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Brain stimulation patterns emulating endogenous thalamocortical input to parvalbumin-expressing interneurons reduce nociception in mice

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ABSTRACT

Background: The bursting pattern of thalamocortical (TC) pathway dampens nociception. Whether brain stimulation mimicking endogenous patterns can engage similar sensory gating processes in the cortex and reduce nociceptive behaviors remains uninvestigated.
Objective: We investigated the role of cortical parvalbumin expressing (PV) interneurons within the TC circuit in gating nociception and their selective response to TC burst patterns. We then tested if transcranial magnetic stimulation (TMS) patterned on endogenous nociceptive TC bursting modulate nociceptive behaviors.
Methods: The switching of TC neurons between tonic (single spike) and burst (high frequency spikes) firing modes may be a critical component in modulating nociceptive signals. Deep brain electrical stimulation of TC neurons and immunohistochemistry were used to examine the differential influence of each firing mode on cortical PV interneuron activity. Optogenetic stimulation of cortical PV interneurons assessed a direct role in nociceptive modulation. A new TMS protocol mimicking thalamic burst firing patterns, contrasted with conventional continuous and intermittent theta burst protocols, tested if TMS patterned on endogenous TC activity reduces nociceptive behaviors in mice.
Results: Immunohistochemical evidence confirmed that burst, but not tonic, deep brain stimulation of TC neurons increased the activity of PV interneurons in the cortex. Both optogenetic activation of PV interneurons and TMS protocol mimicking thalamic burst reduced nociceptive behaviors.
Conclusions: Our findings suggest that burst firing of TC neurons recruits PV interneurons in the cortex to reduce nociceptive behaviors and that neuromodulation mimicking thalamic burst firing may be useful for modulating nociception.

1. Introduction

The investigation of electrical brain stimulation to control central pain is long-standing and often empirical [1–3]. Generally, the mechanism of pain relief is based on interfering with neuronal circuits responsible for pain processing or perception [4,5] with synthetic brain stimulation patterns intended to override

Abbreviations: cTBS, continuous theta-burst-stimulation; iTBS, intermittent theta-burst-stimulation; PV, parvalbumin expressing; PNNs, Peri-neuronal nets; rTMS, repetitive transcranial magnetic stimulation; S1, primary somatosensory cortex; SOM, somatostatin; TC, thalamocortical; TMS, transcranial magnetic stimulation; TRN, thalamic reticular nucleus; VPL, ventroposterolateral.

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endogenous activity. Could novel brain stimulation strategies that correct circuit pathology with patterns emulating endogenous activity enhance therapeutic efficacy? Such an approach derives from a precise hypothesis on disease etiology to identify 1) firing patterns correlated with suppression of pain and, 2) the cellular targets of that patterned activity that mediate pain processing.

Nociception serves vital protective functions against bodily injury. As part of the TC circuit, the sensory thalamus plays a critical role in gating transmission of peripheral nociceptive information to the somatosensory cortex, where representation and perception of pain is assumed to occur [6–10]. This sensory gating function of the thalamus has been suggested to be mediated by the ability of individual TC neurons to fire in tonic and burst firing modes via interconnections with the cortex and thalamic reticular nucleus (TRN) [11–14]. Specifically, the γ-aminobutyric acid (GABAergic) projection from TRN to TC neurons de-inactivates T-type calcium channels, inducing strong inhibition that, in turn, leads to low threshold calcium spike "rebound" bursts [15]. Subsequent *in-vivo* studies suggests that the tonic firing of TC neurons correlates with nociceptive responses [16–18] while the burst firing of TC neurons correlates with suppression of pain responses [16,19–21].

Although studies suggested differential roles for TC tonic and burst firing in pain processing, how the dual firing modes of TC neurons contribute to differential pain processing in the somatosensory cortex, which should be a crucial part of an ascending pain control mechanism, is currently unknown. The sensory cortex is a highly organized structure with layer specific input/outputs and the sensory TC neurons, which directly receive peripheral sensory inputs, primarily synapse onto layer 4 of the cortex [22]. Of the two firing modes of TC neurons, burst firing, compared to tonic firing, has been shown to have greater potency to activate inhibitory interneurons in the cortex [23,24].

