Hard lessons in motor control from the mammalian spinal cord

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Traditionally, spinal control of motor output has been viewed as an attractive testing ground for theories of neuronal computation both because of the opportunities to manipulate identified input and output pathways, and because of the supposed relationships between specific, local neuronal circuits and well-studied reflexive behaviors. However, recent findings concerning the complexity of these circuits and their activity during natural behavior have forced a re-examination of the servocontrol theories that gave rise to the predictions of relative simplicity. Attempts to restore conceptual order have led to a proliferation of anatomical and physiological organizing principles for muscles and their motoneuron pools (e.g. size principle of recruitment, anatomical compartmentalization, partitioning of sensory feedback, task groups, etc.). A better understanding of the mechanics of natural motor behavior is required in order to relate such principles to each other, to consider their implications for supraspinal motor planning, and to appreciate their functional roles for the organism.

For more than a century, students of CNS function in vertebrates have recognized that the spinal cord presents unique advantages for the study of neural circuitry. Complete, functional sensorimotor loops can be found with only one or two serial synapses, and their input and output neurons are readily located and characterized. One such pathway, the excitatory synapse from the primary (group Ia) afferent of the muscle spindle onto the homonymous α-motoneurons (innervating the extrafusal muscle fibers of the same muscle), has served as a model of synaptic transmission and its modulation[1].

It was natural for early investigators to relate such simple spinal circuits to aspects of motor behavior, particularly to those reflexes that were found to persist in decerebrate and spinalized animals. Subsequently, developments in three areas reinforced the commonly accepted notion that the spinal cord consisted of fairly simple 'relays', in which sensory input was immediately converted into reflex reactions that constituted functional elements of more complex natural behaviors[2]:

(1) Clinical studies of reflexes in humans provided evidence of specific sensorimotor deficits resulting from various CNS diseases and traumatic injuries that affected specific pathways and neurons.

(2) Cellular neurophysiological studies identified sets of interneurons with input–output connections appropriate for mediating some known reflexes.

(3) Servocontrol circuits developed by robotics engineers to stabilize torque motors were noted by physiologists to have similarities to the neural circuits that were being traced.

The problem

Within the past twenty years, research developments in three separate areas have seriously challenged this simplistic view of the spinal cord:

(1) Spinal circuits are far more complex than was originally predicted. As neurophysiological and anatomical analyses of interneural circuits have progressed, their complexity has been shown to far exceed that predicted by either the known reflexes or the existing servomotor control theories. Monosynaptic feedback from the muscle spindle Ia afferents onto the homonymous motoneurons was thought to provide a simple 'length servo', but the pathway is now known to be deeply modulated presynaptically by a variety of segmental and descending sources (reviewed in Ref. 3). More complex servo theories such as stiffness
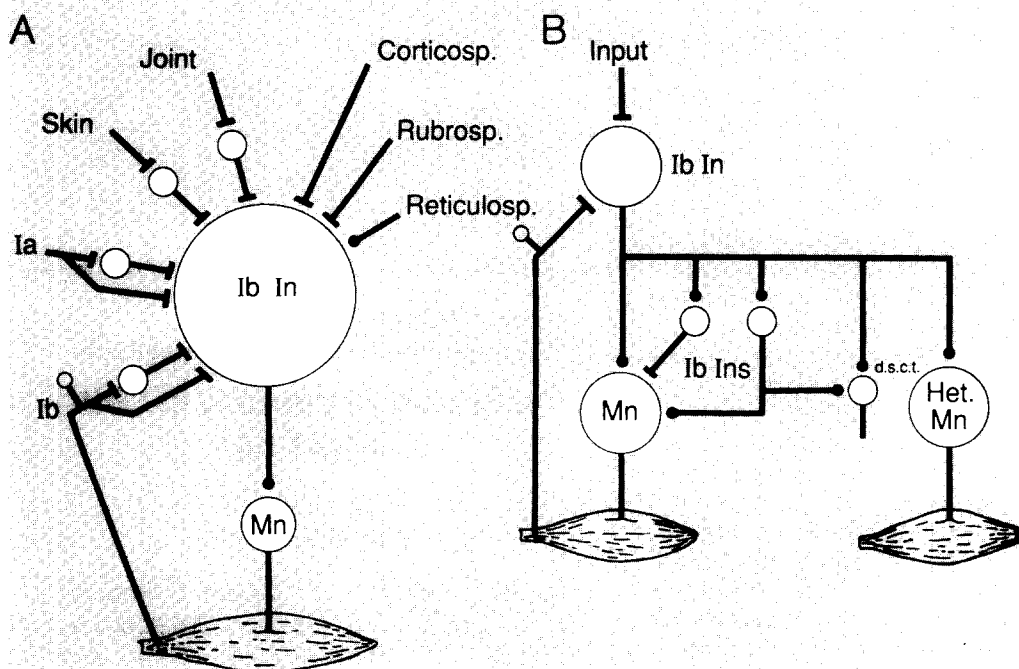

