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

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Abstract

Migraine is a chronic trigeminal pain condition that affects the existence of great part of our population. Its debilitating headache attacks, with increased sensitivity to multiple forms of stimuli, force many of the patients to frequently rely upon over the counter analgesics, and quite frequently resort to abuse of prescribed medications, particularly the 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 its relief on the function of μ-opioid receptor (μOR) mediated neurotransmission, the primary target of opioid medications. This line of enquiry is of particular importance as this neurotransmitter system is arguably the endogenous brain mechanism most centrally involved in pain regulation, as well as the effectiveness of opioid medications. Recently, new advances in molecular

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Compliance with Ethics Guidelines

Conflict of Interest

Dr. Alexandre F. DaSilva, Dr. Thiago D. Nascimento, Dr. Marcos F. DosSantos, and Dr. Jon-Kar Zubieta each declare no potential conflicts of interest relevant to this article.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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; μOR 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 solid 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 to 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 a surprise, since opioid analgesics are widely known for their ability to decrease experimental and, most important, clinical pain perception. Despite all the controversies regarding targeting medicinally the human opioid system, many questions regarding the impact of frequent headache suffering and the directly 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 in large part via μORs. They are found throughout the central and peripheral nervous system and play a crucial role in analgesia and in the successful action of exogenous opiate drugs frequently prescribed to address cancer and non-cancer pain treatment. Recent positron emission tomography (PET) studies have demonstrated that trigeminal pain activates endogenous μOR-mediated neurotrasmission 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 μORs, 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, μOR concentrations have been examined in patients diagnosed with fibromyalgia syndrome [2]. There were significant reductions in the μOR availability of those patients compared to 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 μORs or their elevated occupancy by pain-induced release of endogenous opioids, these reductions in μOR 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 μOR availability (non-displaceable binding potential - BP_{ND}) may be also

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 non-selective opioid radiotracer, in the frontal, cingulate and temporal cortices in association with the inflammatory-related pain levels. In neuropathic pain, reduced μOR BP_{ND} was demonstrated in both hemispheres. In contrast, in central post-stroke pain, reductions with [11C]diprenorphine binding decreased predominantly in the hemisphere contralateral to pain [4]. More recently, and in the opposite direction, increases in μOR availability and reductions in pain anticipation and pain-induced endogenous opioid release were 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 μOR 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 μORs [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 with the notion that this migraine-related process is mediated via activation of μORs. Recently, DaSilva and colleagues have developed a PET protocol that allows us to measure μOR BP_{ND} in migraine patients. They noticed reductions in μOR BP_{ND} during a spontaneous migraine attack compared to the baseline [••12]. There were reductions in μOR 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 evidence that changes in μOR BP_{ND} during a spontaneous migraine attack are reported. These results indicated the acute activation of the endogenous opioid neurotransmission interacting with μOR due to the pain of the migraine attack **(Figure 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 μOR BP_{ND} in the left nucleus accumbens, an area known to be involved in pain modulation and reward/aversive behaviors. In addition, μOR BP_{ND} in the NAcc was negatively correlated with the McGill 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 [^{11}C]diprenorphine, again a non-selective 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 [^{11}C]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 decrease receptor availability as measured by radiotracer binding in the brain of chronic trigeminal pain patients is likely reflecting receptor downregulation in the context of persistent endogenous opioid system activation and chronic pain, while the acute changes associated with an intervention (e.g., motor cortex stimulation) reflect the capacity to active this neurotransmitter system by the stimulus employed. 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 to 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 two relatively large electrodes—anode and cathode. Its effects depend on polarity of stimulation, such as 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 corticospinal tract and thalamus.

