The Energy Requirement for Growth: An Application of Atkinson's Metabolic Price System

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Extract

Atkinson's metabolic price system has been applied to the calculation of the energy costs of growth of a 3-week-old, 3,900-g "male reference baby," growing along the 50th percentile. The increase in weight of liver, brain, lung, spleen, and kidney has been calculated from literature data. The other organs and tissues were assumed to grow proportionally to the gain in body weight corrected for the weight gain of the organs mentioned above. The gross chemical composition of tissues and organs has been used to calculate the increases in specific tissue components, such as proteins, triglycerides, phospholipids, cholesterol, glycogen, DNA, and RNA. Of the total weight gain of 6.9 g/kg body wt/24 hr, 25.2% could be accounted for as solids deposited in the body, the remainder, 74.8%, being water. The energy needed to synthesize these solids has been calculated in terms of ATP equivalents, ATP being the form of energy used in the biochemical synthetic reactions. A total of 0.0614 mol ATP Eq is needed/kg body wt/24 hr in addition to 0.164 g glucose/kg body wt/24 hr. Proteins, which accumulate at a rate of 0.971 g/kg body wt/24 hr, take 87.7% of these ATP Eq. The energy needs for the active uptake of ions has also been calculated and was found to be 0.0108 mol ATP Eq/kg body wt/24 hr, which increases the total to 0.0722 mol ATP Eq/kg body wt/24 hr.

These ATP equivalents can be generated by the complete oxidation of 0.342 g glucose, which sets the total energy need to maintain growth at 0.506 g glucose/kg body wt/24 hr. Assuming an intake of humanized milk containing 69 kcal/100 ml, at 140 ml/kg body wt/24 hr, 2.2% of the total caloric intake is needed to cover the energy cost of normal growth.

Speculation

The metabolic price system theory as developed by Atkinson may prove to be very useful in calculating the energy requirements for specific functions, such as performance of mechanical work, maintenance of ionic equilibrium, and energy costs for replacing body constituents, as more becomes known about the stoichiometry of biochemical reactions in various organs.

An important problem in human nutrition, especially in the rapidly growing individual, is to assess that part of the total caloric intake which is used for specific function such as heat production, basal metabolism, muscle activity, etc. The energy requirement for growth, *i.e.*, the energy needed to synthesize specific cell constituents (proteins, nucleic acids, fats, phospholipids, etc.), is virtually impossible to determine experimentally.

The biochemical pathways for the synthesis of these cell

constituents are, in general, at least, well known. Atkinson (2) has pointed out that "each metabolic sequence may be characterized by its coupling coefficient—the number of moles of ATP, or of ATP equivalents regenerated or used per mol of starting material consumed or of product synthesized." The number of molecules of ATP generated or used can thus be evaluated for each metabolic step. The energy requirements for the synthesis of specific cell constituents can then be calculated in terms of ATP equivalents used.

Provided the body composition is known in some detail, it should be possible to calculate the energy requirement of growth in terms of ATP equivalents, given the known biochemical synthetic pathways. On the other hand, the energy generated by the catabolic pathways is transformed into a form utilizable by the organism, namely ATP and/or NAD(P)H. The yield of ATP equivalents can therefore also be calculated and, thus, the percentage of the total caloric intake needed to cover the requirement for growth. It is the purpose of this communication to explore this line of approach as applied to growth of the human neonate.

CALCULATIONS

GROWTH

Table 1 summarizes the gross body composition of the human neonate. The data have been calculated from those given by Silverman (21).

The growth rate of a 3-week-old human male infant of 3,900 g will be assumed to be 27 g/24 hr, *i.e.*, 6.9 g/24 hr/kg body wt. This is the rate of growth of a human infant, growing along the 50th percentile (11). These figures have been derived from Dutch statistics. The solution to the problem posed can, however, easily be recalculated for other statistics. This gain in weight is not equally distributed over all organs. The data of Schulz *et al.* (18) have been used to calculate the increase in weight of liver, brain, lung, spleen and kidney, and adrenals. In Table 1 nervous tissue has been listed, which includes brain, spinal cord, and peripheral nerves. It is predominantly the brain which shows a rapid postnatal growth (8). The contribution of the brain to total nervous tissue amounts to 113 g/kg body wt (18). The growth of the brain has been calculated from the data of Schulz *et al.* (18). The remainder of nervous tissue is supposed to increase proportional to the body weight. The gain in weight of the other organs has been considered to be proportional to the gain in total body weight, corrected for the gain in weight of the organs mentioned above. This is permissible as long as short time intervals are considered. The results of these calculations are shown in Table 1.