Fig. 1. (A) The 'Ib inhibitory interneuron' (Ib In) actually receives both direct and polysynaptic input from muscle spindle afferents (Ia) and other somatosensory modalities and descending tracts, as well as excitatory input from Golgi tendon organs (Ib). **(B)** In addition to its characteristic inhibitory output to the homonymous motoneurons (Mn), the Ib In projects to heteronymous motor pools (Het. Mn) and to a variety of excitatory and inhibitory interneurons in the spinal cord and ascending tracts, such as the dorsal spinocerebellar tract (d.s.c.t.) (Modified from Ref. 5.)

regulation proposed a dynamic balance between positive length feedback (from spindles) and negative force feedback (from Golgi tendon organs, GTO) that would cause an active muscle to behave like a linear spring in response to perturbing forces or movements[4]. However, the so-called 'Ib inhibitory interneuron' between the GTO and the homonymous motoneurons receives a bewildering variety of cutaneous, proprioceptive and descending inputs, and it projects widely to other types of interneurons and to motoneurons of remote and even antagonistic muscles[5] (see Fig. 1). Furthermore, axonally transported tracers such as HRP have revealed that motoneurons have large dendritic trees and that afferents have widespread terminal arborizations[6], suggesting that, to date, we have identified circuits for only a tiny fraction of the signal traffic through the spinal cord.

(2) The natural behavior of neural elements cannot be predicted from theories. It has recently become possible to record the activity of single, identified afferents and efferents during natural behavior in intact animals[7,8]. The results have been different from and much more diverse than the activity seen in reduced preparations or predicted by pre-existing theories of motor control. For example, the muscle spindle contains intrafusal muscle fibers that modulate the sensitivity of the sensory transduction process. Several competing hypotheses about their activity were developed from control theory and acute neurophysiological observations (reviewed in Ref. 9). However, during natural motor activity in alert animals, spindle afferents show a greater range of response properties than would be predicted by any single theory of fusimotor control[7,9,10]. It has been suggested that the nervous system may employ multiple control strategies to optimize the information flow from afferents under different kinematic conditions, and that it switches between them on the basis of prior motor experience[11].

(3) Servocontrol theory has not even been useful in the control of idealized robotic systems. One possible interpretation of the complexity of biological control circuits is that they reflect the complex and non-linear behavior of the sensors and motors of living organisms. In recent years, it has become possible to build anthropomorphic robots with linear servomotors, precision position encoders, and high-speed digital controllers. However, the performance of such robots has been plagued by problems of instability, noise sensitivity and excess computational load of their control algorithms[12,13].

Engineers are now seeking new control theories, but the magnitude of the problem has caused some to turn to the study of biological systems as welcome proof that dexterity and agility can be achieved by real-time controllers.

Current approaches

Given the setbacks in the reductionistic approach outlined above, it seems important to step back and look for methods and data that offer broader perspectives on the general features of motor behavior and its control and regulation.

The anatomically defined entity of a 'muscle' and its decomposition into a pool of motor units constitutes an historical and logistical focus for most sensorimotor physiology. Experiments are based on the ability to identify and isolate single muscles and their nerves and tendons; motor control theories usually assume that the CNS at some level is geared to regulating the force, length, stiffness, etc., of each muscle as a homogeneous entity. The obvious homologies among muscles and nerves across mammalian species are

Fig. 2.
The sensory and motor apparatus residing within a single muscle may be subdivided according to multiple, somewhat independent, criteria based on anatomical and physiological observations. Each of these has functional implication for the mechanical capabilities and neural control of the muscle (or parts thereof) and may affect the design or interpretation of neurophysiological experiments on its spinal control circuitry.

