INTRODUCTION

A compelling problem in developmental neurobiology during the past few decades has been to resolve how networks of functionally appropriate connections arise during development, and how they are maintained throughout adult life, given that the genetic pre-specification of every connection would require a degree of encoding that could outstrip an organism's genomic capacity. It is more or less taken for granted that the diversity and specificity of functions in the nervous system arise through some degree of selectivity in the formation and use of neural connections (Purves & Lichtman, 1985), but it has been proposed that the full complement of neuronal connections must be determined by epigenetic, trophic dependences of neurones on their target organs (Purves, 1988). According to this 'neurotrophic theory', neurones are predisposed to make broadly selective synaptic connections, but the number of neurones innervating a specific target and the number and diversity of each neurone's connections are regulated by a negative feedback loop: specific nutrients (trophic factors) derived from peripheral targets regulate neuronal survival and growth of dendrites, axon collaterals and synaptic terminals; while orthograde patterns of neural activity limit the production, availability or accessibility of the trophic support (Figs
A general form of the neurotrophic theory, as it might be applied to the motor innervation of smooth or skeletal muscle. The level of neurotrophic factor produced by the target tissue is up- or down-regulated by the level of activity induced in the muscle by its motor nerve supply (MN). Decreased levels of activity give rise to increased levels of neurotrophic factor, and increased levels of activity reduce the level of neurotrophic support. The level of neurotrophic factor acquired by the neurone influences its survival and the number, disposition and strength of its connections. Based on Purves (1988). B and C, schematic illustrations of the principal differences in the distribution of motor innervation to smooth and skeletal muscle, and how this might relate to distribution of neurotrophic resources. In smooth muscle (B), the neurotrophic resource (NGF; stippling of muscle) may be distributed over the entire area of the target tissue, and the autonomic motor nerve terminals compete for this on a consumptive basis, leading to a stable steady state in which the resource is partitioned between the boutons of the nerve supply. By contrast, in skeletal muscle (C) the neurotrophic resource may be restricted to a relatively small area, leading to spatial competition between convergent motoneurones and their terminals, emergence of a dominance hierarchy and, ultimately, exclusion of all but one of the convergent terminals.

Thus neurones and their axons and dendrites appear to flourish in proportion to the capacity of their axon terminals to exploit trophic resources, whose levels they indirectly limit and control. It is customary to describe this potential interaction between neurones and their targets in terms of competition for neurotrophic resources.
Fig. 2. Fluorescence micrographs showing the difference in motor innervation of smooth muscle (A and B) and skeletal muscle (C), as visualized with vital staining. A and B, autonomic motor nerve terminals in a preparation of mouse vas deferens stained with the fluorescent carbocyanine dye DiOC₄(5). Note the extended, beaded distribution of fluorescent nerve terminals. C, somatic motor nerve terminals in a reinnervated and paralysed rat lumbrical muscle stained with the fluorescent styryl dye 4-Di-2-Asp. Note the pair of axons converging on the reinnervated motor endplate on the left (arrow). Calibration bar, 20 μm. (Panels A and B reproduced with permission from Lavidis & Bennett, 1992).

Neurotrophic theory has arisen, at least in part, from the notion that the interplay between neurones and their synaptic connections during development resembles more closely the interactions between organisms in a biological system than the organization of elements in an electrical circuit (Purves & Lichtman, 1985, p. 363). Competitive, Darwinian principles are also the cornerstone of other theories of higher brain function and
development (Edelman, 1987, 1992). Our aims in this review are therefore threefold. Firstly, we explore the possibility that principles used to describe competition in a different biological context – namely the dynamic interactions between members of plant and animal communities (Keddy, 1989) – may be applied to the problem of neuronal or synaptic competition. The intention is to indicate how these principles might be used as basis for further experimental investigation of competitive synaptic mechanisms. Secondly, we consider some potential weaknesses in the way neurotrophic theory is currently applied to thinking about the control of skeletal muscle innervation, particularly in relation to the role of motoneuronal activity. Thirdly, we consider alternative kinds of molecular mechanisms for competition at neuromuscular junctions, and we present a speculative model based on ‘induced fit’ between presynaptic and postsynaptic molecules. This model embodies some of the criteria used in population biology to define the nature of competition between individuals vying for access to limited resources. Finally, we briefly consider the possible relevance of our approach to thinking about the control of convergence and divergence elsewhere in the nervous system during development or nerve regeneration.

A DEFINITION AND SOME GENERAL PRINCIPLES

The essence of the neurotrophic theory is that neurones are supported by substances which are limited in supply, and this implies that a neurone may profoundly influence the access of others to the same neurotrophic factors. In the context of skeletal muscle innervation, a cogent illustration of this kind of influence is provided by the process of reinnervation after partial denervation. Intact motor axons, which first sprout to reinnervate muscle fibres vacated by degenerating terminals, relinquish some of their additional connections only when regenerating axons return (Guth, 1962; Brown & Ironton, 1978; Thompson, 1978; Ribchester, 1988a). Thus the number of muscle fibres innervated by each regenerating motoneurone (motor unit size) gradually increases, at the expense of the intact, sprouted motor units (Fig. 3). At a cellular level, the competition is played out on muscle fibres which receive convergent, functional innervation by regenerating axons and intact or sprouted motor axons (Fig. 4).

This example, which we shall return to in sections below, is sufficient to permit a concise working definition of synaptic competition: the negative effects which one neurone and its terminals have upon others by consuming, or controlling access to, a resource that is limited in availability.

This definition of competition is almost identical to that proposed by Keddy (1989) to describe competitive interactions between organisms in plant and animal communities. As a definition it generates several important questions. First, what is the precise nature of the negative influences between neurones? Second, what is the precise nature of the resources? Third, is synaptic competition based on consumption of resources or on control of access to resources? And finally, what other factors limit the availability of trophic resources and how is this limitation brought about?

‘Resources’ are defined in population biology as substances or factors which lead to increased growth rates as their availability in the environment is increased. ‘Consumption’ and ‘control of access’ refer to two different modes of competition. In plant and animal communities, organisms either consume a fraction of a resource which is distributed over a large available area; or they vie for access to the whole of a resource which is only available in a restricted area. In the first case, the competition is referred to as consumptive competition; in the second case it is referred to as spatial competition. The availability of
resources may be limited by various means: by competitors exploiting resources and removing them from the local environment (competition by exploitation), or by competitors directly or indirectly interfering with other competitors seeking access to the resource (competition by interference).

