SPINAL-CORD INJURY

Locomotion restored after paralysis

Spinal-cord injury can render intact neuronal circuits functionally dormant. Targeted reduction of neuronal inhibition in the injured region has now enabled reactivation of these circuits in mice, restoring basic locomotion.

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When we decide to walk, the brain broadcasts commands through parallel neuronal pathways that cascade to executive centres in the lumbar region of the spinal cord[1]. A spinal-cord injury (SCI) scatters this exquisitely organized communication system, leading to severe locomotor deficits or paralysis[2]. Most SCIs spare islands of intact neural tissues below the injury, which contain nerve fibres that remain connected to executive centres. But for unclear reasons, these anatomically intact connections remain functionally dormant. Writing in *Cell*, Chen *et al.*[3] demonstrate that reducing the excitability of inhibitory neurons within the injured region of the spinal cord enables these dormant connections to relay commands from the brain, and promotes partial recovery of locomotion in mice that have sustained an SCI that causes complete paralysis.

It was long assumed that restoring movement after an SCI would involve precisely reconstituting the circuit connectivity that was in place before the injury. However, evidence of spontaneous circuit reorganization after SCI has challenged this view[4]. For example, consider injuries in which the spine is severed on either side in two staggered places. Although descending pathways from the brain are all severed at either the first or second lesion, new contacts can form between the projections from neurons in the brain that reach the second cut and local neurons that lie between the cuts. These contacts establish 'detour' circuits that relay sufficient information to executive centres to restore basic locomotion[5,6] (Fig. 1). But until now, experimental procedures that trigger the formation and activation of these detour relays either have not been clinically relevant[5] or have acted only transiently[6].

Chen and colleagues set out to find a permanent way to render relay circuits functional following injury. They injected mice that had sustained a staggered SCI with a panel of compounds known to modulate neuronal activity. One of these compounds, a small molecule called CLP290, restored movement in the injured mice.

CLP290 activates a protein called KCC2 (ref. 7), which is a transporter of potassium and chloride ions, and is responsible for maintaining a functional level of the latter in neurons. Neurotransmitter molecules such as GABA or glycine open chloride channels on the surface of target neurons, allowing chloride ions (Cl^-) to flow into the cells down a concentration gradient, resulting in neuronal inhibition. By pumping out Cl^-, KCC2 can control the concentration gradient and so limit how strongly target neurons are inhibited by these neurotransmitters.

SCIs lead to a decrease in the levels of KCC2 in neurons below the injury[8]. Chen *et al.* examined the effects of increasing KCC2 levels in their mice, either in the lumbar spinal cord below the SCIs or in the relay circuits between the staggered injuries. To do this, they used various genetically engineered mice, which enabled them to modulate KCC2 expression in the three main types of neuron in the spinal cord — inhibitory, excitatory and motor neurons. The authors found that increasing KCC2 expression in inhibitory neurons between the staggered lesions could reproduce the effects of CLP290 treatment, whereas no other manipulation could.

It would be intuitive to expect that downregulation of KCC2 following injury would decrease the activity of neurons, by increasing the GABA- or glycine-mediated Cl^- influx. However, KCC2 downregulation actually leads to neuronal excitation if the lack of this transporter increases the concentration of Cl^- in the cells to such a level that GABA- or glycine-mediated opening of Cl^- channels causes an efflux, rather than an influx, of Cl^- (ref. 8). This mechanism enables GABA and glycine to excite neurons during development. After birth, KCC2 upregulation in neurons reduces intracellular Cl^- concentrations, transforming excitation into inhibition.

Similarly, the authors found that injury-mediated downregulation of KCC2 in inhibitory neurons located between the staggered lesions increased the cells' activity, and thus their ability to inhibit local relay circuits, rendering these circuits dormant. CLP290 restored the functionality of relay circuits by preventing downregulation of KCC2 and thus maintaining the balance between inhibition and excitation (Fig. 1). Moreover, the researchers showed that CLP290 did not affect the growth of new neuronal projections — recovery was triggered merely by restoring this balance in relay circuits.

