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BRIEF COMMUNICATION

μ-Opioid activation in the midbrain during migraine allodynia – brief report II

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Abstract

We investigated in vivo the allodynic response of the central μ-opioid system during spontaneous migraine headaches, following a sustained pain threshold challenge on the trigeminal ophthalmic region. Six migraineurs were scanned during the ictal and interictal phases using positron emission tomography (PET) with the selective μ-opioid receptor (μOR) radiotracer [11C]carfentanil. Females were scanned during the mid-late follicular phase of two separate cycles. Patients showed ictal trigeminal allodynia during the thermal challenge that was concurrent and positively correlated with μOR activation in the midbrain, extending from red nucleus to ventrolateral periaqueductal gray matter. These findings demonstrate for the first time in vivo the high μOR activation in the migraineurs' brains in response to their allodynic experience.

Introduction

The use of opioids in clinical practice is not without risk of undesired effects, especially in migraine patients where the recurrent nature of the attacks, and consequently the frequent use of rescue opioid intake, can severely increase the risk of chronification and even allodynia.[1] This augmented cutaneous sensitivity to stimuli that should not cause pain, already present in 65% of migraineurs, turns mundane activities such as washing the face with hot water and combing the hair into distressing tasks during the headache attacks.[2] Our group demonstrated in our previous study that there was an ineffective high release of endogenous μ-opioids at the cortical level to fight the ongoing migraine pain. More precisely, this was noted in the medial prefrontal cortex (mPFC), a cortical area that processes the spatio-temporal and cognitive-emotional inputs related to spontaneous chronic clinical pain.[3] However, information is still lacking regarding the involvement of the endogenous μ-opioid receptor (μOR) system in the allodynic response during migraine attack, which could provide a molecular explanation of why certain patients have increased cutaneous sensitivity. In order to address the technical requirements for molecular

neuroimaging in humans we used a sustained thermal pain threshold (STPT) challenge developed in-house on the trigeminal ophthalmic region. Hence, we were able to examine for the first time in vivo, changes in μOR activity in the brains of migraine patients during the ictal allodynic experience.

Patients and Methods

The methods were previously described elsewhere.[3] Clinical characteristics of the episodic migraine headache for the participants are described in Table 1. The patients were screened first by phone, and later examined by pain specialists, who used the International Headache Society classification to guide the diagnosis of episodic migraine.[4] None of the patients were using contraceptives or opioids for the 6 months prior to the recruitment. Following the initial appointments, subjects were scanned during spontaneous headache (ictal) and nonheadache (interictal) phases of their migraine. Subjects contacted the laboratory early in the morning of the positron emission tomography (PET) sessions to confirm the occurrence or not of the migraine attack, since the PET suite and radiotracers production were scheduled in advance. Only spontaneous and not drug-induced migraine attacks were considered, consequently many scheduled PET sessions had to be canceled. In addition, to minimize the influence of hormone variation, PET sessions for female migraine patients were arranged only during the mid-late follicular phase, within 5–10 days after menstrual onset, of two separate menstrual cycles, with the assistance of a gynecologist with knowledge of molecular imaging protocols. The study was given approval by the University of Michigan Institutional Review Board and by the Radioactive Drug Research Committee.

Ictal and interictal PET sessions

We used the selective μOR radioligand, [11C]carfentanil for the PET sessions.[5] Each session was 90 min, with 40 min of baseline acquisition, followed by 20 min of a STPT challenge (more information below). As described in our previous study,[3] [11C]carfentanil was produced using a cycloton in the vicinity.[6] PET scans were acquired with a Siemens HR+ scanner in 3-D mode (reconstructed FWHM resolution 5.5 mm in-plane and 5.0 mm axially) with septa retracted and scatter correction. Subjects were positioned in the PET scanner gantry and two intravenous (antecubital) lines were placed. Each dose of [11C] carfentanil (15 ± 1 mCi, ≤0.03 μg/kg) was administered fifty percent as a bolus, and the remaining dose was continuously injected across the scan session to achieve steady-state tracer levels around 35 min after tracer administration.

STPT – PET challenge

The STPT in the trigeminal ophthalmic region was developed in-house for various reasons, including technical elements related to receptor quantification PET methods (Fig. 1). Receptor binding measures in PET require the utilization of challenges sufficiently long in duration so that a constant state can be achieved and enough data points collected to permit quantification. The heat intensity was controlled by the individual's experience, from a starting baseline of 32°C, multiple heat cycles occurred at constant rates (1°C/sec ascending and descending), and applied to the forehead area (V1) ipsilateral to the headache using a 16 mm^2 thermal probe system (Pathway Model- MEDOC, Ramat Yishai, Israel). The subjects were instructed to tap the mouse button at the first perception of pain to instantly return temperature to baseline level.

