Regulation of motor neuron dendrite growth by NMDA receptor activation

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SUMMARY

Spinal motor neurons undergo great changes in morphology, electrophysiology and molecular composition during development. Some of this maturation occurs postnatally when limbs are employed for locomotion, suggesting that neuronal activity may influence motor neuron development. To identify features of motor neurons that might be regulated by activity we first examined the structural development of the rat motor neuron cell body and dendritic tree labeled with cholera toxin-conjugated horseradish peroxidase. The motor neuron cell body and dendrites in the radial and rostrocaudal axes grew progressively over the first month of life. In contrast, the growth of the dendritic arbor/cell and number of dendritic branches was biphasic with overabundant growth followed by regression until the adult pattern was achieved. We next examined the influence of neurotransmission on the development of these motor neuron features. We found that antagonism of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor inhibited cell body growth and dendritic branching in early postnatal life but had no effect on the maximal extent of dendrite growth in the radial and rostrocaudal axes. The effects of NMDA receptor antagonism on motor neurons and their dendrites was temporally restricted; all of our anatomic measures of dendrite structure were resistant to NMDA receptor antagonism in adults. These results suggest that the establishment of mature motor neuron dendritic architecture results in part from dendrite growth in response to afferent input during a sensitive period in early postnatal life.

Key words: activity-dependent development, spinal cord, critical period, motor neuron, dendrite

INTRODUCTION

Adult mammalian motor neurons receive input at an estimated 20,000-50,000 synapses located on dendrites and the cell soma (Gelfan, 1963; Shepherd, 1990; Ulfhake and Cullheim, 1988). Both the qualitative and quantitative aspects of this innervation are likely to be a function of the size and geometry of the neuronal dendritic arbor (Purves and Lichtman, 1985b; Purves, 1983; Purves and Hume, 1981). Knowledge of the forces that regulate dendrite growth and maturation will critically impact upon our understanding of the connectivity and computational capacity of motor neurons.

A variety of epigenetic factors have been suggested to influence dendritogenesis, including the location of motor neurons within the spinal cord, their peripheral projection, the afferent inputs, dendritodendritic interactions, humoral and mechanical factors. The participation of synaptic inputs have received much attention because the ingrowth and organization of afferents correlates well with the period of dendritic remodeling during development (Vaughn, 1989). In fact, dendrites from many different neuron types grow as a function of afferent input although it is not clear if this is due to the level of excitatory drive provided by the input, its pattern of activity or by the provision of trophic support (Bodnarenko and Chalupa, 1993; Purves and Lichtman, 1985a; Riddle et al., 1993; Balazs et al., 1988; Smith, 1974; Pearce et al., 1987; Mattson et al., 1989). Several studies have specifically examined the role of patterned afferent activity on dendrite structure. In the cat, visual experience in early postnatal life can modify the orientation of the dendritic field of cortical layer III pyramidal cells and this may determine receptive field properties (Tieman and Hirsch, 1982). Work on frog optic tectum suggests coherent afferent activity acts on individual primary and secondary dendrites to influence their behavior (Katz and Constantine-Paton, 1988). The cellular mechanism(s) that may account for dendrite responses include active inhibition of dendrite extension, dendritic pruning or an effect of selective facilitation of dendrite growth. Thus, the basic process by which afferent activity governs the establishment of dendritic architecture is unknown.

