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Lactate as a Cerebral Metabolic Fuel for Glucose-6-Phosphatase Deficient Children

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Summary

The main substrates for brain energy metabolism were measured in blood samples taken from the carotid artery and the internal jugular bulb of four children with glycogen storage disease caused by deficiency of glucose-6-phosphatase. Multiple paired arterial and venous blood samples were analyzed for glucose, lactate, pyruvate, D-β-hydroxybutyrate, acetoacetate, glycerol and O_2, and the arteriovenous differences of the concentrations were calculated. In the first three patients the substrates were measured in two successive conditions with lower and higher glucose-intake, respectively, inducing reciprocally higher and lower concentrations of blood lactate. In the fourth patient medium chain triglycerides were administered simultaneously with the glucose-containing gastric drip feeding.

Lactate appeared to be taken up significantly. It consumed, if completely oxidized, between 40–50% of the total O_2 uptake in most cases. Only once in one patient the uptake of lactate switched to its release, when the blood lactate level decreased to normal. D-β-hydroxybutyrate and acetoacetate arteriovenous (A-V) differences were small to negligible and these ketone bodies, therefore, did not contribute substantially to the brain's energy expenditure. Glycerol was not metabolized by the brain. Lactate thus appeared to be the second brain fuel next to glucose. It may protect the brain against fuel depletion in case of hypoglycemia.

Abbreviations

A-V, arteriovenous
AcAc, acetoacetate
G6Pase, glucose-6-phosphatase
GDF, gastric drip feeding
MCT, medium chain triglycerides
β-OHB, β-hydroxybutyrate
P, priming dose

Some children with hepatic glycogenosis caused by G6Pase deficiency show a striking tolerance for hypoglycemia. Their brain function remains unimpaired even when the blood glucose concentration is very low. Remarkably, those of our patients who show the most pronounced metabolic disturbances and the highest lactate levels in the blood, appear to be the least susceptible to clinical symptoms of hypoglycemia. On the other hand, patients with a less abnormal metabolic state and only moderately elevated lactate levels show cerebral symptoms as soon as their blood glucose drops to even moderately low levels. We, therefore, wondered whether in some patients, besides glucose, lactate might be utilized as an energy substrate by the brain and thus protect the child against the deleterious effects of glucose depletion. This would be opposite to the situation in normal children (18, 22, 24, 25, 26) and normal adults (4, 9, 23), in whom the brain releases lactate and consumes ketone bodies (β-OHB and AcAc) as soon as glucose, the preferential fuel, becomes insufficiently available. In G6Pase-deficient children, however, this is impossible because there is no physiologic hyperketosis during fasting. Their fasting hypoglycemia is accompanied by *hypo*ketosis (5) and *hyper*lactacidemia (6).

The ability to utilize lactate instead of ketone bodies would therefore be a useful mechanism. If, indeed, substantial cerebral utilization of lactate were found, this might influence the dietary treatment of the patients. The present treatment of frequent high carbohydrate meals during the day and a glucose-containing gastric drip feeding (GDF) at night (10) enhances the glucose dependency of the patients (20) as it suppresses the production of metabolic fuels other than glucose, especially lactate (11). This would deprive the patient of his only other possible brain fuel beside glucose. We considered this issue so important that we decided to test our assumption on four G6Pase deficient children. We measured the concentrations of possible brain fuels during two successive periods characterized by low and high glucose intake, which would induce a reciprocally higher and lower lactate availability, respectively. In one of these patients we administered MCT in order to stimulate ketone body production maximally (3) with the intention of providing the patient with another fuel beside glucose and lactate.

PATIENTS AND TEST PROCEDURES

Four children, aged 4, 5, 8, and 11 yr, with G6Pase deficiency diagnosed by enzyme assay of liver biopsy (type I-A) were investigated. They had the usual abnormalities such as marked hepatomegaly, tendency to hypoglycemia, hyperlactacidemia, hyperlipidemia, and hyperuricemia. They all were on GDF at night.

The investigations were carried out after approval from the medical ethical committee of the University Hospital of Leiden had been obtained, and with the informed consent of the parents. The children were carefully prepared for the test with the assistance of a psychologist, who participated in this study.

