

Topical Review

Neurotrophins and synaptic plasticity in the mammalian spinal cord

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The pathway mediating the monosynaptic stretch reflex has served as an important model system for studies of plasticity in the spinal cord. Its usefulness is extended by evidence that neurotrophins, particularly neurotrophin-3 (NT-3), which has been shown to promote spinal axon elongation, can modulate the efficacy of the muscle spindle–motoneurone connection both after peripheral nerve injury and during development. The findings summarized here emphasize the potential for neurotrophins to modify function of both damaged and undamaged neurones. It is important to recognize that these effects may be functionally detrimental as well as beneficial.

Neurotrophins (nerve growth factor (NGF), brain derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3) and neurotrophin 4/5 (NT-4/5)) constitute a family of molecules (Thoenen, 1991) that have assumed a central role in studies of recovery after spinal cord injury. This emerged from evaluation of their role during development where they act as differentiation and survival factors for sensory and motor neurones (reviewed in Mendell, 1995; McMahon *et al.* 1996). In adults they encourage growth of damaged central axons (Schnell *et al.* 1994; Xu *et al.* 1995; McTigue *et al.* 1998). Neurotrophins signal by binding to low and high affinity receptors in the membrane of their target cells. The low affinity p75 receptor binds all neurotrophins (reviewed in Bothwell, 1996). Neurotrophins also signal via three high affinity tyrosine kinase receptors, known as trk receptors, with affinities as follows: NGF: trkA; BDNF and NT-4/5: trkB; NT-3: trkC (Thoenen, 1991).

Neurotrophins can also exert physiological effects in postnatal animals. Some of these are potentially helpful, i.e. in enhancing synaptic efficacy (see below). However, they may also cause deleterious side effects. For example, NGF and BDNF have been reported to cause hyperalgesia and allodynia (Kerr *et al.* 1999; Mendell *et al.* 1999). Here we review some of the physiological effects of these agents that might support or mitigate against their use in promoting recovery of function. We concentrate on the monosynaptic excitatory postsynaptic potential (EPSP) elicited in motoneurones by spindle afferent (group Ia) fibres. This pathway has served as an important model system in investigations of both central synaptic

transmission and changes in synaptic function after spinal cord injury (Mendell, 1988).

Role of NT-3 in development of sensory receptors

The role of NT-3 as a survival factor for spindle afferent fibres during development has been documented by selective survival of labelled large diameter muscle sensory neurones in culture when NT-3 is provided (Hory-Lee *et al.* 1993), selective loss of muscle afferents projecting to the motoneurone pool after prenatal treatment with a NT-3 antibody (Oakley *et al.* 1995), failure of muscle afferents to survive in mice with null mutations of either NT-3 or trkC (Snider, 1994), and rescue of spindles in NT-3 knockout mice after introducing a NT-3 gene (Wright *et al.* 1997). Recent experiments have demonstrated that animals lacking NT-3/trkC signalling never develop proprioceptive afferent projections to muscle (Kucera *et al.* 1995) suggesting that NT-3 might affect differentiation as well as survival (Ockel *et al.* 1996).

NT-3 is expressed in muscle spindles in adults (Copray & Brouwer, 1994), which could make it available to spindle afferent fibres supplying them. There is now considerable evidence that exogenously administered NT-3 can influence the properties of group Ia fibres whose function is in flux during development or after injury.

NT-3 rescues spindle afferent function after axotomy

When a muscle nerve is cut, both the afferent fibres and the connections they make on intact motoneurones (i.e. heteronymous motoneurones) undergo substantial

