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The effect of gestational age and intrauterine nutrition on plasma free amino acids in the human newborn

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The postnatal changes in plasma amino acids and blood glucose of preterm appropriate for gestational age (PAGA) and small for gestational age (PSGA) infants were compared. The mean blood glucose concentration was significantly depressed ($p<0.001$) in the PSGA infant group. Neither the total concentration of the determined 17 plasma amino acids nor the plasma level of the three important glucogenic amino acids (alanine, glycine, proline) were significantly higher in the premature small for gestational age infants than in those, whose birth-weight was appropriate for gestational age. The mean concentrations of leucine, phenylalanine and aspartate were significantly lower ($p<0.05$) and of glutamate significantly higher ($p<0.05$) in the PSGA group. No correlation was found between blood glucose and the main glucogenic amino acids. Combining the present results for preterm infants with those full term well-nourished and small-for-gestational-age infants, among the 17 amino acids only alanine turned out to be significantly related to gestational age in the combined group of SGA infants.

The results show that hypoglycaemia in preterm SGA infants is not associated with hyperaminoacidaemia as it has been observed in full term SGA neonates. To explain this difference, it is suggested that the duration of intrauterine malnutrition is a decisive factor in the maturation of hepatic gluconeogenesis. This would mean that birth before term, i. e. a short exposure to unfavourable nutritional conditions, does not severely affect the postnatal activation of gluconeogenesis.

In recent studies, the role of impaired gluconeogenesis in the aetiology of hypoglycaemia in SGA infants has been shown [2, 3, 7, 8]. The postnatal accumulation of the gluconeogenic amino acids lactate and pyruvate in the plasma of SGA infants suggested a reduced hepatic uptake of these precursors and a decreased glucose synthesis. The extent of amino acid accumulation in the plasma was directly related to the degree of glucose deficiency and the severity of intrauterine undernutrition [8]. Direct assays of hepatic glocuneogenic enzyme activities in animals [1, 6, 11] and recently in human studies [5] suggest that the defect in gluconeogenesis would probably be due to a delay in induction of the key rate-limiting gluconeogenic enzymes.

Neonatal hypoglycaemia in the full term SGA infant is associated with increased plasma concentrations of

gluconeogenic substrates [3, 8]. No information is, however, available on the quantitative and qualitative amino acid pattern of preterm newborn babies. In the present study we have compared the postnatal changes in plasma amino acids of well nourished and undernourished preterm infants to establish whether gestational age, in addition to the intrauterine nutritional status, had any influence on their plasma aminogram.

Material and Methods

20 newborn infants born before 37 weeks of gestation were studied. Nine infants had birthweights below the tenth percentile according to our local intrauterine growth chart, and showed clinical signs of undernutrition. These infants formed the group of preterm small-for-gestational-age infants (PSGA). The remaining 11 preterm babies were all well nourished with a birth weight appropriate for gestation (PAGA). Mean gestational ages, birth weights and postnatal ages in the two groups of infants are shown in Table I. All the normally grown premature infants were born after uneventful pregnancy. In 5 of the PSGA infants studied, pregnancy was complicated with toxaemia.

A blood glucose level of less than 20 mg/100 ml was accepted as a criterion of hypoglycaemia, and such low levels were observed in 6 PSGA infants between 1—12 hours postnatally. One infant developed convulsions during hypoglycaemia, which did not respond to intravenous injection of glucose.

Peripheral venous blood was taken from all the infants at the time of admission (1—12 hours after birth) before the first feeding. Blood glucose was measured in duplicate by the orthotoluidine method of Price [9]. Amino acid analysis was performed by an automatic Beckman Multichrom Liquid Column Chromatograph and norleucine was used as an internal reference standard. The levels of 17 individual amino acids were quantitated. The standard t test was used for statistical analysis. Regression equations were calculated by the method of least squares.

