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Urs Lucas Böhm, Claire Wyart

► **To cite this version:**

Urs Lucas Böhm, Claire Wyart. Spinal sensory circuits in motion. *Current Opinion in Neurobiology*, 2016, 41, pp.38-43. 10.1016/j.conb.2016.07.007 . hal-01371943

**HAL Id: hal-01371943**

**<https://hal.sorbonne-universite.fr/hal-01371943v1>**

Submitted on 26 Sep 2016

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## **Title**

Spinal sensory circuits in motion

## **Short title**

Sensory-motor integration in the spinal cord

## **Authors**

Urs Lucas Böhm<sup>1,2,3,4</sup> and Claire Wyart<sup>1,2,3,4,#</sup>

## **Affiliations**

<sup>1</sup>Institut du Cerveau et de la Moelle Épine, <sup>2</sup>UPMC Univ. Paris 06, <sup>3</sup>Inserm UMR S1127, <sup>4</sup>CNRS UMR 7225, Campus Hospitalier Pitié-Salpêtrière, 47 bld de l'Hôpital, 75013 Paris, France

#Correspondence: [claire.wyart@icm-institute.org](mailto:claire.wyart@icm-institute.org)

## **Abstract**

The role of sensory feedback in shaping locomotion has been long debated. Recent advances in genetics and behavior analysis revealed the importance of proprioceptive pathways in spinal circuits. The mechanisms underlying peripheral mechanosensation enabled to unravel the networks that feedback to spinal circuits in order to modulate locomotion. Sensory inputs to the vertebrate spinal cord were long thought to originate from the periphery. Recent studies challenge this view: GABAergic sensory neurons located within the spinal cord have been shown to relay mechanical and chemical information from the cerebrospinal fluid to motor circuits. Innovative approaches combining genetics, quantitative analysis of behavior and optogenetics now allow probing the contribution of these sensory feedback pathways to locomotion and recovery following spinal cord injury.

## **Highlights**

- Main channels underlying mechanosensory responses have been identified in dorsal root ganglia
- GABAergic sensory neurons were recently identified as chemo- and mechanoreceptors within the vertebrate spinal cord
- Proprioceptive pathways shaping locomotion appear distributed and multimodal

## **Keywords**

proprioception, locomotion, dorsal root ganglia, cerebrospinal fluid-contacting neurons

## **Introduction**

Locomotion is generated by the oscillatory activity of motor neurons driven by groups of local interneurons in the spinal cord [1]. These premotor networks do not rely on sensory feedback to generate the basic locomotor rhythm as the isolated spinal cord can oscillate without any peripheral input in many species [2]. Nonetheless, in moving animals, there is evidence that sensory feedback provides strong modulation of locomotion and is critical for its proper function. In particular, excitation from peripheral afferents can initiate locomotion [3] as well as reset the oscillatory cycle [4]. Yet, the technical challenges that arise from selectively targeting and manipulating sensory pathways during ongoing locomotion make it difficult to probe the contribution of sensory feedback to natural locomotion. The recent discoveries of new channels and selective markers of sensory cells made it possible to map new pathways and investigate their functions. Here we discuss the latest work on the mechanisms and relevance of peripheral mechanosensory feedback for shaping motor output. In addition, we introduce the recent discovery that cerebrospinal fluid-contacting neurons (CSF-cNs) constitute a new class of GABAergic sensory neurons located within the spinal cord.

## **Peripheral sensory neurons**

In the peripheral nervous system, dorsal root ganglia (DRG) are the primary entry point for somatic sensation in vertebrates. Temperature, pain, itch and touch but also proprioceptive signals like muscle contraction and load are relayed by DRG excitatory afferents to spinal circuits where they are processed (Fig. 1). These diverse signals are carried by different subclasses of DRG types. The sensory diversity of different DRG neurons primarily results from the differential expression of channels and receptors that mediate the different stimuli [5]. While peripheral sensory neurons mediate many different types of sensory inputs such as temperature, pain, itch and chemical irritants, the most relevant for locomotion is mechanical feedback from muscle and skin.

