

ORIGINAL ARTICLES

Cerebral metabolic rate for glucose during the first six months of life: an FDG positron emission tomography study

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Abstract

Aim—To measure the local cerebral metabolic rate for glucose (LCMRGlc) in neonatal brains during maturation using positron emission tomography (PET) and 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG). **Methods**—Twenty infants were studied using PET during the neonatal period. The postconceptional age ranged from 32.7 to 60.3 weeks. All infants had normal neurodevelopment and were normoglycaemic. The development of the infants was carefully evaluated (follow up 12–36 months) clinically, and by using a method based on Gesell Amatruda's developmental diagnosis. LCMRGlc was quantitated using PET derived from FDG kinetics and calculated in the whole brain and for regional brain structures.

Results—LCMRGlc for various cortical brain regions and the basal ganglia was low at birth (from 4 to 16 $\mu\text{mol}/100\text{ g/minute}$). In infants 2 months of age and younger LCMRGlc was highest in the sensorimotor cortex, thalamus, and brain stem. By 5 months, LCMRGlc had increased in the frontal, parietal, temporal, occipital and cerebellar cortical regions. In general, the whole brain LCMRGlc correlated with postconceptional age ($r=0.90$; $P<0.001$). The change in the glucose metabolic pattern observed in the neonatal brain reflects the functional maturation of these brain regions.

Conclusion—These findings show that LCMRGlc in infants increases with maturation. Accordingly, when LCMRGlc is measured during infancy, the postconceptional age has to be taken into account when interpreting the results.

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Keywords: cerebral metabolic rate of glucose, positron emission tomography.

There have only been a few positron emission tomography (PET) studies of 2-[¹⁸F]fluoro-2-deoxy-D-glucose (FDG) during the first months of life in the human infant.^{1,2} All reference values for the normal local cerebral meta-

bolic rate for glucose (LCMRGlc) by various PET centres have been measured in healthy adults.³ However, to describe the normal pattern of LCMRGlc during infancy in infants with neurological disorders LCMRGlc needs to be ascertained. Human brain maturation is incomplete at birth and during development the brain undergoes anatomical and functional changes. Brain development includes proliferation of the neurones, their migration to specific sites, a series of organisational events, and myelin formation.⁴ The timing of these events occurs from the second month of gestation to adult life. During the first three months of life infant development is fastest in behavioural, neurophysiological, and anatomical function.⁴

Previous studies on developing brain have demonstrated a series of changes which affect cerebral glucose utilisation. These changes include increases in the concentrations of the glucose transporter proteins in the blood-brain barrier and in the neurones and glia.⁵ The non-invasive measurement of LCMRGlc with PET,⁶ using FDG as a tracer, is a widely used technique to study LCMRGlc in vivo in the human brain.⁷ LCMRGlc undergoes dynamic maturational changes during development from birth to adulthood: this has been demonstrated in the cat,⁸ and in the human infant.¹ These changes are related to neurobehavioural developmental milestones.

We measured LCMRGlc using PET in newborn infants with suspected hypoxic-ischaemic brain injury⁹ or hypoglycaemia. Preliminary results have been presented in an earlier study.¹⁰ From these studies we have now selected 20 infants who developed normally during follow up. We aimed to determine normal values for LCMRGlc during the first months of life.

Methods

From over 150 infants and children measured for LCMRGlc between 0 and 18 years, we selected retrospectively 20 babies. Of these, 12 were selected from our research protocol designed to evaluate suspected hypoxic-ischaemic brain injury.⁹ The other eight infants were evaluated with FDG-PET after neonatal

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symptomatic hypoglycaemia.¹¹ The outcome of the 20 neonates seemed to be normal during follow up and they remained neurodevelopmentally normal (follow up 12 to 36 months). The developmental assessment included a careful neurological examination by a neuro-paediatrician, or a paediatrician and a physio-therapist. The oldest 12 children were studied according to the *Manual of Developmental Diagnosis*.¹² There were eight girls and 12 boys, and two babies were studied twice; thus altogether, 22 PET studies were included into the study. These infants were born at 25–41 gestational weeks (14 were preterm), and at the time of PET investigation, were aged 32.7–60.3 postconceptional weeks and 1–148 postnatal days (nine preterm babies aged 32–37 postconceptional weeks). Birthweight ranged from 720–4970 g, and the mean weight of infants at the time of PET study was 4128 g (range 1945–7590 g). Three infants were large for gestational age babies and one infant was small for gestational age. Infants were treated at the neonatal ward of Turku University Hospital. The study protocol was approved by the Ethics Committee of Turku University Hospital. Written parental consent was obtained.

