BIOCHEMICAL JOURNAL LETTERS

Evidence against involvement of cytochrome *P*-450 haem in the regulation of synthesis of mammalian liver 5-aminolaevulinate synthase

Although studies of the role of mammalian liver cytochrome *P*-450 in the microsomal mixed-function oxidase-catalysed activation of porphyrogens have been instrumental in the development of the concept of feedback regulation of 5-aminolaevulinate synthase (EC 2.3.1.37) synthesis (see De Matteis, 1975, 1978), there is now sufficient evidence to question the widely held view that the haem moiety of this major haemoprotein participates in the above regulatory process. The following is a summary of this evidence. The marked enhancement of 5-aminolaevulinate synthase activity caused by the porphyrogen 2-allyl-2-isopropylacetamide, which is produced as a result of the initial loss of liver haem, is not potentiated by joint administration of phenobarbitone, despite the ability of the latter agent to potentiate the above loss of cytochrome *P*-450 haem (De Matteis, 1971). By contrast, phenylbutazone is capable of potentiating the enhancement of synthase activity by the porphyrogen 3,5-diethoxycarbonyl-1,4-dihydrocollidine without causing a further early loss of cytochrome *P*-450 haem above that produced by this latter porphyrogen (De Matteis & Gibbs, 1972). Cytochrome *P*-450 and other hepatic cytochromes and haemoproteins (except tryptophan pyrrolase, EC 1.13.11.11) are insensitive to administered 5-aminolaevulinate, despite the concomitant repression of synthase synthesis (Druyan & Kelly, 1972). The diminished ability of 2-allyl-2-isopropylacetamide to enhance markedly synthase activity in the liver of the adrenalectomized (and/or ovariectomized) rat, and the ability of cortisol to exert its permissive effect on this enhancement in these rats, are observed in the absence of any changes in cytochrome *P*-450 haem (Padmanaban *et al.*, 1973). Synthase activity is enhanced by acute administration of hexachlorobiphenyls and by chronic treatment with the organophosphate insecticide fenitrothion in the absence of any loss of cytochrome *P*-450 (Yoshida *et al.*, 1975; Goldstein *et al.*, 1976). Enhancement of synthase activity by small doses of 2-allyl-2-isopropylacetamide is not associated with changes in cytochrome *P*-450 haem (Klinger & Müller, 1980). There is no consistent correlation between the decrease in cytochrome *P*-450 concentration and the enhancement of synthase activity in rats treated with iron–dextran (Bonkowsky *et al.*, 1981). Phenobarbitone causes a prompt enhancement of synthase activity (in chick embryos *in ovo* and in cultured hepatocytes) without any measurable initial destruction of cytochrome *P*-450 haem (Giger & Meyer, 1981). The impaired ability of 2-allyl-2-isopropylacetamide to enhance synthase activity in pregnant rats is not associated with impaired destruction of cytochrome *P*-450 haem (Sardana *et al.*, 1981).

Many of the above findings are in marked contrast with the reported response of tryptophan pyrrolase haem (Badawy, 1978, 1979; Badawy & Morgan, 1980; Morgan & Badawy, 1980). It is therefore proposed that the mammalian liver regulatory-haem pool is not utilized by cytochrome *P*-450, but may be closely associated with tryptophan pyrrolase in the cytosol compartment. Evidence supporting this latter suggestion will be presented in a future publication.

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