Previous work indicates that the molecular development of motor neurons depends on segmental and suprasegmental inputs during a sensitive period in early postnatal life (Kalb and Hockfield, 1988). These effects are mediated by electrical activity within the neuromuscular unit supporting the view that motor neurons undergo activity-dependent development (Kalb and Hockfield, 1994). Pharmacological investigations indicate the involvement of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor in this process (Hockfield et al., 1990; Kalb and Hockfield, 1990). This is of particular note since the NMDA receptor also participates in the activity-dependent development of the cat visual cortex and frog optic tectum (Bear et al., 1990; Kleinschmidt et al., 1987; Scherer and Udin, 1989; Cline et al., 1987; Cline and Constantine-Paton, 1989). Receptor autoradiography reveals that NMDA receptors are transiently expressed at high levels in the devel-
oping ventral horn, and over the first few weeks of life NMDA receptors are lost from all spinal cord regions except the substantia gelatinosa (Kalb et al., 1992). These results suggest the development of motor neurons involves the activation of ventral horn NMDA receptors during a sensitive period in early postnatal life. In the present study we investigated the role of NMDA receptor activation on the postnatal growth of motor neuron dendrites.

METHODS AND MATERIALS

Animals
To study the normal development of quadraceps motor neuron dendrites, we labeled the dendritic tree from animals of both sexes at age (post-natal) P7, P14, P21, P28 and adults (older than 3 months). To maintain optimal care of pups, neonates were taken from litters that were culled to less than 10 pups per dam. Animal were maintained in 12 hours:12 hours light:dark cycle and given ad libitum access to food and water.

Administration of NMDA receptor antagonists
To examine the effects of NMDA receptor antagonism on the development of the motor neuron dendritic tree the effect of two different NMDA receptor antagonists was evaluated. One set of animals received 1 mg/kg of MK-801 or saline by daily intraperitoneal injection from P7 to P21. The second set of animals received aminophosphonovaleric acid (APV). APV does not cross the blood-brain barrier so the drug (or saline) was incorporated into the slow-release plastic matrix elvax and a 50 µm thick slice was implanted at a laminectomy site over the lumbar enlargement at P7 (Cline et al., 1987; Kalb and Hockfield, 1990). Surgical procedures involving the use of animals were approved by the Yale University Animal Care and Use committee according to NIH guidelines. Details of the preparation and implantation of elvax have been described (Kalb and Hockfield, 1990). Briefly, P7 animals were anesthetized by hypothermia and the upper lumbar enlargement was exposed at a laminectomy site. Elvax impregnated with APV or saline was placed over the exposed spinal cord and the site sutured closed. Awake, warm and dry pups were returned to their nursing mother and remained part of the culled litter for 12 days before the labeling procedure. Repeated neurologic evaluation after the surgery showed that the surgical procedures were well tolerated. Less than 5% of animals demonstrated a myelopathy and they were not included in the analysis. APV is released from an implant at a steady rate for at least 14 days (Cline and Constantine-Paton, 1989) and at the APV concentration used no antagonism of non-NMDA glutamate receptors occurs (Hockfield et al., 1990).

To evaluate the effect of NMDA receptor antagonism on the dendritic tree of adult motor neurons, a set of adult animals were implanted with APV-elvax over the lumbar enlargement. For the surgical procedure, adults were anesthetized with Ketamine (50 µg/g body weight) and Xylozine (4 µg/g body weight) and operative and postoperative care was identical to that given to neonates. Operated adults were individually housed. Two weeks later, the dendritic tree was labeled and quantitatively examined.

Histochemistry and morphometry
Since certain neuronal subpopulations may be more sensitive to activity-deprivation than others, we wanted measures of dendrite length and topography from a population of motor neurons. To this end, motor neuron dendrites were labeled with cholera toxin-conjugated horseradish peroxidase (CTHRP, List Biological Laboratories) and camera lucida drawing of labeled motor neuron cell bodies and dendrites were entered into a quantitative image analysis program. Although this method of labeling motor neuron dendrites may not delineate the entire dendritic tree, it is an accurate measure of dendrite arbor that can be used to compare two groups of animals (Kurz et al., 1986; Goldstein and Sengelaub, 1993; Goldstein et al., 1990).

