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CHAPTER 17

The education and re-education of the spinal cord

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Abstract: In normal life, activity-dependent plasticity occurs in the spinal cord as well as in the brain. Like CNS plasticity elsewhere, this spinal cord plasticity can occur at many neuronal and synaptic sites and by a variety of mechanisms. Spinal cord plasticity is prominent in postnatal development and contributes to acquisition of standard behaviors such as locomotion and rapid withdrawal from pain. Later on in life, spinal cord plasticity contributes to acquisition and maintenance of specialized motor skills, and to compensation for the peripheral and central changes associated with aging, disease, and trauma. Mastery of even the simplest behaviors is accompanied by complex spinal and supraspinal plasticity. This complexity is necessary, to preserve the full roster of behaviors, and is also inevitable, due to the ubiquity of activity-dependent plasticity in the CNS. Careful investigation of spinal cord plasticity is essential for understanding motor skills; and, because of the relative simplicity and accessibility of the spinal cord, is a logical and convenient starting point for exploring skill acquisition. Appropriate induction and guidance of activity-dependent plasticity in the spinal cord is likely to be a key part of the realization of effective new rehabilitation methods for spinal cord injuries, cerebral palsy, and other chronic motor disorders.

Keywords: spinal cord; spinal cord injury; plasticity; conditioning; learning; memory; behavior

Introduction

The development of neuroscience over the past 200 years has been marked by the gradual and belated elevation in the status of the spinal cord. Originally thought to be simply a big well-protected nerve through which the brain interacts with the world, the spinal cord evolved first into a way station between the brain and the periphery that harbored a few simple reflexes, and then progressed to a repository of highly stereotyped behaviors such as locomotion. Nevertheless, it remained until very recently a hard-wired structure that simply responded, albeit in complex ways, to inputs from the brain and from the periphery.

Understanding of spinal cord function is now evolving further as part of the growing recognition of the ubiquity of activity-dependent plasticity in the CNS. Appreciation of the multiple mechanisms of synaptic and neuronal plasticity, of their existence in many different regions, and of the frequency with which they are activated, has overturned the traditional view of a hard-wired CNS that stores the effects of past experience by only a few mechanisms at only a few specialized sites. Activity-dependent plasticity, or persistent CNS modification that results from past experience and affects future behavior, is now recognized as a feature of the entire CNS, including the spinal cord.

The spinal cord has capacities for activity-dependent plasticity similar to those found elsewhere in the CNS. During development and later in life, it changes in response to input from the brain and from the periphery. Like plasticity elsewhere in the

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CNS, this spinal cord plasticity involves synaptic and neuronal mechanisms (e.g., long-term potentiation (LTP), modifications in neuronal morphology and electrical properties); it is affected by growth factors, and it is associated with gene activation (e.g., Liu and Sandkühler, 1997; Eyre et al., 2000; Gibson et al., 2000; Inglis et al., 2000; Mendell et al., 2001; Wolpaw and Tennissen, 2001; Tillakaratne et al., 2002; Dupont-Versteegden et al., 2004; Ding et al., 2005.)

Many laboratory and clinical studies have addressed the functional impact of such spinal cord plasticity in health and disease. The main measures of function have been two major classes of spinal cord responses to peripheral inputs: flexion withdrawal reflexes, which are mediated by oligosynaptic nociceptive pathways to spinal motoneurons from unmyelinated C fibers and small myelinated A-delta fibers; and proprioceptive reflexes, which are mediated by mono- and oligosynaptic pathways to spinal motoneurons from larger afferents innervating muscle spindles, Golgi tendon organs, and other receptors that register muscle length and tension and limb position (Matthews, 1972; Baldissera et al., 1981; Burke, 1998; Kandel et al., 2000; Zehr, 2002; Misiaszek, 2003; Sandrini et al., 2005; Voerman et al., 2005).

In the isolated spinal cord, flexion withdrawal reflexes display habituation and sensitization in a variety of stimulation protocols (Mendell, 1984). Most studies have involved pain mechanisms and sensitization of spinal cord responses to C and A fiber inputs (see Chapters by Price and by Lenz and other recent reviews (e.g., Herrero et al., 2000; Zimmermann, 2001; Ji et al., 2003; Melzack et al., 2004; Katz and Rothenberg, 2005; Flor and Andrasik, 2006)). In addition, these reflexes can show classical and operant conditioning phenomena (reviewed in Patterson, 1976; Kandel, 1977; Thompson, 2001). Furthermore, activity in proprioceptive afferents can change the spinal cord (e.g., Lloyd, 1949; Kandel, 1977).

The spinal locomotor pattern generator (LPG), which is normally activated and influenced by descending supraspinal activity, can function autonomously in the isolated spinal cord. This is most apparent in lower vertebrates, but evident also in higher vertebrates such as the cat (Rossignol, 1996; Kiehn and Butt, 2003; Clarac et al., 2004; Juvin et al., 2005; Grillner et al., 2005; Rossignol et al., 2006). A spinal LPG exists in humans as well (Holmes, 1915; Kuhn, 1950; Bussel et al., 1988; Calancie et al., 1994; Dietz et al., 1995; Dobkin et al., 1995; Rossignol, 1996, 2000; Kiehn et al., 1998; Dimitrijevic et al., 1998; Orlovsky et al., 1999; Dietz, 2003; Zehr, 2005). Studies begun 50 years ago and resumed in the 1980s demonstrate that the locomotion produced by the isolated spinal cord improves with training and that this improvement derives from spinal cord plasticity (Shurrager and Dykman, 1951; Lovely et al., 1986; Barbeau and Rossignol, 1987; Barbeau et al., 2002; Rossignol et al., 2002, 2004; Tillakaratne et al., 2002; Edgerton et al., 2004). This work (reviewed in Chapters by Frigon and Brown) implies that the operation of a human LPG could be encouraged and guided in those with spinal cord injuries so as to restore locomotion. Comparable methods for inducing and guiding activity-dependent spinal cord plasticity could promote restoration of bladder, bowel, and other autonomic functions after spinal cord injuries.

Interruption or impairment of descending spinal cord pathways leads to gradual changes in spinal cord function (Riddoch, 1917; Kuhn, 1950; Mountcastle, 1980; Ronthal, 1998; Hiersemenzel et al., 2000). The end result typically includes increased resistance to passive muscle stretch, especially in antigravity muscles (i.e., leg extensors and arm flexors), hyperactive tendon jerks, and increased flexion withdrawal responses. These functional effects make up the syndrome of spasticity. The progressive development of these signs reflects plasticity in the spinal cord caused by loss or distortion of supraspinal input and by associated changes in peripheral inputs. This spinal cord plasticity includes modifications in motoneuron and motor unit properties, in motoneuron synaptic coverage, in primary afferent EPSPs, and in interneuronal pathways (Nelson and Mendell, 1979; Cope et al., 1986; Munson et al., 1986; Boorman et al., 1991; Thompson et al., 1992; Shefner et al., 1992; Hochman and McCrea, 1994a–c; Tai and Goshgarian, 1996; Tai et al., 1997; Hultborn, 2003). Much more rapid activity-dependent spinal cord plasticity occurring in response to the

more focused change in descending input caused by a cerebellar lesion was first described nearly 80 years ago (DiGiorgio, 1929, 1942; Manni, 1950; Gerard, 1961; Chamberlain et al., 1963). This phenomenon, labeled "spinal fixation," was thought by Gerard and others to be an excellent model for the fixation or consolidation of memory. Similar phenomena occur in the spinal cord in connection with other supraspinal lesions and after manipulation of vestibular sensory inputs (Giulio, 1952; Straka and Dieringer, 1995). In sum, altered descending input that persists for a sufficient time causes spinal cord plasticity that remains after the input ceases.

