Spinal Reflexes

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Abbreviations

EPSPs	Excitatory postsynaptic potentials
GABA	Gamma aminobutyric acid (inhibitory transmitter)
EMG	Electromyogram
H-reflex	Hoffmann's reflex
H wave	Component of the H-reflex
M wave	Component of the H-reflex
NA	Noradrenaline
5-HT	Serotonin
VGLUT1	Vesicular glutamate transporter one
VGLUT2	Vesicular glutamate transporter two

Brief History

Observations on spinal reflexes were made together with the earliest observations on functions of the human body and followed the development of medical sciences. Systematic studies of spinal reflexes began more than 100 years ago, with the work of Sherrington, after the basic organization of the nervous system and of the role of various categories of neurons had been outlined by morphological studies of Cajal and Golgi at the end of the nineteenth and the beginning of the twentieth century. A deeper understanding of the mechanisms and organization of spinal reflexes and of their role in motor behavior had nevertheless to await until almost today and to the disclosure of the properties of spinal neurons and their networks by advanced morphological, electrophysiological, immunocytochemical, and developmental

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studies, as well as to the analysis of their changes under different experimental and pathological conditions. Recent investigations of spinal reflexes are also closely related to the rehabilitation of patients with restricted motor abilities, e.g., to attempt to restore their locomotor abilities after spinal injuries or to increase the range of voluntary movements after stroke.

Spinal Cord

Spinal cord is a morphologically distinct part of the central nervous system, as it is contained within the vertebral column and not in the skull and may to a certain extent operate independently of its other parts. The fact that some motor reactions can be evoked even when the spinal cord has been isolated from the rest of the brain led to the concept of the relative autonomy of the operation of the spinal cord. The most spectacular observations on which this concept is based are that even highly complex movements, such as locomotion, are possible when all connections between the spinal cord and the brain are interrupted. However, it is also well established that the spinal cord is intimately linked with all other parts of the nervous system and that even such elementary functions as emptying the bladder or withdrawal reflexes considerably differ after spinal injuries and that all motor reactions subserved by the spinal cord depend on both spinal and supraspinal neurons.

Spinal neurons are of four main functional types: motoneurons, interneurons, propriospinal neurons, and ascending tract cells which develop from different types of embryonic cells, and the knowledge of their properties and of interconnections between them is essential for understanding of all motor reactions. Of these neurons, only motoneurons which are the output neurons of the spinal cord are grouped in nuclei, described as motor nuclei while most of the remaining neurons are widely spread out throughout the spinal gray matter, the core of the spinal cord (Fig. 46.1b) and intermixed with other neurons. However, neurons with input from the upper limbs, trunk, and lower limbs, and commanding movements of these parts of the body are preferentially distributed in the cervical, thoracic, and lumbosacral segments of the spinal cord (Fig. 46.1a), and neurons originating from different embryonic neurons and characterized by similar input and similar axonal projections (see ► Chap. 30, "Spinal Interneurons") are distributed in different Rexed's laminae (see Fig. 30.1d in ► Chap. 30, "Spinal Interneurons").

Selection of Motoneurons Ensuring Properly Coordinated Motor Reactions

As the same muscles and motoneurons that evoke their contractions are used for practically unlimited variants of movements, coordination of motor reactions must depend on which of these motoneurons are activated at a time and in which order.

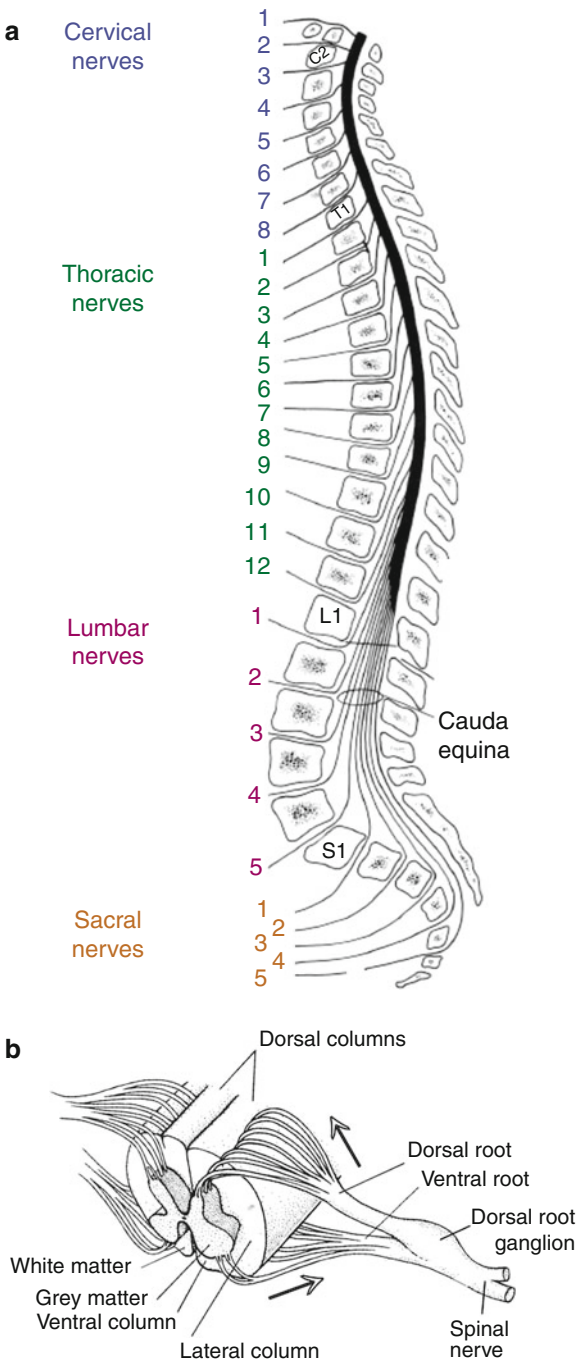

Fig. 46.1 *Basic features of spinal cord morphology.* (**a**) Location of the human spinal cord (*black*) with respect to the spinal vertebrae. Note that the spinal cord does not extend beyond thoracic vertebrae and that most of the spinal segments (defined by their connections with the successive spinal nerves) are located more rostral than the corresponding vertebrae. (**b**) The input–output morphology in the transverse plane. The diagram illustrates that sensory fibers (axons of neurons located in the dorsal root ganglia) enter the spinal cord via the dorsal roots and that axons of motoneurons leave the spinal cord via the ventral roots. *Arrows* indicate the direction along which nerve impulses are conducted within these roots. Nerve fibers interconnecting neurons in the various segments, or neurons in the brain with those in the spinal cord, run through the ventral, lateral, and dorsal columns (Modified from Kandel et al. (1991))

