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Research Article

Orexin-A Levels in Episodic and Chronic Migraine: Implications For Hypothalamic Involvement?

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Summary

Objective: The aim of the study was to demonstrate whether blood Orexin A levels (OX-AL), which are a marker of hypothalamic activity, are altered in patients with migraine and whether they differ ictally and interictally and with the chronification of migraine.
Materials and Methods: A total of 113 patients participated in this study. Orexin A blood samples were taken during a headache-free interval. In 17 patients with episodic migraine a second blood sample for Orexin A was taken during an attack of migraine.
Results: OX-AL were lower in episodic migrane compared to controls but did not differ during an attack and the interictal period.
Conclusion: Our findings of low OX-AL in episodic migrane both ictally and interictally, similar levels of OX-AL in chronic migraine and tension-type headache compared to controls may suggest that OX-AL is probably not released in response to acute pain but its basal levels may modulate the susceptibility to pain. Basal OX-AL are low in patients with episodic migrane which could reflect a suppression of the orexinergic system due to hypothalamic dysfunction but increase with chronification possibly in response to lower Orexin-A receptor density secondary to neurodegeneration. Further larger studies may shed more light on the role of the orexinergic system and the hypothalamus in migraine and the chronification of it.

Key words: Orexin-A, Migraine

Epizodik ve Kronik Migrende Orexin-A Düzeyleri: Hipotalamik Tutulumun Etkisi Mi?

Özet

Amaç: Bu çalışmanın amacı, hipotalamik aktivitenin bir belirteci olan kan Oreksin-A düzeylerinin migren hastalarında değişiklik gösterip göstermediğini ve migrenin kronikleşmesi ile iktal ve interiktal periyotta farklılık gösterip göstermediğini ortaya koymaktır.
Materyal-Metot: Bu çalışmaya 113 hasta dahil edildi. Oreksin-A kan örnekleri baş ağrısının olmadığı dönemde alındı. Epizodik migreni olan 17 hastada migren atağı esnasında ikinci kan örneği alındı.
Sonuçlar: Oreksin A düzeyleri, epizodik migren grubunda kontroller ile karşılaştırıldığında daha düşüktü ama atak ve interiktal periyotta değişiklik göstermedi.
Sonuç: Epizodik migrende iktal ve interiktal Oreksin-A düzeylerinin düşük olması ve kontrol grubu ile karşılaştırıldığında kronik migren ve gerilim tipi başağrısında benzer düzey Oreksin-A düzeyleri, Oreksin-A'nın muhtemelen akut ağrıya cevap olarak salınmadığı ve bazal düzeylerinin ağrıya duyarlılığı modüle edebileceğini önermektedir. Epizodik migren hastalarında bazal Oreksin-A düzeylerinin düşük olması, hipotalamik disfonksiyona bağlı oreksinerjik sistemin baskılanmasını yansıtabilir, ama kronikleşme ile birlikte artması

muhtemelen nörodejenerasyona sekonder düşük oreksin reseptör yoğunluğuna ikincil olabilir.Daha büyük çalışmalar migren ve kronikleşmesinde oreksinerjik sistem ve hipotalamusun rolünü daha fazla aydınlatabilir.

Anahtar Kelimeler: Oreksin-A, Migren

INTRODUCTION

Orexin A (OX-A) and B are a group of peptides which are synthesized in the lateral and dorsal hypothalamus and are widespread in the brain[12]. The orexinergic system plays a role in the modulation of feeding, the sleep-wake cycle, cardiovascular, neuroendocrine and autonomic functions in the body[12,8,25]. It is known that the orexinergic system projects to many structures involved in pain and autonomic modulation like the periaquaeductal gray matter (PAG), ventrolateral reticular formation, paraventricular nucleus, dorsal raphe nucleus, locus coeruleus, nucleus tracti solitarii and the spinal and trigeminal dorsal horns[12,26,18]. Recent studies have shown that the orexins also play an important role in the modulation of pain[3,5,14,27]. Animal studies have shown that Orexin-A has an antinociceptive effect which is mainly activated under inflammatory conditions[3,29]. Despite the research on pain there still is only circumstantial evidence for role of the orexins in primary headaches.

