriched structures such as the corpus callosum and striatal white matter. Animals receiving anti-Nogo-A antibody treatment significantly improved recovery of function on the skilled forelimb reaching task as compared to stroke only and stroke/control antibody animals. These findings show that anti-Nogo-A antibody delivered through the intrathecal route is as effective in restoring lost functions after stroke as the intracerebroventricular route. This is of great importance for the future application of anti-Nogo-A immunotherapy for ischemic stroke treatment.

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Introduction

Annually, 15 million people worldwide suffer from ischemic stroke, a disruption of blood supply to the brain. Of these, 5 million die and another 5 million are left permanently disabled (Mackay and Mensah 2005). Since injured CNS neurons still exhibit the potential to grow (Richardson et al. 1980; David and Aguayo 1981), the main factors causing incomplete functional recovery are thought to be due to the neurite-growth inhibitory environment in the adult CNS. The adult CNS myelin contains abundant growth-inhibitory molecules including proteoglycans (Davies et al. 1999), Nogo-A (Huber et al. 2002), myelin-associated glycoprotein (MAG) (McKerracher et al. 1994; Mukhopadhyay et al. 1994), versican V2 (Schweigreiter et al. 2004) and oligodendrocyte

myelin glycoprotein (Omgp) (Wang et al. 2002). Of particular interest to our laboratory is the inhibitory protein Nogo-A, which is primarily synthesized by oligodendrocytes and localized in the innermost and outermost myelin layers (Huber et al. 2002). Our previous studies showed that anti-Nogo-A Ab treatment delivered intracerebroventricularly (ICV) immediately after ischemic stroke facilitated axonal growth from the contralateral, non-lesioned forelimb cortex into the de-afferented red nucleus and resulted in significant functional improvement (Papadopoulos et al. 2002). A related study applying a different anti-Nogo-A Ab delivered ICV 24 h after stroke in adult rats demonstrated functional improvement in the Montoya Staircase forelimb task and an increase in corticospinal tract (CST) fibers crossing the midline into the de-afferented spinal cord (Wiessner et al. 2003). A similar study targeted the Nogo-66 receptor (NgR), a common receptor subunit for the Nogo-66 domain of Nogo-A, as well as Omgp and MAG (Lee et al. 2004). This study reported functional improvement and cortico-efferent plasticity when an NgR antagonist was delivered ICV 1 week after stroke in adult rat (Lee et al. 2004).

Recent studies from our laboratory also demonstrated that ICV anti-Nogo-A Ab treatment significantly improved motor function in the forelimb reaching task in young adult (Seymour et al. 2005) and aged rats (Markus et al. 2005) when given 1 week after stroke. In an attempt to further the clinical application of anti-Nogo-A Ab immunotherapy, we wanted to determine if Ab delivery could be given intrathecally in a more clinically accessible approach as compared to ICV route. Using an intrathecal route to deliver medical treatment has been widely accepted for other clinical uses, such as for spasticity (Verrotti et al. 2006), chronic pain (Farrow-Gillespie and Kaplan 2006), and cancer therapy (Bergman et al. 2001). However, this delivery system has never been tested in an established rodent stroke model. The purpose of the present investigation was to study this clinically applicable route, i.e. intrathecal instead of ICV, for anti-Nogo-A Ab administration and to determine behavioral outcome of skilled motor function after stroke.

Materials and methods

Animal use was approved by the Institutional Animal Care and Use Committee of Hines Veterans Affairs Hospital. Adult male, Long Evans black-hooded rats (mean weight of 300 g) were first trained on the skilled forelimb reaching task (Fig. 1a) as described previously (Papadopoulos et al. 2002) which requires fine digit movement and intact motor and sensory neural pathways (Whishaw 2005). Limb preference of each animal was determined at the beginning of the training session. Pellets were placed opposite to the preferred limb and 1.0–1.5 cm away from box opening to favor use of the