In a series of pilot experiments we determined that optimal labeling of neonatal and adult motor neurons and their dendritic trees was...
obtained after making injections of CTHRP (0.4% in 5 μl) into multiple sites under direct visualization in the right quadriceps muscle of anesthetized animals. Two days later animals were perfused with cold 0.1 M phosphate-buffered saline (pH 7.4) followed by 1% paraformaldehyde/1.25% glutaraldehyde then 0.1 M phosphate buffer plus 5% sucrose. Spinal cords were embedded in gelatin, cryoprotected overnight in 10% sucrose and sectioned on a Jung-Reichert Cryostat. Horizontal free floating tissue sections (45 μm) were reacted with tetramethylbenzidine (TMB) (Mesulam et al., 1980). To minimize variability of the histochemical reaction, the volume of fixative and reaction times were held constant and tissue from animals in each experimental group were reacted together. After mounting on slides, spinal cord sections were viewed under dark-field illumination and complete drawings of labeled neurites and cell bodies were made with camera lucida at 420× magnification. Drawing began from the first section that had a labeled neurite and every eighth section was drawn thereafter until no further labeled processes or cell bodies were seen. By carefully manipulating the plane of focus at high magnification, the path traveled by individual dendrites could be tracked in all three axes. Points where individual dendrites overlapped could be distinguished from dendritic branching (Fig. 1). These drawings were entered into the MacMeasure program 1.9 (Rasband, NIH) using an ADB graphics tablet (Kurta).

A variety of measures of dendrite architecture were established. The dendritic arbor/cell value was determined by dividing the summed lengths of labeled dendrites by the total number of labeled motor neurons. Cell body cross-sectional area was determined by outlining the perimeter of the labeled motor neuron cell body. The transition from cell body to proximal dendrite may be difficult and arbitrarily determined but the same criteria were applied to all neurons. The greatest radial extent of dendrite was the distance of the tip of the most distal dendrite within a horizontal spinal cord section to the nearest labeled motor neuron cell body. Three measures were made per animal and the average value used. The number of bifurcation points was determined by (1) reviewing all the drawings from an individual animal and finding the drawing with the overall largest dendritic tree, (2) counting the number of unequivocal bifurcations of labeled dendrites in this drawing. The number of labeled motor neurons was determined by counting TMB-stained cell bodies with an unequivocal nucleus. The rostrocaudal extent of dendrites was determined by counting the number of 45 μm thick sections (drawn and undrawn), from the first to last that had a labeled process. Each numerical value in Figs 2, 3 and Tables 1, 2 represents the mean and standard deviation from at least 5 animals in each experimental group.

Statistical analysis consisted of analysis of variance.

RESULTS

Normal development

Postnatal changes in motor neuron dendrite features were evaluated in variously aged neonatal animals until the adult phenotype was attained. These results are displayed graphically in Figs 2, 3. The postnatal growth of motor neuron cell body cross-sectional area increased steadily from P7 through P28 when the adult motor neuron cell body size is essentially achieved. The cross-sectional area of P28 motor neurons is approximately 50% larger than P7 motor neurons (F(1,8)=7.3, P<0.05) and not significantly different than adult motor neurons (F(1,8)=0.006, P>0.5). We next examined the maximal extent of motor neuron dendrites within the segmental cord (radial extent) and in the longitudinal axis (rostrocaudal extent). Dendrite growth in both directions occurs steadily over the first month of life until the adult pattern of greatest extent of dendrites is achieved. The maximal radial extent of dendrites at P28 is approximately 75% greater than at P7 (F(1,8)=33, P<0.001) and is not significantly different than in adults (F(1,8)=0.03, P>0.5). The rostrocaudal extent of dendrites at P28 is approximately 50% greater than at P7 (F(1,8)=7.6, P<0.05) and not significantly different than in adults.

Fig. 2. Postnatal growth of motor neuron cell body (A) and dendrites in the rostrocaudal (B) and radial (C) axes. The growth of these motor neuron features is monophasic and adult values are reached by P28. Bar heights represent mean values from at least 5 animals ± s.e.m.
Over the next week the number of branches approximately halved (F(1,7)=16.2, P<0.01) (Fig. 3). The number of branches at P28 is not significantly different from the value in adults (F(1,8)=0.89, P>0.3). In sum, these motor neuron dendrite measures show biphasic growth with overabundant growth in the first 3 weeks of life then regression until they reach their adult values.