Table 1. Clinical profile of episodic migraine participants enrolled in this study. Sequence of subjects follows figure 2, left image, from left to right.

			Episodic migraine characteristics[1]					
Subjects	Gender	Age	Diagnosis[1]	Pain intensity[2]	Pain frequency[3]	Pain duration (h)	Chronicity in years	Usual abortive medication[4]
1	Male	21	With aura	6	2	12	7	Ibuprofen
2	Female	21	Without aura	8	4	12	5	None
3	Female	26	Without aura	6	8	12	15	Acetaminophen
4	Female	38	With aura	6.2	6	72	20	Acetaminophen
5	Male	22	With aura	6.7	8	24	6	Acetaminophen
6	Male	26	With aura	5	2	5	2	None

[1]Based on ICHD-3 beta (However, none of the participants reported visual aura preceding or during the ictal PET scan).
[2]Pain intensity during ictal PET scan.
[3]Average days per month.
[4]Preventive medication was an exclusion criteria, and abortive medication was not allowed 48h prior to interictal and ictal PET scans.

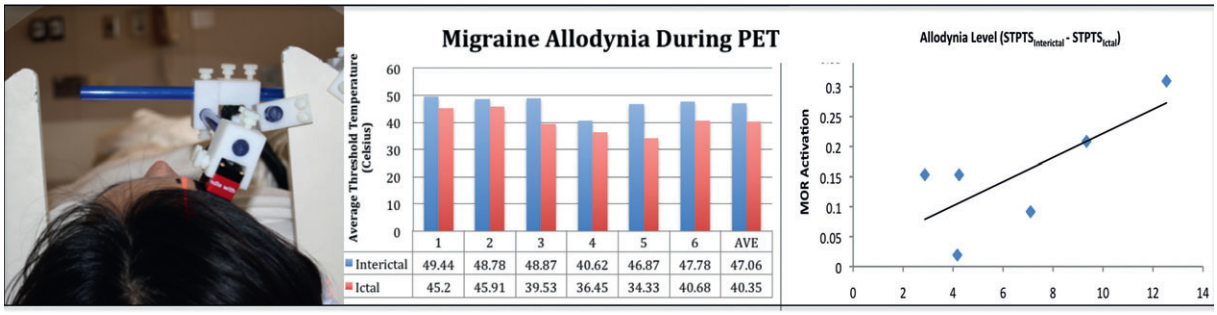

Figure 1. Migraine trigeminal allodynia during PET. *Left*: Sustained thermal pain threshold (STPT) challenge on the ophthalmic trigeminal region of a migraine patient. *Center*: Trigeminal heat allodynia levels. The graph shows six patients that were scanned and concurrently challenged during ictal and interictal phases with the STPT challenge protocol. The average threshold temperature significantly decreased during the headache (ictal) phase in the migraine patients ($P < 0.003$). *Right*: Correlation of μ-opioid activation with migraine trigeminal allodynia. The scatter plot indicates a significant positive correlation between μ-Opioid activation and Allodynia ($r = 0.75$; $P < 0.003$). The allodynia values were based on the difference between average thermal pain threshold levels in °C (STPT) during ictal and interictal migraine phases.

In that manner, individuals with migraine selected their thermal pain threshold based on their current sensitivity, which avoided unnecessary discomfort during the experiment, especially in the allodynic ictal sessions. The challenge cycles were repeated every 10 sec for 20 min during the PET session, and multiple pain thresholds measurements were recorded to provided the average threshold of the session (Fig. 1 – Left).

Electronic mobile pain data entry

At the time of the PET sessions, headache and facial pain intensity and area were recorded and analyzed using a free and interactive Apple mobile application developed in-house (Pain*Trek,* University of Michigan).

MRI acquisition

Magnetic resonance imaging (MRI) scans were acquired on a 3T scanner (General Electric, Milwaukee, WI). These images provide anatomical information for structure identification and were utilized for the anatomical standardization to the ICBM/MNI atlas coordinate system. This established the linear and nonlinear warping transformation matrices applied to the co-registered receptor binding PET maps. The acquisition sequence was axial T1 FAST SPGR MR (TE = 3.4, TR = 10.5, TI = 200, flip angle 25°, FOV 24 cm, 1.5 mm thick slices, NEX = 1), acquisition matrix 256 × 256, 60 slices.

