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Role of Endo-opioid and Endo-cannabinoid Systems in Migraine and Medication-overuse Headache

Endo-opioid ve Endo-kannabinoid Sistemlerin Migren ve İlaç Aşırı Kullanım Baş Ağrısındaki Rolü

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Abstract

Objective: The endo-opioid and endo-cannabinoid systems are important in regulating pain and have been implicated in migraine pathophysiology. Patients with frequent attacks, such as patients with chronic migraine (CM), frequently develop medication overuse headache (MOH). Not all patients with chronic headache develop MOH, the reason for which is not exactly known. We aimed to assess the involvement of these neurotransmitter systems in episodic and CM and in MOH.

Materials and Methods: Patients with (episodic migraine; n=29), (CM; n=15), MOH (n=16) and 31 healthy controls were recruited and blood levels of nociceptin and anandamide (AEA) were compared between groups, as well as their levels with headache parameters.

Results: AEA levels were significantly lower in the combined migraine groups compared to controls (p=0.009), but head to head comparison of the groups revealed no significant difference (p=0.062). Median nociceptin levels were found to be very high in CM (235.76 ng/l) group and very low in MOH (30.08 ng/l) group, but the difference was not statistically significant.

Conclusion: Our finding of low AEA levels in migraine supports the hypothesis of a dysfunctional endocannabinoid system in migraine. Although our results failed to reveal any differences between episodic and CM, an interpretation of findings reported in the literature suggested that this low endocannabinoid inhitory tone might contribute to nociceptive facilitation resulting in maintained central sensitization and therefore sustained pain in CM. Although not significant, nociceptin levels were much higher in CM group and the lowest levels were found in MOH group. It is possible that in CM, the opioid system tries to counterbalance the endocannabinoid dysfunction and if the opioid levels fail to rise, the patient is driven to an excessive use of analgesics and MOH develops. Although we were unable to prove this hypothesis we think it would be worthwhile studying this hypothesis in a larger group of patients.

Keywords: Anandamide, nociceptin, medication overuse headache, migraine, endocannabinoid system

Öz

Amaç: Endo-opioid ve endo-kannabinoid sistemler ağrının regülasyonunda önemli rol oynar ve migren fizyopatolojisi ile ilişkilendirilmişlerdir. Kronik migrende (KM) olduğu gibi sık atak geçiren hastalarda ilaç aşırı kullanım başağrısı (İAKBA) gelişebilmektedir. Ancak tüm kronik başağrısı olan hastalarda İAKBA gelişmemektedir. Bunun nedeni tam olarak bilinmemektedir. Bu çalışmanın amacı bu sistemlerin epizodik ve KM'de ve İAKBA'daki rolünün belirlenmesidir.

Gereç ve Yöntem: (Epizodik migren; n=29), (KM; n=15), İAKBA (n=16) ve 31 sağlıklı kontrol çalışmaya alınarak nosiseptin ve anandamid (AEA) kan seviyeleri ölçüldü ve bunların kan seviyeleri gruplar arasında ve başağrısı parametreleri ile karşılaştırıldı.

Bulgular: AEA seviyeleri tüm migren grupları birleştirilerek karşılaştırıldığında kontrol grubundan anlamlı olarak düşüktü (p=0,009) ancak grupların teke tek karşılaştırılmasında fark bulunamadı (p=0,062). Anlamlılık olmamakla birlikte median nosiseptin değerleri KM grubunda çok yüksek (235,76 ng/l), İAKBA grubunda ise çok düşüktü (30,08 ng/l).

