Orexin-A CSF levels correlate with anxiety but not excessive daytime sleepiness in chronic migraine

Orexina-A se correlaciona com ansiedade mas não sonolência diurna no líquido cefalorraquiano de pacientes com enxaqueca crônica

Mario Fernando Prieto Peres[1,2,3], Domingos Savio Vieira[1,2], Marcelo Rodrigues Masruha[1,2]
André Leite Gonçalves[1,2,3], Juliane Prieto Peres Mercante[1], Maria da Graça Naffah-Mazzacoratti[2]

[1]Instituto Israelita de Ensino e Pesquisa - Hospital Albert Einstein, Sao Paulo, Brazil
[2]UNIFESP, Escola Paulista de Medicina, Department of Neurology, Sao Paulo, Brazil
[3]FMABC, Department of Neurology, Sao Paulo, Brazil

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ABSTRACT

Background: The hypothalamus is a key brain region in the control of energy metabolism, sleep and circadian rhythms, stress and anxiety, food intake, sexual and reproductive behaviors. Orexin-A (hypocretin-1) is a neuropeptide, synthesized in the hypothalamus extensively linked to sleep/wake states, particularly excessive daytime sleepiness. Chronic migraine is comorbid with several conditions but little is known about its mechanisms. We aimed to study the role of orexin-A in the mechanism of chronic migraine and comorbid conditions. **Methods:** We studied orexin-A levels in the CSF of 60 chronic migraine patients, comparing with age and sex matched controls, and comorbidity with anxiety, depression and excessive daytime sleepiness, using appropriate scales. **Results:** Orexin-A levels were inversively correlated with anxiety levels (r=-308, p=0,03), but not depression and excessive daytime sleepiness. Orexin levels in CM patients were not different than controls. **Discussion/Conclusion:** Anxiety in CM may be due to a decrease in orexin-A or may be the cause of its depletion. The orexinergic system may be implicated in anxiety comorbid with migraine.

Keywords: Migraine; Anxiety; Orexin

RESUMO

O hipotálamo é uma estrutura chave para o controle do ciclo sono-vigília, estresse e ansiedade, comportamento alimentar e sexual. A orexina-A (hipocretina-1) é um peptídeo hipotalâmico ligado ao ciclo de sono, especialmente sonolência diurna excessiva e narcolepsia. Enxaqueca crônica é comórbida com diversas doenças, mas pouco se sabe sobre os seus mecanismos. Estudamos o papel da orexina-A na fisiopatologia da enxaqueca crônica e comorbidades dosando seus níveis no líquido cefalorraquiano de 60 pacientes com diagnóstico de enxaqueca crônica, comparados com controles pareados por idade e sexo. Escalas apropriadas foram usadas para mensurar ansiedade, depressão e sonolência diurna associadas. Os níveis de orexina-A foram inversamente correlacionados com os de ansiedade (r=308, p=0,03), mas não houve diferença com as escalas de depressão e sonolência excessiva. Os níveis de orexina-A não foram diferentes em pacientes e controles. **Conclusão:** Ansiedade em enxaqueca crônica pode ser devido a uma diminuição da orexina-A ou ser a causa da sua depleção. O sistema orexinérgico pode estar implicado na comorbidade da ansiedade com enxaqueca.

Palavras-chaves: Migrânea; Ansiedade; Orexina

INTRODUCTION

The hypothalamus is a key region in the central nervous system (CNS) responsible for the regulation of several physiological functions, such as control of energy metabolism, sleep and circadian rhythms, stress and anxiety, food intake, sexual and reproductive behaviors.[1] Orexin (hypocretin) is a neuropeptide, synthesized in a small set of neurons in the perifornical area of the hypothalamus. Recent studies have implicated the orexin system as a critical regulator of sleep/wake states as well as feeding behavior and reward processes.[2] Orexin has been linked to many neurological conditions not only in sleep disorders such as narcolepsy, but also in neurological diseases with associated sleep symptomatology, mainly excessive daytime sleepiness (EDS) including traumatic brain injury, neurodegenerative, neuromuscular and neuroimmunological disorders.[3] Orexin deficiency also cause abnormalities in energy homeostasis and reward systems. Orexin activates waking active monoaminergic and cholinergic neurons in the hypothalamus and brainstem receiving significant input from the limbic system.