Consumptive competition and spatial competition tend to produce different kinds of stable steady state (Keddy, 1989). Consumptive competition commonly leads to a fairly uniform spatial distribution of competing individuals in relation to the resources on which they rely (resource partitioning). This competitive strategy and steady state is illustrated by mobile organisms; for example, in the distribution of whale populations in relation to the plankton resources on which they feed. Spatial competition, by contrast, almost invariably leads to establishment of hierarchies, in which one or more participants becomes dominant over others (dominance hierarchies). This strategy and steady state are commonly experienced by sessile organisms; for example, in the distribution of barnacles adhering to a rock. The establishment of dominance is interesting because it may be thought of in terms of two positive feedback loops (Fig. 5) which contrive further to strengthen the position of
Fig. 4. Examples of intracellular recordings from partially denervated rat lumbrical muscles that were subsequently paralysed by a tetrodotoxin block applied to the sciatic nerve, during regeneration of injured (SN) motor axons. A and F are mononeuronally innervated muscle fibres; B–E are polyeuronally innervated to different extents by sprouted (LPN) and regenerated axons. (From Ribchester, 1993.)

dominant competitors at the expense of others (the subordinates). An essential requirement for dominance – or, in the limit, exclusion of all but one participant – is some initial form of asymmetry between future dominant or subordinate competitors; otherwise the competitors co-exist.

From the above standpoint, it seems to us that if we can describe and explain competitive synaptic interactions in terms of negative influences; identify the molecular nature of the resources; determine the extent to which competitive interactions are regulated by the consumption of, or control of access to, resources; and demonstrate how the resources are limited; then it would be fair to say that we will have achieved a reasonable understanding of synaptic competition. This understanding might then be translated into rational and
beneficial ways of manipulating neurotrophic resources and competition. For example, recent reports have indicated that it may be feasible to treat certain neuromuscular disorders by manipulating levels of activity or by administering neurotrophic factors which may not normally be present in muscle (Sendtner, Kreutzberg & Thoenen, 1990; Gurney, Yamamoto & Kwon, 1992; Sendtner, Holtmann, Kolbeck, Thoenen & Barde, 1992a; Sendtner, Schmalbruch, Stockli, Carroll, Kreutzberg & Thoenen, 1992b).

NEUROMUSCULAR PARADIGMS OF NEUROTROPHIC COMPETITION

Innervation of smooth muscle

An established paradigm for neurotrophic theory is provided by the innervation of smooth muscle targets by autonomic ganglion neurones, especially those arising in sympathetic ganglia. It is well known that the innervation of smooth muscles is a distributed one (e.g. Lavidis & Bennett, 1992; Fig. 2). There is good evidence that smooth muscle regulates sympathetic ganglion cell numbers and the number and disposition of their peripheral (axonal) and intraganglionic (dendritic) branches (Olson & Malmfors, 1970; Hume & Purves, 1988; Voyvodic, 1989). This regulation is evidently mediated, at least in some cases, by a family of structurally related, diffusible growth factors, including ‘neurotrophins’ such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), neurotrophins 3 and 4/5 (NT3, NT4/5), and structurally dissimilar molecules such as ciliary neurotrophic factor (CNTF), leukaemia inhibitory factor (LIF) and fibroblast growth factor (FGF; see Levi-Montalcini, 1987; Korsching, 1993, for reviews). The survival and growth of a sympathetic neurone probably depends on the capacity of its nerve terminals to bind these neurotrophin resources (mediated by specific, tyrosine-kinase-associated neurotrophin receptors), followed by uptake by endocytosis and retrograde transport (Yankner & Shooter, 1983; Berkemeier, Winslow, Kaplan, Nikolics Goeddel & Rosenthal, 1991; Lindsay, Alderson, Friedman, Hyman, Furth, Maisonpierre, Squinto & Yancopoulos, 1991; Thoenen, 1991; Dechant, Biffo, Okazawa, Kolbeck, Pottgeisser & Barde, 1993a; Dechant, Rodriguez-Tebar, Kolbeck & Barde, 1993b; Rodriguez-Tebar, Dechant, Gotz & Barde, 1993). Fractions of the total amount of neurotrophin resource
appear to be partitioned between and consumed by the terminal boutons of the autonomic nerve supply.

The smooth muscle paradigm provides a compelling illustration of neurotrophic theory in its most conventional form (Fig. 1A and B); and it seems to represent a form a consumptive competition based on exploitation of an essential resource. Levels of neurotrophin molecules appear to be regulated by negative feedback: the production of the neurotrophic molecules is down-regulated in the target muscle and consumption is up-regulated by the autonomic innervation. This regulation appears to be activity dependent, although the evidence for this remains indirect (Shelton & Reichardt, 1984; Heumann, Korsching, Scott & Thoenen, 1984; Heumann & Thoenen, 1986; Snider, 1988).

**Innervation of skeletal muscle**

A quite different form of neurotrophic interaction and different competitive pressures appear to prevail at skeletal neuromuscular junctions, where interactions involving more than one motoneurone occur within a much more restricted area of the muscle fibre surface (Figs 1C and 2C). The pattern of innervation of skeletal muscle, and the manner in which it normally emerges, are what one might expect if spatial competition rather than consumptive competition were driving the interaction between motor nerve terminals and muscle fibres.

The events leading to the mature pattern of innervation of motor endplates are quite well documented (reviewed by Jansen & Fladby, 1990). Motoneurones grow selectively into specific skeletal muscles in early development (Lance-Jones & Landmesser, 1980; Landmesser, 1984; Tanaka & Landmesser, 1986). Normally about half these motoneurones subsequently die (Lance-Jones, 1982; Oppenheim, 1991). Motoneurone death is largely a prenatal phenomenon (Hardman & Brown, 1985; Oppenheim, 1986), and neurotrophin growth factors produced by muscle or in peripheral nerve have recently been implicated in it (Oppenheim, Qin-Wei, Prevette & Yan, 1992; Yan, Elliott & Snider, 1992; Sendtner et al. 1992a). Motoneurones which survive cell death provide a transient, focal polynuclear innervation of muscle fibres (Boeke, 1925; Redfern, 1970; Bennett & Pettigrew, 1974). Significantly, the terminals converge on a common synaptic site, the motor endplate, which constitutes about 0.1% or less of the total area of exposed muscle fibre membrane (Bekoff & Betz, 1977; Bixby, 1981). The surviving neurones typically withdraw between one-half and nine-tenths of their initial complement of peripheral branches during postnatal development, a process commonly referred to as synapse elimination (Brown, Jansen & Van Essen, 1976; Korneliusen & Jansen, 1976; Riley, 1977; Betz, Caldwell & Ribchester, 1979; Fladby, 1987). Recent data strongly suggest that the loss of functional input is protracted and occurs by stepwise elimination of individual terminal boutons, rather than by a sudden disconnection of axon collaterals or retraction of the entire terminal. The surviving terminal progressively adds boutons to the endplate over the same period (Balice-Gordon, Chua, Nelson & Lichtman, 1993a; Balice-Gordon, Garriga & Lichtman, 1993b).