Sonuç: Migrende düşük olarak bulduğumuz AEA seviyeleri migrende endokannabinoid sistem işleyişinin bozulmuş olduğu hipotezini desteklemektedir. Epizodik ve KM grupları arasında bir fark bulamamıza rağmen literatürde bildirilen sonuçların yorumlanması bize KM'deki devamlı başağrısının, düşük endokannabinoid inhibisyon düzeyinin katkıda bulunduğu nosiseptif fasilitasyona bağlı süregelen santral sensitizasyon sonucunda oluşabileceğini düşündürmüştür. Anlamlılığa ulaşmamakla birlikte nosiseptin düzeyleri KM grubunda en yüksekken İAKBA grubunda en düşüktü. KM'de bozulmuş olan endokannabinoid sistemi komponse etmek amacıyla endo-opioid sistemin devreye girmeye çalışması ve endo-opioid seviyelerinin yükselememesi durumunda hastanın aşırı ağrı kesici almaya itilerek İAKBA geliştirmesi olasıdır. Bu hipotezi tam olarak doğrulayamamakla birlikte bunun daha geniş çalışmalarda incelenmeye değer olduğunu düşünmekteyiz.

Anahtar Kelimeler: Anandamid, nosiseptin, ilaç aşırı kullanım başağrısı, migren, endokannabinoid sistem

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Introduction

The pathophysiology of migraine is still not fully understood despite numerous studies contributing to a better understanding of the mechanisms underlying migraine attacks. Patients with frequent attacks of migraine, such as patients with chronic migraine (CM), frequently develop medication overuse headache (MOH) which complicates the clinical picture and is difficult to treat (1,2). Not all patients with chronic headache develop MOH, the reason for which is not exactly known (1,2).

Various neurotransmitter systems have been implicated in the pathophysiology of migraine and also MOH (1,2,3,4). The endo-opioid system and recently characterized endocannabinoid system are among the key players in regulating pain (5,6,7,8,9) and are also thought to be involved in migraine (5,6,7,10,11,12,13,14,15).

The endocannabioid system is an important part of the endogenous pain control system and consists of the lipid mediators anandamide (AEA), 2-arachidoglycerol (2-AG) and palmitoylethanolamide (PEA) and the cannabinoid receptors CB1 and CB2 (7). The endocannabinoid system plays an important role in pain and CB1 receptors have been demonstrated in areas known to be involved in pain processing and migraine pathogenesis such as the periaqueductal grey matter (PAG), rostroventromedial medulla, cingulate cortex, frontal cortex, limbic areas and the caudal trigeminal nucleus (6,16) and have been shown to directly or indirectly modulate the release of neurotransmitters such as glutamate and γ-aminobutyric acid, glutamate, dopamine, noradrenaline, serotonin, nitric oxide (NO) and acetylcholine, most of which play an important role in migraine (17,18,19). Recent studies suggest that endocannabinoid deficiency may be an important factor underlying migraine pain and may play an important role in the chronification of migraine and development of MOH (20,21,22,23,24). The fact that the endocannabiod system has been involved in the neurobiology of drug addiction strengthens its role as a key factor in the pathophysiology of MOH (25).

Another system involved in pain and migraine is the opioid system (5,9,14). Nociceptin/orphanin FQ (N/OFQ) is a member of the opioid system which is structurally similar to dynorphin A and has been implicated in cortical spreading depression evoked trigeminal nociception and thefore in the pathophysiology of primary headaches including migraine (14,15). N/OFQ receptors are found not only in the trigeminovascular neurons but also in areas involved in pain perception like the cingulate, insular cortices, amygdala, hippocampus, hypothalamus, thalamus, dorsal raphe nucleus and periaquaeductal gray matter (PAG) (26,27). Nociception microinjection into the PAG has been shown to facilitate C-fibre evoked responses and block analgesia caused by morphine injection (28,29). In *in vitro* studies, nociceptin has been shown to inhibit calcitonine gene related peptide (CGRP) release in the trigeminal ganglion pointing to a possible role in pain inhibition (30). There are only a few studies of nociceptin in migraine and in MOH (31,32).

İn this study we aimed to measure interictal levels of peptides representing the endo-opioid system (nociceptin) and the endo-cannabinoid system (anandamid) in order to asses the involvement of these systems in both episodic and CM and in MOH.

