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The metabolic pattern of premature infants receiving Aminosol-glucose infusion

By

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Total energy metabolism and the contribution to heat production of fat, carbohydrate and protein oxidation have been investigated in three premature infants subjected to Aminosol-glucose infusion for 28 hours. In 15 low-birth-weight infants receiving the same mixture of nutrients only the changge in blood metabolites were followed.

1. Amino acid oxidation, the rate of which was low in the fasting state, gradually increased during Aminosol-glucose infusion, to become an important component of energy metabolism. The changes in nitrogen balance pointed to a marked metabolic stimulation during Aminosol-glucose infusion, leading to an enhanced deamination of amino acids.

2. Only one of the three premature infants showed an increase in total heat production, although amino acid oxidation and urea formation considerably increased during intravenous nutrition. This suggests that the "specific dynamic action" does not primarily reflect the energy cost of protein catabolism.

3. The changes in the utilization pattern of substrates was also reflected by the alterations in blood metabolites. It is concluded that intravenous nutrition with an amino acid mixture may cause marked distortions in the metabolic pattern and biochemical composition of the blood.

In a previous study [10] it has been shown that in premature infants the infusion of a fibrin-hydrolysate-monosaccharide solution (Aminosol-glucose) for a few hours markedly changed the fasting metabolic pattern: the oxidation rate of glucose and amino acids increased, and the rate of lipid oxidation decreased. This shift in substrate utilization was reflected by alterations in the plasma levels of the main nutrients and metabolites.

On the basis of these findings it appeared reasonable to assume that a prolonged administration of an amino acid mixture may cause a further increase in amino acid catabolism leading to a highly unphysiological metabolic state. The increased urea formation and elevated urea level, as well as the enhanced endogenous acid production are well-known biochemical consequences potentially deleterious to premature infants.

Thus, a study was performed in premature infants to determine the participation of amino acid oxidation as the source of energy during the intravenous administration of Aminosol-glucose for 28 hours. It was thought that some quantitative information regarding protein catabo-

TABLE I

Pertinent clinical data of three premature infants in whom energy metabolism and substrate utilization has been studied

No.	Birth weight, g	Gestational age, weeks	Postnatal age, hours	Rate of Aminosol infusion, ml/kg/min	History of pregnancy and delivery
1	900	27	35	0.10	Spontaneous delivery. Hypothermia
2	1850	36	26	0.10	Spontaneous delivery. Premature rupture of membranes. Dysmaturity. Vomiting
3	1880	?	15	0.10	Spontaneous delivery. Premature rupture of membranes

lism would provide a basis for further studies exploring the changes in energetics of parenteral nutrition, and may aid in defining the energetic efficiency of parenteral nutrition in newborns.

MATERIAL AND METHODS

Energy metabolism and the distribution pattern of substrate utilization have been examined in three premature infants, whose pertinent clinical data including volume and duration of Aminosol-glucose infusion are shown in Table I.

Aminosol-glucose was given by an infusion pump into a scalp vein. An umbilical venous catheter was inserted, through which blood samples were withdrawn before and during the infusion. The infusion was started after a 12-hour control period. During Aminosol-glucose administration, urine was separately collected from 0 to 4, from 4 to 16 and from 16 to 28 hours. Collection of urine was continued after the Aminosol-glucose infusion had been stopped. Infant No. 1 received 5% glucose with bicarbonate intravenously during this period.

Oxygen consumption and CO_2 production were measured using the Kipp diaferometer, which allowed a continuous measurement of respiratory gas exchange and of the respiratory quotient. Readings were made every minute, except when reference was made to room air. The studies were performed within the zone of thermoneutrality (34—36°C). The infants were placed in an incubator under a perspex hood through which room air was drawn at a rate of 1.6 to 4.0 l/min. Before the infusion of Aminosol-glucose into a cephalic venous vein, oxygen consumption of the sleeping or resting infant had been followed through a 120-minute control period. During the first 4 hours of intravenous nutrition, gas exchange was measured continuously, thereafter throughout every second hour of the observation period.

