Regulatory Aspects of Glucose and Ketone Body Metabolism in Infant Rat Brain

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Summary

The present study was designed to investigate some of the possible factors responsible for the low rate of the oxidative use of glucose observed in neonatal rat brain.

An evaluation of the role of pyruvate dehydrogenase (PDH, EC 1.2.4.1) showed that at all stages of brain development, the activities of both molecular forms of this enzyme are considerably less than those reported for the enzymes localized above in the glycolytic pathway. The proportion of both molecular forms is not altered during brain maturation. The activities of the active form and of the total enzyme in adult brain are 0.56 and 1.1 $\mu\text{mole}/\text{min}/\text{g}$ brain, respectively. It is concluded that PDH represents the rate-limiting step in the oxidation of glucose by neonatal brain due to a delay in the synthesis of the enzyme protein.

A "cross-over" plot of glycolytic intermediates in neonatal brain showed that only fructose 1,6-bisphosphate concentrations are significantly lower than in adult brain, indicating a block at the level of phosphofructokinase (PFK, EC 2.7.1.11). A marked increase in citrate concentrations in neonatal brain (values ranging from 0.44-0.82 $\mu\text{mole}/\text{g}$ brain) with regard to adult levels (0.28 $\mu\text{mol}/\text{g}$ brain) is suggested to be responsible for the inhibition of the enzyme.

Glucose 6-phosphate concentrations in neonatal brain are not different from adult values. Despite increasing ketonemia neither consistent intracerebral accumulation of glucose nor a decrease in the brain/blood ratio of glucose is observed during brain maturation. These data argue against limitations of glucose use at the level of hexokinase or membrane transport in the neonatal brain.

Speculation

Ketone bodies are major substrates of the neonatal brain in that they fulfill to a large extent both the energy requirements of the brain and provide carbon for the needs of biosynthetic processes. The dual function of ketone bodies cannot be substituted for alternatively by glucose due to a limitation in the oxidative breakdown of glucose observed in young rat brain. Thus, glucose is saved for preferential use in the pentosephosphate pathway, providing hydrogen equivalents for the synthesis of myelin lipids, a process which is very active in neonatal brain.

Ketone bodies are major substrates of the brain of suckling rats fulfilling to a large extent both the energy requirements of the brain and providing carbon for the needs of biosynthetic processes (7, 12, 21). The preferential use of ketone bodies by the brain occurs despite the fact that the blood glucose concentration in neonatal rats after the first day of life is normal or even elevated (21). Little is known about the mechanisms responsible for the low rate of the oxidative use of glucose by the neonatal brain. From observation with the isolated rat heart, under conditions of increased turnover of fatty acids or ketone bodies, it may be expected that the low rate of glucose oxidation in the neonatal

brain results from limitations at several steps. The reactions proposed include membrane transport and the phosphorylation of glucose, the phosphofructokinase reaction and the pyruvate dehydrogenase reaction (10, 24, 35). Data from arteriovenous difference measurements in young rats (21) have shown that when ketone bodies are oxidized by the brain, there is a net output of lactate from brain to blood. Two implications arise from this in terms of regulatory processes. One is that the "blood brain barrier" must be readily permeable to pyruvate and lactate. This assumption has been found valid on the basis of measurements of isotopic exchange between different brain compartments (6). The other conclusion is that the rate of pyruvate oxidation via acetyl-CoA is slower than any preceding step in the glycolytic pathway. The apparent limitation of pyruvate oxidation in infant brain may result from an increase in the cytosol redox state of the brain or from a limitation of the pyruvate dehydrogenase reaction. Pyruvate dehydrogenase in mammalian tissues exists partially in an active (dephosphorylated) and an inactive (phosphorylated) form. Rapid changes in the enzyme activity are achieved by alterations of the ratio of its two molecular forms (27, 30, 35, 36). Thus, an inactivation of the enzyme by phosphorylation of preexisting enzyme molecules could be responsible for a decreased activity of pyruvate dehydrogenase in the brains of young, ketonemic rats. Other mechanisms coming into question are a delay in the synthesis of the enzyme protein or a decrease in the enzyme activity due to metabolites such as acetyl-CoA and NADH which, besides being involved in the regulation of the interconversion cycle, can act by feedback inhibition of PDH_a (25, 30).

