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## The effect of tyramine on phenolic acid and alcohol excretion in man

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Against a background of extensive animal experimentation (Kopin, 1966), the ability of tyramine to liberate noradrenaline from its binding sites has recently been investigated in man (Engelman & Sjoerdsma, 1964; Sandler & Youdim, 1968). The metabolism of tyramine itself has been well documented in the rabbit (Lemberger, Klutch & Kuntzman, 1966), but has not been studied systematically in the human. It would appear that tyramine administration gives rise to two series of metabolites, those deriving from its own degradation and those from the metabolism of other amines liberated by it. The possible implication of tyramine in the pathogenesis of a migraine variant has aroused considerable interest in this area of investigation (Sandler, Youdim, Southgate & Hanington, 1970). The availability of quantitative gas chromatographic procedures (Karoum, Ruthven & Sandler, 1968; Karoum, Anah, Ruthven & Sandler, 1969) has now enabled us to obtain further information about both series of metabolites.

Urine samples were collected at intervals of 1, 3, 6, 9, 12 and 24 h after administration on different days of 5 mg tyramine intravenously and 125 mg tyramine orally, with appropriate placebo experiments, to six healthy adult male volunteers.

No significant increase in 4-hydroxy-3-methoxymandelic acid or 4-hydroxy-3-methoxyphenylglycol output was detected after either route of administration, in general agreement with previous observations in the same volunteers (Sandler & Youdim, 1968) that released noradrenaline is predominantly O-methylated. A significantly increased output of homovanillic acid, probably too large to be accounted for by any direct conversion of tyramine to dopamine (Lemberger, Klutch & Kuntzman, 1966), was observed, however, during the first 9 h after intravenous tyramine, with a peak at 3–6 h. This increase in output of homovanillic acid presumably derives from dopamine release and is in accordance with *in vitro* evidence (Collins & West, 1968); it may have significance in human Parkinsonism.

Of the metabolites deriving directly from tyramine metabolism, the excretion of *p*-hydroxyphenylacetic acid closely paralleled the administered dose of amine; but despite this high output, there was no evidence of the corresponding alcohol, tyrosol. Whether the enhanced excretion of *p*-hydroxymandelic acid during the first hour after intravenous tyramine stemmed directly from its conversion to octopamine (Kopin, 1966) or indirectly from the release of endogenous octopamine stores (Molinoff, Landsberg & Axelrod, 1969) can only be decided by the use of radioisotopically labelled tyramine. Such studies would also be helpful in pinpointing the origin of the increased homovanillic acid output observed after tyramine injection.

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## The use of phenobarbitone to investigate the pathogenesis of unconjugated hyperbilirubinaemia

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An unconjugated hyperbilirubinaemia may result from increased bilirubin production, such as occurs in haemolytic disorders, or from defective uptake or conjugation of the pigment by the liver-cell. However, the factors causing hyperbilirubinaemia in many patients remain obscure, and even in haemolytic states it is difficult to correlate the depth of jaundice with the degree of haemolysis (De Gruchy, 1964). Patients with Gilbert's syndrome may show minor reductions in red cell survival time (Powell, Billing & Williams, 1967), but it is probable that the hyperbilirubinaemia found in the condition is more related to defective conjugation of bilirubin (Black & Billing, 1969) than to increased load. Investigation of four patients with haemolytic disorders revealed two with a defect of conjugation similar to that found in Gilbert's syndrome (Black, unpublished), and the co-existence of this defect in five of ten haemolytic patients studied by Berk, Bloomer, Howe & Berlin (1969) is suggested by their abnormal handling of $^{14}$C-bilirubin. The levels of plasma bilirubin in these cases seemed to be dependent on more than a single factor.

The administration of phenobarbitone to patients with a proven, or suspected, deficiency of the bilirubin-conjugating enzyme, bilirubin UDP-glucuronyl transferase, leads to a reduction in the plasma level of bilirubin (Yaffe, Levy, Matsuzawa & Baliah, 1966; Whelton, Krustev & Billing, 1968). Matsuda & Takase (1969) have also shown a similar effect of phenobarbitone in two jaundiced patients with hereditary spherocytosis. Phenobarbitone has been shown significantly to increase biliburin-transferase activity in man (Black, Perrett & Carter, unpublished), and it is likely that its beneficial effect in these cases was by induction of transferase activity. Indirect evidence in favour of this hypothesis has been obtained by studying the effect of a 2 week course of phenobarbitone (180 mg/day) on the plasma bilirubin levels and $^{14}$C-bilirubin disappearance curves of patients with mild unconjugated