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Sensory and descending motor circuitry during development and injury

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Proprioceptive sensory input and descending supraspinal projections are two major inputs that feed into and influence spinal circuitry and locomotor behaviors. Here we review their influence on each other during development and after spinal cord injury. We highlight developmental mechanisms of circuit formation as they relate to the sensory–motor circuit and its reciprocal interactions with local spinal interneurons, as well as competitive interactions between proprioceptive and descending supraspinal inputs in the setting of spinal cord injury.

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Background

The coordinated activation of peripheral muscles is essential for generating locomotor behaviors that enable us to respond and interact with the external environment. The generation of accurate motor skills requires that diverse brain-originating descending signals be integrated by spinal cord-resident sensory–motor (reflex) circuits, which generate appropriate skeletal muscle contraction during locomotion [1,2,3•,4•]. The process of how descending information interacts with spinal sensory–motor circuits, and ultimately controls motor behavior, has fascinated researchers since the beginning of the last century [5] and remains an active topic of current research.

This review explores how the proprioceptive sensory–motor circuit and descending supraspinal projections coexist and influence each other, and, in particular how spinal reflex circuits are impacted when descending supraspinal tracts are interrupted by injury or disease. We begin by reviewing recent findings that describe how the sensory–motor circuit is established and dynamically maintained. In addition, we will explore the growing literature supporting a signaling role for proprioceptive sensory afferent neurons in both development and plasticity of local spinal circuitry. Lastly, the role of proprioceptive sensory signaling in recovery from spinal cord injury and the re-establishment of descending control over motor output will be discussed.

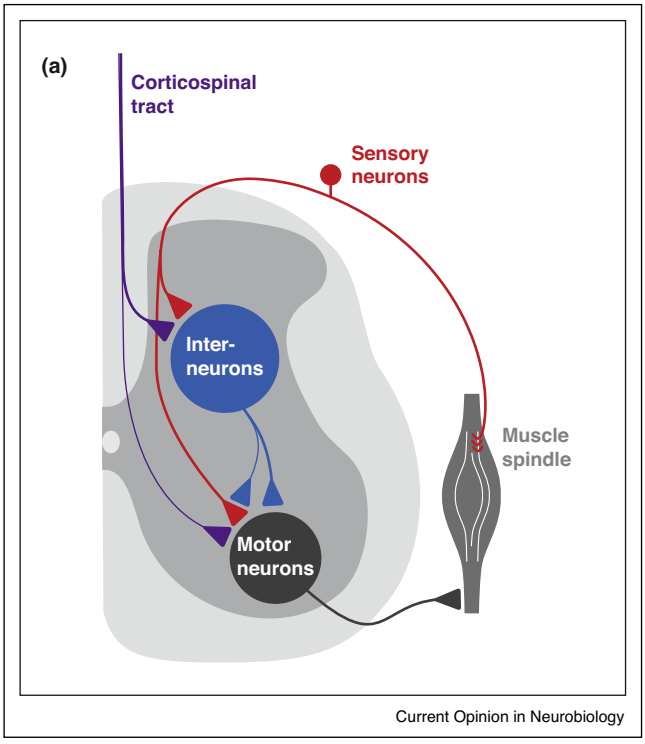
The spinal sensory–motor reflex circuit

Pioneering studies by Eccles and colleagues in the 1950s [6] characterized the spinal sensory–motor reflex circuit and how stretch of a peripheral muscle is relayed via proprioceptive sensory neuron afferents onto specific dedicated spinal motor neurons. This information is then transmitted back to the muscle of origin and thus drives reflex contraction (Figure 1a) [6–9]. The sensory–motor circuit is dedicated to proprioceptive control, the sensing and stabilization of the limb in space. The behavioral relevance of this circuit has been well described, and experimental disruptions of the spinal reflex circuit result in characteristic behavioral and functional abnormalities. Perturbing the targeting of proprioceptive sensory neurons onto motor neurons leads to severe disorganization of locomotor function [1]. If proprioceptive feedback is lost, coordinated stepping movements required for normal walking locomotor behaviors are impaired [3•,4•]. Descending brain-derived information influences the sensory–motor circuit either directly, via motor neurons, or indirectly, via local spinal interneurons [5,10,11]. As a final relay station that forms direct instructive connections with muscles in the periphery, the proprioceptive sensory–motor circuit is of special relevance when considering changes resulting from spinal cord injury or loss of descending information.