PET studies were carried out during post-prandial sleep one hour after feeding, without sedation, as we have described before.^{9, 13} Two venous catheters were inserted, one in a peripheral vein for the injection of FDG and another for blood sampling. For the measurement of brain, 3.7 (SD) 0.5 MBq/kg of FDG was injected intravenously and dynamic scanning was started. Dynamic scanning of the thoracic region was started simultaneously and continued for 7 minutes (12×10 seconds, 10×30 seconds). Thereafter, dynamic scans were taken from the brain (10×120 seconds). The brain study was started about 45 minutes after the tracer injection. Blood samples were obtained five to 10 times during the PET study for the input function, as described before.¹³ Plasma glucose concentrations were measured three times during the study period; these were constant and all patients were normoglycaemic over the period investigated (plasma glucose 5.5 (1.4) mmol/l). Total volume of blood collected did not exceed 5 ml.

FDG was synthesised, as described by Hamacher *et al*.¹⁴ The specific activity at the end of the synthesis was about 2 Ci/μmol and the radiochemical purity exceeded 98%.¹⁵

PET studies were performed, as described before.¹³ The infant was lying supine in an

eight-ring ECAT 931/08-12 tomograph (Siemens/CTI Corp, Knoxville, TN, USA) with the imaging planes oriented parallel to the canthomeatal line. The axial resolution was 6.7 mm and 6.5 mm in the spatial plane (full width of half the maximum), measured according to the method of Spinks *et al* 1988.¹⁶

Regions of interest were drawn on Hanning filtered 256×256 PET reconstructions (cut-off frequency 0.5) which were corrected for deadtime and decay. The attenuation was corrected with the calculated method to avoid extra radiation and to save time. The blood time-activity curve was derived from a region of interest drawn over dynamic PET images of the left heart cavity (0–7 minutes from injection) and venous plasma samples (7–50 minutes from injection).¹³ The whole brain regions of interest were placed on four representative slices around the thalamus. Elliptical regions of interest were drawn on each trans-axial slice visualising different brain structures using anatomical atlases as reference.¹⁷ The mean activity concentrations of these individual regions were calculated. The three compartment model of FDG was used, as described before.^{6, 7} Plasma and tissue time-activity curves were treated with graphic analysis to quantitate the fractional rate of tracer phosphorylation, K_i .¹⁸ The rate of glucose utilisation was calculated by multiplying K_i by the plasma glucose concentration, $[Glc]_p$, and dividing by a lumped constant (LC)¹⁹:

$$rGU = (K_i \times [Glc]_p) / LC.$$

The lumped constant is used to correct for differences in the transport and metabolism of FDG and glucose.⁷ In this study we used an LC of 0.52, the measured value from human studies.²⁰

ANALYTICAL AND STATISTICAL PROCEDURES

Plasma glucose concentrations were measured using the glucose oxidase method with a glucose analyser (GWB micro-stat GM7, Analox Instruments, London, England). Statistical analyses were performed using the BMDP program,²¹ correlations were performed by bivariate plots. A probability level of 0.05 was considered significant. Results are given as mean and standard deviation (SD).