New appreciation of these data and their implications has coincided with and has been encouraged by the energy and optimism now centered on possibilities for restoring spinal cord structure and function after injury (e.g., see Chapter by Merzenich et al., Dobkin and Havton, 2004; Liverman et al., 2005). The expectations for achieving regeneration of damaged pathways and lost neurons inevitably lead to the question of how newly regenerated spinal cord is to become capable of useful function. An effectively functioning adult spinal cord depends on appropriate activity-dependent plasticity during early development and throughout subsequent life. A newly, and probably imperfectly, regenerated spinal cord will almost certainly not support effective function well (Muir and Steeves, 1997); it will probably display diffuse infantile reflexes and/or other disordered and dysfunctional behaviors. Thus, as methods for producing spinal cord regeneration become available, methods for appropriately re-educating the regenerated spinal cord are likely to become essential.

This anticipated need is spurring attention to the activity-dependent spinal cord plasticity that shapes the functional properties of spinal cord neurons and pathways to support behaviors as varied as locomotion, urination, ballet, and playing a musical instrument. Furthermore, new appreciation of the inherent capabilities for plasticity of the injured unregenerated spinal cord gives additional reason for investigating activity-dependent spinal cord plasticity (e.g., Chapter by Frigon and Grillner and Wallén, 2004). Understanding spinal cord plasticity is necessary for understanding both the changes caused by injury and the processes that might be engaged and guided to restore effective function.

Attention to activity-dependent spinal cord plasticity is further encouraged by the growing recognition that acquisition and maintenance of normal motor behaviors depend on activity-dependent plasticity at many sites in the CNS, including the spinal cord. Peripheral and descending inputs during practice change the spinal cord, and these changes combine with changes elsewhere in the CNS to support the new behavior. Thus, understanding the mechanisms of spinal cord plasticity and its interactions with plasticity elsewhere is required for understanding normal motor behaviors as well as the complex motor disabilities that accompany spinal cord injuries and other chronic neurological disorders.

Activity-dependent spinal cord plasticity during normal life

In the normal CNS, descending and peripheral inputs to the spinal cord are a continual barrage of activity in many different pathways. The immediate effects of this activity (e.g., voluntary movements, responses to peripheral disturbances, locomotion, respiration, urination, task-specific adjustments in spinal reflexes) are very obvious. In contrast, the gradual long-term effects of these inputs on the spinal cord are not obvious. Nevertheless, these gradual long-term effects are important: they serve to establish and maintain spinal cord function in a state that supports effective motor behaviors. Gradual activity-dependent plasticity, driven by descending and associated peripheral inputs, shapes spinal cord function during development and continues to adjust it throughout later life.

The next sections review the spectrum of activity-dependent plasticity during normal life, and Table 1 lists representative examples.

Developmental plasticity

In early life, both descending and peripheral inputs have crucial roles in the plasticity that produces a

Table 1. Examples of activity-dependent spinal cord plasticity in normal life

Development

Focusing of proprioceptive reflexes (Myklebust et al., 1986; O'Sullivan et al., 1991)
Directionality of nociceptive withdrawal responses (Levinsson et al., 1999; Waldenstrom et al., 2003)
Lateralization of descending cortical control (Eyre et al., 2001; Martin et al., 2004)
Maturation of bladder reflex pathways (de Groat, 2002)
Motoneuron morphology (Inglis et al., 2000)

Skill Acquisition and Other Experiences Later in Life

Ballet (Nielsen et al., 1993; Koceja et al., 1991; Goode and Van Hoven, 1982)
Athletic training (Rochcongar et al., 1979; Casabona et al., 1990)
Activity level (Yamanaka et al., 1999; Gomez-Pinilla et al., 2002)
Hopping (Voigt et al., 1998)
Backward locomotion (Schneider and Capaday, 2003)
Limb trajectory maintenance (Meyer-Lohmann et al., 1986)
Age-related changes in proprioceptive reflexes (Koceja and Mynark 2000; Morita et al., 1995)
Operant conditioning of proprioceptive reflexes (Wolpaw et al., 1983; Chen and Wolpaw, 1995; Segal, 1997)

normally functioning adult spinal cord, a spinal cord that has characteristic adult reflex patterns, supports basic motor skills like locomotion, and also supports more specialized skills such as dancing or playing the piano.

Rapid withdrawal from painful stimuli is a critical function of spinal cord pathways, and it is acquired early in life. In the neonatal rat, focal nociceptive stimulation evokes diffuse and frequently inappropriate muscle activations and limb movements. In contrast, in the normal adult this stimulation excites only the correct muscles – the muscles that withdraw the limb from the painful stimulus. Schouenborg's group has shown the importance of descending input in achieving these correctly focused adult flexion withdrawal reflexes (e.g., Levinsson et al., 1999; Waldenstrom et al., 2003). When spinal cord transection at birth removes descending input, the adult pattern fails to develop; so that nonspecific and inappropriate withdrawal reflexes are still present in adulthood (Fig. 1A).

Spinal cord proprioceptive reflexes contribute to locomotion and other basic motor behaviors (Rossignol, 1996). In human infants, muscle stretch causes short-latency spinally-mediated stretch reflexes in the stretched muscles and in their antagonists as well (Myklebust et al., 1986; O'Sullivan et al., 1998). The antagonist stretch reflexes gradually disappear during childhood, and the adult is left with standard "knee-jerk" reflexes that are limited to the stretched muscles. However, when perinatal supraspinal damage (i.e., cerebral palsy) disrupts activity in descending pathways, this evolution may fail to occur, and antagonist stretch reflexes may last into adulthood and contribute to motor disabilities. Fig. 1B shows agonist and antagonist stretch reflexes from a normal baby, a normal adult, and an adult with cerebral palsy. Like the normal baby and unlike the normal adult, the adult with cerebral palsy shows short-latency responses in both agonist and antagonist muscles. In this situation, the original damage is supraspinal. Thus, the probable reason for the abnormal persistence of infantile spinal reflexes into adulthood is distortion of the descending input that gradually eliminates these reflexes in the initial years of life.

Intact descending activity is also important for development of urinary function. In newborn animals and humans, voiding is easily evoked by peripheral stimuli through a purely spinal reflex pathway. During postnatal development, this reflex voiding is suppressed and brain control of voiding becomes dominant. The change seems to reflect change in the relative strengths of peripheral and descending excitatory inputs to the preganglionic neurons in the spinal cord that mediate micturition (de Groat, 2002; Vizzard, 2006). The decreased response to peripheral input probably results from a presynaptic decrease in glutamic acid release, rather than from a postsynaptic change. Neonatal spinal cord transection prevents this evolution, and infantile reflex voiding persists into adulthood. The primitive pattern can also reemerge in adults after spinal cord injury.

In development, corticospinal pathways change so that they produce the normal adult pattern of mainly contralateral innervation of limb muscles (Eyre et al., 2001, Eyre, 2003; ten Donkelaar et al., 2004; Martin, 2005). Perinatal damage to sensorimotor cortex on one side can prevent this normal