Migraine is a chronic and debilitating condition affecting a significant proportion of the population.[4] Migraine pathophysiology is multifactorial, genetic, hormonal, environmental aspects are involved, the hypothalamus has been considered to play an important role in migraine mechanisms.[5] The orexin system may be a potentially important target for both mechanisms and treatment of headache disorders.[6] A number of studies in experimental animals showed that orexin is involved in pain modulation within the CNS, and suggested the presence of a link between these peptides and nociceptive phenomena observed in primary headaches.[7-9] Cluster headache has been linked to the orexin system, several polymorphisms were studied in 109 patients, the 1246 G>A polymorphism of the hypocretin receptor 2 (HCRTR2) gene was significantly different between cases and controls. Homozygosity for the G allele was associated with an increased disease risk.[10] Migraine has been studied genetically, but the HCRTR2 G1246A polymorphism has not found to be associated.[11,12] The orexinergic system has been implicated in the comorbidity with migraine and obesity.[13-15] Orexin-A was studied in the cerebrospinal fluid (CSF) of chronic migraine (CM) and medication-overuse headache (MOH) patients showing higher levels in these patients.[16]

Orexin has been linked to anxiety,[17,18] stress,[19] addiction,[20] but to date it has never been linked to migraine psychiatric comorbidity. We therefore aimed to study the role of orexin-A in chronic migraine patients and comorbid conditions.

PATIENTS AND METHODS

Sixty-two patients (10 men and 52 women, ages 15-69 years, mean age 37.9 years) were diagnosed with CM according to International Headache Society criteria 2004[21] and Appendix 2006,[22] and were consecutively enrolled. All patients attending at the Brain Research Institute-Hospital Israelita Albert Einstein, São Paulo, Brazil. Two patients were excluded: a woman who had chronic meningitis due to cysticercosis, and another woman with idiopathic intracranial hypertension with papilloedema, both of whom had migrainous features. Sixty patients were analyzed. All these patients had a history of episodic migraine, but had subsequently developed frequent migraine. The patients were referred from a basic health programme, in a community near the hospital, representative of the general population. Patients were not exposed to previous migraine prevention treatments. All 60 patients suffered from daily headaches at the time of the study. Clinical history was obtained by the authors. Interviews and neurological examinations were performed by two neurologists (D.S.S.V. and M.R.M.), supervised by the senior author (M.F.P.P.). Body mass index (BMI; weight in kilograms divided by the square of height in meters) was recorded in all patients.

COMORBIDITY MEASURES

Patients were interviewed and diagnosed if any psychiatric comorbidity was present according to the DSM-IV. All the patients were submitted to a detailed headache questionnaire and answered the following questionnaires: Epworth sleepiness scale, in order to measure excessive daytime sleepiness which was considered when levels were equal or higher than 10. STAI (State-Trait Anxiety Inventory) measured anxiety levels, 20 questions ranging from 1 to 4 each one, total score would range from 20 to 80, a cutt-off on 40 was stablished for the dicotomous analysis. The BDI-II (Beck Depression Inventory) was used to assess depression severity, the score has 21 questions, each one scoring 0 to 3, the total score ranges from 0 to 63, depression diagnosis has been correlated in the literature with a score higher than 16.

CSF PROCEDURES

All patients had a lumbar puncture (LP), which was performed with the patient positioned in the lateral decubitus position on a level surface. A standard 22-G spinal needle was used. The opening pressure (OP) was recorded by using a manometer positioned at a 90° angle to the spinal canal with the patient's knees and hip in the extended position and neck straightened. CSF pressure was recorded until the patient was relaxed and the pressure values had stabilized. All LPs were performed by the same investigator (D.S.S.V.). Increase in CSF was considered when the OP was > 200 mmH2O.

Controlled CSF specimens were also obtained from 60 age- and sex-matched subjects who underwent lumbar puncture for others diagnostic purposes. Their CSF and blood tests were normal. When necessary, instrumental investigations including neuroimaging also excluded CNS diseases (multiple sclerosis, vasculitis, and other autoimmune diseases affecting the CNS) or systemic diseases (diabetes, renal or hepatic dysfunction, inflammatory diseases). Neurodegenerative diseases, mood, and anxiety disorders were also excluded. Orexin-A was quantified in the CSF using a ultra-sensitive, commercially available ELISA Kit (Peninsula Laboratories, San Carlos, CA).

The protocol was approved by the local Ethics Committee and all patients gave written consent to these study. The subjects' consent was obtained according to the Declaration of Helsinki. All patients were in pain at the time of lumbar puncture.