Finally, Chen *et al.* demonstrated through two experiments that brain commands were being transmitted through the reactivated relays in CLP290-treated mice. First, electrically induced signals in the brain's cortex were relayed to the motor neurons below the injury, resulting in the activation of hindlimb muscles. Second, neurons between the staggered lesions were more active in response to locomotor activity in treated than in non-treated mice.

The authors' results are important. Together, they show that excessive neuron-mediated inhibition of relay circuits in the injured spinal cord is a key mechanism in preventing

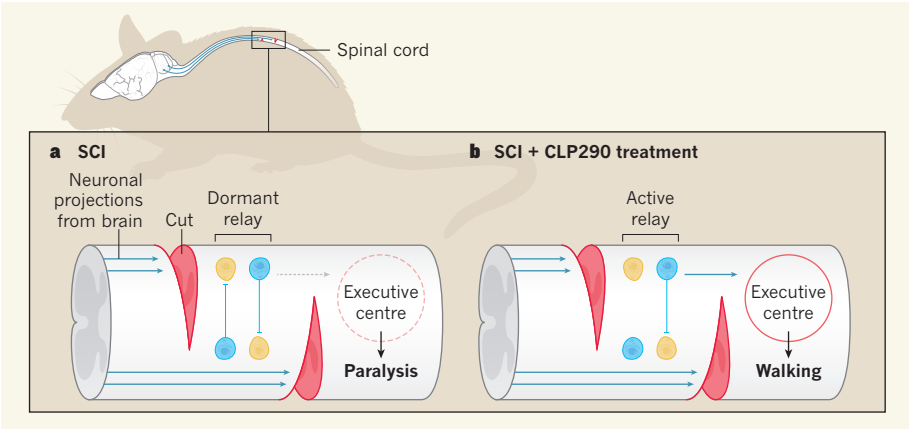

Figure 1 | Restoring balance in neuronal relay circuits. a, In a staggered spinal-cord injury (SCI), two partial cuts in the spine completely interrupt direct neuronal projections from the brain to executive centres that produce locomotion. Excitatory neurons (yellow) and inhibitory neurons (blue) located between the injuries can form relay circuits that, when active, pass brain-derived brain commands past the SCI. But Chen *et al.*[3] show that, in mice with an SCI, excessive activity in inhibitory neurons increases inhibition of the circuits to a level that renders them dormant. Information is not passed to executive centres (indicated by dashed circle), and so the animals are paralysed. **b**, The authors find that treatment with a small molecule called CLP290 reduces the activity of the inhibitory neurons between the cuts. This restores the balance between excitation and inhibition, enabling relay circuits to pass information from the brain to executive centres and so leading to the recovery of basic locomotor movements such as walking.

anatomically intact but functionally dormant neuronal pathways from contributing to movement after an SCI.

What are the clinical implications of the findings? Chen *et al.* used a small molecule that is well tolerated in mice, even at a high concentration[6]. However, the relevance of this treatment for humans with severe SCI remains unclear. The authors' experimental model poorly mimics severe spinal-cord contusions commonly found in humans, in which nearly all the connections from putative relay neurons above the injured site are interrupted[9]. It therefore remains unclear whether Chen and colleagues' results could be reproduced after a clinically relevant SCI. Indeed, because CLP290 does not promote the growth of new neural connections, this treatment would be expected to be effective only after an SCI that spares a substantial proportion of nerve fibres. In addition, SCI causes a cascade of detrimental changes, so effective treatments must target multiple facets of spinal-cord repair and recovery[4], but CLP290 targets a single mechanism.

However, this type of orally administered pharmacological treatment is particularly attractive in combination with complementary strategies — notably, with interventions that promote the formation of relays in the spinal cord. For example, Chen and colleagues predict that CLP290 treatment will act synergistically with rehabilitative training, especially electrical spinal-cord stimulation, which promotes relay formation[6]. Alternatively, neural stem cells grafted into the injured spinal cord can enable reconstitution of relays across an SCI in monkeys[10]. Reducing neuron-mediated inhibition in the vicinity of the grafted relays could aid the functional integration of the relays into the host's neuronal networks.

