

## NCAM as a Target for GDNF-induced Analgesia in Neuropathic Pain

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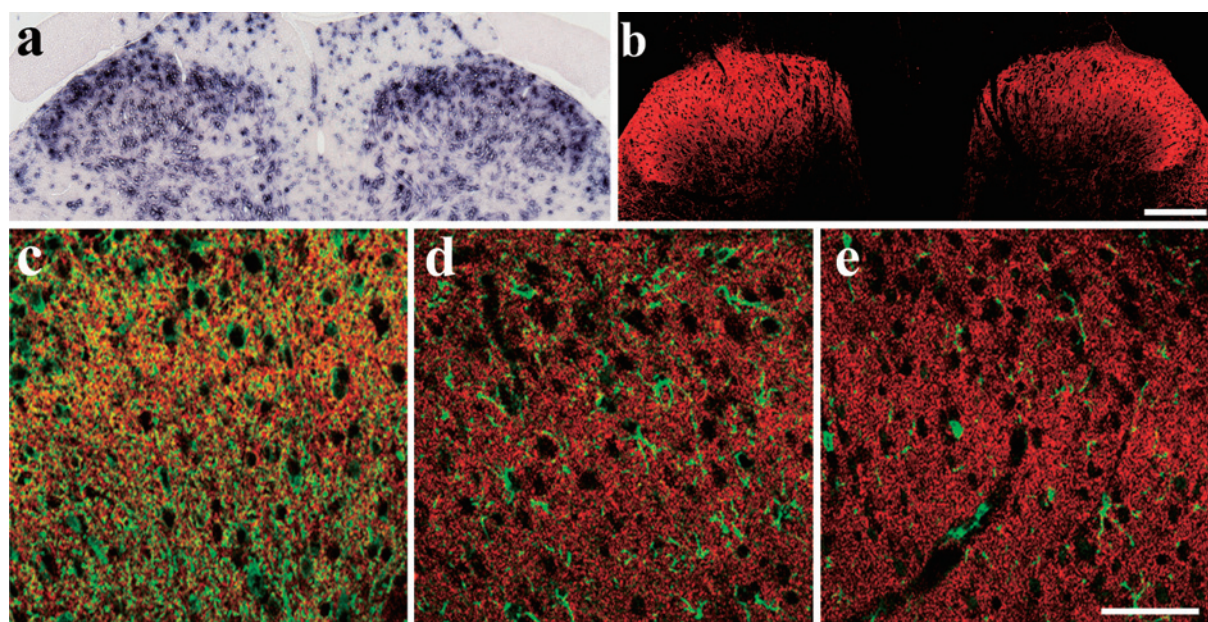


Fig. 1

Glial cell line-derived neurotrophic factor (GDNF) has been shown to exhibit analgesic effects on neuropathic pain, a chronic maladaptive pain syndrome typically caused by damage to the nervous system, although the underlying mechanisms of GDNF-induced analgesia are still largely unknown. We found that neural cell adhesion molecule (NCAM), one of signaling receptors for GDNF, plays a critical role in the analgesic effect of GDNF. Both NCAM messenger RNA and protein are densely expressed in the superficial dorsal horn (**Fig. 1a and 1b**). Immunohistochemical studies show that NCAM is expressed mostly in intrinsic spinal neurons, but not in glial cells, in the dorsal spinal cord (**Fig. 1c–e**). In addition, NCAM is also found in IB4-positive central axon terminals of a subpopulation of small dorsal root ganglion neurons (**Fig. 2a**), which depend on GDNF for their survival *in vitro* and transmit nociceptive information to the spinal secondary neurons. Consistently, *in situ* hybridization reveals that NCAM messenger RNA is expressed in small neurons of the dorsal root ganglion (**Fig. 2b**). When NCAM expression is decreased with an NCAM antisense oligodeoxynucleotide, the analgesic effect of GDNF is abolished (**Fig. 3**). Furthermore, an NCAM-mimetic peptide, C3d, alleviates the neuropathic pain (**Fig. 3**). Therefore, the development of new drugs activating GDNF-NCAM signaling may represent a new strategy for the relief of neuropathic pain.

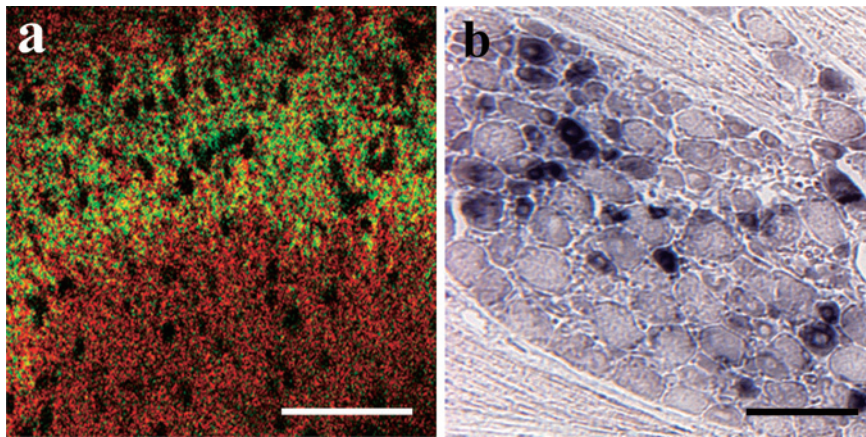


Fig. 2

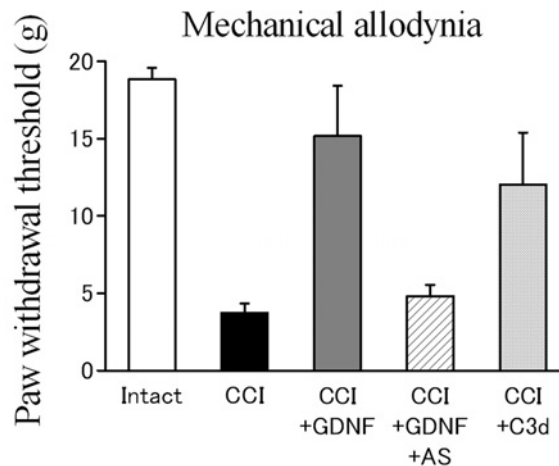


Fig. 3

- Fig. 1** In situ hybridization (a) and immunohistochemistry (b) for NCAM in the fourth lumbar (L4) dorsal spinal cord of the rat. Scale bar, 200  $\mu$ m. Confocal images of double-labeling immunohistochemistry for NCAM (red) and MAP2 (c; a neuronal marker; green), glial fibrillary acid protein (d; an astrocyte marker; green), or Iba1 (e; a microglial marker; green) in the superficial L4 dorsal horn of the rat. Scale bar, 50  $\mu$ m.
- Fig. 2** (a) A confocal image of NCAM immunoreactivity (red) and IB4 binding (green) in the superficial L4 dorsal horn of the rat. Scale bar, 50  $\mu$ m. (b) In situ hybridization for NCAM in the L4 DRG of the rat. Scale bar, 100  $\mu$ m.
- Fig. 3** Effects of GDNF and an NCAM antisense oligodeoxynucleotide or an NCAM-mimetic peptide, C3d, on mechanical allodynia, a characteristic response to neuropathic pain, induced by chronic constriction injury of the rat sciatic nerve. The paw-withdrawal threshold represents the weakest force (g) inducing withdrawal of the hindlimb paw from mechanical stimuli.