The organization of motor pools

	Common term	Determining factor	Teleological purpose
Anatomical bases	Muscle architecture	Kinematics	Optimize mechanical properties
	Motor nuclei	Embryology	Establish initial connectivity
	Nerve branching	Limb milieu	?
Physiological bases	Fiber type recruitment	Frequency of use	Metabolic efficiency
	Compartmentalization	Receptor distribution	Intramuscular regulation
	Task groups	Kinematics	Intermuscular coordination
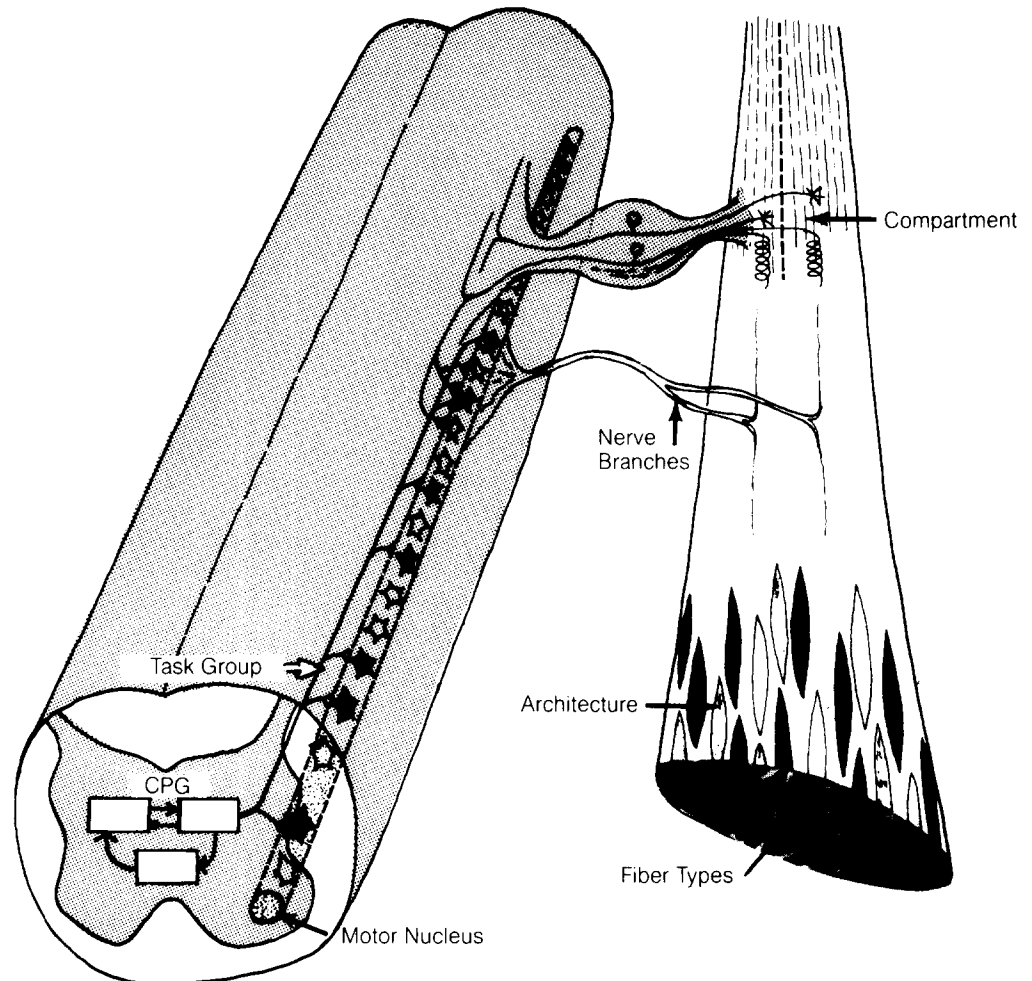
consistent with a central role for the concept of a 'muscle', but it may be that this role relates more to embryological development than to motor behavior. Recent research (see below) has focused on functional as well as anatomical organizations, some of which reveal intramuscular subdivisions while others suggest widespread intermuscular coordination.

Intramuscular organization

It is becoming increasingly clear that motor units are not just a 'final common pathway' in which different control signals from various centers sum to generate tension. Rather, motor units are organized on the basis of multiple anatomical and physiological characteristics into highly specialized entities whose functional properties may shed light on the design goals of the organism. Fig. 2 shows six such organizing principles, three of which (1–3 below) are determined by anatomical features and three of which (4–6) are identified typically by physiological properties.

