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Plasticity from muscle to brain

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Abstract

Recognition that the entire central nervous system (CNS) is highly plastic, and that it changes continually throughout life, is a relatively new development. Until very recently, neuroscience has been dominated by the belief that the nervous system is hardwired and changes at only a few selected sites and by only a few mechanisms. Thus, it is particularly remarkable that Sir John Eccles, almost from the start of his long career nearly 80 years ago, focused repeatedly and productively on plasticity of many different kinds and in many different locations. He began with muscles, exploring their developmental plasticity and the functional effects of the level of motor unit activity and of cross-reinnervation. He moved into the spinal cord to study the effects of axotomy on motoneuron properties and the immediate and persistent functional effects of repetitive afferent stimulation. In work that combined these two areas, Eccles explored the influences of motoneurons and their muscle fibers on one another. He studied extensively simple spinal reflexes, especially stretch reflexes, exploring plasticity in these reflex pathways during development and in response to experimental manipulations of activity and innervation. In subsequent decades, Eccles focused on plasticity at central synapses in hippocampus, cerebellum, and neocortex. His endeavors extended from the plasticity associated with CNS lesions to the mechanisms responsible for the most complex and as yet mysterious products of neuronal plasticity, the substrates underlying learning and memory. At multiple levels, Eccles' work anticipated and helped shape present-day hypotheses and experiments. He provided novel observations that introduced new problems, and he produced insights that continue to be the foundation of ongoing basic and clinical research. This article reviews Eccles' experimental and theoretical contributions and their relationships to current endeavors and concepts. It emphasizes aspects of his contributions that are less well known at present and yet are directly relevant to contemporary issues.

Keywords: John Eccles; Plasticity; Activity-dependent; Memory; Learning; Motor unit; Spinal cord; Muscle

Contents

Abbreviations: CNS, central nervous system; EMG, electromyographic activity; LPG, locomotor pattern generator; PTP, post-tetanic potentiation; SCI, spinal cord injury

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1. Introduction

People come to the study of the nervous system for different reasons. Some want to cure disease and ease disability; others are drawn by the intricate problems of CNS structure and function; still others are attracted to neuroscience by its popularity (or, in other eras, its lack of popularity); or they simply fall into it by chance or circumstance. Sir John Carew Eccles (1903–1997), as he explained many years later, became a neuroscientist because he was interested in himself. He wanted "to understand what I am" (p. 4 in Eccles, 1965). He first tried psychology, but the results were personally unsatisfying and drove him to basic neurophysiology, and more specifically to the laboratory of Sir Charles Sherrington (1856–1952) and the study of the synapse (for review of Eccles' career, see Curtis and Andersen, 2001; Stuart and Pierce, 2006).

Eccles' original motivation is clearly evident late in his career in his resolute devotion to understand the relationships between the mind and brain (see Libet, 2006; Wiesendanger, 2006). It is also evident in his life-long focus on the plasticity induced by neural activity, whether the activity associated with normal experience or the activity induced by lesions of various kinds. Activity-dependent plasticity underlies learning and memory, and thus it shapes capacities and behaviors.

At the time that Eccles arrived, Sherrington and his group were the most prominent and successful proponents of the sensorimotor hypothesis of CNS function. This was first clearly formulated in the middle of 19th century and has largely controlled neuroscience research ever since. According to this hypothesis, the whole function of the CNS is to be the "central exchange organ", in which "the afferent paths from receptor-organs become connected with the efferent paths of effector-organs". That is, the function of the CNS is to connect sensory inputs to appropriate motor outputs; "it is . . . an *organ of co-ordination [sic]* in which from a concourse of multitudinous excitations there result orderly acts, reactions adapted to the needs of the organism" (p. 313 in Sherrington, 1906). Sherrington's work focused on the simplest sensorimotor connections, those produced by spinal reflex pathways, both as models for understanding more complex connections and as essential prerequisites for undertaking studies of such connections. Thus, Eccles began by studying basic neuromuscular interactions. Nevertheless, he focused even at this level on the phenomena of plasticity. And as he moved centrally from muscles and nerves to the spinal cord and then to the brain, he studied plasticity at each level, and at each level he made important contributions.

Eccles' later endeavors at the level of the brain coincided with and contributed to the genesis of the current preoccupations with synaptic plasticity (e.g. long-term potentiation and depression) in hippocampus, cerebellum, and other brain areas (e.g. Andersen et al., 1964a,b; Kitai et al., 1969; Eccles et al., 1972, 1975; Nicoll et al., 1975; also see 2006 reviews by Andersen and Ito in this issue). Eccles' earlier work on plasticity in the periphery and in the spinal cord is less well known, however, and much less properly appreciated. Nevertheless, it was most unique and interesting, and it anticipated fundamental issues that are just now becoming widely recognized by the neuroscience community. Indeed, the remarkable recent success in defining synaptic and other mechanisms of plasticity in the brain raises difficult issues that compel renewed attention to the lower-level plasticity phenomena that engaged Eccles 50 years ago. These phenomena, the timely questions they raise, the insights they offer, and the useful experimental models they provide, are the primary focus of this review.

2. Eccles' studies of plasticity

Eccles' interest in the neurophysiological basis of plasticity is evident throughout his publications. His research on neuromuscular and spinal reflex systems focused on how activity affects these systems. His initial studies of changes in muscle properties during development and after surgical alterations in muscle innervation were the first demonstrations of plasticity in muscle contractile properties caused by neural influences. These studies sparked the beginning of an active field of research into the influences of nerve on muscle and muscle on nerve, the activity-dependence and -independence of these influences, and the way that interruption of these normal influences affects muscle phenotype.

2.1. Muscle plasticity

Eccles and his co-workers pioneered the study of neuronal influences on muscle with their studies of cross-reinnervation of

muscle and the effects of altering neuromuscular activity through spinal cord isolation. Subsequent studies confirmed many, but not all (see below), of his original findings (Buller and Pope, 1977). This was due in part to the fact that his studies of muscle plasticity were based on recordings from whole muscle. Eccles was certainly aware of the concept of the motor unit (Eccles and Sherrington, 1930), but detailed knowledge of the contractile properties of single motor units (Burke et al., 1971; Close, 1967) and methodology for the histochemical identification of contractile proteins in individual muscle fibers (Barnard et al., 1971; Brooke and Kaiser, 1970; Guth and Samaha, 1969) were not developed until after the time that Eccles switched his focus from the periphery and the spinal cord to supraspinal levels. Eccles lacked the contractile and histochemical context for interpreting many of the graded effects he saw (e.g. partial conversions between fast and slow contractile properties). These varied from muscle to muscle, even for muscles with grossly similar contractile properties. The combination of these technologies afforded a fuller appreciation of the significance of Eccles' early work. Over the past 45 years, activity-dependent and -independent plasticity of the contractile and biochemical properties of muscle and its innervating motoneurons have been explored and extensively reviewed (e.g. Roy et al., 1991; Pette and Vrbova, 1992, 1999; Gordon and Pattullo, 1993; Baldwin and Haddad, 2001; Gordon et al., 2004). This section focuses on three key studies from Eccles' laboratory and their impact on research into the role of activity-dependent and activity-independent factors in the control of muscle properties.

2.1.1. Disuse atrophy

By the time Eccles began his studies of muscle disuse, it had already been established that interruption of a muscle's nerve resulted in a decreased number and/or cross-sectional area of muscle fibers (i.e. atrophy) and reduced force production (reviewed by Tower, 1939). Qualitatively similar, although less profound, effects could be achieved with the muscle nerve intact if neuromuscular activity was greatly reduced by transecting the spinal cord above and below the motoneuron pool and cutting the intervening dorsal roots (Tower, 1937b). Eccles confirmed these effects using a similar preparation (i.e. dorsal rhizotomy plus a single spinal transection to isolate the lumbosacral cord) (Eccles, 1941). More importantly, he demonstrated that brief daily electrical tetanic stimulation (lasting from as little as 10 s up to 2 h) largely prevented weight loss in ankle flexor muscles and slightly attenuated the disuse-dependent loss of tetanic force production (Eccles, 1944). Prior attempts to prevent atrophy in denervated muscle by electrical stimulation had been unsuccessful (e.g. Hartman and Blatz, 1920; Hines and Knowlton, 1939). Eccles' demonstration of the ability of electrical stimulation to preserve muscle mass in an atrophy-inducing experimental preparation (along with similar contemporaneous reports from other laboratories: e.g. Fischer, 1939; Guttmann and Guttmann, 1942) revealed the potential for activity-dependent muscle plasticity. It also presaged the development of the present-day field of functional electrical stimulation for normalizing muscle endurance and controlling muscle function after spinal cord injury (SCI) or other disruptions of supraspinal control over lower motoneurons (Barbeau et al., 2002; Stein et al., 2002; Peckham and Knutson, 2005).

Eccles clearly believed that the lack of neuromuscular activity was responsible in large part for the observed atrophy in his preparation, which is consistent with his view of activity-dependent plasticity in the spinal cord (see Section 2.3.3 below). At the same time, he also recognized that other factors could influence muscle properties. The spinally transected and deafferented preparations used by Eccles exhibited minimal, if any, activity, and yet he observed differences among muscles in the effects of electrical stimulation. For example, the same stimulation that largely prevented atrophy in the flexor muscles had little effect on atrophy in extensor muscles. Eccles recognized that because of the design of his experimental paradigm, the flexors were usually held fully lengthened and the extensors were usually fully shortened. Using tenotomy to prevent muscle elongation, Eccles reported that electrical stimulation was more effective in reducing muscle atrophy at long muscle lengths than at short muscle lengths (Eccles, 1944). In addition, he confirmed previous reports that the effects of tenotomy alone were similar to those of disuse. Eccles argued that the disuse-like effects of tenotomy could not be explained by altered activity directly, but were more likely to be related to marked muscle shortening.

Since the time of Eccles' studies of disused muscle, a view of the mechanism of disuse atrophy has emerged that emphasizes mechanical factors and de-emphasizes the direct contribution of reduced activity (Roy et al., 1991; Gordon and Pattullo, 1993; Talmadge et al., 1995). Interruption of spinal circuitry is usually associated with a variable level of reduction in muscle activity below the level of the lesion, and the extent of disuse atrophy is not always consistent with the loss of muscle activity (Alaimo et al., 1984; Lovely et al., 1986; Stein et al., 1992). Paradigms involving contraction of muscle in a shortened and/or unloaded state (e.g. tenotomy, limb immobilization at short muscle lengths, hindlimb suspension, and exposure to reduced gravity) produce muscle atrophy comparable to or even more extensive than that seen with inactivity after interruption of spinal circuitry (Baker, 1983; Pachter and Eberstein, 1984; Winiarski et al., 1987; Martin et al., 1992; Talmadge et al., 1995; Jamali et al., 2000; Duchateau and Enoka, 2002; Ohira et al., 2002). In addition (and as noted by Eccles (1941, 1944)), disuse atrophy is more pronounced in anti-gravity muscles (Lieber et al., 1986; Pierotti et al., 1991; Ohira et al., 2002; Pesce et al., 2002; Roy et al., 2002b), which is consistent with the importance of unloading to development of muscle atrophy.

While changes in activity affect the state of muscle contraction, they also influence muscle length and loading. Eccles' early studies of disuse atrophy highlight the complexity of the issue of designing experimental paradigms that can distinguish among the multiple factors regulating muscle properties. Recent studies that assessed the contractile and biochemical properties of muscle under various combined conditions of neural activity, innervation, mechanical state, and electrical stimulation have provided new insights into the relative contributions of activity-dependent and activity-

independent factors (Pierotti et al., 1994; Roy et al., 1996, 1998a, 2002a; Zhong et al., 2002; see Section 2.1.3 below).

2.1.2. Developmental muscle plasticity

Eccles was aware that the contractile properties of adult muscle are not all fixed at birth. All muscles exhibit slow contractile properties at birth (i.e. longer time from contraction onset to peak force and for relaxation after a single twitch; lower frequency tetanic stimulation adequate for achieving fully fused contractions) (Denny-Brown, 1929a). During the first 5 weeks of post-natal development, they become faster (i.e. shorter single-twitch contraction and relaxation times; higher frequency tetanic stimulation needed to achieve fused contractions (which are also more powerful)). Some muscles retain these fast contractile properties, while others revert to slow contractile properties.

Eccles had previously studied the relationship between the electrophysiological properties of motoneurons and the muscles they innervate (Eccles et al., 1957, 1958a). Motoneurons that exhibit prolonged hyperpolarization after a single action potential (afterhyperpolarization) tend to innervate muscles with slow contractile properties, and motoneurons with short afterhyperpolarizations tend to innervate muscles with fast contractile properties. Motoneurons innervating predominantly fast muscles were known to fire more rapidly than motoneurons innervating predominantly slow muscle (Denny-Brown, 1929b; Granit et al., 1956, 1957). The matching of intrinsic properties of the motoneuron to the contractile properties of the muscle is now well established (Kernell et al., 1999). In the 1950s, it was becoming clear to Eccles that the duration of the afterhyperpolarization plays an important role in regulating the firing rate of a motoneuron (Eccles, 1953, 1959), and that this in turn ensures efficient activation of its muscle fibers (Adrian and Bronk, 1929; Eccles et al., 1958a). This raised the question of whether the developmental change in muscle contractile properties represented an effect of the differences in firing behavior of motoneurons on the properties of their innervated muscles or intrinsic regulation by muscles independent of their pattern of activation.

To address this question, Eccles, his daughter Rose Eccles, and Arthur Buller studied the role of motoneuron activity in developmental changes in muscle by carefully analyzing the time course of change in the contractile properties of hindlimb muscles in kittens (Buller et al., 1960a). They confirmed that all muscles tested were slow at birth and increased their speed of contraction over the next several weeks (Fig. 1A1 and A2). Muscles destined to be predominantly fast (e.g. flexor digitorum longus and flexor hallucis longus in Fig. 1A1) retain this rapid contraction time, while those muscles destined to be predominantly slow (i.e. soleus and crureus in Fig. 1A2) reacquire their slow contractile properties. In order to assess the role of motoneuron activity on the development of the speed of contraction, Buller et al. (1960a) studied the time course of change in muscle properties in kittens in which descending activation of motoneurons was greatly reduced by upper lumbar spinal transection a few days after birth. They found that muscles that were destined to be fast developed normally even in the absence of motoneuron activity (Fig. 1B1). The reversion of soleus and crureus to longer contraction times did not occur (Fig. 1B2), however. Instead, these muscles retained their fast contractile properties so that they were indistinguishable in contraction time from the normally fast muscles. Addition of a dorsal rhizotomy to the spinal transection induced soleus and crureus to become even faster. Eccles interpreted the results of this study as demonstrating that slow muscle differentiation

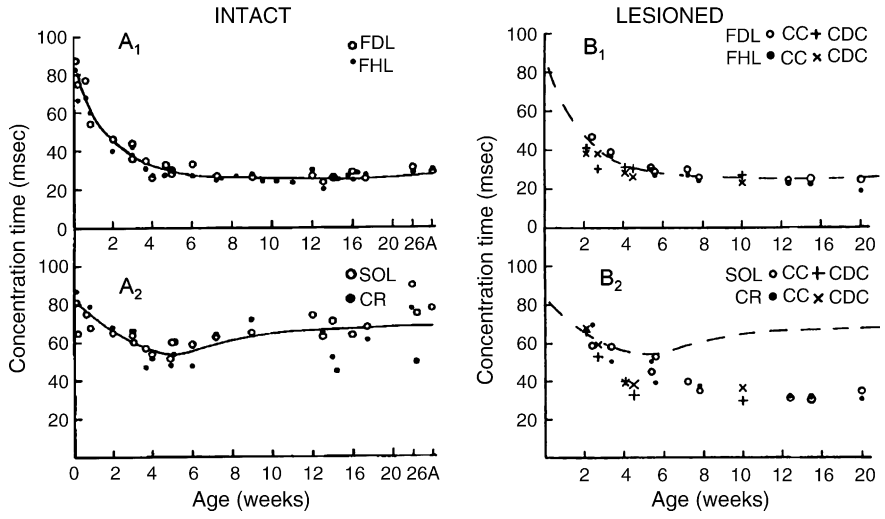

Fig. 1. Differences among muscles in developmental time course of the speed of contraction. Contraction times are shown for four different muscles from cats of different ages with intact CNS (A1 and A2) or with spinal transections alone (CC) or with deafferentation below the level of the lesion (CDC) performed between 1 and 4 days after birth (B1 and B2). All muscles exhibit long contraction times at birth, which become shorter over the next several weeks. In both intact (A1) and lesioned (B1) animals, flexor digitorum longus and flexor hallucis longus (FDL and FHL, respectively) retain their rapid contraction time. Soleus and crureus (SOL and CR, respectively) reacquire their long contraction times in intact animals (A2), but not in lesioned animals (B2). The dashed lines in B1 and B2 show the time course of change in contraction time in intact animals as solid lines in A1 and A2, respectively. Modified from Figs. 3 and 9 in Buller et al. (1960a) with permission of the publishers.

depended on neural influences. The failure of normally slow muscles to revert to the slow phenotype suggested that control over slow muscle was activity-dependent, while the development of the fast muscle phenotype was activity-independent.

