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Vagus nerve stimulation suppresses acute noxious activation of trigeminocervical neurons in animal models of primary headache

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ABSTRACT

Vagus nerve stimulation (VNS) has been reported to be effective in the abortive treatment of both migraine and cluster headache. Using validated animal models of acute dural-intracranial (migraine-like) and trigeminal-autonomic (cluster-like) head pain we tested whether VNS suppresses ongoing and nociceptive-evoked firing of trigeminocervical neurons to explain its abortive effects in migraine and cluster headache. Unilateral VNS was applied invasively via hook electrodes placed on the vagus nerve. A single dose of ipsilateral or contralateral VNS, to trigeminal recording and dural-stimulating side, suppressed ongoing spontaneous and noxious dural-evoked trigeminocervical neuronal firing. This effect was dose-dependent, with two doses of ipsilateral VNS prolonging suppression of ongoing spontaneous firing (maximally by ~60%) for up to three hours, and dural-evoked (Aδ-fiber; by ~22%, C-fiber: by ~55%) responses for at least two hours. Statistically, there was no difference between ipsilateral and contralateral groups. Two doses of VNS also suppressed superior salivatory nucleus-evoked trigeminocervical neuronal responses (maximally by ~22%) for 2.5 h, to model nociceptive activation of the trigeminal-autonomic pathway. VNS had no effect on normal somatosensory cutaneous facial responses throughout. These studies provide a mechanistic rationale for the observed benefits of VNS in the abortive treatment of migraine and cluster headache. In addition, they further validate these preclinical models as suitable approaches to optimize therapeutic efficacy, and provide an opportunity to hypothesize and dissect the neurobiological mechanisms of VNS in the treatment of primary headaches.

1. Introduction

Migraine and cluster headache are two of the most painful and disabling neurological conditions that patients can suffer, affecting a significant proportion of the global population (Lipton et al., 2007; Murray et al., 2012). Some of the best abortive treatment approaches for these headaches include the triptan, 5-$HT_{1B/1D}$ receptor agonist class of drugs, or over-the-counter analgesics. However, in migraine, at best, triptans provide pain-free rates at 2 h of 27–30%, with sustained pain-free (no headache reoccurrence 2–24 h post original dose) rates of 20% (Ferrari et al., 2001). In cluster headache, sumatriptan produces pain-free rates of 46% after 15 min, but its effective use is restricted to mainly parenteral routes of administration (Anon, 1991). Triptans are also contraindicated in many patients with severe vascular disorders. Thus, it is clear that current therapies for the abortive treatment of these headache disorders are inadequate for many patients. Therefore, new therapies are urgently needed to help alleviate this burden, particularly for non-responder patients of these existing treatments.

Vagus nerve stimulation (VNS) is currently approved for the treatment of seizures and depression in the US. In recent years VNS has also been investigated as a novel treatment modality for migraine and cluster headache. In studies of patients with implanted VNS devices to treat epilepsy and depression, many also reported significant improvements in their migraines and cluster headaches (Cecchini et al., 2009; Mauskop, 2005; Sadler et al., 2002). Since then several open-label and controlled trials provide support for the use of non-invasive VNS (nVNS) in the abortive treatment of both migraine (Barbanti et al., 2015; Goadsby et al., 2014; Kinfe et al., 2015) and cluster headache (Gaul et al., 2016; Nesbitt et al., 2015; Silberstein et al., 2016b). However, it is still not known what effects VNS has in rodent models of acute trigeminal pain related to migraine and cluster headache. Furthermore, the mechanism of action of VNS in successfully treating these primary headaches is largely unknown.

Abbreviations: s/s, action potential spikes/sweep; DRN, dorsal raphe nucleus; iVNS, invasive vagus nerve stimulation; LC, locus coeruleus; nVNS, non-invasive vagus nerve stimulation; NTS, nucleus tractis solitarius; PVN, paraventricular hypothalamic nucleus; TCC, trigeminocervical complex; SOC, standard of care; SuS, superior salivatory nucleus; VNS, vagus nerve stimulation.

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Migraine headache is believed to be mediated by activation of trigeminal primary afferents that innervate the nociceptive-specific dural vasculature, and their central projections to the medullary dorsal horn and cervical extension (Bernstein and Burstein, 2012; Goadsby et al., 2009). Noxious stimulation of dural vascular structures in conscious humans results in pain referred to the head, similar to migraine (Penfield and McNaughton, 1940; Ray and Wolff, 1940). Thus, this approach is modeled in preclinical studies, causing activation of trigeminocervical neurons (Burstein et al., 1998; Goadsby and Zagami, 1991), and responses are effectively inhibited by established abortive migraine treatments, including triptans (Burstein and Jakubowski, 2004; Goadsby and Hoskin, 1996; Goadsby and Knight, 1997; Hoskin et al., 1996). The excruciating pain in cluster headache is believed to be mediated by nociceptive activation of the trigeminal-autonomic reflex (Goadsby, 2002; May, 2005). Recently, a preclinical model of trigemino-autonomic nociceptive activation has been developed using stimulation of the brainstem superior salivatory nucleus (SuS); the origin of cells of the parasympathetic vasodilator pathway (Akerman et al., 2009; Akerman et al., 2012). Activation of this cranial parasympathetic projection modeled both nociceptive activation of trigeminocervical neurons and changes in lacrimal flow, indicative of cluster pain and autonomic symptoms. These responses were specifically inhibited by established cluster headache abortives, including triptan and oxygen treatment (Akerman et al., 2009; Akerman et al., 2012). In the present study we used these validated preclinical approaches to determine whether invasive VNS (iVNS) aborts nociceptive responses indicative of migraine and cluster headache, similar to the efficacy of VNS in their abortive treatment. This would provide a platform for these approaches to be used to dissect iVNS's mechanism of action.

