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Placental permeability to metabolites in fed and starved rats

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Feetal growth and oxidative metabolism are supported by the continuous transfer of nutrients from the mother (Battaglia & Meschia, 1978; Munro et al., 1983). The pas-

sage 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) (Hendrix & Schneider, 1978). The net transfer of a metabolite

to the foetus is influenced by the concentration gradient be-

tween mother and foetus (Shelley, 1979), blood fluxes at

both sides of the placenta (Wilkening et al., 1982), and the

placental permeability to that metabolite (Dynes & Schneider, 1978). Thus changes in the concentra-

tion of a metabolite in the maternal circulation lead to vari-

ations in its transfer to the foetus (Bovd 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; Peten & Yudilevich, 1981). These studies have confirmed that, independently of the transport mechanism and the net trans-

fer 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

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 20min through a cannula placed at the level of the left uterine artery with trace amounts of different 14C-labelled metabolites dissolved in 0.9% NaCl. Using the surgical procedure and other methodological details described by Lasun-
ción et al., (1983) in this way, the left uterine horn were 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 right uterine horn was used as an index of the permeability to the infused metabolite (Lasunción et al., 1983; Palacín et al., 1983). D-[U-14C]Glucose, L-[U-14C]alanine and [U-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 α-amino [L-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 [14C]alanine was infused, as indicated by the high plasma

radioactivity difference value (Table 1), demonstrating the expected high placental permeability to these metabolites. When [14C]glycerol or α-amino[14C]isobutyric acid was infused, however, these difference values were much smaller (Table 1), indicating that placental permeability to these compounds is lower than to glucose and alanine. For α-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 α-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-[U-14C]glucose (Table 1), indicating that glucose metabolism does not affect its placental permeability index.

To correct values for a potential unspecified leak, infusion was also performed with L-[1-14C]glucose. As also shown in Table 1, 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 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 1, plasma radioactivity differences between foetuses from the left and 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 unaltered 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

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Table 1. Plasma radioactivity differences between fetuses from the left and the right uterine horn after infusion of d[(U-14C)glucose, 3-O-methyl(U-14C)glucose, 2-amino(14C)isobutyric acid, (U-14C)glycerol or l-[1-14C]glucose in the fed and 48 h-starved 21-day-pregnant rat.

<table>
<thead>
<tr>
<th></th>
<th>Fed</th>
<th>48h-Starved</th>
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<tbody>
<tr>
<td>d-(U-14C)glucose</td>
<td>10973 ± 2144 (6)</td>
<td>8829 ± 460 (6)</td>
</tr>
<tr>
<td>d-(U-14C)Glucose</td>
<td>6141 ± 713 (6)</td>
<td>9929 ± 1635 (6)</td>
</tr>
<tr>
<td>3-O-Methyl(U-14C)Glucose</td>
<td>9576 ± 2398 (6)</td>
<td>7651 ± 913 (6)</td>
</tr>
<tr>
<td>2-Amino(1-14C)Isobutyric Acid</td>
<td>1972 ± 195 (4)</td>
<td>2448 ± 648 (4)</td>
</tr>
<tr>
<td>(U-14C)Glycerol</td>
<td>1944 ± 447 (6)</td>
<td>2026 ± 300 (6)</td>
</tr>
<tr>
<td>l-[1-14C]Glucose</td>
<td>314 ± 65 (3)</td>
<td>—</td>
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</tbody>
</table>

Infusions were performed for 20 min under pentobarbital anaesthesia with the tracers diluted in 0.9% NaCl at the rate of 12.84 μl/min. Values were always corrected by considering 1 x 10¹⁶ c.p.m. as the total infused radioactivity per rat, and are expressed as means ± S.E.M. Numbers of animals per group are indicated in parentheses. Statistical differences between fed and 48 h-starved rats were always not significant (P > 0.05).

Foetal plasma radioactivity differences
(left - right)

consequence of other factors known to affect the transfer, including, among others, availability of metabolites in the maternal side, blood flow, and foetal consumption.

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Studies in humans on the development of the GST1, GST2 and GST3 isozymes

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The GST is a group of enzymes that catalyse the conjugation of xenobiotics with glutathione (GSH). They are primarily found in the liver, kidney, lung, and gut. The GSTs have a wide range of substrates, including drugs, pesticides, and environmental pollutants.

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 pH 4.4 from columns containing Phenyl-BPA-DEAE columns. The fractions were pooled, concentrated, and examined by starch-gel electrophoresis to determine which isozyme was present.

Chromatofocusing resulted in the separation of the different GST isozymes (Fig. 1). The GST isozymes eluted first, usually as two peaks of activity. The first peak was not retained and corresponded to the isozyme with the lowest mobility. The second peak was present in between pH 8.0 and 9.0 (GST 1) and pH 5.90 (GST 2).