**Effects of NMDA receptor antagonism on structural development of motor neurons**

We next evaluated the effects of NMDA receptor antagonism on the anatomical maturation of motor neurons. For these experiments, neonates were implanted with APV-elvax over the rostral lumbar enlargement at P7, injected with CTHRP on P19, killed on P21 and subsequently histochemically reacted with TMB for quantitative analysis.

The most striking finding is that the dendritic arbor/cell from APV-treated neonates (2238±783 µm) was approximately 40% smaller per cell than the dendritic arbor/cell from saline-treated animals (3672±791 µm, n=6) and this difference was significant by ANOVA (F(1,10)=6.54, P>0.03). This is shown in typical stained sections from APV and saline-treated animals (Fig. 4) and in composite camera lucida drawings (Fig. 5). In addition to reducing the dendritic arbor/cell, APV also lead to a significant 25% reduction in motor neuron cell body size (1346±189 versus 1751±182 µm²; F(1,10)=13.46, P<0.004). Although the average size of the dendritic arbor/motor neuron is smaller in the APV-treated animals in comparison with controls, the radial length of the longest dendrite within the segmental spinal cord is not significantly different between APV-treated animals (486±88 µm) and control animals (558±120 µm; F(1,10)=1.28, P>0.29). If the maximal extent of dendrite growth is the same for APV versus control animals but the amount of dendritic arbor/motor neuron is smaller in APV-treated animals, it suggests that control animals have a more highly branched dendritic tree than APV-treated animals. To examine this possibility we counted the number of dendritic bifurcation points in spinal cord section drawings. We found that the number of branches in control animals (122±32) is significantly larger than the corresponding value in APV-treated animals (59±13; F(1,10)=20.0, P<0.002). These findings (summarized in Table 1) indicate that the overall surface area of dendritic membrane is larger in control than APV-treated neonates, in part because it is more highly branched. Motor neurons with more complex dendritic trees are likely to have greater convergent innervation with functional consequences for neuronal activation and neural unit size (Purves and Lichtman, 1985b).

One possible explanation for these observations is that APV inhibits the retrograde transport of CTHRP into the cell body and subsequent distribution into dendrites. For a variety of reasons this does not appear to be the case. First, the longest dendrite in APV-treated animals is not significantly different from the corresponding value in controls. If APV influenced the axonal and dendritic transport of CTHRP then one would expect the longest dendrite to be shorter in the APV-treated animals. Second, we found that the average the number of motor neurons retrogradely labeled with CTHRP in APV (17±5) was not significantly different from the value in control animals (20±4; F(1,10)=1.35, P>0.26). Third, the rostrocaudal extent of the dendritic tree in APV-treated animals (3360±685
µm) was not significantly different from the corresponding value in control animals (3245±603 µm; F(1,10)=0.02, P>0.80). Thus, although the CTHRP labeling method does not provide Golgi-like delineation of the motor neuron dendritic tree, it yields a consistent measure of the dendritic tree where effects of APV on neuritic transport to CTHRP does not appear to be a factor.

In the next set of experiments we examined the effects of a second NMDA receptor antagonist, MK-801. MK-801 has the advantage of crossing the blood-brain barrier after systemic injection and so was administered by daily intraperitoneal injections (1 mg/kg) from P7 through P21. Motor neurons and their dendritic tree were labeled as above by CTHRP.