Most generally, motoneurons may be activated in three ways: (1) by direct actions of sensory nerve fibers, (2) by direct actions of supraspinal neurons, and (3) by spinal interneurons relaying actions of either sensory nerve fibers or supraspinal neurons. However, direct contacts between sensory nerve fibers make up only a few percents of all synaptic contacts on motoneurons and are formed by only one category of sensory fibers (muscle spindle primary afferents activated by muscle stretches, see ▶ Chap. 27, "Kinesthetic Inputs"). Direct contacts between descending tract fibers and motoneurons are also scarce, and they are in addition restricted to only a few coupling combinations: For example, corticospinal tract neurons form such contacts only in primates and mainly with motoneurons innervating distal limb muscles (see ▶ Chap. 37, "Cortical Motor Control"); reticulospinal tract neurons contact predominantly motoneurons innervating flexors, while vestibulospinal tract neurons contact predominantly motoneurons innervating extensors. These preferred connections were originally revealed in electrophysiological experiments, by recording postsynaptic potentials evoked in motoneurons by different categories of sensory fibers and by descending tract neurons, but also in morphological studies. The latter confirmed, for instance, that only a small proportion of contacts between sensory fibers and motoneurons are direct when the majority of synaptic contacts on motoneurons remained after transection and the subsequent degeneration of peripheral afferents. This was also confirmed when immunocytochemistry was used to identify axon terminals in contact with motoneurons. Terminals expressing vesicular glutamate transporters (VGLUT1) which characterize terminals of sensory fibers were found to be scarce, and the majority of synaptic terminals on motoneurons were found to express vesicular glutamate transporters (VGLUT2) of the kind that characterizes terminals of intrinsic spinal interneurons or of supraspinal neurons (see ▶ Chap. 11, "Cell Biology of the Synapse"). There is thus a general consensus that the overwhelming part of the excitatory input to spinal motoneurons is relayed by spinal interneurons. Furthermore, it is more and more firmly established that the premotor interneurons do not operate as passive links between sensory fibers and/or supraspinal neurons and motoneurons but are involved in integrating information from many sources before it is forwarded to motoneurons (see ▶ Chap. 30, "Spinal Interneurons") and that organization of spinal motor output depends on interneuronal networks. The contents of this chapter and of the chapter on spinal interneurons are thus intimately related.

Spinal Reflexes: Reactions Mediated by Spinal Neuronal Networks

Are They Automatic and Stereotype, or Adjustable?

Typical examples of reflex reactions are withdrawal of a hand touching a hot object in order to avoid getting burned, correcting body position after having stumbled to avoid falling, scratching to alleviate skin irritation, blinking to avoid damage of the cornea, or swallowing a piece of food once it got in the mouth. Traditionally, spinal reflex reactions are differentiated from other movements on several bases.

Reflex reactions are contrasted to learned movements because they are innate and occur even in newborn babies. They are contrasted to voluntary intentional movements because they are induced more or less "automatically" in response to stimuli and do not require conscious planning or decisions. Spinal reflexes are also differentiated from visually guided movements, movements following acoustic stimuli, or movements that are in other ways initiated by cortical or brain stem neurons, because they occur even when the connections between the spinal cord and the brain are interrupted. They are also contrasted to centrally initiated movements, such as pharmacologically evoked muscle contractions (e.g., after tetanus toxin poisoning) or similarly pharmacologically evoked alternating flexions and extensions, because they are in response to specific stimuli.

However, even if these features are characteristic for reflex reactions, they should not be taken to indicate that spinal reflexes are always stereotype, invariable, and unmodifiable. For instance, withdrawal of a hand touching a hot object can be prevented by a voluntary effort when it might cause something worse, e.g., that a pot with hot water drops on your feet. Corrections of a limb position after stumbling depend on the position of the whole body so that the proper balance is preserved, and scratching movements may be stopped voluntarily. For these reasons, more and more attention is paid to the state, or task, or context dependence of spinal reflexes (see Burke (1999)), and more and more evidence is also being found for their modifiability by learning.

Modifications of spinal reflexes are important for the adjustments to the requirements of various behavioral situations, but they may also reflect pathological changes in the spinal cord or in the brain, e.g., when some spinal reflexes are exaggerated, or abnormally weak, when connections between the spinal cord and the brain are interrupted after various injuries. These modifications may theoretically occur at different sites along neuronal pathways, commonly referred to as "reflex arcs," between the sites at which nerve impulses are generated in sensory fibers by various stimuli and the motoneurons excited by these stimuli. The sites are indicated in Fig. 46.2. (1) Stronger reflex responses are evoked when the sensitivity of the receptors is increased, e.g., in muscle spindles under influence of gamma motoneurons, with the resulting increasing number and the frequency of nerve impulses in sensory fibers, or when these nerve impulses are evoked by stronger stimuli. (2) Alternatively, the transmission between the sensory fibers and spinal neurons excited by them may be weakened by presynaptic inhibition (see ► Chap. 12, "Molecular Regulation of Synaptic Release"), with the resulting less effective activation of their target cells. (3 and 4) The excitability of both motoneurons and of interneurons mediating excitation of motoneurons may be increased or decreased by excitatory or inhibitory actions of other spinal or supraspinal neurons, with the resulting facilitation or depression of spinal reflexes. Depending on which interneurons and motoneurons are excited or inhibited by these other neurons, the same stimuli may lead to contractions of different muscles, e.g., either on the same side of the body or on both sides. Both the excitability and membrane properties of interneurons and motoneurons may also be modified by modulatory actions of monoaminergic, peptidergic, or cholinergic

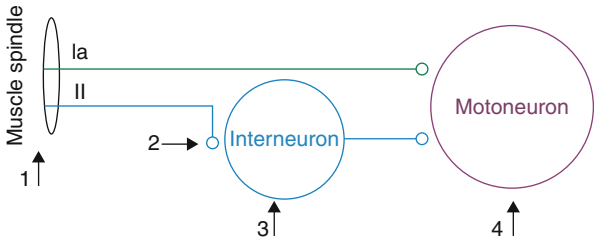

Fig. 46.2 *A diagram of two simplest reflex arcs from muscle spindles to motoneurons*. Neuronal connections in *green* represent direct connections between muscle spindle primaries (group Ia afferents) and motoneurons, while those in *blue* represent disynaptic connections (via single interposed interneurons) in this example between muscle spindle secondaries (group II afferents) and motoneurons. Direct contacts of some group II afferents are not indicated. In all such diagrams, both interneurons and motoneurons represent several (in many cases several hundreds) neurons operating in parallel. *Arrows* indicate where transmission along these pathways can be modified and the resulting reflex actions either enhanced or weakened

neurons (see ▶ Chap. 12, "Molecular Regulation of Synaptic Release"). In order to understand how spinal reflexes are evoked, how they are adjusted under normal physiological conditions, or when they reflect pathological changes in the organism, one has to become familiar not only with their elementary forms and basic mechanisms but also with the mechanisms that allow their modifications and the incorporation of all simple reactions into larger purposeful forms of behavior. In the following sections, these issues will be illustrated for the most representative spinal reflexes.

Different Ways of Analyzing Spinal Reflexes

Spinal reflexes are examined for different purposes. One of these is to understand mechanisms of reactions evoked by various stimuli and how simple reflex reactions contribute to more complex forms of behavior, such as locomotion, postural adjustments, or voluntary movements. However, they are also examined for diagnostic purposes and to monitor the progress of the rehabilitation of motor performance. Analysis of basic mechanisms of spinal reflexes has as a rule been done in greatly reduced preparations, usually in deeply anesthetized animals in which only some neuronal systems operate and by recording postsynaptic potentials or action potentials from single spinal neurons in electrophysiological experiments. However, in order to be able to use knowledge obtained in this way for clinical applications, it had to be verified that results from animal studies do apply to humans. Fortunately, this turned out to be generally true, even if only some features of spinal reflexes can be analyzed in humans, and only indirect experimental approaches can be used to this end. For instance, instead for recording postsynaptic potentials or action potentials evoked in motoneurons themselves, actions of motoneurons on muscle fibers innervated by them are used as their measure. This involves the use of electromyographic techniques to analyze electrical activity of the muscles, measurements of the degree of muscle contractions, or monitoring external effects of these contractions.