Materials and Methods

This study was conducted on patients with episodic and CM with and without medication overuse who met the International Classification of Headache Disorders-3-Beta criteria, were between 18-80 years of age and attended the Akdeniz University hospital, Department of Neurology from February 2018 to September 2020. The study protocol was approved by the Local Ethics Committee of Akdeniz University (decision no: 148, date no: 21.02.2018) and all patients gave their informed consent prior to the study. Inclusion criteria were a monthly attack frequency <6 for episodic migraine (EM); a monthly analgesic/anti-migraine drug consumption of <10 days for CM and being off of any prophylactic medications for at least 2 months for all groups. Exclusion criteria were presence of any of the following: Another primary headache disorder, any known neurological or systemic disease, pregnancy, regular consumption of any drugs, another acute or chronic pain disorder and presence of depression as assessed by Becks Depression scale (patients with a score >16 were excluded). Patients were classified into 3 groups: EM without aura (EM), CM without medication overuse (CM), CM with medication overuse (MOH), and a control group of age and gender matched healthy individuals.

All patients with headache were told to keep a headache diary for one month. Patients categorized the daily intensity of their pain as severe (3), medium (2) or mild (1). The data from those diaries were used to calculate a "headache score" which consisted of the sum of all headache days where days with severe headache were multiplied by 3, medium headache by 2 and mild headache by 1.

Impact of headache on quality of life was determined by the The Migraine Disability Assessment (MIDAS) questionnaire (33).

Blood samples were collected in the morning between 08:00-11:00, after the patients returned the headache diary at least 72 hours after the end of their last migraine attack. Samples taken from the antecubital vein were taken into test tubes containing 6 ml K-EDTA and aprotinin (0.6 TIU/ml), the plasma was seperated by centrifugation at 4000 rpm for 4 minutes and plasma samples were aliquoted and stored at -80 ºC until analysis.

Nociceptin levels were analysed by the ELISA method using MyBioSource kits (MyBioSource.com. P.O. Box 153308. San Diego, California. United States; intra-assay coefficient of variation (CV):<8%, inter-assay CV:<10%; sensitivity 0.59 ng/l; linearity levels 1.00-400.0 ng/l).

AEA levels were analysed by the ELISA method using MyBioSource kits (MyBioSource.com. P.O. Box 153308. San Diego, California. United States; intra-assay CV:<10%, inter-assay CV:<12%; sensitivity 0.93 ng/l; linearity levels 2.47-200.0 ng/l).

Statistical Analysis

Statistical analysis was performed using IBM SPSS 23.0 software (IBM Corp., Armonk, NY). Normality assumption was tested by Kolmogorov-Smirnov test. Because normality could not be achieved, non-parametric tests were used. Mann-Whitney U test was used to compare 2 groups and Kruskall-Wallis test was used to compare 3 or more groups and Bonferroni-Dunn test was used for post-hoc analyses. Correlations between ordinal or not normally distributed parameters were analyzed by Spearman's correlation analysis or multiple linear regression analysis. The level for significance was set at $p<0.05$.

Results

A total of 91 subjects were recruited; 29 in the EM without aura (EM) group; 15 in the CM without medication overuse group (CM); 16 in the CM with medication overuse group and 31 controls. Demographics of the groups are presented in Table 1. There was no difference in terms of age and sex distribution between groups.

Median values for monthly headache frequency, headache years, headache score and MIDAS score were higher in the CM and MOH groups compared to EM, but did not differ between CM and MOH groups (Table 1).

Median AEA and nociceptin levels of the groups are presented in Table 2. AEA levels were significantly lower in the combined migraine groups compared to controls (p=0.009), but head to head comparison of the groups revealed no significant difference (p=0.062). Median nociceptin levels were found to be very high in the CM group (235.76 ng/l) and very low in the MOH group (30.08 ng/l), but the difference was not statistically significant.