The gross chemical composition of these tissues is given in

Table 2. Whenever possible, the tissue composition of the human neonate has been used. Not all data were available, however. In those cases, the composition of the human adult has been used. The specific increases in tissue components of the different tissues can now be calculated from the data given in Tables 1 and 2. The result is given in Table 3.

A total of 1.734 g/kg body wt can be accounted for of the total weight gain of 6.9 g/kg body wt. The remainder, 74.8%, must be water.

ATP EQUIVALENTS

It will be assumed that nutrition provides the growing infant with a balanced amount of amino acids. Such an assumption can be met in practice easily, especially with synthetic diets, such as those used in parenteral nutrition. No ATP equivalents will therefore be calculated for either synthesis or breakdown of amino acids. All other body constituents will be considered to be derived from glucose and/or amino acids, except fatty acids, which will be assumed to be administered in sufficient amounts of the right composition. The fatty acid composition of adipose tissue of the neonate changes rapidly with the fatty acid composition of the food. In this respect the neonate is different from the adult, in whom much slower changes are observed (26). The assumption made, namely that the fatty acids administered with the food are deposited in the body, seems, therefore, to be justified. Minerals, trace elements, and vitamins will be considered to be supplied in adequate amounts.

The calculation of ATP equivalents has been carried out as outlined by Atkinson (2). Every metabolic step associated with the conversion of 1 mol ATP to 1 mol ADP means a loss of 1 ATP Eq; the conversion of ATP to AMP means a loss of 2 ATP Eq. Oxidation of FADH yields 2 ATP and oxidation of

NADH yields 3 ATP, because the P/O ratios for the oxidation of FADH and NADH by the mitochondrial respiratory chain are 2 and 3, respectively. NADPH is valued at 4 ATP Eq because the energy-linked transhydrogenase, catalyzing the transfer of hydrogen from NADH to NADP, requires an additional ATP (15). The formation of 1 peptide bond will be considered to proceed at the expense of 5 ATP Eq. This figure is subject to doubt. There are arguments favoring a figure of 4 (20). By applying the figure of 5, a maximum energy for protein synthesis will be calculated. Any additional ATP equivalents for chain initiation will be neglected. The average molecular weight of amino acids as occurring in proteins will be put equal to 95. This figure has been calculated from the known amino acid composition of a number of proteins (hemoglobin, collagen, and myosin). A total of 0.053 ATP Eq will thus be necessary for the synthesis of 1 g protein.

The synthesis of a triglyceride from fatty acids and glycerol requires 6 ATP Eq. It has been assumed that fatty acids are supplied in adequate amounts, but that glycerol 1-phosphate must be synthesized from glucose at the expense of 8 ATP Eq/mol glycerol 1-phosphate. The synthesis of 1 mol triglycerides requires, therefore, 10 ATP Eq and the expenditure of 0.5 mol glucose. The average molecular weight of a triglyceride will be assumed to be 850. The synthesis of 1 g fat requires thus 0.012 ATP Eq and the expenditure of 0.00059 mol glucose. Fatty acids administered orally as triglycerides are hydrolyzed in the alimentary tract to fatty acids and β -monoglycerides. Resynthesis to triglycerides takes place in the intestinal mucosal cells after uptake of these fatty acids and β -monoglycerides. This process requires an additional 4 ATP Eq/mol triglyceride. The synthesis of 1 g fat before it is laid down in the body consumes, therefore, 0.016 ATP Eq and 0.00059 mol glucose.

Similar calculations can be made for other cell constituents. As outlined previously, it is assumed that these cell constituents are synthesized from glucose, amino acids, and fatty acids. This implies that the synthesis of, for example, cholesterol yields a net gain in ATP equivalents because the conversion of glucose to acetyl-CoA yields 7 ATP Eq/mol acetyl-CoA formed. Similarly, whenever a mole of glucose or amino acid is only partially used, it will be assumed that the remainder of the carbon skeleton is completely oxidized, which will yield a gain in ATP equivalents.

