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PAIN

Transplanted precursors halt neuropathic pain

Neuropathic pain symptoms include persistent hypersensitivity to both noxious stimuli (hyperalgesia) and non-noxious stimuli (allodynia) and are thought to result, in part, from reduced activity in the spinal inhibitory circuits that modulate incoming sensory information. Boosting the activity of these inhibitory pathways by pharmacological means has achieved some success in reducing pain symptoms but is limited by adverse side effects. Bráz *et al.* now report an alternative approach that involves transplanting immature inhibitory neuron precursors into the spinal cord; this technique enhances function in spinal inhibitory circuits and is effective in a mouse model of neuropathic pain.

GABAergic cortical interneuron precursors derived from the embryonic medial ganglionic eminence (MGE) can survive and functionally integrate into host neuronal circuits when transplanted into the adult mouse forebrain. To determine whether these cells can integrate into spinal cord circuits in a similar manner, the authors transplanted MGE cells in which GABA-expressing cells were labelled with green fluorescent protein (GFP) into the dorsal horn of the lumbar spinal cord of adult mice.

One month after transplantation, GFP-positive (MGE-derived) cells were distributed throughout the dorsal horn of the lumbar spinal cord. Most of the cells had differentiated into neurons that expressed a range of markers of cortical interneurons. Similar results were found when the cells were transplanted into the spinal cord of animals in which partial nerve injury (known as spared nerve injury (SNI)) was carried out, although the survival rate of the grafts was lower in these animals. These findings indicated that the transplanted cells could survive and differentiate in the non-native environment of the spinal cord.

Next, the authors asked whether MGE cells integrate with the existing neuronal sensory circuits. They transplanted MGE cells into mice that express a transneuronal tracer (wheat germ agglutinin (WGA)) in the dorsal root ganglion (DRG) neurons that provide sensory input to the spinal cord. One month later, the presence of WGA in MGE-derived cells indicated that the transplanted cells were receiving presynaptic inputs from DRG neurons. The inputs appeared to be functional: expression of FOS (a marker of neuronal activity) was induced in MGE-derived cells by non-noxious and noxious stimuli.

The authors also examined the connections made by MGE-derived cells. They transplanted MGE cells that were engineered to express WGA and found that many postsynaptic spinal neurons took up the marker. Furthermore, they injected a pseudorabies virus, which is transported in a retrograde manner across synapses, into a brainstem target of spinal cord projection neurons and later detected the virus in MGE-derived cells, suggesting that the transplanted cells had become part of the host spinal circuits.

To determine whether the transplants could modify symptoms of neuropathic pain, the authors transplanted MGE cells into the spinal cord of mice that underwent SNI 1 week previously. Within a month of the transplant, the authors observed an attenuation of the reduction in GABA signalling that was present in control injured mice (indicated by reduced levels of GABA-synthesizing enzymes) and a complete reversal of the mechanical allodynia.

These findings suggest an alternative approach to the treatment of neuropathic pain that could have several advantages over a pharmacological strategy. In addition, by altering the spinal circuits thought to be damaged in neuropathic pain, such a transplantation approach might modify the course of the disease.

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ORIGINAL RESEARCH PAPER Bráz, J. M. *et al.* Forebrain GABAergic neuron precursors integrate into adult spinal cord and reduce injury-induced neuropathic pain. *Neuron* **74**, 663–675 (2012)

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