Short report

Serotonin in tension headache

R SHUKLA,* K SHANKER,† D NAG,* M VERMA,† K P BHARGAVA†

From the Departments of Neurology,* and Pharmacology and Therapeutics,† King George's Medical College, Lucknow, India

SUMMARY Serotonin (5-hydroxytryptamine, 5-HT) is implicated in the pathogenesis of migraine; however, its role in tension headache has not yet been studied. The uptake of 5-HT by platelets in patients of tension headache was significantly higher compared with migraineurs as well as controls. The basal platelet 5-HT levels did not show a significant difference. The study implicates the role of serotonin in tension headache.

The involvement of 5-HT in migraine is well established. A decrease in basal platelet 5-HT as well as a reduced uptake of 5-HT by the platelets has been reported.¹⁻⁴ However, platelet 5-HT uptake in tension headache has not so far been explored. It has been suggested that migraine (classical as well as common), tension-vascular and tension headache are a continuum of the same pathophysiology. The precise margins of these clinical entities are elusive.⁵ Hence it was considered appropriate to study the role of serotonin in tension headache. This appears to be the first report of platelet serotonin uptake in tension headache.

Patients and methods

Twenty patients with tension headache, attending the neurology out-patients department, were included in the study. The mean age was 29.5 with a range of 14 to 45 years and male:female ratio was 1:3. Nineteen patients of migraine were also studied. The mean age was 30.7 years (range 16 to 50 years) and male:female ratio 1:1.7. The diagnosis of migraine was based on the criteria given by the World Federation of Neurology⁶ whereas tension headache was diagnosed according to the following criteria based on a modification of those suggested by the ad hoc committee of the headache group.⁷ "Patients with headache lasting for 24 hours, non localised, dull ache described as heaviness or a band being tightened around the head without any nausea or vomiting, precipitated by tension and stressful situations, relieved by sleep or tranquilisers and no relief with ergot alkaloids".

Address for reprint requests: Dr R Shukla, Department of Neurology, KG's Medical College, Lucknow-226 003, India.

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Fifteen age and sex matched controls comprising unpaid healthy volunteers taken from hospital staff and patients suffering from neurological disorders not likely to affect 5-HT metabolism (such as myopathy, peripheral neuropathy and motor neuron disease) were also included.

Patients suffering from hypertension and ischaemic heart disease were excluded. None of those included in the study was taking drugs (analgesics, antidepressants etc.) and food items (banana, tomato, pineapple, nuts, cheese etc) known to effect 5-HT metabolism, for 7 days prior to collection of blood samples.

Blood was collected (9 ml) by venepuncture from the median cubital vein at 9:00 am using a plastic syringe with a 21 gauge needle. It was immediately transferred to plastic tubes, containing 1 ml of 3.8% sodium citrate, and kept in iced containers.

Platelet rich plasma (PRP) was prepared by centrifugation according to the method of Born and Gillson.⁸ All glass equipment used in the experiments was coated with silicone. Platelet counts in PRP were done in a Neubauer haemocytometer at a dilution of 1 in 20. Basal platelet serotonin content was determined using 1 ml of PRP by the spectrophotofluorometric method.⁹ Recovery of 5-HT by the present method was 80-90%. The results are expressed in ng/10⁸ platelets.

Platelet 5-HT uptake was measured by the method of Gujrati *et al*¹⁰ by determination of the content of radioactivity of platelets incubated with H³-5-HT oxalate (specific activity, 26.4 ci/mmol; New England Nuclear Corporation). Solution of labelled amine was made in normal saline. Platelet rich plasma samples (1 ml) were preincubated for 5 minutes at 37°C before addition of labelled 5-HT (200 pmol) at 10, 20 and 30 pmol concentrations. The reaction mixture was incubated for 10 minutes with constant stirring at 37°C. Uptake of amine process was terminated by the addition of 2 ml cold solution of formaldehyde (4%). Tubes were cooled and then centrifuged at 8000 g for 20 minutes at 0°C. The supernatant was decanted and stored, the inner side of the centrifuge tube was wiped with filter paper. The platelet pellet was digested in 0.2 ml formic acid (21 M) and 0.3 ml

distilled water for one hour at room temperature, and then transferred to glass counting vials containing 10 ml of scintillant (dioxane: toluene: methanol: naphthalene: 1,4 bis 2-5-phenyl oxazolyl benzene: diphenyl oxazole). The radioactivity was measured by automatic Packard Scintillation Counter with counting efficiency of tritium (H^3) 33%. The control as well as samples of study group were analysed simultaneously. Statistical analysis was done by Student's *t* test.