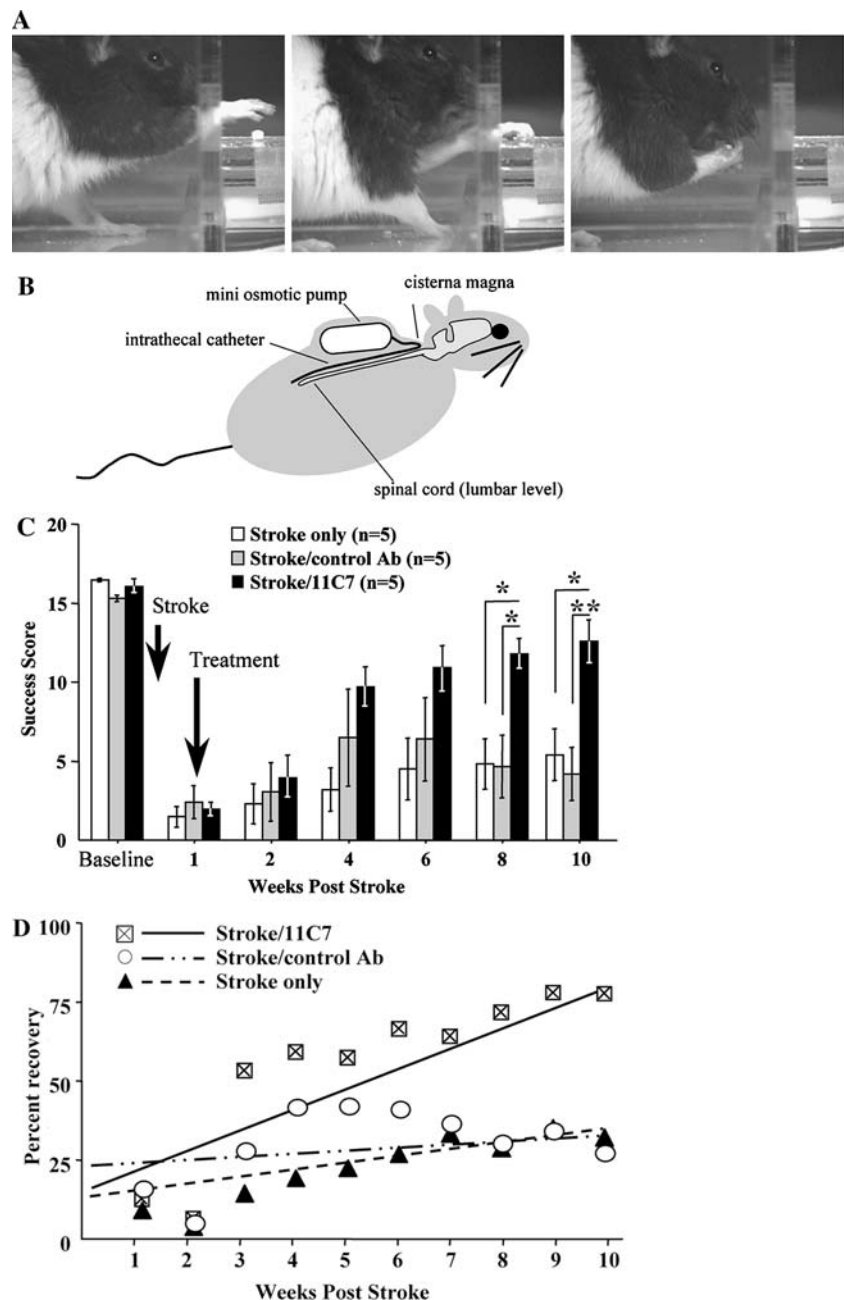
preferred limb and avoid use of the non-preferred one. Animals that used both limbs for reaching were removed from the study. Animals successfully retrieving 15 out of 20 pellets during three consecutive training sessions (averaged to obtain a baseline measure) received middle cerebral artery occlusion (MCAO) surgery to impair the preferred forelimb. For MCAO surgery (Markus et al. 2005), animals were anesthetized (sodium pentobarbital 50 mg/kg, intraperitoneally), and a burr hole was made to expose the MCA, which was permanently ligated by a 10–0 suture and then transected with microscissors. The common carotid artery (CCA) ipsilateral to the MCAO was permanently ligated and the contralateral CCA was temporarily occluded for 60 min. After MCAO, animals continued to use their impaired forelimb to reach, despite showing deficits in performing the task.