Mechanisms of sensory–motor circuit formation

Stimulating sensory fibers of a single limb muscle generally produces monosynaptic reflex responses within the same or a limited subset of functionally-similar muscles [6–9]. The corresponding specificity of anatomical wiring displayed by the sensory–motor reflex circuit has been a rich basis on which to study the developmental mechanisms of circuit formation [12]. Developmental studies of circuit specificity have considered several basic mechanisms by which specific neuronal connectivity is

Figure 1



Proprioceptive and corticospinal tract inputs into spinal circuitry. **(a)** Information about stretch of a peripheral muscle is carried from the periphery to the spinal cord via proprioceptive sensory neurons that transmit the information to motor neurons both directly and indirectly via spinal interneurons. In rodents, corticospinal tract (CST) fibers form rare monosynaptic connections onto motor neurons, while the majority of CST contacts are formed with interneurons [33,49].

established, including: (1) positional targeting, (2) molecular surface recognition between neurons and their targets, and (3) circuit refinement based on neuronal activity.

The clustering and settling position of motor neurons within the spinal cord has been suggested as a determinant in the establishment of sensory–motor specificity [13]. The positional targeting principle posits that sensory afferents project to their final position independent of any target motor neuron-derived cues, and that the clustering and settling position of motor neurons within the spinal cord instead determines the establishment of sensory–motor specificity. Consistent with this, when motor neuron position is scrambled via loss of transcription factor Foxp1, sensory neurons still target their appropriate terminal innervation zones [14]. This principle may be relevant to interneuron connectivity as well: an identified class of spinal interneurons loses their normal sensory input when shifted laterally upon loss of the transcription factor Satb2 [15]. The molecular underpinnings of the positional targeting principle are not yet well understood, however, and a caveat to this model is that when transcription factor expression in a spinal neuron population is lost, molecular characteristics of the neurons themselves are changed, potentially causing aberrant connectivity independent of position. Indeed, in a mouse mutant for the transcription factor Pea3, a population of motor neurons not normally expressing Pea3 is displaced yet continues to receive largely normal proprioceptive inputs [16].

A complementary system that may augment positional targeting mechanisms is that of neuronal recognition-based cues. The targeting of sensory afferents along the dorsal–ventral axis of the spinal cord is controlled by graded sensory neuron expression of the transcription factor Runx3, where increasing expression levels specify sensory afferents to project to more ventral spinal termination zones [17]. Similarly, changes in motor neuron transcriptional identity via mutation of Hoxc9 have been shown to instruct both sensory and premotor interneuron inputs [18], and ectopic expression of Lhx3 in lateral motor column neurons leads to altered motor neuron activity patterns, suggesting alterations in premotor interneuron connectivity [19]. In addition, repulsive receptor/ligand interactions have been reported to corral sensory projections into appropriate laminar positions within the spinal cord. Semaphorins expressed by spinal neurons and glia generate boundaries that repel Plexin-expressing sensory neurons [20–22]. The Semaphorin–Plexin signaling pathway also choreographs a recognition system for sensory–motor specificity. Sema3e expression in a subset of motor neurons, together with proprioceptive sensory neuron expression of its high-affinity receptor PlexinD1, instructs a repellent signaling program [23••,24]. However, this repellent signaling program does not wholly explain the remarkable wiring specificity exhibited in spinal motor circuitry; it is clear that other factors need to be determined.

Lastly, the refinement of circuit connectivity via correlated neuronal activity has been considered as a possible contributor to sensory–motor circuit specificity. However, mature patterns of sensory afferent topography are already present during gray matter innervation [25,26] and sensory–motor specificity is evident at birth [8]. Correlated neuronal activity further plays no role in the segregation of functionally antagonistic motor circuits [27] and only a minor role in the establishment of connections between sensory neurons and functionally similar motor neurons [28].

The intricate and precise wiring of the spinal motor system thus appears to rely primarily on a complex combination of position-based cues and intrinsic molecular identity [13]; this conclusion represents both the most parsimonious synthesis of available data and the challenges of available experimental manipulations, wherein

position can rarely be influenced independent of molecular identity.