After local anesthesia two catheters were introduced by a pediatric cardiologist–one into the femoral artery, the other into the femoral vein–and positioned in the carotid artery and internal jugular bulb, respectively, as described earlier (23, 24). The position of the catheters was ascertained by x-ray with image intensification. Through the catheters, kept open with heparinized sodium chloride solution (10 U heparin/dl NaCl 0.9%, 3 ml/h), paired arterial and venous blood samples were taken and immediately prepared for analysis of oxygen content and determination of metabolic substrates. The tube for the nocturnal GDF was used to administer glucose solutions (three patients) and an emulsion of MCT (MIGLYOL 812, Dynamit Nobel, Troisdorf, W. Germany (one patient). Most fluids were administered by the P-continuous infusion technique in order to accelerate the transition from one condition into the other. Samples

from a peripheral vein were taken for immediate glucose and lactate assay at 30-min intervals when a fluid was being administered; as soon as the glucose assay indicated that a steady glucose concentration had been attained, samples for a complete analysis as described were taken.

The experimental design is presented in Figure 1A for the former three patients, and in Figure 1B for the latter patient. The patients were supervised by a pediatric cardiologist, a pediatrician, and the above mentioned psychologist. They were medicated with diazepam, 5 or 10 mg intramuscularly, at the beginning of the test. Arterial blood pressure and heart rate were monitored continuously. Most of the time the children were awake. They showed no fear. The younger children became rather restless towards the end of the test. Patient 1 vomited and became hypoglycemic 4 h after termination of the test. He recovered rapidly after intravenous administration of glucose and sodium bicarbonate. The other patients showed no abnormalities. A few weeks later the psychologist reexamined the patients and interviewed the parents for an evaluation of the test with regard to its psychologic impact on the children. She found no untoward sequelae.

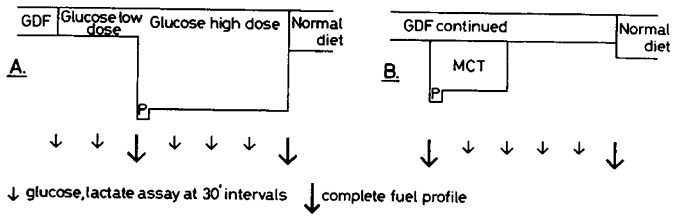

Fig. 1. Procedure of the cerebral substrate utilization test, (*A*) protocol for the first three patients and (*B*) protocol for the fourth patient. GDF, gastric drip feeding; MCT, medium chain triglycerides; and P, priming dose.

METHODS

Glucose, lactate, pyruvate, β-OHB, AcAc, and glycerol in blood (1.0 ml) were measured by spectrophotometry with $NAD(P)^+$, NAD(P)H coupled enzymic methods as described by Bergmeyer (1) with an Aminco-Chance Dual wavelength spectrophotometer. Blood gas analysis was performed on a Radiometer BMS 5Mk2 blood microsystem. Insulin was estimated with antiserum Cavis 51, [^{125}I]pork insulin as tracer, and human MRC insulin as standard. Separation of bound and free insulin was done with dextran-coated charcoal by the method of Herbert et al. (15). Glucagon was estimated by a modification of the method of Heding (13) with antiserum K5563 and ^{125}I-glucagon obtained from Novo Industries (København, Denmark).

RESULTS

The results of the tests are given in Tables 1–4. The A-V differences for glucose were positive irrespective of its concentration in arterial blood in all four patients. The A-V differences for lactate were positive except in patient 3 (period B) when the arterial concentration was low. The A-V differences for the other substrates were small to negligible except for βOHB and AcAc in patient 4 after MCT administration (period B). The sums of calculated O_2 equivalents assuming complete combustion of substrates by the brain, were in reasonable to good agreement with the O_2 actually taken up. The insulin concentration increased when the amount of glucose administered had been increased (period B in the first 3 patients). The glucagon concentration did not correlate with either glucose or insulin concentration.