The present studies were designed to investigate some of the factors presumed to be involved in the control of glucose oxidation by infant brain. Out of these special attention is dedicated to regulations at the level of pyruvate dehydrogenase and phosphofructokinase.

MATERIALS AND METHODS

REAGENTS

All chemicals and enzymes were of analytical grade (37, 38). Arylamine acetyltransferase (EC 2.3.1.5) was prepared from pigeon liver according to the modification by Wieland *et al.* (36) of the original procedure described by Tabor *et al.* (32). The only deviations from these instructions were that 20 mM phosphate instead of 10 mM phosphate was used for the elution of the enzyme from the aluminum hydroxide gel (C₇). The final concentration of the combined eluates was achieved by freeze-drying instead of precipitation by ammonium sulfate. The lyophilisate was then dissolved in distilled water to give an activity of approximately 1 U/ml which corresponds roughly to a specific activity of 0.02 U/mg protein. This solution was finally dialysed against 5 mM phosphate buffer pH 7.8. Arylamine transacetylase activity during purification was measured in the combined assay with acetylphosphate and phosphotransacetylase as described by Tabor *et al.* (32).

ANIMALS

Rats of an albino wistar strain were bred in the animal house of this department. The gestational age of this colony was 22 days and the average birth weight was 6.1 ± 0.4 g. Birth was allowed to proceed naturally at term and the newborn animals remained with their mothers until weaning at 21 days postpartum. Premature animals (gestational age, 19 days) were delivered by uterine section. Adult rats weighing 200–300 g were maintained on laboratory chow (39) and water *ad libitum*. The brains of newborn animals were frozen by immersion of the neonatal rat into liquid nitrogen. This procedure has been described essentially by Ballard (1) for the measurement of gluconeogenesis in newborn rats. Obviously, because the skull of neonatal rat pups is very thin, freezing proceeds so rapidly that tissue hypoxia is prevented. This has been checked by evaluation of the lactate/pyruvate ratio (see *Results* and *Discussion*). Adult rats were killed using the freeze-blowing apparatus devised by Veech *et al.* (34) which removes and freezes brains of conscious rats more rapidly than was here-to-fore possible. Equal numbers of male and female rats were selected randomly and used in each series of the experiments.

PREPARATION OF BRAIN HOMOGENATES

The cerebral hemispheres of neonatal rats were removed from the decapitated heads under liquid nitrogen. For determination of PDH activity the brain of an adult rat or pooled brains of neonatal rats were pulverized in a mortar, cooled with liquid nitrogen and then transferred to a centrifuge tube and weighed. A 9-fold volume of cooled (-20°) 20 mM potassium phosphate buffer pH 7.0 containing 40% (v/v) glycerol was added. Homogenization was carried out with a high speed tissue desintegrator adapted to small tissue samples (40). The blender was driven twice at top speed for 60 sec each, which was sufficient for complete extraction of the enzyme. This homogenate was used for the pyruvate dehydrogenase assay without preceding centrifugation.

EXTRACTION OF BRAIN METABOLITES

For extraction of brain metabolites, pulverized frozen brain tissue was immediately transferred to a centrifuge tube containing 2 ml of 6% (w/v) of ice cold perchloric acid in 1 mM EDTA. The mixture was rapidly stirred with a glass rod, weighed and diluted up to 5-fold (w/v) with the EDTA (1 mM) containing perchloric acid. Homogenization was then carried out in the same manner as described except that temperature was kept in the range of $1-4^\circ$. After centrifugation, the supernatant fluid was neutralized with 5 N KOH and the precipitated perchlorate was removed by centrifugation. For complete extraction of brain metabolites, a 2-fold volume of 3% (w/v) of perchloric acid containing 1 mM EDTA was then added to the pellet obtained after the first centrifugation. Rehomogenization of the brain material was achieved with the motor-driven blender as described and then followed by centrifugation. After neutralization and centrifugation, the supernatants of both extractions were combined, stirred for 10 min, and finally centrifuged. The resulting supernatant fluid was used for assays of metabolites.