2.1.3. Neural influence on muscle plasticity

Eccles performed further studies on neural regulation of muscle properties using an experimental paradigm in cats in which pairs of nerves innervating slow and fast muscle were severed and resutured either to their original nerve (self-reinnervation) (on one side of the animal) or to the opposite nerve (cross-reinnervation) (on the other side of the animal) (Buller et al., 1960b). This paradigm had previously been used to induce a rewiring of spinal circuitry in lower species (for review see Sperry, 1945), and it was being tested in cats to try to induce plasticity in the monosynaptic connections between group I afferents and motoneurons (reviewed in Buller and Pope, 1977). Although the cross-reinnervation elicited little plasticity within the spinal cord, a remarkable change was observed in the contractile properties of the affected muscles (Fig. 2). Normally slow muscles (e.g. soleus) cross-reinnervated by nerves from motoneurons that normally innervated fast muscle (e.g. flexor digitorum longus) acquired fast contractile properties (SOL in Fig. 2A). Normally fast muscles cross-reinnervated by nerves from motoneurons that normally innervated slow muscle developed slower contractile properties, although the transformation appeared to be less complete than that of cross-reinnervated slow muscle (FDL in Fig. 2A). Cutting and rejoining the same nerve did not affect contractile speed—fast muscle stayed fast, slow muscle stayed slow (Fig. 2B). When surgery was performed at different times during development, the results of cross- and self-reinnervation were similar regardless of the age, suggesting that the initial composition of the muscle was not a confounding factor.

The above results clearly indicated that the motoneuron exerted control over the contractile properties expressed by the muscle, but it was not clear whether this control was mediated by neurotrophic influences of the nerve on the muscle or by activity induced in the muscle by the innervating motoneurons. In the latter case, the low frequency tonic firing of slow motoneurons would induce slow contractile properties, and the phasic higher firing frequency of fast motoneurons would induce fast contractile properties. To address this issue, Buller et al. (1960b) performed the same cross-reinnervation experiment with soleus and flexor digitorum longus in cats that had spinal cord transections above L2 and below S2 and an intervening dorsal rhizotomy. The transections and rhizotomy left the motoneurons physically intact but greatly reduced their activity by removing all descending and afferent input to them (spinal isolation; Tower, 1937a). After 9–10 weeks, soleus contraction time was shorter and flexor digitorum longus contraction time was slightly longer on both the crossed and uncrossed sides. In addition, the non-lesioned slow crureus muscle also exhibited shorter contraction times in these preparations, which they interpreted as indicating that the peripheral lesion itself did not interfere with the effects of spinal isolation. Buller et al. (1960b) concluded that the same developmental influence that made muscles slow was related to the effect of cross-reinnervation with a muscle nerve that normally innervated slow muscle. Because there was little consistent difference in the speed of contraction between the crossed and uncrossed sides, they concluded that this effect was dependent on intact neuronal input but could not attribute it solely to differences in firing rates between motoneuron pools. Their hypothesis about differences in firing rate did not hold up. According to this hypothesis, the greatly reduced motoneuron activity after spinal isolation should have increased soleus contraction time, instead of decreasing it, as it actually did. This prompted Buller et al. (1960b) to suggest that a trophic influence from slow motoneurons induces muscles to express slow contractile properties.

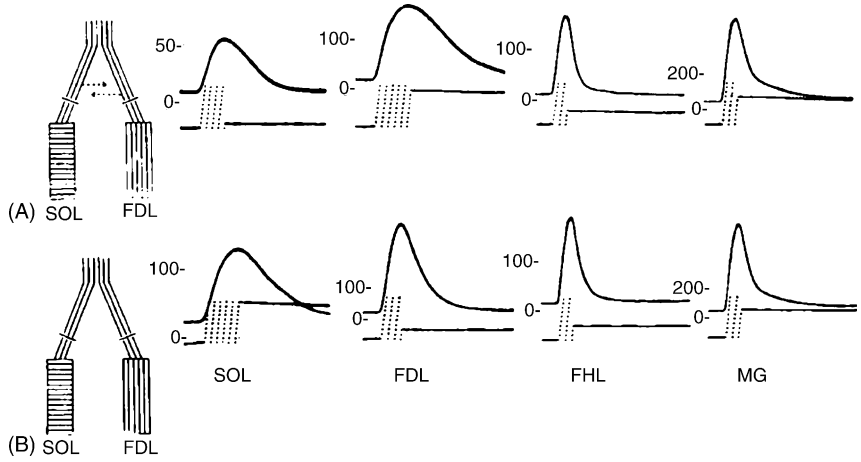

Fig. 2. Effects of cross- and self-reinnervation on muscle twitch characteristics. Shown are single twitch responses (upper trace in each pair of traces) for four different muscles to nerve stimulation 30 days after cutting the nerves to the soleus (SOL) and flexor digitorum longus (FDL) muscles, cross-suturing on one side (A) and self-suturing on the other side (B) in a 21-day-old cat (the cartoons on the left illustrate the surgical preparations). SOL contraction time becomes faster on the cross-reinnervated side than on the self-reinnervated side (contraction time is indicated by the raster counter with 1 ms resolution in the lower of each pair of traces). Conversely, FDL develops a slower contraction time. Neither the unmolested flexor hallucis longus (FHL) nor the medial gastrocnemius (MG) muscles are affected by these procedures. From Fig. 1 in Buller et al. (1960b) with permission of the publishers.

2.1.4. Significance of Eccles' studies on muscle plasticity

Eccles' developmental and cross-reinnervation studies (Buller et al., 1960a,b) firmly established the importance of neural influence on muscle properties. Due to experimental limitations, however, he was never able to determine conclusively the precise contributions of activity-dependent and activity-independent (i.e. trophic) mechanisms. These limitations included: the small numbers of animals in some experimental groups, the measurement of whole muscle contractile properties instead of single motor unit properties, and the difficulties of distinguishing between activity-dependent and activity-independent factors by comparing contractile properties of cross-reinnervated and self-reinnervated muscles in spinally isolated preparations. These limitations led in some cases to confusing observations that confounded the interpretation of results. Even so, Eccles' work on the role of activity and innervation on muscle properties was the impetus for a wide range of subsequent studies of the interplay between activity-dependent and activity-independent influences of nerve on muscle and muscle on nerve.

Many later studies have addressed the influence of neuromuscular activity on muscle. In one of the first demonstrations of the role of neuromuscular activity, Vrbova (1963) showed that cutting the tendon of the soleus muscle shortens its normally long contraction time. Low-frequency, but not high-frequency, stimulation of the muscle nerve restored the slow contraction time. Chronic stimulation of nerves to predominantly fast muscles at low frequencies comparable to the preferred firing rates of slow motor units induces a shift from fast to slow contractile properties (Ausoni et al., 1990; Vrbova, 1966; Salmons and Vrbova, 1969; Pette et al., 1973). The change in contractile properties is associated with a shift in myosin and other contractile sarcoplasmic reticulum protein isoforms (Brown et al., 1983; Leeuw and Pette, 1993; Ohlendieck et al., 1999). Slow-to-fast transformations have been induced by electrical stimulation of the cut muscle nerve (Al-Amood and Lewis, 1987; Gorza et al., 1988; Lomo et al., 1974). In other studies in which the muscle nerve was left intact, Kernell et al. showed that the confounding effect of spontaneous activity was reduced by spinal hemisection and deafferentation (Eerbeek et al., 1984; Kernell et al., 1987a,b). In these studies, the total amount of daily stimulation (more so than the frequency or pattern of stimulation) appeared to play a crucial role in triggering slow-to-fast transformations. Stimulation of the peroneal nerve lasting for 50%, 5%, or 0.5% of each animal's day (roughly corresponding to the normal usage amounts of S, FR, and FF motor units, respectively) for 4 or 8 weeks increased contraction time of the largely fast peroneus longus muscle, regardless of stimulation frequency or pattern. In addition, the degree of slowing was more pronounced at 50% activation than at $\leq$5% activation. Daily stimulation of $\geq$5% increased muscle endurance and increased expression of type I muscle fibers. Thus, the recruitment order-related level of activation of a motor unit had a strong influence on properties related to its contractile speed. On the other hand, the frequency of stimulation had a greater influence on maximal force production: high frequencies (typical of fast motor units) produced less reduction in force than did low frequencies (typical of slow motor units). These data indicated the importance of recruitment order-dependent activation pattern and frequency for determining motor unit phenotype. Even so, there are limitations on the extent to which activity can affect muscle properties. For example, Gordon et al. have shown that chronic low-frequency stimulation of the medial gastrocnemius muscle induces a shift towards S-type motor units (e.g. decreased contractile speed and force, increased endurance), but does not induce any compression of the range of S-type motor unit properties with respect to control animals (Gordon et al., 1997). Thus, a muscle activation pattern that triggers a fast-to-slow transformation is not sufficiently powerful to force all its motor units to have identical properties.

Clearly, imposed patterns of stimulation can have powerful effects on muscle properties. Later attempts, however, to demonstrate the influence of innervation by motoneurons with different activity patterns (e.g. cross-reinnervation of slow muscle with a faster nerve) have been less successful than the early efforts of Buller et al. (1960b). For example, cross-reinnervation of a slow muscle (soleus) with the nerve normally innervating a mixed (medial gastrocnemius) or largely fast (flexor digitorum longus) muscle had little influence on the muscle properties of the slow muscle (Dum et al., 1985; Foehring et al., 1987; Foehring and Munson, 1990).

A more recent series of experiments in the laboratory of Reggie Edgerton has reopened and greatly extended Eccles' investigation into the contribution of activity-dependent and activity-independent factors in the regulation of muscle properties (Graham et al., 1992; Jiang et al., 1990; Pierotti et al., 1991, 1994; Roy et al., 1996, 1998a, 2002a; Zhong et al., 2002). As in Tower's (1937a) study of spinal inactivity, cats received dual spinal transections above and below the motoneuron pools under study and bilateral deafferentation of the intervening spinal segments (i.e. spinal isolation) and were maintained for up to 8 months. Recordings of electromyographic activity (EMG) confirmed that the motoneuron pools were silenced by spinal isolation (Pierotti et al., 1991). Prolonged inactivity produced surprisingly little change in the distribution of functionally identified motor unit types in the largely fast tibialis anterior muscle. The lack of change did not appear to be the result of synaptic rearrangement induced by spinal isolation, in that there was no change in innervation ratio (Pierotti et al., 1991, 1994). In the normally homogenously slow soleus muscle, spinal isolation induced a decrease in contraction time and a change in the pattern of force during an unfused tetanus. About 30% of the motor units were classified as fast, despite the fact that all of the immunohistochemically assessed motor units expressed contractile proteins associated with the slow phenotype (as did all control soleus motor units) (Zhong et al., 2002). These data indicate that activity-independent factors contribute to the maintenance of the wide range of motor unit phenotypes.

The above data also suggest that not all muscle properties are equally affected by inactivity. In general, maximum tetanic force and fiber cross-sectional area are markedly reduced by prolonged spinal isolation, while fatigue resistance is hardly

affected (Pierotti et al., 1994; Zhong et al., 2002). The effects of spinal isolation on glycolytic and oxidative enzyme activities varied widely among muscles, with 25–90% of the spinal isolation-induced variation being activity-independent (Graham et al., 1992; Jiang et al., 1990; Pierotti et al., 1994). Despite the wide range of spinal isolation-induced biochemical changes, these markers remain appropriately aligned with physiologically defined motor unit types, and keep the same overall range of variability as in control muscles. In addition, the changes induced by spinal isolation are not randomly distributed among fibers throughout the muscle, but rather are highly uniform within motor units (Zhong et al., 2002). These studies demonstrated that both activity-dependent (particularly those related to muscle fiber size and force production) and activity-independent factors contribute to the regulation of muscle properties at the level of the motor unit.

The regulation of muscle properties by both activity-dependent and activity-independent factors was demonstrated most clearly by the study of Roy et al. (1996), which assessed the interaction of spinal isolation and cross-reinnervation of a nerve that normally innervates a largely fast muscle (flexor hallucis longus) into the normally slow soleus muscle in cats. The crucial experiment had four treatment groups: spinal isolation with or without cross-reinnervation, and intact spinal cord with or without cross-reinnervation. Both the spinal isolation alone and cross-reinnervation alone induced slow-to-fast transformations (e.g. increased fast myosin isoforms, decreased contraction and relaxation times, and a tendency towards increased fatigability). Spinal isolation alone (but not cross-reinnervation alone) induced signs of atrophy (e.g. reduced twitch and tetanic tension, and reduced specific tension). Combining spinal isolation and cross-reinnervation induced an even greater slow-to-fast shift in contractile and biochemical properties, suggesting that these two treatments had independent, nearly additive effects. This experimental design distinguished between the effects of inactivity and innervation and indicated the existence of both activity-dependent and activity-independent influences of nerve on muscle.

Neural factors are not the only ones that can influence muscle properties. Muscle properties are also sensitive to the mechanical conditions under which muscle activation occurs. In spinally isolated cats, daily short-duration isometric activation is more effective in maintaining normal contractile properties and myosin isoform expression than is the same amount of activation during lengthening or shortening contractions (Roy et al., 2002a). Even passive oscillatory stretching of soleus in the spinally isolated cat can partially restore muscle contractile properties (Roy et al., 1998a). Other factors may also help to determine muscle properties. For example, chronically elevated or depressed thyroid hormone levels are associated with faster or slower MHC isoform expression and contractile properties, respectively, in rat soleus muscle (Caiozzo et al., 1991, 1992).

As a result of a variety of neural and non-neural factors, muscle fibers vary widely in their mechanical, biochemical, and anatomical properties. Although this plasticity is non-associative and is ostensibly less complex than CNS plasticity, it can change behavior and may thereby induce further adaptive plasticity in the CNS itself (see Section 3.4 below).

2.2. Neuronal plasticity

2.2.1. Motoneuron plasticity after axotomy

The morphological changes induced in motoneurons by severing their axons were well known at the time that Eccles began his spinal cord studies (e.g. Cajal, 1928). Changes in neuronal function after peripheral nerve or ventral root section were first demonstrated as a reduction in magnitude and an increase in latency of the monosynaptic response to dorsal root stimulation and an enhancement of the polysynaptic response (Campbell, 1944). Eccles' laboratory performed a series of experiments in cats in which ventral roots were severed and the animals were allowed to recover for 5–56 days (Downman et al., 1951, 1953). Recordings of the L7 or S1 ventral root potential in response to group I strength stimulation of the dorsal roots or hindlimb nerves revealed a progressive decrease in and eventual failure of the monosynaptic component and an increase in central delay over the course of 5–12 days and a progressive increase in a longer latency component during post-lesion days 13–30. Monosynaptic responses elicited at group I strength began to reappear by about 5 weeks and continued to increase; longer latency components were evident, but diminished. These data led Eccles to the conclusion that monosynaptic Ia-motoneuron transmission was temporarily lost and oligosynaptic transmission enhanced in injured motoneurons.

