

Migraine and the Mu-Opioidergic System—Can We Directly Modulate it? Evidence from Neuroimaging Studies

Alexandre F. DaSilva · Thiago D. Nascimento ·
Marcos F. DosSantos · Jon-Kar Zubieta

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Abstract Migraine is a chronic trigeminal pain condition that affects the daily lives of a large part of our population. Its debilitating headache attacks, with increased sensitivity to multiple forms of stimuli, force many patients to rely on over the counter analgesics and resort to abuse of prescription medications, particularly opioid agonists. In the latter case, the indiscriminate medication-driven activation of the opioid system can lead to undesired side effects, such as the augmentation of hyperalgesia and allodynia, as well as the chronification of the attacks. However, we still lack information regarding the impact of migraine attacks and their relief on the function of μ -opioid receptor (μ OR) mediated neurotransmission, the primary target of opioid medications. This line of inquiry is of particular importance as this neurotransmitter system is arguably the brain's most important endogenous mechanism involved in pain regulation, and understanding this endogenous mechanism is crucial in determining the effectiveness of opioid medications. Recently, new advances in molecular neuroimaging and neuromodulation have provided important information

that can elucidate, in vivo, the role of the endogenous opioid system in migraine suffering and relief.

Keywords Migraine · Headache · Brain · Opioid · Neuroimaging · MRI · PET · Neuromodulation · Neurotransmission · tDCS · Stimulation · μ OR BP_{ND} · Trigeminal · Pain · Allodynia · Chronic · Analgesia

Introduction

Opioid use in migraine is highly controversial. Recently, there has been an increased debate of its role in migraine treatment due to strong evidence that its frequent prescription can lead to augmented risk of headache chronification, allodynia, abuse/dependence, and depression/anxiety. For instance, health-care resource utilization is higher for migraine opioid-users compared with nonusers for emergency, primary, and specialty care visits. Nonetheless, the American Academy of Neurology Practice Parameter lists opioids as second- or third-tier treatments for migraine. This is not surprising, since opioid analgesics are widely known for their ability to decrease experimental and, most importantly, clinical pain perception. Despite all the controversies regarding medicinally targeting the human opioid system, many questions regarding the impact of frequent headache suffering and the direct modulation of this system are still unanswered at the molecular level.

How is the Human Opioid System Affected by Acute and Chronic Pain?

The descending inhibitory system modulates pain perception to a great extent via μ ORs. They are found throughout the central and peripheral nervous system and play a crucial role

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A. F. DaSilva (✉) · T. D. Nascimento · M. F. DosSantos
Headache and Orofacial Pain Effort, Biologic and Materials Sciences
Department, School of Dentistry, University of Michigan, 1011 N.
University Ave., Room 1014A, Ann Arbor, MI 48109-1078, USA
e-mail: adasilva@umich.edu

T. D. Nascimento
e-mail: nasci@umich.edu

M. F. DosSantos
e-mail: santosmfh@gmail.com

J.-K. Zubieta
Translational Neuroimaging Laboratory, Molecular and Behavioral
Neuroscience Institute, Department of Psychiatry, University of
Michigan, 205 Zina Pitcher Place, Room 1060, Ann Arbor,
MI 48109-5720, USA
e-mail: zubieta@umich.edu