Results

WHOLE BRAIN

LCMRGlc was strongly associated with post-conceptional age. In preterm infants (postconceptional age ranged from 32–37 weeks), the whole brain LCMRGlc was 5.5 (1.4) μmol/100 g/minute (table 1). In term infants (aged 38–42 postconceptional weeks) the whole brain LCMRGlc was 7.2 (2.6) μmol/100 g/minute (table 1). The whole brain LCMRGlc reached the value of 18.7 (1.6) μmol/100 g/minute in infants aged 56–60 postconceptional weeks. In general, the whole brain LCMRGlc correlated with postconceptional age ($r=0.90$) (fig 2C) and with postnatal age ($r=0.84$; $P<0.001$).

Local cerebral metabolic rates for glucose (μmol/100 g/minute) for selected brain regions during development seen with PET

Structure	Postconceptional age (weeks)				
	32–37 (n=8)	38–42 (n=6)	43–48 (n=2)	49–56 (n=2)	Over 56 (n=4)
<i>Cerebral cortex:</i>					
Frontal	6.5 (1.9)	7.6 (3.4)	8.0 (2.0)	15.1 (0.7)	24.2 (4.6)
Temporal	6.2 (1.9)	8.5 (3.3)	7.2 (0.0)	16.4 (1.7)	20.5 (2.0)
Occipital	5.8 (1.3)	8.7 (3.0)	8.0 (1.5)	15.8 (0.5)	25.0 (3.1)
Sensorimotor	7.4 (3.6)	9.0 (4.4)	12.2 (2.5)	22.0 (5.7)	33.0 (1.7)
Thalamus	9.3 (4.3)	12.1 (4.9)	16.7 (6.1)	20.0 (0.3)	34.4 (3.2)
Brain stem	10.4 (3.5)	13.3 (5.6)	20.1 (0.0)	15.8 (0.4)	23.4 (1.9)
Cerebellum	9.4 (3.5)	11.9 (4.3)	11.1 (4.2)	15.3 (2.9)	14.4 (8.6)
Whole brain	5.5 (1.4)	7.2 (2.6)	7.4 (0.6)	12.2 (0.2)	18.7 (1.6)

*Values represent means (SD). All brain regions were not available in every subject.

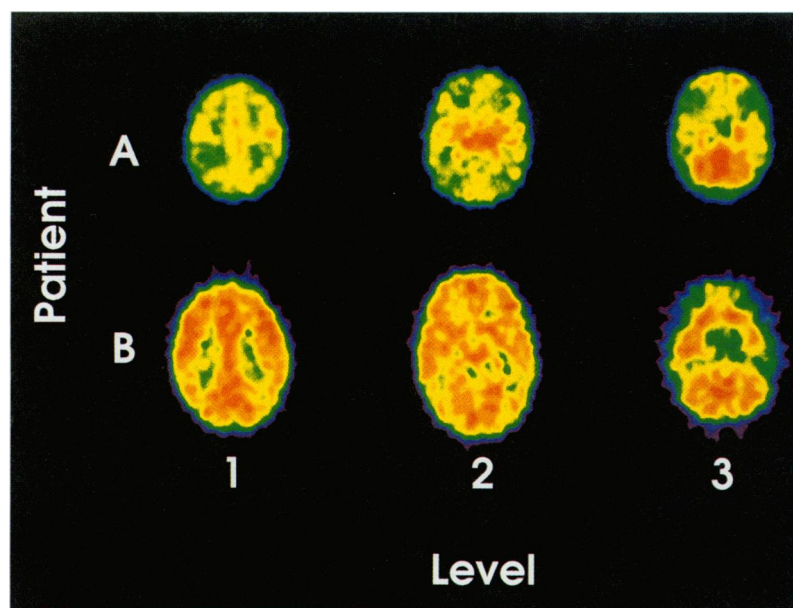


Figure 1 Distribution of FDG and change in LCMRGlc pattern with increasing postconceptional age. For both patients (A is 37 weeks and B is 60 weeks postconceptional age), three tomographic levels of scan were obtained. Level 1 is taken through the cingulate cortex, level 2 through the mid portion of the thalamus, and level 3 through the cerebellum.

Qualitative inspection of the image sets (fig 1) revealed maturational changes in LCMRGlc in infants with increasing age.