Eccles was a pioneer in the use of intracellular recording from mammalian spinal neurons (Brownstone, 2006; Burke, 2006; Hultborn, 2006; Willis, 2006), and he used this approach to study axotomized motoneurons (Eccles et al., 1958b). Stimulation of group I afferents elicited EPSPs in the axotomized motoneuron that rose more slowly and had a more variable time-to-peak than did those in intact motoneurons. The latency from volley arrival at the spinal cord until EPSP onset was similar to that in intact motoneurons, indicating a lack of any abnormality in the arrival of the monosynaptic input. When an action potential was elicited in an axotomized motoneuron, its onset was much more variable and was typically more delayed than that seen in intact motoneurons.

EPSPs of axotomized motoneurons exhibited small depolarizing components that appeared at variable times after EPSP onset (Fig. 3). These were never seen in intact motoneurons. Eccles referred to these events as "partial responses". Their profile varied, ranging from spike-like responses (typically 4–6 ms in overall duration, with a rapid rise to a peak of <5 mV and a more slowly decaying tail; Fig. 3E and K) to longer duration, dome-shaped responses with more irregular shape and slower rise times (Fig. 3A, B and F). The spike-like partial responses were often not easily affected by intracellularly injected hyperpolarizing current (Fig. 3K).

When these partial responses were affected, however, they were blocked in all-or-none fashion (Fig. 3E and K). This led

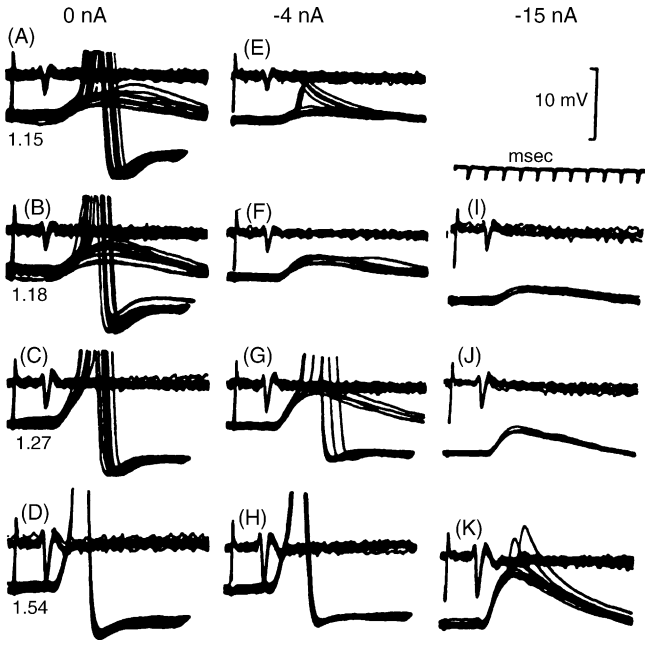

Fig. 3. EPSPs and partial responses recorded from an axotomized motoneuron. This figure shows intracellular recordings from a motoneuron antidromically activated from the lateral gastrocnemius-soleus nerve (lower tracing of each pair) and dorsal root entry zone potential (upper tracing of each pair) 16 days after S1 ventral root lesion. The homonymous nerve is stimulated at different intensities (the stimulus intensity used in each row is shown in the left-most panel of the row as a multiple of afferent threshold) with no current bias (left column) and during hyperpolarizing current pulses of −4 nA (middle column) and −15 nA (right column). Low intensity stimulation elicits broad, dome-shaped potentials (e.g. panels A and B) that are easily blocked by small hyperpolarizing currents (e.g. panels F and I). Hyperpolarization also reveals all-or-none, spike-like partial events (e.g. panel E), which are often difficult to block, even with large hyperpolarizing currents (e.g. panel K). Modified from Fig. 5 in Eccles et al. (1958b) with permission of the publishers.

Eccles to propose that they arose from electrically excitable patches of distal dendritic membrane. His hypothesis was supported by later studies in which stimulation of the bulbar reticular formation, which provided inhibition to the motoneurons' dendritic tree, prevented partial responses to afferent input (Kuno and Llinás, 1970a). Hyperpolarizing current pulses blocked the dome-shaped partial responses more readily (compare Fig. 3A with 3E and Fig. 3B with 3F and 3I), thereby revealing underlying EPSPs that were smaller but similar in shape to the monosynaptic EPSPs seen in intact motoneurons (Fig. 3I and J). Eccles attributed the dome-shaped potentials to somatic and proximal dendritic regions of increased excitability. These findings contradicted Eccles' earlier hypothesis of enhanced polysynaptic transmission in axotomized motoneurons (Downman et al., 1953). According to this hypothesis, the longer latency components of the EPSP should not have been affected by hyperpolarizing current pulses.

The partial responses appeared to reflect an axotomy-induced increase in the electrical excitability of membrane regions outside of those normally responsible for action potential initiation. Evaluation of the intrinsic properties of the axotomized motoneurons illuminated the unexpected neuronal plasticity underlying the enhanced longer latency synaptic input. These neurons differed little from those with intact axons with respect to resting potential, action potential amplitude, and afterhyperpolarization size or duration. The current threshold for eliciting an action potential (rheobase), however, was about 30% lower in axotomized motoneurons than in intact motoneurons. Input resistance increased, but as shown later (Kuno and Llinás, 1970a), not enough to explain the decrease in rheobase.

These findings suggested that axotomy had altered the excitability of membrane components that were ''within the reach'' of intrasomatic current injection. Indeed, abnormalities of action potential initiation were detected at multiple sites; i.e. antidromic action potentials elicited during hyperpolarizing current pulses revealed changes in the first myelinated axonal segment spike, the initial segment spike, and the somatodendritic membrane spike (Coombs et al., 1957). The increased time from axon spike to initial segment spike, the lower maximum slope of the initial segment spike, and the greater susceptibility of the antidromic initial segment spike to hyperpolarizing block all indicated a low safety factor for antidromic invasion of the initial segment. On the other hand, the somatodendritic spike could be initiated at about a 45% lower level of depolarization from resting potential in axotomized than in intact motoneurons, thereby indicating increased excitability of the somatodendritic membrane. The shorter initial segment-somatodendritic latency with orthodromic activation was consistent with the lower initial segment excitability and greater somatodendritic excitability. Separate antidromic and orthodromic spikes could be elicited at the same time in the same motoneuron and became additive when the stimulus timing caused them to overlap. Orthodromic somatodendritic spikes often had no initial segment-somatodendritic break. These observations suggested that axotomy had reduced initial segment excitability and increased somatodendritic excitability enough to allow partial spikes to initiate action potentials, thereby disrupting the normal mode of orthodromic triggering of an action potential in the initial segment.

The widely varying partial response latency and voltage threshold after arrival of the group I volley indicated to Eccles that the partial responses were being elicited from different sites within the same motoneuron. Several partial responses could occur at once and summate to elicit an action potential. In addition, activation of different afferents had different probabilities of triggering partial responses. For example, in the plantaris motoneuron shown in Fig. 4, stimulation of the homonymous nerve (Fig. 4B) or a heteronymous muscle nerve (Fig. 4A) elicited EPSPs of comparable size, but only the homonymous input evoked partial responses. On the other hand, stimulation of a different heteronymous nerve elicited a small EPSP, but reliably elicited partial responses from a less depolarized voltage than did the homonymous input (Fig. 4C, with the partial response revealed during hyperpolarizing current injection in Fig. 4D). Eccles suggested that different groupings of synapses from different muscle nerves accounted for their differing abilities to elicit partial responses.

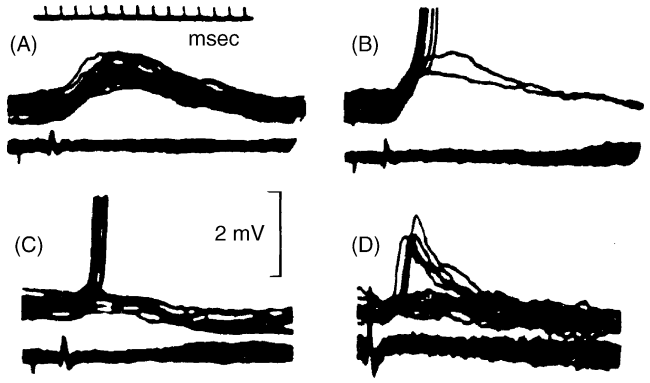

Fig. 4. Firing threshold varies with afferent source in an axotomized motoneuron. Shown are intracellular recordings (upper traces of each pair) of responses evoked in a plantaris motoneuron by stimulation of different peripheral nerves. Stimulation of flexor digitorum longus (A) or plantaris (B) nerve elicits EPSPs of comparable size, but only the latter elicits an action potential orthodromically. Stimulation of the gastrocnemius-soleus nerve (C) elicits only a minimal EPSP, but it initiates action potentials from a less depolarized potential than does homonymous stimulation. Hyperpolarizing current injection blocks the action potential elicited by gastrocnemius-soleus nerve stimulation and reveals an underlying spike-like partial response (D). Lower traces of each pair are extracellular recordings from the dorsal root entry zone. Modified from Fig. 11 in Eccles et al. (1958b) with permission of the publishers.

2.2.2. *Influence of Eccles' studies of plasticity in axotomized motoneurons*

Subsequent studies of the properties of axotomized motoneurons largely confirmed the original observations from Eccles' laboratory on partial responses (Kuno and Llinás, 1970a; Sernagor et al., 1986). Such responses have not always been detected after cutting the motoneuron axon. They are most frequently reported with proximally placed lesions of the ventral roots (Eccles et al., 1958b; Kuno and Llinás, 1970a; Sernagor et al., 1986) and are less common after cutting a peripheral nerve (e.g. Mendell et al., 1974). Thus, the likelihood of partial responses appears to depend on the location of the injury.

Other laboratories have greatly extended Eccles' studies of axotomized motoneurons. Reports vary across species and tissue types, but generally axotomy results in decreased conduction velocity, increased input resistance, shortened afterhyperpolarization duration in S-type motoneurons and prolonged afterhyperpolarization duration in F-type motoneurons, decreased EPSP amplitude, and slowing of EPSP rise time and half-width (Foehring et al., 1986; Pinter and Vanden Noven, 1989; Kuno and Llinás, 1970b; Kuno et al., 1974a,b; reviewed in Titmus and Faber, 1990). Increased membrane resistivity has been suggested to be responsible for the increase in neuronal input resistance and the slowing of the time course of the EPSP (Gustafsson, 1979; Kuno et al., 1974a). The hypothesis that post-synaptic plasticity is responsible for the changes in EPSP properties is supported by quantal analysis and by the fact that partial axotomy of peripheral nerve changes EPSPs in axotomized but not in intact motoneurons (Kuno and Llinás, 1970b; Scott and Mendell, 1976). The EPSP changes may also reflect a decrease in the number of synaptic contacts and/or a distal shift in their distribution on the motoneuron (Kuno and Llinás, 1970b; Sumner, 1975).

In cats, intracellular application of the lidocaine derivative QX-314 at low concentrations blocked partial responses induced by ventral root lesion, indicating that Na^+ channels are required for partial response expression (Sernagor et al., 1986). Studies in other species yielded similar results, and also demonstrated that K^+ and Ca^{2+} channels do not contribute to partial responses (Goodman and Heitler, 1979; Kuwada, 1981; Titmus and Faber, 1986). Unexpectedly, QX-314 was shown to block the presumably dendritic partial responses more effectively than it did the somatodendritic spike (which showed only a modest reduction in amplitude and rate of rise) (Sernagor et al., 1986). The opposite sensitivity would have been predicted based on the drug concentration gradient (proximal > distal). These results have been attributed to a proximal-to-distal decrease in axotomy-induced acquisition of Na^+ channels in the motoneuron membrane (Titmus and Faber, 1990). Newly made Na^+ channels that cannot be delivered to their normal axonal targets after axotomy might be passively distributed into nearby membrane. More would be expected to be inserted in proximal than in distal parts of the membrane, so that higher drug concentrations would be needed to block excitability in the proximal regions. This hypothesis is not entirely satisfactory, because it implies that more Na^+ channels would be inserted into the initial segment and remaining proximal axon, which would be expected to increase their excitability. The reduced initial segment safety factor and slower axonal conduction velocity after axotomy are not consistent, however, with such an increase in excitability (Eccles et al., 1958b).

One of the functional consequences of axotomy is its effect on motoneuron repetitive firing. In non-axotomized motoneurons, current injection above a threshold level induces repetitive firing of action potentials, and the rate of firing increases linearly with increasing current (the ''primary range'' (Kernell, 1965a)). Above a certain level, the slope of the relationship between current and firing frequency increases (the ''secondary range''). In axotomized motoneurons, the slope of the primary range of the current–frequency relationship increases (Heyer and Llinás, 1977; Gustafsson, 1979; Nishimura et al., 1992). In some studies, the entire current–frequency relationship becomes more linear due to the loss of the primary-to-secondary range slope transition and exhibits a slope higher than that of the primary range in intact animals (Heyer and Llinás, 1977; Nishimura et al., 1992).

The mechanism underlying this axotomy-induced change in motoneuron firing behavior is not yet established. Gustafsson proposed that the effect of axotomy on repetitive firing reflects the decrease in the action potential afterhyperpolarization (Gustafsson, 1979; see also Heyer and Llinás, 1977; Nishimura et al., 1992). The duration of the afterhyperpolarization is an important determinant of repetitive firing behavior during sustained depolarization (Kernell, 1965b). Heyer and Llinás (1977) reported, however, that axotomy also affects the time course of the inter-spike membrane potential trajectory. In intact motoneurons, the membrane potential trajectory between sequential action potentials exhibits a hyperpolarization (similar to that observed after a single action potential)

followed by a continuous increase in the firing threshold (Granit et al., 1963). After axotomy, the post-spike hyperpolarization is shorter and the rise to firing threshold is delayed, indicating a disruption of the normal relationship between afterhyperpolarization duration and the interval between adjacent action potentials during repetitive firing (Kernell, 1965b). Disruption of the relationship between firing rate and afterhyperpolarization duration also occurs after an acute partial spinal cord lesion (Carp et al., 1991), suggesting that factors in addition to the afterhyperpolarization can contribute to the regulation of repetitive firing.

The known participation of Na^+ channels in partial responses after motoneuron axotomy raises the possibility that Na^+ channels also contribute to altered repetitive firing behavior. Recent evidence indicates that Na^+- and Ca^{2+}-dependent persistent inward currents play a crucial role in shaping the motoneuron input–output relationship. Of particular relevance here is the finding that persistent inward currents underlie the increased slope of the current–frequency relationship, and descending neuromodulatory influences on the motoneuron affect the transition from primary to secondary firing range (i.e. a slope increase) (Lee and Heckman, 2001; Heckmann et al., 2005; Brownstone, 2006). Thus, the axotomy-induced effects on the shape of the current–frequency relationship could reflect changes in the contribution of persistent inward Na^+ currents to repetitive firing behavior. The lack of voltage clamp studies of Na^+ currents in axotomized motoneurons makes it difficult to assess this hypothesis directly. Although there have been no reports of axotomy-induced sustained membrane potential depolarizations, there are examples of partial responses with durations longer than those initially reported by Eccles (e.g. Fig. 3 in Kuno and Llinás (1970a), and Figs. 1 and 2 in Sernagor et al. (1986)).