The dendritic arbor/cell in MK-801-treated neonates was significantly smaller (1482±451) than saline-injected control animals (3638±322) by ANOVA (F(1,8)=60.4 P<0.001). In

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**Fig. 4.** Dark-field photomicrographs of CTHRP-labeled motor neurons and dendrites within the ventral horn from saline- (A) and APV- (B) treated neonatal rats. Motor neuron cell bodies are located in the lateral ventral horn with groups of dendrites oriented primarily dorsally or medially (up or left respectively). The density of dendrites in APV-treated neonates is reduced in comparison with saline-treated animals, although the length of the longest dendrites in both animals are approximately equal. Bar, 60 µm

**Fig. 5.** Camera lucida composite drawings of CTHRP-labeled motor neurons and dendrites from neonatal rats treated from P7 to P21 with either saline (A) or APV (B) drawn at 315 µm intervals through the quadraceps motor neuron pool. The density of motor neuron dendrites is reduced in APV-treated animals. Bar, 110 µm.
In addition, cell body size and number of dendritic bifurcations were significantly reduced in MK-801 treated animals in comparison with controls. MK-801 did not influence the number of labeled motor neurons, the greatest dendritic extent in the radial or rostrocaudal axes. Quantitative data from MK-801 treated neonates is summarized in Table 1. The finding that two different drugs, which work at different sites in the NMDA receptor channel complex, have the same effects on motor neuron development, strongly supports the view that activation of the NMDA receptor modified the development of motor neuron dendrites.

**Effects of NMDA receptor antagonism on structural features of adult motor neurons**

To determine if the effect of APV treatment on motor neuron dendrites was temporally restricted we examined the effect of 14 days of APV on adult motor neuron dendrites. Twelve days after implanting APV-Elvax over the lumbar enlargement of rats older than 90 days, CTHRP was injected into the quadriceps muscle and 2 days later the tissue stained with TMB. No significant difference in dendritic arbor/cell was seen when comparing APV-treated animals (3364±665 µm; n=6) with saline-Elvax controls (3176±368µm, n=6; F(1.8)=0.26, P>0.5). In addition, APV had no effect on the adult motor neuron cell soma size (2155±117 versus 2047±216 µm²; F(1.8)=0.96, P>0.3), number of labeled motor neurons (14±2 versus 14±4; F(1.8)=0.28, P>0.6), length of the longest radial dendrite (582±89 versus 549±43 µm; F(1.8)=0.20 P>0.6), number of bifurcations (52±12 versus 63±21, F(1.8)=0.54, P>0.46) or rostrocaudal extent of dendrites (3420±402 versus 3330±298 µm; F(1.8)=0.21, P>0.75). These results are summarized in Table 2. Thus once the motor neuron dendritic tree is established, the maintenance of its branching pattern and greatest extent is not dependent upon NMDA receptor activation.

**DISCUSSION**

In the present study we have quantitatively examined the postnatal growth of rat motor neuron dendrites and examined the role of NMDA receptor activation in the maturation of the dendritic tree. We find exuberant growth of dendrites of the first 3 weeks of postnatal life followed by a period of resorption until the adult architecture is achieved. Antagonism of the NMDA subtype of glutamate receptor from P7 to P21 results in a reduction in the dendritic arbor per motor neuron. The reduction in dendritic bifurcations in such animals suggests NMDA receptor blockade reduces the dendritic arbor per cell in part by preventing the elaboration of new branches. The effects of NMDA receptor blockade on dendrites are age-dependent; neonatal but not adult dendrites are influenced by NMDA receptor antagonism. These results provide evidence that motor neuron dendrites mature during an NMDA receptor sensitive period in early postnatal life.

The establishment of the motor neuron dendritic tree may depend upon a balance of growth promoting and growth inhibiting processes. The smaller, less branched dendritic arbor

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### Table 1. Effects of the NMDA receptor antagonists on quantitative measures of neonatal motor neuron cell bodies and dendrites

