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Changes in Plasma PPARs Levels in Migraine Patients

Authors' Contribution:
Study Design A
Data Collection B
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Data Interpretation D
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Literature Search F
Funds Collection G

BCDEF 1,2 **Zhang He-min**
ABCDEF 1 **Bi Guo-rong**
ABCDEF 2 **He Qiu**
BCDEF 3 **Lin Xiang**
BCD 4 **Liu Suli**

1 Department of Neurology, Sheng Jing Hospital of China Medical University, Shenyang, Liaoning, China
2 Department of Neurology, The People's Hospital of Liaoning Province, Shenyang, Liaoning, China
3 Department of Neurology, Dalian Medical University, Dalian, Liaoning, China
4 Department of Neurology, Zhu Madian Center Hospital, Zhu Madian, Henan, China

Corresponding Author: Bi Guo-rong, e-mail: bigr@sj-hospital.org
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Background: The aim of this study was to observe the change in plasma PPARs (peroxisome proliferator-activated receptors) level during various periods and in different subtypes in migraine patients.





Material/Methods: We divided 227 patients with migraine into 2 main groups: the attack period group (n=98) and the attack-free period group (n=129). Patients were further divided into 4 subgroups according to whether they had aura symptoms. The control group consisted of 100 healthy subjects. We collected the clinical data of patients and measured the plasma levels of PPARs using enzyme-linked immunoassay (ELISA). We used SPSS software for statistical analysis.

Results: We found no significant difference in age, BMI, blood pressure, or blood lipid level among migraine patients during the headache attack period and during the headache-free period compared with the control group. The PPAR α and PPAR β/δ levels during the headache attack period were significantly higher than during the headache free period and in healthy controls. The PPAR γ levels during the headache attack period were significantly lower than those during the headache-free period and in the healthy control group. The PPARs levels during the headache attack period were significantly different from those during the headache-free period, regardless of presence or absence of aura. The PPARs levels during the headache-free period were not significantly different from those of the healthy control group. The level of PPARs has no significant differences between migraine with aura group and without aura group, regardless of whether headache attack.

Conclusions: PPARs involved in the pathogenesis of migraine. Presence of absence of aura had no obvious effect on PPARs level.

MeSH Keywords: **Inflammation • Migraine Disorders • Peroxisome Proliferator-Activated Receptors**

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Background

Migraine is a common chronic neurological disease. The pathogenesis of migraine is still not very clear. The brainstem trigeminal nerve/vascular inflammatory theory of migraine pathogenesis is receiving increasing attention, and the expansion of the brain and meningeal arteries and inflammation are the main pathological changes in migraine [1,2]. Peroxisome proliferator-activated receptors (PPARs) were found by Issemann for the first time in 1990. PPARs is a transcription factor in ligand activation and belongs to the nuclear hormone receptor superfamily [3]. It can regulate lipid metabolism after activation, as well as improving insulin sensitivity and antitumor and other biological functions. There are relationships between PPARs and stroke, Alzheimer's disease, and multiple sclerosis [4–6]. Our previous studies have found that PPAR alpha, PPAR beta/delta, and PPAR gamma have strong positive expression in a nitroglycerin experimental rats migraine model in rat trigeminal nerve neck complex [7]. Clinical studies have shown that migraine plasma levels of PPAR gamma vary [8]. Preliminary research suggests PPARs may participate in the onset of migraine. This study further explores the change in plasma PPARs level during the headache attack period and during the headache-free period, explores the relationship and clinical significance of PPARs and migraine, and provides a new train of thought about migraine prevention.

Material and Methods

The research object

Selected cases: Between January 2012 and June 2014 we enrolled a total of 227 migraine patients at the Neurology and Neurosurgery Department at The People's Hospital of Liaoning Province, both as outpatients and hospitalized patients, including 98 patients who were in the headache attack period and 129 patients in the headache-free period, of which 62 had auras and 165 did not have auras. Migraine patients were enrolled according to the diagnostic criteria (second edition) of the International Headache Society Migraine Classification Committee and the 2011 edition with migraine guidelines for diagnosis and treatment in China. During the study period, patients could accept pain management during the headache attack period but could not volunteer for the prevention of migraine. The study was approved by our hospital ethics committee and the patients provided signed informed consent.