Synapse elimination during development ultimately yields a familiar, stereotyped pattern of adult muscle fibre innervation (at least in mammalian skeletal muscle and many of those in birds, reptiles and amphibia) of a single motor nerve terminal attached to each muscle fibre. Similar processes occur during reinnervation of completely or partially denervated adult skeletal muscle: like immature muscle fibres, reinnervated muscle fibres in adult muscles experience a transient polynuclear innervation, which in most cases is subsequently eliminated (Boeke, 1916; McArdle, 1975; Gorio, Carmignoto, Finesso, Polato & Nunzi, 1983; Taxt, 1983a, b). From the viewpoint of either development or
reinnervation, the key (related) questions are: why do terminals of different motoneurones not normally co-exist at a motor endplate and how is it that only one terminal normally persists?

*Indirect evidence for spatial competition in skeletal muscle*

Evidence that neuromuscular synapse elimination results from some form of spatial competition can be deduced from the kinds of experiment which population biologists would call ‘removal’ experiments and ‘additive’ experiments. A removal experiment involves depleting an existing population and then searching for evidence of competitive ‘release’ in the remainder; a result of alleviation of pressure on resources. In the case of muscle, a removal experiment may be instigated by performing a partial denervation. In an additive experiment, the ratio of putative competitors to the level of resource is artificially increased, and the investigator searches for a resulting decrease in some index of performance of the competitors: the predicted result of increased pressure on resources. Additive experiments can be implemented by performing an implant, forcing additional axons to innervate a muscle.

Motor unit size is preserved or may even continue to decline in neonatal muscle after partial denervation at birth: there is no evidence for an expansion of the motor units (Brown *et al*. 1976; Thompson & Jansen, 1977; Betz, Caldwell & Ribchester, 1980a; Fladby & Jansen, 1987). In adults, however, the response to partial denervation is quite different. Rampant sprouting and occupancy of denervated motor endplates by intact axons occurs (Brown, Holland & Hopkins, 1981*a*). In rodents, the transition of the response occurs around 3 weeks after birth, when most of the polyneuronal innervation has been eliminated (Brown, Hopkins & Keynes, 1982).

When excess motor axons are implanted into the endplate region of an adult muscle, elimination of some – actually rather few – of the intact motor terminals occurs (Bixby & Van Essen, 1979). An alternative approach, successfully carried out in frogs, has been to force motor axons from ipsilateral and contralateral sides of the spinal cord to grow into only one hindlimb (Lamb, 1980). This also results in hyperinnervation of muscles, by twice as many motoneurones as normal. Individual motor units are evidently smaller in these muscles, as predicted from an increase in pressure on resources, but the interpretation is complicated because the number of muscle fibres forming during development depends on the number of motor axons innervating the muscle, and nerve implants induce formation of more muscle fibres than normal (Betz *et al*. 1980*a*; Ross, Duxson & Harris, 1987; Sheard & Lamb, 1991).

The reinnervation of partially denervated muscle may be regarded as a combination of a removal and an additive experiment. When regenerating axons return to a partially denervated muscle, they recover innervation of fewer fibres than they innervated initially, evidently because their endplates become occupied by sprouts from intact axons, as described above. It appears that these opportunistic connections are not readily winkled out by the regenerating axons (Fig. 3), and the longer the interim between nerve injury and regeneration, and the fewer the number of regenerating axons, the less competitive they appear to become (Brown & Ironton, 1978; Thompson, 1978; Luff & Torkko, 1990; Ribchester, 1993). The success of the regenerating axons in reinnervating partially denervated muscle is dramatically improved by simply cutting the intact axons immediately before the regenerating ones return, causing the intact terminals and their sprouts to degenerate (Ribchester & Taxt, 1984). Although substantial improvement in the amount of synapse formation by the regenerating axons can also be obtained merely by paralysis of the
muscle during reinnervation – rendering the muscle functionally denervated – the increase is not as great as when sprouts from intact axons are improved by complete, structural denervation (Ribchester & Taxt, 1984; Ribchester, 1993).

The absence of sprouting in neonatal muscles following partial denervation and the difference between the effects of paralysis and surgical denervation on sprouting in adult muscles are findings that are compatible with a mechanism of spatial competition at endplates based on interference (the presence of either a functional or non-functional terminal preventing or inhibiting synapse formation by an ingrowing nerve) but not readily explained by a mechanism based on consumptive exploitation of a trophic resource whose levels are controlled solely by activity. These findings together suggest that the gradual elimination of polyneuronal innervation during normal development or regeneration may be represented as the emergence of a dominance hierarchy (Fig. 5), based on some form of initial asymmetry (not necessarily a size or geometric asymmetry) in the capacity of the convergent axons to respond to the resources concentrated at the developing motor endplate and leading, via positive feedback, to the exclusion of all the subordinate motor terminals.

The proposition that spatial competition regulates the focal innervation of skeletal muscle fibres and that consumptive competition regulates the distributed innervation of smooth muscle is compromised by a few possible exceptions, however. For example, the extensive axon collateral and motor nerve terminal sprouting which occurs following partial denervation or paralysis of adult muscle (Betz, Caldwell & Ribchester 1980b; Holland & Brown, 1980; Brown, Holland & Hopkins, 1981b; Brown, Hopkins & Keynes, 1982), the distributed innervation of tonic muscle fibres in some muscles (Gordon, Perry, Tufferey & Vrbova, 1974; Lichtman, Wilkinson & Rich, 1985), and the distributed motor innervation of intrafusal muscle fibres in muscle spindles (Barker, 1974; Banks, 1981) all provide a superficial resemblance to the distributed pattern of innervation of smooth muscle. A further complication is that supernumerary motor nerve terminals in skeletal muscle are not always eliminated. For instance, following treatment of neonatal male rats with testosterone, muscle fibres in the bulbocavernosus and levator ani muscles acquire a polyneuronal innervation which persists into adulthood (Jordan, Letinsky & Arnold, 1989; Lubischer, Jordan & Arnold, 1992). Also, following reinnervation of partially denervated muscles in normal adults, a small proportion of fibres appear to acquire a stable polyneuronal innervation (Ribchester, 1988a; Werle & Herrera, 1991; Barry & Ribchester, 1994). These exceptions suggest that perhaps different factors regulate the growth and branching of axons in skeletal muscle, independently of the factors which motivate the competition between convergent terminals at neuromuscular junctions. Overall, however, the differences in the patterns of innervation of smooth and skeletal muscle suggest to us that, normally, consumptive competition is the principal basis for the control of innervation in the case of smooth muscle, whereas convergent terminals in skeletal muscle mainly experience a form of spatial competition.