The energy needed for the synthesis of the cell constituents can now be calculated from the data of Tables 2 and 3 (Table 4). An important energy-requiring process is the active uptake of ions. Potassium ions take a predominant position in the intracellular ionic composition. Two K^+ can be taken up per ATP hydrolyzed (19). If an intracellular K^+ concentration of 80 mmol/kg body wt is assumed, a total of 0.55 mmol K^+ must be taken up at the expense of 0.00023 ATP Eq. It will be assumed furthermore, that all amino acids which are deposited in proteins have to be taken up by the cells by an active

Table 1. Gross body composition of human neonate and daily increase in weight of different tissues

Tissue	Weight/body wt, g/kg	Body wt increase/24 hr, g/kg
Blood	93	0.703
Nervous tissue	136	0.677
Muscle	227	1.715
Skeleton	163	1.233
Liver	47	0.120
Kidney + adrenals	11	0.041
Spleen	3	0.026
Lung	18	0.068
Intestine	66	0.499
Skin	70	0.545
Adipose tissue	166	1.273
Total	1,000	6.900

Table 2. Gross chemical composition of human tissues in percentage of wet weight

Tissue	Glycogen	RNA	DNA	Protein	Phospholipids	Cholesterol	Triglycerides	Reference
Blood				22	0.046	0.092	0.080	13
Nervous tissue		0.13	0.19	4.73	1.77	0.85	0.5	6, 25
Muscle	1	0.25	0.04	13	2.0	0.1	1.6	10
Skeleton				17			2.5	10
Liver	5	1.0	0.25	16	2.5	0.6	2.9	6, 23
Kidney + adrenals				18	2.7	0.3	2.3	7
Spleen				18	3.5	0.3	0.5	6
Lung				12.5	4.4	0.4	1.0	6
Intestine				12	1.8	0.6		3
Skin				17			13.0	6, 23
Adipose tissue				12.5		0.4	40	10

Table 3. Increase in tissue components per 24 hr in grams per kilogram of body weight

Tissue	Glycogen	RNA	DNA	Protein	Phospholipids	Cholesterol	Triglycerides
Blood				0.154	0.001	0.001	0.001
Nervous tissue		0.001	0.001	0.032	0.013	0.006	0.004
Muscle	0.017	0.004	0.001	0.233	0.034	0.002	0.027
Skeleton				0.210			0.031
Liver	0.006	0.002	0.001	0.019	0.003	0.001	0.003
Kidney + adrenals				0.007	0.001		
Spleen				0.005	0.001		
Lung				0.009	0.003		0.001
Intestine				0.060	0.009	0.002	
Skin				0.093			0.071
Adipose tissue				0.159		0.006	0.509
Total	0.023	0.007	0.003	0.971	0.065	0.018	0.647

Table 4. ATP equivalents and building blocks used for synthesis of cell constituents for growth of a 3-week-old male infant of 3,900 g¹

	ATP, Eq	Total expenditure, %	Building blocks, g			
			Glucose	Ala	Gly	Asp
Protein	-0.0515	-71.3				
Triglycerides	-0.0104	-14.4	0.069			
Cholesterol	+0.0003	+0.4	0.053			
Glycogen	-0.0003	-0.4	0.029			
Phospholipids	-0.0010	-1.4	0.007			
RNA	+0.0010	+1.4	0.004	0.004	0.001	0.003
DNA	+0.0005	+0.7	0.002	0.002		0.002
K ⁺ uptake	-0.0002					
Uptake of amino acids	-0.0034					
Uptake of Ca ⁺⁺ in bone	-0.0018	× 2				
	-0.0108	-15.0				
Total	-0.0722	100.0	0.164	0.006	0.001	0.005

¹ All values are per 24 hr per kilogram of body weight.

process. There is considerable evidence that the active uptake of amino acids proceeds cooperatively with the uptake of Na⁺ at a one-to-one ratio (*cf.* Reference 14), presumably linked to the Na⁺-K⁺ pump. This sets the stoichiometry for the uptake of amino acids to 3 amino acids/ATP used. As the increase in protein has been calculated at 0.971 g/24 hr/kg body wt, with an average molecular weight of 95 for the amino acids as occurring in proteins, a total of 0.0102 mol amino acids has to be taken up at the expense of 0.0034 ATP Eq.

The skeleton increases in weight by 1.233 g/24 hr/kg body wt (Table 1). The mineral content of bone at birth is 11.4% (I0), predominantly hydroxyapatite. A total of 3.5 mmol Ca⁺⁺ has to be taken up by the bone cells.