in analgesia and in the successful action of exogenous opiate drugs frequently prescribed to address cancer and noncancer pain treatment. Recent positron emission tomography (PET) studies have demonstrated that trigeminal pain activates endogenous μ OR-mediated neurotransmission in cortical and brainstem regions including, for example, the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), anterior and posterior insula, medial and lateral thalamus, hypothalamus, amygdala, periaqueductal gray matter (PAG), and nucleus accumbens. All of these regions have high concentrations of μ ORs, and the degree of their activations correlates with the ability to curb affective and sensory features of pain suffering [1]. Such developments in PET neuroreceptor labeling have permitted the investigation of valuable molecular mechanisms in the brain of other chronic pain disorders *in vivo*. For instance, μ OR concentrations have been examined in patients diagnosed with fibromyalgia syndrome [2]. There were significant reductions in the μ OR availability of those patients compared with healthy subjects in the basal ganglia, amygdala, and dorsal ACC. In a specific region of the basal ganglia, the nucleus accumbens, these results were further correlated with clinical pain. This region is part of the reward system and drug-taking behavior. Either by the loss of μ ORs or their elevated occupancy by pain-induced release of endogenous opioids, these reductions in μ OR availability *in vivo* helps to elucidate why opioid therapy is anecdotally claimed as an ineffectual treatment for patients with fibromyalgia, which is also a divisive fact among clinicians in migraine therapy [3]. These changes in μ OR availability (non-displaceable binding potential, BP_{ND}) may also be present in the brain of patients suffering with other forms of chronic pain disorders, but with slightly different patterns. For instance, in rheumatoid arthritis patients there are significant reductions in [11C] diprenorphine binding, a nonselective opioid radiotracer, in the frontal, cingulate, and temporal cortices in association with the inflammatory-related pain levels. In neuropathic pain, reduced μ OR BP_{ND} was demonstrated in both hemispheres. In contrast, in central poststroke pain, reductions with [11C] diprenorphine binding decreased predominantly in the hemisphere contralateral to pain [4]. More recently, and in the opposite direction, increases in μ OR availability and reductions in pain anticipation and pain-induced endogenous opioid release was observed in the thalamus and amygdala of patients diagnosed with non-neuropathic back pain, which were associated with clinical pain ratings. Such particularities indicate specific dysfunctional opioidergic central changes for each chronic pain disorder, and might underlie their different sensitivity to opiates. Hitherto, scarce information is available on the baseline and release of the endogenous μ -opioids in migraine pain, and how μ OR

availability and endogenous μ -opioid release relate to treatment responses.

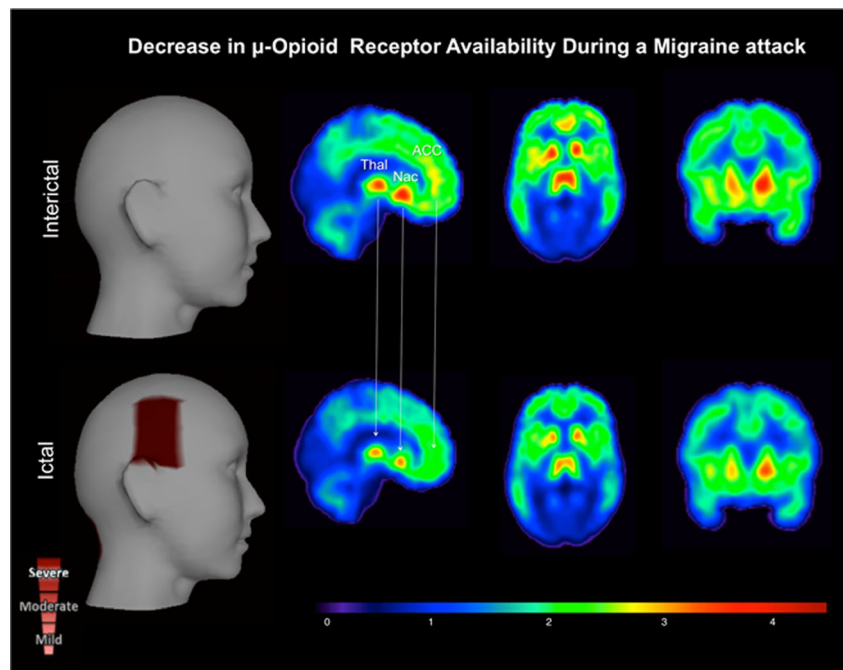
What is the Involvement of the Human μ -Opioid Receptor Mediated Neurotransmission in the Migraine Pathophysiology?

