Insight into B5-I spinal interneurons and their role in the inhibition of itch and pain

Michael C. Chiang[1,2,3]

Junichi Hachisuka[1,2]

Andrew J. Todd[4],*

Sarah E. Ross [1, 2, 5,*]

Affiliations

1. Department of Neurobiology

2. Pittsburgh Center for Pain Research, University of Pittsburgh

3. Medical Scientist Training Program, University of Pittsburgh

4. Institute of Neuroscience and Psychology, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow G12 8QQ, UK

5. Department of Anesthesiology, University of Pittsburgh, 200 Lothrop Street, Pittsburgh, PA 15213, USA

*Correspondence: andrew.todd@glasgow.ac.uk (A.J.T.), saross@pitt.edu (S.E.R.)

1 Introduction

The last few years have seen major advances in our understanding of spinal microcircuits that integrate somatosensory input, resulting in part from availability of mice that allow genetically defined neuronal populations to be marked or manipulated. However, a genetically defined population does not necessarily correspond to a functional population, and defining functional populations remains a major challenge. Here we begin to address this by focusing on a group of inhibitory interneurons in superficial dorsal horn. These have been variously identified as PrP-GFP,[4,9] B5-I,[6,7] or Dyn-cre[2] neurons. However, it now appears that they represent largely overlapping populations stemming from a common lineage. Here, we summarize what is known about these neurons, and consider their roles in the inhibition of itch and pain.

2 Neurochemistry and Development

The transcription factor Bhlhb5 is required for development of ~30% the inhibitory neurons in the superficial laminae, termed B5-I neurons.[7] These cells initially express galanin and dynorphin, but some subsequently express nNOS, with many of these switching off the neuropeptides.[6] Cre expression in the Dyn-cre mouse[2] therefore captures both Gal/Dyn and nNOS populations. It has been shown that around half the B5-I cells express GFP in the PrP-GFP mouse[5] (shown in green in the pie chart). The B5-I neurons are distinct from inhibitory interneurons that express neuropeptide Y, parvalbumin, or calretinin.[6]

3. Anatomy and physiology

B5-I cells are irregular in shape with axons and dendrites generally extending furthest in the rostral-caudal axis.[3,4] The 2 subsets exhibit anatomical differences, because nNOS cells reside more ventrally and have larger axonal and dendritic arbors. Like most superficial dorsal horn inhibitory neurons, they show tonic firing upon current injection.[4,6]

4. Spinal microcircuitry

Several types of primary afferent, including those that express TRPM8, MrgD, TRPV1/TRPA1, as well as low threshold myelinated afferents innervate B5-I neurons, and they are inhibited by several neuromodulators.[5] Paired recording studies suggest that B5-I neurons inhibit vertical cells and have reciprocal inhibitory connections with islet cells.[9] In addition, the nNOS subset strongly innervates 2 types of lamina I projection neuron: giant cells and some of those that express the neurokinin-1 receptor, whereas other neurokinin-1 receptor projection neurons receive weak innervation.[3]

5. Possible functions

Mice lacking B5-I neurons show spontaneous scratching and menthol no longer reduces itch, suggesting that B5-I neurons inhibit itch and mediate its suppression by counterstimuli.[6,7] Different pruritogens act through distinct primary afferent and spinal pathways, but the degree to which these are itch-specific remains unclear, as does the logic of spinal projection neurons, which can receive both pruritic and noxious input.[1] Athough the cellular basis for inhibition of itch by B5-I neurons has not yet been determined, GRPR-expressing interneurons, which are essential for some forms of itch,[8] are a possible candidate. Inhibition of itch is not the only function of B5-I neurons, because their ablation in the adult results in allodynia, highlighting a role in gating mechanical pain.[2] Because B5-I neurons comprise 2 neurochemically distinct populations, it will be of interest to determine the role of each in inhibition of pain and itch.

