The NOS inhibitors such as nitroarginine or Nw-nitro-L-arginine methyl ester (L-NAME) have been shown to prevent the induction of NOS activity and the subsequent motoneuron death after avulsion.[50,51] Taken together, these results indicate the neuroprotective effects of AxCAhGDNF, AxCAmBDNFME, AxCAmTGFβ2, and AxCArGIFM on the injury and death of adult facial motoneurons. In contrast, the treatment with AxCANrCNTF, AxCANrCT1 and AxCAhIGF1 failed to prevent the loss of facial motoneurons after avulsion; neither improvement of ChAT immunoreactivity nor suppression of NOS activity was observed. Additionally, we also examined pairwise combinations of these adenoviral vectors and demonstrated additive neurotrophic effects of AxCAhGDNF and AxCAmBDNFME on injured motoneurons after avulsion (Fig. 6). Such combined effects of GDNF and BDNF have been demonstrated in vitro using fetal rat motoneurons.[52]

Neuroprotective activity of GIF (MT-III)

Among these neuroprotective factors that rescued injured motoneurons in our avulsion experiments, GIF (MT-III) is a unique molecule whose expression is reduced in Alzheimer's disease brains. GIF, a CNS-specific member of MT family, is a 68 amino acid small, cysteine-rich protein that binds zinc and copper with high affinity.[53] GIF exhibits protective effects against glutamate-, nitric oxide-, and b amyloid-induced neurotoxicity.[54,55] GIF acts as a hydroxy radical scavenger and inhibits tyrosine nitration by peroxynitrite.[56] The formation of hydroxy radical-modified DNA and RNA as well as peroxynitrite-modified proteins have been demonstrated in injured motoneurons after avulsion.[13] Our results therefore indicate that GIF may protect injured motoneurons from oxidative stress by hydroxy radical and peroxynitrite.[10]

GIF mRNA is down-regulated in postmortem spinal cord tissues of human sporadic ALS,[57] whereas up-regulated in the spinal cord of human mutant SOD1-tg mice (G93A mice) as the animals age and develop weakness.[58,59] G93A mice deficient of GIF exhibit reduced survival and accelerated motoneuron death compared with G93A mice with normal GIF expression.[60] These reports suggest that GIF may have protective roles against motoneuron degeneration in ALS. In addition, zinc is important in maintaining the SOD1 structure, and some variants of mutant SOD1 in vitro exhibit markedly reduced affinity for zinc and enhanced nitration activity by peroxynitrite.[61] The induction of either wild type or mutant SOD1, depleted of zinc, into cultured motoneurons is found to provoke nitric oxide-dependent neuronal death that is accompanied by elevated level of nitrotyrosine.[1,62] Since GIF is an important regulator of zinc in CNS and has a scavenging effect for peroxynitrite,[56] GIF may protect motoneurons in patients with ALS by modulating zinc and/or preventing tyrosine nitration by peroxynitrite. It is therefore conceivable that GIF may prevent the degeneration of motoneurons in patients with motoneuron injury and motor neuron diseases such as ALS.[10]

ORAL ADMINISTRATION OF T-588

R(-)-1-(benzo[b]thiophen-5-yl)-2-[2-(N,N-diethylamino)ethoxy]ethanol hydrochloride (T-588) has been developed as a candidate for a neuroprotective agent against neurodegenerative diseases. This low molecular weight (330 Dalton) compound is a synthetic derivative of acetylcholine.[63] Orally administered T-588 is efficiently transported into the central nervous system.[64] It has been demonstrated that T-588 promotes neurite outgrowth of cultured spinal ventral horn cells[65] and delays the progression of motor deficits in the wobbler mouse.[64] We investigated whether oral administration of T-588 can protect injured motoneurons after facial nerve avulsion in adult rats.[11]

