The biochemical basis of the acute porphyrias

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The acute porphyrias are a group of hereditary diseases resulting from abnormalities in the pathway of haem biosynthesis. Affected subjects usually enjoy good health, but on exposure to various precipitating factors they become at risk of developing potentially fatal attacks of neurological dysfunction, characterized by severe abdominal pain, mental disturbance and paralysis. Such attacks are associated with the overproduction of porphyrins and their precursors which appear in the urine.

Eight enzymes occur in the pathway of haem biosynthesis, which involves the conversion of glycine and succinyl-CoA firstly into the porphyrin precursors ALA* and PBG, then into the various porphyrins, and finally, with the insertion of iron into haem (Fig. 1). The flux through the pathway is regulated by the activity of the initial enzyme ALA synthase (EC 2.3.1.37), which is under negative feedback control by haem. Four different types of acute porphyria have been described, each characterized by a different pattern of overproduction of porphyrins and precursors owing to partial deficiency of different enzymes of the pathway. In acute intermittent porphyria there is a 50% deficiency of the enzyme uroporphyrinogen I synthase (EC 4.3.1.8), and this results in overproduction and increased urinary excretion of ALA and PBG. Patients with hereditary coproporphyria have deficiency of coproporphyrinogen oxidase (EC 1.3.3.3), and those with porphyria variegata have deficiency of protoporphyrinogen oxidase (EC 1.3.3.3) and sometimes also of ferrochelatase (EC 4.99.1.1). In these latter two forms of porphyria the more distal enzyme block results in the overproduction not only of porphyrin precursors but also of formed porphyrins, which result in cutaneous photosensitivity in addition to neurological manifestations. Though often termed the acute hepatic porphyrias, the enzyme deficiency is not limited to the liver and has been documented in all the extra-hepatic tissues so far examined. Early studies indicated that the liver is the main source of the overproduction of the porphyrins and precursors, but more recently evidence has been presented indicating that the kidney is also important (Day et al., 1981). The three types of acute porphyria mentioned above are all inherited in a Mendelian autosomal dominant fashion, and in each case the activity of the deficient enzyme is approx. 50% of normal. A single well-documented case of homozygous hereditary coproporphyria has been described in which the activity of coproporphyrinogen oxidase was less than 5% of normal, resulting in a particularly severe form of the disorder (Grandchamp et al., 1980). More recently a fourth type of acute porphyria has been described, caused by deficiency of ALA dehydratase (Brandt & Doss, 1981). As the activity of this enzyme must be markedly decreased before it becomes rate-limiting, overproduction of its substrate (ALA) and related clinical manifestations only occur in homozygotes or in heterozygotes where the enzyme activity is further inhibited by an acquired factor such as lead poisoning. There have been only a few studies of the molecular pathology of the enzyme deficiency in the acute porphyrias. Genetic heterogeneity of the uroporphyrinogen I synthase deficiency has been reported in acute intermittent porphyria. In most cases there is a 50% quantitative deficiency of the normal enzyme, but in a few a structural gene mutation results in normal amounts of functionally abnormal enzyme (Anderson et al., 1981).

One of the interesting aspects of the acute porphyrias is the exacerbation of the biochemical and clinical manifestations of
the disorder by various factors. Many commonly prescribed drugs can precipitate attacks in subjects with the genetic trait, and consequently the acute porphyrias can be regarded as pharmacogenetic diseases. The great majority of drugs that are known to be implicated in porphyria attacks share the property of being inducers of the hepatic MFO enzyme system. Induction of the MFO involves increased synthesis of the haemoprotein cytochrome P-450, and the increased rate of haem synthesis required for this results in a marked increase in the accumulation of the porphyrins and precursors formed before the genetically deficient enzyme. Certain other drugs may exacerbate the disorder by directly inhibiting the already deficient enzyme. Ethanol ingestion also precipitates attacks, probably increasing ALA synthase activity by a more direct mechanism such as altering the mitochondrial redox potential. Energy deprivation and various hormonal fluctuations may also increase ALA synthase activity and precipitate attacks, and the hormonal effect explains the increased incidence of attacks in females of child-bearing age.

