Placental permeability to metabolites in fed and starved rats

MANUEL PALACÍN,*
MIGUEL ANGEL LASUNCIÓN† and
EMILIO HERRERA†

*Departamento Investigación, Centro "Ramón y Cajal", Ctra. Colmenar km 9, Madrid-34, Spain, and
†Departamento Bioquímica, Facultad Medicina, Universidad Alcalá de Henares (Madrid), Spain

Juglal growth and oxidative metabolism are supported by the continuous transfer of nutrients from the mother (Battaglia & Meschia, 1978; Munro et al., 1983). The passage of metabolites through the placental barrier may occur by simple diffusion (e.g. for fatty acids), facilitated diffusion (e.g. for glucose) or active transport (e.g. for amino acids) (Dancis & Schneider, 1978). The net transfer of a metabolite to the foetus is influenced by the concentration gradient between mother and foetus (Shelley, 1979), blood fluxes at both sides of the placenta (Wilkenk et al., 1982), and the actual permeability of the placenta to that metabolite (Dancis & Schneider, 1978). Thus changes in the concentration of a metabolite in the maternal circulation lead to variations in its transfer to the foetus (Boyd et al., 1973).

Placental transfer of different substances has been well established in systems which allow simultaneous sampling from both sides of the organ (Battaglia & Meschia, 1978; Johnson & Yudilevich, 1981). These studies have confirmed that, independently of the transport mechanism and the net transfer to the foetus, placental permeability differs for each metabolite (Battaglia & Meschia, 1978; Seeds et al., 1980). It is not yet known, however, whether the placenta itself, as an organ, is able to modify its effective permeability to a metabolite in order to modulate its transfer to the foetus. As the foetal/maternal ratio of circulating metabolites varies and is greatly modified by starvation, in the present work we compared the placental permeability of different metabolites in the rat and determined whether maternal starvation affects this parameter. Fed and 48 h-starved 21-day-pregnant Wistar rats anaesthetized with sodium pentobarbital (33 mg kg body wt) were infused for 20 min through a cannula placed at the level of the left uterine arteries with tracers of different 14C-labelled metabolites dissolved in 0·8% NaCl by using surgical procedure and other methodological details described by Lasunción et al. (1983). In this way, the left uterine horn received the tracer directly, whereas it reached the right horn after dilution in the mother’s circulation. The difference between plasma radioactivity in foetuses from the left and the right uterine horn was used as an index of the permeability to the infused metabolite (Lasunción et al., 1983; Palacin et al., 1983) of [1-14C]glucose, [1-14C]alanine and [1-14C]glycerol were used as tracers because these metabolites are transferred through the placenta by different transport mechanisms (Widdas, 1952; Dancis & Schneider, 1978), and because their concentration in maternal plasma changes with starvation (Herrera et al., 1969; Girard et al., 1977). Two non-metabolizable compounds (3-O-methyl-[U-14C]glucose and 2-amino-[1-14C]isobutyric acid) were also used to determine whether placental permeability to them differed from that of their metabolizable analogues. Plasma radioactivity values were much higher in foetuses from the left than from the right horn when [14C]glucose or [1-14C]alanine was infused, as indicated by the high plasma radioactivity difference value (Table I), demonstrating the expected high placental permeability to these metabolites. When [14C]glycerol or 2-amino[14C]isobutyric acid was infused, however, these difference values were much smaller (Table I), indicating that placental permeability to these compounds is lower than to glucose and alanine. For 2-amino[14C]isobutyric acid, the different results compared with those with L-[14C]alanine may be a consequence of the needs of the placenta to incorporate into its metabolism the amino acid to be transported (Carroll & Young, 1983), although the known difference in the nature of the carrier for 2-aminoisobutyric acid and alanine (Enders et al., 1976) could also influence results. With 3-O-methyl[14C]glucose, which is fully recognized by the D-glucose carrier (Johnson & Smith, 1980), observed values were very similar to those with D-[1-14C]glucose (Table I), indicating that glucose metabolism does not affect its placental permeability index. To correct values for a potential unspecific leak, infusion was also performed with L-[1-14C]glucose. As also shown in Table I, the difference in plasma radioactivity between foetuses from the left and the right uterine horn was very small, which, besides validating the technique used, demonstrates the specificity of placental transport for D-glucose. Experiments in 48 h-starved rats were conducted specifically to determine the eventual effects of starvation on placental permeability, but not to quantify the net transfer of metabolites to the foetus. As shown in Table I, plasma radioactivity differences between foetuses in the left and the right horn were very similar in starved and fed animals for any 14C-labelled compound. This finding indicates that starvation in the rat does not modify placental permeability. Plasma concentration of both glucose and alanine decrease, whereas that of glycerol increases with starvation in the mother (Herrera et al., 1969; Girard et al., 1977), and these changes may secondarily affect the actual metabolite transfer throughout the placenta, even in the presence of unaffected permeability. Therefore the present results suggest that differences in the foetal maternal ratio of circulating metabolites known to be caused by starvation in the pregnant rat are not due to altered placental permeability to metabolites, but are a
Studies in humans on the development of the GST1, GST2 and GST3 isoenzymes