Stretch Reflex

The Basic Mechanisms of the Stretch Reflex Evoked by Group Ia Muscle Spindle Afferents

The stretch reflex consists in contractions of the stretched muscles to resist their lengthening. In its basic and the most elementary form, it is evoked by nerve impulses in primary endings of muscle spindles which form synaptic contacts with motoneurons, with only one synapse between the afferents and the motoneurons, as indicated in Fig. 46.2. It is therefore also referred to as the monosynaptic reflex. All features of the morphological substrate of this reflex combine in making it extremely quick and efficient. Primary endings of muscle spindles are highly sensitive to increases in their length and discharge in response to phasic stretches of only a couple of micrometers (see ▶ Chap. 27, "Kinesthetic Inputs"). Sensory fibers forwarding nerve impulses from primary endings are among the largest and fastest conducting ones: They are called group Ia afferents (see ▶ Chap. 27, "Kinesthetic Inputs") and conduct up to about 100 m/s. Once they enter the spinal cord via a dorsal root, they subdivide so that axon collaterals of a single group Ia muscle spindle afferent make synaptic contacts with a great majority (up to 90%) of motoneurons that innervate the stretched muscle and evoke excitatory postsynaptic potentials (EPSPs) in all these motoneurons. Considering that a stretch of a muscle may result in a simultaneous activation of a considerable proportion of muscle spindles in this muscle, that group Ia afferents from all these spindles induce EPSPs in the same motoneurons, and that these EPSPs summate within a very short time interval, there is a high probability that the resulting compound EPSPs reach the threshold for generation of action potentials in the motoneurons and are followed by a contraction of the stretched muscle. However, simultaneous activation of all of the motoneurons would not be very purposeful because it might cause a too strong muscle contraction, and there are several means to ensure that only a fraction of motoneurons are then activated. The first to be activated are as a rule motoneurons of the S type (most excitable but developing weakest muscle contractions). The stretch reflex is therefore easiest to evoke in extensor muscles in which the proportion of slow motor units is high, e.g., in the soleus muscle. Additional recruitment of less excitable motoneurons that are responsible for stronger muscle contractions is possible when excitability of these motoneurons is increased, e.g., by supraspinal or spinal neurons or by specialized modulatory neuronal systems (see ▶ Chap. 12, "Molecular Regulation of Synaptic Release"). The degree of muscle contractions following a standard muscle stretch is therefore a good measure of the excitability of motoneurons that innervate it and is widely used for diagnostic purposes.

Stretches of muscle spindles that incite stretch reflexes may be evoked in different ways, but in the first hand by pulling the tendon or by tapping the tendon and thereby increasing its length. In clinical practice, tapping the tendon is routinely used to evoke the so-called tendon jerk reflex (which should not be mixed with reflex actions from tendon organs). The easiest to evoke is the stretch reflex that follows tapping the tendon of the knee extensor quadriceps

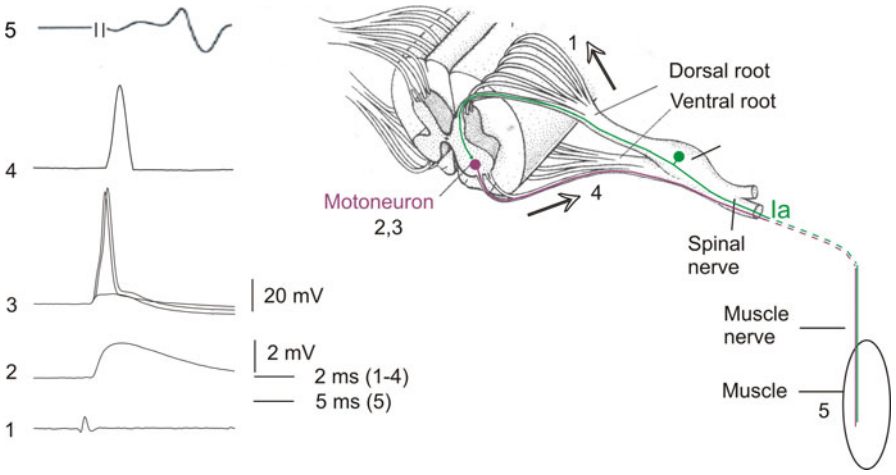

Fig. 46.3 *A sequence of monosynaptically evoked actions of group Ia afferents on motoneurons.* Records to the left are (*1*) afferent volleys (nerve impulses in group Ia afferents at the level of the dorsal root, just prior to their entry to the spinal cord); (*2*, *3*) monosynaptic EPSPs and action potentials induced by them recorded intracellularly in a motoneuron; (*4*) monosynaptic reflexes represented by compound action potentials recorded from axons of several motoneurons in a ventral root; (*5*) the following compound action potentials recorded from the surface of the muscle innervated by the motoneurons (electromyogram, EMG, at a slower time base). Records *1–4* are from different experiments but are normalized (horizontally) to allow comparison of their timing

muscles just below the patella (referred therefore to as the "patellar" or "knee jerk" reflex).

Activation of group Ia afferents may also be evoked by vibrating the belly of a muscle, with the resulting stretching of muscle spindles that they innervate, and by electrical stimulation of the afferents. Under experimental conditions, afferents innervating muscle spindles are most conveniently stimulated at the level of the dorsal roots where they are not mixed with motor axons as in peripheral nerves (see Fig. 46.1b). The resulting activation of motoneurons may be recorded directly from motoneurons, from axons of motoneurons running in the ventral roots (usually referred to as the monosynaptic reflex), from muscle nerves (as "electroneurographs"), or from muscles innervated by the motoneurons (as "electromyographs"). Some of the records obtained in this way are illustrated in Fig. 46.3.

In clinical studies, and for diagnostic purposes, group Ia afferents are usually stimulated at the level of peripheral nerves by transcutaneous stimuli, utilizing the very convenient differences in the excitability of sensory and motor fibers by electrical stimuli. As illustrated in Fig. 46.4, weakest stimuli activate then Ia afferents almost selectively because the excitability of these large afferent fibers is much higher than of smaller diameter axons of motoneurons. Technically, easiest to stimulate are Ia afferents of the soleus muscle by electrodes placed above the peroneal nerve just proximal to the lateral gastrocnemius where it runs most superficially. The effects are analyzed from records of electromyographs obtained