One week after stroke, animals that showed a deficit in skilled reaching with the stroke-impaired limb (retrieval of no more than an average of six pellets during the first week post stroke) received either purified monoclonal mouse anti-Nogo-A antibody (Ab) (IgG1, 11C7 $n = 5$), control Ab (IgG1 against wheat auxin, $n = 5$), or no treatment ($n = 5$). Animals receiving no treatment after stroke were also used for another behavioral study during the same time period. Antibody was delivered using an intrathecal route by inserting a pre-measured 32 G catheter (ReCath CO, Allison Park, PA, USA) through the cisterna magna which was then extended to the lower lumbar level (Fig. 1b). An osmotic minipump (Alzet, 2ML2, Cupertino, CA, USA) was placed in a mid-scapular subcutaneous pocket and connected to the intrathecal catheter. The catheter was stabilized to muscle followed with wound closure. Baseline and weekly behavioral sessions were video recorded. For behavioral data, a repeated-measures ANOVA was used for comparison of the rate of improvement and one way ANOVA with Tukey's post hoc analysis was used to compare the mean of success score at one time point. After completion of behavioral testing, animals were perfused, brains removed, cryosectioned and processed for stroke size analysis using the method of Kawamata et al. (1997) as described in our previous reports (Papadopoulos et al. 2002; Seymour et al. 2005). Additional animals received 11C7 or control Ab and were perfused 3 weeks after stroke and processed to detect Ab distribution. In brief, brain sections were blocked with TBS (pH 7.4, 0.5% Triton-X, 5% normal goat serum) followed by incubation at 4°C overnight with Alexa Fluor 488 conjugated F(ab')₂ rabbit-anti-mouse IgG (Molecular Probe, 1:200) in TBS containing 0.5% Triton-X and 5% NGS.

Results

Analysis of the forelimb reaching task over the 10-week testing period revealed several important findings (Fig. 2a).

Fig. 1 The experimental procedures and behavioral assessment of animals. **a** Forelimb reaching task performed by an adult rat showing animal grasping a pellet. **b** Intrathecal catheter was placed through the cisterna magna and extended to the lumbar space. **c** All groups showed marked deficits in successfully obtaining pellets with the stroke-impaired limb during the first week after stroke surgery, with no significant difference between groups. Animals treated with the anti-Nogo-A Ab 11C7 ($n = 5$) for 2 weeks continued to improve from 4 weeks post stroke, so that by 8 weeks and at the end of the study they were significantly different from the stroke/control Ab group ($n = 5$) and the stroke only group ($n = 5$). There was no significant difference between control groups at any time point (one-way ANOVA with Tukey's post hoc analysis, $* P < 0.05$, $** P < 0.01$). Error bars indicates \pm SEM. **d** Animals receiving anti-Nogo-A Ab treatment demonstrated a statistically significant improved rate of recovery compared with animals receiving stroke only ($P < 0.01$) and stroke/control Ab treatment ($P < 0.01$). There was no difference in the improvement rate between stroke only and stroke/control Ab groups (repeated-measures ANOVA)



Before stroke, animals in all groups showed excellent skilled reaching and no difference in performance. One week after stroke and prior to treatment, all animals showed significant deficits in obtaining pellets with the stroke-affected limb, with no difference between groups. Animals that received the function blocking anti-Nogo-A Ab 11C7 began to improve at 4 weeks after stroke, and showed statistically significant improvement by 8 weeks after stroke when compared with stroke only ($P = 0.02$) or stroke/control Ab treated animals [$P = 0.02$; $F(2,14) = 6.62$]. At the end of the study (10 weeks after stroke) animals treated with the anti-Nogo-A Ab demonstrated an improvement to 78% of their pre-stroke performance, which was significantly

different from the animals receiving no treatment ($P = 0.018$) or control Ab after stroke [$P = 0.007$; $F(2,14) = 8.36$]. There was no significant difference between the two control groups at any time point in the study. Thus, animals receiving anti-Nogo-A Ab treatment demonstrated a statistically significant improved rate of recovery compared with animals receiving stroke only ($P < 0.01$) and stroke/control Ab treatment ($P < 0.01$) (Fig. 2b), with no difference between control groups.

