Gonzalo Lafora would have appreciated the progress made by the explorers so far.

Berge A. Minassian
Division of Neurology,
Department of Paediatrics, and Program in
Genetics and Genome Biology,
The Hospital for Sick Children,
Toronto Canada,
Institute of Medical Sciences,
University of Toronto,
University of Toronto Michael Bahen Chair in Epilepsy Research

Correspondence to: Berge A. Minassian
E-mail: berge.minassian@sickkids.ca

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Removing the brakes on post-stroke plasticity drives recovery from the intact hemisphere and spinal cord

The existence of bilaterally redundant corticospinal pathways suggests a potential means of recovery after unilateral injury such as stroke. However, in the adult brain, plasticity is kept in check by inhibitory factors that provide the stability necessary in neuronal networks to encode memories and retain learned actions. In the current issue of *Brain*, Nicolas Lindau and colleagues use antibodies that block Nogo-A functioning to unlock plasticity within the adult injured brain, leading to a structural and functional re-routing of corticospinal signals to exploit circuit redundancy (Lindau *et al*., 2014).

After a large motor cortex stroke, there is evidence that the intact hemisphere can control the impaired hand and thus facilitate behavioural recovery (Grefkes and Ward, 2014). However, hemiparesis remains a common deficit after stroke, indicating a need for therapies that augment spontaneous recovery. Lindau *et al.* (2014) show that, in rats, promoting axonal sprouting by blocking the growth-inhibitor protein Nogo-A facilitates the emergence of motor pathways that allow the intact hemisphere to drive motor output to the impaired forelimb. Although only 10% of corticospinal projections terminated in the ipsilateral spinal cord before injury, anti-Nogo-A therapy induced the generation of additional ipsilateral motor projections and produced substantial recovery of forelimb function.

During the development and refinement of the nervous system there is extensive axonal sprouting. To curb ebullient outgrowth in the adult, various inhibitory molecules such as Nogo-A keep the system in check. Over the years, the Schwab group has systematically examined the therapeutic potential of inhibiting Nogo-A in a number of disease models, including stroke. Initial efforts were aimed at enhancing sprouting at the cortical level through the expression of Nogo-A antibodies in peri-infarct tissue (Emerick *et al*., 2003). To evaluate a more clinically accessible approach to treatment, Lindau *et al*. (2014) delivered a Nogo-A inhibitor intrathecally to the lumbar spinal cord. This method builds on

previous studies providing proof of principle that intrathecal anti-Nogo-A treatment promotes recovery after cortical injury (Tsai *et al*., 2007). Following unilateral stroke, Lindau *et al*. (2014) observed a remarkable sprouting of axons and rewiring of limb pathways within the spinal cord to take advantage of the spared hemisphere. Widespread switching of corticospinal projections has been observed after injury in more plastic juveniles, which may have lower levels of sprouting inhibitors than adults. Recent evidence suggests that several molecular mediators of plasticity are temporarily upregulated in the spinal cord after cortical stroke (Sist *et al*., 2014) and may therefore act in concert with anti-Nogo-A treatment to promote recovery. Although a spinal site of action is likely based on the data presented, Nogo-A antibodies would also have access to the peri-infarct cortex where other inhibitors of outgrowth such as ephrin-A5 have been shown to act (Overman *et al*., 2012).

Lindau *et al.* (2014) use a multi-pronged approach ranging from detailed kinematic assessment of forelimb movements to tracing of axonal crossings within the spinal cord. Intracortical microstimulation (ICMS) was performed to confirm the contribution of specific cortical sites to motor output and the presence of an enhanced uncrossed functional corticospinal pathway following stroke in anti-Nogo-A treated animals. The anatomical tracing experiments revealed that anti-Nogo-A treatment promoted contralaterally projecting fibres from the uninjured hemisphere to recross at the level of the cervical spinal cord and replace connections lost after stroke. The treatment also produced a 2-fold increase in the number of ipsilaterally projecting fibres from the rostral forelimb area of the uninjured hemisphere. These anatomical changes correlated with significant behavioural recovery and an increase in ICMS evoked motor output from the intact hemisphere to the ipsilateral forelimb in anti-Nogo-A treated animals. To demonstrate that the corticospinal tract from the intact hemisphere was mediating behavioural recovery, the authors severed the tract from the uninjured hemisphere in recovered animals and showed that the deficits re-emerged. This large body of work supports evidence that the intact hemisphere assumes control after a relatively large stroke that leaves little spared sensory-motor cortex (Murphy and Corbett, 2009). Although the ipsilateral hemisphere is involved in forelimb movements in uninjured animals (Ganguly *et al*., 2009), this means of recovery was not observed in the absence of anti-Nogo-A treatment as there was little spontaneous reorganization.

Given the magnitude of the behavioural recovery and apparent axonal sprouting from the intact hemisphere following anti-Nogo-A treatment, it is possible that the normal function of this cortical tissue (controlling the unimpaired paw) is negatively impacted by such reorganization. Although Lindau *et al.* (2014) did not directly evaluate the function of the ipsilesional limb, the single pellet reaching task used likely requires significant bimanual coordination. The non-reaching limb supports and aligns the body while executing the reach, and the kinematic analysis performed by the authors is sensitive to impairments in body posture. Reaches by treated animals resembled the normal reaching pattern more closely than those of untreated animals, suggesting that the intact hemisphere is able to drive output to both forelimbs without producing a gross motor deficit in the ipsilesional limb. In a series of related experiments, Theresa Jones' lab found that engaging the intact hemisphere after stroke by reach-training with the ipsilesional limb blocked all recovery in the contralesional forelimb (Jones *et al*., 2013). One explanation for these seemingly contradictory effects is that the intact hemisphere has limited plasticity after injury, and the allocation of this limited plasticity is a key determinant of functional outcome. Using up plasticity by training the ipsilesional forelimb results in poor recovery of the contralesional forepaw; removing the brakes on plasticity through anti-Nogo-A inhibitors facilitates the recruitment of the intact hemisphere to drive motor output to the contralesional forelimb through ipsilateral projections. One critical test of this hypothesis would be to reversibly silence the intact hemisphere either optogenetically or chemically and determine whether this reinstates the deficit in anti-Nogo-A treated animals. Cortical muscimol infusion was recently used to demonstrate the importance of ipsilateral pathways that emerged after chronic electrical stimulation of the intact hemisphere (Carmel *et al*., 2014).