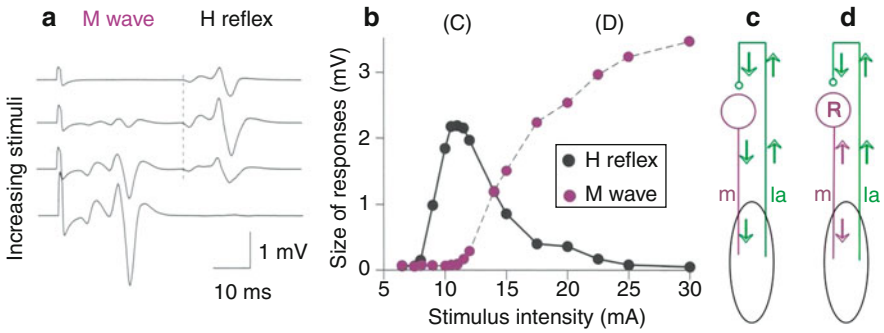

Fig. 46.4 *The relationships between the intensity of electrical stimulation of a muscle nerve in humans with the resulting H and M waves in the electromyographic records from the muscle innervated by this nerve*. H denotes the Hoffmann reflex which is secondary to synaptic activation of motoneurons by group Ia afferents, as diagrammatically indicated by *green arrows* in (**c**). M denotes EMG responses secondary to stimulation of motor axons (m) in this nerve. As axons of group Ia afferents are more excitable, they may activate motoneurons at lower stimulus intensities than those needed to stimulate motor axons and allow the H-reflex to be evoked in isolation from the M wave. At higher stimulus, intensities higher and higher proportions of activated motor axons induce larger and larger M waves (by nerve impulses traveling toward the muscle as indicated by *purple arrows* in (**d**)). Antidromically conducted action potentials invade then motoneurons and counteract their synaptic activation by nerve impulses in Ia afferents during the subsequent refractory period. Submaximal M waves indicate that only some motoneurons are invaded; only some motoneurons are then refractory, and other motoneurons may be synaptically activated. Submaximal M waves are thus followed by smaller than originally H-reflexes. When all motoneurons are invaded, which is indicated by maximal M responses, these are not followed by H-reflexes. The tests of this kind are used to test excitability of motoneurons in clinical studies (Modified from Pierrot-Deseilligny and Burke (2005))

from the surface of the soleus muscle. The technique was introduced by Hoffman so that the reflex responses evoked in this way are most often referred to as H-reflex. These responses are evoked by both lower threshold and longer latency components (H wave) than the much earlier responses of the muscle itself following stronger stimuli (M wave; Fig. 46.4a, b). Note that when the M wave is maximal, it is not followed by the H reflex. The reason for this is explained in Fig. 46.4d, by indicating that motoneurons invaded by antidromically conducted nerve impulses (purple) cannot be reactivated by nerve impulses in sensory fibers (green) reaching them during the refractory period (indicated by R) associated with their antidromic activation. This is in contrast to the situation illustrated in Fig. 46.4c when no such obstacles occur when weak stimuli induce nerve impulses in sensory but not motor fibers. Like responses evoked by muscle stretches/tendon taps, H-reflexes provide a measure for excitability of motoneurons.

Stretch Reflex in Its Wider Context

Monosynaptic activation of motoneurons innervating the stretched muscle is only one of several effects of muscle stretches occurring under any behavioral

conditions. Even if one considers only what happens at a spinal level, it is far from being an isolated phenomenon.

1. It is as a rule associated with excitation of motoneurons of muscles with similar functions (synergists), which evoke movements of the same joint. For instance, motoneurons innervating the soleus may be monosynaptically excited by Ia afferents from not only the soleus itself but also from the medial and lateral gastrocnemius, plantaris, and vastocrureus because group Ia muscle spindle afferents from all of these muscles have synaptic contacts with some of the soleus motoneurons. Motoneurons of the stretched muscle are often referred to as homonymous and those of the synergists as heteronymous.
2. Monosynaptic activation of motoneurons of the stretched muscles is associated with inhibition of motoneurons innervating muscles with opposite actions (antagonists) around the same joint, as illustrated in Fig. 46.5f. Diagram in Fig. 46.5h shows that the same group Ia muscle spindle afferents have synaptic contacts with not only motoneurons but also with interneurons ("Ia interneurons") that inhibit motoneurons innervating antagonists. Inhibitory postsynaptic potentials (IPSPs) mediated via these interneurons are thus evoked via a disynaptic pathway (with one synapse between the afferents and the interneurons and the other one between the interneurons and the motoneurons). As the interneurons are activated as synchronously and as effectively as motoneurons, their actions on motoneurons of antagonists are evoked with a delay that is only a fraction of a millisecond longer than the excitation of homonymous and synergistic motoneurons. The antagonists may then relax so that they do not obstruct contractions of the synergists.
3. The degree of contractions of the stretched muscles is adjusted by inhibitory interneurons (called Renshaw cells) that are activated by nerve impulses in motoneurons' axon collaterals; these are induced in parallel with nerve impulses forwarded to the muscles. Renshaw cells discharge repetitively and may therefore evoke fairly long-lasting IPSPs which decrease the probability of a too early reactivation of motoneurons by Ia afferents in which prolonged muscle stretches may evoke quite high-frequency discharges. They provide thus a negative feedback to motoneurons and thereby also protect the muscles innervated by them. However, Renshaw cells counteract activation of motoneurons of not only a single muscle but of all those that are likely to be coactivated by the same stimuli, thus not only of the homonymous muscle but also of its synergists, and sometimes even antagonists. The negative feedback actions of Renshaw cells are further strengthened and prolonged by another population of interneurons that are activated secondarily to muscle contractions. These interneurons may be activated by nerve impulses from tendon organs (via group Ib afferents) even when the tendons are pulled by contractions of a very small number of motor units (see ▶ Chap. 27, "Kinesthetic Inputs"). IPSPs evoked by these interneurons (see below and ▶ Chap. 30, "Spinal Interneurons") are likewise distributed to motoneurons of both the homonymous muscle and its synergists and further reduce the probability of their reactivation, or at least reduce the frequency of their reactivation during either long-lasting or repeated stretches.

4. Depending on the degree of stretch, muscle spindles may give rise to discharges in not only primary but also secondary sensory fibers (group Ia and II, respectively) that innervate them. In such a case, direct actions of group Ia afferents on motoneurons may be associated with indirect actions of group II afferents evoked via spinal interneurons (see below and ▶ Chap. 30, "Spinal Interneurons").

In addition to these four effects of muscle stretches, the resulting muscle contractions may be followed by a loss of the body balance, or by collision with some objects, and various sequences of additional reflex responses that are then initiated.

Modulation and Role of Stretch Reflexes During Different Motor Tasks

Monosynaptic stretch reflexes may be facilitated or depressed by all of the modulatory actions indicated in Fig. 46.2. Most generally, they are easiest to evoke under conditions when the excitability of motoneurons is highest and the presynaptic inhibition of transmission between group Ia afferents and these motoneurons is lowest. For example, monosynaptic excitation of soleus motoneurons by group Ia afferents is most conspicuous during the stance phase of the locomotor step cycle. The role played by stretch reflexes may also depend on the motor task. Widely distributed projections of group Ia afferents from intrinsic hand muscles on motoneurons of muscles operating at finger, wrist, and elbow levels, but stronger on muscles operating at the wrist than on long flexors and extensors of the fingers, might be used to stabilize the wrist and the elbow. To provide a firm support to hand muscles during grasping and manipulatory movements (Pierrot-Deseilligny and Burke 2005) might thus be the main role of reflex actions of these afferents rather than stretch reflexes of individual intrinsic hand muscles sensu stricto.

Pathological Changes in Stretch Reflexes

Attenuation of monosynaptic reflexes (decrease in amplitude and increase in their latency) occurs primarily after injuries of peripheral nerves, or at the level of the dorsal roots, and in polyneuropathies when the number of group Ia afferents is reduced, or conductance along them is less synchronous (Pierrot-Deseilligny and Burke 2005). In contrast, enhancement of monosynaptic reflexes is primarily linked to the enhancement of excitability of motoneurons, but weaker presynaptic inhibition may be a contributing factor. The enhancement associated with spasticity has been in particular related to changes in motoneurons' membrane properties (bistability developing after injuries of the spinal cord) but also to the increased input from premotor interneurons when they are no longer under descending inhibitory control by noradrenergic neurons (Jankowska and Hammar 2002; Nielsen et al. 2007).