decline in function (reviewed in Titmus & Faber, 1990). Axotomized afferent fibres have reduced conduction velocity (Collins *et al.* 1986; Munson *et al.* 1999) and gradually lose sensitivity to blunt probing and gentle stretching of the neuroma. They also lose their ability to respond with slowly adapting discharge to steady pressure (Munson *et al.* 1999). All these properties recover toward normal when the afferents reinnervate the muscle (Johnson *et al.* 1995), or even if they are misdirected into the skin by cross anastomosis (Johnson *et al.* 1995). Since the mRNA for NT-3 is expressed in both muscle and skin (Schechterson & Bothwell, 1992) and the afferent fibres express the *trkC* receptor (McMahon *et al.* 1994), NT-3 is a candidate to mediate this recovery. Consistent with this is that application of NT-3 at $60 \mu\text{g day}^{-1}$ to the central end of a cut peripheral muscle nerve via an osmotic minipump reverses both the conduction velocity decline and the elevation in mechanical threshold of these afferents in adult cats (Munson *et al.* 1999; Fig. 1). However, the requirement of NT-3 for afferent fibre function has not been confirmed by demonstrating loss of function of intact spindle afferents after neutralizing endogenous NT-3 (see 'NT-3 action on developing spindle afferent fibres').

Axotomized spindle afferent fibres elicit EPSPs of reduced amplitude in intact motoneurons (Goldring *et al.* 1980; Mendell *et al.* 1995, 1999). This decline is reversed if the afferent fibres regain peripheral connections either in

muscle or in skin (Mendell *et al.* 1995). NT-3 has been found to substitute for peripheral targets in re-establishing normal central projections (Munson *et al.* 1997a; Mendell *et al.* 1999). Surprisingly, not only was the decline in amplitude of composite EPSPs elicited by stimulation of the treated afferent fibres prevented, but also the EPSPs became substantially larger than normal (Fig. 1). This suggests that if NT-3 is normally involved in maintaining central projections, either it acts in concert with other factors or the dosage of NT-3 provided (duration and/or concentration) was inappropriate. Recovery of function requires continuous infusion of NT-3 since removal of the pump after 5 weeks causes both EPSP amplitude and axonal conduction velocity to decline to values characteristic of long term axotomy 3–22 days later (Mendell *et al.* 1999).

Individual axotomized afferent fibres treated with NT-3 elicit EPSPs in a larger fraction of the heteronymous motoneurone pool than do intact afferents (Mendell *et al.* 1999). This increased functional connectivity of Ia fibres is consistent with a recent hypothesis advanced by Chen & Frank (1999) who suggested that release of NT-3 from the motoneurone might provide a 'stop and arborize' signal to Ia afferents. This was proposed in the context of development where Ia axons are growing into the spinal cord to synapse on motoneurons. In adult animals one can speculate that peripherally supplied NT-3 acts in a similar manner after transport to the cell body, although