DRG subtypes have mainly been characterized based on their innervation pattern, electrophysiological properties and responsiveness [5]. The identification of genetic markers to label some of the subclasses such as parvalbumin for proprioceptive DRGs [6,7] has been key

to understand the properties and functions of proprioceptive neurons. Recent efforts using single cell RNA sequencing made it possible to divide neuronal subtypes based on their gene expression profiles and provide a more comprehensive and unbiased classification. However, the exact number of subtypes and their functional characteristics remains to be established [8,9].

A recent body of work identified Piezo2 as the main channel responsible for proprioception and touch response. The initial characterization of Piezo2 revealed expression in mouse DRG neurons [10]. Soon after, the channel was determined to be involved in vertebrate touch response in vivo in zebrafish. Knocking down *piezo2b* in zebrafish larvae leads to a loss of light touch but not nociceptive mechanosensation due to a loss of function in touch sensitive neurons [11]. Several studies performed since by the Patapoutian group established Piezo2 as the main channel to transduce touch response in mammals as well. Merkel cells, which are important for light touch sensation in mammals [12,13], rely on Piezo2 to be touch sensitive [14]. In addition to Merkel cells, Piezo2 is also necessary in A $\beta$  fibers which are relaying the light touch response from Merkel cells to the spinal cord. This dual role is likely the reason why only mice lacking Piezo2 in both Merkel cells and A $\beta$  fibers show strong deficits in their touch response [15]. Functionally relevant Piezo2 in Merkel cells and A $\beta$  fibers suggests a two-receptor site model for light touch where Piezo2 in Merkel cells is responsible for the static phase and Piezo2 in A $\beta$  fibers is responsible for the dynamic phase of the response [15]. Interestingly, similar to the observations made in zebrafish, mechanosensation in nociceptive C-fibers remained unchanged in the Piezo2 conditional knockout mice (Piezo2<sup>CKO</sup>), indicating that another yet unidentified channel is responsible for noxious mechanical stimuli.

In addition to mediating light touch response, Piezo2 is also the main mechanosensitive channel underlying proprioception, both in muscle spindles and Golgi tendon organs (GTO) [16]. In response to mechanical stimulation, parvalbumin-positive (PV<sup>+</sup>) proprioceptive neurons [6,7] lose their predominant rapidly adapting mechanical response in Piezo2<sup>CKO</sup> while the less common intermediately adapting currents remained [16]. Consequently PV<sup>+</sup> Piezo2<sup>CKO</sup> DRGs are unresponsive to muscle stretch and Piezo2<sup>CKO</sup> mice have marked limb coordination deficits [16]. It should be mentioned that some of the rare touch sensitive neurons were not explicitly tested in Piezo2<sup>CKO</sup> mice, leaving the possibility of Piezo2 independent mechanosensitive neurons. Also, in neither of these studies, eliminating Piezo2 abolished all mechanically-activated currents [15,17]. These observations suggest that there are probably additional

channels mediating mechanosensation. Furthermore, Piezo2 likely acts in concert with other molecular partners to tune its response in different cell types [18]. Nonetheless, during the last few years Piezo2 emerged as the main channel underlying mechanosensation in DRG neurons.

To what extent proprioceptive feedback contributes to locomotion has long been a debate in the spinal cord field [19]. Recently Akay *et al.* addressed this question in a mutant mouse model that lacks muscle spindle [20]. Mice lacking functional muscle spindle showed specific impairments in the timing of ankle flexor activity. Interestingly, this impairment was much more severe during swimming where proprioceptive feedback from GTO plays less of a role as the gravitational load is reduced. These results indicate that muscle spindles and GTO provide both distinct and redundant feedback when regulating muscle activity.