Predictions regarding plasticity of smooth and skeletal muscle innervation

Our proposals yield some immediate predictions about the scope and extent of on-going, systematic and enduring changes in the structure of neuromuscular connections (i.e. their plasticity) in smooth and skeletal muscle. For example, if the innervation of smooth muscle is regulated by a form of consumptive competition, then, like mobile organisms, their axon terminals might be expected to be continually shifting in their distribution over the surfaces of smooth muscle cells, in response to local changes in the concentration of neurotrophic
resources. By contrast, if the mononeuronal innervation of skeletal muscle arises by spatial competition, then, like sessile organisms, we might expect the motor nerve terminals which exclusively innervate single extrafusal muscle fibres to be structurally rather inert. From similar reasoning we would predict that the motor innervation of muscle spindles and tonic extrafusal muscle fibres should be more labile than that of extrafusal twitch muscle fibres, and that during nerve sprouting after partial denervation there should be continuous remodelling of nerve terminals, with making and breaking of neuromuscular contacts as on-going processes.

There is some supporting evidence for these proposals. Repeated visualization of nerve terminals in mature skeletal muscle in vivo indeed shows that once the basic architecture of a nerve terminal is established it remains quite invariant in form (Lichtman, Magrassi & Purves, 1987; Balice-Gordon & Lichtman, 1990, 1993). There is also evidence, albeit indirect, in support of the prediction that terminals belonging to sprouted axons should be more labile, based on the distribution of sizes of innervated and denervated muscle fibres in partially denervated muscles (Ridge & Rowerson, 1990). Either direct or indirect evidence in support of on-going remodelling of terminals in muscle spindles or in smooth muscle is lacking, however. Interestingly, repeated observation of dendrites and cell bodies of the sympathetic neurones themselves, which also receive a distributed innervation, suggest that their synaptic inputs are quite dynamic in form (Purves, Voyvodic, Magrassi & Yawo, 1987). It would seem to be worthwhile to apply similar repeated-visualization techniques to study the dynamic properties of motor terminals in smooth muscle.

**COMPETITION VERSUS CO-EXISTENCE OF MOTOR NERVE TERMINAL BOUTONS**

We now consider in more detail some of the difficulties in applying neurotrophic theory in its conventional form to the problem of competitive elimination at neuromuscular junctions in skeletal muscle. In particular, we address the proposed importance of neural activity in determining the rate and outcome of elimination, and the possible importance of selective, recognition mechanisms that might influence the competition. The former is a linchpin of neurotrophic theory; the latter is normally excluded from it.

After synapse elimination is completed in early postnatal development, each surviving motor nerve terminal is seen typically to arborize into a number of twigs and boutons. As Purves (1988) has pointed out, this actually poses an interesting paradox. How is it that individual boutons which make up the single surviving presynaptic terminal are allowed to co-exist, while similar boutons belonging to different axons are eliminated? (Co-existence of organisms and species undergoing spatial competition for a common resource is also an intriguing problem to population biologists; Keddy, 1989.) Put another way, what property of a synapse might normally protect intraterminal synaptic boutons from competitive elimination, while simultaneously promoting interterminal competition?

**Role of activity**

Activity and the processes which hinge upon it are natural candidates for explaining the synaptic bouton paradox. When an action potential occurs in a motor axon collateral, it spreads almost simultaneously into all the boutons of the nerve terminal, producing synchronous and uniform exocytosis, release of transmitter and recycling of synaptic vesicles (Betz, Mao & Bewick, 1992; Ribchester, Mao & Betz, 1994). It is possible to imagine a number of mechanisms by which terminal boutons that are synchronously active behave as equals in competition, while boutons that are not simultaneously active will not
have equivalent status with respect to access to neurotrophic resources (for example, see Purves, 1988, p. 157). Such proposals imply that if simultaneous activation of boutons were somehow to inhibit competition, then terminals belonging to different, convergent axons that are compelled to express identical patterns of activity would exert no mutual negative influence, and would therefore co-exist rather than compete. In other words, a prediction is that if individual muscle fibres are innervated by convergent axons expressing identical activity, they should remain polynervously innervated. The available experimental evidence does not entirely support this prediction.

It is generally agreed that paralysis inhibits synapse elimination; thus when the terminals of the same and different axons are synchronously inactive they show a tendency to co-exist (Benoit & Changeux, 1975; Thompson, Kuffler & Jansen, 1979; Brown et al. 1982; Duxson, 1982; Caldwell & Ridge, 1983; Taxt, 1983b; Callaway & Van Essen, 1989). This finding is broadly in accord with the standard form of neurotrophic theory (Fig. 1). However, recent experiments indicate that some synapse elimination can occur in the absence of propagated neural activity. Competition between completely inactive axons was studied by blocking activity in the entire motor nerve supply during reinnervation of partially denervated muscle (Ribchester, 1993). As expected, this procedure increased both the overall amount of synapse formation and the amount of polynervous innervation in the muscles. But the number of *mononeuronally* innervated fibres, exclusively innervated by
regenerating, inactive axons was also increased (Fig. 6). Thus it is apparently possible for some inactive terminals to be displaced during competition with other inactive terminals.

