Energy Metabolism of Brain in Human Protein-Calorie Malnutrition

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Summary

Cerebral blood flow (CBF) and carbohydrate metabolism were studied in 5 normal children and 25 children, aged 40 months or less, with varying degrees of protein-calorie malnutrition (PCM). CBF in normal children and those suffering from grade I PCM was 90.3 ± 5.7 ml/100 g/min, a value comparable with that obtained by other investigators, but the proportion of glucose taken up by the brain which combined with oxygen, the oxygen/glucose index (OGI), was 65.8%, indicating significant conversion of glucose into lactic acid. Cerebral lactic acid production was $45.3 \mu\text{M}/100$ g/min, and the respiratory quotient (R.Q.) was 1.00. With increasing severity of PCM, there was increased glucose utilization and a progressive reduction in the OGI. In grade IV PCM, CBF was 68.7 ± 5.4 ml/100 g/min, and the OGI was 34.7%. Cerebral lactic acid production was $27.4 \mu\text{M}/100$ g/min, and the R.Q. rose to 1.52. These findings suggest that in severe human PCM the proportion of glucose undergoing aerobic oxidation is reduced, and that in addition to being converted to lactic acid, a significant proportion of glucose is transformed by the brain into long chain fatty acids.

Speculation

These results indicate that in chronic, severe PCM, a considerable proportion of glucose utilized by the brain is converted into fatty acids. This alteration in cerebral carbohydrate metabolism may be due to altered function of one or more of the regulatory enzymes within the brain. Acetyl coenzyme A carboxylase, fatty acid synthetase, and the hexose monophosphate shunt dehydrogenases are some of the more obvious candidates for future investigations.

Protein-calorie malnutrition is characterized by a variety of neurologic and behavioral symptoms (14, 15). Apathy, withdrawal, and lack of interest in surroundings are the most constant and earliest neurologic features of the condition, and are common in children whose weight is less than 40% of the expected value (29). The electroencephalogram is usually diffusely slowed during the acute stages, returning to normal after nutritional recovery (13).

Long term studies on children who have experienced PCM early in life demonstrate a variety of cognitive inadequacies. These result in defective intersensory organization and poor school performance (5, 6, 8, 22, 26). As a rule, the younger the child at the time of his hospitalization for malnutrition, the less likely is he to achieve ultimate intellectual parity (4).

Numerous experimental studies have been designed to reproduce the clinical picture of PCM. The brain of an animal subjected to nutritional deprivation in the course of development weighs less, contains fewer cells, and has lesser amounts of protein, nucleic acid, and myelin than the brain of a well nour-

ished animal (10, 21, 31-34). From these studies, it has become evident that when nutritional deprivation occurs at the time of the brain's "growth spurt" these alterations are maximal and irreversible (10).

In order to correlate the data gathered from experimental animals with clinical experience, we undertook to study the effects of PCM on cerebral blood flow and brain energy metabolism.

MATERIALS AND METHODS

Thirty children, 6-40 months of age, were entered into the study. Their ages within the limits of ± 1 month were determined by the help of a local calendar. Their nutritional status was ascertained on the basis of body weight; and the extent of malnutrition determined by expressing body weight as a percentage of standard weight. The latter was assumed to be the 50th percentile from the Stuart Growth Charts and is referred to as 100%.

Five normal children, all relatives of hospital personnel, weighed more than 80% of the expected weight for age. Of the 25 children with PCM, 5 children suffering from grade I PCM weighed between 71% and 80%; 7 in grade II weighed between 61% and 70%; 7 in grade III weighed between 51% and 60% and 6 in grade IV weighed 50% or less than expected for their chronologic age.

Other parameters of growth and nutrition such as height, length, head circumference and left midarm circumference were also measured. In addition, a detailed clinical history and physical examination were carried out to determine the spectrum and profile of nutritional deprivation, and to exclude any primary illnesses that might have induced malnutrition.

The nutritional profile of the children included in the study is summarized in Table 1. Children with grade I PCM were pooled with the control subjects since there were no differences in energy kinetics between these two groups. Urinalysis, Mantoux tests, and radiographs of chest helped exclude urinary infection or tuberculosis. The majority of children with PCM suffered from concurrent illnesses. These usually were diarrhea and respiratory infections. Clinical evidence of vitamin B complex and vitamin A deficiency was noted in five subjects.

