

## Vestibular Deprivation and the Development of Dendrite Bundles in the Rat

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### SUMMARY

Motoneuronal pools of muscles that subserve postural tasks contain dendrite bundles. We investigated in the rat the development of these bundles in the pools of the long back muscles and related this to postural development. Motoneurons and their dendrites were retrogradely labeled by injecting unconjugated cholera toxin subunit B (CTB) into the muscles of 54 normal rats from birth until adulthood and into 18 rats that were vestibularly deprived from the 5th postnatal day (P5). Dendrite bundles coursing in a transverse direction already occurred at P1. From P4, the first longitudinal bundles could be observed, but the major spurt in development occurred between P6 and P9, when conspicuous bundles developed coursing in rostro-caudal and transverse directions. This is the age when rats become able to stand freely and walk a few steps. Around P20, the dendrite bundles attained their adult characteristics. Vestibular deprivation by plugging both semicircular horizontal canals did not lead to a retarded development of dendrite bundles nor to a changed morphology. This finding is remarkable, as behavioral analysis

showed a delay in postural development by about 3 days. We hypothesize that dendrite bundles in the pools of the long back muscles function to synchronize the motoneurons in different spinal cord segments.

### KEYWORDS

neuro-ontogeny, rat, back muscle motoneurons, dendritic reorganization, postural control

### INTRODUCTION

Dendrite bundles can be observed in several brain areas, such as the cortex, thalamus, brain stem, and spinal cord in monkey, cat, rat, and pig; (for review see Roney et al., 1979). In the rat, dendrite bundles were observed in the cervical spinal cord (for example, Anderson et al., 1988) and at lumbosacral levels, large bundles containing more than 1200 dendrites were demonstrated (Kerns & Peters, 1974; Anderson et al., 1976; Bellinger & Anderson, 1987a,b). These bundles probably arise from motoneurons innervating pelvic muscles (Anderson et al., 1976; Schroder, 1980; Nicolopoulos-Stournaras & Iles, 1983; Bellinger & Anderson, 1987b). Other dendrite bundles are connected to motoneurons innervating extremity and trunk muscles.

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In the 1970s, the Scheibels (Scheibel & Scheibel, 1970) demonstrated that the ability of a kitten to walk with its ventral body surface free from the floor occurs by the age when dendrites in the lumbar spinal cord reorganize into bundles. On the basis of this finding, the authors suggested that dendrite bundles are involved in the generation of complex motor patterns. The development of dendrite bundles was studied using the Golgi technique, but this method does not allow the identification of neurons with certainty. More recently, in developing rats, we injected the soleus and tibialis anterior muscles with retrogradely transported cholera toxin subunit B (CTB). This method does permit the identification of the motoneurons, and unconjugated CTB visualizes the dendritic trees to a considerable extent. Motoneurons innervating the soleus muscle appeared to form dendrite bundles around the 16<sup>th</sup> postnatal day (P16), but no such reorganization was observed at any age in the pool of the tibialis anterior muscle (Westerga & Gramsbergen, 1992). In subsequent research in adult rats, we inventoried the occurrence of dendrite bundles in the motoneuronal pools of 21 different muscles. The results from that study demonstrated that dendrite bundles are confined to motoneuronal pools of certain extensor muscles in the extremities, as well as in the trunk muscles (Gramsbergen et al., 1996). The common denominator of the functions of these muscles is opposing gravity and controlling posture, and dendrite bundles might play a crucial role in these functions. As posture and patterned extremity movements develop independently and follow a different time course during early neuro-ontogeny (Gramsbergen, 1998), investigating the development of dendrite bundles in back muscles (which are important for postural maintenance) and relating their development to motor development might give further insight into their physiological significance.