Reflexes Evoked from Other Muscle, Tendon, and Joint Receptors

Reflex reactions evoked from other proprioceptors are much more complex than monosynaptic reflexes from muscle spindles. Their main common feature is that they are not evoked by direct actions of sensory fibers on motoneurons but are

mediated by interneurons operating as links between these fibers and motoneurons. Another common feature of these reflex actions is that they are as a rule not evoked in isolation, because muscle, tendon, and joint receptors are usually coactivated, either simultaneously or successively. Whenever a contracting muscle pulls on a tendon, this is associated with a rotation of a joint and with changes in the length and in the internal pressure within several muscles. In addition, reflex actions from these receptors are mediated by shared interneurons that are coexcited by them. Effects from muscle spindle, tendon, and joint receptors are thus pooled together first on the interneurons and then motoneurons. Only under very special artificial experimental conditions, various categories of muscle, tendon, and joint receptors may be selectively activated and the consequences of information forwarded by them analyzed, as summarized in the following sections.

Reflex Actions from Tendon Organs (Group Ib Afferents)

Nerve impulses from tendon organs are initiated when the junctions between muscles and tendons, or tendons, are pulled by contracting muscle fibers. They reflect increases in muscle tension during muscle contractions (see ▶ Chap. 27, "Kinesthetic Inputs"), but they may also respond when muscles are passively stretched to such an extent that they pull on the tendons. The main effect of nerve impulses from tendon organ is inhibition of motoneurons that innervate the contracting muscles (called autogenetic inhibition); it strengthens recurrent inhibition evoked by Renshaw cells as a part of the negative feedback (see above). However, reflex actions of tendon organs are not restricted to these motoneurons and involve inhibition or excitation of motoneurons of other muscles of the same limb as well. Inhibition is evoked most frequently in extensor motoneurons and excitation in flexor motoneurons, as illustrated in Fig. 46.5d and g, thus favoring the flexion of the whole limb. As nerve impulses from tendon organs are conducted by sensory fibers (the group Ib afferents), reflex actions from tendon organs are often described as "Ib excitation or Ib inhibition."

These reflex actions are mediated by subpopulations of interneurons specialized in assisting contractions of different combinations of muscles (different "motor synergies") and therefore resulting in movements in different directions. The final effects of activation of tendon organs depend on which of these interneuronal subpopulations are selected. Most specialized appear to be interneurons that are monosynaptically excited by group Ib tendon organ afferents and have themselves direct synaptic contacts with motoneurons, i.e., those that mediate disynaptic actions of these afferents on motoneurons. Individual interneurons may coactivate, or coinhibit, motoneurons in several motor nuclei, and patterns of activation of motoneurons depend to a great extent on which of these interneurons are excited and/or inhibited in a given situation (see below and ▶ Chap. 30, "Spinal Interneurons"). It is therefore important that activation of subpopulations of these interneurons may be facilitated by group Ia and II muscle spindle afferents (both providing monosynaptic input to some of the interneurons with input from tendon organs) as well as by skin and joint afferents and a number of descending tract neurons (see ▶ Chap. 30, "Spinal Interneurons"). Additional inhibitory actions of cutaneous

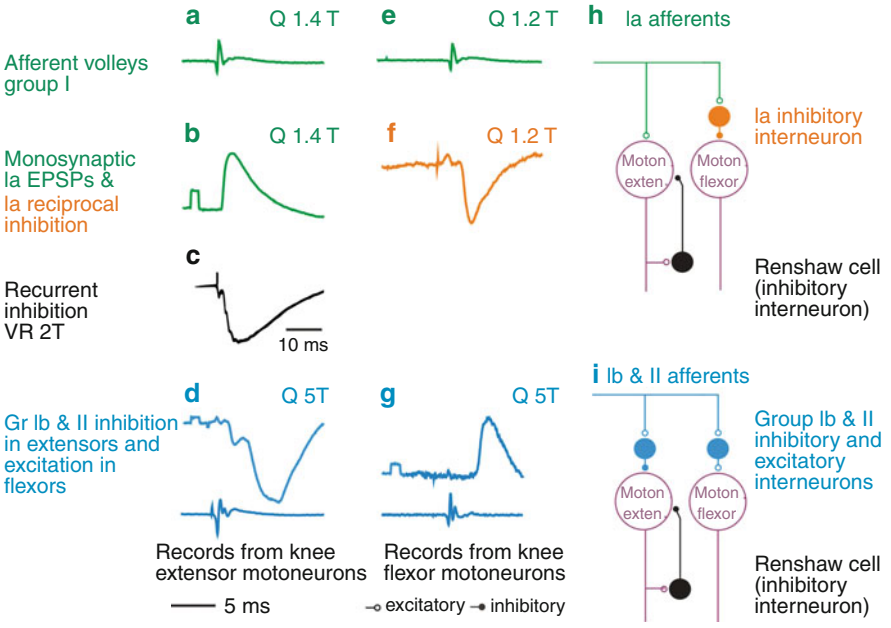

Fig. 46.5 *The sequence of events following a muscle stretch or electrical stimulation of group I afferents*. (**a**, **e**) Afferent volleys in group I afferents. (**b**) Monosynaptic excitation of motoneurons of the homonymous and synergistic muscles by group Ia afferents, as in Fig. 46.3. (**c**) Disynaptic inhibition, via recurrent axon collaterals of motor axons and Renshaw cells, primarily of synergists. It represents negative feedback following activation of motoneurons. (**d**) Disynaptic inhibition after activation of group Ib and II afferents. Ib inhibition represents negative feedback following reflex contraction of the stretched muscle and activation of tendon organs. Inhibition by group II afferents is evoked at longer latencies and is of longer duration, predominantly in extensors, and may thus both strengthen and prolong effects of Ib afferents on extensors. (**f**) Disynaptic inhibition of motoneurons of antagonists accompanying excitation of synergists by the same afferents. (**g**) Predominant opposite effects of group II afferents on motoneurons innervating flexors. The records are from different experiments but are normalized (horizontally) to allow the comparison of their timing. The diagrams to the *right* indicate how the illustrated postsynaptic potentials were evoked. Diagram (**h**) is for (**a**–**c**) and (**f**), while diagram I is for (**d**) and (**g**). For more details on the interneuronal networks involved, see ▶ Chap. 30, "Spinal Interneurons"

afferents might be particularly meaningful during exploratory movements because they might curtail these movements on meeting an obstacle (Pierrot-Deseilligny and Burke 2005). More efficient activation of joint afferents when the joint approaches the extremes of a movement (Pierrot-Deseilligny and Burke 2005) might likewise serve to terminate it.