Proprioceptive feedback from muscle spindle and GTO is not the only source of sensory input shaping limb movement. Recent work also highlighted the importance of cutaneous feedback in grasping and locomotion [21,22]. Retinoid-related orphan receptor (ROR) alpha positive interneurons were shown to receive inputs from both light touch responsive afferents and corticospinal pathways, likely integrating touch sensation and cortical commands [22]. Ablation of ROR alpha reduced the light touch response, while overall motor behavior stayed unchanged. However, corrective paw placement notably deteriorated, indicating the importance of cutaneous feedback for corrective movements. Similarly Bui *et al.* [21] showed another interneuron type, dl3, to contribute to grasping. These interneurons receive low threshold mechanosensitive inputs and their ablation reduces grasp strength while leaving general motor function intact. This and previous work [23,24] highlights the diversity of sensory interneurons and further studies will likely reveal the function and circuitry of additional classes.

In terms of network dynamics, peripheral proprioceptive feedback originating from muscle activation provides glutamatergic input to sensory interneurons, which can indirectly lead to muscle activation. Such excitatory feedback loops are intrinsically prone to oscillation [25]. Presynaptic inhibition of sensory afferents has been shown to function as a gain control system to prevent these oscillations to occur [26]. Altogether this recent body of work adds to the evidence that proprioceptive feedback strongly shapes locomotion [20,26,27].

### **Intraspinal GABAergic sensory neurons**

Since the description of spinal reflexes by Sir Charles Sherrington, mechanosensory feedback was classically thought to originate solely from peripheral sensory afferents projecting to the dorsal spinal cord. Recently, cerebrospinal-fluid contacting neurons (CSF-cNs) have been identified as intraspinal GABAergic sensory neurons in the ventral spinal cord. Even though initially described nearly a century ago in over vertebrate 200 species [28,29], the function of CSF-cNs is still poorly understood. Searching for the sour taste receptor in the mouse tongue, Huang *et al.* first described the expression of the TRP channel PKD2L1 in spinal CSF-cNs [30]. Recent detailed molecular characterization established CSF-cNs as coexpressing GABA and PKD2L1 in the spinal cord of zebrafish, mouse and monkey [31,32]. CSF-cNs originate from two distinct progenitor domains in both mouse and zebrafish, suggesting functionally different subpopulations [33–36].

Based on the observation that PKD2L1 is specific to pH sensitive taste cells in the mouse tongue [37], Huang *et al.* showed increased firing rates when subjecting PKD2L1 expressing CSF-cNs to low pH *in vitro* [30]. More detailed pharmacological analysis in the mouse dorso-vagal complex and the lamprey spinal cord led to the conclusion that acidification actually inhibits PKD2L1 and likely activates ASIC channels [38,39]. This is in accordance with later studies showing that CSF-cNs do not exhibit a proton current after acidification and activation by low pH is most likely due to ASICs [40]. PKD2L1 is instead activated by alkalization as well as hypo-osmotic shocks [38]. Recent work showed that PKD2L1 likely acts as a spike generator in CSF-cNs and that there is a bimodal response of CSF-cNs [41]. This study and following work in lamprey [42], suggests that firing is increased by alkalization through the activation of PKD2L1 and by acidification through the activation of ASIC channels.

The initial *in vitro* studies showed that CSF-cNs are sensitive to changes of pH and osmolarity. Recent work identified mechanosensitive function of CSF-cNs *in vitro* [39] and *in vivo* [43]. In the lamprey spinal cord, CSF-cNs show mechanically-evoked firing [39], suggesting these cells may respond to CSF flow. However, from the *in vitro* studies in mouse and lamprey the relevance of this sensory response for behavior remains unclear. In zebrafish larvae, we showed that CSF-cNs are not recruited during fictive locomotion when muscle contraction does not occur [43]. In contrast, CSF-cNs respond to passive spinal cord bending as well as active muscle contraction. As CSF-cN activation is selective to the side of contraction, the mechanisms by which CSF flow activate CSF-cNs asymmetrically are unclear. Optogenetic