We are reaching an exciting time in SCI medicine, when multiple interventions that have strong synergistic potential are approaching clinical applications. There are now realistic opportunities to develop treatments that improve recovery after SCI in humans. ■

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HIGH-ENERGY PHYSICS

Proton bunches rapidly accelerate electrons

Experiments show that short bunches of protons can produce electric fields that are strong enough to accelerate energetic electrons compactly. This discovery could lead to miniaturized high-energy particle accelerators. SEE LETTER P.363

TOSHIKI TAJIMA

For almost a century, particle accelerators have revealed the microscopic structure of the Universe in ever-increasing detail. This continual improvement has required progressively higher particle energies and, in turn, larger accelerators (the latest accelerator for such exploration[1] has a circumference of 27 kilometres). In conventional accelerators, particles are propelled by electromagnetic waves that are produced by external circuits. To drastically reduce the size of accelerators, scientists are exploring ways to use waves that are instead generated internally, in an ionized gas known as a plasma[2]. On page 363, Adli *et al.*[3] report such a method, which makes use of an experiment in which the plasma waves are driven by bunches of protons — much like a motorboat on a lake drives waves in its wake.

The authors demonstrated their method using the Advanced Wakefield (AWAKE) experiment[4], which is located at CERN, Europe's particle-physics laboratory near Geneva, Switzerland. In this experiment, a proton bunch is injected into a plasma and sets electrons bobbing in its wake (Fig. 1). This electron motion generates a spatial modulation in the electric-charge density of the plasma, which in turn produces an electric field known as a wakefield. If another electron is injected into the plasma a short distance behind the proton bunch, it is captured by the wakefield and is accelerated to high energies.

Because the proton bunch moves at close to the speed of light, the wakefield can be extremely strong. It can even be at the level of the Tajima–Dawson field[2], the amplitude of which is several orders of magnitude larger than that of the fields used in conventional accelerators. This is the reason that scientists see wakefield acceleration as a means of substantially miniaturizing particle accelerators.

The amplitude of a proton-driven wakefield can be so large only when the proton bunch and the plasma's internal clock (in this case, the oscillation period of the plasma waves) are in resonance — a condition that enhances the amplitude of the waves, akin to pushing a child on a swing synchronously with the swing's oscillation period. This condition is met when the length of the proton bunch matches the wavelength of the plasma waves. The plasma's ability to sustain strong fields increases when the plasma density is increased, which decreases the wavelength

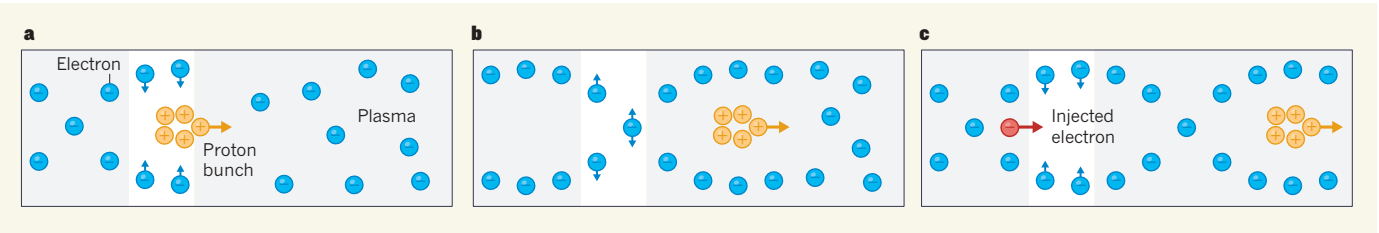

Figure 1 | The AWAKE experiment. **a**, In the Advanced Wakefield (AWAKE) experiment[4], a bunch of protons is injected into an ionized gas known as a plasma. As the proton bunch travels through the plasma, it attracts electrons contained in the plasma, pulling them towards the centre. **b**, By the time these electrons have reached the centre, the proton bunch has moved on. The electrons overshoot and begin to move outwards. **c**, The region that the electrons vacated is now positively charged. The electrons start to move inwards again, and the cycle repeats. Adli *et al.*[3] show that if an electron is injected into the plasma a short distance behind the proton bunch, this cycling of positive and negative charge can rapidly accelerate the injected electron.