Two babies were studied twice, and these two examinations were treated as independent scans in all analyses. To avoid the complications of repeated measures, the correlations were performed without the second scans from these two babies. The correlations do not differ from these results.

THALAMUS, CEREBELLUM, AND BRAIN STEM

In infants aged 2 months and younger, LCMRGlc was active in subcortical areas (thalamus, brain stem) and the sensorimotor cortex (fig 1). The regional thalamic LCMRGlc values ranged from 5 to 20 $\mu\text{mol}/100$ g/minute before the postconceptional age of 42 weeks, and these values reached 35 $\mu\text{mol}/100$ g/minute at the age of 56–60 postconceptional weeks. During the first months of life the LCMRGlc for the cerebellum ranged from 5–16 $\mu\text{mol}/100$ g/minute, and a maturational rise in LCMRGlc was found. The brain stem was relatively advanced already at birth, the LCMRGlc values ranged 4–20 $\mu\text{mol}/100$ g/minute, and reached the value of 23 $\mu\text{mol}/100$ g/minute at the age of 56–60 postconceptional weeks (table 1). The LCMRGlc increased with postconceptional age in the thalamic region ($r=0.86$; $P<0.001$), in the cerebellum ($r=0.62$; $P<0.005$), and in the brain stem ($r=0.72$; $P<0.001$) (fig 2B).

CORTICAL REGIONS

LCMRGlc for all cortical brain regions was low (from 4 to 12 $\mu\text{mol}/100$ g/minute) in the preterm infants (fig 1, table 1). In the preterm and term infants LCMRGlc was the most active in the sensorimotor cortex (fig 1) and it ranged from 4 to 16 $\mu\text{mol}/100$ g/minute. In the

frontal cortex LCMRGlc was low in preterm and also at term infants (from 3.5 to 15 $\mu\text{mol}/100$ g/minute) and it increased with advancing postconceptional age (fig 2A). The temporal and the occipital cortical LCMRGlc values were low at birth (4–10 $\mu\text{mol}/100$ g/minute). LCMRGlc correlated positively with advancing postconceptional age in the sensorimotor cortex ($r=0.89$; $P<0.001$), frontal cortex ($r=0.88$; $P<0.001$), temporal cortex ($r=0.90$; $P<0.001$), and occipital cortex ($r=0.79$; $P<0.001$).

Discussion

Our results show that whole brain and regional LCMRGlc were strongly associated with postconceptional age. We believe that our data are