After avulsion of the right facial nerve, the animals were freely administered solution of 0.05% (w/v) T-588 or received T-588 (3-30 mg/kg/day) through an oral tube for 1-4 weeks. The loss of injured motoneurons was significantly prevented in rats freely administered 0.05 % T-588 solution (62.7 ± 5.3 %, n=8 and 50.1 ± 4.8 %, n=11 at 3 and 4 weeks postoperation, respectively) in comparison with vehicle-treated animals (42.4 ± 6.4 %, n=8 and 31.2 ± 6.4 %, n=10 at 3 and 4 weeks postoperation, respectively). In separate experiments, the loss of injured motoneurons was also significantly prevented by oral tube administration of 30 mg/kg/day T-588 (52.4 ± 8.0 %, n=10) as compared to vehicle (34.8 ± 13.8 %, n=8) at 4 weeks after avulsion. T-588 treatments also ameliorated ChAT immunoreactivity in injured motoneurons and the tissue ChAT enzyme activities at 1-week postoperation examined. These results indicate that oral administration of T-588 ameliorates the survival of injured motoneurons and supports their neuronal function after facial nerve avulsion in adult rats. It has been shown that T-588 activates mitogen-activated protein (MAP)/extracellular signal-regulated kinase (ERK) pathway in cultured rat newborn astrocytes and inhibits astrocyte apoptosis induced by Ca^{2+} stress.[66] T-588 may therefore modify MAP/ERK pathway in injured motoneurons and surrounding glial cells after facial nerve avulsion. Our results indicate that T-588 may be a promising therapeutic agent for motoneuron injury and motor neuron diseases in humans.

CONCLUSION

Using peripheral nerve avulsion models, we have identified neuroprotective activities of GDNF, BDNF, TGFβ2, GIF, and T-588 against degeneration of adult motoneurons. These factors may prevent the degeneration of motoneurons in adult humans with motoneuron injury and motor neuron diseases. Further investigations are required to elucidate pathomechanisms of motoneuron degeneration after peripheral nerve avulsion that may help understand pathogenesis of ALS in humans.

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LEGENDS FOR FIGURES

Fig. 1 Facial nerve avulsion of adult rat. (**a-d**) Avulsion surgery. The right facial nerve (VII) is exposed at its exit from the stylomastoid foramen (**a**). The distal portion of the facial nerve is cut (**b**), and the proximal facial nerve is avulsed by gentle traction using microhemostat forceps (**c**). An arrow in (**d**) indicates stylomastoid foramen after avulsion. Bars = 1 mm. (**e**) Perfusion-fixed brain tissue 4 weeks after avulsion showing the absence of extra-axial portion of facial nerve on the lesioned side (arrow). Bar = 2 mm. (**f-g**) Photomicrographs of facial motoneurons at the contralateral (**f, h**) and ipsilateral (**g, i**) side 4 weeks after the right facial nerve avulsion stained with HE (**f, g**) and immunolabeled with GFAP (**h, i**). Bars = 100 mm. Note the loss of motoneurons with gliosis on the lesioned side.