The impressive efficacy of this treatment in a rat model of stroke opens up the possibility that growth-inhibitor blockade could one day be developed as a treatment for humans with motor cortex stroke. Although the current study provides clear evidence in favour of pursuing this approach, future experiments should assess the impact of stroke risk factors such as age and cerebrovascular health on treatment efficacy. The current study focused on motor pathways, but the treatment may also induce functionally relevant plasticity in fibres mediating sensory processing. Removing key inhibitors of plasticity during a limited time window after stroke offers new hope for unlocking potential plasticity in the adult nervous system, and could provide a powerful intervention when combined with current rehabilitative strategies.

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Gergely Silasi and Timothy H. Murphy
Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver, B.C. Canada V6T 1Z3

Correspondence to: Timothy H. Murphy
E-mail: thmurphy@mail.ubc.ca

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Role of PACAP in migraine headaches

Migraine is a complex disorder with a wide spectrum of clinical symptoms, and affects more than 16% of the general population. Despite its high heritability, the genetic basis of migraine remains unclear in most cases, and appropriate prophylactic and clinical therapy is not always available. Recent years have nevertheless seen considerable progress in understanding the cellular and circuit mechanisms of migraine (Vécsei *et al*., 2013). In this issue of *Brain*, Faisal Amin and colleagues add to this progress by identifying the PAC_1 receptor as a potentially important candidate therapeutic target (Amin *et al*., 2014).

Since the 1990s, a central theme of migraine research has been the trigeminovascular theory (Moskowitz, 1992). The trigeminovascular system provides an important pain-transmission link between the vascular (dural and cortical) and neuronal (brainstem and thalamus) regions. The sensory trigeminal unit is controlled by the descending pathways from the monoaminergic nuclei, and a number of neuropeptides, such as calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and pituitary adenylate cyclase-activating polypeptide (PACAP), have essential roles in activation of the trigeminovascular system (Edvinsson, 2013). PACAP is a member of the VIP/secretin/glucagon neuropeptide family and exists in two biologically active forms: PACAP27 and (predominantly) PACAP38. It is a pleiotropic peptide: it acts as a hormone on the pituitary gland, a neurotransmitter and a neuromodulator in the nervous system, and it exerts neuroprotective, anti-apoptotic and differentiation-inducing effects in the developing nervous system. The effects of PACAP are mediated through G-protein-linked receptors: $VPAC_1$, $VPAC_2$ and PAC_1 (Vaudry *et al*., 2009). PACAP38 is present in the trigeminal ganglion and caudal trigeminal nucleus (Tajti *et al*., 2001), and plasma PACAP-38-like immunoreactivity is increased after electrical stimulation of the trigeminal ganglion (Tuka *et al*., 2012).

Intravenous administration of PACAP38 causes headache in healthy subjects and migraine-like attacks in migraine patients without aura, beginning on average 6 h after the start of the infusion (Schytz *et al*., 2009). PACAP38 infusion also increases the diameter of the superficial temporal arteries and decreases the mean blood flow velocity of the middle cerebral arteries (Schytz *et al*., 2009). Amin *et al*. (2014) compare the vascular and biochemical effects of infusion of PACAP38 to those of the structurally and functionally related neuropeptide, VIP, in female migraineurs without aura. They show that 73% ($n = 16$) of their subjects developed migraine-like attacks after PACAP38 infusion, compared to 18% ($n = 4$) after VIP infusion. Three of four patients who developed migraine-like headache after VIP administration also reported attacks after PACAP38 treatment. Both VIP and PACAP38 are potent vasodilators of cerebral and dural arteries, and all three VIP/PACAP receptors are present on cranial arteries. Amin *et al*. (2014) report that both neuropeptides caused pronounced dilations of the extracranial (the superficial temporal artery, the middle meningeal artery, the external carotid artery and the cervical segment of the internal carotid artery), but not the intracranial arteries. However, VIP-induced dilatation was normalized after 2 h, whereas PACAP38-induced vasodilation was longer lasting.

Plasma PACAP38 levels were increased 1 h after the start of PACAP38 infusion only in those patients who later reported migraine attacks. Blood levels of VIP, in contrast, were unaltered after intravenous administration of PACAP38. This suggests the possibility of *de novo* synthesis or release of PACAP38 during migraine.

These results are consistent with previous evidence implicating PACAP38 in migraine. Markovics *et al*. (2012) compared the effects of nitroglycerol and PACAP on the trigeminovascular system of PACAP knockout and wild-type mice. Nitroglycerol is a well-known NO donor, which causes both immediate and delayed migraine-like attacks in migraine patients without aura. Nitroglycerol administration also induced photophobia in wild-type mice, as well as increases in meningeal blood flow and c-fos expression in the trigeminal ganglion and caudal trigeminal nucleus. These changes were reduced in PACAP-deficient mice compared with wild-type animals. Furthermore, PACAP38 elicited photophobia in wild-type