A preliminarily 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 **(Figure 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 ($1mm^3$) 3T MRI-derived FE from a healthy subject. The spatial focality of the analysis was restricted to 5x7 cm^2 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 3.4 (MA, USA). One good analogy of our forward-tDCS analysis is the prediction of earthquake diffusion, taking into consideration a particular seismic strength, the terrain's geography and geology. On that study, instead, it was the current strength, size/location of electrodes, head/brain anatomy and white/gray matter constitution that dictated the flow of electricity. 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 even 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 their 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 μOR availability *in vivo* in response to an acute motor cortex stimulation, consistent with the acute release of endogenous opioids interacting with μORs [••31]. Concentrations of μOR BP_{ND} in a chronic trigeminal pain patient during a single tDCS application induced a decrease in μOR availability in the thalamus and other pain-matrix structures including NAcc, ACC, and 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 μORs, 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 cold [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 μOR availability in the posterior thalamus compared to 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. μOR 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 μORs to suppress the ongoing headache and pain in general. Further activation of the endogenous μOR-mediated neurotransmission produces an analgesic effect, and changes toward control values in μOR BP_{ND} take place after continued treatment.

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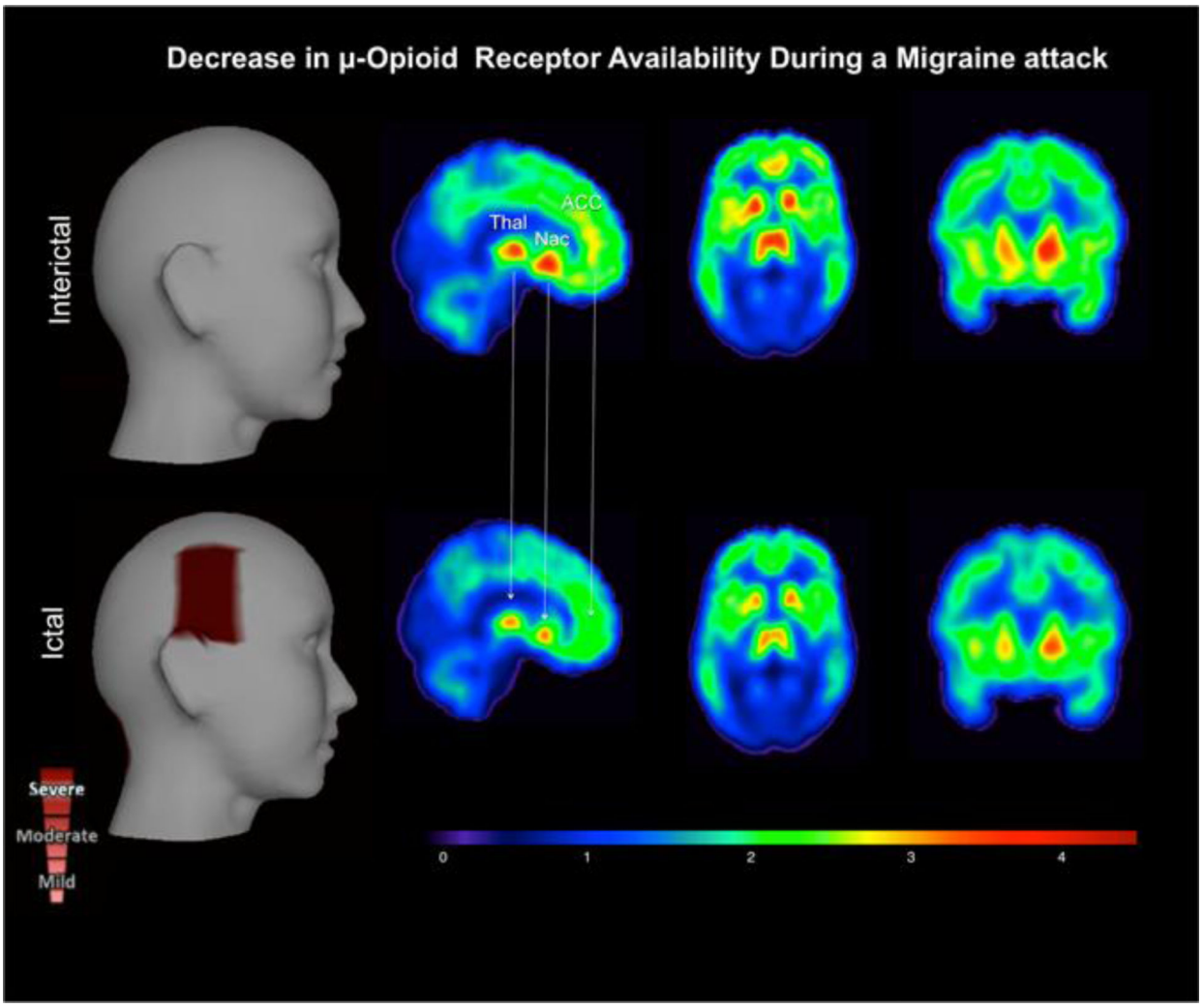

