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Tyramine metabolism and migraine: a metabolic defect

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A possible role for tyramine in the pathogenesis of migraine was suggested by the demonstration, in patients who gave a history of dietary precipitation of attacks, that oral tyramine could induce migraine (Hanington, 1967). Analysis of the urinary metabolites following oral tyramine in subjects with dietary migraine demonstrated a significant decrease in the excretion of conjugated tyramine when compared with normal controls (Smith, Kellow, Mullen & Hanington, 1970). Our present work was aimed at elucidating the nature of the conjugate whose excretion was reduced and determining whether this reduction could be demonstrated, not only in patients with dietary migraine, but also in migrainous subjects who did not relate their attacks to diet.

Four controls and nine migrainous subjects were investigated, the migrainous group consisting of five dietary and four non-dietary cases. All subjects ingested a capsule containing isotopically labelled tyramine (10 μCi *p*-hydroxyphenylethylamine-2-^{14}C) at 10.00 h, and urine was collected over the subsequent 12 hours. Over 98% of the recovered activity was excreted in the first 12 h, therefore we confined our investigations to this period.

When chromatograms of whole urine specimens run in butanol–acetic acid–water (60–15–25) were photographed using a spark chamber scanner (Hesselbo, 1968) four distinct spots were found. After acid hydrolysis two of these spots disappeared suggesting that they were conjugates. Known volumes of each urine specimen were chromatographed and the bands given by the conjugate cut out, and their activity calculated using a TriCarb scintillation counter. The activity of one of these spots was reduced in the migrainous group as compared with the controls. By the use of preparatory chromatograms and elution a quantity of this substance was obtained. It was a single chromatographically pure substance which was totally hydrolysed by acid liberating a single compound which co-chromatographed with tyramine in three different solvents. On enzymic hydrolysis, using either limpet arylsulphatase B or mylase (Koch Light), it was again totally hydrolysed liberating tyramine. Authentic tyramine-O-sulphate (Mattock & Jones, 1970) co-chromatographed with our unknown, confirming that it was indeed tyramine-O-sulphate.

Tyramine-O-sulphate would appear to be a quantitatively important urinary metabolite accounting for about 15% of the ingested dose in normal controls. The migrainous group excreted some 10% of the dose which is significantly less than the controls (P=0·02). Even when considered separately, both the dietary and non-dietary group excreted significantly less tyramine-O-sulphate than controls, though the values for the dietary group tended to be lower than those of the non-dietary group.

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Acute effect of phenytoin on serum folate concentration

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Many epileptic patients have subnormal serum folate concentrations, which have been attributed to long-term anticonvulsant therapy. Klipstein (1964) reported that the highest incidence of subnormal serum folate concentrations occurred in epileptic patients who had been treated with phenytoin for long periods, but found no correlation between drug dose and the concentration of serum folate. The present

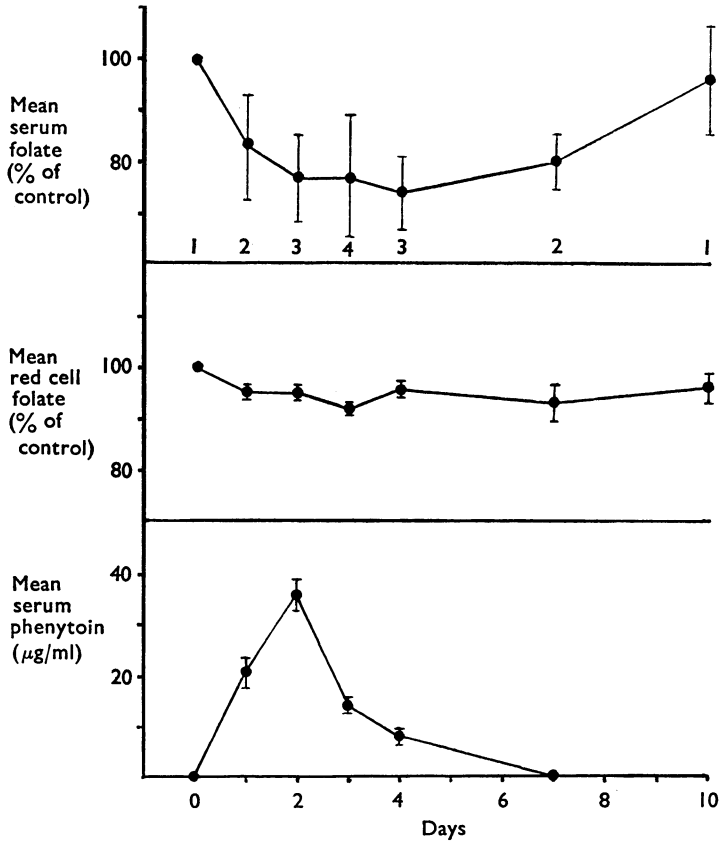

FIG. 1. Mean (±S.E.) values of the concentration of folate in serum, and red cells, and of phenytoin in serum of six subjects receiving 1,600 mg of phenytoin sodium orally during the first 4 days of the experiment. The folate concentrations have been expressed as a percentage of the control before treatment. The figures below the serum folate curve represent the number of subjects having a subnormal serum folate on the respective days.