In order to detect whether anti-Nogo-A Ab given through an intrathecal route distributed well into the CNS parenchyma, additional animals receiving Ab treatments after stroke were sacrificed immediately at the end of Ab

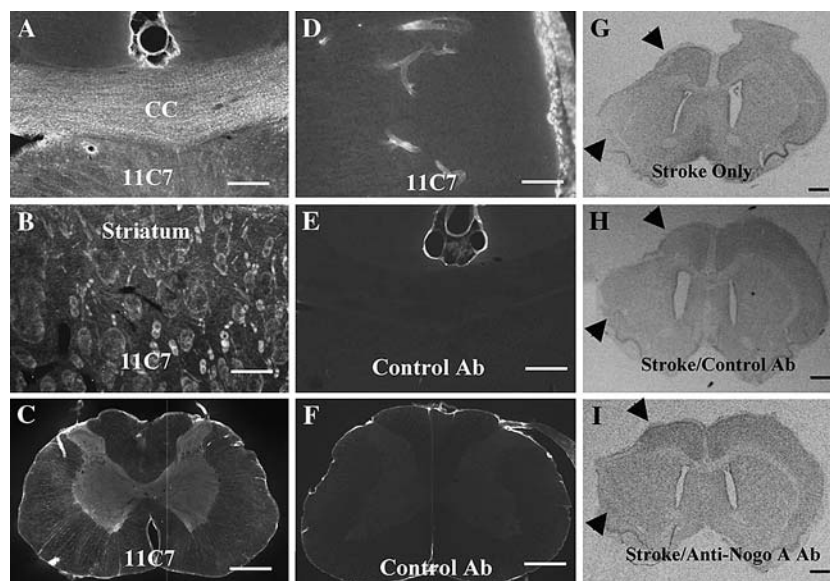


Fig. 2 The Anti-Nogo-A Ab 11C7 penetrated the brain parenchyma and in particular was detected in the white matter fiber tracts of the corpus callosum (a), striatal white matter (b), and spinal cord (c). Grey matter was also labeled in the spinal cord (c). Perivascular labeling of antibody was detected in the cortical parenchyma (d). There was no specific staining in the brain (e) and spinal cord (f) of control Ab treated

animals. Representative photomicrographs of ischemic stroke lesions in the sensorimotor cortex (Nissl stain) showing g stroke-only control; h stroke/control Ab treated; i stroke/anti-Nogo-A Ab treated. Location of the stroke lesion is indicated by arrowheads. No significant difference in lesion size was found between groups (one-way ANOVA). Bars indicate 100 μm (a–f) and 500 μm (g–i)

treatment, and the brains processed for immunocytochemistry. The results showed that the anti-Nogo-A Ab 11C7 penetrated into the CNS parenchyma, and was distributed throughout the fiber tracts such as the corpus callosum and the striatal white matter. In the spinal cord, anti-Nogo-A Ab was detected in both the grey and white matter (Fig. 2a–c). Perivascular labeling was also seen in the brain parenchyma of anti-Nogo-A Ab treated animals (Fig. 2d). No specific labeling in brain parenchyma and spinal cord of control Ab treated animals was observed (Fig. 2e, f).

Lesion analysis showed that all stroke lesions included the sensorimotor cortex without involving subcortical structures (Fig. 2g–i) with no statistical difference in stroke volume between groups (stroke only, $14.17 \pm 6.83\%$ SEM; stroke/control Ab, $13.69 \pm 2.34\%$ SEM; stroke/anti-Nogo-A Ab, $9.40 \pm 2.26\%$ SEM) (one-way ANOVA).

Discussion

The results of the present study show that anti-Nogo-A immunotherapy delivered through an intrathecal route significantly improved function when given 1 week after ischemic stroke. In addition, antibodies delivered at the low lumbar level demonstrated efficient brain parenchymal distribution and binding to structures enriched with myelin including the corpus callosum, striatal white matter, and spinal cord.