To obtain uniform metabolic conditions, all children were not fed for 3 hr before the studies. Studies were performed with the child in the supine position. CBF was measured in 11 additional subjects using the method of Kennedy and Sokoloff (16). Of these, five were normal or grade I PCM, and six suffered from grade IV PCM. Children were allowed to inhale a mixture of 15% nitrous oxide, 21% oxygen, and 64% nitrogen. Arterial samples were obtained from either femoral or radial artery, and venous samples from internal jugular bulb, using the method of Baird and Garfunkel (2). All sample syringes were heparinized and kept capped in ice water until analyzed. CBF was calculated

by plotting nitrous oxide concentrations of arterial and venous blood against time, following the method of Kety and Schmidt (19). Blood samples were analyzed for glucose using the glucose oxidase method. Blood oxygen and carbon dioxide contents were measured by the manometric technique of Van Slyke and Neill (30). Lactic and pyruvic acids were determined enzymatically according to Technical Bulletins 726 and 826 (Sigma Chemical Company, St. Louis). The procedure involved in sampling of blood was explained to the parents before the study was carried out, and at no time were investigations undertaken against parents' wishes. Most children cried and required some restraint during the procedure, particularly at the time of needle punctures. However, no significant changes in PCO_2 were observed in the course of the procedure.

RESULTS

The cerebral arteriovenous (A-V) differences for glucose and oxygen are depicted in Table 2. Values for both are presented in $\mu\text{mol}/100\text{ ml}$ blood, where 1 mg glucose is equivalent to 5.55 μmol and 1 ml oxygen at an ambient temperature of 37° is equivalent to 39.6 μmol . Since, theoretically, 1 molecule of glucose requires 6 molecules oxygen for its complete aerobic combustion it is possible to calculate the proportion of glucose taken up by the brain that has combined with oxygen. This value, following the example of Cohen *et al.* (7), will be referred to as the oxygen-glucose index (OGI) where:

$$\text{OGI} = \frac{(\text{A-V}) \text{ oxygen}}{6 \times (\text{A-V}) \text{ glucose}} \times 100\%$$

An OGI of 100 means that all the glucose taken up by the brain appears to have been oxidized aerobically. In control subjects and children with grade I PCM, the OGI was 65.8%. These values are significantly less than those reported for adults (91.9% (7); 88.9% (18)), but are similar to those obtained by Kraus *et al.* (20) on normal German infants (77.4%). With increasing severity of PCM, there was a fall in the OGI, so that in children with grade IV PCM, the OGI was only 34.7%. Since the A-V difference for oxygen remained relatively unchanged

between the several groups of subjects, the decreased OGI was the result of a progressive increase in the A-V difference for glucose. Cerebral oxygen and glucose consumption were determined for two groups of subjects: Children with normal nutrition and with grade I PCM, and children with grade IV PCM (Table 2). Values for CBF obtained for the former group ($90.3 \pm 5.7\text{ ml}/100\text{ g}/\text{min}$) are comparable with those obtained by Kennedy and Sokoloff (16) for children ($106.4\text{ ml}/100\text{ g}/\text{min}$) and are considerably higher than values obtained for adults. In grade IV PCM, the CBF decreased to $68.7 \pm 5.4\text{ ml}/100\text{ g}/\text{min}$. Although, in the latter group, glucose consumption was significantly greater than in control subjects ($87.6\text{ }\mu\text{mol}/100\text{ g}/\text{min}$ as compared with $65.5\text{ }\mu\text{mol}/100\text{ g}/\text{min}$), oxygen consumption was less ($182.3\text{ }\mu\text{mol}/100\text{ g}/\text{min}$ as compared with $258.7\text{ }\mu\text{mol}/100\text{ g}/\text{min}$). It is evident that whereas the absolute amount of glucose undergoing oxidation remained constant, the proportion of glucose oxidized dropped significantly.

Cerebral carbon dioxide production was measured in four infants with normal nutrition, and in six patients with grade IV PCM (Table 3). There was no significant difference in the arterial CO_2 content between the two groups. The respiratory quotient was 1.00 in the normal children and 1.52 in the group with severe PCM.

The arterial and venous concentration of pyruvic and lactic acids were measured in six normal infants and in six patients with grades II-IV PCM (Table 4). Significant amounts of lactate were produced in both normal infants and infants with PCM. Although there was less lactic acid formed by the brain of patients with PCM, the difference was not significant statistically.