In the pathophysiology of narcolepsy an autoimmune loss of orexinergic cells in the hypothalamus has been shown to lead to low orexin-A levels[11] In narcoleptic patients the prevalence of migraine is much higher compared to the normal population suggesting a common pathophysiological step between these two disorders[6]. Other conditions where the hypothalamus and the orexinergic system seem to be involved, like obesity have also been found to be more prevalent in migraine sufferers[9]. Studies on patients with cluster headache have found increased polymorphism of the hypocretin receptor 2 (HCRTR2) gene but found CSF levels of Orexin A to be normal[24,20,4]. In a study investigating the genetic variants of Orexin Receptor 1, Rainero et al found that the HCRTR1 gene could represent a genetic susceptibility factor for migraine without aura. Results of this study suggest that the orexinergic system may have a role in the pathophysiology of migraine[21]. Hypotalamic activation is well known in the pathophysiology of migraine but it is uncertain until now whether the hypothalamus is involved in the initiation or later phases of the migraine attack[7].

Migraine and tension-type headache are two distinct entities by definition although in clinical practice these two disorders are commonly coexistent and are frequently confused with each other especially when the symptoms of migraine are subtle. Many studies and case demonstrations have shown activity in the hypothalamus in trigeminal autonomic cephalgias and migraine but not so for tension-type headache[7]. Therefore Orexin-A might be involved in the pathophysiology of migraine but not tension-type headache.

In regard of the previous studies we wanted to demonstrate whether blood Orexin A levels, which are a marker of hypothalamic activity are changed in patients with migraine compared to healthy controls and tension-type headache, a primary headache disorder with no presumed hypothalamic involvement. We further wanted to assess whether Orexin-A levels differ ictally and interictally in patients with episodic migraine and if there is a change with the chronification of migraine.

MATERIAL AND METHODS

Study Population:

This prospective cross-sectional study was conducted between November 2009 to January 2011 in the headache outpatient

clinic of the Department of Neurology at the xxxxxx Hospital. The study protocol was approved by the ethics committee and all the patients gave their informed consent prior to the study.

Patients were recruited by headache specialists out of patients they had seen in the outpatient clinic and who accepted to join the study. Patients who accepted were revised a second time in regard to inclusion and exclusion criteria and then included into the study. Healthy controls were recruited from patient relatives, hospital staff and family members who were healthy and were willing to join the study.

Eligible patients were patients between 18-55 years old, fulfilling the criteria of either episodic migraine without aura (n=31), chronic migraine (n=15), episodic tension type headache (n=31) or chronic tension type headache (n=15) according to the ICHD-II criteria[17]. Twenty-one control subjects without a history of primary headache disorder and any exclusion criteria were included. Exclusion criteria were: (i) history of any metabolic diseases, (ii) central nervous system disease, ıı) obesity or cachexia (body mass index <18.5 or >25 kg/m2), (iv) narcolepsy, (v) depression (≥17 points in the Beck depression scale) (vi) use of any prophylactic treatment for migraine within 6 months of recruitment (vii) antidepressant therapy within 3 months of recruitment (viii) and presence other painful conditions that might have interfered with Orexin A levels. As medication overuse (i.e excessive use of analgesic, narcotic or antimigraine drugs according to the ICHD II criteria)[17] and preventive treatment might have influenced blood Orexin A levels patients with medication overuse or on preventive treatment were also excluded.

Assays:

until analysis. Orexin-A levels were determined by enzyme-linked immunoassay ELISA kits.°Venous blood samples of all patients and controls were taken during a headache-free interval of at least 72 hours. In 17 patients with episodic migraine blood samples were also taken during a migraine attack. Ictal samples were only taken if the attack occurred after a pain free period of at least 72 hours. All blood samples of episodic migraine patients were taken within an hour of initiation of the migraine attack prior to symptomatic treatment. Blood sample was drawn from chronic migrane patients during interictal period. Blood samples were treated with 100 µL aprotinin (6 Tripsin Inhibitory Units/mL) per 1 ml of blood and then centrifugated. The separated plasma was stored at -80 C

Statistical analysis:

Statistical analyses were performed using the SPSS software version 16. Demographic and baseline characteristics were summarized as a mean±SD for continuous variables and as a percentage of the group for categorical variables. The normality analysis was performed by Kolmogorov–Smirnov. One-way ANOVA was used to compare the Orexin-A levels among the headache groups. Paired Student's t-test was used to compare Orexin A levels in episodic migraine group. All the hypotheses were constructed as two-tailed and α critical value was accepted as 0.05.

RESULTS

A total of 113 patients participated in this study. Mean age of the study population was 30.23±7.28 /years. There were 34 (30%) males and 80 (70%) females. Mean headache duration was 4.96±3.85/years, median number of attacks per month was 4 and mean BMI was 22.03±1.9 kg/cm2. Median value for Beck depression scale was 6. Diagnoses were episodic tension type headache in 31, chronic tension type headache in 15, episodic migraine without aura in 31 and chronic migraine in 15 patients. Baseline characteristics of the patients are given in Table 1.