Energy metabolism was expressed as kcal/kg/hr which represented the average of the readings of the different periods during which respiratory metabolism was followed. The caloric value for oxygen used for calculation of heat production corresponded to the average RQ of the respective observation period. The relative quantity of calories (fat and carbohydrate) produced was estimated from the non-protein RQ. This quantity was calculated from oxygen consumption and CO_2 production after subtraction of oxygen and carbon dioxide related to protein metabolism, as determined by the excretion of urinary nitrogen minus α-amino nitrogen. The Kjeldahl technique and the method of CLAYTON and

STEELE [2] were used for determination of the total and α-amino nitrogen content of the urine.

In 15 infants in whom parenteral feeding was necessary, only the changes in blood metabolites were followed during Aminosol-glucose infusion. Birth weight in this group of infants ranged from 900 to 1880 g, and gestational age from 26 to 36 weeks. The rate of Aminosol-glucose infusion varied between 0.038—0.12 ml/kg/min, and the postnatal age at which parenteral nutrition was started, between 15 and 48 hours. Five of these infants died between 2 and 9 days of age. The main post-mortem findings were intraventricular haemorrhage, pulmonary haemorrhage, and aspiration pneumonia.

Blood samples were drawn from the umbilical venous catheter before and at the 4th, 16th, 28th hour during the Aminosol-glucose infusion for determination of various plasma metabolites. The blood was placed in tubes containing heparin. Glucose and lactate concentration in 0.2 ml of whole blood each was determined by the o-toluidine method described by PRYCE [9], and that described by HUCKABEE [6], respectively. The remainder of the blood sample was centrifuged for analysis of FFA [3, 8], α-amino nitrogen [11] and urea content [1], as well as for determination of the ratio of the concentration of non-essential glycine + serine + glutamine + taurine to that of the essential leucine + isoleucine + valine + methionine, using paper chromatography [12]. For statistical analysis the means and standard errors were calculated; when it seemed necessary, significance was estimated by Student's *t* test.

RESULTS

Participation of the main nutrients in total heat production

Total energy metabolism and the participation of fat, carbohydrate and protein oxidation in the calories produced by the three premature infants, and expressed as calories per kg body weight per day is demonstrated in Fig. 1. It is seen that in two infants, prior to intravenous nutrition, heat production was dominated by fat utilization, in the third baby (No. 1), carbohydrate was also a major factor in oxidative metabolism.

Only one infant responded to Aminosol-glucose infusion by an increase in heat production. This infant exhibited the lowest metabolism, which became even lower after the administration of fibrin hydrolysate had been stopped. The distribution pattern of energy metabolism, however, showed similar changes in each infant: the participation of carbohydrate and protein oxidation increased, while fat metabolism became the smallest energy-component, or in two infants it did not contribute at all to the calories produced during the later period of intravenous nutrition. It was of interest that the amount of oxidized protein which was very small in the fasting state, gradually increased during the infusion of Aminosol-glucose, and became an important component of energy metabolism. This was particularly evident in infant No. 1, whose energy exchange during the last 12-hour period (from 16 to 28 hours) of parenteral alimentation was dominated by amino acid oxidation. In infants Nos 1 and 2, urine collection and oxygen consumption were followed after Aminosol-glucose infusion for 48 and 24 hours, respectively. During this period of time, infant No. 1 received 5 % glucose solution

