—Photogravure—

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

Atsushi Sakai and Hidenori Suzuki
Department of Pharmacology, Nippon Medical School

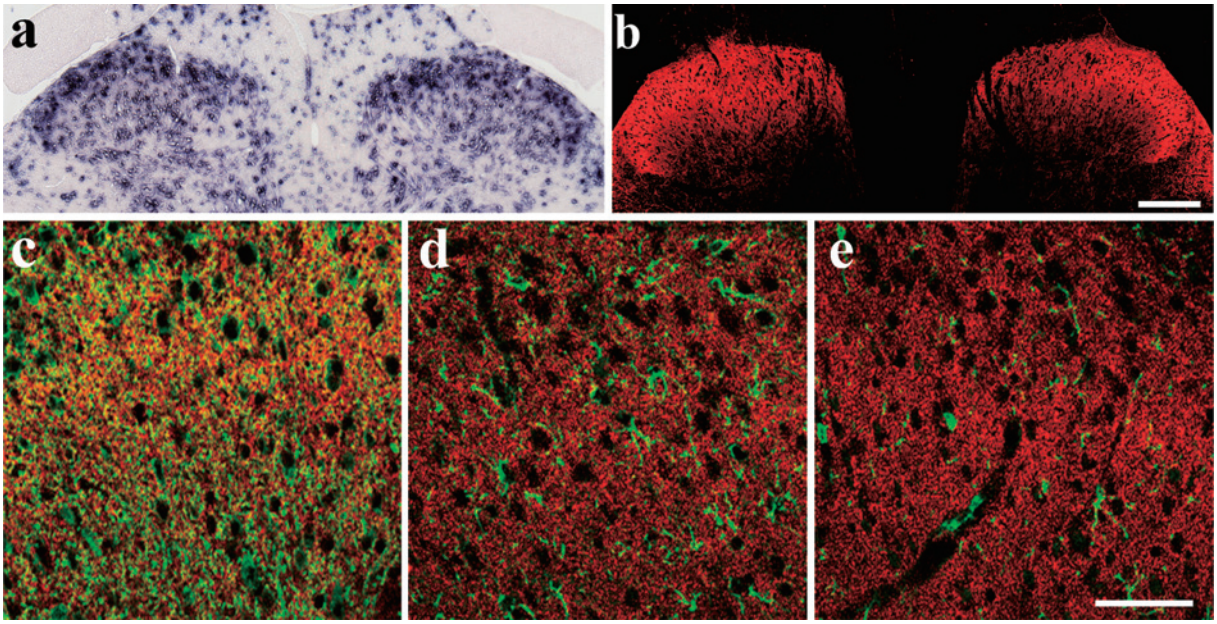

Fig. 1

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.

Correspondence to Atsushi Sakai, Department of Pharmacology, Nippon Medical School, 1–1–5 Sendagi, Bunkyo-ku, Tokyo 113–8602, Japan

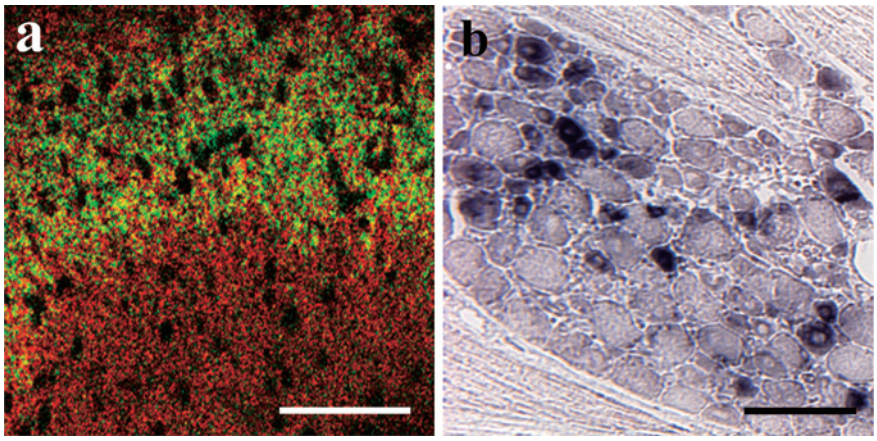

Fig. 2

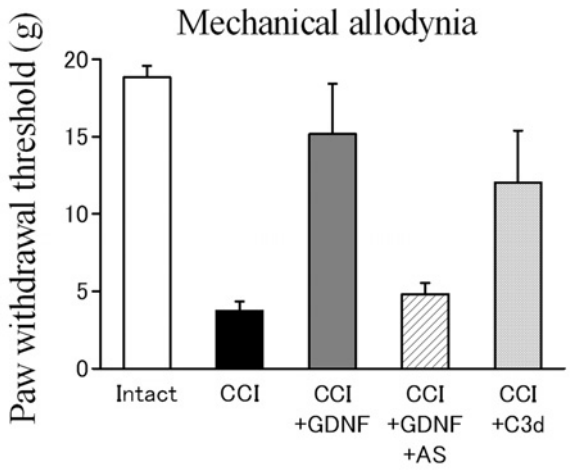

Fig. 3

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 μm. 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 μm.

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 μm. (b) In situ hybridization for NCAM in the L4 DRG of the rat. Scale bar, 100 μm.

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.

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