Neuroimaging analysis

T1-weighted MR and PET images of each subject were co-registered to each other using a mutual information algorithm.[7] For this purpose, K1 ratio images were first aligned to the MR, and the transformation matrix applied to the co-registered non-displaceable binding potential (BPND) scans of the same image set. The MR scans were then anatomically standardized to ICBM brain atlas stereotactic coordinates by nonlinear warping, and the resulting transformation matrix applied to both K1 ratio and BPND image sets.[8,9]

Subsequently, dynamic image data for each of the receptor scans were transformed on a voxel–by–voxel basis into three sets of parametric maps, which were co-registered to each other. These were (1) a tracer transport measure (K1 ratio, proportional to cerebral blood flow; tracer transport = blood flow × tracer extraction) and receptor-related measures (BPND), encompassing data from 45 to 90 post tracer administration (STPT challenge). These parametric images were calculated using a modified Logan graphical analysis[10] with the occipital cortex (a region devoid of μORs) as the reference region.

Results

Seven patients (four females/three males) contacted us by phone in the early morning with spontaneous migraine for their ictal PET scans. They were instructed to tolerate the pain without any rescue pharmacotherapy until the end of the scan sessions. The seventh patient's allodynia phase data was eliminated due to thermal probe displacement during scan.[3] The average pain intensity of the remaining patients was moderate (6.3 ± 0.9; VAS [1–10]) for the headache attacks. With the exception of patient 1, all other patients had migraine predominantly in the right side (Table 1). All the patients showed significant cutaneous heat allodynia during the ictal PET session in the ipsilateral ophthalmic trigeminal area when compared to the interictal phases ($P < 0.003$) (Fig. 1 – Center). No additional headache attacks were recounted by the patients during the 3 days before or after the ictal phase scanned.

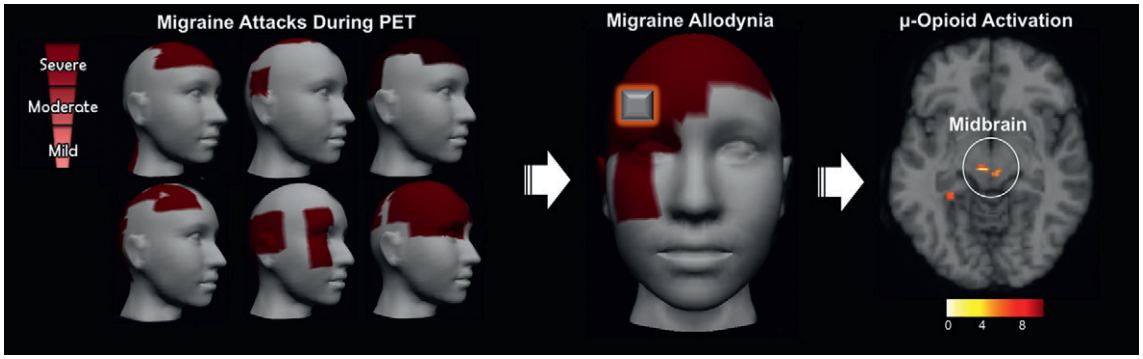

Figure 2. Migraine headache severity and allodynia-induced μ-opioid activation during PET. *Left*: Headache and facial pain intensity and area were recorded and analyzed using a free and interactive Apple mobile application developed in-house (Pain*Trek,* University of Michigan). The average pain intensity was moderate (6.3 ± 0.9; VAS [1–10]) for the headache attacks. *Center*: Placement of the thermode for the sustained thermal pain threshold (STPT) challenge on the patient's ophthalmic trigeminal region ipsilateral to the headache. The 3D image represents the average rating of the pain intensity and location of the migraine headache attacks of all patients at the time of the ictal PET session. *Right*: μ-opioid activation during migraine trigeminal allodynia. The image shows decrease in the μOR BPND of the midbrain region of the six migraine patients during attack as compared with the interictal phase ($P < 0.000$), using our STPT challenge.

We also noticed a decrease in μOR BPND during the cutaneous heat allodynia associated with the spontaneous migraine attack. There were concurrent bilateral clusters of endogenous μOR activation in the midbrain, extending from the red nucleus (RN) to the ventrolateral periaqueductal gray matter (vlPAG) (MNI coordinates with a peak on the left side: *x*: −6; *y*: −20; *z*: −8; $P < 0.000$) (Fig. 2), which was positively correlated with the patients' allodynic levels ($P < 0.003$; $r = 0.75$) (Fig. 1 – Right). These results indicate the acute activation of endogenous opioid neurotransmission interacting with μOR due to the allodynic experience of the migraine attack.