The results of synchronizing neuromuscular activity using chronic electrical stimulation also pose some problems. Chronic electrical stimulation of immature muscles, contrary to the above predictions, does not cause convergent terminals on polyneuronally innervated muscle fibres to co-exist; rather, synapse elimination is accelerated (O’Brien, Östberg & Vrbová, 1978; Thompson, 1983). It could be argued that chronic muscle stimulation merely superimposes some synchronous activity on the natural, asynchronous activation of motor units, and the net effect is to reduce the amount of trophic resource available; thus, in accordance with neurotrophic theory, increasing the competitive pressure and hence increasing the rate of synapse elimination. The outcome of the competition could still be determined by the endogenous asynchronous activity of the convergent axons. This explanation cannot be refuted with available data. It could be tested, however, perhaps by electrically stimulating motor nerve terminals and muscle fibres directly, while remotely blocking the conduction of natural activity in the peripheral nerves which supply the muscles.

The question of a physiological role for differences in the activity in determining the outcome of neuromuscular synaptic competition has been specifically examined in a number of studies. The first studies involved selectively blocking activity in motor axons innervating polyneuronally innervated muscle fibres in reinnervated adult muscles, and these studies suggested that active terminals are preferentially stabilized at the expense of inactive ones (Ribchester & Taxt, 1983, 1984). However, the effects of blocking activity in some axons but not others in neonatal animals have been interpreted differently; apparently the blocked motor axons acquire larger motor units (Callaway, Soha & Van Essen, 1987; but see Ribchester, 1988b).

Experiments with selective stimulation of motor units in neonatal muscle have also been carried out. When some axons but not others are electrically stimulated, the more active terminals appear to have a competitive advantage and their motor units remain expanded, at the expense of the less active axons (Ridge & Betz, 1984). An acute, heterosynaptic depression has also been reported during stimulation of two axons convergently innervating single muscle fibres (Betz, Chua & Ridge, 1989). Selective stimulation of motoneurones making convergent synapses on myotubes in culture has also been reported to stabilize the stimulated synapses and repress the non-stimulated connections (Magchielse & Meeter, 1986; Lo & Poo, 1991; Dan & Poo, 1992). However, it has also been reported that while stimulation of neuromuscular preparations in tissue culture accelerates synapse elimination, there is no effect of selective versus non-selective stimulation on the terminals which survive (Nelson et al. 1993). As yet, there are no reports of the effects of selective stimulation on elimination of polyneuronal innervation in reinnervated adult muscle.

One alternative to presuming a central role for activity is the idea that competitive success might be based on the capacity of the motoneurone cell body to support only a limited number of terminals, and that trophic resources gathered by one collateral or bouton are redistributed or shared among others (e.g. Smallheiser & Crain, 1984). However, such ideas are not very compelling. For example, inactive regenerating axons are additionally disadvantaged in competition with intact axons, even when these have sprouted to their maximum extent (Ribchester, 1988a). Also motoneurones are clearly quite capable of supporting more terminals than they actually do, whether competing terminals are present or not, as shown by the effects of muscle paralysis in delaying or inhibiting elimination of polyneuronal innervation in both neonates and reinnervated adult muscle (Thompson et al. 1979; Taxt, 1983b; Barry & Ribchester, 1994).
Role of selective synapse formation and elimination

An alternative or additional explanation of the one-to-one relationship between a motor nerve terminal and a skeletal muscle fibre is that this arises through some form of selective recognition process, occurring either during synapse formation or synapse elimination. It is very clear that skeletal muscle is not a homogeneous tissue from the viewpoint of developing or regenerating motoneurones. For instance, motoneurones are evidently capable of making crude distinction between muscles on the basis of their position or segmental origin (Bennett & Lavidis, 1984; Wigston & Sanes, 1985; Donahue & English, 1987, 1989; Hardman & Brown, 1987; Balice-Gordon & Thompson, 1988; Bennett & Ho, 1988; Laskowski & Sanes, 1988; Laskowski & High, 1989). Other data suggest that matching of motor terminals to muscle fibres of a pre-specified, complementary type is important in competition, both during postnatal development and following reinnervation in adults. This is due partly to selectivity during synapse formation, and partly to selective synapse elimination, mismatched terminals being preferentially withdrawn in competition with functionally matched motoneurone and muscle fibre types (Thompson, Sutton & Riley, 1984; Gordon & Van Essen, 1985; Jones, Ridge & Rowlerson, 1987a, b; Lichtman & Wilkinson, 1987; Soha, Yo & Van Essen, 1987; Bennett, Davies & Everett, 1989; Fladby & Jansen, 1990; Gates & Ridge, 1992).

In sum, to date most experiments suggest that active motor terminals have an advantage over inactive ones, but differences in propagated activity in motor axons alone appear to be insufficient to ensure persistence of specific terminals at polyneuronally innervated junctions. Thus explanations other than activity appear to be required to account for both competition between terminals and co-existence of boutons belonging to the same motor nerve terminal. Evidence that some form of selective recognition process plays a role in synaptic competition is now quite compelling. A possible molecular basis for activity-dependent adjustment of selectivity of neuromuscular connections is presented in the penultimate section of this review.

MOLECULAR BASIS FOR NEUROMUSCULAR SYNAPTIC COMPETITION

Our conclusion thus far is that criteria used to categorize competition in an ecological context may have utility in a neurobiological context, at least in relation to understanding the control of muscle innervation. Notions of ‘spatial competition’ or ‘consumptive competition’ appear to provide a useful analogy, because they may potentially influence the way we might formulate more detailed hypotheses about the cellular and molecular mechanisms underlying competition in smooth and skeletal muscle.

Diffusible versus fixed molecular resources

According to Keddy (1989), the existence of competition in ecosystems is best demonstrated by showing a dependence of the interacting participants on the level of essential resources. In skeletal muscle, unlike smooth muscle, a critical problem is that we do not yet have any clear idea of the molecular identity of the trophic resources for which motoneurones and their terminals appear to compete. The search for products of skeletal muscle which function as specific motoneurone growth factors continues unabated (Dohrmann, Edgar & Thoenen, 1987; Henderson, 1988; Oppenheim, Haverkamp, Prevette, McManaman & Appel, 1988; Arakawa, Sendtner & Thoenen, 1990; Henderson, Camu, Mettling, Gouin et al. 1993). Interestingly, it has recently been shown that
expression of mRNA encoding the neurotrophin BDNF increases in skeletal muscle following denervation (Funakoshi, Frisen, Timmusk, Zachrisson, Verge & Persson, 1993; Koliatsos, Clatterbuck, Winslow, Cayouette & Price, 1993). BDNF and NT3 have also been shown to increase the efficacy of synapses in tissue culture (Lohof, Ip & Poo, 1993). The mechanism of the synaptic strengthening is unclear. One possibility is that retrogradely transported second messengers are involved (Harish & Poo, 1992). Another is that since neurotrophic factors are normally taken up by receptor-mediated endocytosis, neurotrophins might stimulate activity-dependent synaptic vesicle exocytosis and recycling. Such effects could provide a cellular basis for the kind of positive feedback required to produce exclusive innervation of a motor endplate. Techniques have recently been described for quantitative study and analysis of the control of exocytosis, endocytosis and synaptic vesicle recycling at neuromuscular junctions and synaptic boutons (Betz & Bewick, 1993; Ryan, Reuter, Wendland, Schweizer, Tsien & Smith, 1993; Ribchester et al. 1994), so it should be possible to test this idea.