(1) The gross anatomical description of *musculoskeletal architecture* usually includes only origins and insertions and the joint motion(s) that would be induced by tension in the muscle alone and with the joints at rest and unconstrained. However, the tension-generating potential of a muscle fiber is a complex and non-linear function of the length and velocity of motion of its sarcomeres. To relate the motion of joints to the motion of sarcomeres, one must consider quantitative factors such as the length of the effective lever arms at each joint (a product of the tendon path and the joint angle at the time the muscle is used), plus internal architectural details such as fiber orientation. For example, pinnate muscles pack large numbers of obliquely oriented but relatively short muscle fibers between sheet-like tendinous attachments so that they can generate large tensions for isometric or lengthening work. However, the pinnate architecture magnifies length and velocity at the sarcomere level (it is similar to a lever with a large mechanical advantage). For physiological ranges of motion, the force output of muscles is even more highly modulated by velocity than length. Pinnate architecture is highly inefficient during shortening because sarcomere motion rapidly approaches V_{max}, the maximal rate of shortening at which active tension can be generated[14]. Muscles that normally generate force while shortening rapidly tend to have parallel-fibered architecture. Thus, the diverse and highly specialized architectural forms of muscles have important implications for the work of the muscles under various kinematic conditions. It is interesting to note that in at least some muscles with broad origins or insertions, and hence heterogeneous skeletal lever arms, individual muscle units are usually confined to narrow longitudinal strips within which skeletal action and fiber architecture tend to be homogeneous[15].

(2) At the central end of the motor units, the *motor nuclei* in the spinal cord (and brainstem) also appear to be highly organized, coherent structures. Despite the complex and apparently random coursing and intermingling of motor axons in the ventral roots, plexi and peripheral nerves, the somata providing the α-(extrafusal) and γ-(intrafusal) innervation of a single muscle (or closely related synergistic group) are usually tightly packed into narrow columns that may be adjacent to but never overlap the columns of antagonist muscle motoneurons[16]. Furthermore, the position of motoneurons along the rostral–caudal axis of these nuclei, which may be several segments long, may be topographically related to the location of their muscle units within the target muscle[17].

(3) Many muscles are innervated by nerve trunks that divide near their entry zone into separate *nerve branches* that serve anatomically distinct regions of the muscle[18]. Such branching patterns may be somewhat variable from one individual to another within the same species, perhaps suggesting[15] that such details reflect more closely the vagaries of embryological development rather than organizing principles of motor control. Nevertheless, in some muscles such branches tend to define regions that may have different fiber-type compositions[19] and/ or different patterns of proprioceptor distribution[20].

(4) Mammalian muscle units tend to be histo-chemically and physiologically distinguishable into at least three *muscle fiber types*: slow twitch (type S), fast twitch–fatigue resistant (type FR) and fast twitch–fatiguable (type FF). The orderly recruitment of the different types of muscle fibers via their innervating motoneurons is well established during most motor behaviors (Henneman's size principle[21]) although the underlying mechanism(s) continues to be debated[22–24]. In many muscles, the fast twitch–fatiguable fibers are segregated into the more superficial regions, perhaps because these parts of the muscle have longer skeletal lever arms or because they require less blood supply, thus conserving heat. Efferent activity recorded from these muscle regions or their nerve branches is modulated differently from aggregate activity in deeper, slow twitch regions. The latter contain motor units that are recruited during less vigorous activities, but may tend to saturate during large and/or fast movements[25].

(5) There has been considerable interest in *sensorimotor partitioning* within the anatomical compartments defined by muscle nerve branches. It has been shown that intramuscular proprioceptors, such as muscle spindles and especially Golgi tendon organs, are most sensitive to the motion and forces caused by those muscle units that are in their immediate vicinity[26]. Thus, it seems reasonable to ask whether proprioceptive feedback is centrally 'partitioned' so that afferents contribute a disproportionate share of their sensory feedback to those muscle units that exert direct influence on the sensory signals[27]. In some muscles there appears to be a weak selectivity in the strength of monosynaptic excitatory feedback from muscle spindle primaries that transcends the selectivity that might be expected from the rostral–caudal gradient of the motor nucleus[28]. On the other hand, the short latency inhibitory feedback from the tendon organs (via the 'Ib inhibitory interneurons' mentioned earlier) appears to be spatially non-specific[5,29], despite the even tighter mechanical coupling between each individual tendon organ and the few motor units with fibers ending on it[26].

