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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.

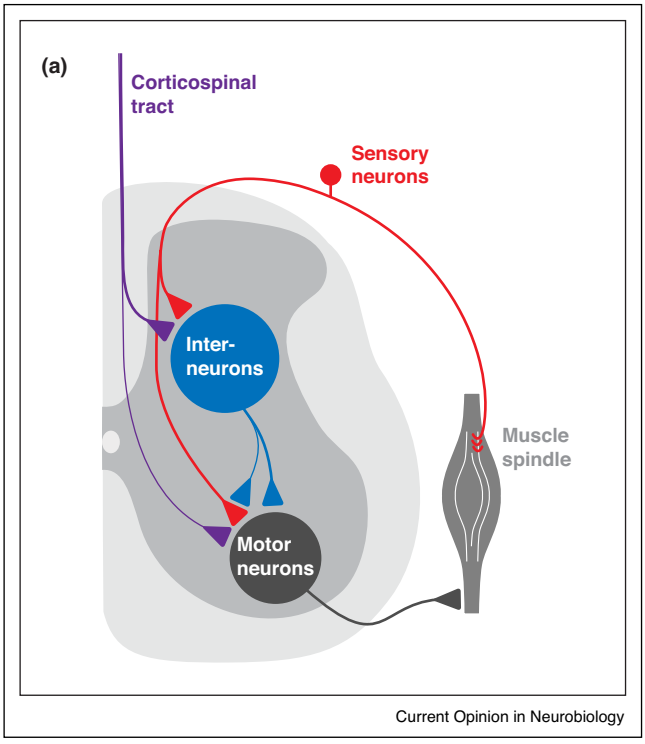
The spinal sensory–motor reflex circuit

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