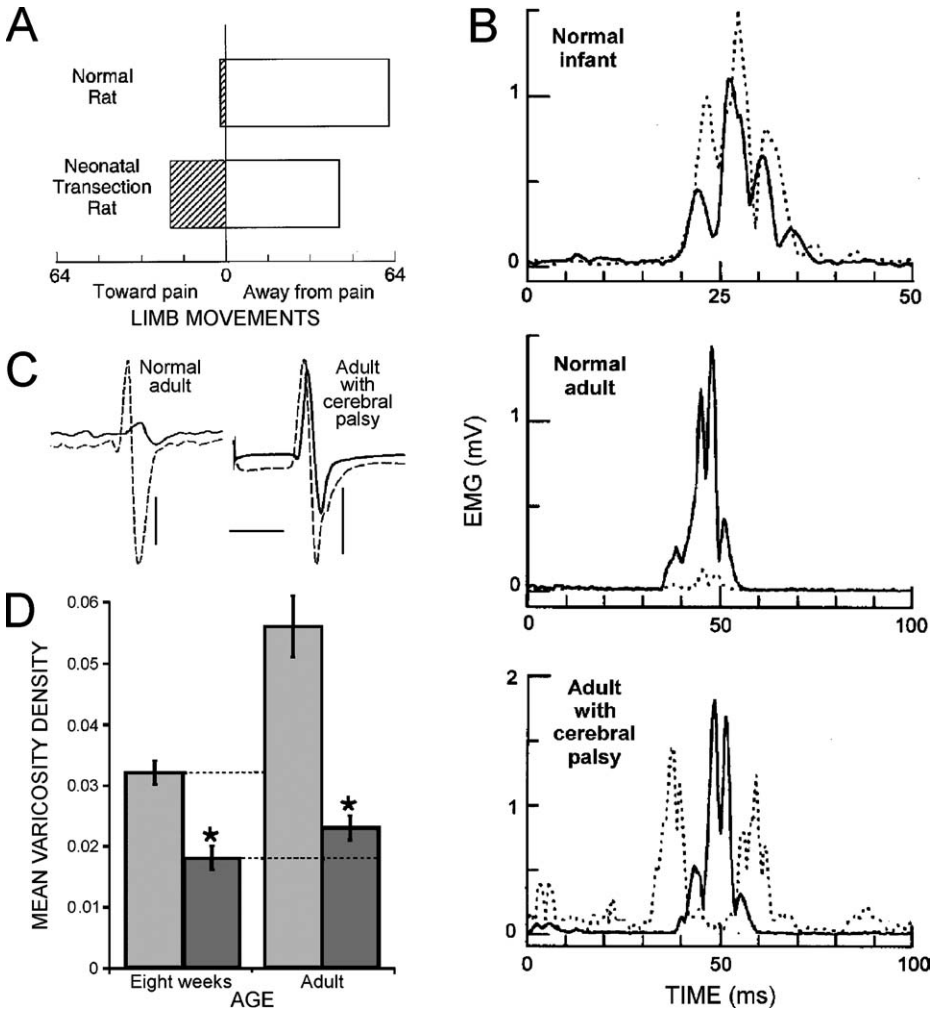

Fig. 1. Activity-dependent spinal cord plasticity during development. (A) Direction of limb movement produced by flexion withdrawal responses to a nociceptive stimulus in normal adult rats and in adult rats that had undergone spinal cord transection just after birth. Direction is almost always appropriate, i.e., away from the stimulus, in normal adults, but is often inappropriate in transected adults. Neonatal transection prevents normal shaping of flexion withdrawal reflexes by descending input (modified from Levinsson et al., 1999). (B) Short-latency electromyographic (EMG) responses of soleus (solid) and tibialis anterior (dotted) muscles to sudden foot dorsiflexion, which stretches the soleus and shortens the tibialis anterior, in a normal infant, a normal adult, and an adult with cerebral palsy. In the normal infant, spinal stretch reflexes occur in both muscles. In the normal adult, a reflex occurs only in the stretched muscle, i.e., the soleus, and little or no response occurs in the tibialis anterior. In contrast, in the adult with cerebral palsy, in whom perinatal supraspinal injury has impaired descending input, the infantile pattern persists: reflexes occur in both muscles. (From B. Myklebust, unpublished data (Myklebust et al., 1982, 1986 for comparable data)). (C) Ipsilateral (solid) and contralateral (dashed) EMG responses (first dorsal interosseus muscle) to transcranial magnetic stimulation over motor cortex in a normal adult (left) and an adult with cerebral palsy (right). Horizontal scale bar is 20 ms, vertical bar is 200 μV. The large ipsilateral response seen in the subject with cerebral palsy indicates abnormal preservation of the strong ipsilateral corticospinal connections that normally disappear early in life (modified from Eyre et al., 2001). (D) Densities in 8-week-old and adult cats of putative corticospinal tract boutons (varicosities) in cervical spinal cord ipsilateral (dark gray) and contralateral (light gray) to forelimb muscle paralyzed from age 3 weeks to 7 weeks. Muscle paralysis during development reduces corticospinal tract innervation and this deficit persists into adulthood. Asterisks indicate significant differences from the contralateral data (modified from Martin et al., 2004).

evolution, and lead to abnormal adult innervation in which the undamaged side has strong ipsilateral as well as contralateral projections to the spinal cord. This abnormal innervation seems to result from the lack of normal activity-dependent competition between ipsilateral and contralateral connections. Fig. 1C, which shows responses to transcranial magnetic stimulation in a normal adult and an adult with cerebral palsy, illustrates the abnormality (Eyre et al., 2001). The normal adult has a large contralateral response and a minimal ipsilateral response, while the adult with cerebral palsy has large responses on both sides. Cerebral palsy can also affect muscle afferent connections in spinal cord, and may in addition affect spinal neuronal properties (e.g., expression of parvalbumin and the early immediate gene c-Jun) (Gibson et al., 2000). The functional effect of the abnormal innervation is especially severe in humans, in whom corticospinal connections become prominent early in development and come to have major roles in movement control (Eyre et al., 2000; Mayer and Esquenazi, 2003). The motor abnormalities caused by perinatal hemispheric damage may be minimal in the infant and only become obvious later on, as complex motor skills fail to develop normally.

Both peripheral and descending inputs contribute to the development of a properly functioning adult spinal cord. In rats, the evolution of normal flexion withdrawal responses depends not only on descending pathways (e.g., Fig. 1A) but on peripheral input as well. Peripheral anesthesia during development prevents development of normal adult reflexes (Waldenstrom et al., 2003). Painful input is not required: tactile input alone can support normal development. Abnormal peripheral input during development caused by paralysis of a particular muscle may also lead to adult abnormalities in corticospinal motoneuronal connections (Fig. 1D) and motor control (Martin et al., 2004).

Plasticity with the acquisition and maintenance of motor skills

Acquisition of motor skills later on in life is accompanied by modifications in spinal cord circuits. These modifications have been demonstrated in animals and humans mainly by measuring the spinal stretch reflex (SSR) (produced largely by the monosynaptic pathway comprised of the Ia afferent from the muscle spindle, its synapse on the motoneuron, and the motoneuron), and its electrical analog, the H-reflex, which is evoked by direct electrical stimulation of Ia afferents (Magladery et al., 1951; Matthews, 1972; Henneman and Mendell, 1981; Brown, 1984; Zehr, 2002). The simple spinal pathway of these reflexes contributes to both simple and complex behaviors. As a result, changes in this pathway change many behaviors and/or change the CNS activity responsible for these behaviors. Many studies indicate that these spinal reflexes are affected by the nature, intensity, and duration of past physical activity and by specific training regimens.

These spinal reflexes differ between athletes and nonathletes and among different groups of athletes (Rochcongar et al., 1979; Goode and Van Hoven, 1982; Casabona et al., 1990; Koceja et al., 1991, 2004; Nielsen et al., 1993; Augé and Morrison, 2000). Nielsen et al. (1993) measured H-reflexes in soleus muscles of people who were sedentary, moderately active, or extremely active and in professional ballet dancers. H-reflexes and disynaptic reciprocal inhibition were larger in moderately active people than in sedentary people, and were even larger in extremely active people. Given that the human soleus muscle is composed largely of slow (i.e., type I) fibers, exercise-induced change in motor unit properties cannot readily explain these reflex increases associated with physical activity. The most notable result, illustrated in Fig. 2A, was that both the H-reflex and disynaptic reciprocal inhibition were smallest in the professional dancers, even though they were much more active than the other groups. The dancers' reflexes were smaller than those of sedentary people, and far smaller than those of people who were physically active in other ways. Beginning from the knowledge that muscle cocontraction (i.e., simultaneous contraction of agonists and antagonists) is associated with increased presynaptic inhibition and decreased reciprocal inhibition, Nielsen et al. (1993) proposed that the prolonged cocontractions needed for the classical ballet postures led to