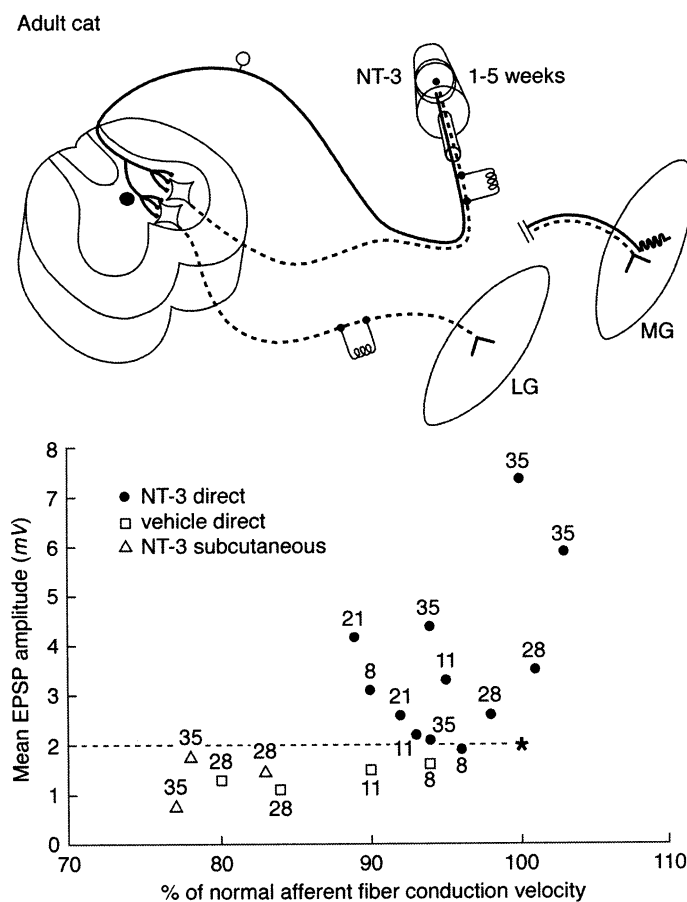


Figure 1. Effects of NT-3 on conduction velocity of and EPSP amplitude elicited by axotomized group Ia afferent fibres

Top panel, schematic diagram of experiments carried out in adult cats. Osmotic minipump containing NT-3 placed on axotomized medial gastrocnemius (MG) nerve affected axotomized MG sensory and motor axons. Response to stimulation of axotomized, treated MG afferents was examined in intact lateral gastrocnemius–soleus (LGS) motoneurons. Response of axotomized MG motoneurons to intact LGS afferents also measured. Bottom panel, treated afferents; intact motoneurons. Each symbol represents mean EPSP amplitude (ordinate) and afferent conduction velocity of large muscle afferent fibres (as % of value in intact nerve) from a single experiment. Numbers represent days after axotomy. In controls (open symbols: vehicle applied to nerve or neurotrophin administered systemically) conduction velocity and EPSP amplitude fell gradually after axotomy. After NT-3 (filled symbols), EPSP amplitude increased and conduction velocity recovered to 100% after initial decline. * Mean values in unoperated cats. Dashed line indicates mean value of EPSP amplitude in intact cats. Data from Mendell *et al.* (1999).

there is probably little axonal elongation occurring in the spinal cord at that time.

Further evidence for the ability of NT-3 to restore the properties of damaged Ia afferents comes from models of large fibre neuropathy induced by cisplatin (Gao *et al.* 1995) or by pyridoxine (Helgren *et al.* 1997). These studies provide evidence that the proprioceptive loss resulting from these treatments can be reversed as measured behaviourally in tasks such as accuracy in walking on a narrow beam, electrophysiologically using H-reflexes and conduction velocity of group Ia afferent fibres, and anatomically by measuring the calibre of large diameter axons in the peripheral nerve and the dorsal columns.

The effects of neurotrophins are very specific in the adult cat. In the same preparations in which NT-3 elicited substantial effects on Ia afferent fibres and their projections to motoneurons, there was no change in the synaptic inputs to or the properties of motoneurons projecting in the same muscle nerve (but see Gonzalez & Collins, 1997; Munson *et al.* 1997*b*). Furthermore, another neurotrophin, NT-4/5, applied in the same way as NT-3, had virtually no effect on group Ia afferent fibres and their central projections.

NT-3 action on developing spindle afferent fibres

Similar electrophysiological analysis has been carried out in the neonatal rat spinal cord where the monosynaptic

