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Brain Metabolism during Fasting *

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Abstract. Catheterization of cerebral vessels in three obese patients undergoing 5–6 wk of starvation demonstrated that β-hydroxybutyrate and acetoacetate replaced glucose as the predominant fuel for brain metabolism. A strikingly low respiratory quotient was also observed, suggesting a carboxylation mechanism as a means of disposing of some of the carbon of the consumed substrates.

Introduction

Numerous studies performed after brief postabsorptive periods have shown that the only significant energy-yielding substrate consumed by brain is glucose, at rates of 110–145 g/24 hr (2–4). In adult man glucose and glycogen stores amount to 150–300 g, and the protein mass is approximately 6–8 kg (5). Although the fat depot may be massive and glycerol from neutral fat can be converted to glucose, net gluconeogenesis from fatty acid carbon has not been demonstrated in mammalian systems. If the central nervous system does maintain an absolute requirement for glucose during starvation, this substrate must be derived from the limited carbohydrate stores, from de novo synthesis from amino acids from protein, and from other precursors such as glycerol from adipose tissue, or lactate recycled from glycolytic tissues.

The use of prolonged starvation for the treatment of obesity has posed a fascinating problem; namely, that man is capable of fasting for periods of time beyond which he would have utilized *all* of his carbohydrate resources and *all* of his proteins for gluconeogenesis in order to provide adequate calories as glucose for the central nervous system.

This study was designed to clarify the apparent paradox, and it was found that β-hydroxybutyrate and acetoacetate replace glucose as the brain's primary fuel during starvation. In addition, a surprisingly low respiratory quotient was observed due to failure to recover substrate carbon as CO_2, suggesting a carboxylation by a pathway not yet defined.

Methods

Subjects. Three obese subjects were admitted for study to The Clinical Center of the Peter Bent Brigham Hospital (Table I). Subject M. B. had intermittent precordial discomfort, initially thought to be angina pectoris; F. N. had hip and backaches attributed to osteoarthritis. He also had mild hypertension, latent diabetes mellitus as detected by a mildly diabetic intravenous glucose tolerance test and electrocardiographic changes compatible with early left ventricular hypertrophy. Subject M.L. had menstrual irregularities unresponsive to uterine curettage and cyclic hormonal therapy.

Before admission, all three were informed of the procedures to be followed and the potential risks. The investigators, and the patients as well, felt that the procedures were warranted in order to elucidate possible metabolic aberrations associated with obesity. On admission, all had normal hemograms, urinalyses, chest and abdominal roentgenograms, electrocardiograms (ex-

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TABLE I

Clinical data

Patient	Age and sex	Starvation	Height	Weight			Body surface area		Per cent deviation from pop. mean wt.*	
				Initial	Final	Δ	Initial	Final	Initial	Final
		days	*cm*		*kg*		*m²*			
M.B.	42, female	41	173.0	123.5	98.8	−24.7	2.33	2.14	+61	+28
F.N.	49, male	38	177.5	132.6	109.8	−22.8	2.45	2.26	+65	+37
M.L.	26, female	40	176.0	147.3	124.2	−23.1	2.54	2.37	+109	+76

* From Metropolitan Life Insurance tables, 1959.

cept F. N.), thyroid indexes, serum enzymes (alkaline phosphatase, lactic dehydrogenase, glutamic-oxalacetic transaminase), and normal concentrations of serum protein, lipids, electrolytes, urea nitrogen, and uric acid before starvation. Intake during starvation consisted of one multivitamin capsule (Unicap, The Upjohn Co., Kalamazoo, Mich.), 17 mEq of NaCl, and 1500 ml of water each day. The subjects were encouraged to participate in occupational therapy, daily walks, and informative dietary sessions.

Catheterization. After the patients had fasted 38–41 days, a Sones No. 7 catheter was placed percutaneously through the right brachial artery and passed into the aortic root. For cerebral blood flow, the aortic catheter was repositioned in the carotid artery. Through the right and left antecubital veins, Goodale-Lubin No. 7 catheters were passed into the internal jugular bulb and hepatic vein. Position of the catheters was repeatedly ascertained visually with image intensification. Blood samples were then drawn simultaneously during 10-sec-timed intervals from the various catheters every 15 min for four to six study periods of time and immediately prepared for analysis of oxygen and carbon dioxide content and determination of metabolic substrates. The subjects were premedicated with 100 mg of sodium pentobarbital and 50 mg of meperidine sulfate intramuscularly 1–2 hr before the procedure. Throughout the procedure, intra-arterial pressure and heart activity were continuously monitored. Blood which was removed for analysis was replaced isovolumetrically by 5% human albumin in isotonic saline.