Reflex Actions from Tendon Organs During Different Motor Tasks and Their Pathological Changes

Because of methodological limitations, reflex actions of tendon organs could not be monitored during movements to the same extent as monosynaptic reflexes. Nevertheless, marked modifications of these reflex actions were found to occur during

locomotion, as for example the reversal from inhibition to excitation of extensors during the stance phase of the locomotor cycle (see McCrea and Rybak 2008). The reversal indicates that interneurons mediating disynaptic inhibition of motoneurons do not act then on motoneurons and that their actions are replaced by actions of excitatory interneurons; the latter strengthen and prolong contractions of the extensors. Depression of inhibition from tendon organs has also been found during voluntary movements in man (Pierrot-Deseilligny and Burke 2005), likely to assist maintained voluntary activation of motoneurons and favor the recruitment of new motor units when an increase in the contraction force is needed.

Changes in the balance between inhibitory and excitatory actions of tendon afferents have also been found under different pathological conditions. For instance, an enhancement of excitation at the cost of inhibition may occur in patients after stroke, with Parkinson's disease or after chronic spinal cord lesions (Pierrot-Deseilligny and Burke 2005).

Reflex Actions from Secondary Muscle Spindle Afferents (Group II Muscle Afferents)

Larger and longer lasting muscle stretches are needed to induce nerve impulses in secondary than in primary muscle spindle afferents (see ▶ Chap. 27, "Kinesthetic Inputs"), but reflex actions from the secondary (group II) afferents are closely associated with the monosynaptic stretch reflexes. Some of these actions are evoked disynaptically and induce similar patterns of motor responses as group Ib afferents, although at longer latencies (see Fig. 46.5d). Their main effect is inhibition of motoneurons that innervate the originally stretched muscles, but they also evoke inhibition of motoneurons innervating other muscles. The dominating effects are inhibition of extensor and excitation of flexor motoneurons. However, reflex actions of group II afferents are mediated polysynaptically to a much greater extent than reflex actions of group Ib afferents, and the polysynaptic actions are relayed by distinct populations of spinal interneurons. These interneurons are coexcited by skin and joint afferents, including nociceptors, and have much wider-spread actions, with contraction of flexors in the same limb associated with contraction of extensors of the opposite limb. They mediate thus ipsilateral flexor and crossed extensor reflexes. An example of excitation of a human muscle expressed in EMG responses from this muscle is shown in Fig. 46.6. The two waves of the EMG responses in the thin trace represent activation of motoneurons by nerve impulses initiated in group Ia and group II afferents by bending the foot. The early wave (SLR) represents the monosynaptically evoked activation, and the later wave (MLR) di- or trisynaptically evoked activation.

Reflex Actions from Secondary Muscle Spindle Afferents During Different Motor Tasks

Similarly marked modifications of reflex actions from secondary muscle spindle afferents as from tendon organs have been found during locomotion – the reversal from inhibition to excitation during some of the phases of the step cycle. Such reversal is thus in keeping with the mediation of a great part of reflex actions of

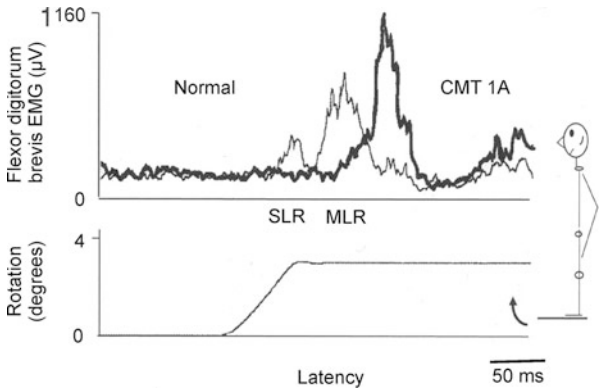

Fig. 46.6 *Components of stretch reflexes in humans*. *Thin gray line*, early and late EMG responses following muscle stretches with the early (group Ia) and late (group II) components in a normal subject; they were evoked by muscle stretches following bending of the foot by rotation of the platform (*lower diagram*). *Thick line*, delayed effects of activation of group II afferents in a patient with the loss of group Ia afferents (Charcot-Marie-Tooth, CMT 1A disease) without the monosynaptic responses (Modified from Pierrot-Deseilligny and Burke (2005))

group II and group Ib afferents by the same interneurons. However, changes in actions from group II afferents occur not only during the stance but also during the swing phase of the step cycle, and not only in extensor but also, or predominantly, in flexor motoneurons. They are therefore consistent with the involvement of some distinct interneuronal subpopulations. In humans, excitatory actions of secondary muscle spindle afferents were found to dominate during postural corrections while inhibitory actions during voluntary movements.

Pathological Changes in Reflex Actions from Secondary Muscle Spindle Afferents

Weaker and delayed excitatory actions of group II afferents and the resulting postural ataxia are caused by peripheral neuropathies, as expected for less effective activation of interneurons that mediate them when the number of afferents is decreased. When such neuropathies are combined with the loss of Ia afferents, group II afferents give rise to quite different responses: delayed and not preceded by earlier components, as illustrated by the thick line EMG response labeled CMT in Fig. 46.6. In contrast, stronger than normally actions of group II afferents are associated with exaggerated stretch reflexes in spastic patients. They are related to lower thresholds of activation of motoneurons and interneurons relaying reflex actions of group II afferents and stronger activation of the interneurons when they become hyperexcitable. These effects may be secondary to a deficient inhibitory control by noradrenergic neurons, but actions of the noradrenergic neurons may be, fortunately, substituted by antispastic drugs, e.g., the NA alpha 2-agonist clonidine, that lower the excitability of the interneurons and subsequently motoneurons and thus counteract exaggeration of reflex actions of group II afferents. These effects

add to the increase in excitability of motoneurons by changes in their intrinsic properties and their deficient serotonergic control. Lack of the serotonergic control may also change the pattern of reflex actions of group II afferents by reducing inhibition of contralateral extensor motoneurons associated with ipsilateral flexion and release bilateral excitation of flexors and extensors. Specific 5-HT agonists may then restore the original pattern of the crossed inhibition (see ▶ Chap. 30, "Spinal Interneurons").

Reflex Actions of Joint Afferents

Receptors in the joints are activated during joint rotation and respond depending on the angle and speed of the rotation (see ▶ Chap. 27, "Kinesthetic Inputs"). Information from these receptors would thus be expected to be very important for the ensuing patterns of muscle contractions. However, there is no evidence that nerve impulses from joint receptors are relayed to motoneurons by separate interneurons; information forwarded by them appears to be as a rule integrated with information from muscle spindles and tendon organs, or with information from nociceptors, thus inducing reflex actions together with them. Like tendon organ afferents and secondary muscle spindle afferents, joint afferents tend to inhibit motoneurons of extensors and excite motoneurons of flexors, contributing to a flexion of the whole limb.

