Serum dopamine β -hydroxylase activity in menstrual migraine

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SUMMARY Migraine has been considered a manifestation of sympathetic dysfunction. Serum dopamine β -hydroxylase (D β H) has been shown to be an index of peripheral sympathetic activity by some workers and there are two reports of elevated activity of the enzyme during the migraine headache as well as in the headache-free interval. We studied the enzyme in seven women complaining of regular attacks of menstrual migraine and eleven controls during the mid-follicular (days 10 ± 2) and premenstrual (days 28 ± 2) phases of the menstrual cycle. Although levels were on average 26% and 10% higher respectively than in control subjects, the difference failed to reach statistical significance because of the large normal range for enzyme activity. However, the premenstrual results were significantly lower ($p < 0.001$) than the mid-follicular measurements in the migraine group, little difference being found in controls. This finding, and the effects of successful therapy with anovulatory doses of oestradiol implants in not only significantly lowering serum D β H but also significantly reducing the difference in enzymic activity between the early and late phases of the menstrual cycle, suggest that if this enzyme is an index of sympathetic activity, it is excessive fluctuations of the sympathetic nervous system that may be relevant in menstrual migraine.

Increased sympathetic activity and altered catecholamine metabolism has been described in migraine, with increased excretion of 4-hydroxy-3-methoxymandelic acid,¹ lowered monoamine oxidase activity in platelets² and elevated plasma noradrenaline concentrations during the migraine headache.^{3,4} The fact that stress is not only an important precipitating factor of migraine attacks, but is also associated with elevated plasma catecholamine concentrations, especially noradrenaline,⁵ adds support to the concept of abnormal sympathetic control in migraine.

The activity of the enzyme serum dopamine β -hydroxylase (D β H) has also been reported to be elevated in migraine. Gotoh *et al*⁶ measured the enzyme during the headache-free interval in patients with migraine, muscle-contraction headache and controls and found raised serum levels

in the migraine group. Anthony⁴ studied the enzyme before, during and after migraine attacks, and demonstrated an average increase in plasma levels of 42% during and 28% after the headache. Serum D β H concentration has been reported to be an indirect measure of peripheral sympathetic activity,^{7,8} and is considered to be a more reliable index than the concentration of noradrenaline, which is rapidly inactivated by pre- and post-junctional uptake.⁹ The enzyme catalyses the conversion of dopamine to noradrenaline, and is highly localised in the chromaffin granules of the adrenal medulla¹⁰ as well as in the storage vesicles of peripheral sympathetic nerves.¹¹ The enzyme is released by exocytosis in proportion to the amount of noradrenaline released by sympathetic nerve stimulation.¹² Resting levels vary greatly in man and appear to be partly under genetic control.¹³ Expansion of the intravascular volume leads to reduced serum D β H levels,¹⁴ while activation of the autonomic nervous system by stress¹⁵ and exercise¹⁶ is associated with a significant increase in activity.

The results obtained in migraine sufferers has been interpreted as further evidence of sympathetic dysfunction in migraine, although the exact mechan-

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ism remains speculative. We studied serum D β H activity (a) in women complaining of menstrual migraine and controls; (b) during the first and second halves of the menstrual cycle as serum levels of the enzyme has been shown to vary during the menstrual cycle;¹⁷ and (c) after treatment with anovulatory doses of subcutaneous implants of oestradiol and cyclical norethisterone which we have reported to be successful in menstrual migraine¹⁸ and other cyclical conditions such as the premenstrual syndrome.¹⁹

Patients and method

Patients Seven women complaining of menstrual migraine and eleven premenopausal control subjects were studied. The two groups were comparable in age (Mean $\pm$ SD: 37 ± 7.8 and 34 ± 6.3 years respectively), none had taken any medication during the month prior to the study, and all were menstruating regularly (cycle length 26–32 days). The patients with menstrual migraine fulfilled the definition of the World Federation of Neurology's Research Group on Migraine and Headache, three having classical and four common migraine, and all complained of regular attacks during the week before or during menstruation, and were headache-free for the remainder of the cycle.

Method 10 ml venous blood was collected after a rest of 30 minutes and the serum stored at -20°C until assay. Measurements were made in both the control and migraine group at a time when the migraine sufferers were expected to be free of headaches (day 10 ± 2) and susceptible to headaches (day 28 ± 2). In four cases of menstrual migraine, the assays were repeated three and six months after treatment with a 100 mg subcutaneous oestradiol implant (Organon Laboratories), the dose that has been shown to inhibit ovulation and be effective as a contraceptive.²⁰ The implants were inserted into the subcutaneous fat of the anterior abdominal wall according to the method described by Thom and Studd.²¹ These four patients were also given cyclical progestogen (norethisterone 5 mg daily during days 20–26 of the cycle) to induce regular endometrial shedding and prevent endometrial hyperplasia.²¹ D β H activity was measured using the method of Kato *et al*,²³ the mean result of two aliquots of each sample being used for analysis. One international unit (IU) of activity represents the formation of $1 \mu\text{mol}$ octopamine per minute per litre of serum after incubation for one minute at 37°C .