The pathophysiology of migraine is not completely understood, but MRI-based studies have reliably demonstrated neuroplastic changes along the trigeminal sensory system [5–7]. There is strong evidence of sensitization in the migraine brain attributable to abnormal trigeminal afferent traffic [8]. In contrast, there is a dysfunctional descending modulatory system that could also explain the headache and allodynic phenomenon in migraine. Under this scenario, descending projections from the dorsolateral prefrontal cortex and brainstem structures, such as the periaqueductal gray (PAG) and the red nucleus, where there is a high expression of μ ORs [9, 10], would be more inefficient in their inhibitory effects on ascending trigeminal sensory neurons [11]. In addition, the dural neurogenic vasodilation usually associated with the migraine pathophysiology can be prevented by the potent opiate analgesic morphine, and afterward be reversed by the opioid antagonist naloxone. These opposing effects of morphine and naloxone on neurogenic inflammation corroborate the notion that this migraine-related process is mediated via activation of μ ORs. Recently, DaSilva and colleagues have developed a PET protocol that allows us to measure μ OR BP_{ND} in migraine patients. They noticed reductions in μ OR BP_{ND} during a spontaneous migraine attack compared with the baseline [12••]. There were reductions in μ OR BP_{ND} in opioid-rich pain-modulatory regions, most notably the thalamus, ACC, NAcc, and Insula. We also found such activation in the midbrain (PAG). This is the first time changes in μ OR BP_{ND} during a spontaneous migraine attack have been reported. These results indicated the acute activation of the endogenous opioid neurotransmission interacting with μ OR due to the pain of the migraine attack (Fig. 1).

What is the Neuroimaging Evidence of Endogenous Opioid System Involvement with Trigeminal Pain and its Relief?

Patients with trigeminal neuropathic pain (TNP) show reduced μ OR BP_{ND} in the left nucleus accumbens, an area known to be involved in pain modulation and reward/aversive behaviors. In addition, μ OR BP_{ND} in the NAcc was negatively correlated with the McGill

Fig. 1 μ -Opioid Brain Profile of a Migraine Headache Attack in vivo. The ictal phase (lower row)—headache phase—shows a decrease in μ -opioid receptor availability (μ OR BP_{ND}) in the pain-matrix regions. This result possibly represents an increase in endogenous μ -opioid release during the migraine attack, as a regulatory response to the ongoing severe headache. DaSilva AF, Nascimento TD, Love TM, DosSantos MF, Martikainen IK, Cummiford CM, et al. Impact of a spontaneous migraine attack in the endogenous μ -opioid system in-vivo. *J Vis Exp.* 2014 [12••]. *Thal* thalamus, *Nacc* nucleus accumbens, *ACC* anterior cingular cortex



sensory and total pain ratings in the TNP patients [13]. Nonetheless, we still lack information regarding the possible long-lasting effects of clinical persistent trigeminal pain upon this and other endogenous regulatory systems, including cases where there is intervention effect. In one of few studies available, Jones et al [14, 15] utilized [11C] diprenorphine, again a nonselective opioid radiotracer, to examine the availability of opioid receptors in a small group of patients diagnosed with chronic pain including trigeminal neuralgia before and following treatment. The authors reported reductions in cortical and subcortical opioid receptor availability at baseline before treatment, which were reversed after the pain subsided. In another study with chronic neuropathic pain patients, surgical motor cortex stimulation decreased [11C] diprenorphine availability in the anterior MCC and PAG [16]. Once more, those central opioid receptor changes following treatment were associated with pain relief. These findings are proof-of-concept that the decreased receptor availability, as measured by radiotracer binding in the brain of chronic trigeminal pain patients, is likely a reflection of receptor downregulation in the context of persistent endogenous opioid system activation and chronic pain. In addition the acute changes associated with an intervention (eg, motor cortex stimulation) reflect the capacity to activate this neurotransmitter system through the employed stimulus. This endogenous opioid-mediated analgesic mechanism has been associated with M1 cortex stimulation, with repetitive transcranial magnetic stimulation (rTMS), as

demonstrated by its blockade with naloxone [17]. The same did not occur when the target area was the DLPFC. The information above indicates that endogenous opioid mechanisms are highly influenced by the type of chronic pain disorder, therapeutic method, and cortical area targeted.