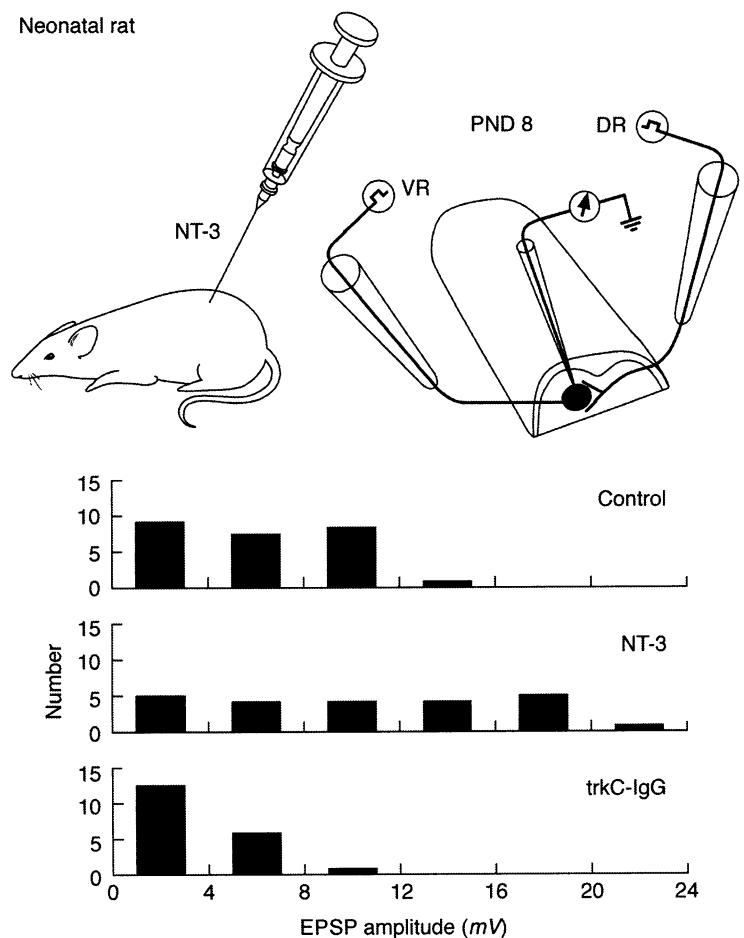
projection from sensory fibres (presumably muscle spindle afferents) is still developing (Seebach & Mendell, 1996). NT-3 was administered systemically on postnatal days 0, 2, 4 and 6, and the monosynaptic EPSP elicited by dorsal root (DR) stimulation was measured 1–3 days later in motoneurons (Fig. 2). EPSP amplitude was larger than in control animals (Seebach *et al.* 1999). When the fusion molecule *trkC*-IgG, which depletes endogenous NT-3 (Shelton *et al.* 1995), was administered according to the same schedule as NT-3, the amplitude of the monosynaptic EPSP was reduced below values in control preparation (Fig. 2). Thus NT-3 is required for normal development of the monosynaptic EPSP. In contrast to NT-3, exogenous BDNF reduced the amplitude of the monosynaptic EPSP whereas depletion of endogenous BDNF with *trkB*-IgG enhanced it. This is in line with recent findings of the direct inhibitory effects of BDNF on the response of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Balkowiec *et al.* 2000) although presynaptic actions of BDNF cannot be discounted (V. L. Arvanov & L. M. Mendell, unpublished observations).

Direct effects of NT-3 in the spinal cord

In studies of NT-3 on axotomized afferents in adult cats its site of action is likely to be the afferent fibres themselves since treatment with NT-3 was effective when delivered directly to the cut end of the peripheral

Figure 2. Systemic administration of NT-3 or *trkC*-IgG during the first postnatal week in rats alters the amplitude of the monosynaptic EPSP

Top panel, neonatal rats treated systemically with NT-3 on postnatal days 0, 2, 4 and 6. On postnatal day 8 the hemisected spinal cord was studied *in vitro*. Bottom panel, EPSP amplitude distribution in controls, NT-3-treated animals and *trkC*-IgG-treated animals. Further details in text. Data from Seebach *et al.* (1999).



nerve, but not when delivered systemically (Mendell *et al.* 1999). In the neonatal rat the situation is less clear since the NT-3 was delivered systemically in very small rats (2–15 g) and the blood–brain barrier is established only at postnatal day 14 (Tonra & Mendell, 1997). Thus NT-3 might be acting directly on spinal cord neurones as in the hippocampus (e.g. Kang & Schuman, 1995).