Blood analyses. Oxygen and carbon dioxide contents were measured manometrically by the method of van Slyke and Neill. For glucose determination, blood was added to tubes containing oxalate-fluoride and analyzed in triplicate within several hours by both the Somogyi-Nelson (6, 7) and Technicon AutoAnalyzer ferricyanide procedures (8). The remainder of analyses were performed by immediately injecting 10 ml of blood into 10 ml of iced 1 M perchloric acid and mixing. After centrifugation in the cold, the supernatant fluid was filtered and stored at −20°C. Pyruvic and lactic acids were measured in the potassium bicarbonate-neutralized supernatant fluid by standard enzymatic techniques (9) and β-hydroxybutyrate and acetoacetate by a modification (10) of the method of Williamson, Mellanby, and Krebs (11) with β-hydroxybutyric acid dehydrogenase. Free fatty acids in serum were measured by the method of Trout, Estes, and Friedberg (12) and α-amino nitrogen by the colorimetric method of Moore and Stein (13), using a supernatant fluid obtained after deproteinization with an equal volume of serum and 0.05 M acetic acid, diluted 1:5, and heated for 5 min in a boiling water bath. All analyses were done in triplicate except those for glucose, which were done in triplicate by both the AutoAnalyzer and Somogyi-Nelson techniques; and the values for glucose are the average of all six determinations for each study period.

Urine analyses. Urine was collected in refrigerated plastic containers; at the end of 24 hr (at 7:00 a.m.) the volume was measured and samples taken for total nitrogen determination (Kjeldahl), ammonia (14), creatinine, uric acid (AutoAnalyzer), and electrolytes. Scant fecal material, composed primarily of mucus, was excreted on three or four occasions by F. N. and M. L. and was not analyzed. After initial colonic evacuation, M. B. passed nothing per rectum for the starvation period.

TABLE II

Caloric expenditure and nitrogen excretion/24 hr

Patient	Calories				Urinary nitrogen					
	Total	Fat	Carbohydrate	Protein	Total	Urea	Ammonia	Uric acid	Creatinine	Unidentified
					g					
M.B.	1985	1888	0	97	3.90	0.70	2.26	0.10	0.35	0.49
F.N.	1707	1607	0	100	4.00	1.32	1.96	0.13	0.63	0.00
M.L.	1773	1691	0	82	3.27	0.86	1.96	0.09	0.41	0.00
Mean*	1822	1729	0	93	3.72	0.96	2.06	0.11	0.46	0.16

* Mean of 3 days measured during last week of fasting before catheterization.

TABLE III

Arterial levels of metabolic fuels

Patient	Glucose	Lactate	Pyruvate	β-Hydroxybutyrate	Acetoacetate	α-Amino nitrogen	Free fatty acids
M.B.*	3.91 ± 0.01	0.65 ± 0.04	0.055 ± 0.003	8.01 ± 0.09	1.71 ± 0.01	2.38 ± 0.06	2.82 ± 0.05
F.N.‡	5.28 ± 0.01	0.57 ± 0.05	0.061 ± 0.001	7.07 ± 0.19	0.96 ± 0.01	3.44 ± 0.04	2.06 ± 0.09
M.L.*	4.27 ± 0.04	0.38 ± 0.04	0.047 ± 0.003	4.92 ± 0.05	0.86 ± 0.04	3.61 ± 0.02	1.32 ± 0.07
Mean	4.49 ± 0.41	0.53 ± 0.08	0.054 ± 0.004	6.67 ± 0.37	1.17 ± 0.27	3.14 ± 0.19	2.06 ± 0.43

Values in mmoles/liter of whole blood (plasma for free fatty acids). Each value is the mean with SE of the mean for 4* or 6‡ observation periods.