Exclusion criteria were: (1) age <15 years or >65 years; (2) body mass index (BMI) <18 kg/m² or >30 kg/m²; (3) routine ECG, blood erythrocyte sedimentation rate (ESR), ASO checked exception; (4) cerebral aneurysm, cerebral infarction, cerebral hemorrhage, vascular malformations, brain tumor, and other

diseases of the nervous system confirmed by TCD examination, CT, or MRI/MRA; (5) complicated with hypertension, hyperlipidemia, diabetes, atherosclerosis, inflammation, rheumatoid arthritis, lupus erythematosus (sle), Hashimoto's thyroiditis or inflammatory bowel disease; (6) smoking, (7) birth control pills; and (8) pregnant or breast-feeding.

Patient groups

Group A: migraine patients during the headache attack period (n=98); Group B: migraine patients during the headache-free period (n=129). According to the presence of aura symptoms, migraine patients were further divided into 4 subgroups: group A1 for patients during the headache attack period without aura phase (n=71), group A2 for patients during the headache attack period with aura (n=27); group B1 for patients during the headache-free period without aura (n=94), and group B2 patients during the headache-free period with aura (n=35). Group C was healthy controls (n=100)

Research methods

We gathered 2 ml of peripheral venous blood, collected into EDTA anticoagulant tubes, and store at -80°C. We assessed the plasma level of PPAR alpha beta/delta/gamma using enzyme-linked immunoassay (ELISA). We collected data on patient age, sex, BMI, blood pressure, and blood lipids (low-density lipoprotein triglyceride) at the same time.

All the specimens were centrifuged at 3000 rpm for 10 min, absorbing supernatant fluid, and repackaging in 0.5-ml EP tubes. We used PPAR alpha beta/delta/gamma kits (purchased from Beijing Tripod Biological Technology Co., LTD) according to manufacturer instructions. The standard enzyme package has a hole without samples and enzyme reagent (the rest of the steps are the same) and a standard hole under the test sample hole. We diluted the standard and the sample under test, incubated them for 30 min at 37°C, washed them, added enzyme reagent, incubated them again for 30 minutes at 37°C, washed them again, added chromogenic agent, avoided light color for 15 min at 37°C, added the liquid and determined wavelength of absorbance (OD value) with a standard enzyme instrument within 15 min under 450 nm.

Statistical processing

We used SPSS 17.0 statistical software for statistical analysis of data with mean standard \pm deviation ($\bar{x}\pm s$). We used single-factor analysis of variance between groups, and 2-sample t test within the groups, with $P<0.05$ as the level of statistically significant difference.

Table 1. Compared of generally condition between groups in migraine.

Group	Case	Gender		BMI (kg/m ² , x̄±s)	Age (years, x̄±s)	BP (mmHg, x̄±s)		Lipid (mmol/L, x̄±s)	
		Male	Female			SBP	DBP	TG	LDL-c
A group	98	34	64	21.62±1.68	29.8±6.9	121.77±14.2	70.9±7.4	1.29±0.39	2.55±0.59
A1 group	71	25	46	21.68±1.8	30.2±6.6	121.46±14.0	71.4±7.5	1.30±0.40	2.55±0.61
A2 group	27	9	18	21.46±1.31	28.8±7.7	122.56±15.0	69.6±6.9	1.26±0.34	2.60±0.57
B group	129	42	87	21.74±1.79	29.3±7.0	119.74±12.7	70.7±7.2	1.31±0.31	2.62±0.55
B1 group	94	31	63	21.63±1.75	28.9±7.1	119.5±12.4	70.6±7.9	1.33±0.29	2.59±0.52
B2 group	35	11	24	22.03±1.91	30.3±6.7	120.29±13.5	70.8±7.8	1.25±0.34	2.69±0.69
C group	100	34	66	21.52±1.81	29.4±6.7	120.74±13.1	71.1±6.2	1.30±0.29	2.67±0.48

Group A – migraine attack period; A1 – migraine attack period without aura; A2 – migraine attack period with aura; B – migraine free period; B1 – migraine free period without aura; B2 – migraine free period with aura; C – the control group. No statistical difference between groups of age, gender, BMI, blood pressure, blood lipid (LDL-C, TG) (P>0.05).