Table I

Gestational age, birth weight and postnatal age of the two groups of infants*

	Preterm AGA infants	Preterm SGA infants
Gestational age (wk)	32.7 (29—35)	33.2 (31—36)
Birth weight (g)	1792 (1250—2450)	1409 (1070—1770)
Postnatal age (hr)	9.7 (3—12)	6.1 (3—12)
No of infants	11	9

* Ranges for age, weight and postnatal age are in parentheses

Results

Table II compares the total and individual plasma amino acids in PAGA and PSGA infant. The latter was not only characterized by a significant weight deficit, but blood glucose concentration was also significantly depressed (54.5 ± 6.3 mg/100 ml versus 24.6 ± 2.6 mg/100 ml). From Table II it is obvious, that neither the sum of concentrations of the 17 amino acids determined, nor the plasma content of the three important gluconeogenic amino acids (alanine, proline, glycine) were significantly higher in the PSGA infants than in those whose birthweight was appropriate for gestational age. The plasma levels of the branched chain amino acids (leucine, isoleucine, valine) tended to be lower in the malnourished group, but except leucine ($p < 0.02$) the differences were not significant statistically. Among the other amino acids, phenylalanine and aspartate were significantly lower ($p < 0.05$) and glutamate significantly higher

Table II

Mean plasma concentrations ($\mu M \pm SE$) of 17 amino acids in the two groups of preterm infants

Amino acid	Preterm AGA infants	Preterm SGA infants
Taurine	257 ± 15	261 ± 27
Aspartate	54 ± 5	40 ± 4*
Glutamate	47 ± 5	68 ± 8*
Citrulline	25 ± 6	23 ± 4
Proline	195 ± 23	187 ± 20
Glycine	285 ± 24	244 ± 12
Alanine	280 ± 23	319 ± 22
Cystine	76 ± 14	93 ± 14
Valine	160 ± 10	138 ± 11
Methionine	24 ± 3	21 ± 3
Isoleucine	51 ± 3	39 ± 6
Leucine	100 ± 9	69 ± 8**
Tyrosine	146 ± 18	103 ± 17
Phenylalanine	114 ± 11	82 ± 8*
Lysine	186 ± 20	217 ± 21
Histidine	61 ± 12	85 ± 13
Arginine	61 ± 10	44 ± 8
Total	211 ± 126	2033 ± 201

* $p < 0.05$
** $p < 0.02$

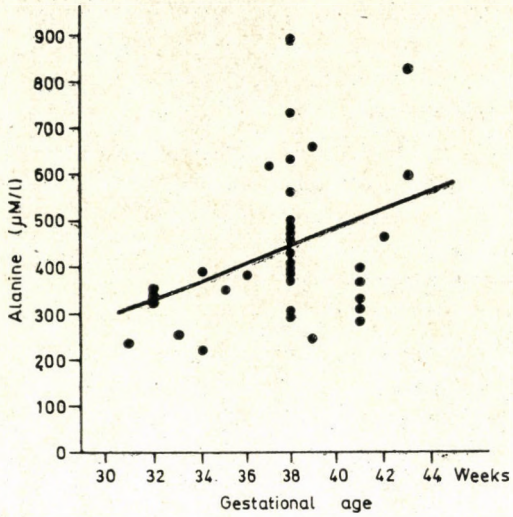

FIG. 1. Relationship between plasma alanine and gestational age in the combined group of SGA (9 preterm and 26 full term) infants: $y = 19.769$, $x - 306.746$; $r = 0.378$; $p < 0.05$.

($p < 0.05$) in the PSGA infants. Thus in the hypoglycaemic preterm SGA infants neither the total plasma amino acid content, nor the individual amino acid concentrations were strikingly different from that of non-hypoglycaemic babies. The significant inverse correlation between blood glucose and the four main glucogenic amino acids observed in full term SGA infants [8] was not demonstrable in preterm SGA infants. It appears that maturity plays an important role in the postnatal changes of the plasma amino acids in relation to blood glucose changes in intrauterine malnourished infants.