stimulation of CSF-cNs in zebrafish indicated that these cells can modulate the occurrence and duration of locomotion by connecting to ventro-lateral premotor glutamatergic interneurons [44,45]. Furthermore, impairing sensory function or vesicular release in CSF-cNs resulted in a decreased tail-beat frequency [43] in freely-swimming zebrafish larvae, indicating that this mechanosensory feedback shapes active locomotion. In mammals, the connectivity and physiological relevance of intraspinal CSF-cNs remain to be investigated.

### **Conclusion and perspectives**

By combining genetics, viral tracing and calcium imaging, the work discussed above reveals how genetically identified sensory pathways feedback onto microcircuits in the spinal cord and shape motor output. Segregated sensory feedback from DRGs is integrated by different subtypes of interneurons, which form an overlapping network to generate the segregated output underlying muscle activation [46,47].

While the different types of sensory afferents reaching the spinal cord have been known for a long time, the investigation of intraspinal GABAergic sensory cells and their corresponding sensory stimuli will likely add complexity to the picture. Changes in pH could be an important signal for spinal cord circuits but to what extent pH varies in the CSF has not yet been extensively measured under physiological conditions. Mechanical feedback from spinal bending can provide important information during locomotion in aquatic animals such as zebrafish and lamprey. However, to what extent spinal bending happens in mouse spinal cord and whether activation of CSF-cNs plays a role in quadruped locomotion remains to be investigated.

Over the recent years, proprioceptive feedback emerged as a focus of research in the field of spinal cord injury. Significant efforts are put into promoting axonal regeneration across the lesion to regain lost drive to spinal circuits. Yet, it has long been recognized that simple training can improve locomotor deficits after spinal cord lesion [48]. This observation has led to the use of epidural stimulation to activate sensory motor reflex circuits to provide the necessary excitation to initiate locomotion in cats and rats [49,50]. These initial findings were followed by epidural stimulations combined with locomotor training in patients with spinal cord injury [51–53]. Improvements to this method were recently achieved in rats by using epidural stimulation in a closed loop system where the stimulation protocol was adapted to the leg position in real time [54] and optimized with computational modeling [55].

As promising as these results are, epidural stimulation remains a relatively crude method and the underlying mechanisms are poorly understood. Continuing efforts in understanding the role of sensory feedback and signal processing in the spinal cord will not only advance our basic understanding of spinal microcircuit computation but should have very direct effects in the treatment of human spinal cord injury in the future.

### Acknowledgements

U.L.B received support from the École des Neurosciences de Paris Ile-de-France (ENP) and the Fondation pour la Recherche Médicale (FRM). This work received support from the Fondation Bettencourt-Schueller, the City of Paris Emergence program, the Atip/Avenir program from CNRS and Inserm, Marie Curie Actions (International Reintegration Grant, IRG #227200), the ERC Starting Grant Optoloco (#311673).

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## Figure legends

### Figure 1

**Sensory feedback circuits in the spinal cord.** Peripheral sensory information is carried by dorsal root ganglion (DRG) neurons and provides excitatory input either directly to motor neurons (MNs) or to the spinal interneuron (IN) network. External inputs include the sensation of temperature, pain, itch and chemical irritants as well as mechanical touch. Internal peripheral sensation comes from mechansosensitive inputs from muscle spindles and Golgi tendon organ (GTO). Inside the spinal cord, inhibitory feedback from cerebrospinal fluid-contacting neurons (CSF-cNs) carry information about the bending of the spinal cord as well as pH and osmolarity of the cerebrospinal fluid (CSF). The IN network integrates peripheral and intraspinal sensory inputs as well as supras pinal commands and provides patterned inhibition and excitation that ultimately lead to rhythmic MN activation.