

β -Thromboglobulin and 11-Dehydrothromboxane B₂ in Tension-Type Headache

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Platelet factor 4, β -thromboglobulin, thromboxane B₂, and 11-dehydrothromboxane B₂ were investigated in tension-type headache. Ten cases of episodic tension-type headache (mean age 42.5 years), 10 cases of chronic tension-type headache (mean age 45.3 years), and 10 age-matched healthy controls were studied. The platelet factor 4, β -thromboglobulin, thromboxane B₂, and 11-dehydrothromboxane B₂ concentrations in the plasma were significantly higher in the episodic tension-type headache group than in the chronic tension-type headache and healthy control groups. Platelets may be involved in episodic tension-type headache.

Key words: tension-type headache, platelet factor 4, β -thromboglobulin, thromboxane B₂, 11-dehydrothromboxane B₂
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Tension-type headache is subdivided into episodic tension-type headache and chronic tension-type headache. There is controversy¹⁻⁵ whether the platelet is involved in tension-type headache or not. The reason for the controversy may be that the platelet is only involved in one of the two subtypes. Because there are no reports on platelet involvement in the two subtypes, we investigated platelet factor 4, β -thromboglobulin, thromboxane B₂, and 11-dehydrothromboxane B₂ in the two subtypes of tension-type headache.

SUBJECTS AND METHODS

Ten cases of episodic tension-type headache (5 men and 5 women, mean age 42.5 years), 10 cases of chronic tension-type headache (6 men and 4 women, mean age 45.3 years), and 10 age-matched healthy controls (5 men and 5 women) were studied with their informed consent. The patients were selected according to the date of visiting our clinic. Some young patients refused to participate in this research because it required them to pay approxi-

mately 20% of the total costs. The mean period from the onset of headache until the examination was 2.6 years (range 1.0 to 4.5 years) in episodic tension-type headache and 3.2 years (range 1.2 to 5.4 years) in chronic tension-type headache. The average monthly frequency of headache attacks in the episodic tension-type headache was four (range, one to eight). The diagnosis was made according to the diagnostic criteria of the International Headache Society.^{6,7} Patients on medication which affects platelet function, such as aspirin, were excluded. No patients were on prophylactic treatment nor hormonal preparations.

Blood was drawn when the patient had a headache and the plasma platelet factor 4, β -thromboglobulin, thromboxane B₂, 11-dehydrothromboxane B₂, serotonin, 5-hydroxyindoleacetic acid (5-HIAA), epinephrine, norepinephrine, dopamine, and 3-methoxy-4-hydroxyphenylglycol (MHPG) were determined at the Special Reference Laboratories ([SRL], Tokyo). Platelet factor 4 and β -thromboglobulin were determined by enzyme immunoassay using international standards⁸; thromboxane B₂ and 11-dehydrothromboxane B₂ were determined by radioimmunoassay; and serotonin, 5-HIAA, epinephrine, norepinephrine, dopamine, and MHPG were determined by high-performance liquid chromatography. The intraindividual variation for the different assays of the above substances was less than 5%, and the platelet and plasma levels for all of the above substances did not

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Clinical Characteristics

	Episodic Tension-Type Headache Group	Chronic Tension-Type Headache Group	Healthy Control Group
Age, y	42.5 ± 6.8	45.3 ± 7.3	43.8 ± 7.1
Headache frequency, per month	6 ± 3	22 ± 5	–
Platelet count, x10 ⁴ /μL	23.2 ± 4.6	24.8 ± 5.1	22.8 ± 4.9
Platelet factor 4, ng/mL	33.1 ± 8.3*	17.3 ± 7.5	13.6 ± 5.7
β-thromboglobulin, ng/mL	96.4 ± 18.2*	48.5 ± 15.9	39.3 ± 10.2
Thromboxane B ₂ , pg/mL	63.8 ± 14.2†	32.4 ± 10.5	27.6 ± 8.4
11-Dehydrothromboxane B ₂ , pg/mL	21.9 ± 6.7†	7.8 ± 3.6	7.1 ± 2.7
Serotonin, μg/mL	0.11 ± 0.08	0.13 ± 0.09	0.12 ± 0.10
5-HIAA, ng/mL	4.2 ± 1.7	4.5 ± 1.5	3.9 ± 1.8
Epinephrine, pg/mL	54 ± 24	67 ± 28	58 ± 18
Norepinephrine, pg/mL	240 ± 72	268 ± 67	256 ± 58
Dopamine, pg/mL	8.3 ± 3.1	9.3 ± 2.8	9.1 ± 3.3
MHPG, ng/mL	5.2 ± 2.1	4.5 ± 1.8	4.7 ± 1.3