Among the interneuron types expressed in the cortex, PV expressing inhibitory interneurons are especially suited to exert feed-forward inhibition to excitatory pyramidal neurons. Of the two main type of GABAergic interneurons expressed in layer 4 of the cortex, PV interneurons are more abundant (constituting 60% of GABAergic interneurons) than somatostatin (SOM) expressing interneurons (constituting 20–30% of GABAergic interneurons) [25,26]. PV interneurons are fast-spiking and synapse onto proximal dendrites or somatic regions of pyramidal neurons [27,28]. Cortical PV interneurons are directly innervated by thalamic projections [29,30] while SOM interneurons only have weak connections with thalamic inputs [31,32]. Together, these properties make PV interneurons ideal for implementing feed-forward inhibition [29] that can be driven by high frequency TC burst firing.

Activity of PV interneurons is reduced or disrupted in the somatosensory cortex of mice with neuropathic pain [33,34] and SOM activation can alleviate neuropathic pain associated allodynia [34]. However, the role of cortical PV interneurons within the TC circuit in gating nociception of non-neuropathic conditions remains uninvestigated. In particular, a circuit level mechanism of how the dynamics between TC tonic and burst dual firings modulate nociception at the cortical level is unknown. The present study examined whether burst, but not tonic, firing mode of TC neurons engages cortical PV interneurons to exert inhibitory modulation of pyramidal neurons in the primary (S1) somatosensory cortex and whether activation of cortical PV interneurons could behaviorally suppress nociceptive responses in mice.

Using electrical stimulation and immunohistochemical methods we investigated whether burst stimulation of TC neurons could significantly activate PV interneurons in the sensory cortex compared to tonic stimulation or sham control conditions. Next we tested whether selective activation or inactivation of cortical PV interneurons with optogenetic or patterned transcranial magnetic stimulations could modulate nociceptive behaviors in mice.

2. Materials and methods

2.1. Animals

Optogenetic experiments employed PV-Cre male mice (8–16 weeks; Jackson Laboratories). All other studies used first generation 129/SvJae x C57BL/6 J hybrid mice (male, 8–12 weeks). Mice were group-housed and maintained at 12 h light-dark cycle (lights on at 8 a.m.) with free access to food and water. Following a surgery, animals were singly-housed. All experiments were conducted in compliance with the Animal Care and Use Committee (Approval number: AP, 2015025). Mice were randomly assigned to experimental groups and based on histology animals with misplaced electrodes or viral injections were excluded from analyses.

2.2. Surgical procedures

All surgical procedures were performed under anesthesia (30 mg/kg Zoletil, IP) and using a stereotaxic instrument (Kopf Instruments) with brain coordinates based on the Paxinos and Franklin (2001) mouse brain atlas [35]. Animals were given Ketoprofen (5 mg/kg SC) right after surgery and daily for a week for post-operative recovery.

For electrical stimulation of the ventroposterolateral (VPL) thalamus, two bipolar stimulating electrodes (0.6 mm apart; Teflon-coated stainless steel, 0.003″ bare 0.055″ coated, A-M Systems) were implanted (AP: −1.34 mm, ML: −1.85 mm, DV: −3.2 mm). The electrodes were secured onto the skull with stainless steel screws and dental cement.

For optogenetic experiments, AAV-DIO-ChR2−eYFP and AAV-DIO−eYFP purchased from the University of North Carolina Vector Core were injected into the primary somatosensory cortex corresponding to the hind limb region (S1HL; AP: −0.5 mm, ML: −1.64 mm, DV: −0.5 mm). The virus injections were made slightly lateral to the optic fiber implantation site, avoiding major arteries. Using glass pipettes (tip size 20–38 μm), a total of 200 nl was injected over 10 min using a Nanoliter Injector (World Precision Instruments). After a week of recovery, an optic fiber (GIF 625; Thor Labs) was chronically implanted into the S1HL (AP: −0.5 mm, ML: −1.6 mm, DV: −0.4 mm).

For TMS, a plastic baseplate was permanently affixed to the skull with Loctite 454 and dental cement. Later, a solenoid coil was connected to the baseplate for magnetic stimulation centering on the S1HL (AP: −0.5 mm, ML: −1.6 mm).

2.3. Electrical stimulation

Mice were habituated to tethering, mockup IP injection (using a syringe without needle), and the experimental apparatus for 30 min daily for a week. On the experiment day, mice were anesthetized with urethane (1.5 g/kg IP), connected to a stimulation cable, and after 10 min received either tonic or burst stimulation for 5 min. Mice in the sham control group were attached to the stimulation cable for the same duration without receiving stimulations. All stimulating pulses were biphasic square pulses with 100 μA current amplitude and 100 μs duration. Burst stimulation consisted of 3 ms intervals of 5 burst pulses with 600 ms interval between the 5 burst pulses, while tonic stimulation was 600 pulses at 2 Hz.

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