Discussion

This is the first in vivo demonstration of the μ-opioid system involvement in cutaneous migraine allodynia during spontaneous attacks. Increased endogenous μ-opioid neurotransmission interacted with μORs particularly in the vlPAG and RN, important midbrain areas related to migraine pathophysiology and allodynia modulation. Moreover, these flawed μOR activations were positively correlated with the severity of the patients' trigeminal allodynia. These findings indicate that, in addition to the migraine headache attack, the abnormal allodynic cutaneous experience was concurrent with ineffective high release of endogenous μ-opioids.

The PAG is a crucial supraspinal site of the antinociceptive descending pathway that also includes the rostral ventromedial medulla (RVM) and the dorsal horn of the spinal cord. The RN participates in cognitive circuits related to salience and executive control, as well as in the modulation of allodynia.[11–13] In migraine patients, there is a significant increase in iron deposition in both regions, which positively correlates with the duration of the illness.[14] The authors speculated that the impaired iron homeostasis may be attributed to neuronal damage caused by the frequent attacks. The activation in these midbrain regions during different migraine phases has been hypothesized as a dysfunctional response to the sensory inputs they receive from activated trigeminal neurons.[15,16] Our study corroborates this theory as there was an increased endogenous μ-opioid neurotransmission interacting with μORs accompanying the intensification of the trigeminal allodynic experience and the migraine suffering. In animal studies, morphine has been shown to modulate meningeal neurogenic inflammation associated with migraine, by attenuating brainstem neuronal activity and trigeminal nucleus caudalis neuronal sensitization, which are significantly reversed by naloxone.[17] Conversely, the sustained exposure to exogenous opioids induces pronociceptive trigeminal neural adaptations in animal migraine models[18] with generalized states of cutaneous allodynia that are blocked by inactivation of the RVM.[19] This persistent exposure to morphine induces reduction in the threshold for the activation of neurons at the medullary dorsal horn and in extension of the receptive field of those cells.

μOR BPND is a measurement in vivo of endogenous μOR availability,[8] and its instant decrease reflects the triggering of this neurotransmitter system during allodynic migraine suffering. The same cohort of migraine patients was previously used to report reduced μOR BPND in the mPFC solely during the headache phase before the thermal challenge, which was found to be negatively correlated with the combined measure of pain area and intensity (Pain Area and Intensity Number Summation – P.A.I.N.S).[3] It is known that μOR activation of the mPFC increases connectivity with the

PAG in analgesia.[20] Remarkably, we found a key difference regarding the level of μ-opioid release in those regions when a brief migraine allodynic experience takes place. Although μ-opioid release weakened with the extension and severity of the migraine pain in the previous study, the system showed the opposite behavior with the focal allodynic experience. This was demonstrated in this study by the positive correlation we found between μ-opioid releases in the vlPAG cluster with the ictal allodynic severity. It is possible that the salient and dysfunctional cutaneous sensory experience during our migraine protocol triggers further activation of the central μ-opioid system to respond to a potential external threat and ongoing pain, possibly represented by the additional ascending trigeminal sensory inputs. This explains the partial ineffectiveness of antimigraine medication once central sensitization with cutaneous allodynia is established in the late phase of headache attack, since there is already a concurrent overflow of endogenous μ-opioids acting on the existent μOR.[21] Despite targeting arguably one of the most important analgesic receptor-based mechanisms in the brain, these drugs are competing with the patients' own endogenous pain-relieving systems. In fact, the prior use of opioids alters treatment resistance to even nonopioid analgesic drugs in migraine patients.[21] Hence, opioids are not recommended as the first choice for the treatment of migraine by the U.S. Headache Consortium Guidelines, and it should be reinforced that their use in clinical practice is not evidence based.

In conclusion, we found additional release of endogenous μ-opioids acting on μOR during cutaneous migraine allodynia in the midbrain region, including the vlPAG and RN, which was positively correlated with the ictal changes in skin sensitivity to heat pain. Further studies should be conducted to evaluate how this endogenous μ-opioid mechanism is related to allodynia in other pain disorders and migraine subtypes, including chronic migraine. These novel results in vivo oppose the common practice of using opioids as rescue therapy for episodic migraine patients 1, especially for those with established allodynia, as there is already a high central occupancy of μORs.

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Conflict of Interest

None declared.

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