Application of NT-3 to fluid superfusing the isolated hemisectioned spinal cord from neonatal (0–1 week) rats increases the amplitude of the DR-evoked monosynaptic AMPA/kainate receptor-mediated EPSP within minutes (Arvanov *et al.* 2000). This increase lasts for at least several hours beyond washout of NT-3. The NT-3-induced increase requires the presence of active *N*-methyl-D-aspartate (NMDA) receptors since it is blocked by the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (APV). The crucial NMDA receptors are in the motoneurone membrane since

potentiation is abolished if the NMDA channel blocker MK-801 is infused into the motoneurone via the microelectrode. NT-3 also enhances the response of neonatal motoneurons to bath-applied NMDA in the presence of tetrodotoxin to eliminate indirect synaptic responses (Arvanov *et al.* 2000), indicating that NT-3 directly potentiates the response of NMDA receptors. Several potential mechanisms exist for interaction of NT-3 and NMDA receptors: via the glycine site of the NMDA receptor (Jarvis *et al.* 1997) or at the level of second messengers (Suen *et al.* 1997).

Other evidence implicating NMDA receptors in mediating the effects of NT-3 comes from the specificity of its action as a function of synaptic input and of age (Arvanian & Mendell, 2001). The same motoneurons whose DR-evoked EPSPs are enhanced by NT-3 also respond with monosynaptic AMPA/kainate receptor-mediated EPSPs to stimulation of descending fibres in the ventrolateral fasciculus (VLF) (Pinco & Lev Tov, 1994). However, these EPSPs are not potentiated by NT-3, nor are those elicited by DR or VLF stimulation in animals older than 1 week. The difference between EPSPs that are and are not potentiated by NT-3 is that the former are also associated with synaptic NMDA receptor-mediated responses whereas the latter are not (Arvanov *et al.* 2000; Arvanian & Mendell, 2001). Preliminary data indicate that removal of Mg^{2+} from the bathing solution strongly enhances NMDA receptor-mediated responses by removing the Mg^{2+} block of the NMDA receptor (Ault *et al.* 1980). In parallel, AMPA/kainate receptor-mediated responses become more susceptible to acute enhancement by NT-3 (Arvanian & Mendell, 2001).

Discussion

From the effects of NT-3 on damaged Ia axons in the adult cat, it might be anticipated that intrathecal NT-3 could enhance axonal growth and sprouting of sensory fibres (Ramer *et al.* 2000). Axotomized afferents can thus provide a valuable model for studying the effects of neurotrophins on damaged spinal neurones. Although NT-3 is required continuously to maintain the recovery of the Ia fibres (see above), its necessity for maintenance of intact axons is not known. Thus it is not clear whether the effect of NT-3 on axotomized afferents is an exaggeration of a normal trophic action or whether it represents revival of a mechanism operating during development. This distinction is important both in terms of understanding the underlying mechanisms as well as in predicting whether undamaged axons would also be influenced by exogenously administered neurotrophins. For example, if NT-3 affects undamaged spindle afferents when administered exogenously in the spinal cord to encourage elongation of spinal axons, it might strengthen the stretch reflex pathway. This could exacerbate spasticity, a serious problem experienced by spinal injured patients.

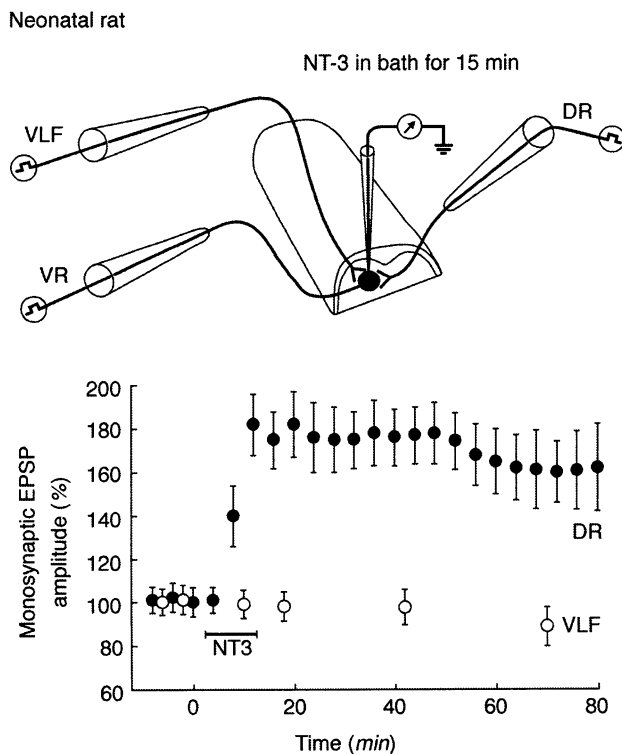


Figure 3. Synapse-selective effect of acutely administered NT-3 on amplitude of EPSPs produced in motoneurons