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<th>Neonate</th>
<th>Adult</th>
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<tr>
<td></td>
<td>APV</td>
<td>Saline</td>
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<tr>
<td>Dendritic arbor/cell (µm)</td>
<td>2338±783</td>
<td>3672±791</td>
</tr>
<tr>
<td>Cross sectional cell body area (µm²)</td>
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<td>Longest radial dendrite (µm)</td>
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<td>558±120</td>
</tr>
<tr>
<td>Rostrocaudal extent of dendrites (µm)</td>
<td>3360±685</td>
<td>3245±603</td>
</tr>
<tr>
<td>Number of labeled cells</td>
<td>16.8±5</td>
<td>20±4</td>
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Values for cross sectional cell body area, dendritic arbor/cell and number of dendritic bifurcations are statistically significantly smaller in APV- and MK-801-treated animals than in controls (*=P<0.05, **=P<0.01). Values for longest radial dendrite, rostrocaudal extent of dendrites, and number of labeled cells do not differ significantly between drug treated and control animals.

### Table 2. Effects of the NMDA receptor antagonist on quantitative measures of adult motor neuron cell bodies and dendrites

<table>
<thead>
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<th>Saline</th>
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<td>Cross sectional cell body area (µm²)</td>
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<td>14±2</td>
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None of the values differ significantly between APV-treated and control animals.
in drug-treated animals suggests that over the first 3 weeks of postnatal life, NMDA receptor activation normally provides a growth promoting or differentiation signal to developing motor neurons. Without such a signal the motor neuron dendritic arbor is stunted either due to intrinsic growth limitations or the unopposed action of a growth inhibiting signaling system. Our results suggest that NMDA receptor activation can selectively facilitate dendrite growth, possibly through promoting the formation of new branches or stabilizing otherwise transient dendritic structures.

During the first month of postnatal life we find an approximate 50% increase in motor neuron cell body cross sectional area and a concomitant monotonic increase in dendritic growth in the radial and rostrocaudal axes. In contrast, the growth of dendritic arbor/motor neuron and the number of dendritic branches is biphasic; these characteristics increase markedly during the first 3 weeks of postnatal life followed by a period of regression. These results generally agree with previous studies that have employed a variety of techniques to examine the postnatal growth of the motor neuron and its dendrites. A monotonic increase in motor neuron cell body size and overall dendritic growth was found in the mouse cervical spinal cord (Sakla, 1959), rat thoracic (Cummings and Stelzner, 1984) and lumbar cord (Goldstein and Sengelaub, 1993), and cat triceps surae motor neurons (Ulfhake et al., 1988). In contrast, biphasic motor neuron dendrite growth has been noted in rat genioglossal (Nunez-Abades et al., 1994), phrenic (Lindsay et al., 1991), forelimb (Curfs et al., 1993) and cat phrenic (Cameron et al., 1991) motor neurons. The discrepancies between these studies can be accounted for by differences in: (1) species, (2) labeling techniques (3) methods of analysis and (4) heterogeneity intrinsic to different types of motor neurons. Despite the differences, virtually all studies provide evidence for remodeling of the dendritic tree during early postnatal life. For example, overgrowth followed by resorption has been found for dendritic spines (Cummings and Stelzner, 1984) or terminals (Cameron et al., 1991), the longest radial dendrite (Lindsay et al., 1991; Curfs et al., 1993), dendritic arbors/cell (Goldstein et al., 1990), and dendrite branches (Nunez-Abades et al., 1994; Ulfhake et al., 1988). Similarly our results identify features of the rat quadriceps motor neuron dendritic tree that are transient and undergo remodeling during early postnatal life.