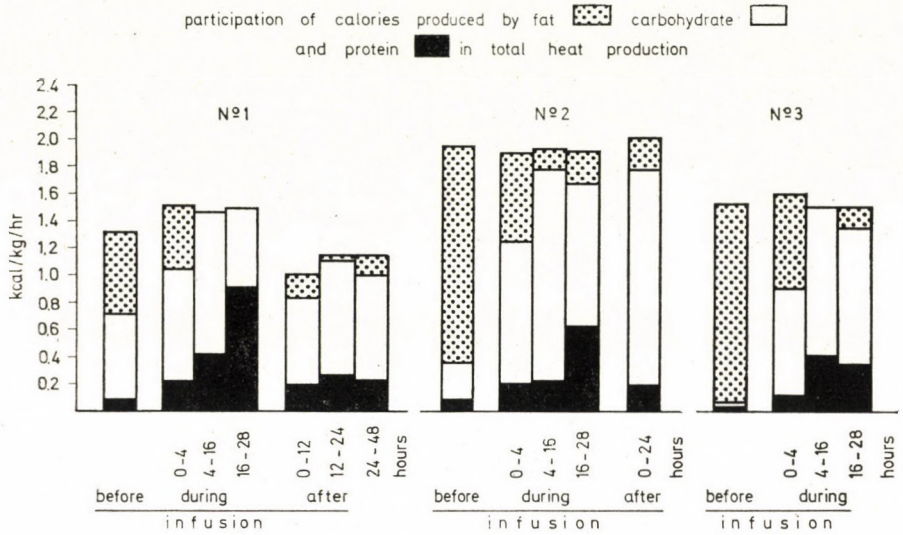

FIG. 1. Participation of calories in total heat production produced by fat, carbohydrate and protein in three premature infants receiving Aminosol-glucose for 28 hours

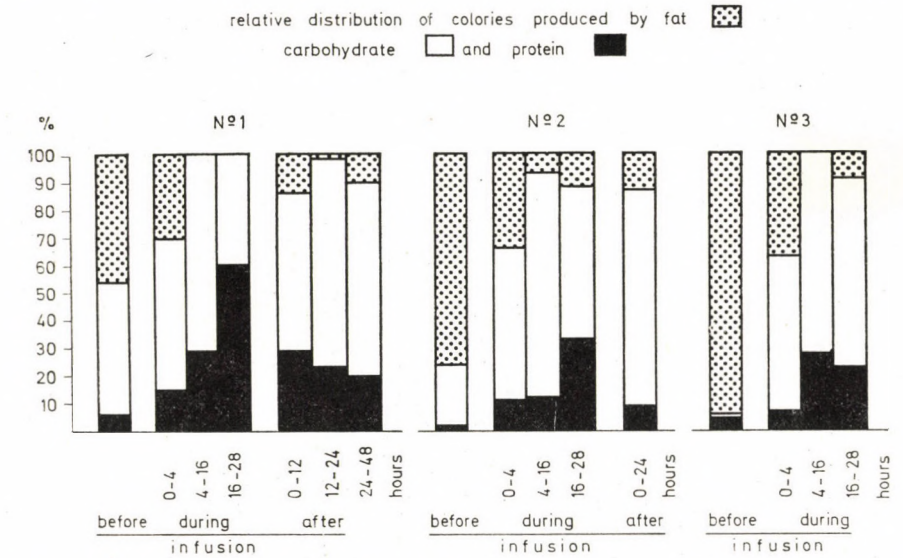

FIG. 2. Relative distribution of calories produced by fat, carbohydrate and protein in three premature infants receiving Aminosol-glucose

intravenously. It is obvious from Fig. 2, that the contribution of amino acid oxidation to the total metabolism was still greater than in the preinfusion period, suggesting that the catabolism of retained amino acids continued after Aminosol-glucose administration had been stopped. This was particularly distinct in infant No. 1. The relative contribution of the three main nu-

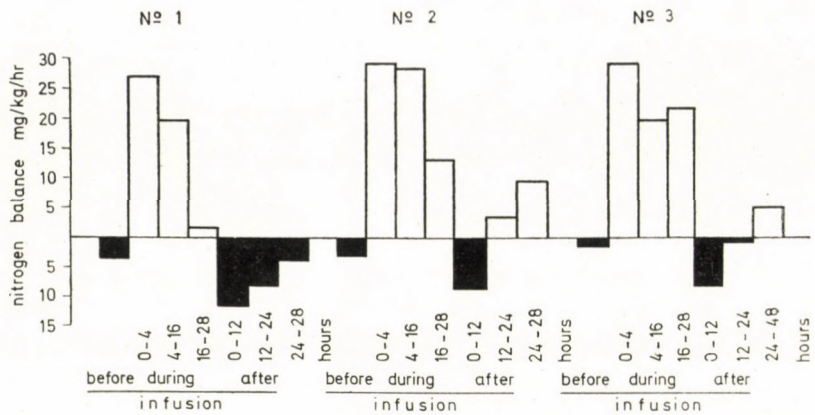

FIG. 3. Nitrogen balance of three premature infants before, during and after Aminosol-infusion

trients to the total heat production is demonstrated in Fig. 2. It can be seen that the proportion of amino acid oxidation increased, and in two infants had reached its maximum (32 and 60%) during the second and third period of Aminosol-glucose infusion.