Selection of Interneurons Mediating Reflex Actions of Group I, Group II, and Joint Afferents

Modulation of reflex actions from these receptors differs from the modulation of stretch reflexes in three respects. First, modulation by gamma motoneurons at the level of the receptors plays an important role in adjusting the sensitivity of the secondary muscle spindle afferents, while possibilities of increasing or decreasing excitability of tendon organs and of joint and other muscle receptors are minimal. Second, modulation of transmission from these receptors by presynaptic inhibition is mediated by different populations of GABAergic interneurons than transmission from group Ia afferents (see ▶ Chap. 12, "Molecular Regulation of Synaptic Release") and is highly differentiated. For instance, because presynaptic inhibition from group II afferents is evoked predominantly by group II afferents, transmission from secondary muscle spindle afferents may be considerably weakened during prolonged muscle stretches, leaving reflex actions of other afferents greatly unchanged, even though they are relayed by the same interneurons. Modulatory actions of monoaminergic, peptidergic, or cholinergic neuronal systems (see ▶ Chap. 12, "Molecular Regulation of Synaptic Release") may likewise selectively weaken or enhance them. For example, noradrenergic neurons may block transmission from group II afferents and let motoneurons respond to nerve impulses in group I but not II afferents. Modulation at the level of interneurons is the third feature differing modulation of reflex actions from group Ib, group II, tendon, joint, and other muscle receptors from monosynaptic actions of group Ia afferents. Reflex actions mediated by interneurons have the great advantage by allowing cortical and

brain stem neurons to select various combinations of interneurons that are best suited in a particular motor task and counteract activation of those that would interfere with this task. For example, during precise finger movements, supraspinal neurons may select interneurons and motoneurons that steer finger movements while dampening movements of the arm. Supraspinal neurons may also weaken or strengthen reciprocal inhibition between flexors and extensors. To this end, Renshaw cells may counteract not only reactivation of motoneurons but also activation of interneurons due to inhibit their antagonists. In this way, they may promote coactivation of flexors and extensors that is needed to stabilize a joint. Renshaw cells may also prevent inhibition of contralateral motoneurons by other interneurons and favor bilateral extension (needed in some postural reactions) or bilateral flexion (as in crouching or hopping) instead of ipsilateral flexion associated with contralateral extension.

Reflexes Evoked by Skin Stimulation

The variety of skin receptors are associated with a broad range of sensations evoked by them but also with highly differentiated reactions induced by skin stimulation. Historically, the attention has focused on two main kinds of these reactions: scratching and withdrawal reflexes. Both became particularly good examples of the "local sign" of responses to skin stimulation. The local sign means that pattern of movements evoked by skin stimulation depends on the site of this stimulation. In the case of scratching, it means that the movements are directed toward the site of the skin irritation to allow the removal of its source (e.g., a mosquito or a thorn). However, the kind of the movements depends also on other factors. As illustrated in Fig. 46.7a, b, different muscles are used by a frog to wipe away a piece of paper from a forelimb stretched forward, and when this limb is held back, even when the same part of the forelimb is stimulated. Different muscle combinations are also used by a turtle for scratching more caudal or more rostral parts of the body (Fig. 46.7c). Contacts with harmful stimuli (e.g., too warm, too cold, or too sharp objects) will likewise evoke withdrawal movements in different directions, always away from these stimuli, to avoid the pain as well as the damage.

Basic Organization

Skin afferents have been found to project to different Rexed's laminae, at least partly depending on their receptor origin. Thus, projection areas of fibers activated by light or moderate touch are mainly in Rexed's laminae IV and V, at the base of the dorsal horn, while C and delta fibers activated by high-threshold mechanical and pain stimuli terminate preferably within the first three laminae and rarely reach more ventrally located neurons. Skin afferents activated by various categories of tactile stimuli might thus affect partly the same and partly different neurons. High degree of convergence of these afferents on spinal interneurons has been further demonstrated in electrophysiological studies of input to individual neurons at

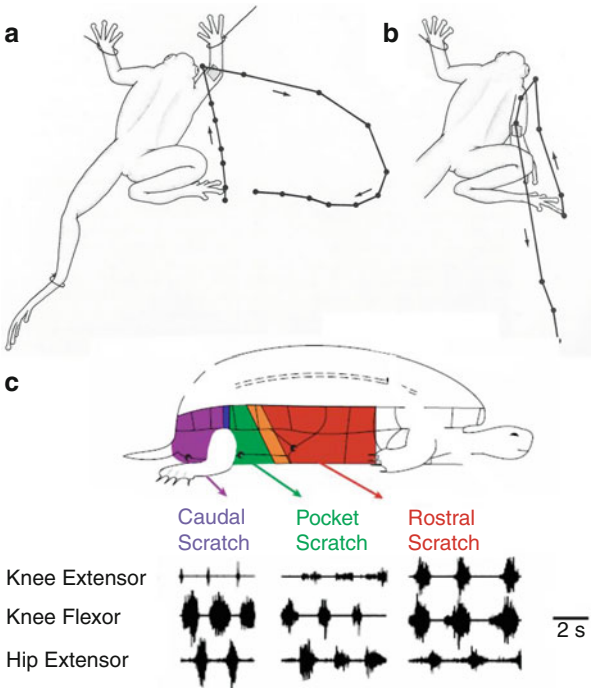

Fig. 46.7 *Examples of the local sign of a wiping and the scratch reflexes.* (**a**, **b**) Different movement trajectories and synergies of muscle contraction during movements of wiping out of a piece of paper from the surface of the frog forelimb when the limb was stretched forward or placed parallel to the trunk (Modified from Kandel et al. (1991)). (**c**) Illustration of the involvement of different combinations of muscles during scratching movements evoked by stimulation of different parts of turtle's body (marked by different colors) (Modified from Berkowitz (2008))

various locations. The term "wide dynamic range neurons" has sometimes been used to denote neurons with the widest convergence patterns, especially those excited by both innocuous and nociceptive stimuli. However, it should be kept in mind that practically all neurons in pathways from skin receptors display some degree of convergence, of afferents from different skin receptors, or from the same category of receptors but from different skin areas, or from both skin and muscle or other nociceptors. All neurons in these pathways integrate thus different kinds of information before they forward it to next neurons, and this is true for both spinal interneurons and for ascending tract neurons.

Diversity of Reflexes Evoked by Skin Afferents

Spinal interneurons with monosynaptic input from skin afferents appear only exceptionally to make direct contacts with motoneurons, i.e., enabling actions from skin afferents on motoneurons to be evoked disynaptically. In addition, such disynaptic actions have been found in only some motoneurons innervating most distal hind limb muscles and to be evoked from skin over the most distal parts of the hind limbs (Fleshman et al. 1984; Moschovakis et al. 1991). On the contrary, actions of the overwhelming majority of interneurons with monosynaptic input from skin afferents are relayed via other interneurons, some of which mediate the above described reflex actions of muscle, tendon, and joint afferents, or by nociceptors. By selecting subpopulations of interneurons initiating different