A one-way analysis of variance (ANOVA) was conducted to evaluate the relationship between Orexin-A levels and the headache types (Episodic Migraine, Chronic Migraine, Episodic tension type headache, Chronic Tension type headache, Control subjects) and statistically significant difference was observed between episodic migraine during ictal period and control groups (p=0.03). Post-Hoc tests were performed using Tukey's test and the results revealed a statistical significant difference between episodic migraine and the control groups (p=0.03) (Table 2).

A second blood sample was collected from 17 of 31 patients with episodic migraine during the attack. There was no statistically significant difference between Orexin-A levels in the episodic migraine group during the attack and the interictal period. There was no statistically significant relation between gender and Orexin A levels.

Table 1: Baseline characteristics of the patients

	Episodic Migraine	Chronic Migraine	Episodic TTH	Chronic TTH	Controls
Number of Patients	31	15	31	15	21
Male/Female	7/24	3/12	12/19	4/11	8/13
Mean age/years	31.06±7.82	29.47±8.76	29.55±5.73	31.93±9.69	29.33±5.60
Mean disease duration/year	6.39±4.53	6.00±4.29	3.77±2.43	3.40±3.15	N/A
Median attack number /month	3	19	3	27	N/A
Mean Body Mass Index	22.47±1.58	22.34±1.80	21.42±2.26	24.47±5.65	21.90±1.97
Median Beck Depression Scale	6	12	6	9	1
Mean Oreksin A level (ng/mL)	0.69±0.32*	0.91±0.37	0.90±0.33	0.84±0.41	0.96±0.22*

* Tukey's test revealed a statistical significant difference between episodic migraine and the control groups. N/A: not applicable

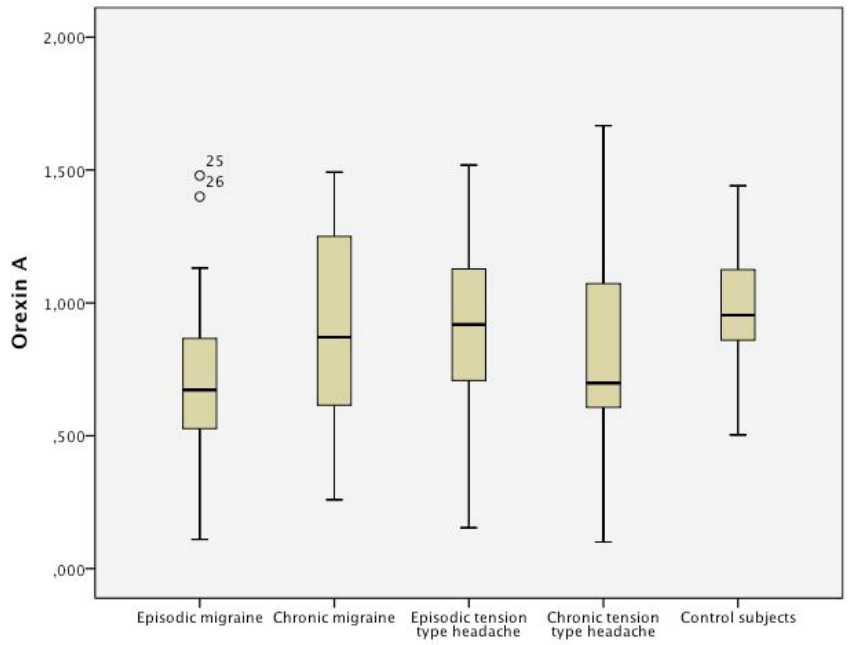

Figure 1: *Comparison of Orexin-A levels according to headache groups*

DISCUSSION

Our finding of lower OX-A levels in episodic migraine may explain why migraine sufferers are more susceptible to migraine attacks. The reason for the lower OX-A levels in episodic migraine is difficult to explain. Given the normal OX-A levels in chronic migraine we would suggest that the dysfunction in the hypothalamus is not primary and persistent. It is possible that the orexinergic system is suppressed in episodic migraine. If this was the fact, one would expect no raise in OX-A levels in response to acute inflammatory pain as during an attack of migraine. Our finding of unchanged OX-A levels during migraine attacks compared to the interictal phase supports this hypothesis. The reason for the low orexin-A levels in episodic migraine and if present, the reason for the hypothalamic suppression has yet to be elucidated in other studies.