Nitrogen balance

Fig. 3 shows the nitrogen balance of the three premature infants in different periods. The positive balance declined during intravenous Aminosol-glucose alimentation, in accordance with the gradually increasing amino acid oxidation. Rate and magnitude of the decrease were different in the three infants. After discontinuing intravenous nutrition, a negative balance exceeding the preinfusion values was observed, pointing to a continuing catabolism of the previously retained amino acids. This is clear from the balance data of infant No. 1. In the other two infants the balance showed a transient negativity, since after the first 12-hour collection period oral feeding was started which led again to nitrogen retention.

Response of plasma nutrients and metabolites

The mean values ± SE for blood glucose, plasma FFA and lactate are shown in Fig. 4. As expected, a fall in FFA concentration occurred in response to a rise in blood glucose ($p < 0.001$). The increment in glucose ($p < 0.001$) fell gradually during intravenous nutrition, while FFA remained at the decreased level attained during the 4 hours of infusion. Blood lactate concentration showed a decreasing tendency ($0.01 < p < 0.05$).

As shown in Fig. 5, the mean α-amino nitrogen content of plasma was nearly doubled at 4 hours ($p < 0.001$) and remained practically at this level throughout the Aminosol-glucose ad-

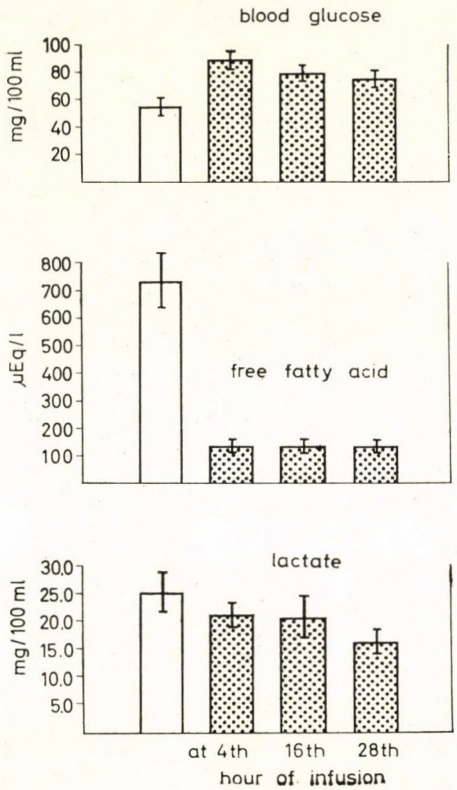

FIG. 4. Mean (±SE) concentration of blood glucose, FFA and lactate before and during Aminosol-glucose infusion

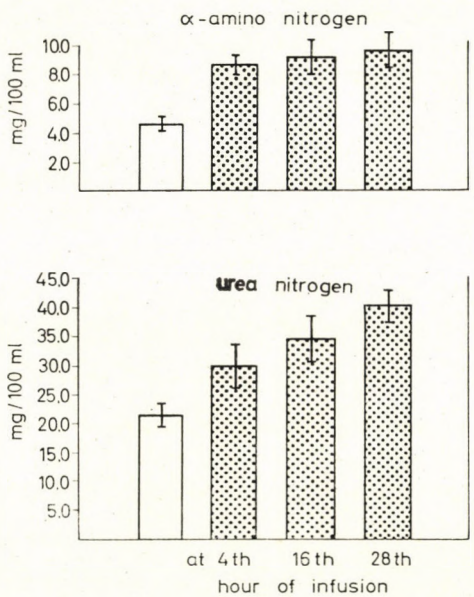

FIG. 5. α-amino nitrogen and urea content of plasma before and during Aminosol-glucose infusion