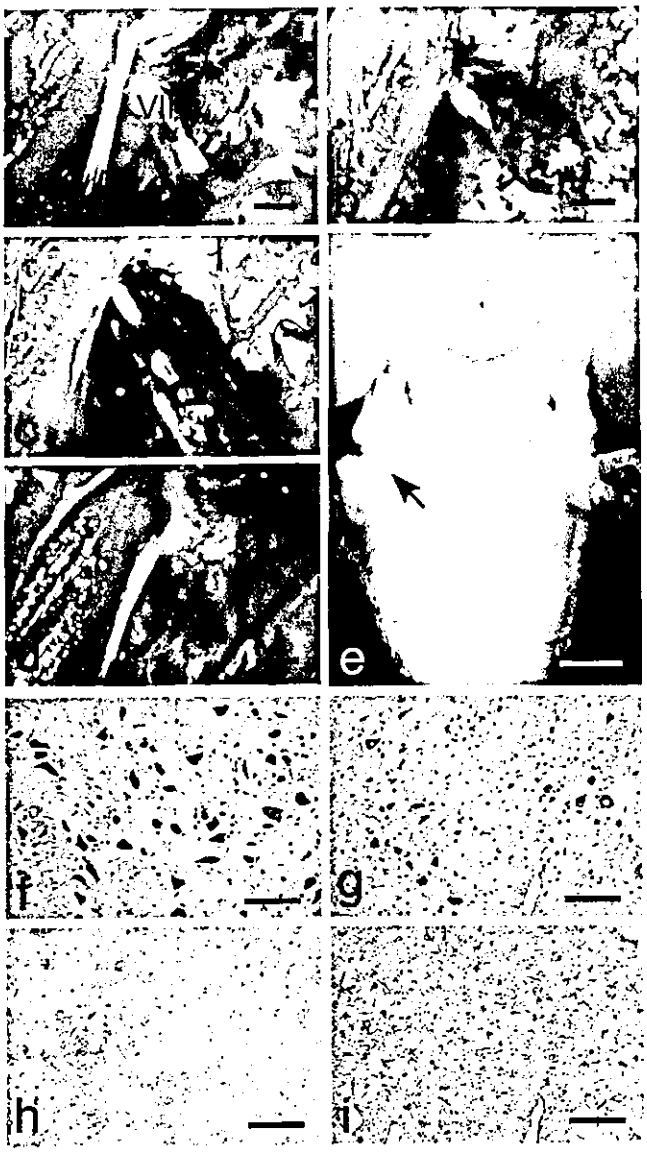
Fig. 2 Spinal root avulsion of adult rat. (**a-d**) Avulsion surgery. The right sixth (C6) and seventh (C7) cervical segment nerves are identified underneath the ventral plate (vent.pl.) (**a**). The C7 distal portion is cut, lifted upon the phrenic nerve (ph.n.) (**b**), and the C7 nerve is exposed until the point where the vertebral foramen was identified. Using microhemostat forceps, the C7 ventral and dorsal roots and dorsal root ganglia (DRG) were avulsed and removed (**c**). An arrow in (**d**) indicates C7 intervertebral foramen after avulsion. Bars = 1 mm. (**e, f**) Perfusion-fixed spinal cord tissue 6 weeks after avulsion showing the absence of C7 ventral (**e**) and dorsal (**f**) roots and DRG on the lesioned side (arrows). Bars = 2 mm. (**g, h**) Photomicrographs of spinal cord 6 weeks after C7 root avulsion stained with KB (**g**) and immunolabeled with GFAP (**h**). Bars = 200 mm. Note the atrophy of C7 ventral horn with loss of motoneurons and gliosis on the lesioned (right) side.

Fig. 3 Photomicrographs of Epon-embedded semithin sections of facial nucleus at the contralateral (**a**) and ipsilateral (**b-d**) side 1 (**b**), 2 (**c**), and 4 (**d**) weeks after avulsion. Shrunken motoneurons show dispersed Nissl substance, nuclear caps (arrows) and intracytoplasmic granules (arrowheads) but no morphological features of apoptosis after avulsion. Decreased numbers of neurites in neuropil and degradation of myelin are also noted. Toluidine Blue stain. Bars = 30 mm.

