INHIBITED INDUCTION OF HEPATIC δ-AMINOLEVULINATE SYNTHETASE IN PREGNANCY

S. PAUL, D. R. BICKERS, R. D. LEVERE and A. KAPPAS
The Rockefeller University, New York, N.Y. 10021, USA

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1. Introduction

The mitochondrial enzyme, δ-aminolevulinate synthetase (ALAS), which is rate-limiting in heme biosynthesis is susceptible to induction by a variety of structurally unrelated chemicals [1–4]. Early studies by Granick [1] using a chick embryo liver cell culture system demonstrated that this induction effect is mediated by de novo formation of the enzyme and not by activation of latent ALAS. The mechanism of drug induction of ALAS may involve, in part, interference with the feedback repression control of enzyme production exerted by the end-product of the pathway, heme, through drug competition for a heme binding site on a postulated aporepressor protein [4]. This would then presumably lead to enhanced activity of the structural gene coding for ALAS and increased production of the enzyme protein. Other mechanisms for inducer effects on ALAS synthesis have also been proposed [5].

Previous studies from this laboratory [6] showed that rats were refractory to the hepatic ALAS induction effect of the potent porphyrinogenic drug allylisopropylacetamide (AIA) during the neonatal period but no experiments were done to determine whether there was a concomitant reduced susceptibility to induction of ALAS in the liver of the mother in pregnancy. The present study was designed to examine this question and the results indicate that there is a progressive and marked inhibition of hepatic ALAS induction in the maternal liver during gestation.

2. Experimental

Female Sprague-Dawley rats (250–300 g), virgin or sperm-positive pregnant, were obtained from Holtzman Farms. The animals were fasted for 24 hr before intraperitoneal injection of AIA (400 mg/kg) and then sacrificed 16 hr later. Controls received solvent injections alone. ALAS activity 16 hr after AIA injection was determined in whole liver homogenates according to Marver et al. [7]. ALA was separated from amino-acetone by solvent-extraction [1]. Animals were studied at 4 day intervals until day 20 of pregnancy and similarly until day 24 post-partum.

3. Results and discussion

The effect of AIA treatment on hepatic ALAS activity at selected times in pregnancy in the post-partum period is shown in fig. 1. Each bar represents the mean ± S.E. of enzyme activity of 6 rats; enzyme activities determined in groups of non-pregnant control animals are shown for comparison. Basal levels of ALAS activities were approximately equal in both non-pregnant and pregnant rats. AIA-treated non-pregnant rats showed the expected 10–15-fold induction of the enzyme at 16 hr. Pregnant animals also demonstrated normal ALAS inducibility until approximately day 8 of pregnancy; thereafter however a progressive and marked decrease in ALAS induction was observed such that by day 20 inducibility was less than two-fold above non-treated

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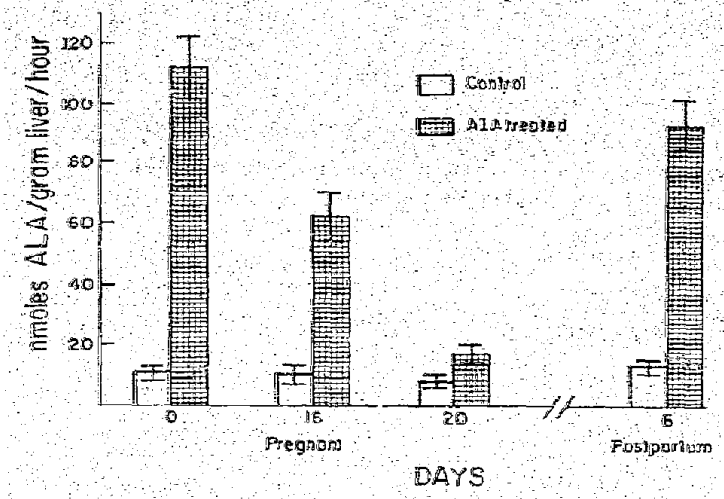

Fig. 1. The effect of gestation on the reduction of hepatic ALAS after a single injection of AIA (400 mg/kg) in rats. Each column represents the mean ± S.E. of ALAS activity in 6 animals. At the time intervals indicated the rats were sacrificed and enzyme activity determined as described in the text.

controls, or more than 80% less than the inducibility of non-pregnant animals. Measurements of ALAS activity at 4 hr intervals up to 72 hr following AIA injection in late gestation revealed no shift in the time-course of enzyme response to the drug as compared with non-pregnant controls. There was rapid recovery of inducibility of ALAS in the post-partum period so that by day 6 responsiveness of the enzyme to AIA had returned essentially to normal.

The mechanism whereby ALAS becomes progressively refractory to AIA induction during pregnancy is not clear but the effect is consistent and pronounced with this chemical inducer. Previous studies have shown that hepatic ALAS induction can be altered by a variety of dietary [8,9] endocrine [2,3] and genetic factors [10]. In addition earlier studies from this laboratory showed that neonatal rats are refractory to AIA induction of ALAS; this capacity to respond to the drug slowly 'matures' so that by 5 to 6 weeks of age adult levels of induction as ALAS can be demonstrated [6]. It is possible that the diminished inducibility of ALAS in the early neonate may reflect in part the residual effects of factors – presumably humoral – which inhibit the induction of this enzyme in the maternal liver.

Pregnancy is an extremely complex endocrine-metabolic state characterized by profound alterations in the production and metabolism of steroid and polypeptide hormones. Many of these hormones i.e. prolactin and growth hormone, significantly affect glucose metabolism and it is possible these changes in glucose metabolism may in some fashion impose a restriction on ALAS inducibility comparable to that produced by glucose ('glucose effect') [7]) on ALAS induction in non-pregnant animals. Alterations in hemoprotein metabolism – specifically cytochrome *P*-450 – could also be involved in the diminished inducibility of hepatic ALAS in pregnancy. AIA has been shown to cause a rapid and transient decrease in the levels of cytochrome *P*-450 prior to the rise in activity of ALAS [11], and this catabolism of heme-protein is thought to underlie the mechanism of AIA-induced induction of this enzyme. Pregnancy may in some manner interfere with this AIA-induced destruction of cytochrome *P*-450 or alter the biotransformation of the inducer itself to active metabolites [10]; we are exploring these questions further. Whatever the proximate mechanism of the effect described here it is evident that a major alteration in hepatic response to AIA occurs during pregnancy and that this altered responsiveness may be useful in exploring the mechanisms of drug and other chemical regulation of porphyrin–heme synthesis in the liver.

Acknowledgements

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