Behavioral studies in the rat show important changes in movement patterns and in postural control in the first 3 weeks of life (Almli & Fisher, 1977; Altman & Sudarshan, 1975; Blanck et al, 1967; Westerga & Gramsbergen, 1990). In the first postnatal days, locomotion is effected by vigorous and rhythmic trunk movements and crawling with the paws (Gramsbergen et al, 1970; Gramsbergen, 1998). From P8 to P11, rats are able to stand with their ventral body surface free, but they walk staggeringly. At around P15 to P16, this immature pattern of locomotion is suddenly replaced by an adult-like walking pattern, characterized by fluent leg and trunk movements and a remarkable increase in walking speed (Westerga & Gramsbergen, 1990). We suggested that this shift from immature locomotion into fluent walking probably is related to developmental changes in postural control (Gramsbergen, 1998). Before P15, electromyogram (EMG) recordings in the long backmuscles show that these muscles are tonically active during bouts of locomotion, but only from P15 to P16 does burst activity occur, which is phase-linked to the leg movements (Geisler, et al., 1996). Even stronger support for the hypothesis that postural control is the limiting factor for the fluent walking pattern to occur was obtained from experiments in which we vestibularly deprived rats from P5 (by plugging the horizontal semicircular canals). Such deprivation leads to a retardation in postural development (Geisler, et al., 1997). The fluent adult-like walking pattern in these deprived rats is delayed by about 3 days, and this holds as well for the development of the specific EMG patterns in the longissimus muscles during locomotion (Geisler & Gramsbergen, 1998).

The long back muscles play an important role in the fixation of the trunk and the maintenance of body posture during standing and walking, and the research question of the present study is at what age the dendrite bundles in the pools of these

muscles develop. The second question is whether vestibular deprivation from P5, which causes a considerable delay in postural development, induces retardation in the development of dendrite bundles as well.

## METHODS

### Animals

Hooded rats of the Lister strain were used. The animals were kept in an animal room that was lighted from 08:00 h until 18:30 h. All experimental procedures had been reviewed and approved by the Ethics Committee of the Faculty of Medical Sciences of the University of Groningen (FDC 091). Pregnant females were inspected for offspring at least twice daily. The day of birth was designated as postnatal day 1 (P1). The rats were weighed daily. Before P10, the rats were identified with non-toxic ink, and thereafter the black and white pattern of their skin enabled identification of the individuals. A total of 54 normal rats were studied at postnatal days 1, 2, 3, 4, 6, 7, 9, 10, 12, 14, 16, 20, 36, 60, and 180. At the youngest ages (until P6), we refrained from verifying the sex of the animals; 17 of the rats of older ages were males and 20 were females. At most ages, we studied four animals. In two rats, the medial multifidus muscle was injected and in the other two the lateral longissimus muscle. In a few animals, the multifidus muscle at the right side and the longissimus muscle at the left side were injected. Material from male and female rats was equally distributed over the age groups and the two muscles.

In addition, we studied 8 male and 10 female rats that were vestibularly deprived. At P5 in these rats, the left and right horizontal semicircular canals were exposed under ether narcosis, and the canals were plugged with a gutta percha point

(Maillefer, Switzerland; for further details on the operation see Geisler, et al., 1997). Motoneurons of the multifidus and longissimus muscles in this group of rats were labeled at P7, P9, P15, and P25.

### Labeling of Motoneurons

Up to 2 weeks of life, rats were anesthetized with ether, and at later ages with fluanisone (10 mg/mL) and fentanyl (0.2 mg/mL): 0.1 ml per 100 g body weight (Hypnorm; Janssen Pharmaceuticals, Tilburg, The Netherlands). Motoneurons and their dendrites were retrogradely labeled with unconjugated subunit B of Cholera Toxin (CTB). A quantity of 2 to 4  $\mu$ L in 3 to 5 injections of a 0.1% solution of CTB was injected into the muscles by means of a pulled glass pipette connected to a manually operated injection system. After the injections, the area was rinsed with saline, dried carefully, and the wound was closed. After survival times ranging from 12 h in rats injected at P1 to 3 d in rats injected from P6, the rats were deeply anesthetized with ether and perfused transcardially with a solution containing 0.8% NaCl, 0.8% sucrose, 0.4% d-glucose in phosphate buffer (0.05M, pH 7.5) (ranging from 40 mL in the case of the youngest rats to 200 mL in the older rats), and thereafter with 40 to 200 mL fixative (4% paraformaldehyde, 0.2% glutaraldehyde in phosphate buffer [0.1M, pH 7.5]). The spinal cord was removed and immersed overnight in phosphate buffer (0.05 M) containing 30% sucrose. The spinal cord was embedded in Tissue Tek (Sakura, Tokyo, Japan), and longitudinal sections (40  $\mu$ m) were prepared on a freezing microtome. In normal rats, at P3, P6, P12, and P20, we also made transversal sections. The material was further processed with a three-stage immunological technique and counterstained with Nissl stain (for further details of the method see, Westerga & Gramsbergen, 1992).