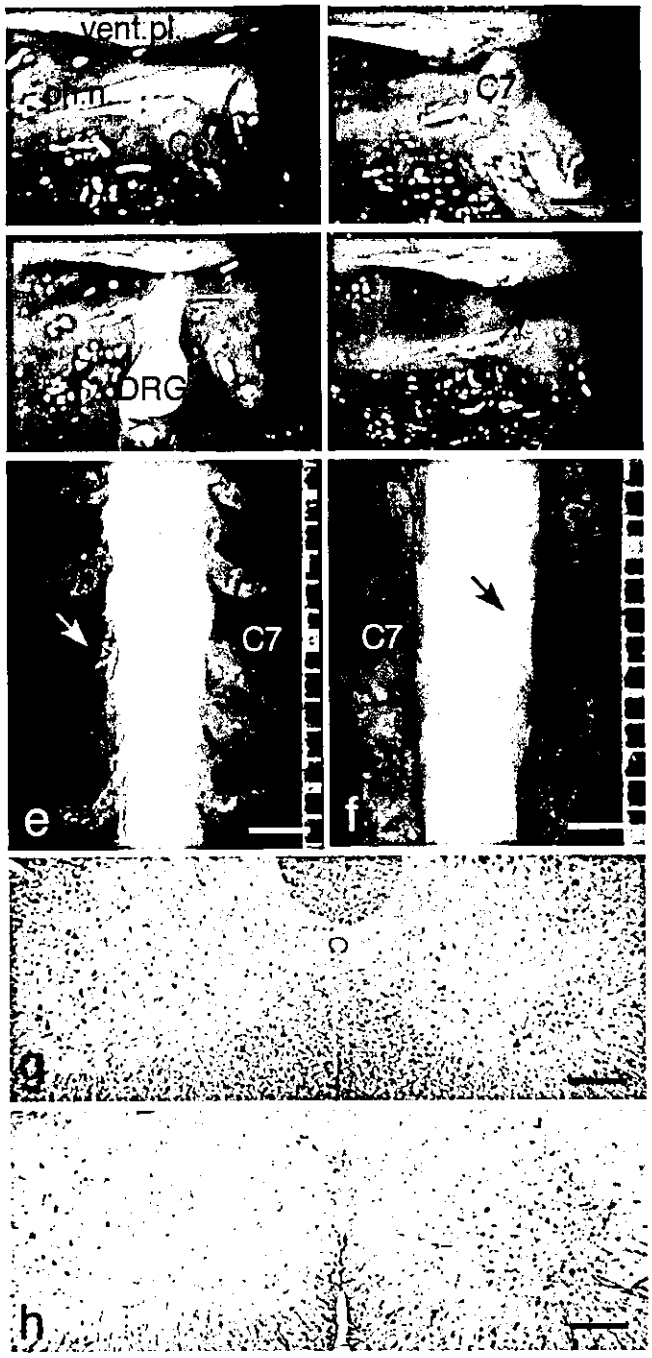
Fig. 4 The percentages of surviving facial motoneurons at the ipsilateral (lesion) side relative to the contralateral (control) side after facial nerve and seventh cervical (C7) root avulsion.

Fig. 5 Adenoviral vectors encoding human glial cell line-derived neurotrophic factor (AxCAhGDNF), mouse brain-derived neurotrophic factor (AxCAmBDNFME), rat ciliary neurotrophic factor (AxCANrCNTF), rat cardiotrophin-1 (AxCANrCT1), respectively), human insulin-like growth factor-1 (AxCAhIGF1), mouse transforming growth factor-b2 (AxCAmTGFb2), and rat growth inhibitory factor (AxCArGIFM).
mNGF-ss; mouse nerve growth factor (NGF) signal sequence.

Fig. 6 The percentages of surviving facial motoneurons at the ipsilateral (lesion) side relative to the contralateral (control) side after avulsion and treatment with PBS, AxCALacZ (white bars), AxCAhGDNF, AxCAmBDNFME, AxCANrCNTF, AxCANrCT1, AxCAhIGF1, AxCAmTGFb2, or AxCArGIFM (shaded bars) as well as pairwise combinations of these vectors (black bars). Results are presented as mean ± SD (PBS: n=8, others: n=4). Statistical comparison was done by Mann-Whitney U test. *$p<0.05$ vs. PBS-, AxCALacZ-, AxCANrCNTF-, AxCANrCT1- and AxCAhIGF1-treated groups; **$p<0.05$ vs. AxCAhGDNF- and AxCAmBDNFME-treated groups.



Watabe Fig 1.



