and we look forward to the innovative approaches that social neuroscience will continue to bring to these problems.

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Sensory-motor control: a long-awaited behavioral correlate of presynaptic inhibition

P Ken Rose & Stephen H Scott

Presynaptic inhibition of cutaneous afferents influences sensory-motor responses in the spinal cord. *In-vivo* recordings in monkeys now show that this process suppresses the transmission of cutaneous signals generated during volitional movement.

A survey of popular neuroscience textbooks suggests that presynaptic inhibition is either rare or a figment of the imagination of physiologists and anatomists of the 1960s. To the contrary, considerable progress has been made in unraveling the cellular and molecular details of this neural process[1,2], but little is known about its role in behavior[3,4]. A report in this issue by Seki *et al.*[5] provides an important functional face to presynaptic inhibition by showing how it modulates cutaneous afferent input to spinal neurons during behavior.

In its most conventional form, presynaptic inhibition involves axo-axonic synapses made by GABAergic interneurons[2]. Although the precise actions of GABA remain open to debate, the end result is clear: GABAergic interneuron activity reduces neurotransmitter release from the postsynaptic axon. As compared to inhibitory synapses directly on the postsynaptic neuron, these axo-axonic synapses selectively reduce input from a particular presynaptic neuron without influencing other inputs to the same postsynaptic neuron.

Seki *et al.*[5] studied the behavioral features of presynaptic inhibition by applying procedures pioneered in the lumbar spinal cord of anesthetized cats to the cervical spinal cord of monkeys trained to execute flexion and extension movements of the wrist. This is no small feat and is arguably one of the most challenging experimental preparations in neuroscience today. The cells that the authors studied receive monosynaptic connections from large-diameter cutaneous afferents. These cells occupy a strategic location (**Fig. 1**); they are the first cells in the spinal cord to relay information from mechanoreceptors to the brain, and they are also the first cells in a circuit that terminates on spinal motor neurons. By regulating the flow of cutaneous signals at this location, descending commands can simultaneously influence motor behavior and the perception of somatosensory stimuli. The key question is under what circumstances do descending commands use presynaptic inhibition via GABAergic interneurons to regulate this flow of information?

The authors[5] used several approaches to show that presynaptic inhibition influences the transmission of cutaneous input to spinal interneurons. First, the effect of stimulating a cutaneous nerve on the activity of spinal neurons was task dependent (**Fig. 1**). When the monkey actively flexed or extended its wrist, cell discharge increased up to 8-fold, but the influence of simultaneous nerve stimulation decreased by 50% from the rest condition. In contrast, comparable passive wrist movements did not affect the influence of nerve stimulation. Because cell discharge was similar during active and passive movements, changes in cutaneous input cannot be simply due to increased refractoriness caused by high-frequency discharge during active movements. Rather, the results suggest that cutaneous input to the spinal neuron was suppressed during volitional movement. This leads to two important questions: what is the source of this suppression and how does it occur?

Seki *et al.*[5] answer the first question by showing that descending commands to the spinal cord are at least partially responsible for suppressing cutaneous input to the spinal cord. The GABAergic interneurons shown in **Figure 1** are known to receive connections from descending systems and primary afferents supplying the skin[2]. Thus, activity in either of these connections could inhibit the responses of first-order interneurons during wrist movement. The transmission of cutaneous signals was not reduced during passive movements, suggesting that descending commands were responsible for presynaptic inhibition during active movement. However, the key observation is that the effect of nerve stimulation was reduced by 20% even before the onset of movement. This pre-movement modulation could not be generated by peripheral afferents and provides definitive proof that descending commands are at least partially responsible for modulating cutaneous input to the spinal cord during movement.

The trickiest part of the study was to demonstrate that modulation of cutaneous input during movement is due to presynaptic rather than postsynaptic inhibition. The finding that cutaneous responses are suppressed at the very time that the interneurons are highly active during extension and flexion suggests that postsynaptic inhibition is not responsible for modulation of cutaneous nerve input. If postsynaptic inhibition is not