Table 2. Plasma level of PPARs concentrations (ng/L, x̄±s).

Group	Cases	PPAR α	PPAR β/δ	PPAR γ
A group	98	572.3±68.1 ^{*,**}	591.1±72.2 ^{*,**}	157.2±104.4 ^{*,**}
A1 group	71	574.9±68.5 [#]	588.5±70.5 [#]	159.8±101.6 [#]
A2 group	27	565.3±67.6 ^{##}	597.9±77.6 ^{##}	150.1±113.2 ^{##}
B group	129	306.3±69.2	233.1±105.6	230.3±97.2
B1 group	94	308.8±70.2	242.7±109.7	233.2±96.4
B2 group	35	299.6±66.8	207.4±90.0	222.6±100.4
C group	100	301.49±74.3	245.68±101.7	221.86±95.6

Group A – migraine attack period; A1 – migraine attack period without aura; A2 – migraine attack period with aura; B – migraine free period; B1 – migraine free period without aura; B2 – migraine free period with aura; C – the control group. * Statistically significant between group A and group B (P<0.05); ** statistically significant between group A and group C (P<0.05); # statistically significant between group A1 and group B1 (P<0.05); ## Statistically significant between group A2 and group B2 (P<0.05).

Results

1. General situation: There was no statistically significant difference among migraine attack period groups, migraine-free period, and healthy control group for general conditions such as age, BMI, blood pressure, or blood lipids (low-density lipoprotein triglyceride) (P>0.05) (Table 1).
2. The plasma level of PPAR alpha beta/delta/gamma: Plasma PPAR alpha beta/delta level in the migraine attack period group was higher than that in the migraine-free period group and healthy controls (P<0.05). The PPAR gamma level in the migraine attack period group was lower than that in the migraine-free period group and healthy controls (P<0.05);

The plasma level of PPAR alpha/beta/delta in the migraine attack period group was higher than in the migraine-free period

group regardless of aura presence. The plasma level of PPAR gamma in the migraine attack period group was lower than that in the migraine-free period group regardless of aura presence. Compared with the group with aura, plasma level of PPAR alpha/beta/delta/gamma was not significantly different in the group without aura (P>0.05). The plasma level of PPAR alpha/beta/delta/gamma was not significantly different between patients in the migraine-free period group and healthy controls (Table 2).

Discussions

Migraine is a common functional disorder of the nervous system, and breaks out repeatedly and protractedly during the course of the disease. Its pathogenesis is not yet fully elucidated. The etiological theory of brainstem trigeminal nerve/vascular

inflammation is recognized by major pathogenesis, and proposes that lack of part of the pain control circuits in the trigeminal nerve vasculature lead trigeminal spinal nerve transmitters to excessively stimulate neurogenic inflammation, and then make the trigeminal nerve stimulation conduct pain to the brain cortex retrogradely and anterogradely [9]. Recent studies found that a variety of vascular active substances, such as nuclear transcription factors-kappa B, IL-6, IL-10, TNF alpha, and TNF beta factor, play an important role in the neurogenic inflammation mechanism of migraine [10]. Our previous animal experiments and clinical studies found that 5-HT, NF-kappa B, and intercellular adhesion molecule-1 (ICAM-1) are involved in the pathogenesis of the migraine process [11,12]. We have also discussed relations between migraine and PPARs in animal experiments [7]. Preliminary clinical trials found that PPAR gamma may affect the incidence of migraine.