It is unlikely that changes in persistent inward currents are due to changes in tonic descending modulatory inputs, since descending activity is greatly reduced in the pentobarbital-anesthetized preparations used to study axotomized motoneurons. In experimental animals and humans, persistent inward currents are more pronounced after SCI (Bennett et al., 2001a,b; Li and Bennett, 2003). This could reflect a denervation supersensitivity-like phenomenon that changes Na^+ channel expression or gating characteristics. Na^+ channel function can be readily modulated by neurotransmitter-gated mechanisms (Cantrell and Catterall, 2001; Cantrell et al., 2002; Carr et al., 2003). Motoneuron firing threshold depolarizes and axonal conduction velocity slows when an animal is rewarded for decreasing the size of monosynaptically evoked excitation of motoneurons. Both of these effects can be explained by an alteration in Na^+ channel activation voltage (Carp and Wolpaw, 1994; Halter et al., 1995; Carp et al., 2001a; also see Section 3.3.4). There is also growing evidence of injury-induced changes in Na^+ channel expression in sensory neurons (Waxman et al., 2000, 2002), but little comparable information is available for axotomized motoneurons (but see Hains et al., 2002). Given the growing interest in neuronal plasticity and its role in acquisition of normal behaviors and in the functional effects of injury, these data are likely to be forthcoming. Taken together, the extensive work briefly summarized in this section reflects the continuing and growing interest in the issues of neuronal plasticity initially raised in Eccles' studies of axotomized motoneurons.

2.3. Synaptic plasticity

During the 1950s, the synaptic transmission between Ia afferent fibers and spinal motoneurons became the most thoroughly studied synaptic connection in the vertebrate CNS. This connection between primary afferent fibers from the muscle spindle and spinal cord motoneurons is perhaps the most accessible synapse in the vertebrate CNS, and is the only one for which both input and output can be monitored at the periphery. It served then and continues to serve as an invaluable model for defining the properties of central synapses. Eccles made major contributions to this endeavor (see Burke, 2006). His interest in plasticity led him to study in particular the frequency dependence of Ia-motoneuron transmission.

2.3.1. Frequency-dependence of synaptic transmission

Using intracellular recordings from motoneurons, Eccles characterized the frequency-dependence of the EPSP elicited by muscle nerve stimulation at group I strength (Curtis and Eccles, 1960). EPSPs tended to be enhanced during the first few hundred ms after the onset of repetitive stimulation, but subsequently fell to a lower steady-state level. EPSPs were depressed by low-frequency (0.3–20 Hz) stimulation, facilitated by stimulation frequencies from 20–30 Hz up to 100 Hz, and depressed by frequencies above 100 Hz. These changes in synaptic efficacy were all quite brief, reaching their steady-state within a few hundred milliseconds. Eccles speculated that such changes played a role in the short-term regulation of synaptic transmission. Subsequent analyses have revealed that the frequency-dependence of Ia afferent-motoneuron transmission is asymmetrically distributed across the motoneuron pool (Fleshman et al., 1981; Collins et al., 1984). This differential frequency-dependence at physiological rates of stimulation appears to help determine the afferent contribution to motoneuron recruitment (Collins et al., 1986).

2.3.2. Post-tetanic potentiation (PTP)

High-frequency (100–500 Hz) stimulation of the Ia-motoneuron connection elicits more profound changes in synaptic efficacy on a much longer time scale. Post-tetanic potentiation (PTP) is a transient enhancement of a synaptic response triggered by high-frequency orthodromic stimulation. PTP had been identified at a variety of synapses, including the neuromuscular junction (Liley and North, 1953) and sympathetic ganglion (Larrabee and Bronk, 1947) but has been probably best characterized at the Ia afferent-motoneuron synapse, initially by David Lloyd (1911–1985) (see Lloyd, 1949). High-frequency stimulation of a dorsal root (at least 100 Hz, typically 200–500 Hz, for 10–30 s) elicits a large increase lasting up to several minutes in motoneuron output as reflected in the peripheral nerve potential (see time course of

amplitude of evoked responses shown by "+" symbols in Fig. 5A). As the duration of the stimulation is increased, the magnitude of potentiation increases to a plateau. Further increases in stimulus duration only lengthen the duration of the potentiation. Lloyd proposed a presynaptic mechanism for PTP at the Ia-motoneuron synapse. His hypothesis was based on two observations: (1) the presynaptic extracellularly recorded volley increased in concert with the potentiated response and (2) PTP was restricted to the afferent pathway stimulated; it was not found when heterosynaptic pathways that had not received the high-frequency stimulation were activated with test stimuli.

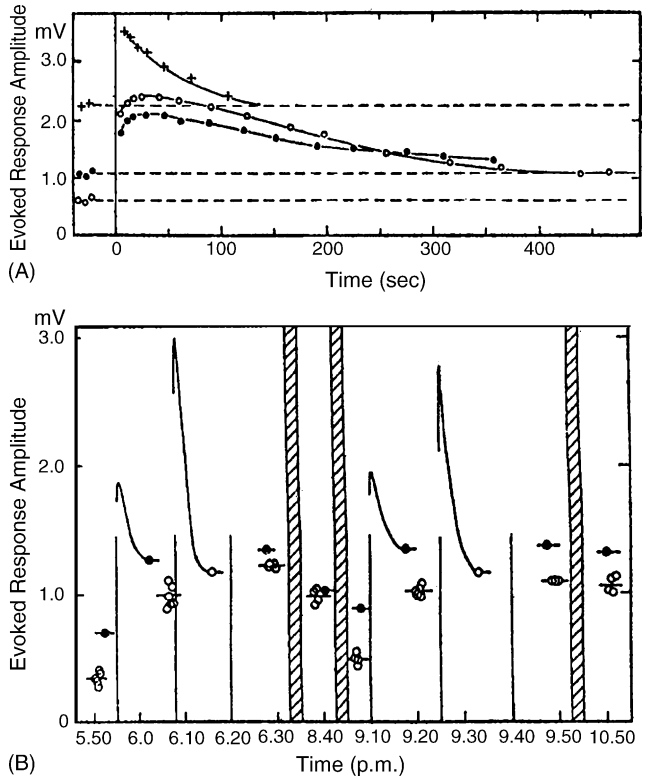

Fig. 5. Time course of amplitude of response of muscle nerves to dorsal root stimulation before and during post-tetanic potentiation (PTP) in cats with chronic unilateral dorsal rhizotomy. (A) The responses of the gastrocnemius nerve prior to (symbols to the left of the vertical line at zero time) and after 15 s 400 Hz stimulation of the L6-S1 dorsal roots are both smaller on the chronically deafferented side (L6-S1 dorsal roots cut 40 days prior to recording) than on the intact side. The time to maximum potentiation is longest and the duration of potentiation is prolonged on the deafferented side (open circle for first instance of potentiation, filled circle for second instance of potentiation several hours later) in comparison to the intact side (+). Note that the responses after the first instance of high-frequency stimulation do not fully recover to the pre-tetanic level and they remain elevated through a several-hour delay until the pre-tetanic responses prior to the second instance of high-frequency stimulation. (B) In another cat with L7-S1 dorsal rhizotomy 38 days prior to recording, six instances of high-frequency stimulation (500 Hz for 15 s, indicated by straight vertical lines) of the previously lesioned dorsal roots elicit PTP of responses from gastrocnemius (filled circles) and biceps-semitendinosus (open circles) muscle nerves. The time course of PTP recorded from one or the other nerve is shown by the curved lines. The three hatched vertical columns indicate 120, 20, and 60 min time breaks from left to right, respectively. The potentiation of both responses evident after the third instance of high-frequency stimulation (responses just prior to 6:30 p.m.) is little diminished even after 2 h (responses at 8:40 p.m.). Subsequent supplemental anesthesia reduces the evoked responses to nearly original levels (compare responses just prior to 9:10 p.m. with those just after 5:50 p.m.). An additional three instances of high-frequency stimulation reinstates long-lasting potentiation of the evoked responses (compare responses at 10:50 p.m. with those just prior to 9:10 p.m.). Figures from Figs. 4(A) and 6(B) in Eccles and McIntyre (1953) with permission of the publishers.

Eccles and Rall confirmed and extended Lloyd's initial observations (Eccles and Rall, 1950, 1951a). With Curtis, Eccles subsequently used intracellular recordings from motoneurons before and during PTP to reveal that the EPSP increased in amplitude after high-frequency stimulation (Curtis and Eccles, 1960). The growing potentiation of the EPSP was sufficient in some cases to elicit an action potential, thereby recruiting the motoneuron to participate in the evoked response. The potentiation of the EPSP and orthodromic activation of the motoneuron lasted over the same several-minute time course as the increased evoked response recorded from groups of motor axons in the ventral root or peripheral nerve. The orthodromic firing threshold did not change during the rise and fall of post-tetanic excitation, confirming that PTP was not dependent on changes in processes controlling motoneuron excitability downstream from the synaptic activation. In addition, application of shorter duration stimulus trains revealed the complex dynamics of the effect of high-frequency nerve stimulation (Eccles and Rall, 1951a,b; Curtis and Eccles, 1960). Use of a very few stimuli revealed an initial post-tetanic depression. An intermediate number of stimuli evoked a brief initial potentiation followed by a delayed, but longer lasting potentiation. Furthermore, PTP was not limited to the monosynaptic connection from group Ia afferents to motoneurons; it was detected also in polysynaptic segmental pathways (Eccles and McIntyre, 1953; Downman et al., 1953).

Eccles' studies of the early 1950s with "Archie" McIntyre (1913–2002) and Charles Downman (1916–1982) were consistent with Lloyd's hypothesis (1949) that PTP was due to a change in presynaptic efficacy and gave some additional insight. With Krnjevic, Eccles used intra-axonal recording from low threshold afferents in the spinal cord to show that PTP was associated with hyperpolarization of the presynaptic terminal and increased action potential amplitude (Eccles and Krnjevic, 1959). Hyperpolarizing current pulses mimicked the effect of PTP on axonal action potential amplitude. From these studies, Eccles proposed that enhanced nerve terminal excitability contributed to PTP. His observation that changes in extracellular field potentials associated with presynaptic activation did not last as long as response potentiation (Eccles et al., 1959) led him to the conclusion that PTP could not be explained entirely by altered electrical activity in the presynaptic terminal. Prompted by the finding of "A.V." Hill (1886–1977) that volume changes due to water influx occur after electrical stimulation of giant squid axons (Hill, 1950), Eccles suggested that water influx during high-frequency stimulation altered the spatial relationship of terminals to the post-synaptic membrane and thereby allowed more transmitter to be released. While this specific concept has little credibility today, it is generally consistent with Eccles' conviction and current evidence that activity-dependent plasticity involves structural changes in neural elements, rather than merely changes in activity recirculating through neuronal loops (see Section 3.1).

Over the many years since Eccles' and others' early studies of PTP, it has been generally accepted as a presynaptic phenomenon, but its exact mechanism remains unclear. Hyperpolarization of the presynaptic terminal could in theory contribute to PTP by increasing Ca^{2+} entry, but hyperpolarization is not always found with PTP at other synapses (Martin, 1977). High-frequency stimulation has been suggested to reduce branch-point block of axonal conduction in the presynaptic arbor (Lüscher et al., 1979, 1983). This mechanism could account for the greater degree of potentiation of EPSPs in large versus small motoneurons, because the more extensive arborization of afferent inputs to large motoneurons would presumably experience a greater degree of relief from transmission failure. The role of relief of branch-point block during PTP has not been universally accepted (Lev-Tov et al., 1983). PTP appears to reflect an enhanced probability of transmitter release from a given site, rather than an increase in the number of release sites (Hirst et al., 1981).

It is generally accepted that PTP and other shorter-term facilitatory processes depend on Ca^{2+} dynamics in the presynaptic terminal, but their precise mechanisms are still unclear (Zucker, 1999; Zucker and Regehr, 2002). Rapid buffering of intra-terminal Ca^{2+} terminates both facilitation and PTP (Kamiya and Zucker, 1994). Ca^{2+} chelators that equilibrate slowly attenuate high frequency-dependent enhancement of synaptic transmission without affecting pre-stimulation transmission efficacy (Delaney and Tank, 1994; Jiang and Abrams, 1998). The transient accumulation of intraterminal Ca^{2+} after trains of stimuli (i.e. the ''residual Ca^{2+} hypothesis'') may account for short-term facilitation but does not appear to be sufficiently long-lived to account for the prolonged time course of PTP (Atluri and Regehr, 1996). The slower kinetics of Ca^{2+} handling by mitochondria are more consistent with the time course of PTP. Tetanic stimulation causes Ca^{2+} accumulation in mitochondria, while blockade of Ca^{2+} fluxes in mitochondria prevents PTP (Tang and Zucker, 1997). Mitochondrial membrane conductance is elevated during a train of action potentials, continues to increase after the end of the stimulation, and then returns toward the initial level over tens of seconds (Jonas et al., 1999). An increase in the number of mitochondria after deafferentation appears to be an adaptive response to increased intra-terminal Ca^{2+} loading (Mostafapour et al., 1997).

2.3.3. *The activity hypothesis*

In the 1950s and early 1960s, Eccles' laboratory and others set out to test a simple and straightforward hypothesis about synaptic plasticity as the mechanism of memory: that synaptic strength depends on past activity; i.e. more activity strengthens synapses while less activity weakens them. They tested this hypothesis by changing activity at the Ia-motoneuron connection. As Sections 2.3.1 and 2.3.2 indicate above, Eccles had previously studied this synapse in a variety of contexts.

2.3.3.1. PTP after chronic deafferentation. The sensitivity to high-frequency stimulation of Ia-motoneuron transmission is a simple model of short-term, activity-dependent plasticity. Eccles considered changes in activity to be a crucial factor in the initiation of plasticity. PTP in intact animals lasts only a few minutes, however. Nevertheless, it is substantially more long-lived than the ephemeral frequency-dependent changes seen at lower rates of stimulation, and it provided Eccles with a simple model of CNS plasticity with which to test his hypotheses about the role of activity in determining synaptic strength.

In order to test the effect of long-term elimination of activity in Ia afferent fibers, Eccles and McIntyre (1953) performed a unilateral L7 dorsal rhizotomy just distal to the dorsal root ganglion and then 3–6 weeks later studied the reflex responses to dorsal root stimulation. The response to low-frequency L7 dorsal root stimulation was smaller on the deafferented side than on the other (i.e. intact) side. PTP took two to three times as long to reach its maximum value on the deafferented side (in Fig. 5A, compare time course of PTP on intact side (+) with deafferented side (open circles and filled circles for first and second application of high-frequency stimulation, respectively)). The peak potentiated amplitude was also reduced on the lesioned side, but the magnitude of potentiation was proportionally larger than on the intact side. In the example shown in Fig. 5A, maximum potentiation was about 300% and 60% above the pre-tetanic level on the deafferented and intact sides, respectively. PTP on the deafferented side decayed much more slowly than that on the intact side. In addition, the evoked responses during PTP on the intact side (+) returned to the pre-tetanic level within 2 min (comparable to PTP in unoperated animals). On the other hand, the post-tetanic responses on the deafferented side (open circles) were still 80% larger than their pre-tetanic responses more than 7 min after the first tetanic stimulus and remained at that level for several hours (see pre-tetanic response level just prior to second bout of high-frequency stimulation). Eccles referred to this long-lasting enhancement of the evoked potential as ''residual potentiation''. This effect was specific to the injured afferent pathway, in that PTP elicited by stimulation of an intact dorsal root adjacent to the chronically lesioned root did not last as long as that elicited by stimulation of the lesioned root.

Fig. 5B further illustrates the longevity of this residual potentiation in another deafferented preparation. After three bouts of tetanic L7 dorsal root stimulation (indicated by solid vertical lines), the responses evoked in gastrocnemius (filled circles) and biceps-semitendinosis (open circles) nerves more than 2 h after the last tetanic stimulus were about 50% and 190% larger than their pre-tetanic responses, respectively. An additional dose of anesthetic reduced the low-frequency test responses to nearly the pre-stimulation levels. Additional bouts of high-frequency stimulation reinstated the long-lasting residual potentiation of the monosynaptic reflex pathway.