Results

Lower platelet counts in PRP were observed in patients with tension headache as compared to controls and migraineurs. The basal platelet 5-HT values were higher in tension headache than patients of migraine. Migraineurs had a lower basal 5-HT as compared with tension headache as well as controls. Platelet count and basal 5-HT changes were not statistically significant.

The uptake of 5-HT by platelets was significantly higher in tension headache at all the concentrations of H^3 -5-HT (table). The platelet 5-HT uptake in tension headache did not show a significant difference (fig) with respect to age (less than 30 and more than 30 years), sex (male and female) and duration of disease (less than 5 and more than 5 years).

Discussion

Platelet serotonin has been the focus of attention in vascular headaches particularly migraine; however, it has not been fully explored in tension headache. An isolated report mentions lower basal 5-HT levels in patients suffering from frequent attacks of tension headache as compared with controls.¹¹ While the basal 5-HT level in tension headache did not differ significantly from controls and migraineurs, the uptake of 5-HT by the platelets was significantly higher in the present study.

Emotional factors are important in patients with tension headache and are present in nearly all the cases.¹² The increased amount of endogenously released 5-HT as a result of stress, may be taken up by

Fig Histogram showing platelet 5-HT uptake (mean $\pm$ SEM) in patients of tension headache in relation to age (A = less than 30 years; B = 30 years and above), Sex (C = male; D = female) and duration of disease (E = less than 5 years; F = 5 years and above). The differences in each group were not significant.

the platelets and also lead to vasoconstriction and ischaemia of the temporal muscles, since serotonin has been shown to be a potent vasoconstrictor of the human temporal artery.¹³ However, it cannot be stated whether the increased uptake of 5-HT is due to a platelet abnormality (such as alteration in the permeability of membrane) or to some other metabolic or biochemical factor present in the plasma.

Vascular reactivity is important in tension headache and the amplitude of pulsation of scalp vessels is reduced in these patients.¹⁴ This suggests that patients of tension headache are unable to "summon up the blood" necessary to nourish the hyperactive scalp musculature.¹⁵ The occurrence of alteration in vascular contractility is also supported by the observation that the pain of tension headache is aggravated by

Table Platelet counts in PRP basal platelet 5-HT and uptake of 5-HT

	Tension headache (n = 20)	Migraine (n = 19)	Controls n = 15)
Platelet counts (in 1×10^8 /ml)	2.08 $\pm$ 0.16	2.39 $\pm$ 0.22	2.70 $\pm$ 0.31
Basal platelet 5-HT* (in ng/ 10^8 platelets)	53.3 $\pm$ 9.26	33.2 $\pm$ 7.12	53.1 $\pm$ 6.70
Platelet 5-HT uptake (in CPM/ 10^8 platelets)			
at 10 pmol	719.8 $\pm$ 74.26 +	419.9 $\pm$ 45.68	478.4 $\pm$ 55.70
at 20 pmol	1161.1 $\pm$ 101.62 + +	691.2 $\pm$ 82.56	737.6 $\pm$ 132.72
at 30 pmol	1867.8 $\pm$ 173.58 + + +	1227.3 $\pm$ 177.50	1200.9 $\pm$ 147.73

The values in each group represent Mean $\pm$ SEM.
*Basal 5-HT estimations were done in 14 patients of tension headache, 12 with migraine and 11 controls.
The differences in platelet counts and basal 5-HT were statistically not significant.
+ $p < 0.01$, + + $p < 0.001$, + + + $p < 0.02$ as compared with migraineurs and + $p < 0.02$, + + $p < 0.01$ as compared with controls.

vasoconstrictor agents and improved by vasodilators.¹³

Differentiation between patients of common migraine and tension headache may not always be easy; moreover, it is now felt that they may be the polar forms of a continuum of the same clinical spectrum rather than well defined separate entities. Thus while migraine has been termed as a "low serotonin syndrome"¹⁶ tension headache on the other end of the clinical spectrum may be called as "high serotonin syndrome". Serotonin is considered to be important in maintaining the vascular tone of the extracranial vessels in normal man.¹³ Thus while migraine is due to excessive vasodilatation, tension headache may be due to excessive vasoconstriction. Whereas in the former the platelet 5-HT- uptake is reduced, in the latter it is increased.

Sicuteri¹⁷ has suggested that there may be a central deficiency of monoamines or endorphins in the brain-stem which may be responsible for the syndrome of non-organic central pain (which includes the entity described as tension or muscle contraction headache). Platelets have been suggested to be a suitable model to study the serotonergic mechanisms of brain 5-HT neurons.¹⁸ The findings of the present study are compatible with the nociceptive theory of Sicuteri. It is possible that increased uptake of 5-HT in the serotonergic neurons in tension headache may lead to lower levels of 5-HT at the synapses causing facilitation of nociceptive impulses.

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