Spearman correlation test found no correlation between headache parameters and nociceptin levels in any of the groups. For AEA levels there only was a negative correlation with monthly headache frequency in the CM group (r=-0.559; p=0.03).

Discussion

We found significantly lower AEA levels in patients with migraine and high nociceptin levels in the CM group and very low levels of nociceptin in the MOH group, although we were unable to demonstrate significance. Circulating levels of endocannabinoids have been shown to be altered in several painful conditions including migraine (8,10,12,20,22,31,34). AEA has been shown to inhibit dural vasodilatation induced by CGRP and NO and that this action can be reversed by a CB1 receptor antagonist in experimental studies (35). Animal studies showed that electrical stimulation of the PAG resulted in release of AEA and led to analgesia (8) and that the injection of a CB1 receptor agonist into the ventrolateral PAG led to inhibition of nociceptor trigerred activation in the trigeminocervical complex (11,36). In a rat model, pretreatment with AEA was effective in reducing c-fos expression induced by nitroglycerin in the trigeminal caudal nucleus (13).

Platelets of female patients with EM have been shown to have increased activity of fatty acid amide hydrolase (FAAH), the enzyme that deactivates AEA, and AEA membrane transporter (AMT) which is responsible for the cellular uptake of AEA, which of both may lead to reduced levels of AEA (12). Gouveia-Figueira et al. (10) however could not demonstrate any difference in interictal blood AEA and other fatty-acid ethanolamide levels in patients with EM compared to controls. On the contrary FAAH and AMT activity have been found to be reduced in patients with MOH and CM without MOH (24). In accordance with this, Rossi et al. (20) reported that AEA and 2-AG levels in platelets were low in patients with MOH and CM without MOH compared to controls. A central dysfunction of the endocannabinoid system has been suggested by the finding of lower levels of AEA in the cerebrospinal fluid of patients with CM (22). This was also confirmed in animal studies where nitroglycerine induced biochemical alterations in the dorsal horn were reversed by AEA, pointing to the role of AEA in reversing central sensitization (16). Perrotta et al. (21) showed that dysfunction in the endocannabinoid system could lead to acute medication overuse and hypothesized that a dysfunctional endocannabinoid system would result in the development and maintainance of central sensitization leading to the chronification of migraine.

Cannabinoid receptor gene and protein expression as well as gene expressions of enzymes involved in the synthesis of endocannabinoids have been shown to be elevated in patients with

Table 1. Demographics and headache parameters in the study groups

	Controls (n=31)	EM (n=29)	CM (n=15)	MOH (n=16)	p
Age	32.1±8.1	30.4±8.7	31.1±8.5	37.9±13.0	NS
Gender (female)	24 (77.4%)	24 (82.8%)	11 (73.3%)	14 (87.5%)	NS
Monthly headache days (median)	NA	4 (1-6)*	15 (10-28)*	17 (10-29)*	<0.001*
Headache years (median)	NA	6 (2-25)*	10 (3-20)*	15 (4-37)*	0.023*
Headache score (median)	NA	9 (2-20)*	34 (24-73)*	44 (27-93)*	<0.001*
MIDAS score (median)	NA	13.5 (1-47)*	51 (12-87)*	57.5 (9-157)*	<0.001*

*CM and MOH compared to EM group.
CM: Chronic migraine, MOH: Medication overuse headache, EM: Episodic migraine, MIDAS: The Migraine Disability Assessment, NS: Not significant

Table 2. Median AEA and N/OFQ levels in the study groups

	Controls (n=31)	EM (n=29)	CM (n=15)	MOH (n=16)	Migraine combined (n=60)	p
AEA (ng/l)	15.9 (1.12-192.92)	3.9 (0.89-181.32)	7.64 (1.13-53.1)	5.18 (0.41-31.9)	5.22 (0.41-181.32)	NS
N/OFQ (ng/ml)	81.82*,† (2.13-384.69)	83.42† (7.41-396.87)	235.76† (7.63-391.4)	30.08† (6.96-339.11)	50.45* (6.96-396.87)	0.009* 0.062†