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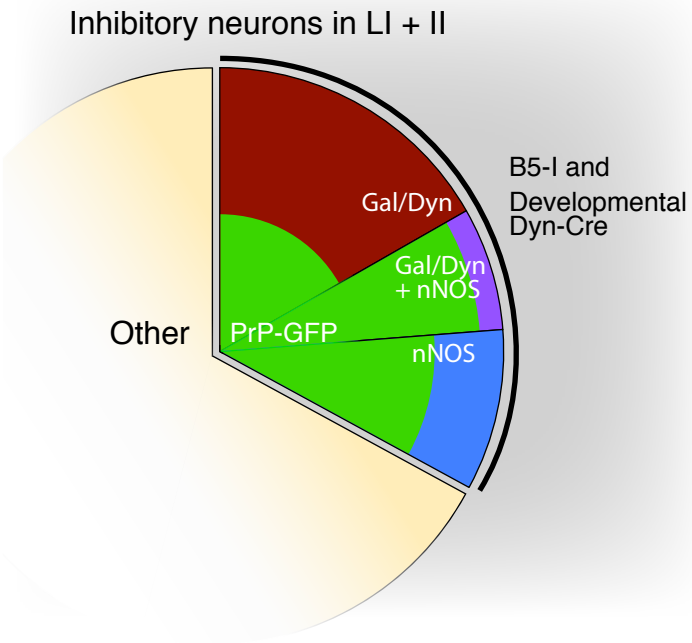
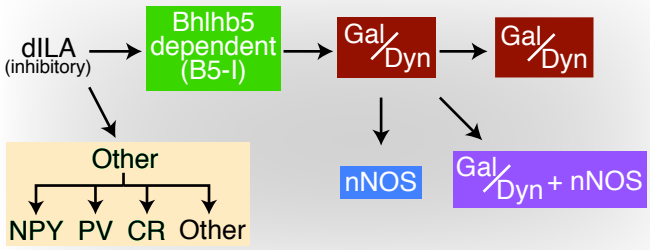
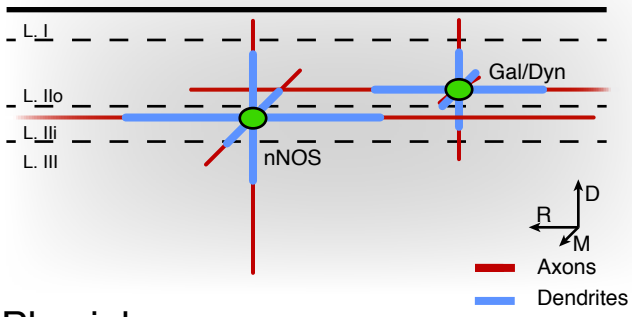
Neurochemical classification



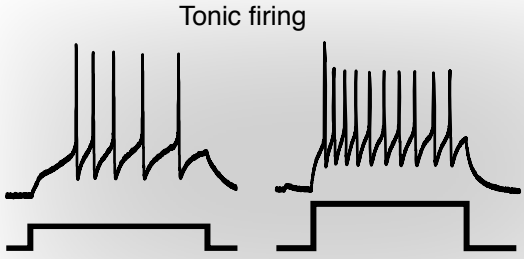
Development



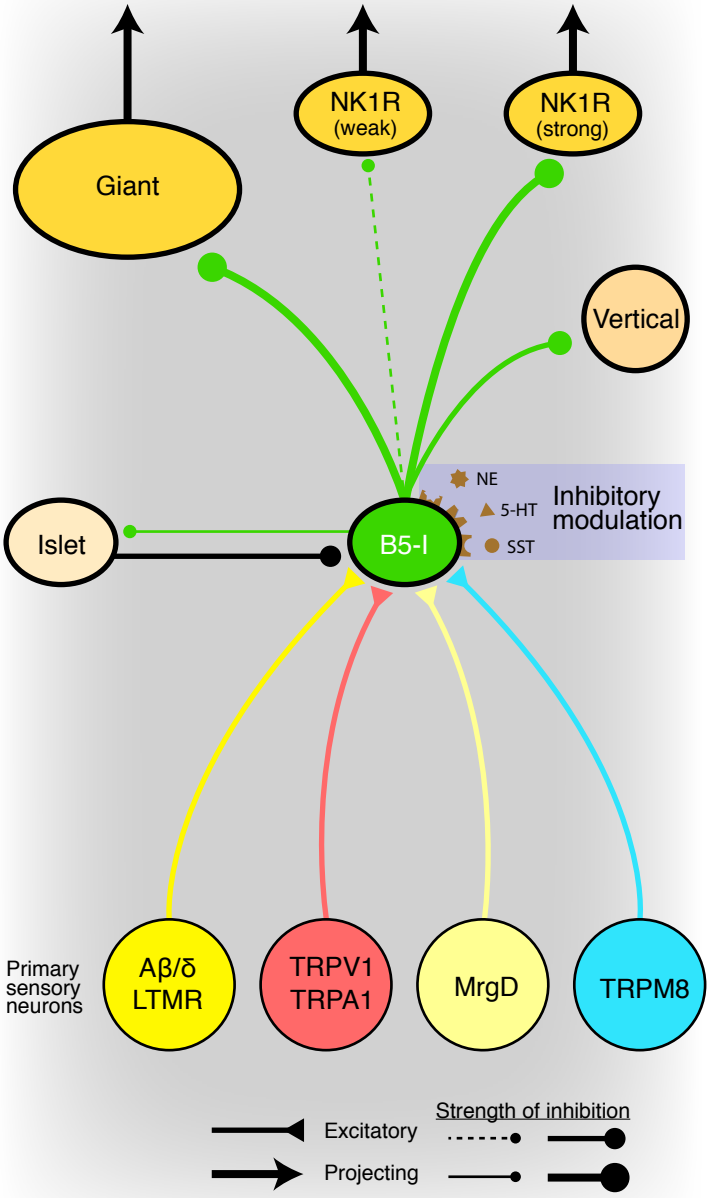
Anatomy



Physiology



Spinal microcircuitry



Possible functions