The motoneurons and their dendritic trees at both the right and left sides were analyzed. We considered the dendrites to be bundled when at least three dendrites coursed in parallel (and sometimes in apposition) for at least a few hundred  $\mu\text{m}$  and with a distance of less than 1 dendrite diameter between the dendrites (for further details see Gramsbergen et al., 1996).

## RESULTS

### General Remarks

At all ages, injection of CTB muscles resulted in a dense labeling of spinal motoneurons of both the multifidus and the longissimus muscles and in an extensive labeling of their dendrites. Up to P20, we regularly observed motoneurons that were labeled at the contralateral side after injections in either of the two long back muscles. Beyond this age, contralateral labeling was observed only after injections into the multifidus muscle. Up to P20, sometimes a few smaller neurons were labeled outside the pools. Undoubtedly these neurons were sympathetic preganglionic neurons and situated dorso-laterally to the central canal. The dendrites of these neurons ran in rostro-caudally oriented longitudinal and transverse dendrite bundles.

The motoneuronal dendrites (and particularly those running in transverse directions) can best be followed in thick horizontal sections as they run more or less in the horizontal plane. The descriptions in the following sections, therefore, are based mainly on horizontally cut sections or reconstructions from horizontal sections.

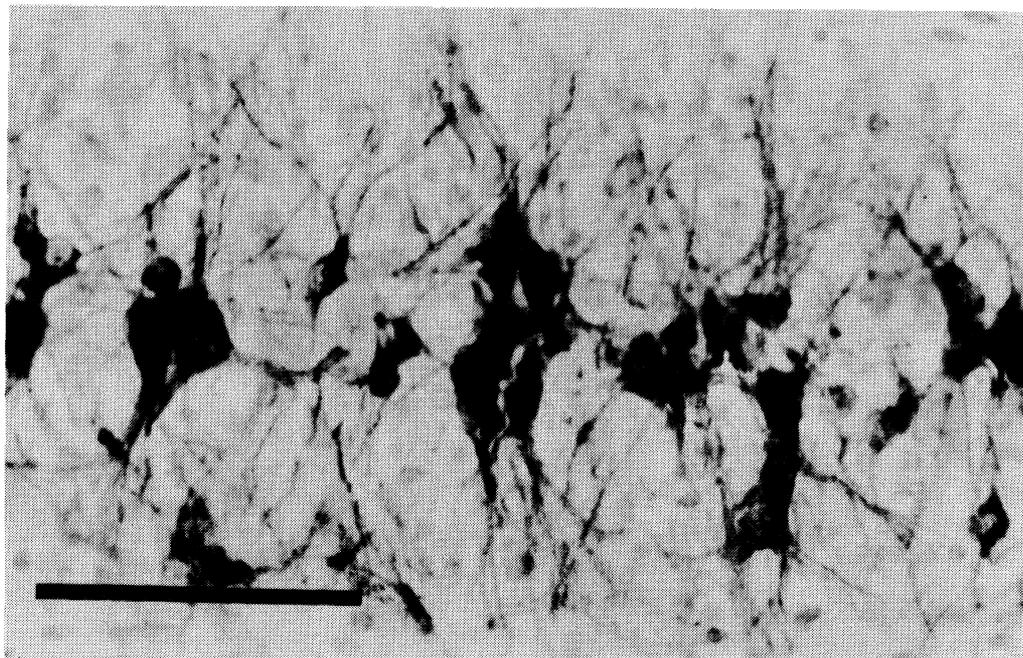
### Development of Dendrite Bundles in Normal Rats

During the first few postnatal days, the motoneurons innervating the multifidus muscle were

