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Neurochemical dynamics of acute orofacial pain in the human trigeminal brainstem nuclear complex

Nuno M.P. de Matos [a,b,*,1], Andreas Hock [c,d,1], Michael Wyss [c], Dominik A. Ettlin [a], Mike Brügger [a,c]

[a] Center of Dental Medicine, University of Zurich, Zurich, Switzerland
[b] Institute for Complementary and Integrative Medicine, University Hospital Zurich and University of Zurich, Zurich, Switzerland
[c] Institute for Biomedical Engineering, University of Zurich and ETH Zurich, Zurich, Switzerland
[d] Philips Healthcare, Hamburg, Germany

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ABSTRACT

The trigeminal brainstem sensory nuclear complex is the first central relay structure mediating orofacial somatosensory and nociceptive perception. Animal studies suggest a substantial involvement of neurochemical alterations at such basal CNS levels in acute and chronic pain processing. Translating this animal based knowledge to humans is challenging. Human related examining of brainstem functions are challenged by MR related peculiarities as well as applicability aspects of experimentally standardized paradigms.

Based on our experience with an MR compatible human orofacial pain model, the aims of the present study were twofold: 1) from a technical perspective, the evaluation of proton magnetic resonance spectroscopy at 3 T regarding measurement accuracy of neurochemical profiles in this small brainstem nuclear complex and 2) the examination of possible neurochemical alterations induced by an experimental orofacial pain model.

Data from 13 healthy volunteers aged 19–46 years were analyzed and revealed high quality spectra with significant reductions in total N-acetylaspartate (N-acetylaspartate + N-acetylaspartylglutamate) (−3.7%, $p = 0.009$) and GABA (−10.88%, $p = 0.041$) during the pain condition. These results might reflect contributions of N-acetylaspartate and N-acetylaspartylglutamate in neuronal activity-dependent physiologic processes and/or excitatory neurotransmission, whereas changes in GABA might indicate towards a reduction in tonic GABAergic functioning during nociceptive signaling.

Summarized, the present study indicates the applicability of ^{1}H-MRS to obtain neurochemical dynamics within the human trigeminal brainstem sensory nuclear complex. Further developments are needed to pave the way towards bridging important animal based knowledge with human research to understand the neurochemistry of orofacial nociception and pain.

1. Introduction

Pain in general and orofacial pain in particular are complex multifaceted phenomena encompassing sensory, affective, cognitive and motor processes. Worldwide costs, suffering and psychosocial distress especially in chronic forms are immense (Maixner et al., 2011; Murray and Lopez, 2013). Related brain mechanisms have been disentangled up to a certain degree, with several (predominantly cortical) areas being involved in decoding specified information from the underlying pain cascade (Peyron et al., 2000; Wager et al., 2013; Denk et al., 2014). In contrast to these quite well described (pain related) neuronal correlates, the brainstem still remains scarcely characterized, particularly in humans (Beissner and Baudrexel, 2014).

As neuronal gate to and from the cortex, this structure is involved in a multitude of vital functional processes and of crucial importance for our daily survival. The functional spectrum of this area covers co-control of breathing, sleep-wake rhythms, blood pressure, heart rate, pain modulation and even higher cognitive and psychological functions (Sessle, 2005; Fairhurst et al., 2007; Hurley et al., 2010).

Listed as one of the most prevalent pain conditions, orofacial pain seems strongly associated with maladaptive brainstem processing (Sessle, 2000; Maixner et al., 2011). The collective term “orofacial pain”

* Corresponding author. Center of Dental Medicine, University of Zurich, Zurich, Switzerland.
E-mail address: nunomiguel.pratesdematos@zzm.uzh.ch (N.M.P. de Matos).
[1] Contributed equally to the study.

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encompasses a variety of pain types perceived in the face, jaw and oral cavity including acute (eg. dental pain) and chronic conditions (eg. trigeminal neuralgia; trigeminal neuropathic pain; burning mouth syndrome; temporomandibular disorders) (Zakrzewska, 2013). One commonality of these different pain types is that their nociceptive information is exclusively transmitted to the brain via the trigeminal brainstem sensory nuclear complex (TBSNC) (Sessle, 2000). This intricate nuclear cluster represents the first relay station in the brain for peripheral somatosensory afferents from the trigeminal nerve (and to a smaller extent from the facial and glossopharyngeal nerves) (Sessle, 2000; DaSilva and DosSantos, 2012). It consists of three nuclei ranging from the mesencephalon down to the cervical dorsal horn, namely: mesencephalic, principal and spinal trigeminal nucleus (Nieuwenhuys et al., 2008). The spinal trigeminal nucleus (Sp5) is further subdivided into three subnuclei in a rostral to caudal fashion: Subnuclei pars oralis, pars interpolaris and pars caudalis (Dubner and Bennett, 1983; Beck et al., 1997; Nieuwenhuys et al., 2008). The TBSNC (Sp5 in particular) receives nociceptive signals from the ipsilateral site of the face and mouth via Aδ and C-fibers and forwards them via 2nd-order neurons to the contralateral ventral posteromedial nucleus (VPM) of the thalamus from which the stimuli are further projected to several cortical structures (Nieuwenhuys et al., 2008).