The A-V differences of glucose and lactate of all patients have been plotted as functions of the respective arterial concentrations in Figure 2. The amount of glucose taken up (A-V difference) did not vary much and was not correlated with its arterial concentration or that of lactate (Fig. 2A and B). Lactate uptake,

Table 1. *Patient 1. (all concentrations in mmol/l, mean ± SD)**

	Arterial blood	A-V difference†	O_2 equiv. calculated‡	% of total O_2‡
Period A§				
Glucose	4.21 ± 0.06	+0.19 ± 0.07**	1.14	65
Lactate	8.83 ± 0.11	+0.21 ± 0.05***	0.63	35
Pyruvate	0.45 ± 0.02	+0.02 ± 0.02		
βOHB	0.68 ± 0.07	+0.03 ± 0.13		
Acac	0.26 ± 0.01	0.00 ± 0.003		
Glycerol	0.06 ± 0.002	+0.01 ± 0.001		
O_2	6.53	+1.93	1.77	
Insulin¶ venous	4			
Glucagon¶ venous	7			
Period B‖				
Glucose	10.81 ± 0.55	+0.15 ± 0.06**	0.90	55
Lactate	4.85 ± 0.07	+0.24 ± 0.05***	0.72	45
Pyruvate	0.36 ± 0.01	+0.04 ± 0.03		
βOHB	0.23 ± 0.08	−0.01 ± 0.11		
Acac	0.18 ± 0.02	−0.01 ± 0.03		
Glycerol	0.04 ± 0.001	0.00 ± 0.004		
O_2	6.60	+1.72	1.62	
Insulin¶ venous	45			
Glucagon¶ venous	<5			

* Part of the results of this patient has been published earlier (7).

† Triplicate paired arterial and venous blood samples were taken at the end of periods A and B for the assay of all substrates. Samples for O_2 determination were taken *in simplo.*

‡ O_2 equivalents and % of total O_2 were calculated if A-V differences of substrates were significant.

§ Period A, 3 mg glucose·kg^{-1}·min^{-1} during 2 h.

‖ Period B, 15 mg glucose·kg^{-1}·min^{-1} during 2 h.

¶ Insulin (mU/l) and glucagon (ng/l) were determined in peripheral venous blood. Significance (Student's *t* test): $^{**}P < 0.1$ and $^{***}P < 0.05$.

Table 2. *Patient 2 (all concentrations in mmol/l mean ± SD)*

	Arterial blood	A-V difference*	O_2 equiv. calculated†	% of total O_2†
Period A‡				
Glucose	5.35 ± 0.12	+0.18 ± 0.06***	1.08	52
Lactate	9.21 ± 0.27	+0.33 ± 0.14***	0.99	48
Pyruvate	0.53 ± 0.03	−0.02 ± 0.04		
βOHB	0.35 ± 0.02	0.00 ± 0.01		
Acac	0.24 ± 0.02	+0.03 ± 0.03		
Glycerol	0.08 ± 0.01	−0.01 ± 0.01		
O_2	4.54 ± 0.03	+1.82 ± 0.03	2.07	
Insulin‖ venous	<1			
Glucagon ‖ venous	22			
Period B§				
Glucose	6.16 ± 0.12	+0.14 ± 0.08**	0.84	54
Lactate	3.46 ± 0.13	+0.24 ± 0.07***	0.72	46
Pyruvate	0.24 ± 0.01	−0.01 ± 0.04		
βOHB	0.08 ± 0.01	0.00 ± 0.01		
Acac	0.10 ± 0.02	0.00 ± 0.01		
Glycerol	0.07 ± 0.01	0.00 ± 0.01		
O_2	4.76 ± 0.10	+1.35 ± 0.15	1.56	
Insulin‖ venous	15			
Glucagon‖ venous	27			

* Quintuple paired arterial and venous blood samples were taken at the end of periods A and B for the assay of all substrates. Samples for O_2 determination were taken in triplicate.

† O_2 equivalents and % of total O_2 were calculated if A-V differences of substrates were significant.

‡ Period A, 3 mg glucose·kg^{-1}·min^{-1} during ½ h.

§ Period B, 15 mg glucose·kg^{-1}·min^{-1} during 2½ h.

‖ Insulin (mU/l) and glucagon (ng/l) were determined in peripheral venous blood. Significance (Student's t test): ** $P < 0.1$ and *** $P < 0.05$.