Figure 1. μ-Opioid Brain Profile of a Migraine Attack *in vivo*

The ictal phase (lower row) – headache phase - shows a decrease in μ-opioid receptor availability (μOR 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. Key words: thalamus (Thal), nucleus accumbens (NAcc), and anterior cingular cortex (ACC). (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. 2013;In Press)

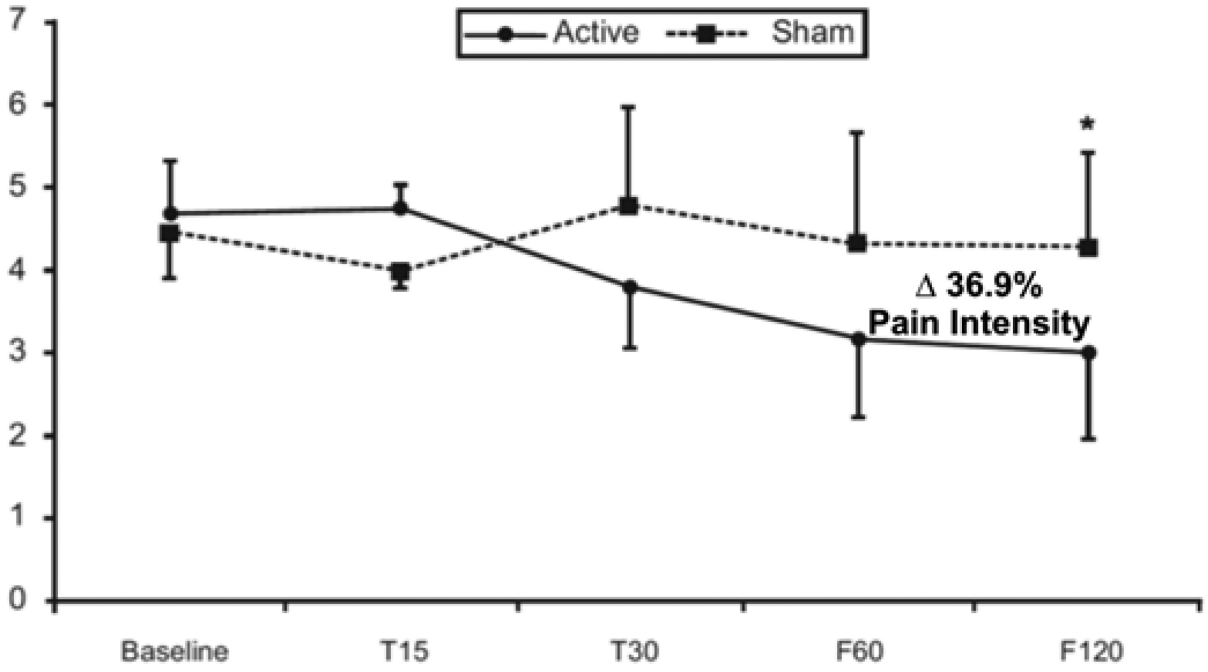

Figure 2. Positive response of chronic migraine to M1-tDCS

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 [••30].