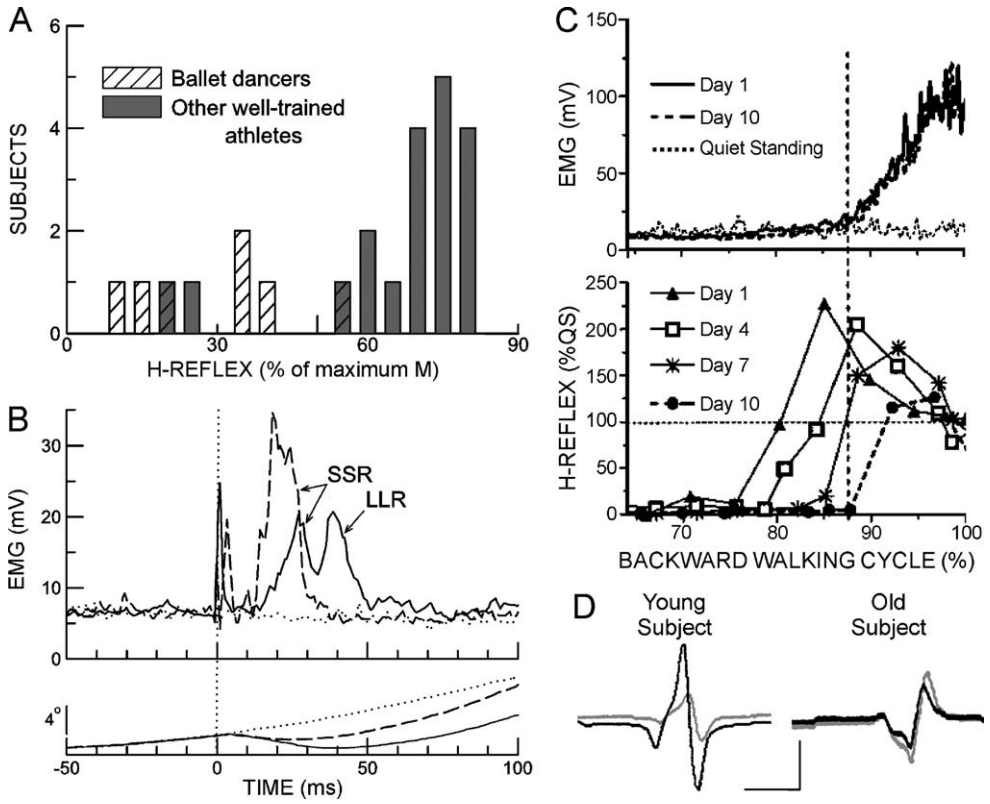

Fig. 2. Activity-dependent spinal cord plasticity associated with skill acquisition and with aging. (A) Soleus H reflexes are much smaller in professional ballet dancers than in other well-trained athletes (e.g., runners, swimmers, cyclists) (H-reflexes of sedentary subjects fall in between.) (modified from Nielsen et al., 1993). (B) Working for reward, monkeys performed an elbow flexion-extension task on which brief perturbations were randomly superimposed. Biceps EMG and elbow angle (flexion upward) for an unperturbed trial (dotted), a perturbed trial early in training (solid), and a perturbed trial late in training (dashed) are shown. Early in training, perturbation elicits both a spinal stretch reflex (SSR) and a long-latency polysynaptic response (LLR). After intermittent training over several years, the SSR is much larger and the LLR has disappeared. The SSR has gradually taken over the role of opposing the perturbation. This improves performance: the disturbance in the smooth course of elbow flexion is smaller and briefer (modified from Meyer-Lohmann et al., 1986). (C) Change in soleus H-reflex size as a function of time in the backward-walking step cycle as a person masters backward walking over 10 days. Top: Soleus EMG of Day 1 and Day 10 just before and after onset of the soleus burst associated with the stance phase of the step cycle. Dotted line shows soleus EMG for quiet standing. Bottom: H-reflex size (as % of size during quiet standing) versus time in the backward-walking step cycle for Days 1, 4, 7, and 10 of training. Soleus EMG does not change with training. In contrast, the marked increase in H-reflex size prior to the soleus burst that is seen on Day 1 disappears by Day 10. (D) Soleus H-reflexes in prone (black) and standing (gray) positions from a young person and an old person. In old subjects, the H-reflex tends to be smaller and to be less affected by body position (modified from Koceja et al., 1995).

persistent decreases in synaptic transmission at Ia synapses, and thus to weak H-reflexes and weak reciprocal inhibition. The decreased direct peripheral influence on motoneurons that is reflected in the smaller reflexes may increase cortical control and thereby enable more precise movements.

In studies of people with different histories of physical activity, it is difficult to rule out the possible confounding impacts of differences in basic genetic endowments (e.g., between dancers and other people, or between dancers and runners). Carefully controlled investigations of the effects of specialized training regimens do not face this difficulty, and such studies provide further evidence of activity-dependent spinal cord plasticity. In an early experiment, monkeys learned to make

smooth repetitive flexion and extension movements about the elbow, and random brief perturbations were superimposed (Meyer-Lohmann et al., 1986). Over months and years, the SSR evoked by the perturbation gradually increased and essentially took over the task of responding to the perturbation, while longer-latency reflex responses gradually disappeared. As Fig. 2B shows, the larger SSR was adaptive, that is, it was associated with faster recovery from the disturbance in trajectory caused by the perturbation. The paper concluded (p. 398) that the results "demonstrate a growing role for fast segmental mechanisms in the reaction to external disturbances as motor learning progresses."

Subsequent studies in humans have described reflex changes occurring over days and weeks due to specialized training regimens (Pérot et al., 1991; Voigt et al., 1998; Yamanaka et al., 1999; Schneider and Capaday, 2003). Fifteen min/day of practice in a backward walking task produced a gradual change in the dependence of H-reflex amplitude on the point in the step cycle at which the reflex was elicited. On the first day of backward walking training, the soleus H-reflex was large well before the onset of the soleus burst associated with the stance phase of the cycle. By the tenth day, the H-reflex was not detectable until the onset of the burst. Fig. 2C illustrates this change. The early increase in the H-reflex on the first day may represent compensation for uncertainty as to when the stance phase of the step cycle, with its need for greater soleus activity, will start. The greater sensitivity of the reflex arc helps ensure a rapid excitatory response to foot contact. As training goes on, and the time of contact becomes more predictable, this compensation becomes less important.

More evidence for adaptive spinal cord plasticity in response to particular demands in adult life is provided by studies of reflex changes in humans that occur during aging (Sabbahi and Sedgwick, 1982; DeVries et al., 1985; Koceja et al., 1995; Morita et al., 1995; Angulo-Kinzler et al., 1998; Zheng et al., 2000; Koceja and Mynark, 2000; Scaglioni et al., 2003; Kido et al., 2004). The age-related modifications in reflex strength and task-related reflex modulation described in these studies and illustrated in Fig. 2D probably reflect both direct and indirect effects of aging, i.e., direct effects on the neuronal circuitry of the reflexes and indirect effects secondary to the effects of aging elsewhere in the CNS or in the muscles, joints, and nerves that implement motor acts.

Sites and mechanisms of activity-dependent spinal cord plasticity

The phenomena summarized in the last section show that activity-dependent changes in spinal cord function accompany the acquisition and maintenance of motor skills throughout life. However, these phenomena do not differentiate between the respective contributions to modifying spinal cord function of: (1) plasticity in the spinal cord itself; (2) changes in descending input to the spinal cord resulting from supraspinal plasticity; and (3) peripheral neuromuscular changes that alter sensory inputs or the effects of spinal cord output. Progress in understanding how plasticity of particular kinds at particular anatomical sites underlies the acquisition and maintenance of particular behaviors, depends on studies of the same spinal cord reflexes that are used to recognize this plasticity.