ASSAY OF PDH_A IN BRAIN

Pyruvate dehydrogenase activity was determined by coupling the reaction with the arylamine acetyltransferase reaction as described by Schweet and Cheslock (28). The assay mixture contained in a final volume of 0.8 ml, potassium phosphate buffer 40 mM, pH 8.0; p-nitroaniline 0.15 mM; NAD⁺ 1 mM; thiamin-pyrophosphate 1 mM; mercaptoethanol 10 mM; MgCl₂ 0.4 mM; CoA-SH 0.3 mM; lactate dehydrogenase 10 μ g; 50–100 mU of arylaminetransacetylase and 50 μ l of brain extract. The reaction was started by addition of 15 μ l of a 1 M solution of sodium pyruvate, which was replaced by water for the blanks. The decrease in the absorbance of p-nitroaniline was recorded in an Eppendorf photometer at 405 nm at 37° . The absorption coefficient (ϵ_{405}) of p-nitroaniline under these conditions was $12 \text{ cm}^2 \times \mu\text{mol}^{-1}$ in agreement with others (26).

ASSAY OF PDH_{TOTAL}

The original activity of a freshly prepared homogenate was defined as the activity of the active form (PDH_A) of the enzyme. Reactivation of the inactive, phosphorylated form of pyruvate dehydrogenase was achieved by incubation of the extracts with 10 mM Mg²⁺ which results in the activation of pyruvate dehydrogenase phosphatase present in the homogenate. Under the conditions used in this study, the homogenate contained sufficient PDH phosphatase to convert all the inactive PDH to the active form within 45 min at 25° . The reactivation assay contained in a final volume of 1 ml 10 mM MgCl₂, 8 mM potassium phosphate buffer pH 7.0, and 0.5 ml of the brain homogenate. Total PDH activity was immediately measured at the end of the incubation period as described.

DETERMINATION OF BRAIN METABOLITES AND OF PROTEIN

All brain metabolites were determined by standard enzymic methods (3). Protein concentrations were measured by the procedure of Lowry *et al.* (16).

In general, the data were presented as individual observations with the mean value obtained in each age group. In the case of PDH activity in the adult brain, the 95% interval of all values was listed. Statistical comparison of the concentrations of metabolites in neonatal and adult brain was performed with the *U* test of Mann and Whitney (17). In the case of the glucose concentrations in the brain and blood which were normally distributed, the *t* test of Student was employed.

RESULTS

By comparing the original activity of a freshly prepared homogenate with that obtained after incubation of the homogenate in the presence of 10 mM Mg²⁺, it can be clearly demonstrated that, like in other tissues, PDH in the brain exists partially in an inactive (phosphorylated) and an active (dephosphorylated) form. Low activities of both molecular forms of the enzyme can be demonstrated in fetal brain tissue as early as 2 days before birth at term (Fig. 1). During the early period of life, the activities of both the active form and of the total enzyme in the brain are low accounting only for about 10–20% of the values observed in the adult brain. After the first week of life, the activities of both molecular forms of the enzyme gradually increase in parallel, adult levels being reached after 3 wk of age, coincident with the time of weaning. Except for the first postnatal day where the active form approximates 70% of the total enzyme activity, the proportion of the two molecular forms remains fairly constant throughout the observation period, *i.e.*, the active form accounts for approximately 40–50% of the activity of the fully activated enzyme. Because the water content of the rat brain decreases during postnatal maturation and the protein content increases (22), the rates of both molecular forms of PDH in the brain are also expressed relative to protein content. As may be seen (Fig. 2), even on the basis of the protein content of the brain, there is still a 3–4-fold increase in the activities of the two molecular forms of the enzyme in brain. Thus, the enzyme exhibits a true differentiation in that the PDH activity increases at a faster rate than general protein in the brain cells. The developmental pattern of PDH activity in the brain is different from that observed for the enzymes of ketone body use, which reach a maximum around 25 days of age and then decline to much lower values in the adult (11, 18). Thus, if one compares the maximal rates of mitochondrial acetoacetyl-CoA thiolase with that of pyruvate dehydrogenase, the ratio is in favor of the former at all times investigated, but it declines with maturity (Table 1).

A cross-over plot of glycolytic intermediates in the neonatal brain (Fig. 3) demonstrates that the lactate/pyruvate ratio and the

concentration of phosphoenolpyruvate in the infant brain are not different from the values observed in the adult brain. Only fructose 1,6-bisphosphate concentrations are significantly decreased (calculated at the 5% level with the *U* test of Mann and Whitney (17)) in respect to adult fed controls. No significant differences in the concentrations of both glucose 6-phosphate and fructose 6-phosphate have been found between the infant and the adult brain. Citrate concentrations in the infant brain are significantly increased (at the 5% level of the *U* test) in respect to adult fed controls with maximal values being 2–3-fold higher than those found in the adult brain (Fig. 4). Regarding regulations of glucose metabolism in the neonatal brain possibly exerted at the level of hexokinase and membrane transport, the following observations are of interest. No significant differences have been found in the concentrations of glucose 6-phosphate between the infant and the adult brain. The distribution of glucose between blood and brain is not consistently altered during the period of brain maturation. Increasing rather than decreasing brain/blood ratios of glucose are observed during the infant period (Table 2).