Similar results were obtained after chronic peripheral nerve lesion (Eccles et al., 1959). For example, cutting the medial gastrocnemius nerve reduced the EPSP caused by stimulation of either the medial gastrocnemius nerve or the lateral gastrocnemius-soleus nerve. EPSPs elicited by high-frequency stimulation of the previously lesioned medial gastrocnemius nerve showed much greater potentiation than did those elicited by high-frequency stimulation of the intact lateral gastro-

cnemius-soleus nerve. In addition, the duration of the PTP of EPSPs elicited by stimulating previously cut medial gastrocnemius afferents was markedly prolonged (up to 20 min) compared to that after stimulation of the intact lateral gastrocnemius-soleus nerve (Eccles et al., 1959; Eccles, 1961). These effects developed gradually; they were not evident in the first week after surgery but were consistently present by 2 weeks after surgery.

Eccles and McIntyre (1953) found that spinal cord plasticity was not limited to the chronically lesioned pathways. In animals with chronic L7-S1 dorsal rhizotomy, stimulation of the intact L6 dorsal root elicited pre-tetanic and post-tetanic responses that were larger on the lesioned side than on the control side. Eccles incorporated this finding into his model by attributing this to an activity-dependent compensatory effect. He argued that the lesion-induced loss of reflex extensor support increased the load on synergist muscles, thereby chronically increasing afferent input to motoneurons innervated by the spared afferents. Results consistent with Eccles' hypothesis were found in intact spinal pathways to lateral gastrocnemius and flexor digitorum longus after chronic lesion of medial gastrocnemius, plantaris, tibialis posterior, and flexor hallucis longus nerves (Eccles and Westerman, 1959).

Thus, after chronic deafferentation, high-frequency stimulation not only reinstated the prior level of excitability, but also rendered the disused synapses ''capable of 'learning' to operate more effectively as a result of intensive presynaptic stimulation'' (p. 209 in Eccles, 1953). Eccles viewed the prolonged duration of this effect (at least in comparison to the more fleeting effects evident at lower frequencies of stimulation) as tantamount to learning in the spinal cord (Eccles, 1961).

2.3.3.2. Altered afferent input after tenotomy. Beránek and Hnik (1959) reduced primary afferent input to the motoneurons of a cat's gastrocnemius muscle by simply cutting the muscle's tendon, waiting 4–6 weeks, anesthetizing the animal, and measuring in the ventral root the motoneuron response to stimulation of the afferent nerve. The authors expected that tenotomy, by removing all tension from the muscle spindles, would abolish primary afferent input, thereby weakening the inactive synapse. Much to their surprise, the results were exactly the opposite; the reflex was larger after tenotomy. Fig. 6A from the work of Eccles et al. (1962) illustrates this result. The obvious first explanation was that tenotomy had in fact not reduced afferent input but rather increased it. Further experiments initially confirmed and then finally ruled out this possibility (Hnik et al., 1963), and the investigators were left with an apparent paradox; disuse seemed to strengthen rather than weaken a synaptic connection. This puzzling result has been confirmed by subsequent studies of tenotomy (Kozak and Westerman, 1961; Robbins and Nelson, 1970; Goldfarb and Muller, 1971).

Eccles' surprise was further compounded by experiments conducted in his laboratory in which tenotomy was combined with spinal cord transection, so that the spinal cord motoneurons were separated from any interaction with the brain (Kozak and Westerman, 1961). In this case, the reflex increase seen previously did not occur; the reflexes on the tenotomized and opposite sides were the same size. Thus, it appeared that the brain's influence, exerted through descending pathways, was essential for the synaptic strengthening following tenotomy to occur.

In the light of subsequent findings and present-day issues, three aspects of these results deserve mention. First, the

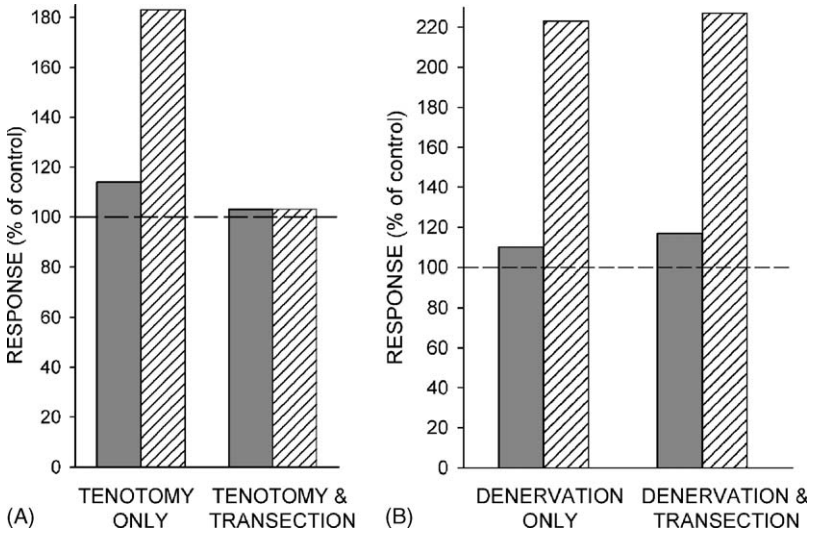

Fig. 6. Descending influences on the effects of tenotomy and partial hindlimb denervation. (A) Tenotomy in cats increases the monosynaptic ventral root response to stimulation of the nerve from a tenotomized muscle (hatched) after 1–4 weeks. The response to stimulation of the nerve from a non-tenotomized muscle (solid) does not change. The increase does not occur in cats in which the spinal cord was transected just prior to tenotomy. Thus, descending input appears to be necessary for the increased monosynaptic response to occur. Modified from Fig. 2 in Kozak and Westerman (1961) with permission of the publishers. (B) Partial denervation increases the monosynaptic ventral root response to stimulation of intact nerves from synergist muscles (hatched) 1 month later. The response to stimulation of the nerve from non-synergist muscles (solid) does not change. The increase also occurs in cats in which the spinal cord was transected. Thus, descending input (and the muscle activity it produces) does not appear to be necessary for the increased monosynaptic response to occur. Modified from Fig. 4 in Eccles et al. (1962) with permission of the publishers.

opposite, non-tenotomized side may not constitute an adequate control. While the other side is not lesioned in any way, the two sides of the spinal cord can affect each other both through direct intrasegmental pathways and by indirect routes involving other segments or the brain itself. Furthermore, the motor functions of the unlesioned side are almost certain to be affected by the functional abnormalities (e.g. defective stance) that occur, at least transiently, after tenotomy of extensor muscles. Clinical and laboratory evidence of such contralateral effects of ostensibly simple unilateral lesions was available long before Eccles' time (Mitchell, 1872; Greenman, 1913). A very recent study also illustrates the bilateral reflex effects of unilateral peripheral nerve lesions (Oaklander and Brown, 2004). Second, the reflexes were measured under anesthesia, which removes or otherwise modifies the normal tonic influence of brain regions over the spinal arc of the reflex. This raises the possibility that the effects observed were state-dependent and might not have been found under other circumstances, such as the absence of chemical anesthesia. Third, the responses measured depended not only on the strength of the synapse but also on the responsiveness of the motoneuron. Thus, any change noted might be due to change in the motoneuron itself rather than the synaptic connection. As subsequent sections illustrate, these issues have figured in many later studies and remain important.

2.3.3.3. Muscle overload by partial deafferentation. A second series of studies in Eccles' laboratory (Eccles et al., 1962) tested in another way the hypothesis that synapse strength correlates with past activity. They examined the effects of an intervention designed to increase activity of the primary afferent-motoneuron connection. By denervating several of the calf and ankle extensor and flexor muscles and thereby eliminating their contributions to locomotion, their experiment sought to increase stress on the muscles that retained their innervation and thus to increase the primary afferent input from their muscle spindles. The expectation was that monosynaptic reflexes elicited by stimulating the nerves to those overworked muscles would also increase. The results confirmed this expectation; 3–5 weeks after partial denervation, the responses elicited by stimulating the nerves to the muscles still innervated were markedly greater than the corresponding responses on the contralateral, unlesioned side. Comparable responses from nerves to other muscle groups remained bilaterally symmetrical. Thus, in this situation, increased activity did appear to strengthen the synapse. A parallel study greatly complicated the interpretation of the results, however. In some cats, the spinal cord was transected at the time of the partial denervation. This additional procedure essentially abolished hindlimb muscle activity in the subsequent weeks, so that the muscles that retained their innervation were not overworked in any way. Nevertheless, despite the fact that these animals were inactive, the result was the same; the responses elicited by stimulating their nerves were increased over those of the opposite leg. This surprising result is summarized in Fig. 6B. Again, it should be noted that the questions of whether the other side constituted an adequate control, of the effects of the anesthesia during reflex measurement, and of changes in the motoneuron itself exist for this study as well.

2.3.3.4. Eccles' synaptic plasticity studies: then and now. Eccles' hypothesis about synaptic strengthening by activity and weakening by disuse was not universally accepted at the time. There was considerable evidence from studies of the neuromuscular junction and autonomic ganglia that supported the opposite hypothesis (i.e. that inactivity enhanced synaptic strength and high activity weakened it; see review by Sharpless, 1964). The main criticism of Eccles' hypothesis was that spinal root and peripheral nerve lesions have degenerative effects on the afferent and/or efferent neuronal elements of the pathway under investigation, which are in addition to the interruption of transmission they produce. His only effective counterargument was that the effects of chronic afferent lesions were comparable in axotomized and intact motoneurons (Eccles et al., 1959). Eccles acknowledged this deficiency in experimental design (Eccles, 1953) and admitted that he had to ''block the afferent pathways without cutting them'' but lacked the methodology to do so (p. 350 in Eccles, 1961).

Eccles' studies of spinal cord synaptic plasticity, which set out to confirm the simple expectation that synaptic strength would correlate with the level of past activity, produced results at once both less satisfying and more interesting. Tenotomy, which decreased primary afferent activity, increased the motoneuron response, and this increase required intact connections with the brain. Denervation of synergist muscles, which probably increased primary afferent activity, also increased the response, but this increase was not abolished by spinal cord transection, which presumably prevented the increased afferent activity.

Furthermore, these studies coincided with a short-lived revival of interest in a remarkable and related phenomenon of spinal cord plasticity first described by Di Giorgio (1897–1961) in the late 1920s (Di Giorgio, 1929, 1942; Eccles, 1965; Gerard, 1961; Chamberlain et al., 1963). She showed that the hindlimb asymmetry produced by a hemicerebellar lesion survived spinal cord transection if at least 45 min passed between the lesion and the transection. Subsequent studies established that this persistent asymmetry was due to change in the spinal cord created by the short period of altered descending activity (Manni, 1950; Gerard, 1961). In still another intriguing development, Shurrager and Dykman (1951) transected the cat spinal cords at different low thoracic-upper lumbar levels and then showed that the hindlimbs could learn to walk as a result of training. This was striking further evidence of plasticity in spinal cord connections that was apparently activity-dependent.

Eccles did not pursue the study of prolonged PTP in lesioned animals much beyond the early 1960s. It became apparent in his writing that he had become disenchanted with the model. Thousands of stimuli are needed to maximize PTP; and its prolongation by chronic lesions requires days or weeks to occur (Sections 2.3.2 and 2.3.3.1). On the other hand, simple forms of learning, such as classical conditioning, can occur with only a few presentations of paired stimulus and reward. Furthermore, PTP is short-lived in intact animals, and only becomes prolonged after injury to afferents.

The dual effects of nerve transection, i.e. loss of activity and interference with trophic influences between nerve and muscle, have been addressed and expanded upon in many studies over the years since Eccles' initial studies on the effects of deafferentation or peripheral nerve lesions. Consistent with Eccles' earlier finding, Gallego et al. (1979) showed that a chronic medial gastrocnemius nerve lesion decreased composite homonymous and heteronymous amplitudes of Ia-EPSPs elicited by medial gastrocnemius nerve stimulation. The decrease in the Ia-EPSP amplitude was not prevented by stimulation of the sciatic nerve, however. On the other hand, chronic application of tetrodotoxin to block transmission of neural impulses in the medial gastrocnemius nerve without interrupting axonal transport or inducing physical damage increased medial gastrocnemius Ia-EPSP amplitude. This finding was reported by Manabe et al. (1989) and later confirmed more definitively by Webb and Cope (1992). It clearly contradicts Eccles' hypothesis that disuse decreases synaptic efficacy.

Given the sensitivity of PTP at the Ia-motoneuron transmission to chronic injury of the afferent and efferent portions of the pathway, it is not surprising that chronic interruption of descending influences also affects transmission at this synapse. Fujimori (1910–1986) et al. showed that chronic spinal hemisected cats exhibit on the lesioned side lower thresholds for mono- and polysynaptic reflexes, increased monosynaptic reflexes at maximum PTP, and less paired-pulse inhibition (Fujimori et al., 1966). Spinal hemisection in rats increases the monosynaptic reflex at low stimulation frequency but has no effect on PTP (Malmsten, 1983). EPSPs are increased in cats with chronic low spinal transection (Nelson and Mendell, 1979). Mid-thoracic spinal cord contusion injury in rats increases the monosynaptic reflex elicited at low frequency, decreases its maximum potentiated amplitude and the duration of PTP, and reduces frequency-dependent depression at frequencies below the threshold for eliciting PTP (Thompson et al., 1998).

Magladery (1911–1977) observed comparable changes in humans with abnormal descending control over the spinal cord. H-reflex recovery curves are increased in patients with spasticity (Magladery, 1955). In humans with recent (<8 weeks post-injury) SCI, composite Ia-EPSPs are increased, although this is not well correlated with spasticity (Mailis and Ashby, 1990). Patients with the most severe spasticity show less pronounced rate depression of the composite Ia-EPSP and also marked facilitation of a group I volley-induced EPSP that occurs after the component of the response attributable to monosynaptic Ia afferent-motoneuron transmission. That acute SCI patients do not show altered rate depression of Ia afferent-motoneuron transmission while patients with chronic injury do (Mailis and Ashby, 1990; Schindler-Ivens and Shields, 2000) suggests that the plasticity that develops after the acute loss of descending input to the spinal cord contributes to the development of this abnormal spinal synaptic transmission.

3. Activity-dependent CNS plasticity and its effects on behavior

3.1. Eccles' focus on the synapse and his abandonment of the spinal cord

The above studies of the 1950s and early 1960s gave new insight into the reflex pathways of the spinal cord and into the effects of activity on neuronal and synaptic function. At the same time, however, Eccles and others found them disappointing in their failure to uncover substantial and consistent evidence of long-term synaptic plasticity. PTP was an interesting phenomenon with possible functional implications, but getting it to last longer than a few minutes required deafferentation (Eccles and McIntyre, 1953). The effects on synaptic function of other manipulations of activity were confusing and beset by frustrating experimental uncertainties. As a result, Eccles grew disenchanted with the spinal cord as an arena for pursuing the phenomena underlying learning and memory and turned his attention, for the remainder of his long career, to the brain and to its ostensibly much richer capacities for long-term plasticity.

This fundamental shift by Eccles from the spinal cord to the brain paralleled and contributed to a comparable shift by the greater neuroscience community. For the next 40 years, studies of learning and memory, and of neuroplasticity in general, focused on the brain and on a variety of invertebrate models. For the most part, the spinal cord lay fallow as a site for exploring plasticity, and it is only recently that interest in its possibilities and appreciation of its advantages have revived.

In September of 1963, during the time of this transition, Eccles and other prominent neuroscientists gathered for The First Conference on Learning, Remembering and Forgetting, which was sponsored by the American Institute of Biological Sciences and held in Princeton. The participants included scientists with widely varying expertise and interests, ranging from behavioral psychology to basic synaptic physiology and anatomy, and including all the major areas in between. The conference resulted in an uncommonly informative book entitled "The Anatomy of Memory" (Kimble, 1965). It comprises thematic sets of chapters, with the chapters consisting in large part of discussion. The first and longest chapter is by Eccles (1965). Entitled "Possible ways in which synaptic mechanisms participate in learning, remembering, and forgetting", this chapter and its accompanying vigorous discussion comprise an excellent summary of Eccles' thinking about plasticity and his reasons for moving supraspinally.