DISCUSSION

Studies on cerebral energy metabolism in adults indicate that glucose is the major oxidative substrate, and that the adult brain utilizes glucose exclusively. Under basal conditions, the measured ratio of oxygen uptake to glucose consumption is 5.5; the difference between this value and the theoretic ratio of 6 can be accounted for by a small amount of lactate production (17). In children, the brain may oxidize substrates other than glucose,

Table 1. Nutritional profile of subjects¹

Nutritional status	Mean age in months, mean $\pm$ SEM	% Standard height	Left midarm circumference, % of standard	Serum albumin, g/100 ml	Hemoglobin, g/100 ml
Normal and grade I (10)	11 $\pm$ 2	94.1 $\pm$ 1.2	84.3 $\pm$ 2.3	2.9 $\pm$ 0.1	11.3 $\pm$ 0.6
Grade II (7)	18 $\pm$ 3	87.7 $\pm$ 1.3	72.8 $\pm$ 2.2	2.9 $\pm$ 0.2	9.6 $\pm$ 0.5
Grade III (7)	21 $\pm$ 4	86.6 $\pm$ 2.0	64.7 $\pm$ 1.8	2.7 $\pm$ 0.2	10.7 $\pm$ 0.5
Grade IV (6)	23 $\pm$ 5	78.1 $\pm$ 1.7	60.6 $\pm$ 0.5	3.3 $\pm$ 0.3	10.9 $\pm$ 1.0

¹ Figures in parentheses indicate number of subjects studied.

Table 2. Effect of protein-calorie malnutrition (PCM) on cerebral arteriovenous (A-V) differences for glucose and oxygen

Nutritional status	Cerebral blood flow, ml/100 g/min (mean $\pm$ SEM)	A-V glucose, $\mu\text{mol}/100\text{ ml}$ (mean $\pm$ SEM)	Glucose consumed, $\mu\text{mol}/100\text{ g}/\text{min}$	A-V oxygen, $\mu\text{mol}/100\text{ ml}$ (mean $\pm$ SEM)	Oxygen consumed, $\mu\text{mol}/100\text{ g}/\text{min}$ (mean $\pm$ SEM)	Glucose equivalents of A-V oxygen difference, $\mu\text{mol}/100\text{ ml}$ (mean $\pm$ SEM)	Glucose burnt aerobically, $\mu\text{mol}/100\text{ g}/\text{min}$	Oxygen/glucose index, %
Normal and grade I (10) ¹	90.3 $\pm$ 5.7	72.6 $\pm$ 5.3	65.6	286.5 $\pm$ 17.6	258.7	47.7 $\pm$ 2.9	43.1	65.8
Grade II (7)		59.3 $\pm$ 6.6		210.9 $\pm$ 33.4		35.5 $\pm$ 5.5		59.2
Grade III (7)		70.9 $\pm$ 11.4		227.9 $\pm$ 40.2		37.9 $\pm$ 6.7		53.6
Grade IV ² (6)	68.7 $\pm$ 5.4	127.5 $\pm$ 19.0	87.6	265.3 $\pm$ 24.0	182.3	44.3 $\pm$ 4.0	30.4	34.7

¹ Figures in parentheses indicate the number of subjects studied.

² There was a significant difference between PCM grade IV and normal and grade I PCM subjects with respect to cerebral blood flow ($P < 0.02$), cerebral A-V glucose difference, and percentage of glucose burnt aerobically ($P < 0.02$).

Table 3. Effect of protein-calorie malnutrition (PCM) on cerebral carbon dioxide production and respiratory quotient¹

	A	V	V-A	Respiratory quotient
Normal (4)	1,568.1 ± 134.6	1,857.2 ± 130.6	289.0 ± 27.7	1.00
PCM (6)	1,793.8 ± 43.5	2,197.8 ± 114.8	403.9 ± 95.0	1.52

¹ Values are in micromoles per 100 ml whole blood. Figures in parentheses indicate the number of subjects studied.

Table 4. Cerebral pyruvate and lactate production in protein-calorie malnutrition (PCM)¹

	Pyruvate			Lactate		
	V	A	V-A	V	A	V-A
Normal (6)	10.2 ± 1.7	9.35 ± 1.6	0.85 ± 0.23	230.4 ± 20.8	179.6 ± 31.5	50.7 ± 1.5
PCM (6)	13.4 ± 1.9	12.7 ± 3.6	0.70 ± 0.45	194.1 ± 27.8	153.7 ± 16.7	40.4 ± 19.4

¹ Values are in micromoles per 100 ml whole blood. Figures in parentheses indicate number of subjects studied.

notably ketone bodies (9, 11, 20, 24), and possibly also glycerol and fatty acids (25). Since the normal infant brain converts a considerable proportion of glucose to lactate and pyruvate, it is not surprising that the OGI in the control group was only 65.8% as compared with adult values of approximately 90% (7, 17).

The subjects of this study were infants between the ages of 6 months and 40 months whose nutritional status was classified on the basis of body weight for age (12). Children with severe PCM were considered on clinical grounds to have marasmus or marasmic kwashiorkor. None of our subjects had frank kwashiorkor. This distinction is important as some of the biochemical and metabolic abnormalities observed differ between the two groups (23).