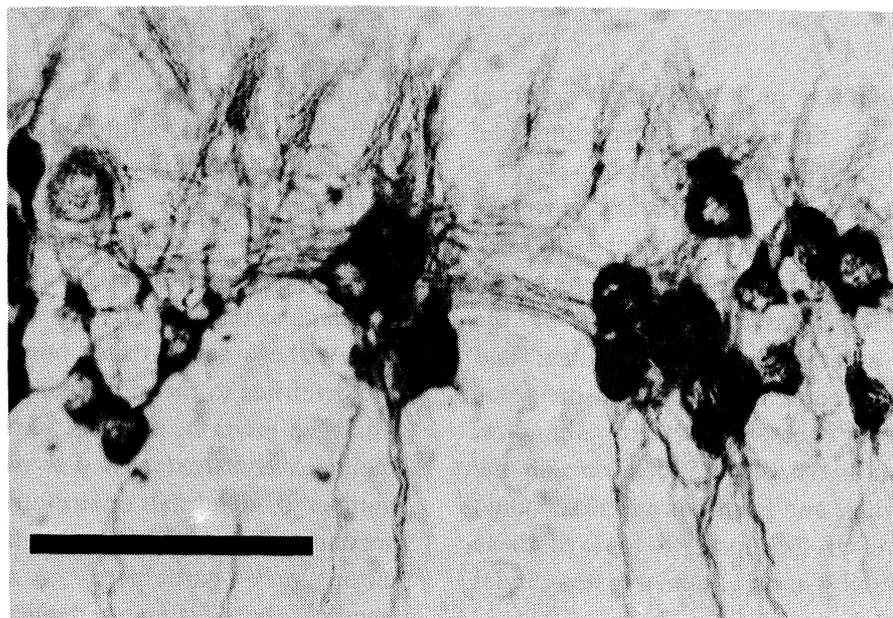
round or elliptical in shape, and most of the neurons were arranged in clusters, obviously in somato-somatic contact with each other (Fig. 1). The motoneurons innervating the longissimus muscle had a similar morphology. The motoneurons—the motoneuronal ‘pool’—innervating the multifidus muscle was located medio-ventrally and clearly separated from that of the longissimus muscle, which is located more ventrally. Most dendrites in both pools coursed in a transverse direction. The dendrites at this age may surpass the median plane and laterally extend as far as the boundary of the gray matter. Some of these dendrites formed bundles consisting of a few dendrites. Dendrites coursing in a rostrocaudal, longitudinal direction occasionally occurred, but they were never organized in bundles.

At P4, transverse dendrite bundles consisting of up to 6 dendrites occurred in the pools of both long back muscles. At this age, several motoneurons were clearly separated from each other, and this led to a stretching of the pools in a rostro-caudal dimension. No important changes occurred with regard to the transverse bundles but at P4 for the first time, a few longitudinal dendrite bundles—consisting of maximally three to four dendrites—could be observed.

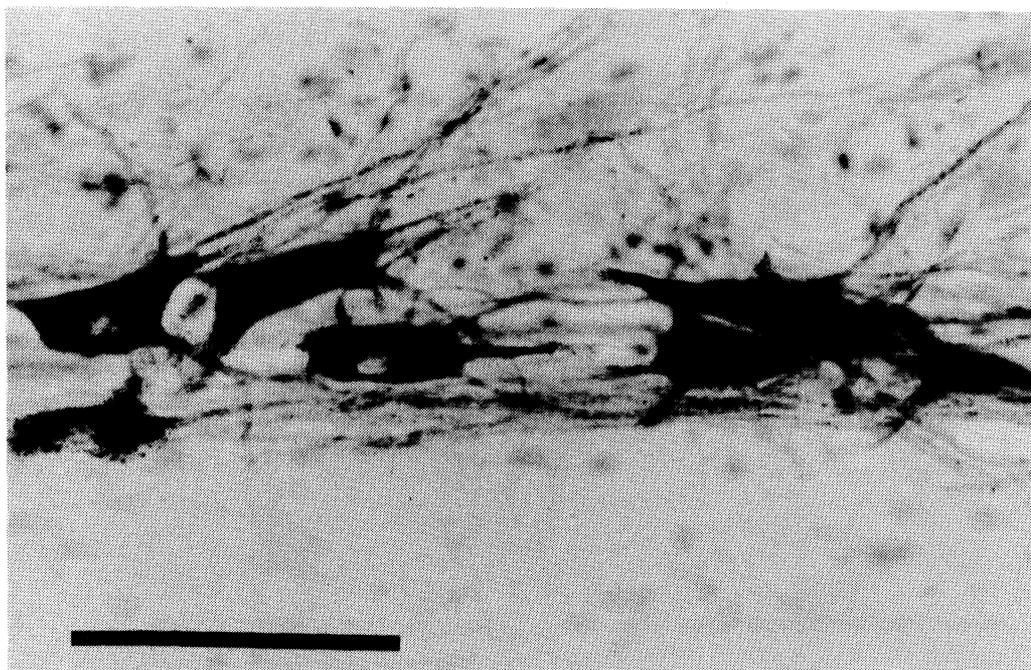
The major development occurred between P6 and P9 and after the latter age, the vast majority of the dendrites were organized in bundles, either coursing in longitudinal or in transverse directions. Only a few dendrites taking a separate course could be observed (Fig. 2). Particularly, at P9 and thereafter, the presence of longitudinal bundles consisting of up to 15 dendrites was a conspicuous feature of the pools of both long back muscle pools. Several of these longitudinal bundles coursed in parallel, and we regularly observed dendrites from the same motoneuron participating in two or three of these longitudinal bundles. Transverse bundles maximally contained eight dendrites. This shift in the organization of the