(6) Recently it has been proposed that the pools of α- and γ-motoneurons innervating the various muscles might also be organized into purely functional *task groups* that do not necessarily correspond to their anatomical segregation in the muscles, their nerve branches, or the motor nuclei[30]. This notion was

developed to account for the observation that motoneurones serving the anatomically homogeneous anterior sartorius muscle of the cat hindlimb are recruited during only one or the other of the two bursts of electromyographic activity generated by this muscle during each step cycle of walking[31]. The EMG burst during the swing phase occurs as the muscle rapidly shortens whereas the burst during stance phase occurs during rapid lengthening. It has been suggested that these two kinematic conditions might consitute separate control problems, even though both occur during the same behavioral task. Thus the tasks are more usefully defined kinematically, and the task groups denote functional associations based on the need for specialized control circuitry in the spinal cord.

Both the anatomical and the physiological organizing principles face problems with definition of terms. Even as simple an entity as a muscle actually represents a rather arbitrary definition, based on gross dissection of fascial planes and nerve branches that may be incomplete and variable. Physiological findings such as partitioning of sensory feedback depend methodologically upon the presence of accessible nerve branches for electrical stimulation and recording, but as mentioned above, these branches may actually reflect embryological influences that are only circumstantially related to motor control principles embodied in the spinal cord circuitry. Concepts such as task groups based upon patterns of natural recruitment are useful only if all natural behavioral tasks can be broken down into a reasonably small set of control problems, but the biomechanics are largely lacking for identifying the kinematic similarities and differences among the roles of muscles during many natural motor activities.

Intermuscular dynamics

All of the organizing principles above share the common presumption that the individual muscle (however it is defined) constitutes a useful level of sensorimotor control, which may be further subdivided into more locally controlled entities. The emphasis on the length, force, stiffness, etc., of individual muscles stems from the traditional analytical approach of dividing a complex system into a collection of individually simple, hopefully linear processes. However, in a multiarticulated limb, the relationship between tension in a muscle and its effect on limb trajectory is anything but simple. The apparently simple act of walking results from a complex set of recruitment patterns in muscles that can be distant and not obviously related to the part of the skeleton that must be moved. For example, dorsal-ward acceleration of the cat foot that occurs at the end of the locomotor swing phase in order to orient it for footfall may be mostly a product of the hamstring muscles, which cross the knee and hip joints but not the ankle[32,33]. The late swing-phase activation of the hamstrings to arrest the forward momentum of the shank results in a whiplike torque at the ankle. Thus, it is not at all clear how much utility there is to a 'first level' of control operating at the single muscle or even single compartment or task group level.

Instead of describing the mechanical state of a limb by the tension or stiffness of individual muscles or even the net torques at each joint, it may be useful for the investigator (and perhaps for the CNS controllers) to consider the generalized mechanical impedance presented by the end point of the limb (e.g. hand or foot). The mechanical impedance opposing the motion of a point contact in three-dimensional space can be specified by a three-dimensional vector for each of three terms: a spring-like elasticity proportional to the magnitude of any displacement from equilibrium, a viscous-like reaction proportional to the velocity (first derivative) of displacement, and an inertial component proportional to the applied acceleration (second derivative). Hogan has suggested that the role of the motor controller is not just to achieve some target trajectory of position in space, but to set up the posture of the whole body and the recruitment of all the musculature to establish a desired pattern of mechanical response to various kinds of perturbations likely to be encountered[34]. An impedance-controller operating on such principles would place much less reliance on the on-line calculation of reflex responses to perturbations, but would presumably require a great deal more experience and sophistication to generate the largely open-loop program that establishes the desired time-course of impedances. This might account for the relatively low gain of the segmental reflexes noted in some experiments[35].

At an even higher level of abstraction, it may be useful to consider performance goals of the whole behavior. Raibert has noted that for behaviors such as locomotion, the goal is really dynamic stability rather than slavish adherence to a specific posture and trajectory of limb motion[36]. He has constructed single and multilegged hopping and running machines that maintain such stability at high speeds through the use of remarkably simple control algorithms, thus avoiding the almost insurmountable computational problems encountered when using inverse-dynamic analysis to explicitly calculate the torques required to produce a particular trajectory.