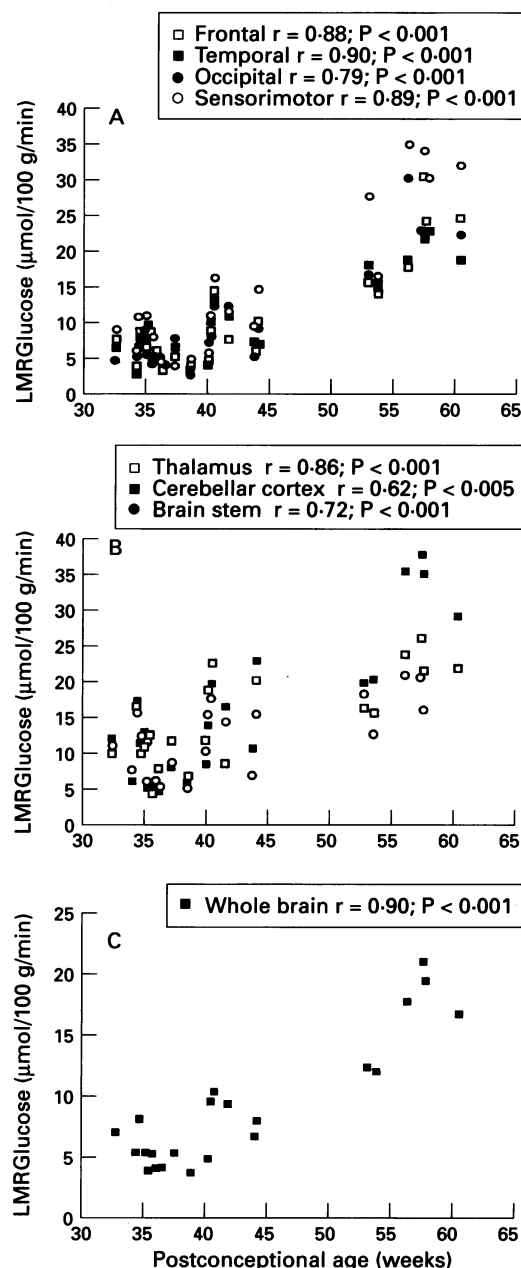


Figure 2 Values of LCMRGlc for selected brain regions plotted as a function of postconceptional age (weeks) for all infants. Points represent individual values of LCMRGlc. (A) Selected regions of cerebral cortex: frontal, temporal, occipital and sensorimotor; (B) thalamus, brain stem, and cerebellum; (C) whole brain.

representative of the normative state, because all infants were normoglycaemic, received no drugs during the time of the PET study, and developed normally during the follow up. For ethical reasons, entirely asymptomatic normal children cannot be studied with PET. The age related changes in cortical glucose metabolism have been studied in humans³ and also in animals.²² Our data on the pattern of the neonatal frontal LCMRGlc show a temporal maturational rise in other cortical regions. In the neonatal period (the first four weeks of life), the frontal cortex developed slower in a previous study of five infants under 5 months old. The maturational increase in LCMRGlc was seen in the anterior parietal, temporal, and calcarine cortical regions by about 3 months.¹ In that study three infants were taking anticonvulsive phenobarbital daily. In animal studies early neonatal phenobarbital exposure decreased LCMRGlc by 12 to 43%. Phenobarbital also changed the maturation pattern seen in local cerebral glucose utilisation compared with controls.²³ The effect of phenobarbital on cerebral glucose metabolism has also been studied in adult patients using PET with FDG, and it reduced LCMRGlc by 37%.²⁴ For these reasons it was important to select patients without any medication for this study.

The effects of maturation on brain glucose metabolism in children have been studied using PET and FDG. These studies have documented the age related changes in children aged 5 days to 15 years. Unfortunately these studies have consisted of only a few newborn infants.^{1,2} The correlation with postconceptional age and regional LCMRGlc was also shown in the present study, reflecting the cerebral maturation already seen in preterm infants. Our data were based on postconceptional age and our studies show that conceptional age is a major determinant of glucose utilisation. LCMRGlc values are very low in the youngest babies, especially in preterm infants. Our results complete the previous findings and illustrate the changes of LCMRGlc, especially in the youngest infants.

Quantification of the cerebral glucose metabolism by PET is technically very demanding in children. Ethically it is not possible to use invasive arterial catheters or to sample large blood volumes in small infants for PET alone. To minimise the need for blood samples we used the combined curve where left ventricular activity concentration during the first 5 minutes of the study was combined with two to 10 venous whole blood samples during the rest of the study.¹³

LC is a mathematical factor that accounts for differences in the transport and phosphorylation of FDG and glucose. In newborn infants LC may differ greatly from normal adult values. Furthermore, the value of LC may vary considerably in ischaemic and infarcted tissue, and during hypoglycaemia and hyperglycaemia. Errors in calculated glucose metabolism can occur unless individual constants are measured. The measurement of LC values in children is difficult to perform

and requires substantial blood volumes. We used measured LC for young adult brain.²⁰ Our patients were normoglycaemic over the period investigated; LC is relatively stable under normoglycaemic physiological conditions.¹⁹ Although we studied infants who were not completely normal, we believe that the data are reasonably representative of the normal state, because all these infants had episodic neurological events but remained neurodevelopmentally normal.

Our study contributes to the data of maturational changes in cerebral glucose metabolism in infants under 7 months old. These results also provide insight into the LCMRGlc values in preterm infants and also show a new finding of the developmental change of LCMRGlc in the frontal cortical region. The postconceptional age rather than postnatal age is the major determinant of glucose utilisation rate. The change of glucose utilisation is uniform and correlates with normal functional maturation.

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