**Fig. 1:** Motoneuronal pool of the longissimus muscle at P1. Horizontal section. Most dendrites course in medio-lateral directions. Scaling bar, 100  $\mu\text{m}$ ; this bar also indicates the medial side.



**Fig. 2:** Motoneuronal pool of the multifidus muscle at P9; horizontal section. Nearly all dendrites are organised in transversal or longitudinal dendrite bundles. Scaling bar, 100  $\mu\text{m}$ ; this bar indicates the medial side. dendrites, taking place in 3 to 4 days, occurred simultaneously in the pools innervating the multifidus muscle and the longissimus muscles.



**Fig. 3:** Motoneuronal pool of the multifidus muscle at adult age in a horizontal section. Scaling bar, 100  $\mu\text{m}$ ; this bar indicates the medial side of the spinal cord.

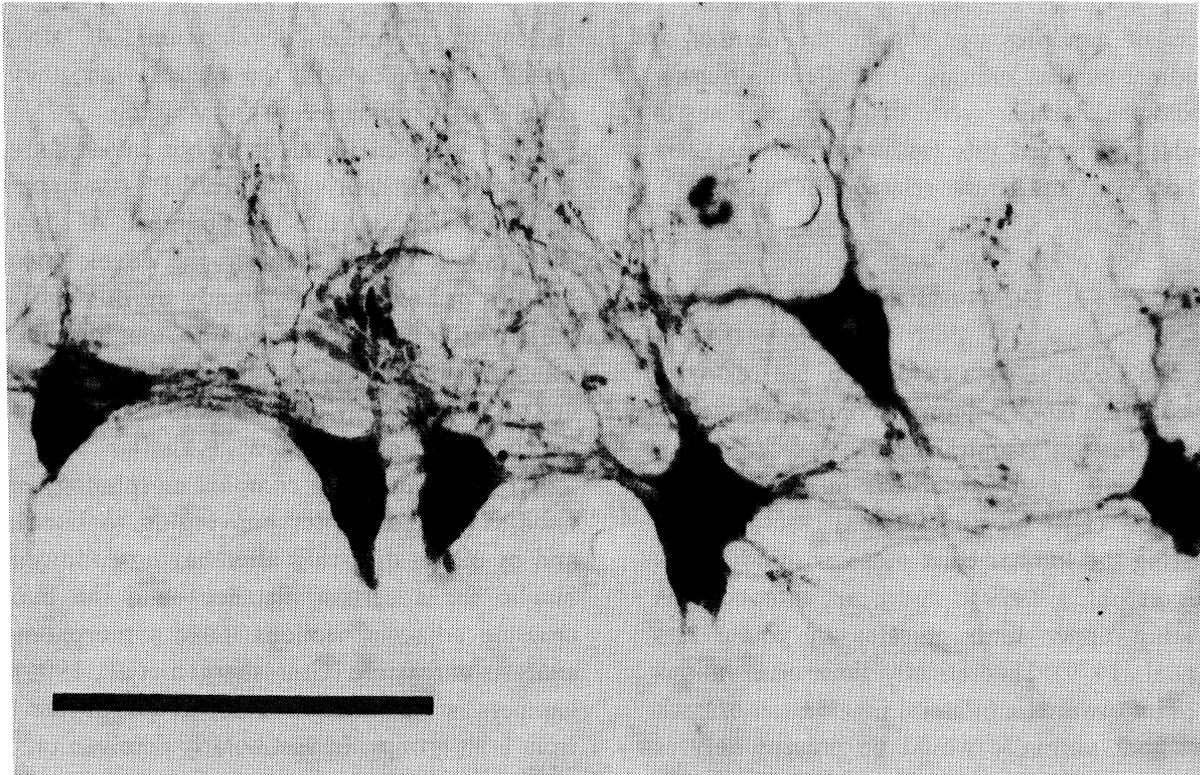
dendrites, taking place in 3 to 4 days, occurred simultaneously in the pools innervating the multifidus muscle and the longissimus muscles.