The hypothalamus may be responsible for maintaining a basal nociceptive treshold via the orexinergic system[3,16]. The orexinergic system has been supposed to facilitate an increase in pain thresholds in the CNS under inflammatory conditions, contributing to antinociception[3,29]. Experimental evidence has shown that in prepro-orexin knockout mice there is no difference in pain thresholds under normal conditions compared to wild type mice while prepro-orexin knockout mice demonstrate increased hyperalgesia when exposed to peripheral inflammation[29]. Orexin- A has been shown to inhibit neurogenic vasodilation at the dura, release of CGRP from trigeminal neurons and transmission of nociceptive responses to dural stimulation at the TNC, all phenomena involved in peripheral sensitization in the pathophysiology of an acute migraine attack[14,1,10,11]. Descending projections of the orexinergic system to the second order neurons in the spinal and trigeminal dorsal horns have been shown[26,18] This raises the possibility that the orexinergic system also exerts its antinociceptive effect at the level of the

second order neurons[12] and is only activated during inflammatory conditions[3,29]. It is therefore possible that orexin-A exerts an inhibitory effect on peripheral sensitization.

In the light of the data above low levels of OX-A would be expected to result in lower pain thresholds leading to a greater susceptibility to triggers and after initiation of an attack of migraine to a facilitated onset and prolonged duration of peripheral sensitization.

The trigeminal nucleus caudalis is in close connection with pain modulating centers like the PAG, and the latter is repetitively activated with increased firing of trigeminal neurons as in repeating frequent migraine attacks[15,13]. Repetitive activation of antinociceptive areas in the brainstem has been suggested to cause degenerative changes in these areas as has been shown by increased iron accumulation in the PAG with chronification of migraine and studies of biochemical markers have pointed to a possible neurodegenerative process in migraine[28,30].

In our study Orexin A levels were found to be no different between chronic migraine patients and controls while they were significantly lower in the episodic migraine group. Higher levels of an analgesic peptide in a chronic pain condition compared to an episodic one seem to be contradictory, as it would be expected that low orexin-A levels should facilitate occurrence of pain. This contradiction may be explained by a hypothalamic compensatory response to chronic pain or the stress resulting from it. Corticotrophin releasing factor (CRF) and Orexin A levels have found to be increased in the CSF of chronic migraine patients. Chronic stress in chronic migraine may increase secretion of CRF, which in turn activates the orexinergic system leading to increased Orexin A levels[22]. On the contrary in episodic migraine where peripheral sensitization is an important part of an attack, low Orexin A levels may facilitate pain resulting from inflammation. It is also probable that low Orexin A levels, may lead to decreased stimulation of pain modulating centers like PAG and may cause inadequate antinociception and prolongation of the pain via central sensitization. Chronification of migraine has been shown to cause degeneration of pain modulating centers in the brainstem[30]. Degeneration of pain modulating areas in the brain may result in decreased Orexin A receptor numbers which in turn could lead to increased release of Orexin A as a feedback response to achieve better pain control. But because other neurotransmitter systems involved in pain would also be dysfunctional, this would explain the chronic pain despite higher Orexin A levels.

In our patients with episodic and chronic tension-type headache (TTH) we found Orexin A levels to be no different compared to controls. It has been proposed that in the pathophysiology of TTH prolonged repetitive nociceptive input from pericranial myofascial structures and dysfunction of pain modulating areas in the brain and brainstem may be the cause of the pain[2,23]. No evidence exists so far associating TTH to the hypothalamus or the orexinergic system[23].

Some limitations of our study warrant mentioning. First as this was a preliminary single center study and we had financial limitations our patient numbers were small. It would be interesting to reproduce our findings in a larger, multicenter study. Second, we could have taken ictal samples for the tension-type headache and chronic migraine group as well but our thought was that in tension-type headache the headache is of much less intensity compared to migraine so that chances are that orexin levels will not change much. As this was a small study with limited resources we decided to focus on migraine attacks and maybe address the subject of ictal differences in later studies. We took our ictal samples in the migraine group after a

pain free period of at least 72 hours. İn chronic migraine, because of the high attack frequency, it is difficult to reliably judge an attack has occurred after a refractory period of 72 hours, so we decided not to assess this group during an attack.

Our findings of low levels of Orexin A in episodic migraine both ictally and interictally, similar levels of Orexin A in chronic migraine and tension type headache compared to controls may lead to the following conclusions. Orexin A is probably not released in response to acute pain but its basal levels may modulate the susceptibility to pain. Orexin A levels are low in patients with migraine due to hypothalamic dysfunction but increase with chronification possibly in response to lower Orexin A receptor density secondary to neurodegeneration. High Orexin A levels in chronic migraine are ineffective in preventing the pain possibly due to reduced numbers of Orexin A receptors or due to other dysfunctioning neurotransmitter systems involved.

This is the first study comparing Orexin A levels between episodic and chronic migraine and tension-type headache. Further larger studies may shed more light on the role of the orexinergic system and the hypothalamus in migraine and the chronification of it.

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