Top panel, electrode arrangement for study of acute effects of NT-3 *in vitro*. Bottom panel, mean change in amplitude of EPSPs elicited in same motoneurone (identified by antidromic response from ventral root (VR)) by DR and VLF stimulation after NT-3 superfusion ($n = 5$). Note change in DR-evoked EPSP and lack of change of VLF-evoked EPSP. Data from Arvanov *et al.* (2000).

The acute effect of NT-3 on the monosynaptic EPSP via NMDA receptors may represent a mechanism whereby NT-3 plays a role in activity-driven plasticity considered to be important in the development of neuronal connections (e.g. Carmignoto & Vicini, 1992; Hestrin, 1992). The reduced EPSP size after neutralization of endogenous NT-3 by trkC-IgG in neonatal animals (Seebach *et al.* 1999) indicates that NT-3 is necessary for development of the monosynaptic reflex occurring during the first postnatal week (Seebach & Mendell, 1996). This raises the question as to where NT-3 normally comes from. Motoneurons express NT-3 mRNA (Buck *et al.* 2000); thus NT-3 might be released constitutively (Farhadi *et al.* 2000) into the vicinity of the Ia fibre/motoneurone synapse. It would be interesting to know whether NT-3-driven strengthening of AMPA/kainate responses might be revived in the adult spinal cord using procedures that allow NMDA receptors to regain function, e.g. by depolarization of the target cells to remove Mg²⁺ block. This might be a mechanism by which exercise improves function in the damaged spinal cord (Edgerton *et al.* 1997).

The role of synaptic activity in the NT-3-driven potentiation of the AMPA/kainate receptor-mediated response is unknown. Potentiation of the C-fibre dorsal root NMDAergic component of the EPSP (but not the AMPA/kainate receptor-mediated component) has been reported in response to repetitive stimulation (Lozier & Kendig, 1995), although the effects of neurotrophins on this are not known.

The uniform acute and chronic effects of NT-3 in enhancing the amplitude of the monosynaptic AMPA/kainate receptor-mediated EPSP stand in sharp contrast to the effects of BDNF on the same system. Chronic application of BDNF in neonates leads to depression of the monosynaptic EPSP (Seebach *et al.* 1999). Recent studies indicate that acute application of BDNF to membrane patches from neurones in the medulla reduces their response to AMPA (Balkowiec *et al.* 2000). However, BDNF has been suggested to increase the NMDAergic response in spinal neurones (Kerr *et al.* 1999; V. L. Arvanov & L. M. Mendell, unpublished observations), presumably via an effect on tyrosine phosphorylation (McGlade-McCulloh *et al.* 1993; Lin *et al.* 1998). Given the evidence that activation of NMDA receptors enhances the response of AMPA/kainate receptors (Arvanov *et al.* 2000), it follows that BDNF may have a dual action on AMPA/kainate responses, a direct inhibitory effect and an indirect excitatory one. This 'push-pull' mechanism may allow BDNF to have a strong influence on the sensitivity of the AMPA/kainate receptors in motoneurons.

In conclusion, it is now clear that neurotrophins are naturally occurring substances that can exert powerful effects in normal development as well as encouraging recovery of function after injury. Their physiological

actions can enhance their usefulness in promoting functional recovery but may also lead to undesirable side effects (e.g. pain, spasticity). These considerations point to the necessity to obtain a comprehensive understanding of their physiology as well as their trophic actions in order to fully exploit the opportunities they provide for promoting recovery of the injured spinal cord.

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