SHORT COMMUNICATION

Total body-glucose turnover in normal and intra-uterine growth-retarded neonatal piglets

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Summary

1. Because studies of the metabolic problems of the human intra-uterine growth-retarded neonate are limited by ethical considerations we have used the intra-uterine growth-retarded piglet as an animal model. Total body-glucose kinetics were measured in 16 intra-uterine growth-retarded and 11 normal piglets from the same litters with $[3H]$glucose as a tracer.

2. The intra-uterine growth-retarded animals had marginally smaller brains than their normal littermates, but substantially smaller livers. Liver weight was reduced in proportion to body weight.

3. Total body-glucose turnover rate was significantly lower ($P < 0.001$) in the intra-uterine growth-retarded animals in comparison with their normal littermates, but was appropriate for their smaller body and liver weights. Brain weight was only slightly reduced in the intra-uterine growth-retarded group so that glucose turnover adjusted to a common brain weight was significantly lower ($P < 0.001$) in these animals.

4. Total body-glucose pool size was lower in the intra-uterine growth-retarded animals ($P < 0.01$), but was appropriate for their body and liver weights. It was significantly reduced in relation to brain weight ($P < 0.001$).

5. Resting plasma glucose concentration was lower in the intra-uterine growth-retarded animals ($P < 0.001$). There was no relationship between concentration and turnover in either group.

6. It is suggested that the observed differences in total body-glucose turnover may be associated with profound differences in cerebral metabolism in the intra-uterine growth-retarded animals.

Key words: glucose, intra-uterine growth retardation, neonatal piglet.

Introduction

Neonatal hypoglycaemia is a well recognized clinical problem that occurs most frequently in light-for-dates infants (Neligan, Robson & Watson, 1963; Oh, 1977). A variety of possible causes have been postulated, but investigations have been limited by ethical constraints. For this reason a number of different animal models have been used, such as the puppy (Hetenyi, Varma & Cowan, 1972), the rhesus monkey (Robinson, Sherwood, Mayes, Freire, Oei & DiBattista, 1980), the lamb (Warnes, Seamark & Ballard, 1977) and the rat (Vernon & Walker, 1972). None of these species is entirely satisfactory for reasons of cost, size at birth, differences in physiology or state of development at birth. Few investigations have been carried out with the neonatal piglet, although this species seems likely to provide a suitable animal model since it has certain morphological and physiological similarities to man and naturally develops neonatal hypoglycaemia (Goodwin, 1957). Furthermore glucose turnover relative to body weight is similar in human neonates and piglets (Flecknell, Wootton & John, 1980). Many litters of piglets contain one or more animals that have experienced intra-uterine growth retardation and these animals show a similar pattern of growth retardation to that which occurs in the human neonate (Widdowson, 1971). Like the human intra-uterine growth-
retarded infant they are also more prone to the development of hypoglycaemia (P. A. Flecknell, unpublished work). To investigate possible differences in glucose metabolism we have measured steady-state glucose kinetics in 16 intra-uterine growth-retarded piglets and 11 normal controls.

Materials and methods

After natural parturition, one or more growth-retarded piglets and one normal littermate were obtained from each of 11 litters of piglets. Growth-retarded animals were identified by their characteristic clinical appearance (Cooper, John, McFadyen & Wootton, 1978) and in general were at least half the mean body weight of their normally developed littermates. Sixteen intra-uterine growth-retarded and 11 normal piglets, aged between 24 and 36 h, were studied. Catheters were inserted into the external jugular vein and carotid artery to facilitate stress-free blood sampling and injection of tracers (Flecknell, 1979). The animals were housed in a thermoneutral environment and were given water ad lib. but no food for 16 h before the experiment. They were weighed at the time of study and their rectal temperatures monitored to ensure that the environmental temperature was high enough to prevent chilling.

After a background blood sample, D-[2-3H]glucose (100 μCi; 3.7 MBq, The Radiochemical Centre, Amersham, Bucks., U.K.) was injected through the jugular catheter and nine arterial blood samples were taken at 5, 10, 15, 30, 60, 90, 120, 150 and 180 min postinjection. At the end of this period the animals were killed and the brain and other major organs removed and weighed. The procedures for sample processing have been described previously (Flecknell et al., 1980). The total body-glucose turnover rate and total body-glucose pool size were calculated from the plasma specific radioactivity values by conventional compartmental methods with a computer program written in Fortran IV.

Statistical methods

Since some litters contained more than one intra-uterine growth-retarded piglet, the statistical design was unbalanced making use of Student’s paired t-test inappropriate for the comparison of normal and intra-uterine growth-retarded animals. We therefore carried out a two-way analysis of variance with the computer program GLIM 3 (Royal Statistical Society, 1978) to compare the differences between the two groups after allowing for the interlitter variation. Analysis of covariance was also carried out with GLIM 3 to compare the two groups of animals after adjusting for differences in body weight.