Our laboratory first reported that ICV anti-Nogo-A Ab immunotherapy given immediately after ischemic stroke resulted in new projections from the contralateral, unlesioned forelimb cortex to de-afferented subcortical structures. Such expanded axonal projections were correlated with functional improvement (Papadopoulos et al. 2002). Further studies confirmed this result and showed that ICV anti-Nogo-A Ab treatment delayed for either 24 h (Wiessner et al. 2003) or 1 week (Seymour et al. 2005) after stroke resulted in significant improvement in the Montoya staircase task and skilled forelimb reaching test. A corresponding increase in midline-crossing CST fibers targeting the de-afferented cervical spinal cord (Wiessner et al. 2003) and corticorubral fiber density in the de-afferented red nucleus (Seymour et al. 2005) were also reported. Our present result of behavioral improvement to 78% of baseline at 8 weeks after stroke in the anti-Nogo-Ab treated animals is similar to these previous studies and suggests that the intrathecal route is just as efficacious as the ICV route for delivery of anti-Nogo-A immunotherapy post stroke.

The skilled forelimb reaching task is a series of complex movements that can be broken down into several components for analysis (Whishaw 2005). Experimental studies have showed that animals can improve their success in the skilled forelimb reaching tasks by adjusting/compensating their postures and motor movements after motor cortical lesion (Metz et al. 2005; Gharbawie and Whishaw 2006). We did attempt to study whether subtle changes in postural

support mechanisms enabled our rats treated with anti-Nogo-A Ab to perform better than control Ab treated animals, but were unable to show any conclusive differences (data not shown). Additional studies will be necessary to determine whether enhanced compensatory mechanisms play a pivotal role in the functional improvement of animals receiving anti-Nogo-A Ab therapy after stroke.

The exact relationship between increased neuroplasticity and functional improvement after stroke and anti-Nogo-A antibody therapy is not entirely clear. Our previous studies using intracortical microstimulation and functional MRI indicated reorganization in the sensorimotor cortex (Emerick et al. 2003) and thalamus (Markus et al. 2005) in animals treated with anti-Nogo-A antibody after brain injuries. Additionally, animal receiving anti-Nogo-A therapy showed an increased dendritic arborization and spine complexity in neurons of the contralateral, unlesioned forelimb cortex (Papadopoulos et al. 2005), a finding that other investigators have shown to be important for recovery after ischemic stroke (Biernaskie and Corbett 2001; Gonzalez et al. 2006).

The intrathecal route has been widely used to deliver treatments for neurological disorders such as baclofen for spasticity (Verrotti et al. 2006), morphine for chronic pain management (Farrow-Gillespie and Kaplan 2006), and in particular the use of antibodies in the treatment of leptomeningeal neoplasms (Bergman et al. 2001; Sorkin et al. 2002). The distribution of intrathecally delivered large molecules such as antibodies to higher levels of the CNS has not been well studied. Reports indicate that pulsations of the cerebral arteries can drive CSF flow in and out of the perivascular spaces and enable large proteins administered to the subarachnoid space to enter the brain parenchyma (Rennels et al. 1985; Ichimura et al. 1991). Therefore, transport between the subarachnoid and perivascular space may serve as an important mechanism for the transport of large molecules such as antibodies and enable them to travel distances in CNS parenchyma much further than predicted by diffusion (Koh et al. 2005). A recent report showing brain parenchymal distribution of anti-Nogo-A antibodies given intrathecally at the mid-thoracic level in rats and the cervical level in Macaque monkeys further supports these reports (Weinmann et al. 2006). In our present study, detection of intrathecally delivered anti-Nogo-A Ab in white matter and perivascular spaces in the brain parenchyma is consistent with these findings.

Anti-Nogo-A Ab immunotherapy has been shown to be effective in improving functional recovery, neuroregeneration, and neuroplasticity after CNS injuries in adult rats (Kartje et al. 1999; Wenk et al. 1999; Schwab 2004; Liebscher et al. 2005), and primates (Fouad et al. 2004; Freund et al. 2006). Our present results strongly suggest that anti-Nogo-A immunotherapy delivered through the more accessible

intrathecal route is an effective way to restore neurological function following stroke and may greatly impact the future treatment of patients suffering from CNS injuries.

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