Values given as mean ± SD.

* $P < 0.05$ versus chronic tension-type headache group and $P < 0.01$ versus healthy control group.

† $P < 0.01$ versus chronic tension-type headache and healthy control groups.

change depending on the time of day in which the samples were drawn. We did not add internal standards to the freshly obtained blood.

The blood drawing was performed using a polystyrene syringe and a 20-gauge needle according to published precautions.⁹ It was left for 15 to 30 minutes in iced water and then was centrifuged at 2000g for 30 minutes at a temperature of 2° to 4°C.

Statistical analysis was performed using Mann-Whitney tests.

RESULTS

The platelet factor 4, β-thromboglobulin, thromboxane B₂, and 11-dehydrothromboxane B₂ concentrations in the plasma were significantly higher in the episodic tension-type headache group than in the chronic tension-type headache and healthy control groups (Table). The ranges of the platelet factor 4 concentrations in the episodic tension-type headache group were 7.8 to 59.2 ng/mL, β-thromboglobulin 40.2 to 153.4 ng/mL, thromboxane B₂ 17.4 to 108.2 pg/mL, and 11-dehydrothromboxane B₂ 2.1 to 42.8 pg/mL. The range of values for subjects in each group did not show that one or two subjects were excessively weighting the final results. We did not measure the test substances in the platelet fractions (2000g pellet).

The platelet count, serotonin, 5-HIAA, epinephrine, norepinephrine, dopamine, and MHPG did not show any significant difference among the three groups.

COMMENTS

Platelet factor 4 and β-thromboglobulin are platelet-specific proteins in the alpha granules of platelets. When a platelet is activated, platelet factor 4 and β-thromboglobulin, in approximately the same amounts, are released into the blood. The ratio of platelet factor 4 and β-thromboglobulin is approximately 1:1 in the case of platelet activation in vitro. In the case of platelet activation in vivo, the ratio is approximately 1:3 because the released platelet factor 4 combines with the endothelium of the blood vessel. In the present study, the ratio of platelet factor 4 and β-thromboglobulin was approximately 1:3 and suggests platelet activation in vivo.

Thromboxane A₂ is produced mainly in platelets and is metabolized to thromboxane B₂ with a half life of approximately 30 seconds in the blood. Thromboxane B₂ is metabolized to 11-dehydrothromboxane B₂ and other metabolites in the liver and other organs. Thromboxane B₂ also increases in the case of platelet activation in vitro, but 11-dehydrothromboxane B₂ does not increase under these circumstances. In the present study, thromboxane B₂ and

11-dehydrothromboxane B₂ concentrations were increased in the episodic tension-type headache group, suggesting platelet activation in vivo.

Platelet activation has been reported in migraine.¹⁰⁻¹² It is in controversy whether platelet activation is present or absent in tension-type headache.¹⁻⁵ There is no report on the difference in platelet activation between episodic tension-type headache and chronic tension-type headache. The present study suggests platelet activation during headache episodes in episodic tension-type headache. Episodic tension-type headache may have pathogenetic components of both chronic tension-type headache and migraine. The comparison between during headache episodes and during headache-free periods in episodic tension-type headache could not be performed because many patients refused to repeat expensive examinations during headache-free periods.

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