Calorimetry. Energy expenditure was measured by indirect calorimetry, using the sampling routine validated by Kinney (15). The patients were allowed to become accustomed to the face mask during the prestarvation period. Hourly, from 7:00 a.m. to 7:00 p.m., with the patient reclining in bed, a 5 min sample of expired air was collected in an aluminized plastic bag. The samples were passed through an analysis train composed of an American Meter Company wet test flowmeter, a modified Beckmann LB-2 carbon dioxide analyzer, and a Beckmann E-2 oxygen analyzer. Two standard gas mixtures were analyzed before each sample was measured. The conventional calculations of indirect calorimetry were applied. The usual assumptions are not strictly correct in the fasting patient, but the resulting error is far smaller than the sampling error. For example, if one corrects Loewy's original calculations (16) for subject M. B. by allowing the decreased fecal nitrogen and altered urinary nitrogen partition, 100 g protein oxidation requires only 112 g of O_2, rather than the 138 g needed in the fed state. In addition, ketonuria depresses the nonprotein respiratory quotient, and the energy expenditure calculated from total oxidation of fat is overestimated. In M. B., this amounted to approximately 70 kcal/day, again an insignificant quantity compared to daily energy expenditure.

Blood flow. Cerebral blood flow was determined in subjects F. N. and M. L. using Krypton (^{85}Kr). ^{85}Kr was dissolved in sterile saline and injected rapidly into the right common carotid artery. The clearance rate of ^{85}Kr was monitored by a 2 inch external gamma scintillation detector with a 1 inch collimation tube placed over the right temporal region. In F. N., simultaneous integrated sampling from the right jugular bulb was also done. Flow rates were calculated using the formulas of both Lassen et al. (17) and Zierler (18).

Results

In Table II are listed the mean daily caloric expenditures, their calculated sources, and mean daily nitrogen excretions, as well as the identified and unidentified nitrogenous components in the urine for each subject. The data are not corrected for body surface area, but this can be derived from the data presented in Table I. Urinary nitrogen averaged between 3.3 and 3.9 g/24 hr, of which the main component was ammonia.

Table III gives the arterial concentrations of the metabolic fuels, and Table IV presents the cerebral arteriovenous differences with the mean and standard errors of the means of the multiple-paired arteriovenous analyses for each of the four

TABLE IV

*Brain arteriovenous differences**

Patient	Oxygen	Carbon dioxide	Respiratory quotient	Glucose	Lactate	Pyruvate	β-Hydroxy-butyrate	Acetoacetate	α-Amino nitrogen	Free fatty acids
M.B.	2.41 ±0.23	−1.26 ±0.27	0.52 ±0.09	0.21 ±0.03	−0.09 ±0.01	−0.023 ±0.003	0.36 ±0.14	0.08 ±0.03	0.08 ±0.03	0.060 ±0.081
F.N.	3.57 ±0.12	−2.57 ±0.17	0.72 ±0.15	0.28 ±0.02	−0.26 ±0.05	−0.032 ±0.003	0.43‡ ±0.10	0.05‡ ±0.05	0.05 ±0.07	−0.010 ±0.037
M.L.	2.89 ±0.02	−1.87 ±0.26	0.65 ±0.08	0.29 ±0.03	−0.24 ±0.08	−0.033 ±0.004	0.23 ±0.03	0.04 ±0.01	0.15 ±0.06	0.000 ±0.029
Mean	2.96 ±0.34	−1.90 ±0.37	0.63 ±0.06	0.26 ±0.02	−0.20 ±0.05	−0.029 ±0.003	0.34 ±0.06	0.06 ±0.01	0.09 ±0.03	0.023 ±0.019

* Values in mmoles/liter whole blood (plasma for free fatty acids). Each value is the mean with SE of the mean for four observation periods.

‡ Six observation periods.

TABLE V

Brain oxygen substrate equivalents in mmoles/liter of blood
Mean values of three subjects after 38–41 days of fasting.

