The Perinatal Development of Haem Biosynthesis in Rats, Guinea Pigs and Humans

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It is known that δ -aminolaevulinate synthetase (EC 2.3.1.13) activity is elevated in the neonatal rat and during the perinatal period in rat, rabbit and guinea-pig liver (Woods & Dixon, 1970). In mice Freshney & Paul (1971) have shown that hepatic δ -aminolaevulinate synthetase, δ -aminolaevulinate dehydratase (EC 4.2.1.24) and ferrochelatase (EC 4.99.1.1) activities are elevated maximally at 14, 15 and 17 days of gestation respectively. These elevated activities fall to normal values shortly after birth.

In the present study the activity of δ -aminolaevulinate synthetase (the initial and normally the rate-limiting enzyme of haem biosynthesis), the activity of ferrochelatase (the terminal enzyme of haem biosynthesis) and the concentration of porphyrins were measured in the perinatal period in rat and guinea-pig liver. δ -Aminolaevulinate synthetase activity was measured by determining the formation of δ -aminolaevulinate from glycine in a whole liver homogenate (Moore, 1970), ferrochelatase activity by measuring the incorporation of ^{59}Fe into protoporphyrin to form haem (Goldberg *et al.*, 1956), porphyrins by the method of Rimington (1961). In the prenatal period the activities of the two enzymes in the foetal liver are sequentially greater than those in the maternal livers, and these increased activities are associated with elevated concentrations of hepatic porphyrins. These porphyrin concentrations are again sequentially elevated, with that of uroporphyrin elevated first about 10 days before birth, then that of coproporphyrin about 5 days before birth and finally that of protoporphyrin about 2 days before birth. All of these elevated concentrations fall to the maternal values shortly after birth. When the mother rats were treated with 2-allyl-2-isopropylacetamide (a potent porphyrogenic drug; Goldberg & Rimington, 1954) it was found that, although there was a large elevation of the activity of the maternal δ -aminolaevulinate synthetase, there was little increase in that of the foetal enzyme. In newborn rats there was a similar lack of effect.

In humans, erythrocyte porphyrins were measured in maternal blood and in umbilical-cord blood. It was found that there was a significantly higher concentration of protoporphyrin in the newborn babies than in the maternal blood and that this was increased in premature births. These results suggest that in the perinatal development of haem biosynthesis there is a sequential induction of the enzymes of the pathway,

each becoming rate-limiting at a given period, this all being associated with a de-repressed activity of δ -aminolaevulinate synthetase and leading to an excessive porphyrin production.

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Lead, Ethanol and δ -Aminolaevulinate Dehydratase

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It has long been accepted that lead has a direct effect on haem biosynthesis (Goldberg, 1968), and in particular it has been shown, both in direct studies and in measurement of excreted δ -aminolaevulinate in the urine, to depress severely the activity of δ -aminolaevulinate dehydratase (the second enzyme of haem biosynthesis; Haeger-Aronsen *et al.*, 1971) both *in vitro* and *in vivo*. It has further been shown that ethanol also depresses δ -aminolaevulinate dehydratase activity (Moore *et al.*, 1971). For this reason it was decided to examine the effects of these two substances, separately and together, on δ -aminolaevulinate dehydratase activity in rats.

A significant depression of δ -aminolaevulinate dehydratase activity at a mean blood lead concentration of $122 \pm 48 \mu\text{g}/100\text{g}$ of blood and at a blood ethanol concentration of $192 \pm 51 \text{mg}/100\text{ml}$ of whole blood was observed. When these are combined at the similar concentrations of $133 \pm 50 \mu\text{g}$ of lead/100g of blood and 199mg of ethanol/100ml of blood, the activity of δ -aminolaevulinate dehydratase is significantly elevated over the two separate depressed activities, although lower than the control value. In a subsequent experiment *in vitro*, with rat liver as a source of the enzyme, it was found that δ -aminolaevulinate dehydratase activity was again depressed by both ethanol and lead separately but elevated by these compounds together. The linking factor in both of these experiments seems to be the concentration of GSH in the system. Lead is known to bind to thiol groups, and other workers have shown that the addition of GSH to systems in which δ -aminolaevulinate dehydratase activity is being measured