PPARs is a ligand-activated transcription regulatory factor of the nuclear receptor superfamily. It plays an important role in fatty acid oxidation, cell proliferation and differentiation, lipid and lipoprotein metabolism, and maintaining glucose steady-state. At present there are 3 known subtypes: PPAR alpha, PPAR beta/delta, and PPAR gamma, which each have different functions. PPAR alpha regulates inflammation, cell proliferation and differentiation, and metabolic processes such as oxidative stress reaction expression [13–15]. PPAR beta/delta plays an important role in the process of cell growth, tissue injury and repair, atherosclerosis, vascular inflammation, tumor formation and inflammation caused by the endoplasmic reticulum stress, and insulin resistance [16–18]. PPAR beta/delta can reduce oxidative stress and exerts anti-inflammatory effects through regulating the interaction between neutrophils and endothelial cells in the acute inflammatory response. PPAR gamma is involved in acute or chronic injury and inflammation of the central nervous system, and has a protective effect on the proliferation and differentiation in fat or glucolipid metabolism, cerebral ischemia and reperfusion injury, and immune systems [19].

Our study detected the plasma level of PPAR alpha/beta/delta/gamma in migraine patients, and compared PPARs level between migraine attack period, migraine-free period, and healthy controls. The results show that plasma level of PPAR alpha beta/delta increased, and PPAR gamma levels dropped during the migraine attack period. Our previous studies found that PPAR alpha/beta/delta/gamma was strongly expressed in the trigeminal nerve neck complex in a nitroglycerin experimental migraine model in rats [7]. The results of the present study are consistent with our previous clinical trials [8]; PPAR gamma in human plasma levels drop, but in the rat trigeminal nerve neck complex it is expressed positively. This may be related to species, different tissue distribution, or different experimental methods, and needs to be investigated further in future experimental studies.

This study suggests PPARs levels are closely associated with migraine, and plasma level of PPARs differ among different subtypes, which may be related to the different effect of PPARs on the occurrence of migraine. Plasma level of PPAR alpha was elevated during migraine attack period. PPAR alpha may effectively reduce levels of proinflammatory factors such as interleukin 1 (IL 1), tumor necrosis factor (TNF-a), cyclooxygenase enzyme (cox-2), induced type nitric oxide synthase (iNOS), and leukocyte adhesion molecule - 1 (ICAM 1). It plays an anti-inflammatory role through inhibiting P38 mitogen-activated protein kinase and activating nuclear factor-K B [20]. PPAR beta/delta may inhibit phosphorylation of ERK1/2 to block the NF-kappa B induced by LPS activated, and then inhibiting the expression of traumatic inflammatory factor TNF alpha, IL-1 beta, and IL-6, increasing the protective cytokine expression of IL-10, increasing the activity of antioxidant enzyme SOD, reducing MDA content, and controlling the expression of inflammatory factors and inflammatory response [21]. Plasma level of PPAR gamma drops during migraine attacks, which lessens the inflammatory response in the inhibition of migraine, and thus accelerating the onset of migraine.

Our study also found that the plasma levels of PPARs have no statistical difference in migraine attack period or migraine-free period, with or without aura. This indicates that plasma level of PPARs with migraine has nothing to do with migraine aura. The pathophysiology of migraine aura is the activation of the trigeminal vascular system and mediating the brain stem and cortex involvement in migraine pain. This may be because the excitability of neurons in the occipital lobe cortex is high, allowing easy cortical spreading, and aura symptoms eventually arise [22]. The results further illustrate that PPARs involved in migraine may be due to its participation in the inflammatory reaction, rather than the excitement of neurons; therefore, there was no significant difference in plasma level of PPARs in patients with or without aura.

Conclusions

Our study results show that PPARs are involved in the pathogenesis of the migraine process. Based on previous research results and our current findings, we suggest that the elevated levels of plasma PPAR alpha/beta/delta may have a protective effect, and that PPAR gamma significantly accelerates the onset of migraine. The conclusions of this study may provide a theoretical basis for understanding the pathogenesis of migraine and in developing new migraine medications. Further studies need to elucidate the correlation between plasma levels of PPARs and other inflammatory factors, and may lead to development of migraine pharmacotherapy involving PPARs receptors. With further in-depth research, the value of PPARs in treatment of migraine will gradually become clear.

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