The stoichiometry of the energy-linked Ca⁺⁺ uptake by mitochondria has been well documented and was found to be 2/ATP (4). If it is assumed that a similar mechanism is operative in bone cells, 0.0018 ATP Eq are needed for the calcium deposition in bone.

The uptake of ions deposited in the body during growth is, however, not limited to the uptake by the cells where these ions are finally stored; uptake of these ions by the gastrointestinal tract requires ATP equivalents as well. Therefore, the total amount of ATP equivalents calculated for the active uptake of ions has to be doubled to obtain the ATP equivalents needed for the active uptake of ions to maintain growth.

The complete oxidation of 1 mol glucose yields 38 ATP Eq.

ENERGY REQUIREMENT FOR GROWTH

The increase in weight of a 3-week-old male infant of 3,900 g growing along the 50th percentile requires 0.0722 ATP Eq/kg body wt/24 hr and 0.164 g glucose.

These 0.0722 ATP Eq can be derived from 0.342 g glucose. A total of 0.506 g glucose/kg body wt/24 hr is therefore needed for the energy requirements of growth.

The daily consumption of a humanized milk containing 69 kcal/100 ml is assumed to be 140 ml/kg body wt. Of the total caloric intake, 2.2% is needed to cover the energy costs of normal growth.

DISCUSSION

The present calculation rests on several assumptions. The gross chemical composition of the tissues of the neonate as given in Table 2 may be subject to criticism. Protein and fat make up the greater part of the total increase in weight as illustrated in Table 3. When the total protein content per kilogram of body weight is recalculated from the data of Tables 1 and 2, a protein content of 13.7% is found. This agrees well with the figures given by Widdowson and Dickerson (24), obtained from total body analyses. The same calculation for fat (phospholipid + cholesterol + triglycerides) yields a fat content of 10.0%, again in good agreement with the analyses of Widdowson and Dickerson (24). The increase in protein of 0.971 g/24 hr/kg body wt (Table 3) is likewise in

good agreement with the calculation given by Fomon (10) for the average rate of protein synthesis in the male reference infant during the first 6 months of life. Proteins and triglycerides take the largest part of the ATP equivalents needed for growth. The comparisons given above therefore lend support to the approximations as used here.

A second source of uncertainty is the active uptake of ions. Potassium ions, an important ionic species of intracellular water, contribute only an insignificant percentage to the total ATP equivalents needed. It has furthermore been assumed that the uptake of all amino acids deposited in proteins proceeds by an energy-dependent mechanism. This presumably overestimates the energy requirements for amino acid uptake because such an energy requirement has not been demonstrated for all amino acids in all tissues.

It has furthermore been assumed that the biochemical reactions proceed at optimal efficiency. Suboptimal efficiencies will occur if futile cycling takes place. Such futile cycling has been demonstrated at the level of the phosphoenolpyruvate to pyruvate ratio (9, 17) and at the level of the fructose 6-phosphate to fructose 1,6-diphosphate ratio (5). The latter may amount to 50% under catabolic conditions (5). Another example is the leakage of K^+ out of the cell which has to be recovered at the expense of ATP. However, these factors do not contribute to the energy requirements of growth because they may be considered as part of the energy requirements of maintenance. Although the exact figure of 2.2% of the total caloric intake needed to maintain growth may need correction when more detailed knowledge on the stoichiometry of various biochemical reactions becomes available, its ultimate value will not differ much from the figure presented. This figure of 2.2% is considerably lower than previous estimates, which amounted to up to 30% (13). However, this figure includes the caloric equivalents of the nutrients deposited in the body. When this is taken into account in the present calculation, a figure of 13.4% is obtained, again considerably lower than previous estimates, which amounted to up to 30% (13).

Part of this discrepancy may be explained by the assumptions made in the present calculation, namely that nutrition provides the growing infant with a balanced amount of nutrients. Energy-requiring metabolic interconversions are therefore not necessary. It may also explain why, as observed by Widdowson (22), the older growing animal on a diet different from mother's milk needs more of its caloric intake to cover the energy costs of growth than the newborn animal on mother's milk. Futile cycling and leakage of ions do not enter the calculation either. These processes do, however, take place and decrease the efficiency of the utilization of nutrients. If these factors were included in the calculation, a higher percentage of the total caloric intake needed for growth would result. The data given represent, therefore, the true energy costs of growth and may not be directly compared with growth requirements from experimental approaches (16), because these figures include contributions by futile cycling and ion leakage. The figure of 2.2% is more in line with clinical experience, that is, that only a slight increase in caloric intake will promote growth in the human neonate on a calorie-restricted diet.