DISCUSSION

The small capacity of the neonatal rat brain for the oxidative use of glucose may be attributed to limitations at the level of both phosphofructokinase and pyruvate dehydrogenase. Pyruvate dehydrogenase catalyzes the rate-limiting step as evidenced by the following observations. At all stages of brain development, the total activity of pyruvate dehydrogenase in the brain is by far lower than that reported for all the enzymes of the glycolytic sequence, as measured *in vitro* (2). The rate of pyruvate oxidation by brain mitochondria prepared from neonatal rats at different ages (14) closely follows the developmental pattern of PDH activity. Brain lactate production continuously observed during the nursing period ends at the time of weaning. At this stage of development, ketone bodies, major substrates of the brain of suckling rats, are gradually replaced by glucose (21). Both events come at that time, where the activity of PDH, originating from low neonatal rates, attains the value observed in adult rats. Because the ratio of the two molecular forms of PDH is not altered during brain maturation it may be concluded that the limitation of the PDH reaction results from a maturational delay in the synthesis of the enzyme protein rather than from inactivation (by phosphorylation) of preexisting enzyme molecules. Thus, the molecular mechanism of PDH regulation in the infant brain differs from that effective in adult rat tissues where the rate of the enzyme is

Fig. 1. Activities of PDH in the brain during pre- and postnatal development of the rat. Prenatal values were obtained from fetal animals delivered by uterine section before term (T). Values of PDH_a (O) and PDH_{total} (▲) from pre- and postnatal rats represent individual determinations performed on 3–5 pooled brains in each age group. The dotted values of PDH_a and PDH_{total} obtained from the same pooled brains are connected by short lines. The vertical bars represent the 95% interval of all (*n* = 33) individual determinations in adult rats. The mean values of PDH_a (□) and of PDH_{total} (■) of each age group are also listed and connected by crossing lines.

Fig. 2. Specific activities of both active PDH (O) and total PDH (▲) in 17-day-old rat brain during postnatal development. The homogenates were the same as those used in Figure 1.

Table 1. Activities of acetoacetyl-CoA thiolase and pyruvate dehydrogenase in brain during development¹

Age	Acetoacetyl-CoA	Pyruvate dehydrogenase	Acetoacetyl-CoA thiolase Pyruvate dehydrogenase
1	1.0	0.19	5.3
3	1.6	0.31	5.2
7	1.8	0.20	9.0
14	3.5	0.45	7.8
21–25	4.9	0.91	5.4
Adult	2.0	1.10	1.8

¹ Activities are given as $\mu\text{mole}/\text{min} \cdot \text{g}$ fresh weight of brain. Values for acetoacetyl-CoA thiolase are from Middleton (18) for the mitochondrial enzyme. Values for pyruvate dehydrogenase are the "total activities" shown in Figure 1.

Fig. 3. Cross-over plot of glycolytic intermediates in neonatal brain. Neonatal values (means of 8 determinations) are expressed as percent levels of adult fed controls. Adult values (means of 12 determinations) expressed as μmol per gram of brain are listed under the abscissa.

Fig. 4. Citrate concentrations in the developing rat brain. The dotted values (●) represent determinations in individual rats. The mean values (■) obtained in each age group are also given and are connected by a crossing line.

Table 2. Concentrations of glucose in blood and brain of adult and neonatal rats¹

	Adult rats fed		Neonatal rats			
			1 day	3 days	7 days	14 days
Blood glucose (μmole/ml)	5.02 ± 0.18 (8)	3.17 ± 0.13 (7) ²	4.10 ± 0.17 (8)	5.05 ± 0.04 (9)	5.27 ± 0.25 (8)	6.23 ± 0.28 (12) ³
Brain glucose (μmole/g)	1.08 ± 0.09 (9)	0.32 ± 0.05 (7) ²	1.23 ± 0.09 (8)	1.47 ± 0.09 (9) ³	1.48 ± 0.04 (8) ³	1.27 ± 0.07 (12)
Brain/blood ratio	0.22 ± 0.01 (8)	0.13 ± 0.02 (7) ³	0.20 ± 0.03 (8)	0.27 ± 0.02 (9) ³	0.26 ± 0.01 (8)	0.26 ± 0.01 (12)

¹ Results are means $\pm$ SE with number of observations in parentheses. No correction was made for that portion of brain glucose present in the vascular space. Values for blood glucose are for whole blood.