To date, however, while there is suggestive evidence that neurotrophins may play a role in promoting motoneurone survival and possibly in the control of nerve branching, there is no clear indication that neurotrophins have anything to do with competitive elimination of terminals at endplates. Indeed, if the mode of competition at polyneuronally innervated neuromuscular junctions is predominantly one of spatial competition— for the reasons outlined in sections above— it would seem inherently more likely that competitive synapse elimination should involve motor nerve terminals vying for access to fixed molecules in their local environment.

What sorts of molecule might fixed neurotrophic resources comprise, and where might they be located? The neural cell adhesion molecule (N-CAM) is a plausible candidate. Tight adhesions form between motoneurone growth cones and muscle fibre membranes within a few minutes of contact (Buchanan, Sun & Poo, 1989). Neural cell adhesion molecule has been implicated in the control of nerve growth and branching in muscle, both during development and following partial denervation in adults (Booth, Kemplay & Brown, 1990; Landmesser, Dahm, Tang & Rutishauser, 1990; Tang & Landmesser, 1993), and the distribution of N-CAM changes in skeletal muscle after denervation, from a restricted distribution to the endplate region in innervated muscle to a more diffuse distribution in denervated muscle (Sanes, Schachner & Covault, 1986). Activity also regulates the expression of N-CAM (Covault & Sanes, 1986). There are presently thought to be about 200 molecular forms of N-CAM, based on alternative splicing and/or variable glycosylation. Some of these isoforms promote and others inhibit neurite growth (Small & Akeson, 1990; Saffell, Walsh & Doherty, 1991; Walsh, Furness, Moore, Ashton & Doherty, 1992; Zorn & Krieg, 1992). Different isoforms of N-CAM are expressed in neonatal muscles, compared with mature or ageing muscles (Andersson, Olsen, Zhermosekov, Gaardsvoll, Krog, Linnemann & Bock, 1993).

Another possibility is that acetylcholine receptors (AChR) or molecules tightly associated with them may provide a substrate for spatial competition, and there is some evidence in support of this. It is well known that junctional AChR become locked into the endplate region during early postnatal development (Slater, 1982). Forms of AChR differing in subunit composition or metabolic half-life are selectively expressed at endplates under different conditions (e.g. Witzemann, Bremner & Sakmann, 1991; Andreose, Xu, Lømo, Salpeter & Fumagalli, 1993). Data from J. W. Lichtman’s laboratory support a hypothesis, originally proposed by Stent (1973), that local activation of junctional ACh receptors feeds into an intracellular mechanism which eliminates inactive receptors (Lichtman & Balice-
Gordon, 1990). Repeated visualization of nerve terminals in living animals, either during postnatal development or during nerve regeneration in adults, appears to show that acetylcholine receptors in the postsynaptic membrane are eliminated prior to retraction of disadvantaged terminals (Rich & Lichtman, 1989; Balice-Gordon & Lichtman, 1991, 1993). Remaining terminal boutons evidently fail to occupy the synaptic space vacated by the retreating terminals. Interestingly, when a patch of receptors at an intact endplate is inactivated by focal binding of α-bungarotoxin, the patch of receptors is removed, the overlaying terminal boutons are withdrawn and the remaining boutons fail to occupy the vacated postsynaptic space (Balice-Gordon & Lichtman, 1991). Complementary approaches also indicate that junctional ACh receptors are inherently or potentially more labile in their spatial distribution in mature muscle than presumed hitherto. Junctional receptors spread from motor endplates in muscle fibres stripped of their basal lamina and cultured (Lupa & Caldwell, 1991). Interestingly, the junctional AChR reaggregate at sites where newly synthesized receptors and myonuclei are co-localized (Anderson & Ribchester, 1993). Junctional ACh receptors also become redistributed beneath nerve terminal sprouts in muscles poisoned with botulinum toxin (Balice-Gordon et al. 1993b).

However, to date there are no experiments which definitely show that either N-CAM or AChR are the molecules which subserve spatial competition at endplates. We know that genes expressed by myonuclei localized to motor endplates are regulated in a different way from those expressed by extra-junctional myonuclei (Merlie & Sanes, 1985; Sanes, Johnson, Katzbaunier, Mudd, Hanley & Martinou, 1991; Witzemann et al. 1991), and, not surprisingly, a number of molecules, in addition to N-CAM or acetylcholine receptors, are known to be selectively expressed at endplates. For example, numerous sodium channel isoforms are expressed in muscle fibre membranes and these are concentrated at neuromuscular junctions (Caldwell & Milton, 1988; Schaller, Krzemien, McKenna & Caldwell, 1992; Lupa, Krzemien, Schaller & Caldwell, 1993). Acetylcholinesterase (Massoulie & Bon, 1983), cytactin (Sanes et al. 1986), s-laminin (Hunter, Shah, Merlie & Sanes, 1989) and acetylgalactosaminyl transferase activity (Scott, Balsamomo, Sanes & Lilien, 1990) are also localized to the neuromuscular junction. It would be interesting to know whether any of these components is selectively up-regulated or down-regulated during synapse elimination, or whether experimentally induced manipulation of these potential resources influences the rate or the outcome of elimination.

Are there growth inhibitory factors in skeletal muscle?

Neurotrophic theory is normally discussed in terms of competition between nerve endings for growth-promoting factors. Yet inhibition of growth is arguably as important a part of synapse formation and stabilization (Watson, 1976; Patterson, 1988). Perhaps the competition is so intense because the perijunctional or extra-junctional membrane or extracellular matrix provide more than just a non-permissive environment for growth.