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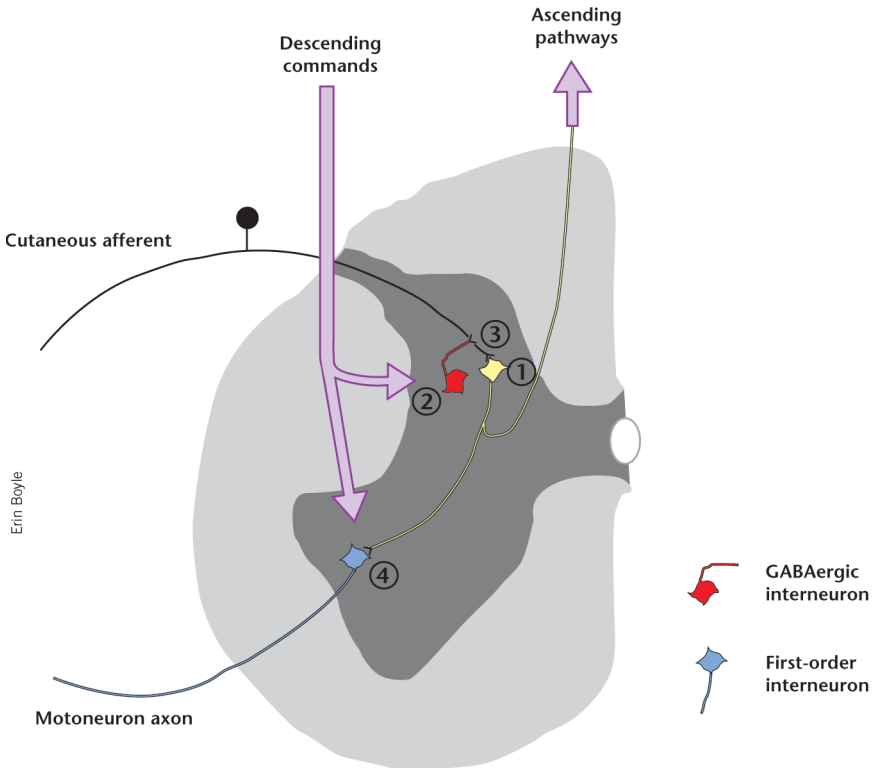

Figure 1 Key neurons involved in the relay of cutaneous input, via first-order interneurons in the spinal cord, to segmental motor systems and higher sensory systems. The numbers (1–4) identify the anatomical loci of critical experiments performed by Seki *et al.*[5] that led to the conclusion that transmission from cutaneous afferents to first-order neurons is dynamically regulated during voluntary motor tasks by presynaptic GABAergic interneurons.

involved, the inhibition must be presynaptic. Easy to say, hard to prove!

The solution to this obstacle lies in a well-described biophysical corollary of presynaptic inhibition. If we assume that the GABA released by the axo-axonic synapse binds to $GABA_A$ receptors, the axon will depolarize due to the opening of chloride channels. (The equilibrium potential for chloride ions in these axons is typically more positive than the resting membrane potential, so the stimulus is depolarizing.) This depolarization, commonly known as primary afferent depolarization or PAD, increases the excitability of the axon. Under these circumstances, a small electrical stimulus in the vicinity of the depolarized axon will be more likely to elicit an antidromic action potential. Despite formidable technical problems, Seki *et al.*[5] provide persuasive evidence that the probability of evoking antidromic potentials increases during the active phase of extension or flexion. Thus, the data fulfill a critical criterion for presynaptic inhibition as the mechanism responsible for modulation of cutaneous signals on first-order interneurons.

What is the advantage of presynaptic inhibition? Postsynaptic input would reduce the influence of cutaneous inputs, but would also modulate all other inputs to the neuron. Presynaptic inhibition allows selective suppression of a specific input to a neuron without influencing other synaptic inputs. Thus, the findings of Seki *et al.*[5] indicate that other inputs to first-order interneurons should be immune to the presynaptic inhibition acting on cutaneous axons. Testing this possibility will require even more demanding experiments. However, such efforts may reap significant rewards. Separate populations of GABAergic interneurons form axo-axonic synapses on secondary muscle spindle afferents and cutaneous afferents[6]. Thus, the results reported by Seki *et al.*[5] set the stage for a much more comprehensive understanding of the selective control of transmission of sensory inputs to spinal interneurons.

Because some dorsal spinal neurons project to the dorsal column nuclei[7], presynaptic inhibition of cutaneous input of spinal neurons likely contributes to the well-documented observation that perceptual thresholds of cutaneous input increase during self-induced movements[8,9]. Further, cutaneous afferents that project directly to the dorsal column nuclei are also influenced by presynaptic inhibition from cortex[10]. Therefore, presynaptic inhibition provides an important mechanism to suppress cutaneous input before it has any opportunity to influence neural processing throughout the central nervous system.

Feedback on the effects of motor performance can only be provided by afferents, so why inhibit this feedback signal? Seki *et al.*[5] observed that intraspinal stimulation at the site of recorded neurons inhibited motoneuron activity to limb muscles used to generate wrist movement (**Fig. 1**). This finding suggests that cutaneous afferent activity during movement would tend to inhibit ongoing motor commands. In theory, descending commands could compensate for this inhibitory cutaneous input, but the strategy appears to be that descending commands presynaptically inhibit cutaneous signals, and thus reduce their influence on the motor system. This may be related to a general strategy of reducing self-generated sensory information, in this case to guide action.

Body movement is generated by muscle activity under the direct control of alpha-motor neurons, the final common output pathway from the spinal cord. It is easy to assume that the focus of descending commands is only to control this output either directly or through spinal interneurons. However, the work by Seki *et al.*[5] highlights the much broader role of descending commands in controlling spinal processing[11]. Corticospinal projections from somatosensory cortex would provide a likely source for presynaptic inhibition of cutaneous input. However, cutaneous responses were reduced well before EMG activity onset, before movement-related activity is normally observed in somatosensory cortex[12], suggesting that the sparse motor cortical projection to dorsal spinal regions may also modulate sensory input at the spinal level[13].