Simple spinal cord reflexes, such as stretch reflexes and flexion withdrawal reflexes are normally activated as parts of complex behaviors. At the same time, they are in themselves simple behaviors, the simplest of which the mammalian CNS is capable; and adaptive changes in these reflexes are basically simple skills (i.e., "adaptive behaviors acquired through practice" (Compact Oxford Engish Dictionary, 1993)) that may be used as laboratory models of the plasticity underlying skill acquisition. Operant conditioning of the SSR, or its electrical analog the H-reflex, which has been described in monkeys, humans, rats, and mice, provides clear evidence of activity-dependent plasticity at particular sites in the spinal cord, and is elucidating the mechanisms and interactions of the spinal and supraspinal plasticity that underlies these simple skills (Wolpaw et al., 1983; Wolpaw, 1987; Evatt et al., 1989; Wolf and Segal, 1996; Segal, 1997; Wolpaw and Tennissen, 2001; Carp et al., 2005; Chen and Wolpaw, 2005; Wolpaw and Chen, 2006).

In the basic paradigm, used in monkeys, humans, rats, and mice, SSR or H-reflex amplitude is measured as electromyographic activity (EMG), and reward is given when the size is greater than (for up-conditioning) or less than (for down-conditioning) a specific criterion. The primary observation is that, after imposition of the reward criterion, the amplitude of the reflex changes appropriately over days and weeks (Fig. 3A). This adaptive change has two phases, a small rapid phase-1 change that occurs in the first few hours or days (believed to reflect rapid appropriate change in descending influence on the spinal reflex pathway), and a much slower phase-2 change that continues to grow for weeks (and appears to reflect gradual spinal cord plasticity caused by the long-term continuation of the descending influence responsible for phase 1) (Wolpaw and O'Keefe, 1984; Chen et al., 2001). This descending influence is conveyed by the corticospinal tract (CST); other major descending pathways are not needed (Chen and Wolpaw, 1997, 2002). Conditioning is possible in humans or rats with partial spinal cord injuries, but does not occur in people with strokes involving sensorimotor cortex or in rats in which contralateral sensorimotor cortex has been ablated or the CST has been transected (Segal and Wolf, 1994; Segal, 1997; Chen et al., 2002, 2006).

This spinal cord plasticity includes alterations in motoneuron properties (Carp and Wolpaw, 1994; Halter et al., 1995; Carp et al., 2001a, b). Down-conditioning is associated with a positive shift in motoneuron firing threshold and a decrease in axonal conduction velocity. Both of these changes suggest a positive shift in sodium channel activation voltage. As illustrated in Fig. 3B, the threshold change (and an accompanying small decrease in EPSP size) could largely account for the smaller reflex amplitude. Although activity-dependent synaptic plasticity has received the most attention in the past, the occurrence and importance of plasticity in neuronal properties (such as in neuronal voltage-gated ion channels) is now being recognized (Spitzer, 1999; Cantrell and Catterall, 2001; Carr et al., 2003). The shift in motoneuron firing threshold with H-reflex down-conditioning is an example of such plasticity, and indicates its behavioral significance. Other physiological and anatomical studies suggest that SSR or H-reflex conditioning also changes the Ia afferent-motoneuron synapse, other synaptic terminals on the motoneuron (e.g., Fig. 3C), motor unit properties, and interneurons that carry oligosynaptic Group 1 input to the motoneuron (Carp and Wolpaw, 1995; Feng-Chen and Wolpaw, 1996; Carp et al., 2001b).

The most recent studies have shown that the cerebellum is essential for acquisition and long-term maintenance of H-reflex down-conditioning, probably through its connections to sensorimotor cortex (Chen and Wolpaw, 2005; Wolpaw and Chen, 2006), and that the basal ganglia are essential at least for acquisition (Chen et al., 2004). Furthermore, these studies suggest that cortical plasticity induced and maintained by the cerebellum is responsible for the long-term survival of the spinal cord plasticity that is directly responsible for the altered H-reflex. Fig. 3D summarizes present understanding of the hierarchy of spinal and supraspinal plasticity that appears to underlie the acquisition and maintenance of this ostensibly simple skill of H-reflex conditioning.

Principles underlying activity-dependent plasticity and their relations to behavioral change

The evidence that activity-dependent plasticity occurs at multiple spinal and supraspinal anatomical sites (with acquisition of even the simple skill of an H-reflex decrease or increase) is consistent with the rapidly increasing evidence that activity-dependent plasticity is ubiquitous in the CNS and occurs at multiple sites with simple learning in invertebrates and vertebrates (Wolpaw and Lee, 1989; Lieb and Frost, 1997; Thompson et al., 1997; Cohen et al., 1997; Carrier et al., 1997; Whelan and Pearson, 1997; Lisberger, 1998; Garcia et al., 1999; Hansel et al., 2001; King et al., 2001; Wolpaw and Tennissen, 2001; Medina et al., 2002; van Alphen and De Zeeuw, 2002; Vaynman and Gomez-Pinilla, 2005). Given that the primary CNS function is to produce appropriate behaviors and that activity-dependent plasticity is ubiquitous in the CNS, complex plasticity, especially in the spinal cord, appears to be both necessary and inevitable.