Since the accumulation of glucogenic amino acids seemed to characterize the hypoglycaemia only in full term SGA infants, it may be a reflexion of gestational age rather than of a lack of glucose. To test this possibility, individual amino acid levels were related to gestational age which has been extended up to 43 weeks by combining the results of the present two study groups of preterm infants with full term, well-nourished and small-for-gestational-age infants. Among the 17 amino acids only alanine turned out to be significantly related to gestational age ($r = 0.378$ $p < 0.05$) in the combined group of SGA (9 preterm + 26 full term) infants (Fig. 1). In contrast, no significant correlation was obtained in the normally grown (11 preterm + 15 full term) neonates.

DISCUSSION

Our previous results not only showed that hypoglycaemia was associated with hyperaminoacidaemia

mainly due to the increased levels of the glucogenic amino acids, but also revealed a close inverse correlation between blood glucose and the most important amino acid precursors e. g. alanine, proline and glycine. Such a relationship between hypoglycaemia and total plasma amino acid content on the one hand, and between blood glucose and glucogenic amino acid concentration on the other hand, could not be demonstrated in SGA infants born before term. This difference between the two groups of hypoglycaemic underweight infants points towards the importance of gestational age or maturity in relation to the postnatal changes of glucose and amino acid metabolism. It should, however, be emphasized, that the difference in the metabolic behaviour applies only to intrauterine malnourished infants; in the normally grown babies the postnatal changes of plasma amino acids are quite similar and appear to be independent of gestational age.

There are several possibilities to explain the lack of an increase in the plasma glucogenic amino acid levels in hypoglycaemic preterm SGA infants. Since hyperaminoacidaemia in hypoglycaemic full term SGA infants is considered to result from an impaired or delayed activation of hepatic gluconeogenesis, it appears reasonable to assume that the postnatal initiation of endogenous glucose synthesis in preterm SGA babies is as efficient as in well-nourished full term infants. Otherwise the increased flow of amino acids to the liver elicited by fasting and their decreased hepatic uptake should lead to elevated plasma levels as it occurs in mature SGA infants. Since this is not the case, either a rapid activation of gluconeogenesis occurs together with an increased disposal of glucogenic amino acids like in normal full term infants, or the reduced capacity for endogenous glucose synthesis due to immaturity does not induce an increased mobilization of amino acid precursors and therefore the plasma levels do not increase after birth. But like in the normal full term infants, the postnatal fall in the concentration of alanine, the most important glucogenic amino acid, suggest that hepatic glucose synthesis becomes active soon after birth in well-nourished and undernourished premature neonates. If this explanation reflects the real situation, than why does not intrauterine malnutrition affect the postnatal activation of gluconeogenesis in babies born before term?

It appears that the duration of intrauterine malnutrition is a decisive factor in the impairment or delay of the biochemical maturation of the liver and hence in the less efficient metabolic transition from the intrauterine to the extrauterine environment. A long exposure to unfavourable nutritional conditions may not only result in a more severe undernutrition of the fetus, but can also lead to perinatal complications, which may threaten survival of the fetus, or cause various disturbances in neonatal adaptation.

Perinatal asphyxia is a common

occurrence in the second half of the third trimester of pregnancies complicated by placental insufficiency, which is often superimposed on the somatic consequences of intrauterine malnutrition, and may contribute to the biochemical and physiological abnormalities interfering with various processes induced by birth and extrauterine conditions. In view of the possible role of asphyxia in the transitory impairment of neonatal gluconeogenesis in full-term underweight infants, the anaerobic metabolism leads to similar quantitative and qualitative alterations in the plasma aminogram as the alterations associated with hypoglycaemia [10]. It is conceivable that in these infants in contrast to those born prematurely, hyperaminoacideamia and hyperalaninaemia are partly due to manifest or subclinical hypoxia, which has been shown to reduce the hepatic uptake of alanine and to increase its synthesis and release in the muscle by enhanced conversion of lactate to alanine [4]. These metabolic consequences of asphyxia superimposed on the impaired glucose homeostasis caused by malnutrition deserve careful consideration in explaining the difference of the plasma amino acid profile associated with hypoglycaemia in term and preterm undernourished neonates.

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