Unpaired and paired Student's *t* tests were used for statistical analysis.

Results

The results are expressed as Mean $\pm$ SEM, and are set out in figs 1–3.

Migraine group before treatment Both on days 10 ± 2 (52.04 ± 4.34 IU) and days 28 ± 2 (45.07 ± 4.53 IU) mean serum D β H concentrations were higher than in the control group (41.15 ± 5.41 IU and 40.99 ± 4.53 IU respectively), but the results

Fig 1 Serum D β H activity during the mid-follicular (days 10 ± 2) and premenstrual (days 28 ± 2) phases of the menstrual cycle in controls and women with menstrual migraine.

Fig 2 The effect of treatment with anovulatory doses of oestradiol implants on serum D β H activity in women with menstrual migraine.

Fig 3 Changes in serum D β H activity between the mid-follicular (days 10 ± 2) and premenstrual (days 28 ± 2) phases of the menstrual cycle in controls and women treated with oestradiol implants for menstrual migraine.

failed to reach significance because of the large range of the readings (Control: 22.0–82.9 IU; Migraine: 28.4–66.9 IU). However, while there was little difference between the two time periods in the control subjects (Mean difference: 0.16 ± 1.56 IU), serum D β H activity was significantly higher on days 10 ± 2 than days 28 ± 2 in the migraine group (Mean difference: 6.97 ± 0.91 IU, $p < 0.001$).

Migraine group after treatment The effect of treatment with oestradiol implants was significantly to reduce D β H activity both on days 10 ± 2 and 28 ± 2 after three months (Days 10 ± 2 : 51.85 ± 5.17 IU; Days 28 ± 2 : 48.25 ± 5.27 IU; $p < 0.05$). By 6 months both sets of results were comparable with the control group (Days 10 ± 2 : 41.95 ± 6.09 IU; Days 28 ± 2 : 38.72 ± 5.02 IU). The difference in the serum concentration of the enzyme between the two time periods in the cycle also became insignificant by six months (3.23 ± 1.18 IU). Symptomatically, all four women treated with oestradiol implants and cyclical progestogen became headache free within six weeks of treatment, but all complained of mild recurrence of their migraines by six months, at which time further implants of oestradiol were administered.¹⁸

Discussion

The role of the sympathetic nervous system in the autoregulation of cerebral blood flow was demonstrated by Gotoh and colleagues.²⁴ It was subsequently shown that the cerebral vessels have a rich adrenergic innervation,²⁵ stimulation of α -receptors resulting in vasoconstriction and of β 1-receptors in vasodilatation.²⁶ It has also been shown that D β H is localised in blood vessels, including the cerebral vasculature.²⁷ These considerations, together with the findings of previous studies of elevated serum D β H activity in migraine,^{4,6} make the enzyme a possible factor in the pathogenesis of these headaches.

Although mean values for serum D β H activity in women with menstrual migraine were greater than in control subjects both in the mid-follicular and premenstrual phases of the menstrual cycle by 26% and 10% respectively, we could not show a statistically significant difference. Furthermore, D β H concentrations were significantly lower on days 28 ± 2 than 10 ± 2 in the migraine group, which is opposite to what would be expected if the enzyme, and thus sympathetic activity, had a role in the pathogenesis of menstrual migraine. The specimens were not collected during the migraine headaches, but these findings are in agreement with the study of Lamprecht *et al*¹⁷ showing that in healthy menstruating women D β H activity increases during the follicular phase, peaks soon after ovulation, and then

decreases to a minimum during the premenstrual period.

From the above data it would seem that the absolute level of D β H activity may not be directly relevant in menstrual migraine. Instead our data would support the concept that if there is a relationship between D β H activity and menstrual migraine, it is excessive fluctuations of this enzyme during the menstrual cycle that may be important. Prior to treatment, there was a significant difference in serum D β H activity between days 10 ± 2 and 28 ± 2 of the cycle. Successful therapy with an anovulatory dose of oestradiol implant not only lowered the absolute level of the enzyme by up to 26%, but also reduced the fluctuation of enzymic activity between the various phases of the menstrual cycle by up to 55%, such that after six months there was no significant difference between the mid-follicular and premenstrual phases.

Such an interpretation must be speculative. Firstly, a temporal relationship between a symptom and a particular variable may be incidental and not necessarily an implication of aetiology. Secondly, by inducing anovulation, oestradiol implants affect many parameters that fluctuate during the menstrual cycle, and thus some as yet unidentified action may be responsible for its therapeutic effect on menstrual migraine.²⁸ For instance, we have shown that therapy with oestradiol implants alters the kinetics of platelet aggregation to 5-HT,²⁹ when migraine has been considered a disorder of platelet function.³⁰ The finding that symptoms disappear while there are still significant fluctuations in D β H concentrations (as at three months) and conversely migraines recur, albeit in a milder form, when these fluctuations are minimal (as at six months), also argue for at best a minor role for possible peripheral sympathetic dysfunction in menstrual migraine. Circulating D β H levels do not appear to reflect central sympathetic activity,³¹ and it is dysfunction of this system that may be relevant in migraine.

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