By examining the activity patterns of motor neurons of eye muscles and working systematically backward through the oculomotor brainstem circuit that controls eye movements, Robinson and colleagues unraveled the neural basis of oculomotor control[14]. Similar progress has not been attained in the limb motor system, partially due to the difficulty of recording the activity of neurons in the spinal cord in awake, behaving animals. Although limb motor control is inherently more complex than oculomotor control, the techniques pioneered by Seki and colleagues[5] to record neural activity in the spinal cord of awake, behaving non-human

primates will continue to lead to important advances in understanding spinal function during volitional motor control. Perhaps it is time to acquaint fledgling neuroscientists with the intricacies of presynaptic inhibition and other features of spinal processing. We hope that the editors of introductory texts in neuroscience are listening.

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Doublecortin finds its place

Magdalena Götz

Confusing results from gene deletion experiments have left the importance of doublecortin (DCX) during brain development unclear. A report in this issue establishes a definitive function for DCX and highlights limitations of gene knockout approaches.

Migration is a daunting task. Billions of neurons in the developing brain must leave their place of birth and travel to precise locations to form the circuits of a mature functioning nervous system. Frequent impairment of this complex process is perhaps not surprising, and migration disorders are among the most common causes of developmental neurological defects[1]. One such defect leads to the so-called 'double cortex' (or subcortical band heterotopia), in which neurons accumulate inappropriately within the white matter beneath the normal cortical layers (**Fig. 1**). A mutation in the doublecortin gene (*DCX* in humans)[2] seems to be the cause, but oddly, mice with a targeted deletion of this gene (*Dcx*) have an apparently normal neocortex[3]. It might have been a simple species difference—molecules indispensable for the long distances traveled by migrating neurons in the human cortex may not be needed for the shorter distances in a rodent brain. However, Bai *et al.*[4] report in this issue that DCX protein is indeed important for normal cortical development in rodents and provide a cautionary note for more general gene-knockout approaches.

Targeted deletions used in gene-knockout studies are often difficult to interpret because the insertion of foreign DNA into a genome can have unexpected effects on neighboring genes[5,6], leading to compensation and absence of a phenotype, or possibly to a phenotype unrelated to the gene of interest. Deleting a gene throughout the entire life span of an organism can also give different results than altering the gene during a certain critical time period. Therefore, to examine the function of DCX, which interacts with the cytoskeleton and is expressed specifically in vertebrates by young neurons of the central and peripheral nervous system[7,8], Bai *et al.*[4] took advantage of recent advances in RNA interference (RNAi), a technique that allows acute targeting and disruption of a specific RNA, while leaving genes untouched[9].

The authors delivered a short hairpin RNA to rats *in utero* to specifically interfere with rodent *Dcx* mRNA. Within one day, DCX protein expression was reduced to 20% of the levels found in cells transfected with control RNAs. Despite the rapid decrease, the initial migration of affected neurons appeared normal. However, several days later, most cells were stuck within the intermediate zone, the future white matter (**Fig. 2a**). There they remained, eventually forming the characteristic band of ectopic neurons seen in adult animals. The similarity of this phenotype to the human double cortex condition is striking, in particular given the large number of phenotypes associated with neuronal migration disorders[1]. Admittedly, the RNA interference technique

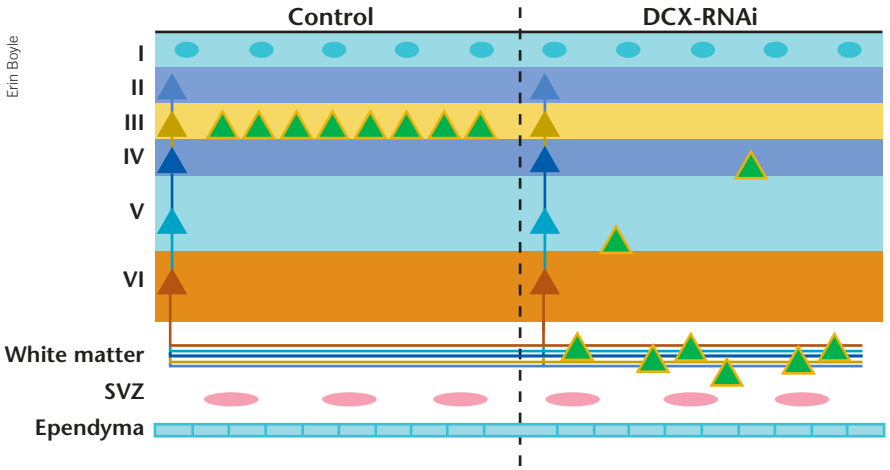

Figure 1 The 'double cortex' mutation. Bai *et al.*[4] used a short hairpin RNA to interfere with doublecortin expression in embryonic rats and found that by adulthood, affected cells accumulated in the white matter, or were scattered among the cortical layers compared to their normal positions in the cortex of control animals.

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