Substrate	A-V difference	Calc. O_2 equivalent	CO_2 equivalent
Glucose	0.26 ± 0.02		
Lactate	−0.20 ± 0.05		
Pyruvate	−0.03 ± 0.003		
Glucose + (L + P)/2	0.145	0.87	−0.87
β-Hydroxybutyrate	0.34 ± 0.06	1.53	−1.36
Acetoacetate	0.06 ± 0.01	0.24	−0.24
α-Amino nitrogen	0.09 ± 0.03	0.42	−0.34
Total substrate equivalents		3.06	−2.81
Measured oxygen consumption or CO_2 production		2.96 ± 0.34	−1.90 ± 0.37

A-V, arteriovenous; L, lactate; P, pyruvate.

to six periods of study. The concentration of the metabolites showed no significant decrease or increase throughout the catheterization study, supporting our desire that the values represent true steady-state conditions and therefore not be subject to the problems incurred by changes in levels or pool sizes. Also presented are the means of the arteriovenous differences for the three subjects. Of note in Table IV are the relatively reduced glucose uptake of 0.26 mmole/liter (4.7 mg/100 ml), the significant production of lactate and pyruvate, and the significant uptake of β-hydroxybutyrate and acetoacetate. The large error in the determination of α-amino nitrogen, as well as the variations in the differences for each study period, diminishes the significance of the uptake of this substrate. Of more importance is the large standard error in each subject for the uptake of free fatty acids, the mean being insignificant for each individual subject, as well as an insignificant mean arteriovenous difference for the average of all three subjects.

Cerebral blood flow was determined by the external techniques in subjects F. N. and M. L. and also by internal monitoring in F. N. Accidental unavailability of ^{85}Kr prevented similar measurements in M. B. By these techniques, cerebral blood flow in both subjects was exactly 45 ml/100 g per min. This is slightly lower than the mean value reported in the literature (19), but yet within the normal range. It should be emphasized, however, that the flow determinations are only approximations, since only a single assay was performed in each subject in contrast to the repeated steady-state values for gases and substrates. Nevertheless, the fact that F. N.'s flow was the same when calculated from both internal and external techniques gives validation to the observation.

Table V presents the calculated mean values for substrates removed and produced for each liter of blood perfusing the brain. Also presented are the calculated oxygen equivalents which would be needed for total combustion of the substrates to CO_2, as well as the amount of CO_2 theoretically produced from each substrate. Appropriate corrections are made for the lactate and pyruvate produced from glucose. The total calculated oxygen consumption of 3.06 mmoles/liter (6.85 volumes/100 ml) agrees well with that determined directly, 2.96 mmoles/liter (6.63 volumes/100 ml). In contrast, the calculated CO_2 which should have been produced, 2.81 mmoles/liter (6.30 volumes/100 ml), is far in excess of that directly determined, 1.90 mmoles/liter (4.25 volumes/100 ml). This striking discrepancy in recovery of expected CO_2 is also reflected in the extremely low respiratory quotients listed in Table IV.

Discussion

Assuming a quantitatively minimal loss of nitrogen by routes other than urine, one can simply calculate a theoretical value for glucose synthesized from nitrogen loss by simply equating 1 g of nitrogen to 6.25 g of protein. Theoretically, 57 g of glucose may be derived from 100 g of protein (20). The average nitrogen loss per 24 hr in these three subjects during the last week of fasting was 3.72 g, and this would yield about 14 g of glucose. Although in good agreement with the glucose: nitrogen ratio of Stiles and Lusk (21), it is possibly in excess since a considerable per-

centage of the nitrogen loss in the urine is not from glucogenic sources, e.g., creatinine and uric acid.

Another source of glucogenic precursor is adipose tissue glycerol, which in fat approximates 10% of the weight of the triglyceride molecule. Table II shows that about 1729 cal are derived from fat daily, producing 19 g of glycerol which can be incorporated into glucose, for a total, when added to that derived from nitrogen, of approximately 33 g of glucose synthesized daily. A third source for glucose is lactate and pyruvate returning to the liver and kidney from glycolysis, the greatest proportion of which is produced by the red cell mass, a quantity approximately 30–40 g/day (22). However, these two substrates are quantitatively reincorporated into glucose, and therefore are not lost by terminal oxidation and do not contribute to net carbohydrate loss. The fourth source of potential glucose is the stored liver and muscle glycogen (the latter available by glycolysis to lactate and pyruvate and then by resynthesis to glucose in the liver); since the total sum, as stated earlier, is only about 150–300 g, by the 5th or 6th wk of fasting this amount probably does not contribute significantly to daily glucose production. Thus, a sum of approximately 33 g of glucose or less is available for terminal oxidation by the body.