It should be pointed out that the figure of 2.2% applies only to the energy requirements of growth for the male reference infant of 3 weeks, of 3.9 kg body/wt, growing along the 50th percentile, and only for the following weeks of life. A different calculation should be made for other ages because body composition and growth rate may be different. Preliminary calculations have shown that with increasing age the percentage decreases because body composition changes with age as does the growth rate of various organs. The calculation as presented here may also not be applied to

malnourished children because there again body composition and growth rate of various organs and the increase in specific constituents of these organs is different from that of the male reference infant. Indeed, a higher caloric requirement for children recovering from protein-calorie malnutrition has been determined (1). The method as applied here proves its value, however, and may find further applications to other ages and other functions, e.g., the energy requirements for replacement of body constituents.

SUMMARY

The energy required for the synthesis of specific cell constituents has been calculated in terms of ATP equivalents used. This has been applied to the growth of a male reference baby, 3 weeks old, 3,900 g, growing along the 50th percentile. From the gross body composition and the gross chemical composition, the increase in protein, triglycerides, phospholipids, cholesterol, glycogen, DNA, and RNA per organ has been calculated and thus the total ATP equivalents required to synthesize these components.

If it is assumed that nutrition provides the growing infant with a balanced amount of amino acids and fatty acids, 2.2% of the total caloric intake is needed to cover the energy costs of growth. When the caloric equivalents of the nutrients deposited in the body are included in the calculation, a figure of 13.4% is obtained.

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Arginine infusion hypoglycemia
dysmaturity insulin
glucagon

Levels of Glucose in Blood and Insulin in Plasma and Glucagon Response to Arginine Infusion in Low Birth Weight Infants

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Extract

Arginine infusions (0.5 g/kg body wt) have been performed in low birth weight infants in order to study the insulin and glucagon control of the glucose homeostasis in the transient hypoglycemia of small for gestational age infants. To evaluate the glucose output by the liver, intramuscular glucagon injection (0.1 mg/kg body wt) was also effected. Twenty-six appropriate for gestational age infants (AGAI) and 29 small for gestational age infants (SGAI), 11 of which were affected by hypoglycemia during the first few days of life, were selected.

In the hypoglycemic SGAI the mean level of glucose in blood showed an evident decrease after arginine, the means being significantly lower at 30 ($P < 0.001$) and 60 ($P < 0.001$) min of the test than those of the AGAI and nonhypoglycemic SGAI. The mean levels of insulin in plasma of the nonhypoglycemic SGAI were significantly lower than those of the AGAI during the whole arginine test ($P < 0.001$ at 0 min, $P < 0.05$ at 30 min, $P < 0.01$ at 60 min); however, when the hypoglycemic SGAI were compared with the AGAI such differences no longer existed.

The mean levels of glucagon in plasma were high at fasting and showed a significant ($P < 0.05$) increase after the arginine infusion without any difference among the means of the three groups of infants at any time of the test. The mean insulin to

glucagon molar ratio (ratio between the simultaneous molar concentrations of insulin and glucagon in plasma) was relatively reduced in comparison with the values reported in the adult and did not show any significant variation after arginine, nor was there any significant difference among the three groups of infants at any time of the test.

After glucagon injection an increase of the blood glucose values was observed in AGAI and nonhypoglycemic SGAI, without any significant difference of the means. In the hypoglycemic SGAI the mean levels of glucose in blood throughout the test were lower than those of the other two groups of neonates, but their mean increase on the basal level did not differ significantly from that of the control subjects.

These results offer evidence to exclude an impairment of the modulation of the bihormonal pancreatic secretion as an important factor of the hypoglycemia of low birth weight infants and to confirm the inability of hepatic response to glycogenolytic stimuli.

Speculation

During intravenous arginine infusion the mean values of the insulin to glucagon molar ratio in plasma of hypoglycemic SGAI infants did not differ significantly from those of control infants. The insulin to glucagon molar ratio could indicate, more than the examination of the single hormones, that in