Local inhibitory influences on sensory–motor spinal circuitry

The proprioceptive sensory–motor circuit has been shown to receive input from a large variety of local spinal interneurons [29•,30]. A class of GABAergic interneurons has been a source of insight into the molecular mechanisms of interneuron targeting. This class of GABAergic interneurons, called GABApre, synapses with the terminals of proprioceptive sensory afferents and, through an inhibitory strategy known as presynaptic inhibition, directly controls proprioceptive sensory output (Figure 2a) [31–34]. In the absence of the sensory target, GABApre interneurons fail to contact alternate targets and ultimately retract (Figure 2a′) [33]. The recruitment of GABApre synapses to sensory terminals depends on a cell adhesion molecule complex including sensory-derived Cntn-5 (NB2)/Caspr4 and GABApre interneuron-derived NrCAM and CHL1 [35••]. In the absence of any one of these proteins, the density of GABApre synaptic contacts on sensory terminals is reduced, indicating an essential function for this protein interaction complex (Figure 2a″). Similar reductions in GABApre synaptic contacts were found in a genetic mouse model of dystonia, potentially through disrupted adhesive signaling [36]. Dysregulated presynaptic inhibition of mechanosensory afferents by spinal interneurons has also been shown to result from mutation in several autism spectrum disorders-associated genes [37]. These data point to the clinical relevance of presynaptic inhibition by spinal interneurons and the importance of understanding the complex adhesive signaling interactions that may specify or refine interneuronal wiring.

Proprioceptor influences on local spinal circuitry

Neurons of the sensory–motor circuit also serve a signaling role and influence other local spinal circuit components. These signaling functions are relevant in contexts of both developmental change and dynamic plasticity.

Developmentally, proprioceptive sensory neurons serve to generate and maintain the functional specificity of downstream spinal interneurons, such that developmental disruption of proprioceptor connectivity results in altered premotor interneuron distribution. Tripodi and colleagues [30] mapped premotor interneuron location throughout the spinal cord by injecting monosynaptically-restricted trans-synaptic viruses. They observed that medio-lateral spinal segregation of extensor and flexor premotor interneurons was disrupted in mice in which proprioceptive afferents were developmentally ablated (Figure 2b,b′). Specifically, medially-localized extensor premotor interneurons that usually receive proprioceptive input spread laterally into the domain that is occupied by flexor premotor interneurons.