The capacity of nerve terminals to form synapses ectopically, outside the normal endplate region is germane to this issue. Ectopic synapses will form when a foreign nerve is implanted into skeletal muscle, but in adults this only occurs when the muscle is denervated (Frank, Jansen, Lømo & Westgaard, 1975), and in neonatal muscle ectopic synapse formation normally occurs only when the nerve implant is positioned more than about 1 mm from the native endplates. Thus distance between endplates seems to be a regulated variable (Brown et al. 1976; Kuffler, Thompson & Jansen, 1977, 1980; Grinnell, Letinsky & Rheuben, 1979; Haimann, Mallart, Ferre & Zilber-Gachelin, 1981; Werle & Herrera, 1988). Paralysis reduces the allowable distance between endplates in such muscles.
(Jansen, Lømo, Nicolaysen & Westgaard, 1973; Srihari & Vrbová, 1978; Ding, Jansen, Laing & Tonnesen, 1983). It is interesting that ectopic synapses do not readily form in denervated adult fast-twitch muscle; instead the implanted axons grow along the muscle surface and synapse preferentially on the motor endplates originally innervated by the native nerve (Taxt, 1983a).

There is no direct evidence that endogenous neurite-growth inhibitors have anything to do with these findings, indeed they do not allow us to distinguish this interpretation from one based on the effects of a passive, non-permissive environment. However, taking these observations together with data from other systems brings into sharper focus the possibility that active, growth inhibitory mechanisms operate in muscle.

First, neurite growth inhibitors are expressed on axons and on neurogla in the central nervous system, and such molecules may be responsible for the failure of nerve regeneration in the CNS (Caroni & Schwab, 1988a, b; Schnell & Schwab, 1990). A specific role for astrocytes in providing a ‘stop growth’ or inhibitory signal in the CNS has been proposed (Luizzi & Lasek, 1987). Neuroglial cells, specifically terminal Schwann cells, also overlie motor nerve terminals at all neuromuscular junctions, and there is evidence that when Schwann cells are added to neurones and muscle fibres in co-culture this either inhibits synapse formation or promotes synapse elimination (Chapron & Koenig, 1989).

Secondly, during early development, growing sensory and motor axons are selectively steered into the anterior half of the somites (Keynes & Stern, 1984). This appears to be due to the production of a specific, peanut-lectin binding molecule by cells in the posterior half of the somite (Davies, Cook, Stern & Keynes, 1990). Peanut-lectin binding activity is also found at vertebrate motor endplates (Ko, 1987), but it is not known whether this has neurite growth inhibiting activity.

Finally, there is some evidence that a balance between the activity of proteases secreted by growth cones and protease inhibitors in the extracellular environment can determine whether neurites will extend or withdraw (Monard, 1988; Fawcett & Housden, 1990). A group of hypotheses for an explicit role for proteases in synapse elimination have been proposed, based on the reported effects of ions and protease inhibitors on the time course of synapse elimination (O’Brien et al. 1978; O’Brien, Östberg & Vrbová, 1984; Connold, Evers & Vrbová, 1986; Vrbová, Lowrie & Evers, 1988; Zhu & Vrbová, 1992; Navarette & Vrbová, 1993).

The possibility that the peri-junctional region of the motor endplate might constitute some sort of ‘terminal exclusion zone’, constraining terminals to the endplate and intensifying competition, could be further explored experimentally by determining whether ectopic synapses will fail to form in this region even when the native nerve supply is removed by denervation. It would also be interesting to know whether growth cone collapse (Kapfhammer & Raper, 1987), a useful indicator of growth inhibiting activity, occurs when a foreign axon is presented ectopically to an innervated muscle, compared with an ectopic presentation to a previously denervated muscle. It would additionally be interesting to know whether Schwann cells play a role in regulating the activity of proteases and protease inhibitors, like that proposed for astrocytes and growing axons in the CNS. Repeated observations of identical terminals (Lichtman et al. 1987) or of selectively labelled Schwann cells (e.g. Mirsky & Jessen, 1984) in muscles treated with proteases or protease inhibitors could provide a useful approach here.
AN 'INDUCED-FIT' MODEL OF NEUROMUSCULAR SYNAPTIC COMPETITION

While most experiments are consistent with a mechanism of competitive synapse elimination based on control of access by terminals for a spatially restricted resource, a number of unanswered questions remain about the qualitative nature of this mechanism. For example, how can neuromuscular synapse elimination occur under some circumstances in the absence of neural activity? Why do no muscle fibres become completely denervated during the period of synapse elimination? Why, after partial denervation, do regenerating axons not recover innervation of many of the muscle fibres they once innervated? How is it that some observations suggest that particular terminals are advantaged through selective synapse formation, while other data suggest that innervation is non-selective but elimination is selective?

In an attempt to reconcile observations such as these, we should like to propose a mechanism based on induction of selective adhesion as a plausible alternative to other hypotheses. By analogy with enzyme kinetic studies, and recent insights into antigen–antibody interaction, we will describe our hypothesis as an 'induced-fit' model.

There are four principal elements to the hypothesis. The first is that motor nerve terminals may induce a selective change in the nature of adhesion molecules in the muscle fibres they contact at motor endplates. The goodness-of-fit for nerve terminals provided by these molecules could be determined by the expression of unique isoforms, generated by alternative splicing and/or differential glycosylation, or by a conformational change induced by the binding of a specific ligand on the nerve terminal to a complementary adhesion molecule expressed on the surface of the muscle fibre (Fig. 7). The second element of the hypothesis is that competing axons may be allowed to occupy synaptic space because there is partial fit between dissimilar isoforms or conformations of the adhesion molecules initially expressed at an endplate. In other words, weak ('noisy') fits would be allowed between different, competing terminals and a muscle fibre. The third element of the hypothesis is that with time, a conformational change in a particular isoform is induced to become more permanent. This would lead to preferential adhesion by one of the terminals innervating an endplate and a progressive loss of adhesion and withdrawal of the remainder. This process would represent a form of positive reinforcement of a terminal, mediated by the muscle fibre, based on an initial asymmetry in the strengths of adhesions of competitors, as required of a mechanism based on spatial competition. The fourth element of the hypothesis allows for activity in competing terminals to accelerate the conformational change or synthesis of the appropriate complementary isoform, thereby providing the competitive edge that is normally observed when active and inactive terminals are pitted against one another.