Table 3. *Patient 3 (determination of substrates, see Table 2).*

	Arterial blood	A-V difference	O_2 equiv. calculated	% of total O_2
Period A*				
Glucose	6.41 ± 0.17	+0.20 ± 0.15**	1.20	58
Lactate	4.24 ± 0.22	+0.25 ± 0.06***	0.75	36
Pyruvate	0.33 ± 0.02	+0.05 ± 0.01‡***	0.13	6
βOHB	0.07 ± 0.02	−0.02 ± 0.02		
Acac	0.05 ± 0.01	0.00 ± 0.01		
Glycerol	0.10 ± 0.01	+0.01 ± 0.01		
O_2	6.41 ± 0.07	+2.07 ± 0.22	2.08	
Insulin venous	11			
Glucagon venous	<5			
Period B†				
Glucose	7.66 ± 0.18	+0.29 ± 0.13**	1.74	100
Lactate	1.23 ± 0.16	−0.05 ± 0.08		
Pyruvate	0.11 ± 0.02	+0.02 ± 0.02		
βOHB	0.05 ± 0.03	0.00 ± 0.02		
Acac	0.05 ± 0.01	0.00 ± 0.01		
Glycerol	0.06 ± 0.01	−0.01 ± 0.01		
O_2	6.46 ± 0.10	+1.68 ± 0.14	1.74	
Insulin venous	29			
Glucagon venous	<5			

* Period A, 3 mg glucose·kg^{-1}·min^{-1} during 1 h.

† Period B, 15 mg glucose·kg^{-1}·min^{-1} during 2 h.

‡ ** $P < 0.1$ and *** $P < 0.05$.

however, varied greatly; it was correlated positively with the arterial lactate concentration (Fig. 2C) and negatively (not significantly) with the glucose concentration (Fig. 2D). Lactate release occurred only once in one patient, when the arterial lactate concentration decreased to a normal value, which is exceptional in these patients (Table 3).

DISCUSSION

Lactate is taken up by the brain of G6Pase-deficient children as is evident from the positive A-V differences found in all four patients. Its significant contribution to the total fuel supply of the brain can be inferred from its O_2 equivalent as percentage of

Table 4. *Patient 4 (determinations of substrates, see Table 2).*

	Arterial blood	A-V difference*	O_2 equiv. calculated	% of total O_2
Period A†				
Glucose	3.46 ± 0.14	+0.25 ± 0.17**	1.50	55
Lactate	9.99 ± 0.10	+0.35 ± 0.14**	1.05	38
Pyruvate	0.60 ± 0.01	+0.08 ± 0.03**	0.20	7
βOHB	0.12 ± 0.03	+0.01 ± 0.04		
Acac	0.08 ± 0.01	−0.01 ± 0.02		
Glycerol	0.11 ± 0.01	−0.01 ± 0.01		
O_2	5.19 ± 0.09	+2.95 ± 0.16	2.75	
Insulin venous	2			
Glucagon venous	107			
Period B‡				
Glucose	1.69 ± 0.06	+0.19 ± 0.06***	1.14	40
Lactate	12.86 ± 0.12	+0.46 ± 0.20**	1.38	49
Pyruvate	0.49 ± 0.01	0.00 ± 0.02		
βOHB	0.69 ± 0.02	+0.04 ± 0.02**	0.18	6
Acac	0.33 ± 0.01	+0.03 ± 0.01**	0.12	4
Glycerol	0.17 ± 0.01	+0.01 ± 0.01		
O_2	4.94 ± 0.04	+2.87 ± 0.04	2.82	
Insulin venous	3			
Glucagon venous	36			

* Quintuple paired arterial and venous blood samples were taken before starting the extra MCT drip and 1½ h after having stopped the MCT administration.

† Period A, gastric drip feeding (GDF) containing 6 mg glucose·kg^{-1}·min^{-1} throughout the night and the test.

‡ Period B, medium chain triglycerides (MCT) 1.5 g/kg, administered during 1 h, was added to the GDF (see Fig. 1B).