At P16, all motoneurons were clearly separated, and the clusters of neurons in contact with each other disappeared altogether. The number of dendrites further increased, and most of the dendrites were organized into longitudinal and transverse bundles, but a few additional dendrites then occurred that coursed apart from bundles. Still, we counted maximally 15 dendrites in the longitudinal bundles, and from this age we counted in reconstructions of the pools, 5 to 8 of these large bundles, running in parallel in a rostro-caudal direction.

At P20, the morphology of the motor columns had essentially attained its adult characteristics. The cell bodies of the motoneurons had an elongated, stellate appearance and all were

localized separately. The orientation of the transverse bundles shifted in a somewhat oblique orientation (and this was even more pronounced at older ages). Because of the increased distances, the longitudinal dendrite bundles were elongated. Morphology at P36, P60, and P180 essentially was the same as that on P20 (Fig. 4).

At these ages, it was possible to easily trace the dendrites to the motoneuron of their origin. At this age, however, it is still impossible to follow a bundle over its extent and to reliably estimate the number of dendrites contributing to the different sections of the bundles. Dendrites of one motoneuron may participate in different dendrite bundles, but different dendrites of the same motoneuron may also participate in the same bundle. Transverse sections of the spinal cord revealed that transverse bundles coursed in a ventro-dorsal direction.



**Fig. 4:** Motoneuronal pool of the multifidus muscle in a vestibularly deprived rat, at P7. Scaling bar, 100  $\mu\text{m}$ ; horizontal section; the bar indicates the medial side.

From P7 we did not detect systematic differences between female and male rats, neither in the development nor in the morphology of dendrite bundles in the pools of the long back muscles.

#### **Effect of Vestibular Deprivation**

At P7 (2 d after the vestibular deprivation was effective), motoneurons of both long back muscles were closely packed and most were arranged in clusters (Fig. 4). Longitudinal dendrite bundles, consisting of 6 to 8 dendrites, could already be observed at this age. The dendrite bundles running in transverse directions were less conspicuous and only contained 4 to 8 dendrites. At P9 the moto-neuronal

pools were similar to those in control rats, with several bundles coursing in parallel. From P15, longitudinal bundles consisted of maximally 15 dendrites, and the dendrites of 1 motoneuron were able to participate in several dendrite bundles. At this age, the clusters of motoneurons dissolved because the motoneurons had drifted apart. In vestibularly deprived rats at P25, the morphology of the dendrite bundles is similar to that in normal adult rats.

When comparing the data from vestibularly deprived rats with those of normal rats, we could not detect any systematic difference in the development of dendrite bundles. On P7 (2 d after the semicircular canals were plugged), the longitudinal bundles were already present and this held for normal rats as well. Also at adult age, the

numbers of dendrites per bundle, the number of longitudinal bundles running in parallel, and further morphological details were strikingly similar. In vestibularly deprived rats (as in normal rats), we could not detect any gender-related differences.