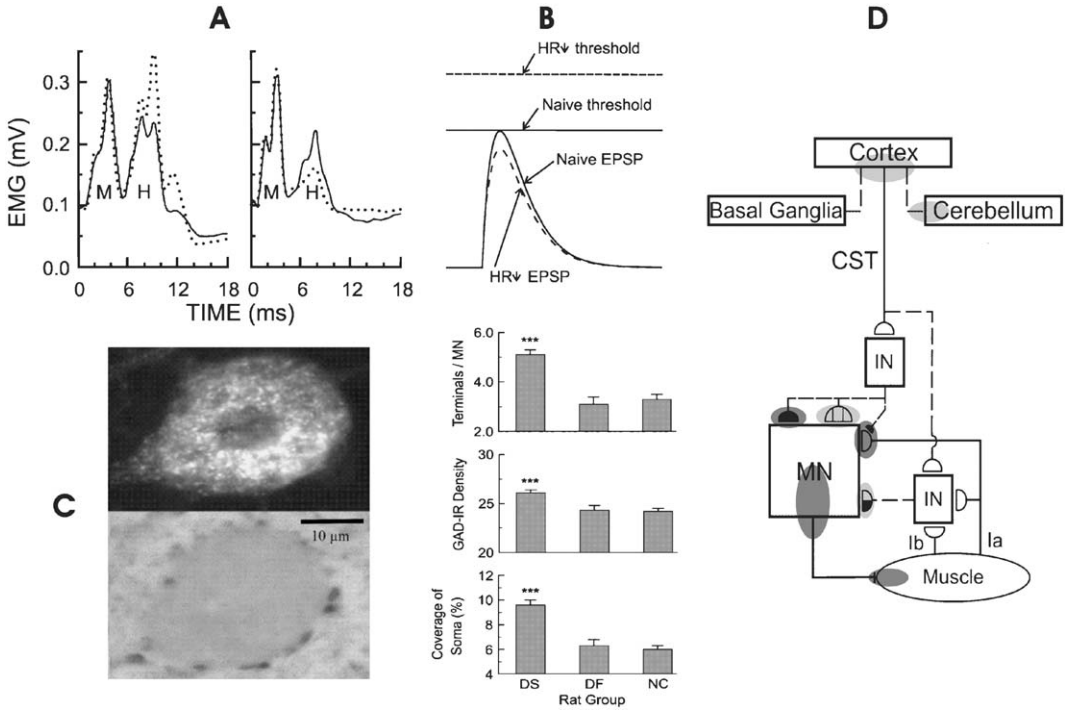

Fig. 3. Operant conditioning of the spinal stretch reflex (SSR)/H-reflex pathway and the associated spinal and supraspinal plasticity. (A) The graphs show average poststimulus soleus EMG for representative days before (solid) and after (dotted) soleus H-reflex conditioning from a rat in which the H-reflex has been increased by the up-conditioning mode (left) or decreased by the down-conditioning mode (right). The H-reflex is much larger after up-conditioning and much smaller after down-conditioning, while background EMG (indicated here by EMG at zero time) and M responses (i.e., direct muscle responses) are unchanged. (B) Triceps surae motoneurons on the conditioned side of H-reflex down-conditioned (HR) monkeys were found to have more positive firing thresholds and slightly smaller Ia EPSPs. Together, these two findings can explain why the H-reflex became smaller (A and B from Wolpaw, 1997). (C) Effects of successful down-conditioning on GABAergic terminals on soleus motoneurons (assessed by glutamic acid decarboxylase (GAD_{67})-immunoreactivity (GAD-IR). Top left: Soleus motoneuron labeled by Alexa Fluor-488 conjugated with CTB injected into the muscle. Bottom left: Same motoneuron showing GAD-IR (i.e., GABAergic) terminals (dark) located on the periphery of the motoneuron.(Bar = 10 Fm.). Right: Average ($\pm$SEM) values for: down-conditioning successful (DS), down-conditioning failed (DF), and naive control (NC) rat groups for: number of GABAergic terminals per motoneuron; terminal GAD density; and GABAergic terminal coverage of soma (expressed as percent of perimeter). (***$P < 0.0001$; compared to the NC group.) After successful down-conditioning, soleus motoneurons have more GABAergic terminals, and these terminals are more densely labeled and occupy more of the soma (from Wang et al., 2006)). (D) Spinal and supraspinal sites (shaded ovals) of plasticity associated with operant conditioning of the SSR or its electrical analog, the H-reflex. "MN" is the motoneuron, "CST" is the main corticospinal tract, and each "IN" is one or more spinal interneuron types. Open synaptic terminals are excitatory, solid ones are inhibitory, half-open ones could be either, and the subdivided one is a cluster of C terminals. Dashed pathways imply the possibility of intervening spinal interneurons. The monosynaptic and probably oligosynaptic SSR/H-reflex pathway from Ia and Ib afferents to the motoneuron is shown. Definite (heavy shading) or highly probable (light shading) sites of plasticity include: the motoneuron membrane (i.e. firing threshold and axonal conduction velocity), motor unit properties, C terminals on the motoneuron, the Ia afferent synaptic connection, and terminals conveying disynaptic group I inhibition or excitation to the motoneuron. The essential roles of the corticospinal tract (originating in sensorimotor cortex) and of cerebellar output to cortex are indicated (updated from Wolpaw, 1997). See Plate 17.3 in Colour Plate Section.

Along with its homologous brainstem nuclei, the spinal cord is the final assembly point for neuromuscular behaviors, both simple and complex. It is, to use the term Sherrington originally applied to the motoneuron itself, "the final common path" (Clarke and O'Malley, 1996, p. 375), assembling and executing the end product of activity elsewhere in the CNS. For example, the motoneurons,

interneurons, and synapses of the lumbosacral spinal cord produce all the many kinds of locomotion and postural maintenance, withdraw the legs from painful stimuli, contribute to actions involving all four limbs, support bladder and bowel function, and produce numerous specialized actions. The fact that the spinal cord supports these many behaviors, and incorporates new ones throughout life, implies that its neuronal and synaptic elements are continually adjusted and readjusted to serve the current repertoire of behaviors. That such adjustments take place in the short-term as the organism shifts from one behavior to another or cycles through the different phases of a single behavior is indicated by studies like those demonstrating the changes in presynaptic inhibition from standing to walking to running, and the changes in responses to primary afferent input that occur over the step cycle (Capaday and Stein, 1987; Stein, 1995; Faist et al., 1996; Rossignol, 1996; Pearson and Ramirez, 1997; Zehr, 2002). As the data reviewed above indicate, both long-term and short-term adjustments occur. Gradual activity-dependent plasticity, initiated and guided by descending and peripheral inputs, presumably maintains spinal cord circuitry in a state appropriate for its current roster of behaviors. The long-term control – a consensus resulting from the different patterns of activity associated with the different behaviors – seems to operate as a coarse adjustment, setting ranges over which fine adjustments specific to each behavior are made. For example, at a given time, the strength of primary afferent input to soleus motoneurons has a range that includes values appropriate for standing, walking, and running (Zehr, 2002).

In this situation, the neural activity that adds a new behavior to the repertoire is likely to induce plasticity that supports the new behavior and, in addition, plasticity that preserves the old behaviors. This is true whether the activity results from daily practice and the behavior is an athletic skill or the activity is produced by peripheral or central damage and the behavior reflects or compensates for a functional abnormality. For example, the increased motoneuron response to primary afferent input that underlies H-reflex up-conditioning (e.g., Fig. 3A (left)) affects other behaviors that involve the same input pathway (Chen et al., 2005a) (Fig. 4). These effects may lead to additional "compensatory" activity-dependent plasticity that restores these other behaviors. The still mysterious plasticity that maintains a normal contralateral H-reflex in a monkey that has undergone H-reflex down-conditioning (Wolpaw and Lee, 1989; Wolpaw et al., 1993) could be compensatory, serving to preserve normal contralateral function. In addition, because activity-dependent plasticity may occur at many places in the spinal cord, the modifications in activity caused by the plasticity responsible for a new behavior or for maintaining old behaviors are likely to lead to further "reactive" plasticity at other sites. Thus, the smaller stretch reflexes in the ostensibly unaffected arm contralateral to an arm paralyzed by a hemispheric stroke (Thilmann et al., 1990), may result from reactive plasticity caused by change in activity in the spinal pathways that connect the two sides of the spinal cord.

These considerations imply that acquisition of a new behavior probably involves three categories of plasticity: primary plasticity that supports the new behavior, compensatory plasticity that preserves old behaviors in spite of the impact of the primary plasticity, and reactive plasticity that is caused by changes in activity due to primary and compensatory plasticity. This etiological categorization explains the multisite plasticity that accompanies even the simplest behavioral change. It indicates that multisite plasticity is necessary to preserve the complete repertoire of behaviors and inevitable due to the ubiquitous capacity of the CNS for activity-dependent plasticity. It also helps to explain why some instances of plasticity (e.g., the contralateral spinal cord plasticity with H-reflex conditioning (Wolpaw and Lee, 1989)) may bear no ostensible relationship to the behavioral changes that they accompany. Recognition of these three etiological categories of plasticity may help define factors affecting the efficacy of new rehabilitation methods (see below).

The normal activity-dependent spinal cord plasticity occurring during development, during skill acquisition later in life, or induced in the laboratory, is largely created and guided by descending input from the brain, sometimes accompanied by associated peripheral inputs to the spinal cord.