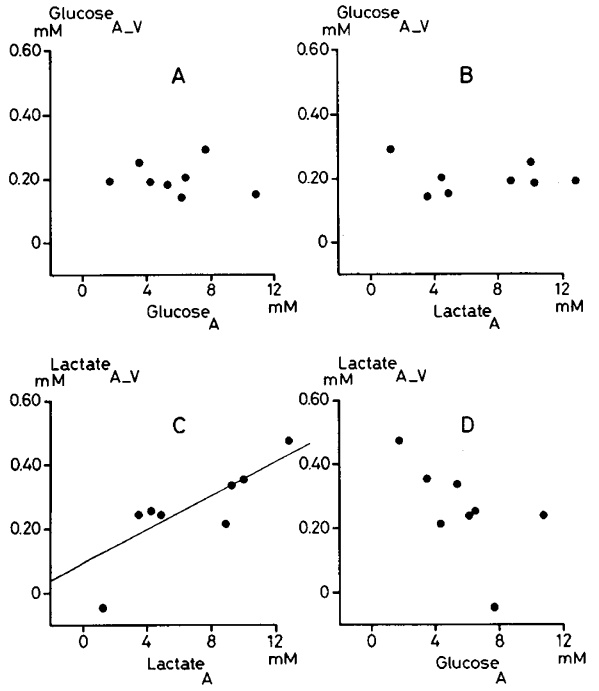

Fig. 2. A-V differences of glucose and lactate as functions of their arterial concentrations, (*A*) no correlation; (*B*) no correlation; (*C*) $[lactate_{A\text{-}V}] = 0.031\ [lactate_A] + 0.04$, $r = 0.83$; $P < 0.01$; and (*D*) no correlation.

total O_2 consumption. Its contribution, together with the much smaller contribution of pyruvate, approached the share of glucose to the brain's total requirement. The prevailing lactate uptake in these patients is surprising because lactate release is the normal event both in children (18) and in adults (4) even during fasting (23). No exceptions from this rule have been described, except in newborn baboons (21), calves (8), and dogs (14), in which a temporary lactate uptake has been observed. There was only a slight, if any, contribution of βOHB and AcAc to brain energy metabolism in the G6Pase-deficient children. Only the combined stimulation of fatty acid oxidation by orally administered MCT and an unintentional hypoglycemia produced a moderate increase of blood ketone bodies and a low to moderate cerebral extraction of ketone bodies (Table 4). This finding is in line with the well-known fact that G6pase-deficient children, when hypoglycemic, are hypoketotic and *not* hyperketotic as is the case in other types of glycogen storage disease (5). As for glycerol, this substrate did not contribute significantly to brain energy metabolism (Tables 1–4), as had been found earlier (19). Free fatty acids have not been determined in our patients as they are not utilized by the brain (9, 19). Neither have amino acids been determined as their uptake by the brain is insignificant, arginine and histidine excepted (25). The error of not taking into account the contribution of amino acids in the cerebral energy expenditure of our patients cannot be large, because the oxygen needed for total combustion of the other substrates to carbon dioxide and water (calculated O_2 equivalents) was in good agreement with the O_2 equivalents actually taken up.

Variabilities in activity and mental alertness of the patients and particularly the possible influence of MCT ingestion on the rate of glucose absorption in patient 4 may have interfered with the attainment of steady state conditions during the experiments. Comparison of one period with another should, therefore, be made with more reservation than in anesthesized animals in which different amounts of lactate, administered intravenously entail steady conditions, which can be compared with more confidence (14). Taking this into account, it can still be concluded that lactate is the next important fuel after glucose for the cerebral energy requirement of patients with G6Pase-deficiency whereas ketone bodies make little or no contribution. The usefulness of lactate for these patients may be compared with the usefulness of ketone bodies as alternative fuels for the brain of the normal child. The development of a physiologic ketosis in a normal child is a gradual process that can compensate for a gradual glucose depletion during fasting. In contrast, the development of glucose depletion in G6Pase-deficient children is often precipitous; therefore, the continuous presence of lactate as an alternative fuel may be very important to save glucose and to compensate for glucose depletion. A more liberal glucose supply, exceeding the basic requirement, leads to an undesirable fall of lactate in the blood. Indeed, if this is done, the child is brought

into a more satisfactory metabolic state but becomes more susceptible to hypoglycemic convulsions. In the presence of an elevated lactate level, on the other hand, brain function would remain intact even when the glucose concentration becomes alarmingly low. Some caution may be in order, however, because the maintenance of an elevated lactate level may conceivably lead to other secondary metabolic abnormalities such as hyperlipidemia and hyperuricemia, the latter being elicited by excessive glycolysis (12) and impaired urinary excretion of urate (16).

We consider the reduction of susceptibility to hypoglycemic convulsions so important that the diet of the patients should be adjusted in such a way as to keep the blood lactate level moderately elevated, for instance from about 4–6 mM (Fig. 2C), in order to keep this alternative fuel available in case of sudden hypoglycemia. The simplest and safest way to maintain this lactate level would seem to restrict the glucose content of the night drip feeding to the basic production rate of glucose, as found in normal children (2), which is higher than the glucose production found in one G6Pase-deficient patient (17). This covers the brain's requirement for glucose, which is estimated to be 60–80% of the normale production rate (2).

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