2. Materials and methods

2.1. Ethics statement

All experiments were conducted under license of the NYU Institutional Animal Care and Use Committee, and conforming to the National Institute of Health Guide for the Care and Use of Laboratory Animals, and adhered to the guidelines of the Committee for Research and Ethical Issues of IASP (Zimmermann, 1983), and adhering to ARRIVE guidelines (Kilkenny et al., 2010).

2.2. General surgical preparation

The surgical preparation, recording methods and analyses have been reported in detail previously (Akerman and Goadsby, 2015; Akerman et al., 2012). Briefly, a total of 55 male Sprague-Dawley rats (265–423 g, Charles River laboratories, USA) were housed in pairs in a light and temperature controlled environment for at least seven days prior to use, with access to food and water ad libitum. They were anesthetized with sodium pentobarbital (80 mg/kg, intraperitoneal, Diamondback Drugs, AZ) and maintained with propofol (PropoFlo™ 15–25 mg/kg/h intravenous infusion). During electrophysiological recording in response to dural electrical stimulation, they were also paralyzed with gallamine triethiodide (Sigma-Aldrich) 25 mg/kg initially and maintained with 15 mg/kg every 35–40 min. To maintain full physiological functionality of the outflow from the superior salivatory nucleus (SuS), which is partly via the facial nerve and predominantly the greater petrosal nerve, the subgroup of animals which had SuS stimulation were not paralyzed. All rats were prepared for physiological measurement and drug administration with cannulation of a femoral artery, and both femoral veins, and received a tracheal cannulation. They were placed in a stereotaxic frame and continuously monitored for blood pressure and body temperature, and were artificially ventilated with oxygen-enriched air. Expired CO_2 was measured and kept between 3.5 and 4.5%. A sufficient depth of anesthesia was judged by the absence of paw withdrawal and corneal blink reflex, and during muscular paralysis, by fluctuations of blood pressure and changes to expired CO_2.

2.3. Cranial surgery preparation for electrophysiological recording

To model the dural intracranial pain believed to be responsible for migraine-like headache we used stimulation of the trigeminal innervation of the dural vasculature. For this, the skull was exposed and a partial craniotomy of the parietal and temporal bones was performed with saline-cooled drilling to expose the dural middle meningeal artery, and the area was covered in mineral oil (Fig. 1A). To model trigeminal-autonomic nociception, thought to involve activation of similar neurophysiological pathways in cluster headache, we used stimulation of the superior salivatory nucleus (SuS). This is the origin of cells of the parasympathetic projection to the cranial vasculature. We have shown previously that stimulation of the SuS causes neuronal activation in the TCC and cranial autonomic symptoms, similar to cluster headache that are mediated specifically by activation of this cranial parasympathetic projection and respond specifically to treatments (Akerman et al., 2009; Akerman et al., 2012). A small hole was drilled in an area above the cerebellum to allow access for a concentric stimulating electrode to be stereotaxically positioned in the SuS (Fig. 1B). To access the trigeminocervical complex (TCC), for electrophysiological recording, the muscles of the dorsal neck were separated and a C_1 laminectomy was performed and the dura mater incised to expose the brainstem at the level of the caudal medulla.

A tungsten recording electrode (0.5–1 MΩ, tip diameter 0.5 μm, World Precision Instruments, Inc. USA) was lowered into the TCC region of the brainstem at 5 μm increments with a piezoelectric motor controller (Burleigh Inc., USA). The neuronal signal was amplified, filtered and fed to a gated amplitude discriminator and analogue-to-digital converter (Micro 1401, Cambridge Electronic Design, UK) and to a microprocessor-based computer for analysis using Spike 2 v8. Additionally the signal was fed to a loudspeaker for audio monitoring and displayed on an analogue oscilloscope to assist isolation of action potentials from adjacent cell activity and noise. Post and peri-stimulus time histograms of neural activity were displayed and analyzed.

2.4. Characterization of neurons

Extracellular recordings were made from multi-unit neuronal clusters in the TCC and were identified as having cutaneous and deep facial receptive fields, and were assessed in all three trigeminal regions (Fig. 1C). The receptive field was assessed for both non-noxious, with gentle brushing using a cotton tip applicator, and noxious inputs, with pinching with forceps that was painful when applied to humans. Neuronal clusters identified as being sensitive to stimulation of at least the ophthalmic facial dermatome of the trigeminal nerve were then tested for convergent nociceptive input from the dura mater or SuS. Nociceptive-responsive trigeminal afferents were activated using electrical stimulation of the dura mater adjacent to the middle meningeal artery through an open cranial window, with a bipolar stimulating electrode using square-wave stimuli (100–200 μs pulse, 0.25 Hz and 4–15 V). To stimulate the SuS a concentric bipolar tungsten stimulating electrode (impedance 10–15 KΩ, tip diameter 3–4 μm) was stereotaxically positioned into the SuS (AP 10.20–10.80 mm from bregma or 1.2–1.8 mm from interaural, DV 9.2–9.6 mm and ML 2.1–2.4 mm, (Paxinos and Watson, 2004)). Constant current stimulus was applied (0.5 Hz, 150 μS duration and 20–55 μA) and neuronal responses in the TCC were recorded. Having established neuronal clusters sensitive to stimulation of the ophthalmic dermatome of the trigeminal nerve, and inputs from either the dura mater or SuS, baseline responses were characterized under test conditions. This consisted of trains of 20 stimuli delivered at 5-min intervals, stimulating either dura mater or SuS. Responses were analyzed using post-stimulus histograms with a sweep length of 100 ms and a bin width of 1 ms that separated Aδ-fiber and C-fiber