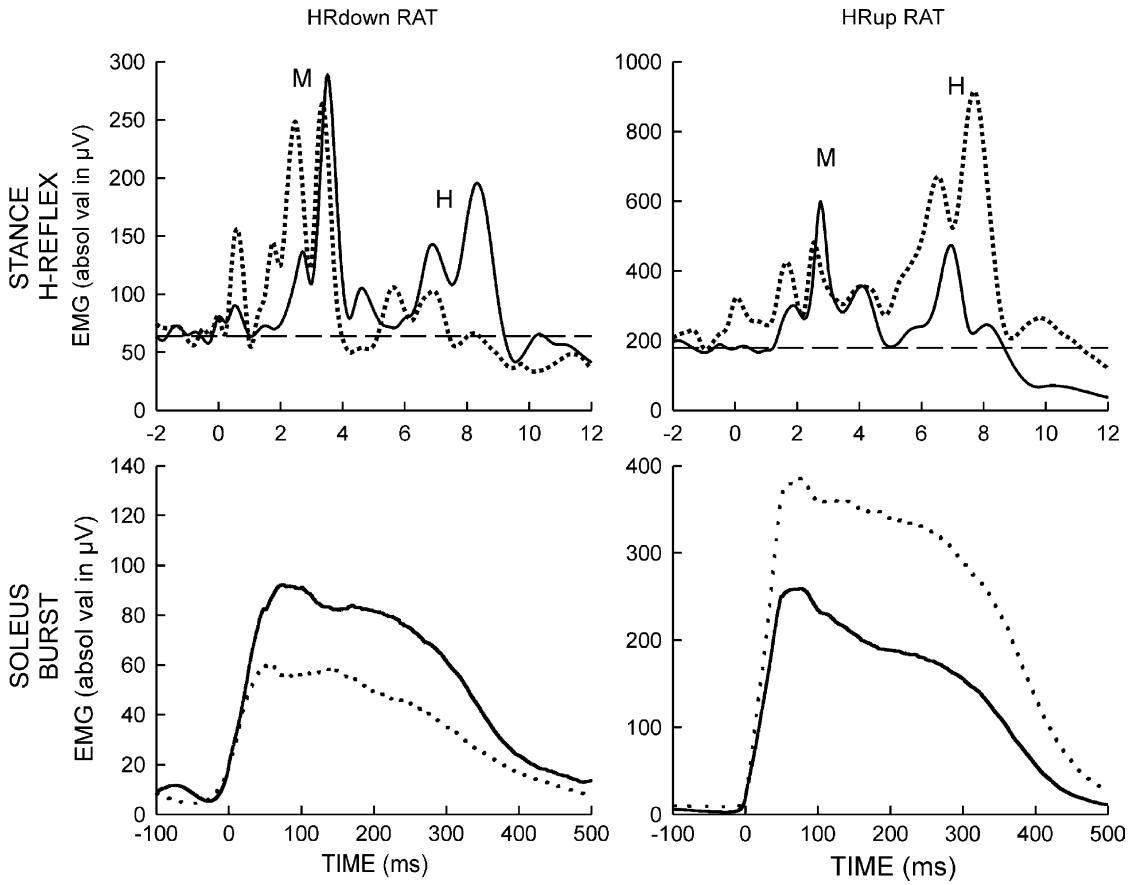

Fig. 4. H-reflexes during the stance phase of locomotion and right soleus bursts during undisturbed locomotion before (solid) and after (dotted) conditioning from a down-conditioned (HRdown) and an up-conditioned (HRup) rat. The stance H-reflexes are each the average of 109–166 trials and the stance bursts are each the average of 131–462 bursts. After conditioning, both the stance H-reflex and the soleus burst are smaller in the HRdown rat and larger in the HRup rat. (from Chen et al., 2005a).

This descending influence is likely to be associated with, and may often depend on, plasticity in cortex, cerebellum, and/or other brain areas. The behavioral effects associated with spinal cord plasticity seem to reflect the complex interactions of plasticity at multiple spinal and supraspinal locations (Carrier et al., 1997; Whelan and Pearson, 1997; Wolpaw and Tennissen, 2001; Wolpaw and Chen, 2006).

Theoretical significance of activity-dependent spinal cord plasticity

The spinal cord's impressive capacity for activity-dependent plasticity suggests that most motor skills, particularly those acquired through prolonged practice, depend to some degree on spinal cord plasticity. This inference is consistent with the strong evidence that activity can gradually change the spinal cord. It seems to explain why intense practice over a long time is needed for acquisition and maintenance of athletic skills and other motor skills such as playing the piano and other musical instruments. In fact, such skills probably cannot be fully understood solely on the basis of plasticity in cerebral cortex, cerebellum, or other brain areas. The plasticity in the spinal cord must also be taken into account. The role of spinal cord plasticity has rarely been accorded any, much less adequate, recognition in studies focused on the role

of cortical plasticity in accounting for new behaviors. The fact that spinal cord plasticity can, and probably often does, contribute to normal and pathological behavioral changes complicates investigations of such changes. Nevertheless, without adequate recognition of and attention to spinal cord plasticity, efforts to clarify how CNS plasticity explains behavioral changes are likely to yield only incomplete or misleading insights.

The fact that motor skills depend on multisite and multilevel (i.e., spinal and supraspinal) plasticity suggests that intellectual skills, like language mastery or mathematical facility, may also depend on widely distributed plasticity. The rapid behavioral changes that traditionally engage most research attention, like single-trial acquisition of a new word, may merely reflect small adjustments in patterns of plasticity slowly created by prolonged practice, adjustments comparable to the change in presynaptic inhibition associated with the transition from standing to running, or the change in descending input that produces phase-1 change in the SSR (see above). As a result, elucidation of many skills may require investigation of gradually acquired activity-dependent plasticity in the brain similar to that found in the spinal cord. Indeed, such investigation might logically start with simple motor skills and with the spinal cord, for its relative simplicity and accessibility and its well-defined connections to the brain facilitate studies of activity-dependent plasticity and of how multiple sites of plasticity conspire to produce behavioral changes.

Possible clinical uses of activity-dependent spinal cord plasticity

In developing new rehabilitation methods for long-term neuromuscular disorders such as spinal cord injury or cerebral palsy, the spinal cord's capacity for activity-dependent plasticity is both a challenge and an opportunity. On the one hand, this capacity may add to the disabilities that follow spinal cord injury and will certainly influence the results of new therapeutic methods that induce regeneration of spinal cord pathways and neurons. On the other hand, it offers the opportunity to induce and guide restoration of function, and could enable imperfect regeneration to support significant functional recovery. For both reasons, the effective engagement of activity-dependent plasticity in the spinal cord is likely to be a key part of new rehabilitation programs for people with spinal cord injuries or other chronic neuromuscular disorders. Therapeutic initiation and guidance of activity-dependent spinal cord plasticity will depend on training protocols that create appropriate patterns of peripheral and descending inputs to the spinal cord. The development of such methods has just begun for locomotion (see Chapter 15 and 16). Other important behaviors, such as urination, have not yet been addressed.

Poirrier et al. (2004) evaluated the effect of repetitive transcranial magnetic stimulation (rTMS) on locomotion in rats with high or low thoracic spinal cord compression injuries. rTMS (10 Hz × 5 s every 2 min for 20 min) was delivered 5 d/wk for 8 weeks. In rats with low thoracic injury, locomotion improved substantially more in TMS rats than in unstimulated rats. Fig. 5 shows this result. In contrast, rats with high thoracic injury, which normally recovered better than those with low thoracic injury, showed no benefit from TMS. Supported by histological data, the investigators hypothesize that TMS improves locomotion in rats with low thoracic injuries by increasing the strength of descending serotonergic input to the lumbosacral locomotor pattern generator.

Another recent study (Chen et al., 2005b) explored the possibility that operant conditioning of a spinal reflex can improve locomotion in spinal cord-injured rats. Mid-thoracic transection of the right lateral column (LC) caused a persistent asymmetry in treadmill locomotion. Rats were then either exposed or not exposed to an H-reflex up-conditioning protocol that greatly increased right soleus motoneuron response to primary afferent input, and locomotion was re-evaluated. H-reflex up-conditioning, which increased the right soleus burst, eliminated the locomotor asymmetry. In contrast, the asymmetry persisted in the unconditioned rats. These results suggest that appropriate reflex conditioning protocols could improve function in people with

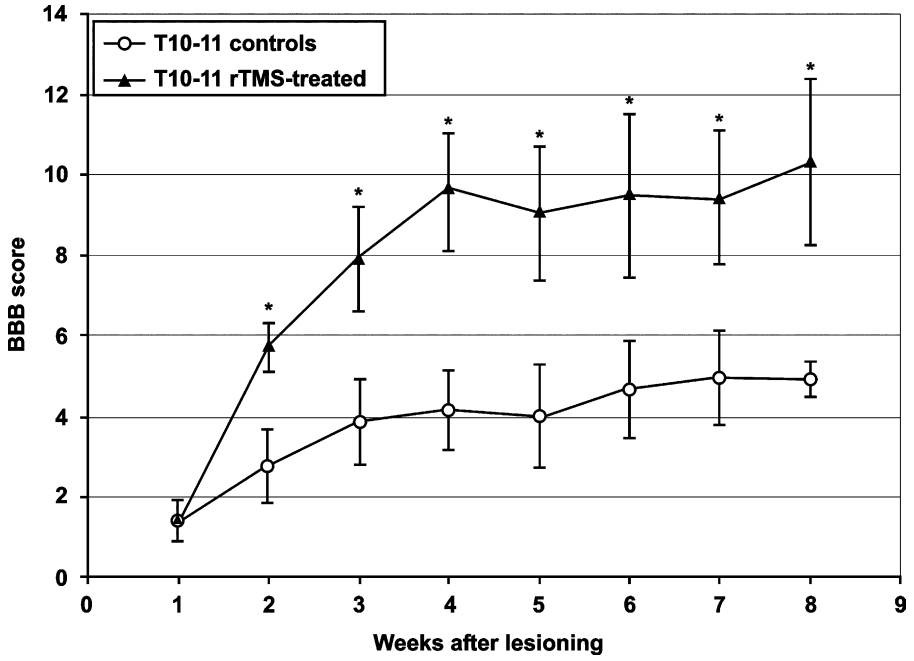

Fig. 5. BBB scores (mean ± SEM) (reflecting locomotor function (Basso et al., 1995)) for control ($N = 6$) and rTMS-treated ($N = 6$) rats with low thoracic spinal cord lesions. BBB scores were significantly higher for the stimulated rats from the second week postinjury onward (from Poirrier et al., 2004.).

partial spinal cord injuries. They could be especially useful when regeneration becomes possible and precise methods for re-educating the regenerated spinal cord become essential for restoring effective function.