By combining the measurement of blood flow with the arteriovenous differences, the rate of utilization or production of specific metabolites can be quantitatively estimated. Turning to Table V, the average glucose uptake, after subtracting the amount glycolyzed to lactate and pyruvate, is 0.145 mmole/liter (2.6 mg/100 ml). This is markedly less than the usual 9–10 mg/100 ml observed in our laboratory while the techniques which little or no production of lactate or pyruvate was observed (25–28). Similar data were observed in our laboratory while the techniques and methods used to study these fasted subjects were validated. With measured cerebral blood flow of 45 ml/100 g of tissue per min, and assuming a brain size of 1400 g the 24 hr glucose oxidation would approximate 24 g, which agrees well with the theoretical maximum of 33 g calculated from nitrogen execretion and glycerol from adipose tissue as described above. The third confirmatory evidence for this marked reduction in glucose metabolism has been data, which obtained from hepatic and renal vein catheterization studies,[1] demonstrated that the liver almost totally ceases to synthesize glucose from amino acids and that the kidney assumes the role of the major source of this diminished amount of glucose daily produced and consumed during starvation.

Of interest are the data presented in Tables IV and V, which relate to the respiratory quotient and carbon balance across the brain. If we add together the calculated O_2 equivalents needed for combustion of the glucose consumed (corrected for lactate and pyruvate production) and the equivalents needed for combustion of the β-hydroxybutyrate, acetoacetate, and amino acid assuming the α-amino nitrogen as alanine, and compare this sum to the oxygen directly determined, the two numbers are in good agreement, 3.06 and 2.96 mmoles/liter of blood, respectively. Also, as stated before, 2.81 mmoles/liter of CO_2 should have ben produced, with a theoretical respiratory quotient of 0.92 instead of the observed 1.90 mmoles/liter, resulting in a quotient of 0.62. To our knowledge, this deficit in CO_2 production can only be explained by a carboxylation reaction with the venous effluent transporting the CO_2 in a form not liberated by the acidification used in the standard manometric technique for determination of CO_2 and HCO_3.

According to most observations, the respiratory quotient of brain, which glucose serves as sole energy source, is close to unity (2, 3, 25). Brain, however, contains enzymes for all the major metabolic pathways (29–31), including fixation of CO_2 (31, 32); and oxidation of keto acids has been demonstrated in vitro (30, 33, 34). In addition, Kety et al. (35) noted decreased respiratory quotients in patients in diabetic ketoacidosis; but direct utilization of keto acids has not been found in this condition (3) or in fat-fed animals (36). Göttstein et al. also observed decreased respiratory quotients in patients with cerebral arteriosclerosis (37). Additional indirect evidence for a novel carboxylation reaction which would result in a low quotient has been Sacks' studies on glucose-^{14}C oxidation in human brain whereby only 50% of glucose-carbon that

[1] O. E. Owen, A. P. Morgan, H. G. Kemp, J. M. Sullivan, M. G. Herrera, and G. F. Cahill, Jr. Data in preparation.

is oxidized is recovered in effluent CO_2 and HCO_3 (38).

A possible objection to this study is the use of obese subjects and the utilization of these data as representative of normal man, but it is extremely doubtful if these subjects do differ from normal, nonobese individuals fasted over the same duration. Indirect evidence of this fact is the nitrogen excretion of Benedict's nonobese subject (39), the nitrogen loss of the other nonobese "professional" fasters studied at the turn of the century (40), and in addition our own prior study of nitrogen loss during a shorter period of fasting in normals (10), which suggest the same progressive decrease in gluconeogenesis as brain adapts to keto acid utilization, and which are superimposable with our observations in the three obese subjects.

Finally, a few general comments seem in order. Man's capability to survive marked extremes in caloric intake depends, at least in part, on his ability to store fuel in an economical form. This means that the depot should have the highest calorie : weight ratio, should be capable of meeting substrate requirements for all tissues, and should be expendable without adverse effects. Survival during prolonged fasting, particularly in a primitive setting, obviously necessitates maximal sparing of nitrogen depots, of which the major portion is muscle. Fat has the greatest caloric potential per unit weight and is readily expendable. β-Hydroxybutyrate and acetoacetate utilization by the brain shows that fat products may even satisfy the central nervous system's substrate requirement, and therefore circumvent the need for gluconeogenesis and concomitant nitrogen depletion. Finally, our subjects failed to show any deficit on psychometric testing, and electroencephalographic tracings remained unchanged, which suggests that the keto acids did fulfill the predominant energy requirement in a satisfactory fashion.

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