*Migraine combined vs controls, †Controls, EM, CM and MOH compared. NS: Not significant,
CM: Chronic migraine, MOH: Medication overuse headache, EM: Episodic migraine, AEA: Anandamide, N/OFQ: Nociceptin/orphanin FQ

EM and CM with MOH with a more pronounced expression of genes involved in endocannabinoid metabolism in the CM group (23). In the same study, *FAAH* gene expression was found to be lower in migraineurs compared to controls with significantly lower levels in CM compared to EM (23). These findings explain the low activity of FAAH reported in previous studies and suggest an effort for compensation, by decreasing AEA degradation, for the low endocannabinoid tone in CM.

Our results are in part consistent with previous studies finding low interictal plasma levels of AEA in patients with migraine. Unfortunately, we were unable to show any difference in head to head comparison of the EM, CM and MOH groups with the control group and therefore could not verify any role for AEA in the chronification of migraine or the development of MOH.

N/OFQ is a member of the opioid system which has also been implicated in the pathophysiology of pain and possibly migraine (14,15).

Nociceptin levels seem not to increase in response to acute pain as N/OFQ levels have been reported to be unchanged during labour (37). However, in some chronic pain conditions such as in fibromyalgia and during the interictal phase of a cluster period, N/OFQ levels seem to be reduced (38,39). Ko et al. (9) reported that N/OFQ levels were significantly higher in patients with pain compared to controls and were much higher in patients with chronic pain syndromes compared to patients with acute pain.

There are only a few studies of nociceptin in migraine. In an experimental study, a selective nociceptin receptor agonist was effective in blocking both allodynia and decreasing light sensitivity in nitroglycerin-induced migraine attacks (40). Circulating levels of N/OFQ have been shown to be decreased in the interictal phase of migraine, further decreasing at the onset of an attack (31). Munksgaard et al. (32) reported no difference in N/OFQ and CGRP levels in a group of patients with MOH before and 6 months after successful detoxification and concluded that altered levels of these peptides did not cause an increase in headache frequency in MOH. The high dropout numbers in that study however still leave room for debate that the post-treatment levels may have changed.

Although we found nociceptin levels to be very high in patients with CM and very low in patients with MOH, our results failed to reach significance. Therefore, we stand on shaky ground reaching any firm conclusions about the role of nociceptin in migraine.

Study Limitations

Several limitations of our study warrant mention. Firstly and most importantly, our subject numbers were too small to detect a statistical difference, causing our high intersubject variability despite great inter-group differences in peptide levels. Secondly, we did not determine the levels of other endocannabinoids such as 2-AG and PEA due to financial reasons. This would have strenghtened our study.

Conclusion

Our finding of low levels of AEA in migraine supports the hypothesis of a dyfunctional endocannabinoid system in migraine. Although our results failed to reveal any differences between episodic and CM, an interpretation of findings reported in the literature suggested that this low endocannabinoid inhitory tone might contribute to nociceptive facilitation resulting in maintained central sensitization and therefore sustained pain in CM. Although not statistically significant, our nociceptin levels were much higher in the CM group and the lowest levels were found in the MOH group. It is possible that in CM the opioid system tries to counterbalance the endocannabinoid dysfunction and if the opioid levels fail to rise, the patient is driven to an excessive use of analgesics and MOH develops. Although we were unable to prove this hypothesis we think it would be worthwhile studying it in a larger group of patients.

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Ethics

Ethics Committee Approval: The study protocol was approved by the Local Ethics Committee of Akdeniz University (decision no: 148, date no: 21.02.2018).

Informed Consent: Informed consent from all participants was obtained.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.H., Concept: D.D-D., S.Ö., B.D., Design: D.D-D., S.Ö., B.D., Data Collection or Processing: G.H., S.Ö., Analysis or Interpretation: G.H., B.D., Literature Search: G.H., B.D., Writing: G.H., S.Ö., B.D.

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