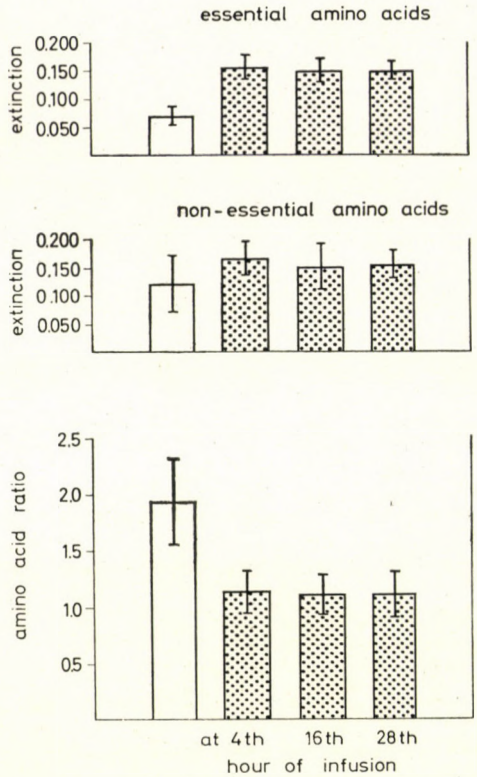

FIG. 6. Responses to Aminosol-glucose of the combined plasma concentration of the essential leucine, isoleucine, valine and methionine, and of the non-essential glycine, serine, glutamine, taurine. The changes in the ratio of these two groups of amino acids are also shown

ministration. The changes in serum urea concentration are also shown in Fig. 6. An increase was evident at 4 hours, thereafter a further rise occurred with a peak of 40 mg/100 ml by the end of the Aminosol-glucose infusion ($p < 0.01$). Since the preinfusion urea level varied considerably, a wide range of values was observed throughout the observation period.

Fig. 6 demonstrates the changes in mean combined plasma concentration of the non-essential glycine + serine + glutamine + taurine and that of the essential leucine + isoleucine + valine + methionine. However, the rise in the plasma level of these two groups of amino acids was not proportional; the greater rise in the combined level of essential leucine + isoleucine + valine + methionine resulted in a marked fall in the plasma amino acid ratio ($p < 0.05$).

DISCUSSION

The present results substantiated our previous observations on the changes in substrate utilization in response to a four-hour period of

Aminosol-glucose infusion [10]. The prolonged administration of the protein hydrolysate-monosaccharide solution caused a profound change in energy metabolism as far as the oxidation of the three main nutrients is concerned. While the energy demand of the fasting newborn infants was mainly covered from the metabolism of fat, parenteral feeding with such a mixture caused a progressive increase in the contribution of carbohydrate and protein utilization to the calories produced.

Amino acid catabolism already increased during the first four hours of infusion, and its proportion amounted to 15, 12 and 7% of the total metabolism which in each infant represented a threefold rise of the preinfusion oxidation rate of amino acids. This was in complete agreement with the findings of our previous study performed during a four-hour Aminosol-glucose load. During the rest of the infusion period, a further substantial increase occurred in the participation of amino acids as sources of energy. The maximum percentage reached amounted to 60, 32 and 28% in the infants Nos 1, 2 and 3, respectively.

The response in urinary nitrogen excretion (total minus α-amino nitrogen) and blood urea level, either in magnitude or in timing, was similar to that of protein metabolism, pointing to the close connexion between urea formation and the changes in distribution pattern of substrate utilization. The changes in nitrogen balance during intravenous nutrition also pointed towards an increasing contribution of amino acid oxidation to the energy expenditure of the premature infants. The time course of the responses in these parameters of protein metabolism suggested a marked metabolic stimulation during Aminosol-glucose infusion leading to an increaseddeamination of amino acids. In this respect, one has of course to reckon with individual differences too, as it was shown by the behaviour of the three infants studied. In infant No. 1, the positive nitrogen balance fell nearly to zero, indicating that during the last fractional period (from 16 to 28 hours) an intensive stimulation of amino acid oxidation had occurred.

According to the balance data, after discontinuing the intravenous nutrition, urinary nitrogen excretion still exceeded the preinfusion value, as a sign of a continuing catabolism of the retained amino acids. The twofold increase in plasma α-amino nitrogen level indicated a distinct retention of amino acids, a portion of which certainly continued to enter the process of oxidative deamination.

