DEVELOPMENT OF ENZYMES AND DRUG ACTIONS

ENZYME INDUCTION IN HUMAN FETAL LIVER IN ORGAN CULTURE. N.C.R. RAIHA and A.L. SCHWARTZ. Dpts of Obstetrics and Gynecology and Medical Chemistry,

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Dibutyryl cyclic AMP in the presence of theophylline was found to induce tyrosine aminotransferase and phenylalanine hydroxylase activities in human fetal liver in organ culture. These effects were completely inhibited by simultaneous incubation with cycloheximide. Corticosteroids were also found to increase tyrosine aminotransferase activity. These results demostrate the competence of mid-term human fetal liver to respond to certain drugs by increasing specific enzyme activity. The potential importance of these findings will be discussed in relation to clinical neonatal problems caused by immature liver function.

INDUCTION OF DRUG METABOLIZING ENZYME ACTIVITIES IN THE HUMAN FOETUS AND IN THE NEWBORN INFANT. F.Sereni,M. Mandelli, N. Principi G. Tognoni, G. Pardi and P.L. Morselli.

The problem of induction of microsomal enzyme activities in the human fetus and in the neonate was studied by measuring diazepam metabolites in the urine of five subjects pretreated with phenobarbital, either during fetal life or after birth.

A very considerable increase of urinary excretion of hydroxylated and conjugated compounds was observed. These findings may be considered as an indirect evidence of induction of drug metabolizing enzyme activities during the last part of gestation and shortly after birth. Present knowledge on liver enzyme induction in fetuses and neonates are critically reviewed.

ACQUISITION OF AN EMBRYONAL BIOCHEMICAL FEATURE IN THE RAT LIVER AFTER PORTACAVAL SHUNT.

J.P. Colombo and J. Bircher.

In the adult rat liver the enzyme-glutamyltranspeptidase (GGTP) is bearly measurable, whereas the newborn rat exhibits about 20 times more activity.A derepression of this enzyme has been reported in rat hepatomas. GGTP was measured in adult rats after an end to side portacaval shunt (PCS). Enzyme activity was almost unmeasurable in the control group whereas already ten days after PCS a tenfold increase was observed.The hypothesis is advanced that this increase after PCS may be regarded as a reacquirement of an embryonal biochemical feature,which predominates in the fetal liver and is repressed in the adult life, but may be activated following PCS.

CHLOROQUIN INACTIVATES LYSOSOMAL FUNCTION(S) IN NORMAL CULTURED HUMAN FIBROBLASTS. Sverre O. Lie and Brian Schofield,Oslo 1,Norway, and Baltimore, Md. 21205, USA.

The lysosomal function of mucopolysaccharide degradation in normal cultured human fibroblasts can specifically be inhibited without affecting over-all cell viability or growth. We have earlier shown that an increase in medium pH will progressively inhibit this function(PNAS 69:2361,1972).It is now shown that chloroquin($1\text{-}2 \times 10^{-5}$) also strongly interferes with mucopolysaccnaride degradation in the living cell when the pH is kept around 6.8. Electron microscopy shows that a morphological picture resembling a lysosomal storage disease develops in these cells after less than two days exposure to the drug.We propose that the antimalarial effect of chloroquin (and quinacrine and quinine) and at least some of the major side effects of the drug are due to the same basic mechanism: An inhibition of normal lysosomal activities in the parasite as well as in the human cell.Our results support the hypothesis that chloroquin is concentrated in the lysosomes of the living cell and inactivates the acid hydrolases of this organelle by increasing the intralysosomal pH.

CONTROL OF PYRUVATE OXIDATION IN FETAL AND MATERNAL TISSUE BY THE THIAMINE LEVEL. D.Hoekstra,R.Berger and F.A. Hommes,Laboratory of Developmental Biochemistry,Department of Pediatrics,Univ.of Groningen,The Netherlands.

Especially during the later stages of pregnancy a fair amount of lactate is transported via the placenta from the foetus to the mother.This extra lactate has to be oxidized by the mother or converted to glucose by gluconeogenesis.The oxidation of pyruvate is controlled by the pyruvate dehydrogenase(PDH) by phosphorylation and dephosphorylation.The phosphorylated enzyme is inactive.Thiamine diphosphate(TPP)inhibits the phosphorylation.It was found the mitochondria of the liver of pregnant rats contain less TPP than controls.The TPP content of fetal rat liver mitochondria was found to be in between that of controls and pregnant rats.The mitochondrial TPP content corresponded to the degree of inhibition of mitochondrial PDH by ATP.Intraperitoneal injection of thiamine to pregnant rats resulted in an increase in TPP content of the fetal rat liver mitochondria,but hardly of the liver mitocondria of the mother animal.These results can be interpreted as a physiological control mechanism of the TPP level on PDH activity. The increased supply of lactate from the foetus to the mother calls for a higher rate of gluconeogenesis by the mother.Pyruvate oxidation must than be shut down to prevent waste of substrate.

IMMUNOLOGY

"B" AND "T" CELLS IN NORMAL ADULTS,NEWBORNS AND IMMUNE DEFICIENCY STATES.
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By means of cytotoxicity studies with antiserum to "T" cells, certain patterns of heterogenecity of "T" cell populations (Thymus-dependent) in normal persons and those with immunedeficient states,have become evident. Quantitation of "T" cells in peripheral blood has also become possible.
By means of immunoenzymatic staining of immunoglobulin receptors on "B"-cell (Thymus-independent),membranes, a method of "B" cell quantitation is described in newborns, and patients with immune deficiencies. These new technics allow for better delineation of the immune status by studies of the lymphocytes in the peripheral blood. It also demonstrates immune deficiency patterns in conditions previously not shown to have involvement of the Immune System.