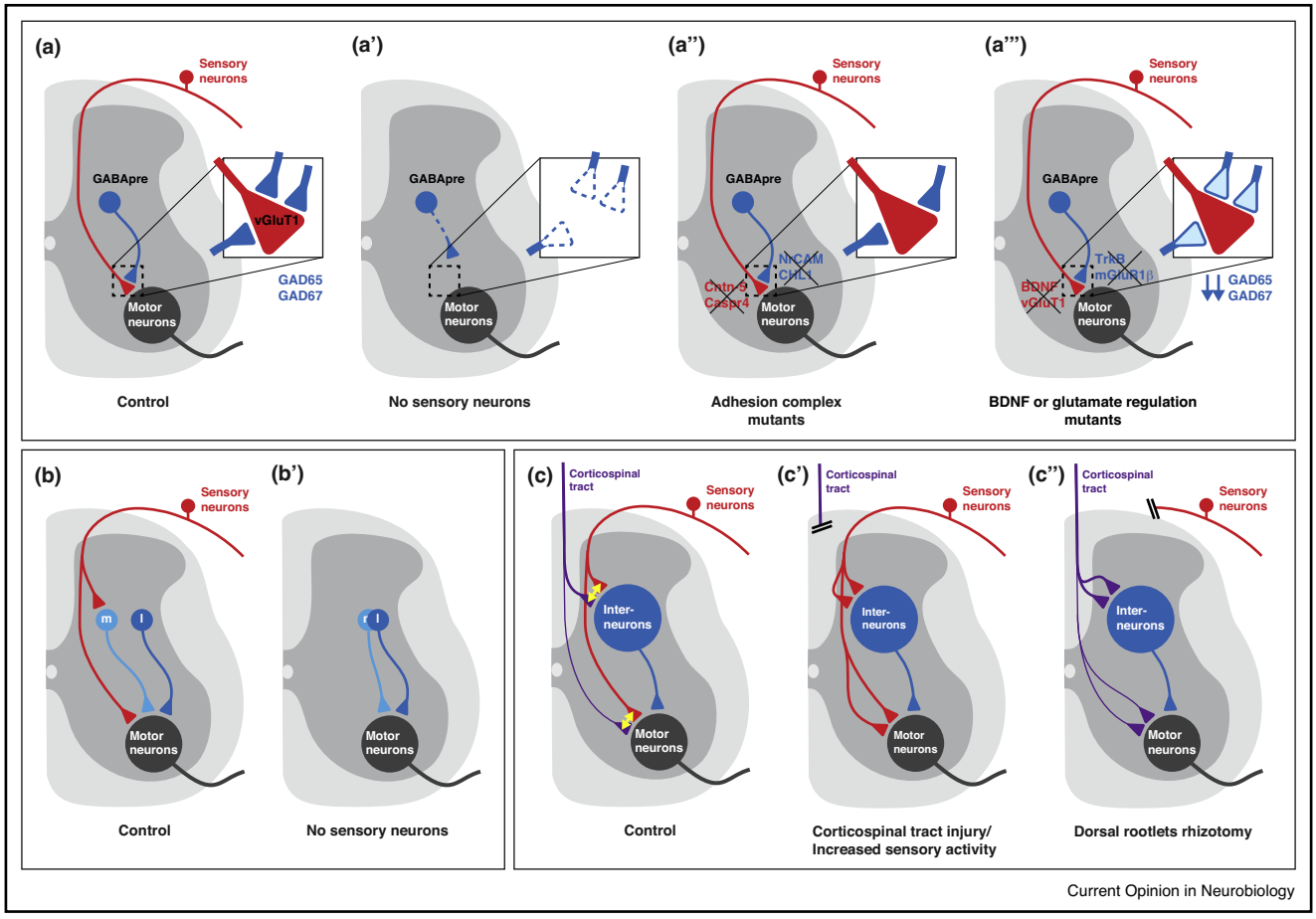
Dynamically, parallel retrograde signals from proprioceptive sensory neurons to local GABApre inhibitory interneurons serve to regulate excitatory signaling across the sensory–motor synapse [38•]. GABApre terminals on proprioceptive sensory afferents express two GABA synthetic enzymes, glutamic acid decarboxylase (GAD)65 and GAD67 [33], and expression levels of these enzymes correlate with electrophysiologically measured GABApre-mediated presynaptic inhibition [38•]. BDNF emanating from proprioceptive sensory neurons controls the synaptic localization of GAD65 [33], while release of sensory terminal-derived glutamate controls the synaptic accumulation of GAD67 [38•] (Figure 2a‴). Reduction of either BDNF or glutamate release from sensory terminals results in reduced GAD65 and GAD67 and decreased presynaptic inhibition. Such a dynamic change may be relevant following spinal cord or brain injury. For example, when descending corticospinal projections are lost following an ischemic cortical lesion in a mouse model of cerebral palsy, GABApre inputs onto sensory neurons show increased levels of the GABA-synthetic enzyme GAD65 [10], suggesting a requirement for increased output from GABApre interneurons, perhaps reflecting increased sensory afferent activity.

Proprioceptor-mediated plasticity and supraspinal interaction following spinal cord injury

The capacity for proprioceptive sensory neuron signals to regulate or organize downstream spinal circuitry is relevant for circuit changes and recovery following spinal cord injury. Proprioceptive sensory neuron feedback has been suggested to help reorganize motor circuits and to be essential for behavioral locomotor recovery following spinal cord injury [2,39–41]. Recent data further supporting this by Takeoka and colleagues [4•] used *Egr3* mutant mice to explore the role of muscle spindle feedback on locomotor recovery after incomplete spinal cord injury. They found that in the absence of muscle spindle feedback, spontaneous locomotor recovery after incomplete spinal cord injury is limited, largely due to an inefficient reorganization of descending projection neurons.