Both the performance-based and the impedance-based control theories deserve particular attention from neurophysiologists because each provides a rationale for the existence of intermediate nodes in the calculations (i.e. interneurons), with convergence of multimodal sensory inputs and descending controls, and divergence of output to remote actuators. For example, in one of Raibert's control circuits, position feedback from one actuator is combined with attitude-sensing (vestibular) and command (descending) signals and gated by a contact-sensor (cutaneous) before changing the output level of another actuator (motoneuron pool)[36].

The challenges

Sensorimotor neurophysiology is in a state of great flux, ranging from its methodology to its theory. Those whose experiments have forced us to confront the 'embarrassment of riches' in the workings of the spinal cord must ask whether it is useful to continue to collect yet more inexplicable data. Those who believed the spinal cord and peripheral motor plant to be well-understood and thus turned their attentions to higher centers of motor planning and coordination (e.g. cerebral cortex and cerebellum) now find that their edifices are built upon 'the shifting sands of spinal segmental circuitry' (Stuart, D. G., unpublished).

Perhaps the answer lies in breaking out of the parochial concerns of these subspecialites and broadening the inquiry into the following three areas:

(1) Development and application of quantitative analyses of natural behavior. The few instances in which neurons, muscles and limbs have been studied during natural motor behaviors unconstrained by artificial limitations have been sobering experiences for sensorimotor neurophysiologists. However, the methods required to collect and to analyse such data are difficult and largely foreign to traditionally trained researchers in this field, so the reports remain fragmentary and even anecdotal. It will probably be necessary for neuroscientists to expand upon their usual methodologies by entering into multidisciplinary collaborations in which complex experiments are designed and performed by teams including surgeons, kinesiologists, motor psychologists, mechanical engineers, and roboticists.

(2) Development and adoption of generalized conceptual tools. The traditional training of neuroscientists imparts much information about how the parts of the nervous system work but very little about what jobs the whole must thereby perform. Mechanical concepts such as impedance, stiffness, impulse, and work provide access to a wealth of analytical engineering tools, but only if the terms are used rigorously. Similarly, signal theory provides sound and powerful tools for quantifying information transmission from sensors and determining the resolution of motor controllers, but it is almost never applied to neurophysiological hypotheses about the function of a particular system. Unfortunately, the traditional arrangement of mathematical and engineering curricula makes courses that cover these concepts relatively inaccessible to neuroscience students who already must cope with an information glut. If neuroscientists of the future are going to lead those interdisciplinary teams, they need at least the vocabulary and the subjective familiarity that will provide access to these other fields of expertise.

(3) Recognition of 'top-down' design strategies. Despite our enthusiastic embrace of reductionism as a philosophy, most of our hypotheses do not, in fact, result from the reduction of a high order phenomenon into its constituent entities. Rather, we tend to start with an almost random collection of bits of data *in medias res* and then extrapolate and generalize upward to 'principles' having no necessary place in the greater scheme of the organism. 'Principles' such as stiffness regulation[4] and $\alpha-\gamma$ co-activation[37] are interesting observations of conditions obtained in one or a few muscles under one or a few behavioral conditions, usually highly constrained and artificial. They may shed light on the larger sensorimotor goals of the organism, but only from perspectives in which we can appreciate how the original observations fit into the whole behavioral repertoire of the organism.

In studying the visual system, Marr found it necessary to develop a 'theory of computation' as an overview from which to examine the virtually infinite set of specific transformations and algorithms that could be employed in image analysis[38]. This top level provides criteria for judging the desirability of the alternative computational approaches and for devising experiments to differentiate among them. This is because it is at the top level where we factor in the

crucial but indirect design criteria and tradeoffs concerning the relative importance of competing performance goals (speed, reliability, efficiency, etc.) and 'technology' limitations (the phylogenetic heritage of biochemical, cellular, and embryological options).

Half a century ago, Nicholas Bernstein identified most of the top-level motor considerations in his studies of the skeletal dynamics of human locomotion[39]. His analyses identifed explicitly the futility of placing too much reliance on reflexive or preprogrammed control schemes having 'unequivocal' (invariant) input–output relationships. Western researchers, largely unaware of this work, concentrated on reductionistic studies of the electrophysiological and microanatomical organization of precisely such control circuits. Thus, the chasm between kinesiological studies of whole mechanical systems and the recruitment and regulation of individual muscles remains unbridged. In theorizing about the motor system, we cannot start with 'length follow-up servos' and 'Ib inhibitory interneurones'. We must first confront the larger framework of sensorimotor behavior and find the proper places to hang these insights and observations.