Based on animal studies, cellular and neurochemical alterations in the TBSNC were suggested being crucially involved in processing acute pain as well as in maladaptation mechanisms leading to pain chronification. Neurochemicals released in the TBSNC by afferents, interneurons and (pain) modulatory pathways – most notably GABA, 5-HT and opioids – alter the processing of nociceptive input on that basal CNS level (Sessle, 2000). Exemplary are various investigations demonstrating changes in GABAergic neurotransmission associated with trauma, inflammation and partial deafferentation (Sessle, 2000; Viggiano et al., 2004; Takeda et al., 2011). Additionally, evidence is given by chronic neuropathic pain models. Using a constriction injury model of the rat infraorbital branch of the trigeminal nerve (CCI-ION), only baclofen (a $GABA_B$-receptor agonist) but not carbamazepine, morphine or tricyclic antidepressants were able to reduce the allodynia-like behavior (Idänpään-Heikkilä and Guilbaud, 1999). Using a similar model, Martin et al. (2010) found a decrease in GAD65 immunoreactivity in the caudal nucleus of the Sp5 suggesting a disruption in GABA-mediated inhibitory circuits.

Few human neuroimaging studies addressed the specific functional/anatomical contributions of the TBSNC in acute and chronic orofacial pain by applying functional magnetic resonance imaging (fMRI) (DaSilva et al., 2002), diffusion tensor imaging (DTI) and voxel-based morphometry (VBM) (Wilcox et al., 2015). However, none of the performed neuroimaging studies provided insights regarding neurochemical alterations in the human TBSNC thus corroborating some results provided by animal studies. But this question could be addressed by proton magnetic resonance spectroscopy (^{1}H-MRS), a powerful method able to simultaneously quantify neurochemical compounds in a defined brain region. Typically measured neurochemicals provide for example information about neuronal density and viability (N-acetylaspartate), energy metabolism (creatine/phosphocreatine), membrane turnover and integrity (choline), antioxidant status (glutathione), glial cell proliferation (Myo-inositol) or neurotransmission (Glutamate, GABA, N-acetyl-aspartyl-glutamate) (Stagg, 2013). Theoretically, ^{1}H-MRS allows observing neurochemical processes and alterations associated with acute and chronic (orofacial) pain conditions within relevant brainstem nuclei. Thus a bridge from human research to the animal studies on TBSNC might be in reach.

However, in-vivo measurements on brainstem levels face a series of significant challenges as technical, structural and physiological characteristics of the brainstem and spinal cord impede proper MR acquisitions. Blood flow in adjacent arteries/venes and CSF pulsation in and around the brainstem induce inhomogeneity in the static magnetic field (B_0) thus causing frequency shifts resulting in poor spectral resolution (Brooks et al., 2013; Beissner and Baudrexel, 2014; Hock et al., 2013a,b). Furthermore, the signal obtained by ^{1}H-MRS is in general very minute, demanding large measurement volumes (usually voxel sizes of 8 ml) in order to achieve sufficient signal-to-noise ratios (SNR) in a reasonable acquisition time (Kreis, 2004; de Matos et al., 2016). But, measuring the TBSNC with the adequate anatomical and functional specificity demands smaller voxel sizes and hence requires adaptations towards long acquisition times. Those, in turn enhance the likelihood for temporal changes in the B_0 field caused by subject motion and B_0 drifts resulting in frequency and phase shifts between single free induction decays (FIDs). All these facets hamper spectral quality aspects and require careful planning and adequate measurement strategies (Hock et al., 2013a,b).

In this feasibility study, we provide a brainstem optimized ^{1}H-MRS sequence and data post processing scheme in combination with a reliable experimental dental pain model in healthy volunteers. The following two questions were pursued: 1) ^{1}H-MRS measurability aspects of a small brainstem area from a technical perspective and 2) possible alterations in the neurochemical milieu induced by experimental dental pain.

2. Materials and methods

The present study was conducted from March 2015 to December 2015 according to the Declaration of Helsinki and was approved by the local ethics committee.

2.1. Subjects

26 healthy males (mean age: 27.35 ± 6.84, range: 19–46) were recruited for the study. Inclusion criteria required the test tooth (right upper canine) to be vital, caries free, sensorically intact and free of previous dental treatments. Exclusion criteria were psychiatric and neurologic diseases, regular pain medication intake, pain syndromes, claustrophobia and general contra-indications for MR. No female volunteers were recruited due to possible variability in pain perception caused by menstrual cycle associated variation in hormonal levels (Wiesenfeld-Hallin, 2005).

All subjects received detailed information about the experimental procedure, aim of the study and provided their written informed consent before any procedure was performed. Subjects were instructed not to consume alcohol, analgesic medication and other drugs 24 h before the start of the MR experiment and to be fed before participation. Participants were explicitly informed to have the possibility to terminate participation and withdraw from the study at any time. They were financially compensated (40 Swiss francs/hour) for the effective time of participation.

From the initial 26 recruited participants, 8 were excluded after the test session due to insufficient and/or inconstant pain intensity perception; therefore 18 subjects were included in the study. Two subjects had to be excluded due to spectral artifacts and two others due to insufficient spectral resolution ($FWHM_{NAA} > 10$ Hz). An additional subject had to be excluded due to strong movements during the experimental conditions, resulting in a total of 13 (mean age: 27.69 ± 7.89, range: 19–46) data sets for analysis.

2.2. Dental stimulation setup

Dental stimulation was administered to the right upper canine. For this purpose, individual dental splints with non-ferromagnetic stainless steel electrodes embedded directly at the center of labial and palatal surfaces were fabricated. To reduce electrical resistance, small portions of hydrogel (size ca. 3 × 3mm) covering the electrodes were applied before splint insertion.

In addition to the tooth stimulating electrodes, a small 2 MΩ resistor (surface-mount device, SMD, KOA Corporation, Tokyo, Japan) was placed on the left side of the dental splint over the second left incisor tooth and sealed with Blu-Mousse (thixotropic vinyl polysiloxane; Parkell, Edgewood, USA). This resistor served as “dummy tooth” enabling