Results

Table 1 lists the mean total body-glucose turnover and pool size for the animals, their mean body, brain and liver weights and their basal plasma glucose concentrations. On comparing the intra-uterine growth-retarded piglets with their normal littermates, the former were found to have a significantly lower total body-glucose turnover rate ($P < 0.001$). This difference is explained by the lower body weight of the intra-uterine growth-retarded group, since analysis of covariance showed that there was no difference after adjusting the two groups to a common body weight ($P > 0.05$). Although brain weight was slightly lower in the intra-uterine growth-retarded animals, it was greater than normal relative to body weight (Table 1) so that glucose turnover adjusted to a common brain weight was significantly lower in the intra-uterine growth-retarded group ($P < 0.001$). Liver weight, conversely, was reduced roughly in proportion to body weight in the intra-uterine growth-retarded animals (Table 1) and analysis of covariance confirmed that there was no difference in liver weight after adjusting for the differences in body weight ($P > 0.1$).

Glucose pool size was significantly lower in the intra-uterine growth-retarded animals ($P < 0.01$), but was not different after adjusting for body weight ($P > 0.25$). Glucose pool size adjusted to a common brain weight was lower in the intra-uterine growth-retarded animals but not different ($P > 0.1$) when adjusted to a common liver weight because of the proportional reduction in the weight of the liver.

Plasma glucose concentration was significantly lower in the intra-uterine growth-retarded animals

<table>
<thead>
<tr>
<th>Variable</th>
<th>Normal</th>
<th>Intra-uterine growth retardation</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>1.149 ± 0.107</td>
<td>0.567 ± 0.080</td>
<td>$&gt;0.05$</td>
</tr>
<tr>
<td>Brain weight (g)</td>
<td>31.7 ± 3.0</td>
<td>28.5 ± 2.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Liver weight (g)</td>
<td>31.9 ± 7.8</td>
<td>15.2 ± 3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose turnover (μmol/min)</td>
<td>39.5 ± 9.6</td>
<td>17.7 ± 6.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose pool (mmol)</td>
<td>7.01 ± 0.74</td>
<td>0.67 ± 0.31</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Plasma glucose (mmol/l)</td>
<td>3.77 ± 0.86</td>
<td>1.95 ± 1.00</td>
<td>&lt;0.001</td>
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</tbody>
</table>
The intra-uterine growth-retarded piglet appears to be a particularly appropriate model for the study of glucose homeostasis in the perinatal period and both human and porcine intra-uterine growth-retarded neonates tend spontaneously to develop hypoglycaemia. Although none of the intra-uterine growth-retarded piglets in the present study exhibited clinical signs of hypoglycaemia, they all had significantly lower basal plasma glucose concentrations than their normal littermates. It has been suggested that neonatal hypoglycaemia is not the result of glucose overutilization, based on the good correlation between turnover per unit body weight and plasma glucose concentration in the newborn rhesus monkey (Robinson et al., 1980). Unfortunately, the correlation may be spurious since adjustment for animals of differing body weight was made by simple division rather than by analysis of covariance which allows for the possibility of a non-zero intercept in the linear relation between turnover and body weight. In contrast Hetenyi et al. (1972) concluded that there was no relation between hepatic glucose production and plasma glucose concentration in the newborn dog and suggested that this might result from a deficient feedback mechanism. In the steady state hepatic glucose production rate is equivalent to glucose turnover rate and in the neonatal piglet our results show a similar lack of relation between plasma glucose concentration and glucose turnover after allowing for body weight, for differences between litters and for the putative difference between intra-uterine growth-retarded and normal animals (r = -0.05, P > 0.1).

Discussion

The intra-uterine growth-retarded piglet is more or less normal in terms of its liver weight-glucose turnover (Flecknell et al., 1980) so these findings suggest that hepatic glucose production in the intra-uterine growth-retarded piglet is more or less normal in terms of its liver and body weight.

In contrast, growth retardation has relatively little effect on brain weight in both piglets and in man and as a consequence, glucose turnover adjusted for brain weight was significantly lower in the intra-uterine growth-retarded animals. The brain is thought to be a major consumer of glucose (Kety, 1957; Schwartz & Kalhan, 1975), estimates ranging from 15 to 50% of hepatic output, although no measurements of cerebral glucose utilization in the neonatal piglet have been reported. Since the intra-uterine growth-retarded piglets have disproportionately large brains, total body-glucose turnover might be expected to be higher relative to body weight. Our results show that this is not the case. Either the rate of cerebral glucose metabolism is appropriate for the weight of the brain and metabolism in other tissues is lower than normal, or vice versa, or use is being made of alternative substrates. In the latter context it has been suggested that ketone bodies...
are a major source of energy for the neonatal brain (Stumpf, Kraus, Kasten & Ahrens, 1979).

In the intra-uterine growth-retarded human neonate hypoglycaemia is a common phenomenon and if uncorrected can lead to cerebral damage or death (Warshaw, 1979). Our studies in the piglet indicate that although both the rate of glucose utilization and the total body-glucose pool size are reduced in intra-uterine growth-retarded animals they are appropriate for their reduced body weight. Since brain weight is only marginally smaller in growth-retarded neonates, it seems possible that there may be profound differences in cerebral metabolism so that further studies of brain glucose utilization are indicated.

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References