Following spinal cord injury, supraspinal tracts such as the corticospinal tract (CST) are known to interact with proprioceptive afferent inputs in a reciprocal manner (Figure 1a and Figure 2c). The CST has been reported to decrease its connections while afferent fibers spread into deafferented areas in the spinal cord (Figure 2c′) [42]. In a recent report by Jiang and colleagues [43••], proprioceptive sensory afferents were shown to have the capacity to remodel corticospinal axon terminals in the mature spinal cord through direct competition. Electrical stimulation of proprioceptive afferents increased afferent

Figure 2



Changes in circuit connectivity as a result of alterations in sensory or cortical input. **(a–a‴)** GABApre terminals (blue) express the GABA synthetic enzymes GAD65 and GAD67 and form axo-axonic contacts on vGluT1-expressing sensory afferent terminals (red) in the ventral spinal cord [33] (a). In the absence of their normal sensory terminal targets, GABApre interneurons initially project into their usual ventral target zone, but eventually retract [33] (a′). GABApre-sensory terminal specificity is controlled by an adhesion complex, consisting of sensory neuron expression of Cntn-5/Caspr4 and GABApre neuron expression of NrCAM/CHL1 [35••] (a″). The inhibitory efficacy of GABApre terminals, as measured by expression of GAD65 and GAD67, is regulated by BDNF and glutamate from sensory neurons via BDNF receptor TrkB and glutamate receptor mGluR1β in GABApre neurons [33,38•] (a‴). **(b,b′)** Extensor and flexor premotor interneurons segregate into medial (m) and lateral (l) domains respectively. Proprioceptive afferents form connections preferentially with extensor premotor interneurons in the intermediate spinal cord (b). In the absence of sensory input, the position of premotor interneurons is altered such that those usually positioned medially move laterally [30] (b′). **(c–c″)** Proprioceptive sensory fiber input and corticospinal projections (purple) innervate similar domains (yellow double arrows) in the spinal cord (c). Corticospinal injury by unilateral pyramid transection increases sensory fiber input to the spinal cord [42]. Also, increased proprioceptive afferent activity via electrical stimulation results in afferent sprouting and corticospinal axon withdrawal [43••] (c′). Deafferentation of sensory input by dorsal rootlet sectioning increases input of corticospinal fibers predominantly onto interneurons [43••] (c″).

sprouting and eliminated CST connections through axonal withdrawal (Figure 2c′). A complementary experiment demonstrated that by eliminating proprioceptive afferents using a dorsal root transection, more CST connections were formed and a doubling of functional motor output was seen (Figure 2c″). This is in agreement with previous findings from primates, wherein CST sprouting was observed after partial digit deafferentation [44]. Lastly, competitive interactions also seem to determine a balance between proprioceptive and descending vestibular inputs onto spinal motor neurons. When proprioceptor function is genetically degraded, increased vestibular input onto motor neurons typically targeted by proprioceptors is observed; in a complementary fashion, when proprioceptive afferent inputs are increased by genetic means, vestibular inputs are correspondingly reduced [11].

The above studies suggest that — by contrast to the developmental wiring of sensory–motor circuitry, where positional cues or neuronal recognition-based cues may determine specific connectivity in a manner independent of activity — activity patterns play a significant role in larger scale balance of descending supraspinal relative to

sensory afferent inputs. Even so, differences in descending neuronal populations related to their cortical location of origin may yet have a significant organizing role. In particular, recent data has suggested that the origin of the CST projections (Somatosensory (S1) or Motor (M1)) directly influences the level of CST sprouting in the macaque [45•]. Indeed, the extensive sprouting seen from S1 CST after a central spinal injury may have significant implications for recovery of function following spinal cord injury. Do these S1 CST neurons have distinct molecular identities? We currently lack substantial understanding of the molecular mechanisms underpinning axonal sprouting and retraction, and we have much work ahead to fully explore the dynamic and plastic interactions between spinal sensory and motor inputs. These questions deserve closer examination, particularly if one believes that medicines, cells or rehabilitative strategies might be designed to harness this intrinsic capacity for growth in injured tissue.

Conclusions

We are rapidly developing an increasingly detailed understanding of specific neuronal populations, their transcriptional profiles and their connectivity in the spinal cord. The ongoing development of advanced genetic models, allowing control over gene expression in ever-more specific neuronal subpopulations, together with new genetic tools for targeting light- and chemical-based stimulation, silencing and ablation techniques [46–48], means that we are entering an intriguing time for understanding the fine balance required between sensory and motor pathway development and plasticity after injury.

Conflict of interest statement

Nothing declared.

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