### DISCUSSION

In one pool, at ages before P6, we regularly observed a few labeled neurons contralateral to the side of injection. Contralaterally located motoneurons were also observed in horseradish-peroxidase (HRP) studies on motoneurons innervating the lumbar back muscles in adult rats (Brink et al., 1979) and on motoneurons innervating upper limb muscles in young rats (Tada et al., 1979). Theoretically, these observations could point towards a bilateral innervation of back muscles that normally would be present only at younger ages (see Tada et al., 1979). The other possibility is that this labeling is caused by leakage from the injection site and the diffusion of CTB toward muscles at the contralateral side. The experiment to rule out one of these possibilities is to transect the nerves on one side before labeling the contralateral muscle.

One of the main results of our study is that the reorganization of dendrites in the motoneuronal pools of the long back muscles takes place between P6 and P9. This time is much earlier than a similar development in the pool of the soleus muscle around P16, paralleling the development of the fluent, adult-like walking pattern (Westerga & Gramsbergen, 1992). The reorganization in the pools of the long back muscles coincides with a transition in the control of the trunk muscles. Before P6 rats have their trunks consistently in contact with the floor, but after this age they can stand and make a few steps (Geisler et al., 1993). Our results are in line with those of a Golgi study by Scheibel and Scheibel (1970) in kittens,

indicating that the development of dendrite bundles coincides with the age at which they are capable of standing freely and walking.

The other main result of our investigation is that vestibular deprivation from P5 does not lead to retardation in the development of dendrite bundles. At P7 the spurt in the development of bundles has started and already by this age—and particularly from P9—both the longitudinal and transverse bundles occur abundantly. Also at adult age, the morphology of bundles in both vestibularly deprived rats and normal rats is similar.

Unfortunately, the complex morphology of the bundles with dendrites converging to bundles—and of others diverting after having followed the bundle for a certain distance—and the bundles crossing adjacent sections make a morphometric analysis unfeasible (Gramsbergen et al., 1996) and hampers a quantitative comparison of the data from both groups. In vestibularly deprived rats and control rats, meticulous analysis of qualitative aspects, however, did not indicate any systematic difference in the dendrite bundles.

The undisturbed development of dendrite bundles in vestibularly deprived rats is remarkable, as this treatment does induce a delay in postural development. Rearing (standing on the hindpaws) with support from the wall of the cage normally develops between P5 and P9 (Geisler et al., 1993) but after vestibular deprivation this behavior only emerges after P9 (Geisler et al., 1997). Also the development of grooming (self-manipulation) and the adult-like walking pattern was retarded in these rats. Such motor patterns require highly complex adjustments between the extremity muscles and the trunk muscles. As dendrite bundles develop at the normal age in vestibularly deprived rats, this finding indicates that these bundles are not involved in the postural control mechanisms effective in these behaviors.

Several theories have been developed regarding the functional significance of dendrite

bundles (Roney et al., 1979; Westerga & Gramsbergen, 1992). Scheibel and Scheibel (1970) suggested that dendrite bundles might be the substrate for a central programming of movement patterns. Reback et al. (1982), however, showed in kittens a poor development of dendrite bundles or even their absence after spinal cord transection at 2 wk, but alternating leg movements remained intact. We studied in rats the effects of movement restriction on the development of dendrite bundles in the pool of the soleus muscle (Westerga & Gramsbergen, 1993). In a group of five rats, the left hindleg was immobilized from P1 until P20 by means of a boot of thermoplastic material. Such immobilization leads to longlasting changes in the walking pattern, but the development of dendrite bundles of the pool of the soleus muscle is not affected (Westerga & Gramsbergen, 1993). The results also indicated that dendrite bundles are not involved in central programs of coordination.

Other hypotheses point to the role that dendrodendritic connections might play in electrotonical coupling of motoneurons. Electrophysiological recordings demonstrated that motoneurons in the spinal cord of adult cats are electrotonically coupled (Gogan et al., 1977). Matthews, Willis, and Williams (1971) detected in an electron microscope (EM) study narrow spaces and long appositions between motoneuronal dendrites, and the authors suggested that dendrite bundles might be the substrate for this coupling. Recently, we demonstrated in rats by EM that elongated gap junctional complexes occur over long distances in the dendrite bundles of the longissimus muscle (Van der Want et al., 1998). It could well be argued that electrotonic coupling is an essential prerequisite for the synchronization of motoneurons of the long backmuscles, given that they are spread over several spinal cord segments. On the other hand, it seems that electrotonic coupling would lead to synchronized firing at low frequencies (depending on the after-hyperpolarization