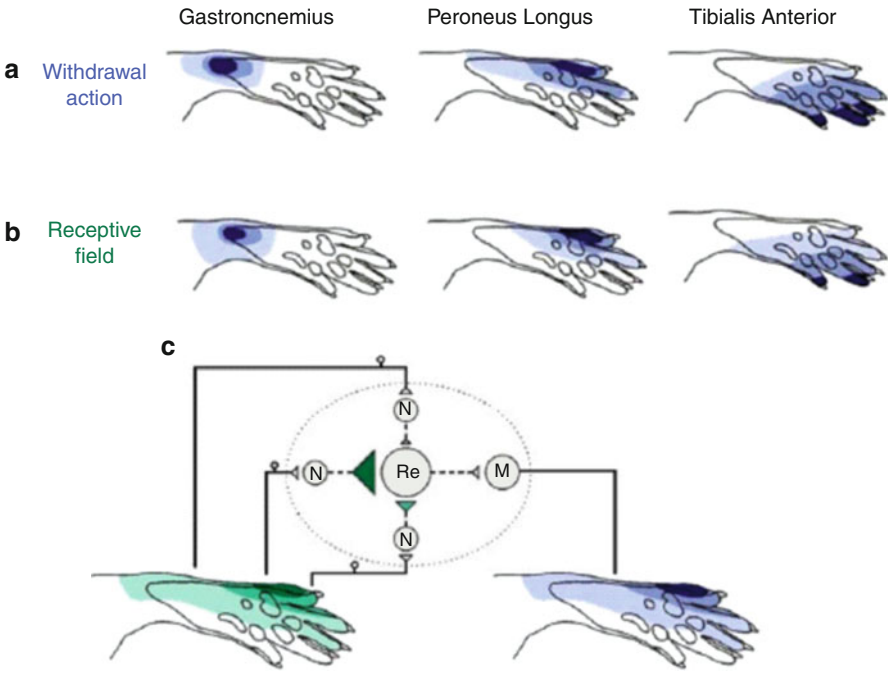

Fig. 46.8 *Input–output relationships in discrete withdrawal reflexes*. (**a**) Maximal withdrawal of the shaded parts of the rat foot following standard mechanical stimuli applied within the *darkest shaded areas* in (**b**). The latter represent skin areas from which contractions of gastrocnemius, peroneus longus, and tibialis anterior muscles were most effectively induced. (**c**) Diagram linking the most selective withdrawal reactions to actions of interneurons that are most effectively activated by the stimuli (Modified from Schouenborg (2008))

synergies of muscle contractions, input from skin afferents may thus be in the most economical way directed to provide the local sign of these reactions. Some interneurons fulfilling such requirements have been found in various species, and they were proposed to have preferential actions on selected motoneurons, as illustrated in Fig. 46.8. However, organization of their neuronal networks has so far been analyzed primarily for interneurons mediating scratch movements evoked from different receptive fields in the turtle illustrated in Fig. 46.7c.

Complex organization of neuronal networks underlying reflex reactions evoked from skin has been already found in the earliest clinical studies. The most interesting of these reactions is that described as the Babinski's sign. It appears in patients in which the corticospinal system is injured and consists in the dorsiflexion rather than in the normally occurring plantar flexion of the toes in response to stroking of the lateral part of the foot sole, as diagrammatically indicated in Fig 46.9. As this reaction is very consistent, it is of great diagnostic value for concluding whether the corticospinal system is, or is not, injured. As the two patterns of movements are opposite in healthy subjects and after injuries to the corticospinal system, this indicates also that the same skin stimuli affect interneurons mediating two different

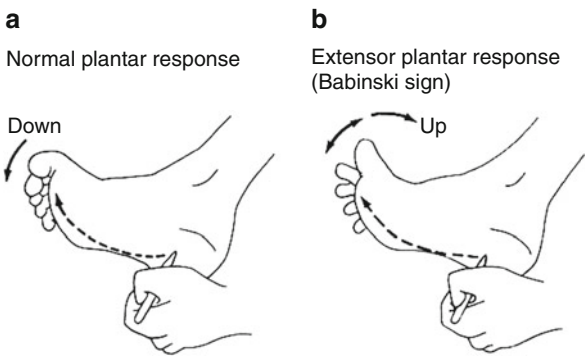

Fig. 46.9 *Examples of movements in opposite directions evoked by the same cutaneous stimuli*. (**a**, **b**) movements evoked by stroking the foot sole in healthy subjects (**a**; plantar flexion) and following injuries of the corticospinal system (**b**; dorsiflexion and fanning of toes) (Modified from Kandel et al. (1991))

motor synergies and that activation of interneurons mediating plantar flexion requires facilitation by corticospinal neurons, as well as the depression of activation of interneurons mediating toe dorsiflexion. Dorsiflexion and fanning of toes occurs also in infants, before the full development of the corticospinal system and/or before axons of corticospinal neurons reach the lumbar segments and/or are fully myelinated.

As there are indications that neuronal networks mediating other reflex responses evoked by skin stimulation are similarly organized, alternative reactions may be expected to be evoked from any skin areas, with the most appropriate ones to be selected in a given situation. However, reflex actions from skin receptors are as a rule mediated via polysynaptic pathways so that detailed analysis of neuronal networks behind these actions is much more difficult than of the disynaptically or trisynaptically evoked actions from muscle receptors.

Spinal Reflexes Are Intrinsic Components of All Motor Acts

When the knowledge of the nervous system was at its early stages, there were strong tendencies to ascribe various functions to distinct parts of the nervous system, distinct neuronal networks, and even distinct neurons. Location of the spinal cord outside the brain suggested therefore that functions of the spinal cord and of the brain are essentially different and that the spinal cord provides primarily output stages of all centrally initiated movements in addition to the more primitive reflex reactions. The supraspinal descending commands were expected to be sent to motoneurons either directly or via separate sets of spinal relay neurons. Even if this was not as explicitly expressed, diagrams of connections between the motor cortex and the peripheral motor apparatus often reflect such views, in the past, but not infrequently even in the most recent publications.

The dramatic change in the understanding of how spinal neuronal networks operate, and of their role more generally, has been incited by studies of A. Lundberg and his research group in the decades 1960–1980. These studies revealed firstly that

neurons mediating spinal reflexes do not operate independently of supraspinal neurons but are under their control and that practically all reflex reactions may be facilitated and/or depressed in different behavioral situations and under different pathological conditions. They were shown to be under control of all of the major supraspinal descending systems, including the cortico-, rubro-, reticulo-, and vestibulospinal, that are classically considered as the main components of the motor systems, but also by monoaminergic, peptidergic, and other descending modulatory systems. However, these studies went even further, by showing that centrally initiated movements, including voluntary movements in humans, are generally not relayed by separate populations of spinal neurons but by the same neurons that relay spinal reflexes. Some spinal neurons are specialized in relying supraspinal commands to forelimb muscles, such as the C3–4 propriospinal neurons, and are particularly important for visually guided reaching movements (see ▶ Chap. 30, "Spinal Interneurons"). Nevertheless, these neurons share this function with interneurons mediating spinal reflexes and/or may operate via these interneurons. In addition, there is no evidence that centrally initiated movements of hind limbs, including voluntary leg movements in humans, are relayed by separate, "private" populations of spinal neurons. In contrast, there are strong indications that these centrally initiated movements, including voluntary movements, are relayed by the same interneurons that mediate spinal reflexes. Neuronal networks mediating various muscle synergies during reflex reactions may accordingly be delegated to mediate the same synergies during movements induced by descending commands, without the need to multiply the spinal output machinery. In addition, as the supraspinal neurons have access to a variety of neurons in spinal neuronal networks, they have also possibilities to combine the networks responsible for various synergies, adjust the degree of activation of subsets of neurons in these networks, and select the optimal activation parameters. It should thus be unthinkable to consider mechanisms of centrally initiated movements without trying to define their spinal interneuronal networks.

Considering the most efficient procedures of rehabilitation after central injuries, it should be also most beneficial for the recovery of motor functions if the involved neuronal networks were activated using all of the available sources of input to their constituent neurons – supraspinal, intraspinal, as well as peripheral. However, only first steps have been made in these directions.

Outlook

A fuller understanding of mechanisms of spinal reflexes and their organization will require further detailed studies. However, the main challenge will be to apply the knowledge based on experiments on animals, including those that are genetically modified, to clinical practice. This will not be an easy task because it will require integration of knowledge from several fields of research and/or intricate collaboration of those with such knowledge, to assist people suffering from different motor disabilities in the best possible ways.

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