There are precedents for some of the elements of the induced-fit hypothesis in other systems. First, it has long been recognized that the goodness-of-fit between the reactive site of an enzyme and its substrate can be altered by a conformational change in the enzyme. In fact the term 'induced fit' was first introduced in the context of enzyme–substrate reaction kinetics (Koshland, Nemeth & Filmer, 1966; Koshland, 1973). Second, it has recently been shown that antigens can change their conformation when antibodies bind to them, in a way that facilitates the antigen–antibody binding (Rini, Schulze-Gahmen & Wilson, 1992). Third, studies on T-lymphocytes show that binding of these to the intercellular adhesion molecule ICAM-1 is enhanced by an induced fit between the adhesion molecule and the cell surface ligand LFA-1, and this is facilitated by an intracellular signalling process activated by binding of different antigens to other T-cell receptors (Cabanas & Hogg, 1993).
How might an induced-fit mechanism work in relation to, say, reinnervation of partially denervated muscle? When an adult muscle is partially denervated, reactive changes leading to motor nerve sprouting occur, and denervated endplates become occupied by sprouts. Functional contact could be allowed because the denervated endplates permit a 'noisy fit', perhaps as a result of change in the isoform of adhesion molecule expressed or the conformation of the existing isoforms. With time, the sprouted terminals would transform the expression of the complementary adhesion molecules by an activity-dependent induction of gene expression in the endplate nuclei. This could be mediated by intracellular second messengers. It is known, for example, that second messengers play a crucial role in determining which major isoform of acetylcholine receptor is expressed at an endplate, and this is mediated in part by neural activity (reviewed by Laufer & Changeux, 1989). Regenerating axons returning to the muscle may reinnervate their old sites, but their goodness-of-fit may depend on how long the sprouts had had to respecify the fit on at the motor endplate, and on how active the sprouted terminal had been. Thus in a paralysed muscle more 'noisy fits' by regenerating axons would be allowed compared with an active muscle, and multiple terminals would persist for longer. But the longer the interim between
nerve injury and the return of the regenerating axons, the more likely it is that the nature of the adhesion molecules would be transformed and the less the likelihood that a noisy fit by regenerating axons would be allowed.

The induced-fit hypothesis seems to us to provide a plausible basis for explaining why terminals do not normally co-exist at an endplate and why one and only one terminal ultimately persists in an essentially invariant form. Testing the hypothesis is feasible, although difficult, mainly because it is not clear which molecular isoforms would be the best candidates for mediating the induced fit. However, as a start, it would be interesting to know whether muscles normally express alternatively spliced isoforms of N-CAM or AChR in proportion to the number of motor units they contain, and whether partial denervation at birth (which permanently reduces the numbers of motor units) reduces the numbers of isoforms expressed.

**Concluding Discussion**

Neurotrophic theory in its conventional form (e.g. Purves, 1988) has been highly successful in providing a framework for thinking about the control of innervation of targets where these receive a distributed innervation, as in the case of smooth muscle, where NGF and related neurotrophins have been identified as important neurotrophic resources. However, the mode of competition presumed to occur in smooth muscle is perhaps too restrictive to account for stabilization and maintenance of connections which are initially focused in more restricted areas of cell surfaces.

In our view, the terminology used by Keddy (1989) to describe competition in an ecological context helps us to focus on the options to be considered for understanding neuromuscular synaptic competition. Specifically, the terminology and conceptual framework which he (and we) recommends help us to view the competitive interactions between motor nerve terminals from a number of different standpoints, and place contemporary approaches to the study of skeletal muscle innervation into perspective. This is a necessary exercise if the challenge of integrating molecular, cellular and organismic physiology is to be met (Boyd & Noble, 1993). For example, adopting the definition of competition that we propose not only underscores the importance of identifying the nature of the molecular resources for which motoneurones compete; it also indicates that success in this endeavour will not provide all the answers to the problem of synaptic competition. Nonetheless it would be helpful to know whether nerve terminals consume neurotrophic molecules, or whether the competition is based on control of access to specific isoforms of adhesion molecules that are spatially restricted in the region of the endplate. We need to know whether there is more than one type of chemical factor driving the interactions between terminals – for example, whether there are both endogenous growth-promoting and endogenous growth-inhibiting molecules in muscle – and to what extent other cell types (like Schwann cells, for example) might influence the outcome of competition. Also, it still remains important to establish how and to what extent the use and disuse (activity) of nerve terminals or muscle fibres are able to limit the availability or access to neurotrophic resources and to regulate the number and disposition of terminal boutons at a motor endplate; and to establish the role of activity-dependent competitive remodelling of neuromuscular junctions in the overall function of motor units in the control of movement.

Finally, although these ideas about consumptive and spatial competition may be applied to the problem of synaptic competition in the peripheral nervous system, it is important to
ask whether they are also likely to be of value in understanding the control of convergence and divergence in the central nervous system. In contrast to skeletal muscle, each neurone in the CNS normally receives many different kinds of synaptic input, and there is burgeoning evidence that a membrane protein not expressed in skeletal muscle, the N-methyl-D-aspartate (NMDA) receptor, plays a critical role in many forms of synaptic plasticity in the CNS (Daw, Stein & Kox, 1993; Malenka & Nicoll, 1993). Activity-dependent, competitive elimination of convergent, homologous inputs is common during critical periods of development in the CNS, for instance in visual cortex, auditory nuclei, and in the cerebellum (Jackson & Parks, 1982; Shatz, 1990; Rabbachi, Bailly, Delhaye-Bouchaud & Mariani, 1992). In adults, even profound lesions to the CNS may bring about only a minor partial denervation of individual target cells, because of the plethora of synaptic inputs to any given neurone by local interneurones. For example, complete spinal transection brings about only a minor partial denervation of lower spinal motoneurones, because the large number of synapses provided by local interneurones and peripheral sensory afferents are unaffected by the lesion. It seems probable that at least some of these synapses undergo continuous remodelling (cf. Purves et al. 1987), and sprouting of axons in the injured spinal cord is now quite well documented (Schnell & Schwab, 1993; Schwab, 1993). Some form of competition will surely occur when (if?) regenerating axons are able to reform connections on neurones partially denervated by a spinal lesion. So there may well be closer parallels than realized hitherto between, say, the competitive reinnervation of partially denervated skeletal muscle and the processes required to re-establish functionally appropriate innervation of partially denervated cells in the injured CNS. In the past, the neuromuscular junction has admirably served neurobiologists seeking explanations for a number of general neurobiological phenomena (such as the mechanism of chemical synaptic transmission; Katz, 1969; Eccles, 1990). Perhaps a clearer understanding of the principles and mechanisms of synaptic competition at neuromuscular junctions will therefore make a significant contribution towards explaining how the numbers and disposition of connections elsewhere in the nervous system are regulated and maintained.

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