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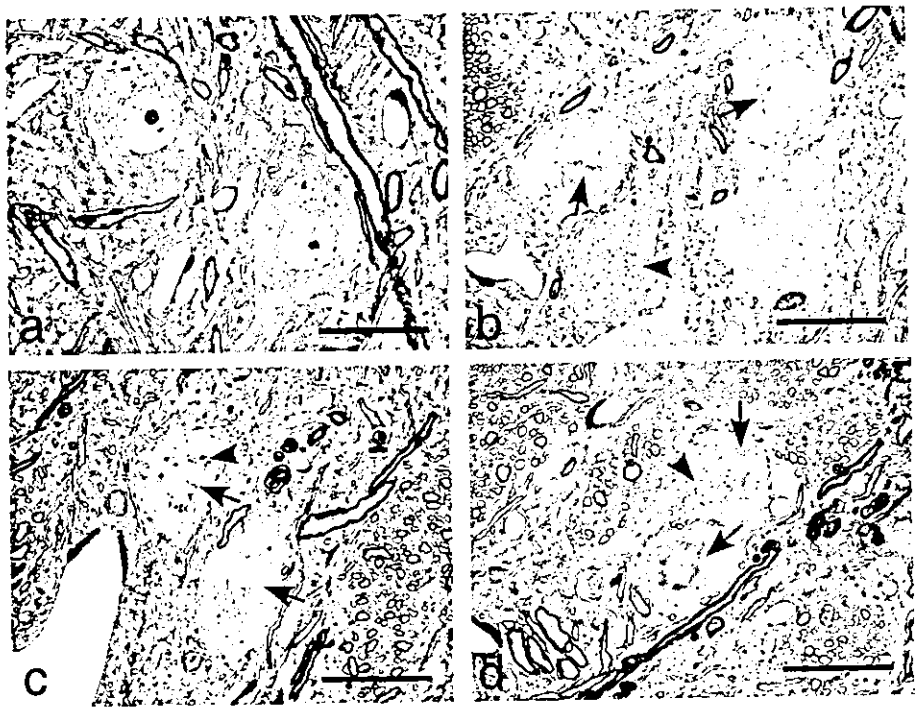

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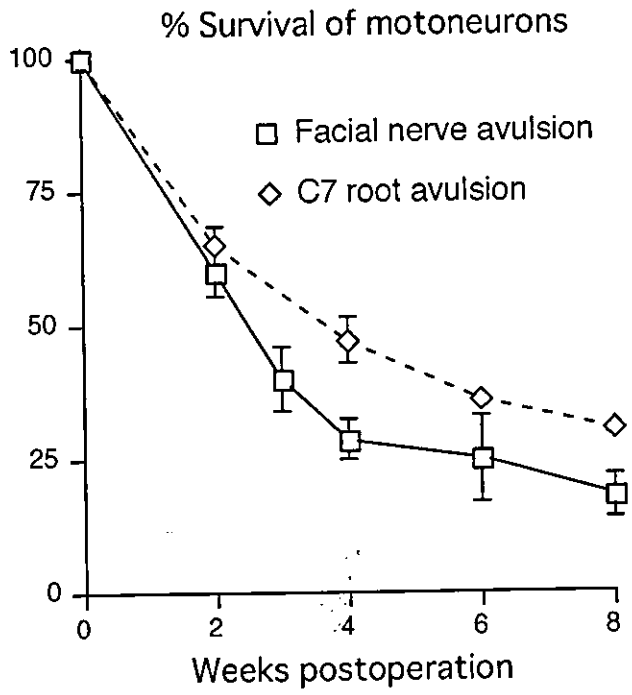