² Values are significantly different from those of adult fed rats at the 0.1% level.

³ Values are significantly different from those of adult fed rats at the 1% level.

controlled by interconversion of its two molecular forms without significant changes in total PDH activity (27, 35, 36).

Cremer and Heath (6) reported that the flux from pyruvate to acetyl-CoA in the brain of the 18-day-old rat is in the range of 0.52–0.94 $\mu\text{mol/min/g}$ of brain. At the same stage of development PDH_a and PDH_{total} account for 0.5 and 0.9 $\mu\text{mol/min/g}$ of brain. Because there is a continuous overflow of lactate from brain to blood, these values which are in the range of or slightly below the glycolytic flux again strengthen the view that PDH is rate-limiting. In a study of PDH activities in the brain, Cremer and Teal (8) found 0.9 $\mu\text{mol/min/g}$ of brain for PDH_{total} in the 18-day-old rat in accordance with our observations. The developmental pattern of PDH_a activities published by these authors differs from our findings because large daily fluctuations in the enzyme activities were recorded, which probably are due to the fact that only single determinations have been done. Furthermore, PDH in the neonatal brain was predominantly found in the active form. Most likely the presence of 2 mM Mg^{++} in the assay system may be responsible for this difference in respect to our results. Concentrations of Mg^{++} in the range of 2 mM lead to considerable activation of PDH phosphatase which, in turn, results in reactivation of inactive PDH (29). Most recently, mitochondrial enzyme activities in developing rat brain were studied by Land *et al.* (14). The adult value of the total PDH activity reported by these authors is approximately three times higher than those determined by the authors or by others (8, 30). This discrepancy may chiefly be due to differences in the methodologic approach because these authors determined the enzyme activity after preincubation of brain mi-

tochondria maintained in respiratory state 4 and not in rapidly frozen tissue.

An increase in the cytosol redox does not account for the apparent limitation of pyruvate oxidation in the infant brain, as the lactate/pyruvate ratio determined in young rat brain agrees well with the value observed in the adult brain. Inhibition of pyruvate oxidation in young rat brain is not expected to result in increased tissue levels of pyruvate and/or lactate because it has been clearly demonstrated by isotopic exchange measurements in the 18-day-old rat *in vivo* that lactate, once formed, is rapidly transported from the brain to the blood (6). Thus, a continuous outflow of lactate from the brain to the blood is observed during the suckling period (11). Furthermore, the lactate/pyruvate ratio found in the infant brain, which is in line with the value found by the authors and by Veech *et al.* (34) in the adult brain, implies that the techniques used for the removal and freezing of the neonatal rat brain are as efficient in preventing tissue hypoxia as does freeze-blowing in adult rats.

It cannot be inferred from our experiments whether acetyl-CoA which inhibits PDH in a dual manner, competitive with CoA (3) and through phosphorylation of the enzyme (25), is implicated in the regulation of pyruvate oxidation in young rat brain. The latter possibility, however, seems unlikely because the ratio of both molecular forms of PDH is fairly constant throughout brain development and because, even in the adult fasted (30) or diabetic rat (13), the interconversion state of the enzyme in the brain is not changed.

Inhibition of cerebral glycolysis at the level of PFK is evidence

by a dramatic decrease in fructose 1,6-bisphosphate concentrations seen in the neonatal brain when compared with adult fed controls. The fact that intracellular accumulations of hexose phosphates to be expected as a consequence of PFK inhibition are not detected may be explained by the high rate of the pentosephosphate cycle in young rat brain when compared with the rate determined in the adult brain. An assessment of glucose fluxes through different enzymic steps reveals that two molecules of glucose out of three entering the infant brain are used by the pentosephosphate pathway (12). Thus, as the mass-action ratio of the phosphohexose-isomerase-reaction found in the neonatal brain (0.24) corresponds to the value of the thermodynamic equilibrium (0.36–0.47, reference 19), glucose 6-phosphate once formed may be rapidly bypassed by the pentosephosphate pathway.