In our previous study concerning the calorigenic effect of Aminosol-glucose infused for four hours, only a mean increase of 13.4% in basal heat production was observed. There was a considerable variation, and in some infants no response was obtained. Among the three infants investigated in the present study, only one responded to the nutritive solution by a definite and lasting increase in heat production. The absence of a regular calorigenic effect of the amino acid mixture does not seem to fit into the

prevailing concept concerning the mechanism of the "specific dynamic action" of protein. It has been postulated [7] that extra heat production elicited by protein consumption represents the energy requirement of urea formation, more generally the energy cost of the oxidation of amino acids. On the basis of this explanation one would expect a regular and considerable thermogenic effect whenever amino acid catabolism increases. Although the present investigations have been performed under conditions associated with a considerably enhanced amino acid oxidation and urea synthesis, in two infants heat production did not increase at all. This appears to be against the above contention and supports the observation of a lack of a regular connexion between the responses of urea formation and oxygen consumption to a test meal in adults.

The pattern of the utilization of metabolic fuels during Aminosol-glucose infusion was also reflected by the alterations in blood metabolites. The increase in blood glucose and glucose oxidation resulted in a decrease of FFA utilization, in accordance with the concept of a glucose-fatty acid cycle. In infant Nos. 1 and 2, after 4 hours of infusion the oxidation of FFA was completely suppressed, and carbohydrate and protein served as metabolic fuels.

The twofold rise in α-amino nitrogen reflected a considerable increase in the size of the free extracellular amino acid pool, which in this early neonatal period was, in all probability, mostly diverted to the catabolic processes. GHADIMI et al. [5] using ion exchange chromatography have recently reported a significant elevation in the majority of plasma amino acids, and emphasized the possible detrimental effects of hyperaminoacidaemia. In addition to these quantitative changes, profound qualitative alterations in the plasma aminogram were also caused by the administration of Aminosol, as it was shown by the decreased ratio of the non-essential and the essential amino acids. It is reasonable to assume that these marked distortions of the free amino acid pattern exert a number of deleterious effects on various cellular functions among which the regulation of protein synthesis might be the most important in causing permanent and irreversible changes in various tissues.

REFERENCES

1. CERIOTTI, G.: Ultramicro determination of plasma urea by reaction with diacetylmonixide antipyrine without deproteinization. Clin. Chem. **17,** 400 (1971).
2. CLAYTON, C. C., STEELE, B. F.: A modified method for the estimation of amino nitrogen in urine. Clin. Chem. **13,** 49 (1967).
3. DALTON, C., KOWALSKI, C.: Automated calorimetric determination of free fatty acids in biologic fluids. Clin. Chem. **13,** 744 (1967).
4. GARROW, J. S., HAWES, S. F.: The role of amino acid oxidation in causing "specific dynamic action" in man. Brit. J. Nutr. **27,** 211 (1972).
5. GHADIMI, H., ABACI, F., KUMAR, S., RATHI, M.: Biochemical aspects of intravenous alimentation. Pediatrics **48,** 955 (1971).
6. HUCKABEE, W. E.: Relationships of pyruvate and lactate during anaerobic metabolism. I. Effects of infusion of

pyruvate of glucose and of hyperventilation. J. clin. Invest. **37**, 244 (1958).
7. Krebs, H. A.: In Mammalian Protein Metabolism (H. N. Munro, J. B. Allison, eds). Vol. I., p. 125. Academic Press, New York 1964.
8. Laurell, S., Tibbling, G.: Calorimetric microdetermination of free fatty acids in plasma. Clin. chim. Acta **16**, 57 (1967).
9. Pryce, J. D.: A simple rapid method for determining glucose in blood or plasma. Analyst **92**, 198 (1967).
10. Rubecz, I., Mestyán, J.: Energy metabolism and intravenous nutrition of premature infants. The response of oxygen consumption, respiratory quotient and substrate utilisation to infusion of Aminosol-glucose. Biol. Neonate. In press.
11. Rubinstein, H. M., Pryce, J. D.: The calorimetric estimation of amino nitrogen in tissue fluids. J. clin. Path. **12**, 80 (1959).
12. Whitehead, R. G.: Rapid determination of some plasma amino acids in subclinical kwashiorkor. Lancet **1**, 250 (1964).

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