Eccles began by reviewing the traditional two-possibilities approach to learning and memory; the assumption that the responsible CNS substrate could be either functional ("dynamical" in Eccles' terminology) or structural (i.e. anatomical). The functional hypothesis went back at least as far as Aristotle, who believed that memories were located in the heart (which he believed to be the site of the mind; see p. 14 in Finger, 1994; pp. 8 and 127 in Neuburger, 1897; and pp. 8 and 21 in Clarke and O'Malley, 1996). In 1963, the functional hypothesis had been relatively recently resurrected in the idea of Lorente De Nó

(1902–1990) and others that memories are patterns of excitation continuously cycling around closed loops of neurons (Lorente De Nó, 1934, 1938; Rashevsky, 1938). This possibility seems implausible, however, given that common experience informs us that memories survive severe disruption or even complete cessation of neuronal activity due to generalized seizures or deep anesthesia. This supports the hypothesis that memory depends on structural changes in the CNS.

At present, it is clear that the traditional distinction between structural and functional theories of memory is not viable. It was always in fact a distinction without a difference; structure at one level of analysis is function at the next level down (Churchland, 1986). A change in synaptic size is both a structural change at the neuronal level and a functional change at the intraneuronal or synaptic level (i.e. the level of the biochemical processes that determine and maintain synaptic size). In a similar fashion, a change in protein phosphorylation is structural from the perspective of the protein and functional from the perspective of the responsible kinase. This reality underlies the widespread adoption of the general term ''plasticity'' to mean lasting change in the nervous system. The term embraces the many kinds and levels of change now known to exist in the nervous system, and it avoids the specious distinction between structure and function. More importantly, this term accommodates the close continuing interactions between functional and structural changes even at the same level of analysis. Thus, the persistent pre- or post-synaptic changes in synaptic structures responsible for long-term potentiation (LTP) or long term depression (LTD) are produced and may be continually modified by activity and can in turn affect activity (Malenka and Bear, 2004).

In considering the mechanisms of memory specifically and CNS plasticity in general, Eccles focused exclusively and unapologetically on the synaptic connections between neurons. He argued that ''These synaptic connections are the only way in which we know that cells at the highest levels do, in fact, influence one another in a significant manner'' (p. 17 in Eccles, 1965). For Eccles, the operative part of this conclusion was the ''we know'' part. Certainly, he knew that changes in neurons themselves or even in glia might modify neuronal interactions and thus contribute to changes in CNS output. He emphasized the synapse because it was the best bet—much new physiological and anatomical data suggested its complex possibilities for plasticity and offered fertile avenues for investigation.

This emphasis on synaptic plasticity has continued into the present, to the extent that many neuroscientists appear to assume that learning and memory are entirely synaptic phenomena. Nevertheless, the importance of neuronal, glial, and even vascular plasticity in changing CNS output is becoming increasingly evident (e.g. Müller, 1992; Carp and Wolpaw, 1994; Spitzer, 1999; Cantrell and Catterall, 2001; Marder et al., 1996; Marder and Thirumalai, 2002; Dahms et al., 1999; Jones, 1999; Jones and Schallert, 1992, 1994; Jones et al., 1996, 1999; Withers and Greenough, 1989; Kolb and Whishaw, 1998; Swain et al., 2003; Leme and Chadi, 2001; Dong and Greenough, 2004; Sutton and Shuman, 2005). Had persuasive evidence of such contributions existed 40 years ago, Eccles would doubtless have happily addressed them. He concentrated on synaptic plasticity because it was obviously important, and presented a host of possibilities and questions well-suited to newly available models and methods.

Eccles concluded that the spinal cord was not a good place to study synaptic plasticity and henceforth applied himself to exploring hippocampus, cerebellum, and other supraspinal areas (e.g. Andersen et al., 1964a,b; Kitai et al., 1969; Eccles et al., 1972, 1975; Nicoll et al., 1975; see also Andersen, 2006; Ito, 2006). His move to them was both traction and pulsion; that is, he was drawn by characteristics that they seemed to have that the spinal cord lacked, and he was pushed away from the spinal cord by the results of studies he and others had carried out.

Eccles identified three special features of supraspinal synapses that he thought marked them as likely to be involved in memory processes. First, they displayed frequency potentiation much greater than that found in the synapses of spinal neurons. He noted (Eccles, 1965) specifically the striking potentiation found in corticomotoneuronal synapses and in entorhinal-dentate granule cell connections in the hippocampus (Phillips and Porter, 1963; Andersen et al., 1963a, 1966). Second, inhibitory synaptic phenomenon appeared to be much stronger and more prominent supraspinally and to involve transmitters not thought to be present in the spinal cord. For example, the IPSPs that occurred in hippocampal pyramidal cells in response to several different synaptic inputs were much larger and long lasting than those produced in spinal cord motoneurons by Ia inhibitory interneurons (Kandel et al., 1961; Andersen et al., 1963a,b; Hamlyn, 1963). Third, Eccles was impressed by the immense dendritic structures of many supraspinal neurons (e.g. in hippocampus) and even more impressed by the specialized complexities (e.g. dendritic spines) of their synapses and the localizations of different synaptic inputs on different parts of the dendritic trees (e.g. Hamlyn, 1963).

Some of the contrasts between spinal and supraspinal synapses that so impressed Eccles are now known to be less marked than they appeared to be 40 years ago. Activity-dependent potentiation akin to that found in the brain does indeed occur in the spinal cord (Mendell and Wall, 1965; Liu and Sandkühler, 1997; Ji et al., 2003; Rygh et al., 2005). A variety of inhibitory synapses employing the same major transmitters present in the brain are well-represented in the spinal cord (Rekling et al., 2000). The dendritic structures of spinal cord neurons, particularly motoneurons, can be quite immense, extending up to several mm from the soma (e.g. Chen and Wolpaw, 1994). Specific dendritic regions are contacted by a diverse variety of descending, interneuronal, and primary afferent axons (Hamos and King, 1980; Starr and Wolpaw, 1994; Brown and Fyffe, 1984). Spines have been observed on spinal cord motoneurons and interneurons, though they appear to be much less frequent than spines elsewhere (e.g. the hippocampus) (Rose and Richmond, 1981; Cameron et al., 1983; Rastad et al., 1990; Luo and Dessem, 1999).

While the reasons that drew Eccles to the brain may be less compelling now than they were at the time, the reasons that pushed him away from the spinal cord are more immediately interesting and important, for they helped determine the nature of memory research for the next 40 years and are related to very contemporary issues that are now reshaping that research. Eccles left the spinal cord not simply because the results of plasticity studies were disappointing but also because they were puzzling. In particular, the effects of tenotomy and partial deafferentation, summarized in Sections 2.3.3.2 and 2.3.3.3 above, did not appear amenable to any simple activity-based explanation.

Eccles and other luminaries agreed that these results warranted further study. Many people (including Eccles), however, saw the problem of plasticity as mainly a problem of synaptic plasticity and more specifically as a problem of the mechanism(s) of plasticity at the individual synapse. As a result, they were interested in the spinal cord mainly because it appeared to be a relatively simple and convenient model system with well characterized and experimentally accessible synapses. When the first studies gave puzzling results that implied considerable complexity, the appeal of the spinal cord faded. This, combined with the new evidence suggesting that supraspinal synapses were qualitatively different and probably had greater intrinsic capacities for plasticity, led to the almost total abandonment of the spinal cord as a model system for studying plasticity. Eccles and others departed for the brain, while still others, including Eric Kandel, moved to invertebrate models, which seemed to offer simplicity and accessibility even greater than that of the spinal cord (e.g. Kandel, 1976; Alkon, 1987).

In the decades that followed, these approaches have defined mechanisms of synaptic plasticity, such as long-term potentiation and depression, and they have revealed as well a variety of other kinds of CNS plasticity, including plasticity in neurons and glia. Some of Eccles' contributions to this work are discussed in associated reviews (see Andersen, Ito, and Wiesendanger in this volume). At the same time, all this new knowledge has not proved sufficient in itself to explain learning and memory. Rather, its proliferation has complicated the problem and has prompted new attention to the puzzling phenomena of spinal cord plasticity that disconcerted Eccles 40 years ago, and new interest in the spinal cord as a model system.

3.2. The gap between describing plasticity and explaining behavior

Until recently, most studies of the CNS substrates of learning and memory have been largely correlational. Beginning from the now discredited belief that the nervous system is hard-wired and can change only in few ways at a few sites, they have sought to explain memory phenomena by defining changes associated with them. In a nervous system in which activity-dependent plasticity is ubiquitous and continual, however, this correlational strategy is inadequate for addressing the central problem: how does plasticity at the synapse, in the neuron, or for that matter at any site, actually account for the changes in behavior that result from past experience? Exactly how does LTP in the hippocampus, or Hebbian behavior at mossy fiber-Purkinje cell synapses, lead to a monkey moving to the correct alternative or a rat navigating a maze without errors? The hippocampus and the cerebellum are a long way from the muscles that produce these behaviors; they affect action through connections that are themselves highly plastic, and they continually interact with other CNS areas that also contribute to behavior and themselves possess capacities for plasticity that are also likely to contribute to behavioral changes. Thus, memory is likely to involve plasticity at multiple sites and to depend on their interactions. The problem is to understand how this distributed plasticity conspires to influence the neurons that are directly responsible for behavior, the motoneurons in the ventral horn of the spinal cord. These are, as Eccles' mentor Sherrington (1906) emphasized, the final common pathway. The problem is to bridge the gap between the many kinds and sites of plasticity associated with any new behavior and the actual production of that behavior.

This focus on how activity-dependent plasticity actually produces modified behaviors has drawn attention back to the spinal cord; first because this is where the final common pathway is located, and second because the spinal cord offers, as it always has, advantages of accessibility and relative simplicity. This attention has been further augmented by the excitement generated by new possibilities for restoring function after SCI (Dobkin and Havton, 2004; Liverman et al., 2005).

3.3. The brain and the spinal cord

The primary theme that underlies and connects these new studies is the dependence of behavior on interactions between brain and spinal cord plasticity. This theme was revealed early on by the evidence that spinal cord transection alters the effects of long-term changes in afferent input, the evidence that Eccles found so disconcerting (Kozak and Westerman, 1961). It is now clear that the brain shapes spinal cord plasticity during early development and throughout life, and that, as a result, behavior is a combined function of brain and spinal cord plasticity. The early development of standard motor skills and the later acquisition and maintenance of more specialized skills involve and appear to depend on appropriate spinal cord plasticity. Indeed, the long-term shaping of spinal cord function by the brain seems to be an important function of descending input, perhaps as important to appropriate motor behavior as is the short-term interactive brain control that has engaged research attention since Fritsch (1838–1927) and Hitzig (1838–1907) first showed that cortical stimulation causes movement (Fritsch and Hitzig, 1870).

3.3.1. Plasticity during development

In the first year of life, descending input from the brain gradually shapes spinal cord pathways to produce the normal adult reflex pattern. Studies of both flexion withdrawal reflexes and muscle stretch reflexes reveal the importance of this influence. In a neonatal rat, focal nociceptive stimulation cause widespread and often inappropriate muscle contractions and

limb movements. In an adult, however, the same stimulation excites only the appropriate muscles, which withdraw the limb from the painful stimulus. As Fig. 7A shows, neonatal spinal cord transection abolishes the development of the adult reflex pattern; and inappropriate withdrawal reflexes remain in the adult (Levinsson et al., 1999; Waldenstrom et al., 2003). Recent work suggests that the brain's contribution is in large part permissive, promoting the spontaneous muscle twitches that drive the spinal cord plasticity underlying the adult reflex pattern (Petersson et al., 2003). At the same time, this process appears to involve corresponding supraspinal plasticity that leads to close correspondence between the cutaneous nociceptive receptor fields of spinal reflex modules and cerebellar climbing fibers (Garwicz et al., 2002).

The effects of the perinatal supraspinal damage underlying cerebral palsy also show the role of descending input in shaping spinal cord circuitry. In normal infants, sudden muscle stretch causes short-latency spinally mediated stretch reflexes in both the muscles stretched and their antagonists (Myklebust et al., 1986; O'Sullivan et al., 1991; Eyre, 2003). Normally, the antagonist reflexes are lost during childhood, and a normal adult displays standard "knee-jerk" reflexes only in the muscles stretched. When perinatal damage abolishes or distorts descending activity, however, the normal evolution can fail to occur, and antagonist stretch reflexes may be retained in adulthood and contribute to movement abnormalities (Fig. 7B).

The importance of the plasticity that results from the combination of appropriate descending and peripheral input during development is also illustrated by the long-term deficits in motor control associated with neonatal brachial plexus injury (Brown et al., 2000; Rollnik et al., 2000; Noetzel and Wolpaw, 2000). Normally, in early life, the peripheral inputs and brain/spinal cord interactions associated with arm movements produce activity-dependent plasticity in the brain and spinal cord that supports normal adult motor control. When brachial damage prevents or distorts these arm movements, the appropriate plasticity does not occur. As a result, even when nerve regeneration eventually reconnects the denervated muscles and restores nearly normal gross strength, motor control often remains impaired.

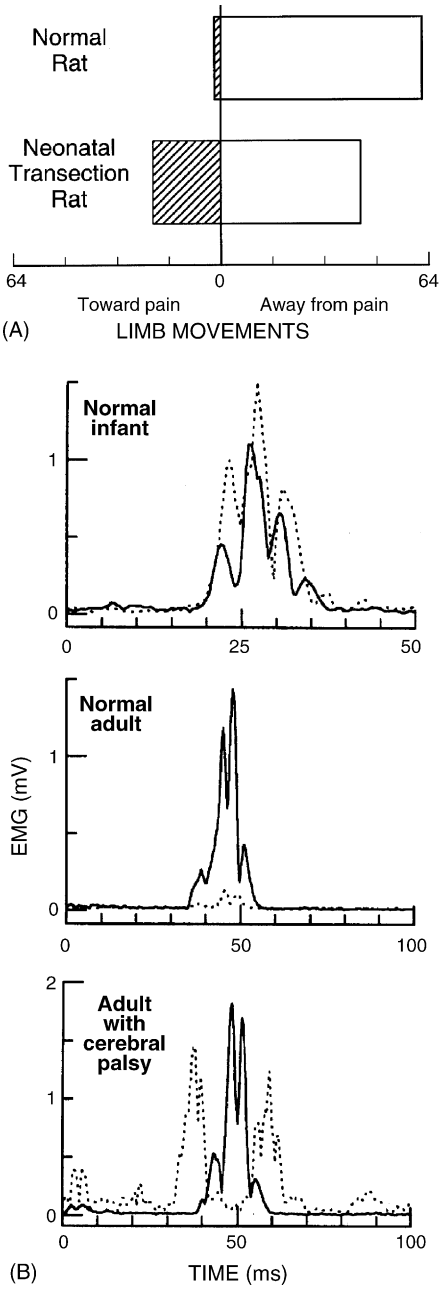

Fig. 7. Activity-dependent plasticity produced by descending input during development. (A) Direction of limb movement produced by flexion withdrawal responses to a nociceptive stimulus in normal adult rats and in adult rats subjected to spinal cord transection just after birth. Direction is almost always 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 Fig. 2 in Levinsson et al. (1999) with permission of the publishers. (B) Short-latency electromyographic 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 a normal adult, a reflex occurs only in the stretched muscle, i.e. the soleus. Little or no response occurs in the tibialis anterior. In contrast, in an adult with cerebral palsy, in whom perinatal supraspinal injury has impaired the descending input needed for development of normal adult reflexes, the infantile pattern persists; reflexes occur in both muscles. From unpublished data of Myklebust as illustrated in Fig. 3 in Wolpaw and Tennissen (2001) with permission of the publishers. For comparable data see Myklebust et al. (1982, 1986).