of the motoneurons), which would be in contrast with to the tonic activation patterns that have been observed in the long back muscles (Geisler et al., 1996). It should be realized, however, that dendrite bundles connect several subsets of motoneurons in parallel, which could lead to smooth and tonic activation patterns. Another factor might be that because of different cable properties of the dendrites in bundles and different distances to the somata, the effects of electrotonic coupling will be scaled (Westerga & Gramsbergen, 1992). The net effect of such coupling therefore could lead to a desynchronization of motor units and to a fused tetanus even at low levels of activation.

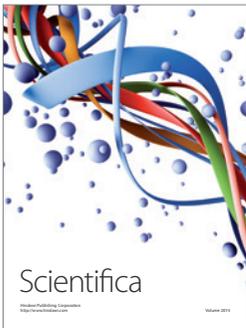
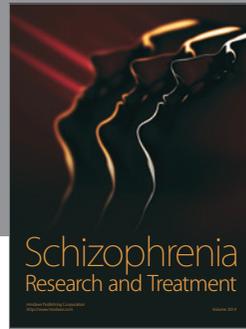
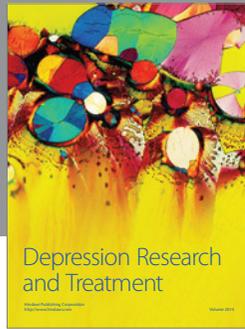
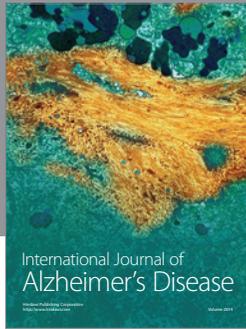
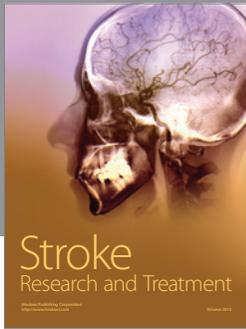
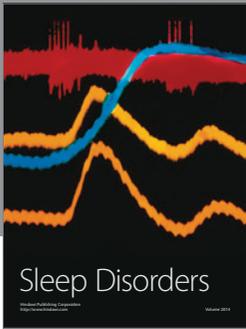
An important but yet unsolved problem is which factor induces the reorganization of dendrite bundles between P6 and P9. Reback et al. (1982) reported that in kittens of 2 weeks, spinal cord transections interfere with the development of dendrite bundles. Similarly, spinal cord transection in rats at P5 abolished the development of dendrite bundles in the pool of the soleus muscle (Gramsbergen et al., 1995). This finding suggests that influences from descending projections induce the development of dendrite bundles. Motoneurons of the back muscles are innervated (mainly indirectly) by vestibulospinal and reticulospinal projections (for review, Holstege, 1988). In the developing rat, these descending projections have reached lumbar levels already several days before birth (Kitao et al., 1993) but reach maturity only after birth (Floeter & Lev-Tov, 1993). Possibly, changes in the organization of these projections around P6 elicit the formation of dendrite bundles. Alternatively, changes in descending systems containing serotonin, norepinephrine and thyreo-tropic hormones might induce their development. Andersson and Bennett (1994) demonstrated that these supraspinal systems specifically innervate motoneuronal columns with dendrite bundles. Selective lesions in either system, or chemical interference with transmission might elucidate this problem.

We conclude that the development of dendrite bundles in the pools of the long back muscles in vestibularly deprived rats proceeds undisturbed from P6, and irrespective of a considerable retardation in postural development. Dendrite bundles, therefore, are not involved in central mechanisms related to postural control. On the other hand, they are a specific feature of motoneurons innervating muscles with important postural functions. A common property of these muscles is that they contain elevated proportions of fatigue-resistant type I muscle fibres (Gramsbergen et al., 1996). Whether retrograde influences from such muscles might play a role in the organization of dendrite bundles is not known. Cross innervation experiments at early age might test the feasibility of this hypothesis. An additional function of dendrite bundles in the long stretched pools of the long back muscles might be to synchronize the motoneurons located in distant spinal cord segments.

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