

Publications de l'U 075 (Inserm) (1999-2000)

2000

TRELUYER J.M., BENECH H., COLIN I., PRUVOST A., CHERON G., CRESTEIL T.

Ontogenesis of cyp2c-dependent arachidonic acid metabolism in the human liver: relationship with sudden infant death syndrome.

Pediat. Res., 47 (5), 677-683, 2000

(Services cités : CUDR, U075)

A modification of the human monooxygenase system have been previously associated with the sudden infant death syndrome (SIDS): the hepatic CYP2C content was markedly enhanced and resulted from an activation of CYP2C gene transcription. To determine the possible consequence of the up-regulation of CYP2C in SIDS, we examined the metabolism of arachidonic acid (AA) an endogenous substrate of CYP2C involved in the physiologic regulation of vascular tone. The overall AA metabolism was extremely low during the fetal period and rose after birth to generate 14,15 epoxyeicosatrienoic acid (EET), 11,12 EET and the sum of 5,6 dihydroxyeicosatrienoic acid (diHETE)+omega/omega-1 hydroxy AA. In SIDS, the accumulation of CYP2C proteins was associated with a significant increase in the formation of 14,15 and 11,12 diHETE, which were shown to be supported by individually expressed CYP2C8 and 2C9 and HETE1 (presumably 15 METE). This increase was markedly inhibited by addition of sulfaphenazole, a selective inhibitor of CYP2C9. So, we propose that the higher CYP2C content in SIDS stimulates the production of EETs and diHETEs and might have severe pathologic consequences in children. [References: 36]

ZADEH M.S., KOLB J.P., GEROMIN D., D'ANNA R., BOULMERKA A., MARCONI A., DUGAS B., MARSAC C., D'ALESSIO P.

Regulation of ICAM-1/CD54 expression on human endothelial cells by hydrogen peroxide involves inducible NO synthase.

J. Leukocyte Biol., 67 (3), 327-334, 2000

(Services cités : U075)

Expression of the inducible isoform of nitric oxide synthase (iNOS) is stimulated by cytokines in human epithelial cells. This work indicates that incubation of human umbilical cord endothelial cells with combinations of interleukin-1 beta, tumor necrosis factor alpha, and interferon-gamma stimulated the synthesis of iNOS mRNA, as detected by reverse transcriptase-polymerase chain reaction. It is important to note that 50, 100, and 200 mu M hydrogen peroxide was able to stimulate iNOS directly. Furthermore, 100 mu M H₂O₂ enhanced synthesis of the oxidation products, nitrite (NO₂⁻) and nitrate (NO₃⁻) at 12 and 36 h, iNOS protein, detected by Western blot analysis, as well as L-citrulline levels, were also increased. When endothelial cell monolayers were incubated for 1 h with 100 mu M H₂O₂ and subsequently with cytokines, iNOS mRNA was further augmented. Under the same conditions, we regularly observed an inhibition (25%) of intercellular adhesion molecule-1 (ICAM-1/CD54) expression. The latter was reversed when the NOS inhibitor N-G-monomethyl-L-arginine was added, as shown by flow cytometry. These data suggest a specific effect of endogenous hydroperoxides on the biosynthesis and processing of the human endothelial iNOS isoform. We propose that H₂O₂ induces a temporary NO-dependent modulation of adhesion molecule expression to limit the tissue destruction that accompanies the vascular recruitment of leukocytes. [References: 39]

1999

BAUNE B., FLINOIS J.P., FURLAN V., GIMENEZ F., TABURET A.M., BECQUEMONT L., FARINOTTI R.

Halofantrine metabolism in microsomes in man: Major role of CYP 3A4 and CYP 3A5.

J. Pharm. Pharmacol., 51 (4), 419-426, 1999

(Services cités : Pharmacie, U075)

We have clarified the contribution of the different enzymes involved in the N-debutylation of halofantrine in liver microsomes in man. The effect of ketoconazole and cytochrome P450 (CYP) 3A substrates on halofantrine metabolism has also been studied.

PINARD J.M., MARSAC C., BARKAOUI E., DESGUERRE I., BIRCH-MACHIN M., REINERT P., PONSOT G.

Riboflavin-response Leigh syndrome and leukodystrophy associated to partial succinate dehydrogenase deficiency.

Archives Pédiatrie, 6 (4), 421-426, 1999

(Services cités : U075)

Succinate dehydrogenase (SDH) deficiency is rare. Clinical manifestations can appear in infancy with a marked impairment of psychomotor development with pyramidal signs and extrapyramidal rigidity.