3.3.2. *Plasticity with skill acquisition*

Skills are adaptive behaviors that are acquired through practice (Compact Oxford English Dictionary, 1993; Grillner and Wallén, 2004; Chen et al., 2005). They range from standard skills such as locomotion that are acquired early in life, to more specialized skills such as ballet or playing the piano that are acquired later on. The hallmark of skills is that they are not acquired quickly, they need prolonged practice, often for many months or even years. Practice is associated with and essential for gradual changes in spinal circuitry; spinal reflexes are affected by the nature, intensity, and duration of training. In accord with Eccles' conviction about the importance of activity, spinal reflex strengths do correlate with the nature of past physical activity but in more complicated ways than he originally envisioned (Rochcongar et al., 1979; Goode and Van Hoven, 1982; Casabona et al., 1990; Koceja et al., 1991;

Nielsen et al., 1993; Earles et al., 2002). The reflexes studied most often have been the spinal stretch reflex (SSR) produced largely by the Ia-motoneuron monosynaptic pathway, which Eccles studied so productively, and its electrical analog, the H-reflex, which is produced by direct electrical stimulation of the Ia afferents (Magladery et al., 1951; Matthews, 1972; Henneman and Mendell, 1981; Brown, 1984).

These proprioceptive reflexes differ in athletes and non-athletes and among different groups of athletes. For example, the soleus H-reflex, and disynaptic reciprocal inhibition as well, are larger in moderately active people than in sedentary people and even larger in extremely active people (Nielsen et al., 1993). Exercise-induced plasticity in motor unit properties cannot easily account for the reflex increase observed with activity, because the human soleus is made up almost entirely of slow (i.e. type I) fibers. Furthermore, and most remarkably, both the H-reflex and disynaptic reciprocal inhibition are smallest in ballet dancers, even though they are far more active than any other group. Their reflexes are smaller than those of sedentary people and much smaller than those of active people. Given that co-contraction of muscles is associated with greater presynaptic inhibition and lessened reciprocal inhibition, it is possible that the persistent co-contractions essential for ballet postures lead to lasting decrease in transmission at the Ia synapse, and thus explain the H-reflex and reciprocal inhibition decreases. From the viewpoint of performance, the lessened peripheral impact on motoneurons represented by the smaller reflexes might augment cortical control and thereby improve movement precision.

A range of short-term and long-term laboratory studies provide further evidence for training-induced spinal cord plasticity (reviewed in Wolpaw and Tennissen, 2001; Koceja et al., 2004). In a long-term study, monkeys were trained to make smooth repetitive flexion and extension movements about the elbow while brief perturbations occurred at random times. Over many months, the SSR to the perturbation gradually grew so that it took over the task of correcting the perturbation, and later reflex responses slowly disappeared. As shown in Fig. 8A, the larger SSR was adaptive; it produced a faster and better correction of the disturbance. The study concluded that the data "demonstrate a long-term functional plasticity of the sensorimotor system of adult animals and suggest a growing role for fast segmental mechanisms in the reaction to external disturbances as motor learning progresses" (p. 398 in Meyer-Lohmann et al., 1986).

In another impressive study, Ung et al. (2005) showed in humans that training to walk backward gradually changes the H-reflex elicited at different points in the step cycle. As Fig. 8B illustrates, over several weeks of training the H-reflex elicited during the stance and late-swing phases of locomotion becomes markedly smaller, without corresponding change in soleus background EMG or in the motor potentials evoked in soleus by magnetic stimulation of cortex. The H-reflex change appears to represent an adaptive response and may reflect change in presynaptic inhibition of Ia afferent input.

Further evidence for adaptive spinal cord plasticity during life, and in response to particular demands, comes from studies

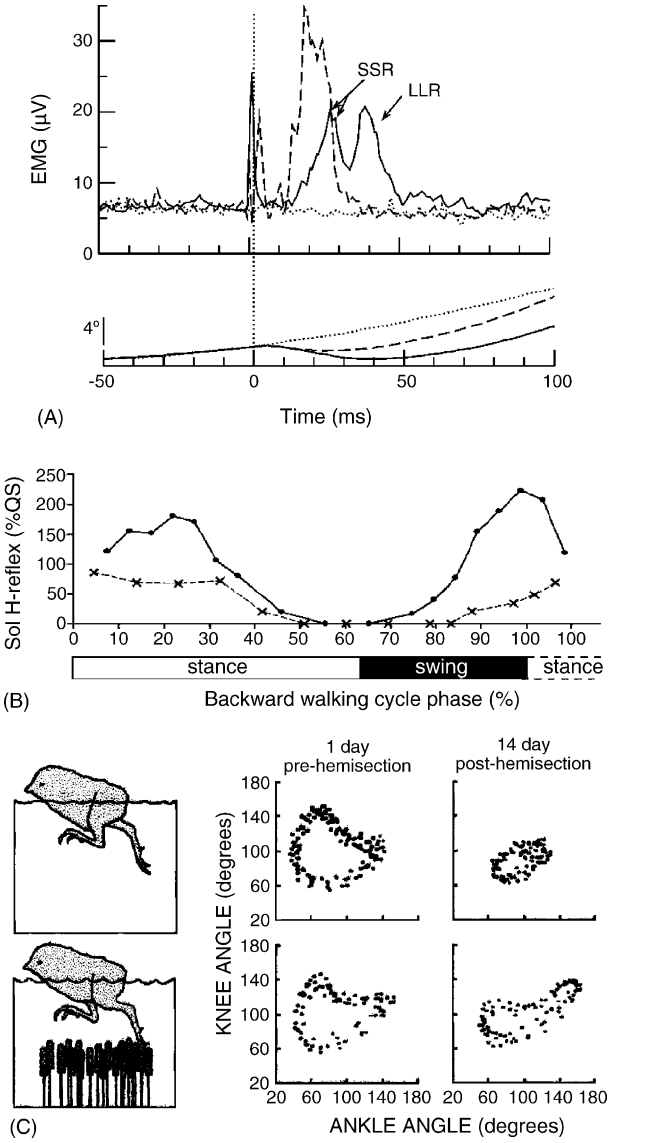

Fig. 8. Training effects on spinally mediated behaviors. (A) Working for reward, monkeys performed an elbow flexion-extension task on which brief perturbations were randomly superimposed. Biceps electromyographic activity and elbow angle (flexion is upward) for an unperturbed trial (dotted), a perturbed trial early in training (solid), and a perturbed trial late in training (dashed) are shown. Early in training, perturbation produces 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 perturbation of the smooth course of elbow flexion is smaller and briefer. Modified from Fig. 1 in Meyer-Lohmann et al. (1986) with permission of the publishers. (B) Soleus H-reflex sizes (in percent of size during quiet standing (QS)) during the step cycle from one subject for a session before (solid) and a session after (dashed) several weeks of backward-walking training. Before training, the H-reflex begins to increase early in the swing period (well before soleus EMG rises). After training, the H-reflex is smaller throughout the step cycle and markedly smaller in midswing and early stance. Soleus EMG during the cycle was similar for the two sessions. Modified from Fig. 3 in Ung et al. (2005) with permission of the publishers. (C) Knee and ankle excursions during swimming in normal chicks and in the same chicks after spinal cord hemisection followed by 14 days of swim training with (bottom) or without (top) plantar stimulation during the phase of movement equivalent to the stance phase of walking. After training, movement is closer to normal in hemisected chicks that have received plantar stimulation. Modified from Fig. 1 in Muir (1999) with permission of the publishers.

of reflex alterations in humans associated with aging, space flight, and specialized training protocols (Sabbahi and Sedgwick, 1982; DeVries et al., 1985; Resche et al., 1986; Trimble and Koceja, 1994; Angulo-Kinzler et al., 1998; Yamanaka et al., 1999; Zheng et al., 2000; Mynark and Koceja, 2002).

These studies all imply that the acquisition and maintenance of motor skills involve spinal cord plasticity: i.e. gradual activity-dependent changes driven and shaped by descending and peripheral inputs. The gradual time course of these changes and their dependence on repetition can help explain the prolonged and intensive practice required for acquisition and maintenance of athletic skills, musical skills, and other highly specialized behaviors. On the basis of these studies alone, it remains possible that the clear changes in spinal cord reflex function might simply be imposed by ongoing descending activity or merely reflect peripheral changes in muscles or sensory receptors. The spinal cord itself might undergo no enduring change. Two other bodies of evidence demonstrate, however, activity-dependent spinal cord plasticity in response to peripheral or descending inputs. Furthermore, these data, which are reviewed below, have made it possible to relate the puzzling results that helped drive Eccles away from the spinal cord to the phenomena of learning and memory that he sought so vigorously to understand.

3.3.3. Plasticity produced by peripheral input

Locomotion, whether walking, swimming, or flying, is produced in large part by interconnected spinal neurons that comprise a locomotor pattern generator (LPG) (Rossignol, 1996; Kiehn et al., 1998; Orlovsky et al., 1999; Dietz, 2003). A spinal LPG is most evident in lower vertebrates, such as the lamprey or chick, and also evident in higher vertebrates such as the cat, in which the lumbosacral spinal cord can support well-coordinated treadmill locomotion after spinal cord transection has eliminated supraspinal control. An LPG appears to exist in humans as well (Holmes, 1915; Kuhn, 1950; Bussel et al., 1988; Calancie et al., 1994; Dietz et al., 1995; Dobkin et al., 1995; Dimitrijevic et al., 1998; Gurfinkel et al., 1998; Rossignol, 2000; Dietz and Harkema, 2004). Extensive evidence now indicates that, in the spinal cord isolated from the brain, LPG operation can be encouraged and shaped by appropriate patterns of peripheral inputs, and that this functional change is due largely to spinal cord plasticity.

As noted in Section 2.3.3.4 above, Shurrager and Dykman (1951) reported that locomotion in cats with transected spinal cords improved with practice. This striking observation drew little substantive interest for more than 30 years, until growing optimism about possibilities for restoring function after SCI encouraged its further exploration. In the past 20 years, the impact of treadmill training on locomotion in spinalized cats and in humans with spinal cord injuries has been studied extensively (Lovely et al., 1986; Barbeau and Rossignol, 1987; Barbeau et al., 1999; Rossignol et al., 2004; Edgerton et al., 2004). In the standard design, cats with complete thoracic spinal cord transection walk on a treadmill with their hindlimbs for 30–60 min/day. The primary observation is that coordinated locomotion develops and improves over days and weeks. The animals gradually walk faster, with longer steps, and for longer periods. Although subtle differences from normal walking can be detected, locomotion after treadmill training in spinalized cats is in major respects comparable to that found in normal animals and much better than in cats that have not undergone this training (Bélanger et al., 1996; de Leon et al., 1998). The training-induced improvement persists for months following the end of training and is not explained by changes in muscle strength or other motor unit properties (Roy and Acosta, 1986; Roy et al., 1991, 1998b; de Leon et al., 1999a). It appears to be due mainly to activity-dependent plasticity in the spinal cord. In humans with partial spinal cord injuries, comparable training seems capable of producing comparable improvements (Barbeau and Fung, 1992; Dietz et al., 1995; Harkema et al., 1997; Dobkin, 1998; Wernig et al., 1995, 1998; Field-Fote, 2000; Dobkin et al., 2006).

The spinal cord plasticity responsible for the improved locomotion depends on the pattern of afferent, efferent, and interneuronal activity that occurs during training. A minimum level of appropriately timed sensory input is essential (Bouyer and Rossignol, 2001). The importance of sensory input has been demonstrated in chicks with spinal cord hemisection. For these animals, training to walk is far more effective than training to swim, although the two skills are very similar (Muir and Steeves, 1995; Muir, 1999). The difference is due to the greater phasic sensory input during walking: that is, the input caused by foot contact and the associated excitation of cutaneous and proprioceptive receptors. When similar input is provided during swim training, performance markedly improves (Fig. 8C).

The functional effects of locomotor training in spinalized cats result at least in part from marked changes in glycinergic and GABAergic inhibition in the spinal cord. The glycinergic inhibitor, strychnine, improves locomotion in untrained spinalized cats, while it does not affect locomotion in trained cats (de Leon et al., 1999b). Furthermore, locomotor training is associated with a marked decrease in GABAergic innervation near the spinal motoneurons involved in locomotion (Tillakaratne et al., 2002). Indeed, this GABAergic innervation is increased above normal levels in untrained spinalized cats and returns toward normal levels with locomotor training.

These studies of locomotion in spinalized animals reveal relationships between spinal and supraspinal plasticity. Carrier et al. (1997) reported that spinalization followed several weeks later by unilateral denervation of ankle flexor muscles has minimal lasting effect on treadmill locomotion, while denervation followed by spinalization leads to markedly abnormal locomotion that does not improve with practice. This contrast implies that the plasticity that accounted for the return of effective locomotion after denervation includes both spinal and supraspinal changes; spinal and supraspinal plasticity combine to compensate for the denervation. Then, when spinalization removes the contribution of the supraspinal plasticity, the spinal cord plasticity functions by itself, and the outcome is grossly abnormal locomotion.

Further insight into the interaction of spinal and supraspinal plasticity comes from study of the effects of partial denervation on the strengths of primary afferent input (Whelan and Pearson, 1997). In the stance phase of walking in the cat, stimulation of primary afferents in the nerves from ankle extensor muscles (the nerves from the lateral gastrocnemius and soleus and from the medial gastrocnemius) excites the leg extensors and delays the onset of the swing phase. Lateral gastrocnemius-soleus nerve stimulation is normally more effective than medial gastrocnemius nerve stimulation. When the lateral gastrocnemius-soleus nerve is cut, however, and the cat continues treadmill walking, the lateral gastrocnemius-soleus nerve's ability to prolong stance nearly disappears over 1 month, while the medial gastrocnemius nerve's ability increases markedly in 5 days and stays high. Furthermore, if the cat is spinalized, the decreased effect of lateral gastrocnemius-soleus nerve stimulation always persists and the increased effect of medial gastrocnemius nerve stimulation sometimes persists. This indicates that spinal cord plasticity is wholly or partly (depending on the cat) responsible for the changes in the effectiveness of nerve stimulation. Spinal cord plasticity comparable to that revealed here or other denervation-induced plasticity probably underlies the grossly disordered locomotion that occurs when spinalization follows ankle flexor denervation (Carrier et al., 1997).

Taken together, this growing body of research is elucidating the complex activity-dependent plasticity that Eccles encountered in the first studies of partial denervation (Sections 2.3.3.1 and 2.3.3.3).

3.3.4. Spinal cord plasticity in a laboratory model

The puzzling results of the 1950s and early 1960s concerned surprising changes in spinal reflex connections induced by manipulations of peripheral input and unexpected relationships between these changes and descending influence from the brain. The subsequent evidence (i.e. Sections 3.3.1–3.3.3) implying that descending and peripheral inputs during development and later on in life lead to spinal as well as supraspinal plasticity consists mainly of changes in spinal cord reflexes (i.e. SSRs, H-reflexes, and flexion withdrawal reflexes). While these reflexes normally serve as parts of complex behaviors, they are themselves simple behaviors, indeed the simplest behaviors of which the nervous system is capable, and adaptive changes in them are simple skills that may be used as laboratory models for exploring the plasticity responsible for skill acquisition (see Section 3.3.2 above). Operant conditioning of the SSR, or its electrical analog the H-reflex, has now been described in monkeys, humans, rats, and mice (Wolpaw et al., 1983; Evatt et al., 1989; Wolpaw, 1987; Chen and Wolpaw, 1995; Carp et al., 2005). It has provided incontrovertible evidence of activity-dependent spinal cord plasticity and is now providing new insight into the complex patterns of spinal and supraspinal plasticity that underlie skill acquisition in normal life and the disordered motor function associated with CNS lesions and other long-term disorders.