These endeavors will be greatly affected by the complexity of the activity-dependent plasticity that accompanies even simple training protocols (e.g., Fig. 3D). They will also be affected by a distinctive feature of activity-dependent spinal cord plasticity as it functions in normal life and in response to disease: the slow rate of its impact on behavior. In spite of the rapidity of activity-dependent processes like LTP (which are known to occur in the spinal cord), the behavioral changes due to activity-dependent spinal cord plasticity develop gradually, probably because each one is the result of multiple activity-dependent processes. Changes in spinal reflexes during development and during the learning of skills like ballet occur gradually over months and years; those caused by H-reflex operant conditioning or other specialized training regimens occur over days and weeks. Although reflexes like the H-reflex can differ substantially between established behaviors (e.g., standing and running (Zehr, 2002)), or even between different phases of one behavior (e.g., stance and swing phases of walking (Faist et al., 1996)), the specification of the reflex strengths associated with a particular behavior develops slowly. This feature is probably fortunate: rapid, large changes in specific reflexes independent of the contexts of specific behaviors could wreak havoc with motor control and necessitate prodigious supraspinal compensation.

At the same time, the characteristically gradual effect of activity-dependent spinal cord plasticity on behavior implies that laboratory studies and clinical applications need to extend over sufficient time periods. Furthermore, the ubiquity of activity-dependent plasticity and the inevitable interactions among primary, compensatory, and reactive plasticity, imply that functional effects are likely to change over time. Early gains will not always evolve into long-term improvements; and, conversely, early deleterious effects may give way to long-term benefits.

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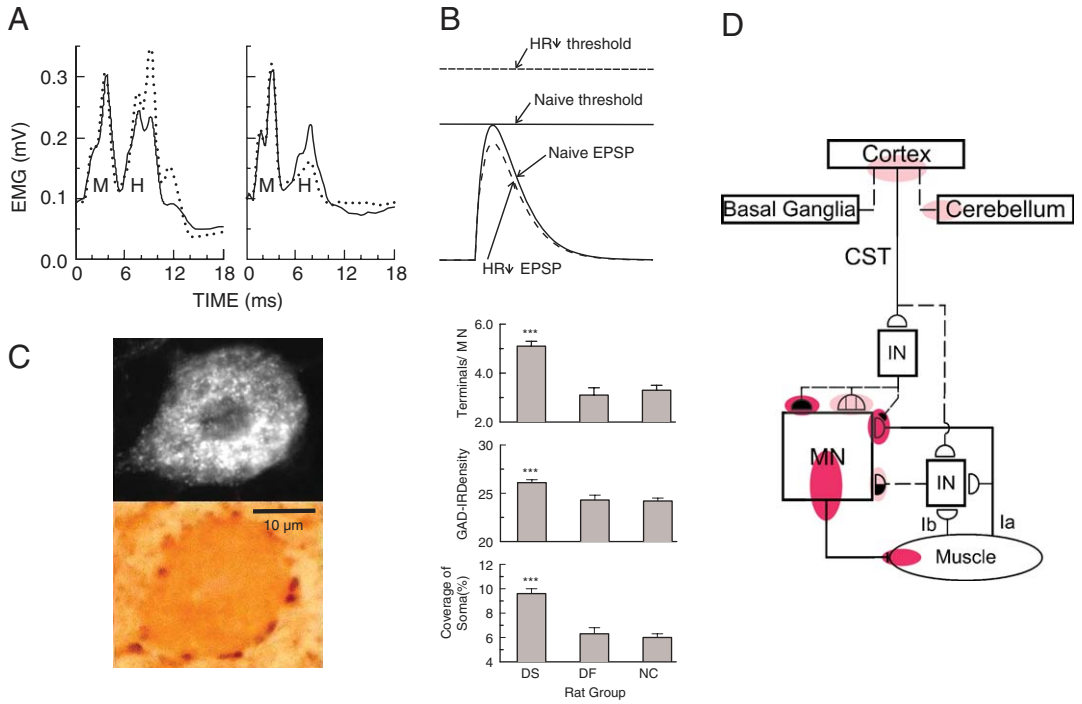

Plate 17.3. Operant conditioning of the spinal stretch reflex (SSR)/H-reflex pathway and the associated spinal and supraspinal plasticity. (A) The graphs show average poststimulus soleus EMG for representative days before (solid) and after (dotted) soleus H-reflex conditioning from a rat in which the H-reflex has been increased by the up-conditioning mode (left) or decreased by the down-conditioning mode (right). The H-reflex is much larger after up-conditioning and much smaller after down-conditioning, while background EMG (indicated here by EMG at zero time) and M responses (i.e., direct muscle responses) are unchanged. (B) Triceps surae motoneurons on the conditioned side of H-reflex down-conditioned (HR) monkeys were found to have more positive firing thresholds and slightly smaller Ia EPSPs. Together, these two findings can explain why the H-reflex became smaller (A and B from Wolpaw, 1997). (C) Effects of successful down-conditioning on GABAergic terminals on soleus motoneurons (assessed by glutamic acid decarboxylase (GAD_{67})-immunoreactivity (GAD-IR). Top left: Soleus motoneuron labeled by Alexa Fluor-488 conjugated with CTB injected into the muscle. Bottom left: Same motoneuron showing GAD-IR (i.e., GABAergic) terminals (dark) located on the periphery of the motoneuron.(Bar = 10 Fm.). Right: Average ($\pm$SEM) values for: down-conditioning successful (DS), down-conditioning failed (DF), and naive control (NC) rat groups for: number of GABAergic terminals per motoneuron; terminal GAD density; and GABAergic terminal coverage of soma (expressed as percent of perimeter). (***$P < 0.0001$; compared to the NC group.) After successful down-conditioning, soleus motoneurons have more GABAergic terminals, and these terminals are more densely labeled and occupy more of the soma (from Wang et al., 2006)). (D) Spinal and supraspinal sites (shaded ovals) of plasticity associated with operant conditioning of the SSR or its electrical analog, the H-reflex. "MN" is the motoneuron, "CST" is the main corticospinal tract, and each "IN" is one or more spinal interneuron types. Open synaptic terminals are excitatory, solid ones are inhibitory, half-open ones could be either, and the subdivided one is a cluster of C terminals. Dashed pathways imply the possibility of intervening spinal interneurons. The monosynaptic and probably oligosynaptic SSR/H-reflex pathway from Ia and Ib afferents to the motoneuron is shown. Definite (heavy shading) or highly probable (light shading) sites of plasticity include: the motoneuron membrane (i.e. firing threshold and axonal conduction velocity), motor unit properties, C terminals on the motoneuron, the Ia afferent synaptic connection, and terminals conveying disynaptic group I inhibition or excitation to the motoneuron. The essential roles of the corticospinal tract (originating in sensorimotor cortex) and of cerebellar output to cortex are indicated (updated from Wolpaw, 1997).