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Biology and structure of the mammalian glycine receptor

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Glycine is a major inhibitory neurotransmitter in the central nervous system of vertebrates and invertebrates. The postsynaptic receptor for this amino acid is an oligomeric glycoprotein which, upon binding of an agonist, forms an anion-selective transmembrane channel. After affinity purification from mammalian spinal cord, the glycine receptor (GlyR) has been shown to contain three polypeptides of 48, 58 and 93 kDa. Biochemical and immunological data have shown that these polypeptides have different functional properties and/or topologies in the postsynaptic membrane of the glycinergic synapse. Monoclonal antibodies against the GlyR have allowed its ultrastructural visualization in the CNS. GlyR deficiencies have been implicated in the pathogenesis of spasticity and spinal cord degeneration in man and mouse.

In 1965, Aprison and Werman[1] suggested that the amino acid glycine acts as a neurotransmitter in mammalian spinal cord. Since then, numerous studies have established glycine as a major inhibitory transmitter in the CNS of vertebrates and many invertebrates (reviewed in Ref. 2). In mammals, glycinergic synapses are abundant in the lower part of the neuraxis, i.e. brain stem and spinal cord, whereas the other major inhibitory transmitter, GABA, predominates in the brain[2]. Both glycine and GABA inhibit neuronal firing by increasing the chloride conductance of the neuronal membrane.

Over ten years ago, a postsynaptic receptor protein specific for glycine was identified by ligand binding studies[3,4] and was shown to be different from the GABA receptor[5]. More recently, our laboratory has focused on the biochemical and immunological investigation of the mammalian GlyR[6,7]. Here, the data currently available on the biology and structure of this chemically gated neuronal ion channel are summarized.

Physiology and pharmacology

In 1955, Eccles and collaborators[8] showed that postsynaptic inhibition is mediated by ion channels permeable to chloride and other small monovalent anions. Intracellular recordings[9] and recent patch clamp experiments[10] have established a relative conductance sequence of $Cl^->Br^->I^->SCN^->F^-$ and have revealed kinetic properties that are similar for both glycine- and GABA-activated chloride channels. However, the elementary conductances and the pharmacology of these channels are different, indicating that the GlyR and the GABA receptor are indeed separate molecules. Patch clamp data have also shown that upon ligand binding both receptors exhibit multiple active conductivity states[11]. The open channel of the GlyR is estimated to have a maximal pore size of 5.2 Å and to possess at least two different anion binding sites[10]. Its channel gating displays some voltage sensitivity[10]. In lower vertebrates, a regulation of GlyR conductance by intracellular chloride has also been demonstrated[12].

The pharmacological properties of the GlyR are still poorly investigated. Besides glycine, the amino acids β-alanine and taurine (Fig. 1A) are efficient agonists of the GlyR (K_d values 5–20 μM)[13,14]. Alanine, serine and proline are less potent, and GABA has little effect below 1 mM. Non-amino acid agonists of the GlyR have not been found.

The number of selective GlyR antagonists is small. Strychnine, a convulsive alkaloid (Fig. 1B) from the Indian plant *Strychnos nux vomica*, is the most potent specific antagonist known so far (K_i 5–10 nM)[2,14]. The neurotoxic effects of this alkaloid can be attributed to a block in glycinergic transmission in different regions of the CNS[15]. In 1973, Young and Snyder demonstrated high-affinity binding of [³H]strychnine to synaptic membrane preparations[3]. This binding was inhibited by glycine and other agonists and modulated by chloride and related anions capable of mediating glycinergic responses[4,5]. Strychnine binding has therefore been postulated to occur at an allosteric site associated with the ion channel of the GlyR[4,13]. Several studies have used [³H]strychnine binding to quantitate and localize the GlyR in various regions of the rodent and human CNS[3,15,16]. We have found strychnine and its derivatives to be potent tools for analysing and purifying the GlyR protein (see below).

Recently, another class of selective GlyR antagonists albeit of lower affinity than strychnine has been described[17]. Derivatives of 4,5,6,7-tetrahydro-

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