Inhibition of cerebral glycolysis at the level of PFK is confirmed by the observation that, in the brains of neonatal rats made hyperketonemic, no changes in the concentrations of adenine nucleotides and of glucose 6-phosphate occurred, but the fructose 1,6-bisphosphate levels were significantly decreased in respect to the (normal ketonemic) controls (33).

The regulation of PFK is very complex and even the inhibitory mode of action of citrate is not fully understood as the effect of citrate may be both diminished and intensified by other effectors (4, 10, 20, 23). Nonetheless, studies of situations with increased turnover of fatty acids or ketone bodies in the heart as well as in the brain have shown that, even in the presence of physiologic ATP-concentrations, citrate may cause PFK inhibition (5, 10, 23, 24, 31). Because the markedly elevated citrate levels observed in the infant brain are all found in the inhibitory range, it seems reasonable to assume that the low activity of PFK in the neonatal brain, as measured *in vitro* (2), is further decreased *in vivo* as a consequence of inhibition by citrate.

It cannot be inferred from our data that further limitations of glucose use in the brains of young ketonemic rats occur at the level of hexokinase or membrane transport. Both the failure of consistent increases in cerebral glucose concentrations in neonatal rats and the failure of significant changes in glucose 6-phosphate concentrations between the infant and adult rat brain argue against a limitation of hexokinase. If glucose transport is regulatory due to interference with ketone bodies, it should be removed from equilibrium. In contrast, increasing rather than decreasing mass-action ratios, *i.e.*, brain/blood ratios of glucose are observed during infancy though the cerebral ketone body use of nursing rats increases with age (21). These findings which argue against a regulatory role of glucose transport in neonatal brain are confirmed by the observation *in vitro* that glucose use by infant brain-cortex slices is not diminished upon addition of acetoacetate (12). Obviously, the capacity of glucose transport in the brain is far in excess of physiologic needs, as a limitation could be only observed as a consequence of an abnormal stimulation of glycolysis by cyanide intoxication (19). This is, in contrast to the situation prevailing in the heart, where increased rates of oxidation of fatty acids or ketone bodies are associated with both inhibitions of hexokinase and of glucose transport (24).

Finally, a few general comments seem in order. Rat milk is rich in fat, but poor in carbohydrate (11). Because hepatic ketogenesis in neonatal rats operates at a high rate (15), a plentiful supply of ketone bodies is available to the growing brain being used both as a major fuel and as sources of carbon for cholesterol synthesis and lipogenesis (7, 12, 21). The diminished availability of glucose is compensated by a decrease in the oxidative use of glucose by the infant brain due to limitations at the level of PFK and PDH. As a consequence, because the glucose flux above the level of PFK is not further controlled, glucose is preferentially used by the pentosephosphate pathway, thus, providing hydrogen equivalents for the synthesis of lipids. After weaning the quantitative contribution of the two cerebral substrates to the metabolic needs of the brain is inverted in favor of glucose. These changes in brain metabolism are paralleled by and probably adapted to an alteration in the composition of the diet because the high fat intake

associated with the nursing period is now replaced by a diet in which carbohydrate is prevalent. The age-dependent relationships of glucose and ketone body metabolism in the brain are also reflected by the ratio of the actual activities of the rate-limiting enzymes (see Table 1).

CONCLUSION

The decrease in the oxidative use of glucose by the brain observed in neonatal ketonemic rats despite normal or even elevated blood glucose concentrations mainly results from a limitation at the level of PDH due to a maturational delay in the synthesis of the enzyme protein. Besides PDH, which catalyzes the rate-limiting step, additional control of glucose use in the neonatal brain is exerted at the level of PFK, obviously mediated by a 2–3-fold accumulation of citrate in the neonatal brain in respect to adult fed controls. The observation that glucose 6-phosphate levels in the infant brain are not different from adult fed controls and the fact that the brain/blood ratio of glucose does not decrease during the nursing period despite increasing ketonemia do not favor the view that glucose use by the young brain is further controlled at the level of hexokinase or membrane transport. Both the preferential use of ketone bodies and the limitation of glucose oxidation by the young rat brain may be interpreted as adaptations to the nutritional intake of the suckling rat because rat milk is rich in fat, but poor in carbohydrate.

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