In children with grade IV PCM, oxygen consumption was significantly lower than our control values, whereas glucose consumption was increased. This resulted in a reduction of the OGI from a control value of 65.8% to 34.7%.

Normal infants convert a significant amount of glucose (22.7 μ M/100 g/min) to lactate. Lactic acid production accounted for the difference between the total amount of glucose utilized by the brain (65.6 μ M/100 g/min) and the amount burnt aerobically (43.1 μ M/100 g/min). In children with PCM, the amount of lactic acid formed fell, and a lesser proportion of glucose utilized by the brain was converted to lactic acid (13.7 μ M/100 g/min). In patients with PCM, of the total amount of glucose consumed by the brain (87.6 μ M/100 g/min), 30.4 μ M/100 g/min were burnt aerobically, and 13.7 μ M/100 g/min were converted to lactic acid. The remaining amount of glucose is therefore unaccounted for. In view of the high R.Q. of children with PCM (1.52), a significant amount of glucose may be presumed to be converted to fatty acids such as palmitate.

These findings are compatible with the observations that feeding of high carbohydrate diet after fasting stimulates hepatic fatty acid biosynthesis. Up to now, no experimental studies have been directed towards a description of the alteration in cerebral carbohydrate metabolism in the developing infant with PCM. Barkai *et al.* (3) failed to demonstrate a significant change in the flow of glucose carbon into protein in adult rats subjected to 72 hr of starvation and Stone *et al.* (2) found that cerebral protein labeling from glucose was increased in adult dogs recovering from hypoglycemia. Obviously, human PCM is sufficiently different from the experimental conditions used in these two studies that they are not comparable.

Since the activity of a number of cerebral enzymes is altered under conditions of chronic undernutrition (1, 28), it would not be surprising that abnormalities in carbohydrate metabolism found in severe PCM result from changes in the function of one or more of the enzymes involved in metabolic control and regulation.

CONCLUSION

Cerebral blood flow and carbohydrate metabolism were studied in five normally nourished children and 25 children aged 6–40 months with PCM of different stages of severity. Cerebral blood flow in control subjects was 90.3 ± 5.7 ml/100 g/min. In the most severe stage of PCM, the cerebral blood flow was reduced to 68.7 ± 5.4 ml/100 g/min. In control subjects, the ratio of oxygen uptake to glucose consumption was 4.0, and there was a significant conversion of glucose into lactate. With increasing severity of PCM, a progressively smaller proportion of glucose was subjected to aerobic oxidation, but the amount of lactate formed did not increase. The unusually high cerebral R.Q. obtained under these conditions suggests that a significant proportion of glucose was converted into long chain fatty acids.

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Aspartate transcarbamylase
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pyrimidine biosynthesis
thymidine kinase
thymidylate synthetase
uridine kinase
undernutrition

Pyrimidine Metabolism during Restorative Brain Growth after Neonatal Undernutrition in the Rat

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Summary

Three litters of 20 Wistar rat pups each were maintained until age 6 days at which time only the 4 lightest and 4 heaviest pups from each litter were left with the mother until age 13 days. Three control litters of eight pups each were also maintained for 13 days. At that time, the undernourished light pups showed body weight, cerebellar weight, and cerebellar DNA, respectively, of 79.2%, 86.6%, and 90.4% compared with a "combined control" group consisting of control pups plus undernourished heavy pups which were statistically indistinguishable with regard to these three measurements. After the week of "catch-up" or restorative body and brain growth, activities of enzymes from metabolic pathways leading to pyrimidine and nucleic acid biosynthesis were measured in cerebella from all three groups (control, undernourished heavy, and undernourished light). The salvage pathway enzyme thymidine kinase (TK) and the inter-conversion pathway enzyme thymidylate synthetase (TS) in the undernourished light group showed significant elevations of 32% and 11%, respectively, above activity in the combined control group. The salvage pathway enzyme uridine kinase (UK) and the *de novo* pathway enzyme aspartate transcarbamylase were

not significantly different in cerebella from these two groups. The significant elevation in TK and TS in undernourished pups suggests that these enzymes are critical for restorative brain growth. The significant elevation of TS indicates that the inter-conversion pathway converting available uridylate, a ribonucleotide, to thymidylate, a deoxyribonucleotide, is activated in order to augment DNA biosynthesis.

Speculation

These findings suggest that certain metabolic pathways may have special importance in restorative brain growth. These biochemical relationships may be extrapolated to the condition of human perinatal undernutrition and restorative brain growth whereby it might be expected that certain critical enzymes and metabolic pathways may be selectively affected.

The ability of the brain to undergo restorative or "catch-up" growth following undernutrition during critical periods of development has recently become a subject of increasing interest. Although somatic growth acceleration following illness or under-