Statistical analysis

The values in μmol/l were expressed as mean ± SD. The chi-square test ($\chi 2$) (without Yates correction) was used for categorical data comparisons. Mean differences of continuous measurements were tested by the one-way analysis of variance - ANOVA (F). Whenever the ANOVA showed significant differences, the Bonferroni's multiple comparison test was used to verify between which groups the differences were found. The Pearson's product-moment correlation coefficient (r) was used to assess the relationship between two continuous variables, and point-biserial correlation coefficients (rpb) were used to assess the relationship between orexin levels and dichotomic categorical variables. A p value of less than 0.05 was considered to indicate statistical significance; all tests were two-tailed. Ninety-five percent confidence intervals (CI) were calculated for the difference between means and the regression coefficients. All statistical analyses were performed on a personal computer with the statistical package SPSS 11.5.1 for Windows.

RESULTS

The mean age of patients was 42.9 years, SD 11.6, mean frequency of headache 28.9 days per month, SD 2.43 days; mean baseline pain intensity (0 to 10) was 5.1, SD 1.3; mean exacerbations pain intensity 9.2, SD 0.8.

All CSF studied presented normal levels of protein, glucose, lactate, as well as the cell count.

Orexin levels were not signifficantly different in CM patients versus controls (p=0.278), no other demographic variable was statistically significant.

Orexin-A levels were inversively correlated with anxiety levels (r=-308,p=0.03). Depression levels (BDI-II) and Epworth Sleepiness scale levels were not significantly correlated with orexin-A levels (r=-0.215; p=0.139, r=0.105; p=0.245, respectively). Body Mass index was not correlated with orexin-A levels.

No significant correlation with analgesic intake and orexin levels were determined.

DISCUSSION

The more anxious the chronic migraine patient the less orexin-A levels were found in the CSF in our study, suggesting a role of hypothalamic orexinergic neurons in migraine comorbidity, particulatly in anxious behaviour. We can hypothesised a hypoactive orexinergic system underlying anxiety in chronic migraine patients.

In a study in CM and MOH patients, significantly higher levels of orexin-A were found in the CSF of MOH and to a lesser extent in patients with CM compared with control subjects. A significant positive correlation was also found between CSF orexin-A values and monthly drug intake group (R=0.39; P < 0.03) and scores of the Leeds Dependence Questionnaire (LDQ), an instrument to measure dependence of substances, in the MOH group (R=0.68; P < 0.0003). The authors interpreted the higher orexin-A levels found in CM and MOH as a compensatory response to pain or a hypothalamic overexpression to stress 16. In this study anxiety was not specifically assessed. Intracerebroventricular injection of orexin-A in two major anxiety tests, the light-dark exploration test (mouse) and the elevated plus-maze test (mouse, rat) suggested an anxiogenic effect of orexin.[23]

In contrast, a recent study in combat related postraumatic stress disorder showed the opposite. CSF and plasma orexin-A concentrations were significantly lower in the patients with PTSD as compared with healthy subjects, as wel as strongly and negatively correlated with PTSD severity as measured by the Clinician-Administered PTSD Scale (CAPS) in patients with PTSD.[19] These findings, in the same direction as our study, suggest a low orexin-A activity in anxiety.

The hypothalamus is a key region in the brain regulating important aspects of defense mechanisms and survival such as pain, sleep-wake cycle, appetite, hormonal and metabolism balance, reproduction. Although limited evidence is found in the literature, it is not surprising that an important defense mechanism such as anxiety might be regulated in the hypothalamus and possibly in orexinergic neurons. One can hypothesize orexin could play a role in regulating anxiety in CM, and migrainous patients with lowered orexin-A levels could develop anxiety because orexin is deficient. On the other hand, the excess of anxiety commonly experienced by CM patients could lead to a depletion in orexin levels.

Lowered orexin-A levels have been extensively linked to excessive daytime sleepiness in narcolepsy and other conditions due to a loss of orexinergic neurons.[24] We have not found a difference in patients versus controls, nor a correlation with BMI and EDS in our sample. It is less likely that a loss in orexinergic neurons happen in this chronic migraine context.

We could not find a difference between patients and controls, these could be due to the lack of an adequate control population, our controls were not absolutely free of symptoms; they underwent a LP to rule out a neurological condition and they could have experienced pain and anxiety during the procedure.

This orexinergic system has been considered as a potential target for the treatment of sleep disorders, it may be also a potentially important therapeutic agent for migraine and anxiety in the future.

We hope to encourage further studies focusing the orexinergic system and the hypothalamus in migraine and anxiety.

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Correspondence

Dr. Mario Fernando Prieto Peres
Joaquim Eugenio de Lima, 881cj 708
Sao Paulo, SP, Brazil
http://cefaleias.com.br/
marioperes@cefaleias.com.br