Can We Directly Target the Opioid-Regulated Regions in the Migrainous Brain? Evidence from Neuromodulation and Forward Neuroimaging-Analysis

Transcranial Direct Current Stimulation (tDCS) has potential advantages for the research of migraine in comparison with TMS, including small portable size, low cost and, most importantly a more reliable placebo control condition [18]. Several well-controlled studies have shown the efficacy of tDCS in pain alleviation [19, 20]. tDCS is based on the application of a weak direct current to the scalp that flows between 2 relatively large electrodes—anode and cathode. Its effects depend on the polarity of stimulation, for example, cathodal stimulation induces a decrease in cortical excitability, and anodal stimulation induces an increase in cortical excitability that may last beyond the duration of the stimulation. In fact, application of tDCS for 13 minutes to the motor cortex can modulate cortical excitability for several hours [21, 22]. Nonetheless, the efficacy of tDCS depends critically on parameters such as electrode position and current strength (<http://www.jove.com/details.php?id=2744>)

[23–25]. For example, M1 is a reliable target to modulate the sensory and motor subthalamic activity associated with chronic pain, independent of the type of stimulation applied [26–29], which also affects other pain-related structures. This occurs directly and indirectly because of the multiple connections between the corticospinal tract and thalamus.

A preliminary investigation, using a blind sham-controlled study, showed significant analgesic effects of tDCS over the primary motor (M1) cortex in chronic migraine (CM) [30••]. Patients were randomized to receive 10 sessions of active or sham tDCS for 20 minutes with 2 mA over a period of 4 weeks. The primary outcome measure was pain intensity (VAS ratings). There was a significant interaction term (time vs group) for pain intensity ratings and also for length of migraine episodes. Post-hoc analysis showed a significant improvement in the follow-up period for both outcomes in the active tDCS group only. In addition, patients in the active group showed a significant improvement in the clinician global impression scale ratings when compared with the sham group (Fig. 2). Using a finite element (FE) program, the authors analyzed the effect of their M1 cortex electrode montage on the current flow in the brain taking into consideration the electrical properties of cortical and subcortical structures. The human head model was based on a single high spatial resolution (1 mm³) 3 T MRI-derived FE from a healthy subject. The spatial focality of the analysis was restricted to 5×7 cm² pads placed exactly as described: anode electrode over the motor cortex and the cathode electrode at the contralateral supraorbital area (SO).

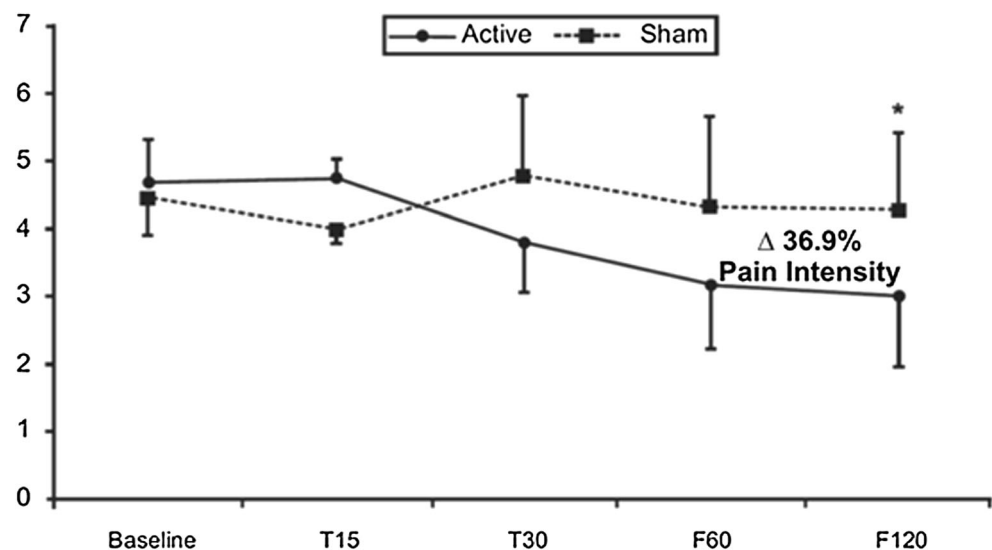
Afterward, the head was segmented into compartments representing the brain tissues, cerebrospinal fluid, skull,