One of the major unanswered questions in this field is the relationship between the clinical manifestations of the acute porphyrias and the underlying biochemical abnormalities (Bonkowsky & Schady, 1982). All of the features of the clinical attacks can be explained by neurodysfunction involving the autonomic, peripheral and central nervous systems. Post-mortem studies of patients dying in attack have shown areas of axonal degeneration and demyelination involving the peripheral and autonomic nervous system and neuronal loss; glycosis has been noted in the central nervous system. There is considerable circumstantial evidence that the neuropathy is due to neurotoxic effects of ALA. Serum ALA concentrations are highest during clinical attacks, and no convincing attacks have been reported unaccompanied by overproduction of ALA. In the non-acute porphyrias, where there is overproduction only of formed porphyrins and not of ALA, neurological attacks do not occur and the patients only suffer cutaneous photosensitivity. The association of increased concentrations of ALA and neuropathy is also seen in lead poisoning and hereditary tyrosinaemia. The main objection to the ALA-neurotoxicity theory is the inability as yet to demonstrate any neurotoxic effects of ALA in laboratory animals. ALA is structurally similar to the inhibitory neurotransmitter GABA, and has been shown to have partial GABA-agonist effects in concentrations seen in acute porphyria. However, the relevance of this neuropharmacological effect of ALA to the structural neuronal changes seen in the clinical attack must remain in doubt. The other main theory to explain the neuropathy of acute porphyria is that it is due to disordered haem biosynthesis within the nerve cell itself. Since the characteristic abnormality of haem biosynthesis has been demonstrated in all tissues so far examined, it is likely to be present in nerve cells. Impaired haem biosynthesis within nervous tissue could result in deficiency of essential haemoproteins, such as mitochondrial cytochromes required for oxidative phosphorylation or microsomal cytochromes that catalyse mixed-function oxidation. Impaired microsomal cytochrome P-450-dependent mixed-function oxidation has been demonstrated in patients in clinical attack. If the neuropathy of acute porphyria is due to impaired intra-neuronal haem biosynthesis, then the precipitating factors of acute attacks must be capable of modifying neuronal haem biosynthesis. The few studies so far performed have failed to show any induction of ALA synthase in nervous tissue following administration of phenobarbitone or alcohol, or starvation, all of which induce clinical attacks. At this time there is insufficient knowledge of neuronal haem biosynthesis to assess its role in porphyric neuropathy.

The management of the acute porphyrias involves both the prevention of attacks and the treatment of any that may occur. A prerequisite to the prevention of attacks is the identification of subjects with the porphyric trait, and this involves the screening of all blood relatives of newly discovered cases. Screening by quantitative measurement of porphyrins and precursors in urine and faeces is inadequate, as increased excretion only occurs in 30% of asymptomatic subjects with the genetic trait. However, the activities of the enzymes of haem biosynthesis can now be measured in peripheral blood cells obtained from a venous-blood sample, and this permits the detection of about 95% of patients with the genetic trait (McColl et al., 1982). These subjects can then be advised to avoid the various factors that could precipitate attacks. Various biological models are available for assessing the likelihood of substances to induce porphyric attacks, and all involve the detection of increased ALA synthase activity after administration of the appropriate agent.

In patients presenting in an established attack, it is essential to identify any precipitating factors and where possible remove them. Drugs are the commonest of these factors. Energy deprivation can precipitate and also aggravate attacks, and in view of the nausea and vomiting which are constant features of attacks it is essential to take measures to ensure adequate energy intake. The intravenous administration of laevulose has been shown to improve both the biochemical and clinical manifestations of attacks and should be used at an early stage of the attack. Over the past 10 years the administration of haematin has been advocated as a means of terminating an attack. It is prepared from human blood cells and is administered intravenously in dosages of 4 mg/kg every 12 or 24 h for several days. The haematin is bound by haemopexin in the plasma, which carries it to the liver cells, where it enters the mitochondria and by increasing the haem pool represses ALA synthase activity and thus decreases the overproduction of porphyrins and precursors. Biochemical improvement is a constant feature after haematin administration, and clinical improvement is experienced in most acute attacks (McCoy et al., 1981). It is of less value in subacute attacks or long-standing attacks with established neuropathy.

Elucidation of the basic biochemical mechanisms involved in the acute porphyrias has provided significant advances in the diagnosis, prevention and treatment of these pharmacogenetic disorders.