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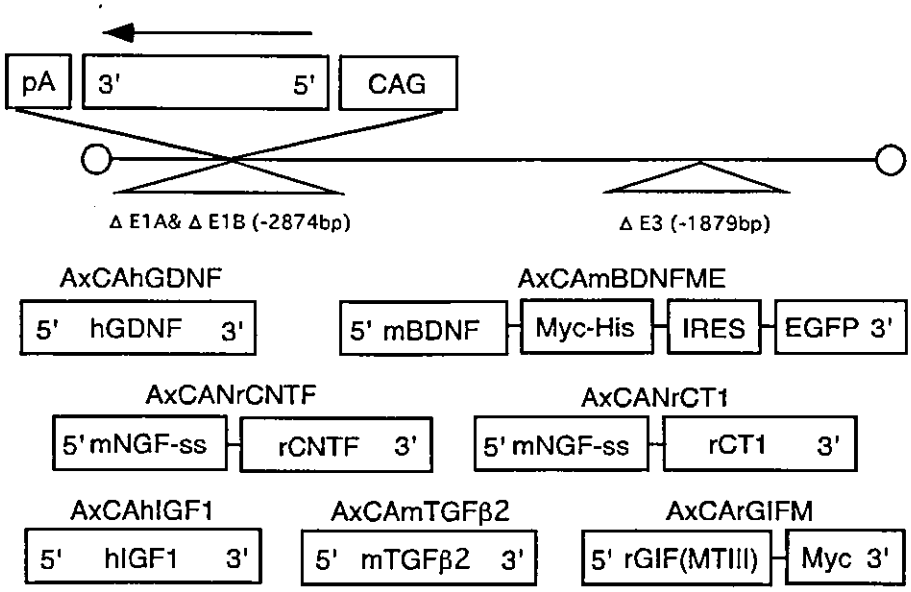

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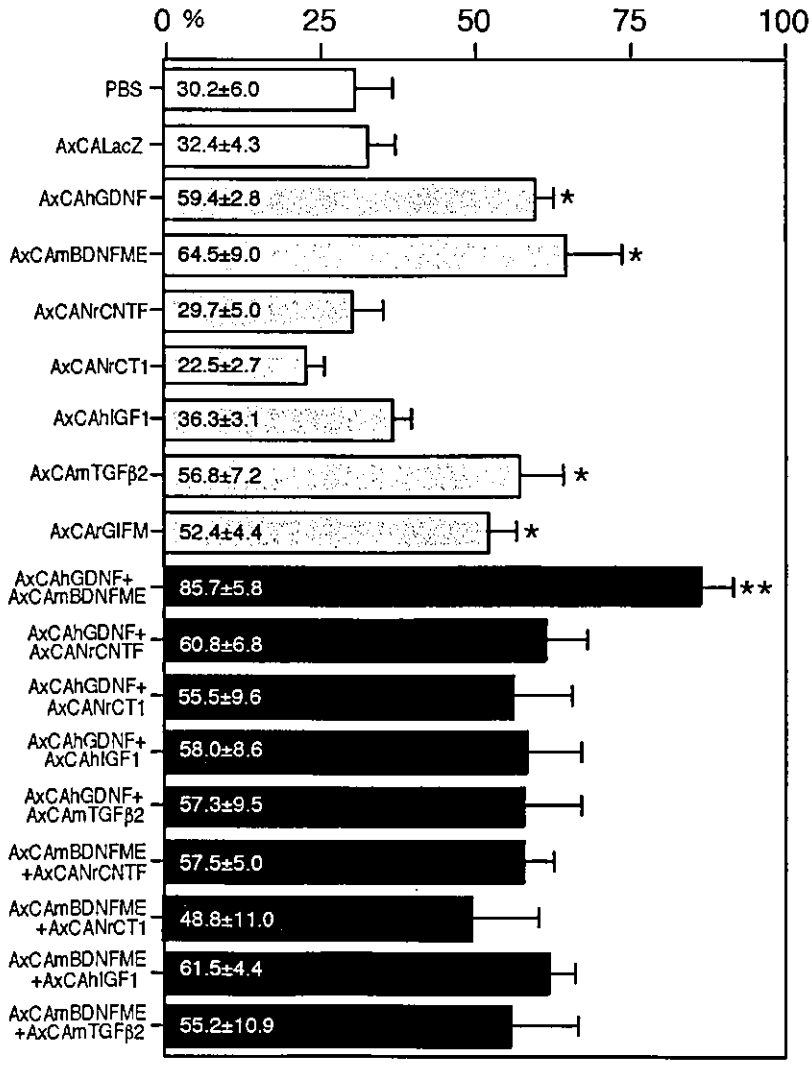

Watabe Fig 6.