muscle, fatty tissue, eyes, blood vessels, and the scalp, respectively. The stimulation pads were imported as CAD models, and volumetric meshes were generated from the segmented data, and later exported to COMSOL Multiphysics 3.4 (Burlington, MA, USA). A good analogy for our forward-tDCS analysis is the factors used in the prediction of earthquake diffusion, such as seismic strength and the terrain's geography and geology. Similarly current strength, size/location of electrodes, head/brain anatomy, and white/gray matter constitution were the factors that dictated the flow of electricity in our previous study. The results showed that significant electric fields are generated, not only in target cortical regions (M1) as was reported before, but also in the posterior thalamus (VPM) and other pain-matrix regions: Insula, ACC, and the brainstem. Derived from the tDCS forward analysis, this direct modulation of the pain-related regions may explain the analgesic effects on migraine pain measures associated with our protocol [30••].

Can We Directly Modulate the Endogenous Opioid-System? Evidence from MRI and PET Studies

When 20 minutes of M1-tDCS stimulation are administered during the PET imaging session, there is an immediate reduction in μ OR availability in vivo in response to an acute motor cortex stimulation, consistent with the acute release of endogenous opioids interacting with μ ORs [31••]. Concentrations of μ OR BP_{ND} in a chronic trigeminal pain patient during a single tDCS application induced a decrease in μ OR availability in the thalamus and other pain-matrix structures, including the NAcc, ACC, and

Fig. 2 Positive response of chronic migraine to M1-tDCS. Mean pain levels (as assessed by VAS) at baseline, T15, T30, F60, and F120 in the 2 groups of stimulation (active & sham tDCS). Error bars indicate standard error of the mean. DaSilva AF, Datta A, Mendonca ME, Zaghi S, Lopes M, DosSantos MF, et al. Chronic migraine alleviation by tDCS is predicted to be associated with current flow through pain-related (sub) cortical regions. *Headache*. 2011;51:48–9 [30••]



Insula, as predicted in the forward tDCS model, which were coupled with pain relief. Such analgesic effect of tDCS on pain measures are likely due to the acute release of endogenous opioids, activating μ ORs, by direct and indirect effect of M1 stimulation on the thalamus and other regions. tDCS over M1 induced immediate changes in thermal sensory perception, especially to cold sensation [32]. Lately, Polania and colleagues have additionally reported that tDCS regulates functional connectivity depending on the specific montage [33]. For instance, cathodal M1-tDCS diminishes functional coupling between ipsilateral M1 and contralateral putamen. On the other hand, anodal stimulation over M1 instantly increases functional coupling between ipsilateral M1 and thalamus.

The same active M1-tDCS montage significantly reduced μ OR availability in the posterior thalamus compared with placebo tDCS [31••]. Interestingly, the single M1-tDCS session improved threshold for acute cold pain in the allodynic area, but the analgesic effects did not alter the patient's clinical pain. This result implies that the endogenous opioid system activating effects of a single tDCS session are subclinical, and multiple sessions are likely necessary to address neuroplastic cortical changes related to a chronic pain state, including migraine.

Conclusions

The μ -opioid system plays a pivotal role in migraine pain pathophysiology and relief. μ OR BP_{ND} is an objective PET measurement in vivo of endogenous μ -opioid availability, and its acute reduction reflects the activation of this neurotransmitter system [1]. Clinical and experimental trigeminal pain suffering induces, at different levels, the release of endogenous opioids acting on μ ORs to suppress the ongoing headache and general pain. Further activation of the endogenous μ OR-mediated neurotransmission produces an analgesic effect, and changes toward control values in μ OR BP_{ND} take place after continued treatment.

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Compliance with Ethics Guidelines

Conflict of Interest Alexandre F. DaSilva, Thiago D. Nascimento, Marcos F. DosSantos, and Jon-Kar Zubieta each declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article contains two studies involving human subjects that were performed by the authors. Both studies were approved by the Institutional Review Board (IRB) at the University of Michigan.

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