In the standard protocol used in humans, monkeys, rats, and mice, reflex size is determined from the EMG response, and reward occurs when this response is above (for up conditioning) or below (for down conditioning) a criterion. The fundamental finding is that when the reward criterion is imposed, reflex size changes appropriately over days and weeks (Fig. 9A). This adaptive change seems to happen in two phases, a small rapid phase 1 in the initial hours or days, and a much more gradual phase 2 that continues for weeks (Wolpaw and O'Keefe, 1984). Phase 1 probably reflects rapid mode-appropriate change in descending influence on the spinal reflex pathway, while phase 2 reflects gradual spinal cord plasticity caused by the prolonged continuation of that descending influence. This critical descending influence appears to come from the sensorimotor cortex via the corticospinal tract (Chen and Wolpaw, 1997, 2002; Segal and Wolf, 1994; Segal, 1997).

Like the Di Giorgio phenomenon (Section 2.3.3.4), the reflex asymmetry caused by this conditioning persists even after the spinal cord is isolated from the brain (Wolpaw and Lee, 1989). Thus, the conditioning modifies the spinal cord. This spinal cord plasticity includes alterations in motoneuron properties (Carp and Wolpaw, 1994; Halter et al., 1995; Carp et al., 2001a). With down conditioning, there is a positive shift in motoneuron firing threshold (Fig. 9B) and a decrease in axonal conduction velocity. Both changes could reflect a positive shift in Na^+ channel activation voltage, and the altered threshold could largely account for the smaller reflex. While synaptic plasticity has received the most attention as the likely basis of learning, the probability that learning also involves plasticity in neuronal voltage-gated ion channels has drawn attention (Spitzer, 1999; Cantrell and Catterall, 2001). The positive shift in motoneuron threshold with down conditioning seems to be an instance of such neuronally based learning. Further physiological and anatomical data imply that SSR or H-reflex conditioning also modifies the primary afferent and other synaptic terminals on the motoneuron (Fig. 9C), interneurons conveying oligosynaptic group I input to the motoneuron, and motor unit properties (Carp and Wolpaw, 1995; Feng-Chen and Wolpaw, 1996; Carp et al., 2001b). Recent work indicates that the cerebellum is essential for down conditioning, and suggests that this conditioning depends on a hierarchy of supraspinal and spinal cord plasticity (Wolpaw and Chen, 2006).

This simple laboratory model is helping to expose the complex relationships between spinal and supraspinal plasticity, and thereby offers new insight into the puzzling interactions suggested by the studies of the 1950s. A diverse variety of manipulations of supraspinal control reveal the importance of supraspinal influence for the existence and expression of the spinal cord plasticity associated with H-reflex conditioning. For example, down conditioning of the H-reflex in one leg does not change the H-reflex in the other leg of the awake monkey (Wolpaw et al., 1993), and if the spinal cord is then transected, the reflex asymmetry created by conditioning is still evident. After transection, however, the reflexes on both sides are unexpectedly large, and the reflex in the other (i.e. unconditioned leg) is much larger than normal (Wolpaw and Lee, 1989). By removing supraspinal influence, transection uncovers a previously hidden effect of conditioning on the contralateral side of the spinal cord. Fig. 9D illustrates this surprising effect. The nature of this plasticity and how it results

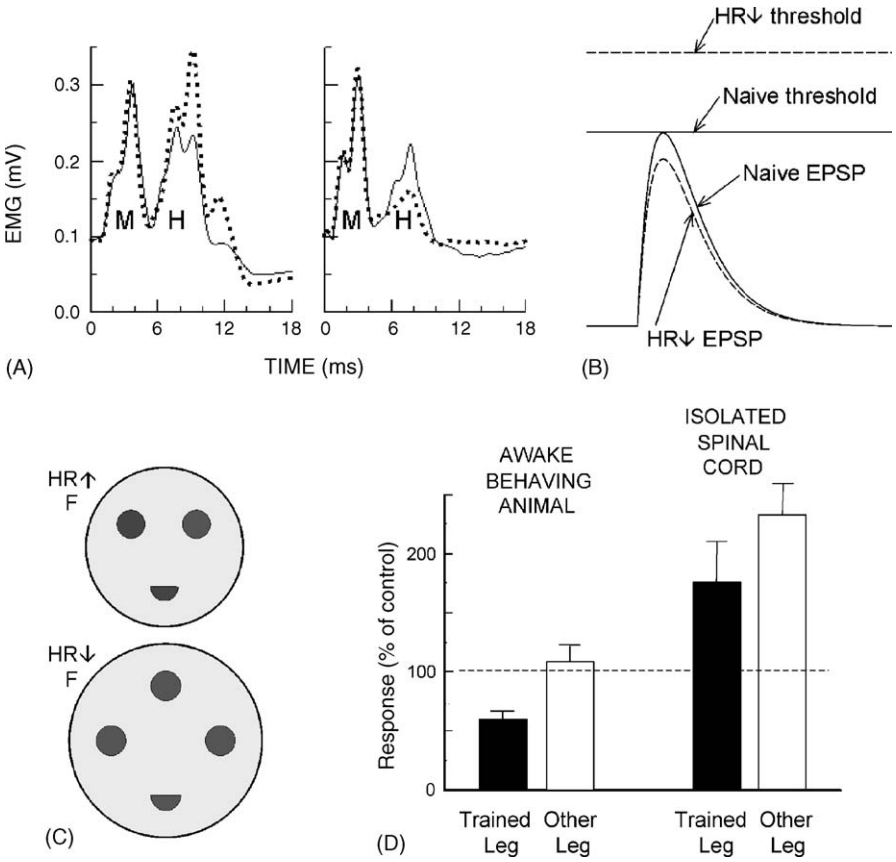

Fig. 9. H-reflex operant conditioning as a laboratory model of spinal cord plasticity. (A) The graphs show average post-stimulus soleus EMG for representative days before (solid) and after (dotted) soleus H-reflex conditioning from a rat in which the H-reflex has been increased by the up conditioning 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. From Fig. 2 in Wolpaw (1997) with permission of the publishers. (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. From Fig. 4 in Wolpaw (1997) with permission of the publishers. (C) The contacts of idealized average F terminals (putative inhibitory terminals) and their active zones on the cell bodies of triceps surae motoneurons on the conditioned sides of H-reflex up conditioned (HR↑) and down conditioned (HR↓) monkeys. HR↑ F terminals are smaller and have fewer active zones. Active zone size is not different. The diameter of the HR↓ F terminal is 2.2 μm. From Fig. 4 in Wolpaw (1997) with permission of the publishers. (D) Reflex responses from monkeys after H-reflex down conditioning. Left side: average triceps surae H-reflexes of the awake behaving monkeys in the down conditioned (trained) leg and the other leg. The H-reflex in the trained leg is much smaller than its control value, while the H-reflex in the other leg is not changed from control. Right side: average maximum triceps surae reflex responses to dorsal root stimulation from the same monkeys under anesthesia and after mid-thoracic spinal cord transaction. The reflex asymmetry created by down conditioning is still present, but the reflexes in both legs are much larger than those from the isolated spinal cords of naïve (i.e. unconditioned) monkeys. (D) shows data from Wolpaw and Lee (1987, 1989) and Wolpaw et al. (1993).

from the conditioning protocol (which bases reward simply on the ipsilateral reflex) remain unknown.

Other evidence of the hidden effects of conditioning has emerged. The corticospinal tract (CST) is needed for the acquisition and maintenance of a smaller H-reflex. If the CST is transected after down conditioning has occurred, however, the H-reflex does not simply return to its original control size; within 5–10 days it becomes substantially larger than its original size (Chen and Wolpaw, 2002). Again, removal of supraspinal influence (in this case partial removal) reveals a previously hidden effect of conditioning. Unlike the effect noted in monkeys after complete transection, this effect could reflect spinal cord plasticity and/or supraspinal influence through pathways other than the CST.

Still more striking evidence of the complexity of the relationship between spinal and supraspinal influence comes from studies of reflex conditioning after supraspinal lesions. If contralateral sensorimotor cortex is ablated and rats are then exposed to down conditioning, the H-reflex neither decreases nor remains unchanged, rather it gets larger (Chen et al., 2004). Sensorimotor cortex ablation alone has no long-term effect on the H-reflex. Thus, this increase is due to down conditioning in the absence of contralateral sensorimotor cortex and is further evidence of the complex supraspinal influence over the spinal cord, even during acquisition of such an apparently simple skill.

3.4. The origins of complexity

In considering the puzzling results of efforts to demonstrate that synaptic strength correlates with the intensity of past synaptic activity, Eccles made a comment that has turned out to be remarkably prescient. Each of his experiments had set out to do, and apparently had done, a single very simple thing, such as reducing primary afferent input through tenotomy. Eccles

cautioned, however, that "... the nervous system is infinitely complex, and when we think we have done just one thing, in fact, we have initiated a whole series of consequential adaptive kinds of reactions which may be largely the cause of the observed responses" (p. 49 in Eccles, 1965). By parsing this comment, we encounter essentially all the major issues raised by subsequent investigations of nervous system plasticity and come finally to the questions of most importance at present.

It is now clear that activity-dependent plasticity has numerous mechanisms involving essentially all the elements that comprise the nervous system and that it is ubiquitous throughout the CNS (Section 3.1). Synaptic plasticity, which has received the most attention, itself includes short-term and long-term phenomena, pre- and post-synaptic mechanisms, and subtractions, additions, and anatomical reorganizations in the connections themselves. Neuronal plasticity, in generalized properties such as firing threshold as well as in localized forms such as dendritic architecture, is of comparable intricacy and impact. Furthermore, activity-dependent plasticity extends beyond neurons and synapses to involve glia and vasculature, CNS components traditionally viewed as merely passive supporting components.

The result of the existence of these many kinds of plasticity is that even the simplest intervention is likely to have multiple consequences, ranging from those that are very localized to those involving other regions of the CNS. For example, a change in the intensity of synaptic activity may lead by entirely local mechanisms to change in the number or other properties of the post-synaptic receptors (e.g. Huganir and Greengard, 1990). Such sensitization or desensitization, while arising from entirely local events, may have wider consequences. The change in synaptic activity, by affecting the activity reaching other spinal and supraspinal areas, can lead to further plasticity, both by initiating other local phenomena and also by producing behavioral consequences that require adaptive responses. For example, a change in the strength of primary afferent input to the motoneuron, by affecting motoneuron firing, may affect the motoneuron's contribution to a wide variety of behaviors, and thereby necessitate compensatory adjustments in the activity of motoneurons innervating other muscles that contribute to these behaviors. Also, activity-dependent changes in a muscle could require adaptive responses in other muscles and in their motoneurons.

That interventions as apparently simple as tenotomy or H-reflex conditioning lead to plasticity at multiple sites was at first surprising; the prevailing expectation was that a simple intervention would produce a simple change in the CNS. Nevertheless, the occurrence of multi-site plasticity seems to be a general principle that applies in even the simplest cases (Lieb and Frost, 1997; Thompson et al., 1997; Cohen et al., 1997; Lisberger, 1998; Garcia et al., 1999; Pearson, 2000; Wolpaw and Tennissen, 2001).

As implied above, this complexity has basically two categories. First, simply because activity-dependent plasticity is ubiquitous in the CNS, the change in activity caused by any intervention is likely to trigger additional, or "reactive", plasticity at other sites. For example, the larger reflex contralateral to an H-reflex that has been down-trained, evident only with anesthesia and spinal cord transection (Wolpaw and Lee, 1989), or the smaller stretch reflexes found in the ostensibly normal arm contralateral to an arm paralyzed by a hemispheric stroke (Thilmann et al., 1990) may reflect reactive plasticity caused by change in activity in pathways connecting the right and left sides of the spinal cord.

Second, the activity-dependent plasticity resulting directly from an intervention (whether the intervention is daily practice or a lesion) is likely to cause further "compensatory" plasticity that is adaptive and thereby maintains effective CNS function. For example, the stronger motoneuron response to Ia afferent input that underlies a larger H-reflex (e.g. Fig. 9A (left)) is likely to affect the many other behaviors involving primary afferent input to the motoneuron, and these effects are likely to trigger further activity-dependent plasticity that maintains these other behaviors. The additional plasticity that produces a normal contralateral H-reflex in the awake monkey (Fig. 9D) may reflect such compensatory plasticity. Similarly, after chronic dorsal root injury, the increase in pre-tetanic and post-tetanic responses to stimulation of an adjacent intact dorsal root may reflect plasticity that compensates for the diminished transmission from the injured dorsal root (Eccles and McIntyre, 1953; Eccles and Westerman, 1959).

Thus, the complex plasticity associated with even the simplest intervention is both inevitable, due to the ubiquity of activity-dependent plasticity and necessary, due to the adaptations needed to preserve the entire repertoire of behaviors.

The final part of Eccles' comment—"... the observed responses"—is perhaps the most interesting. The keyword is "observed", for it implies that the effects of an intervention that leads to CNS plasticity depend on how you assess them. The features of an assessment include both the units of measurement, or more specifically, what the responses are compared to, and the circumstances, or state, in which they are assessed. In the case of the effects of tenotomy, the responses on the lesioned side were compared to the responses on the unlesioned side, which was assumed to provide a control. A variety of studies suggest, however, that the contralateral side is not always unchanged (Sections 2.3.3.2 and 3.3.4).

The circumstances of assessment are also crucial. After down conditioning, the reflex on the other side is unchanged from normal when it is measured in the awake behaving animal, and it is much larger than normal when it is measured under anesthesia after spinal cord transection (Wolpaw and Lee, 1989). Similarly, partial denervation has no apparent long-term effect on locomotion in the otherwise intact cat. The isolated spinal cord preparation, however, is no longer able to master treadmill locomotion (Carrier et al., 1997). In the context of more complex learning phenomena, the circumstances of assessment are often subsumed under the concept of "state dependence".

In sum, the ubiquity of activity-dependent CNS plasticity and the numerous and varied behaviors that the CNS must produce ensure that any intervention, whether physiological or

pathological, will lead to complex multi-site plasticity, and that any behavior, however simple, will depend on complex multi-site plasticity.

4. Conclusions

As Eccles stated it (Section 1), his work was driven by a desire to understand himself. In the context of the sensorimotor hypothesis that underlies modern neuroscience (i.e. that the entire function of the nervous system is to ensure that sensory input (experience) leads to appropriate motor output (behavior)), understanding oneself means understanding the origins and mechanisms of one's behaviors. Neither his efforts nor the efforts of others since, energetic and productive though they have certainly been, come near to reaching this goal. Nevertheless, the nature of the problem is now considerably clearer than it was even a few decades ago, and Eccles' attention to the problem of activity-dependent plasticity in the nervous system has contributed substantially to this progress.

When Eccles began, activity-dependent plasticity was assumed to be synaptic plasticity, and simple interventions, whether physiological or pathological, were assumed to have simple effects. Through efforts to which Eccles substantially contributed, it is now clear that activity-dependent plasticity involves much more than just the synapse; it indeed involves essentially all the elements of the nervous system and occurs ubiquitously from neuromuscular connections, through spinal cord reflex pathways, to the cerebellum, hippocampus, neocortex, and other brain areas. As a result, any intervention, whether a normal experience or an imposed lesion, is likely to have multiple and continually evolving effects that may extend throughout the CNS and affect many different behaviors. This complex plasticity is both inevitable, due to the ubiquity of activity-dependent plasticity in the CNS and necessary, due to compensatory adaptations that preserve effective performance of the entire repertoire of behaviors.

This reality renders wholly inadequate the traditional concepts of memory storage and consolidation that still underlie much research, and it compels attention to simple experimental models in which potential sites of plasticity are defined and accessible. Furthermore, it requires a mechanistic research strategy that goes beyond simply correlating behaviors with plasticity to focus on explaining exactly how changes at multiple sites conspire to produce specific behaviors.

In this effort, the neuromuscular and spinal cord models that Sir John Eccles developed and studied so productively, and the phenomena he described have much to offer and are drawing renewed attention. His work supplies a rich resource of observations and insights that will continue to be mined well into the future.

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