The behavior of motor neuron dendrites during development is likely to be due to the interplay of cell autonomous and epigenetic factors. Most investigations indicate that the number and orientation of primary dendrites are intrinsically determined, while branching and number of terminal dendrites are potentially influenced by extrinsic factors. One of the clearest examples of an epigenetic factor influencing dendrite growth occurs in motor neurons of the sexually dimorphic spinal nucleus of the bulbocavernousus, where testosterone strongly promotes dendrite growth (Goldstein et al., 1990). For other motor neurons, the afferent projections have been proposed to play an important role in dendritogenesis by providing trophic support and/or through synaptic activity. Support for the view that synaptic activity can influence dendritic architecture comes from in vitro studies in the hippocampus (Mattson et al., 1989) cerebellum (Pearce et al., 1987; Balazs et al., 1988; Schilling et al., 1991) and retina (Bodnarenko and Chalupa, 1993) and in vivo studies in the lateral superior olive (Sanes and Chokshi, 1992) and neocortex (Harris and Woolsey, 1979; Van der Loos and Steffen, 1980). The present in vivo study demonstrates that activation of NMDA receptors during development promotes motor neuron dendrite growth. These findings expand upon previous work showing that the molecular maturation of motor neurons occurs during an activity-dependent critical period (Kalb and Hockfield, 1994).

The NMDA receptor has been implicated in the activity-dependent segregation of afferents and refinement of topographic maps in the developing feline and frog visual systems (Cline et al., 1987; Bear et al., 1990; Cline and Constantine-Paton, 1990; Cline and Constantine-Paton, 1989; Scherer and Udin, 1989; Kleinschmidt et al., 1987). The nearly synchronous visually evoked electrical activity of neighboring retinal ganglion cells could provide the appropriate drive to target cells to activate NMDA receptors. It has been proposed that during development synapses are selectively stabilized when NMDA receptors are activated (Constantine-Paton et al., 1990; Constantine-Paton, 1990). Although these studies emphasize the instructive effects of NMDA receptor-mediated activity on axon morphology there is reason to believe that target cell morphology could be similarly regulated in an activity-dependent manner. Rearing kittens in a visual environment composed solely of vertical lines, for example, modifies the orientation of cortical layer III pyramidal cell dendrites in comparison with controls, and these structural changes may subserve electrophysiological orientation preferences (Tieman and Hirsch, 1982). In frogs, when two eyes are forced to innervate the same tectum, the retinal afferents segregate into stripes so that terminals with similar activity patterns are grouped together (Constantine-Paton and Law, 1978). The ramification of individual dendrite branches of neurons within such tecta respect boundaries of segregated retinal afferents (Katz and Constantine-Paton, 1988). These studies illustrate the plastic behavior of developing dendrites and suggest activity-dependent processes can regulate dendrite geometry. The present observations on developing motor neuron dendrites suggest that one mechanism of regulating postsynaptic cell morphology can be through a pathway involving NMDA receptor activation. We suggest the basic rules underlying activity-dependent changes in axon structure during development may be similarly employed in the establishment of the dendritic structure of the postsynaptic cell.

The major changes in dendrite structure that occur during early postnatal life have marked effects on the pattern of synaptic inputs onto neurons (Purves and Lichtman, 1985b). The recognition that activity participates in this process raises the possibility that one function of NMDA receptor-mediated development of motor neuron dendrites may be to sculpt or fine tune synaptic connectivity. We propose a Hebbian model (Hebb, 1949) of dendrite maturation: portions of the dendritic tree behave as units of synaptic integration with individual dendritic branches growing when local patterned afferent input leads to the activation of NMDA receptors. The view that developing motor neurons share some of the plastic features exhibited by hippocampal (Nicoll et al., 1988; Bliss and Collingridge, 1993) and neocortical neurons (Kirkwood et al., 1993; Mooney et al., 1993) is supported by the demonstration of both long-term potentiation and depression in the ventral horn of neonatal rats (Pockett and Figurov, 1993).

An alternative view is that NMDA receptor antagonist

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Activity-dependent plasticity of the development of spinal circuitry may provide insights into the underlying cellular and molecular mechanisms. Activity-dependent plasticity of the development of spinal circuitry may have implications for attempts to overcome spinal cord injury by promoting synaptic reorganization.

The availability of a rodent system for studying NMDA receptor mediated developmental events may provide insights into the underlying cellular and molecular mechanisms. Activity-dependent plasticity of the development of spinal circuitry may have implications for attempts to overcome spinal cord injury by promoting synaptic reorganization.

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