Charles G. Faulder,* Brian A. Davis,* William Cotton,* A. D. Bain,+ Robert Humé+ and Richard C. Strange*  
*Department of Clinical Biochemistry, Central Pathology Laboratory, North Staffordshire Hospital Centre, Hanover Road, Stoke-on-Trent ST4 7PA, U.K., and †Department of Child Health and Life, University of Edinburgh, Edinburgh EH3 9D, Scotland, U.K.

The GST are dimeric detoxicating enzymes that in humans are present in the products of three autosomal loci, GST1, GST2 and GST3 (Pearson, 1981). These isoenzymes exhibit variability, but only in the case of GST1 does this appear to be genetically determined (Strange et al., 1984). Although studies have reported GST activity in human foetal tissues, no systematic study of the development of these loci has been described and little is known of the details of their expression in utero. We now describe experiments to separate, by chromatofocusing, the products of these different gene loci in foetal and neonatal liver cytosol and determine their relative concentration among other factors known to affect the transfer, inclusion, among others, availability of metabolites in the maternal state. Blood flow, and foetal consumption.

The present study was performed with grants from the Fondo de Investigaciones Sanitarias de la Seguridad Social and the Comisión Nacional de Investigación Científica y Técnica, Ministerio de Educación y Ciencia, Spain. We thank Caroline S. Delgado for her editorial help.

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<tr>
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<th>Fed</th>
<th>48h-Starved</th>
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<tr>
<td>l-[14C]Glucose</td>
<td>10973 ± 2144 (6)</td>
<td>8800 ± 460 (6)</td>
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<tr>
<td>d-[14C]Glucose</td>
<td>5614 ± 713 (6)</td>
<td>9729 ± 1635 (6)</td>
</tr>
<tr>
<td>3-O-Methyll-[14C]Glucose</td>
<td>9456 ± 7298 (6)</td>
<td>7689 ± 913 (6)</td>
</tr>
<tr>
<td>2-Aminol-[14C]Aesobutyric acid</td>
<td>1972 ± 195 (4)</td>
<td>2448 ± 64 (4)</td>
</tr>
<tr>
<td>l-[14C]Glycerol</td>
<td>1944 ± 647 (6)</td>
<td>2028 ± 300 (6)</td>
</tr>
<tr>
<td>l-[14C]Glucose</td>
<td>314 ± 65 (3)</td>
<td>—</td>
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Cytosol was prepared from samples of liver obtained with the permission of the Ethics Committee of the Simpson Memorial Maternity Pavilion, Royal Infirmary, Edinburgh, U.K. They were eluted at 6°C from columns containing Polybuffer exchanger 94 (Pharmacia Fine Chemicals, Uppsala, Sweden, 1 l) previously equilibrated with start buffer (25mmimidazole buffer, pH 7.3). The pH gradient was formed by using Polybuffer 74 adjusted to pH 4.0 with HCl (5M). Fractions were analysed for enzyme activity and pH. In initial experiments each peak of activity was pooled, concentrated and examined by starch-gel electrophoresis to determine which gene products were present. Chromatofocusing resulted in the separation of the different GST isoenzymes (Fig. 1). The GST isoenzymes eluted first, usually as two peaks of activity. The first peak was not retained and corresponded to the isoenzyme with faster cathodal mobility, the second peak where present (eluted between pH 6.70 and 6.95) to the isoenzyme with slower cathodal mobility. The GST1 isoenzymes eluted between pH 6.25 and 6.50 (GST1 2 phenotype) or between pH 5.90