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Integration and regulation of fuel metabolism in maintaining homeostasis in human body

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Abstract
Maintenance of energy level, paying regards tohomeostasis is critical for the survival of species. Therefore, multiple and complex mechanisms have evolved to regulate energy intake and expenditure to maintain body weight. For weight maintenance, not only does energy intake have to match energy expenditure, but also macronutrient intake must balance macronutrient oxidation. However, this equilibrium seems to be particularly difficult to achieve in individuals with low fat oxidation, low energy expenditure, low sympathetic activity or low levels of spontaneous physical activity, as in addition to excess energy intake, all of these factors explain the tendency of some people to gain weight. Additionally, large variability in weight change is observed when energy surplus is imposed experimentally or spontaneously. Clearly, the data suggest a strong genetic influence on body weight regulation implying a normal physiology in an 'obesogenic' environment. In this study, we also review evidence that carbohydrate balance may represent the potential signal that regulates energy homeostasis by impacting energy intake and body weight. Because of the small storage capacity for carbohydrate and its importance for metabolism in many tissues and organs, carbohydrate balance must be maintained at a given level. This drive for balance may in turn cause increased energy intake when consuming a diet high in fat and low in carbohydrate. If sustained over time, such an increase in energy intake cannot be detected by available methods, but may cause meaningful increases in body weight. The concept of metabolic flexibility and its impact on body weight regulation is also presented.

Keywords: substrate oxidation, carbohydrate balance, fat balance, energy balance, food intake

Introduction
Throughout evolution, humans and animals have evolved redundant mechanisms promoting the accumulation of fat during periods of feast to survive during periods of famine. However, what was an asset during evolution has become a liability in the current 'pathoenvironment' or 'obesogenic' environment [1] This hypothesis of the 'thrifty genotype' has, however, recently been challenged by Speakman [2] who offers an alternative explanation called the 'predation release' hypothesis. Speakman [2] argues that around 2 million years ago, predation was removed as a significant factor by the development of social behaviors, weapons, and fire. The absence of predation led to a change in the population distribution of body fatness due to random mutations and genetic drift. According to Speakman [2], such random drift, rather than directed selection, explains why some individuals are able to remain thin while living in an obesogenic environment.

Regardless of the origin of the genetic predisposition to obesity, the recent abrupt change in environmental conditions in which high-fat food is readily available and in which there is little need for physical activity has allowed obesity to reach epidemic proportions in both industrialized countries and in urbanized populations around the world [3]. This epidemic is the result of a normal physiology (genetic variability) in a pathoenvironment. In the United States, in the early 2000's, two out of three adult Americans were overweight or obese [6] More alarming, the prevalence of obesity is drastically increasing among children [7]. The World Health Organization has identified obesity as one of the major emerging chronic diseases of the 21st century [3]. Obesity increases the risk for a number of noncommunicable diseases, such as type 2 diabetes mellitus, hypertension, dyslipidemias and cardiovascular disease, and reduces life expectancy [8].

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Obesity results from a chronic imbalance between energy intake and energy expenditure. Hyperphagia, a low metabolic rate, low rates of fat oxidation and an impaired sympatheticnervous activity characterize animal models of obesity. Similar metabolic factors have been found to characterize humans who are susceptible to weight gain. In this manuscript, we review the current knowledge of the role of daily energy expenditure and nutrient oxidation in the regulation of energy and substrate balances, and therefore, in the etiology of obesity. We will first introduce the concept of substrate balance by opposition to energy balance and its implication on body weight homeostasis. Then, we review studies in which energy balance has been perturbed by overfeeding, with particular focus on the variability in weight change. Finally, we discuss evidence about the potential role of carbohydrate balance on energy intake and body weight regulation in humans.

1. Interrelationship of carbohydrate, lipid, and protein metabolism:
1. Interconversion of the macronutrients (Fig 1)
1) Krebs cycle: Amphibolic pathway
(1) Oxidative catabolism of carbohydrates, fatty acids, and amino acids
(2) Provision of precursors for many biosynthetic pathways, particularly gluconeogenesis

2) Glucose: Precursor for both the glycerol and the fatty acid components of triacylglycerols
(1) Dihydroxyacetone phosphate (DHAP): 3-carbon intermediate in glycolysis
(2) Conversion of pyruvate to acetyl CoA by pyruvate dehydrogenase complex

3) Only glycerol portion of fat: Conversion into carbohydrate via DHAP
 * during the fasting state, when fat catabolism is accelerated, this conversion assumes greater importance in maintaining a normal level of blood glucose.
(1) Conversion of fatty acids into carbohydrate: Not possible due to the irreversibility of the pyruvate dehydrogenase reaction
(2) Acetyl CoA: Used for energy, lipogenesis, cholesterogenesis, or ketogenesis (Fig 2)

4) Certain amino acids: Synthesized from carbohydrate or fat
(1) Conversion of fatty acids into amino acids via acetyl CoA: Impossible
(2) Amino acids producing acetyl CoA directly: Isoleucine, threonine,phenylalanine,tyrosine,lysine,leucine; indispensable amino acids

5) Most amino acids: Precursors for carbohydrate or fat synthesis
(1) Glucogenic amino acids: Production of glucose
(2) Ketogenic amino acids (potentially lipogenic amino acids):Production of ketone bodies via their conversion to acetyl CoA or acetoacetyl CoA
¨ç Leucine, lysine: purely ketogenic amino acids
(3) Several amino acids: Both glucogenic and ketogenic
 * Only when protein is supplying a high percentage of the calories would one expect glucogenic amino acids to be used in fat synthesis

2. The interconversion of the energy-producing nutrients appears to be skewed toward providing the organism with an energy source that can be easily stored (fat), thereby proving times when food is not readily available.
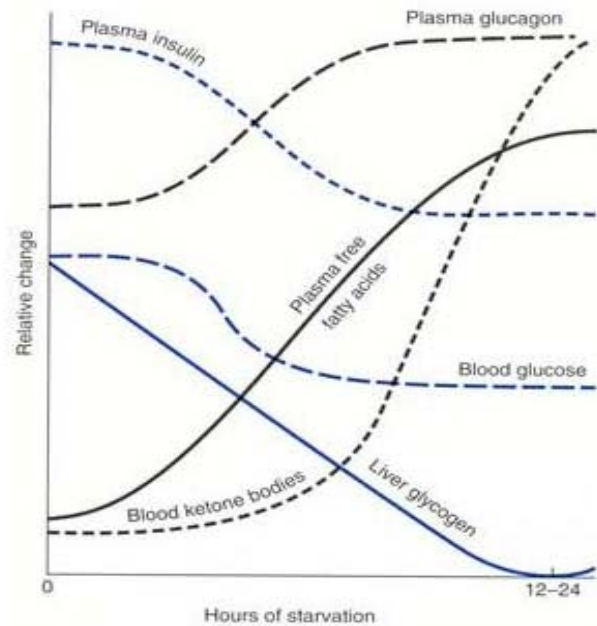

Fig 1. Interconversion of the macronutrients.

2. The Central role of the liver in metabolism
1. Metabolic pathways for glucose 6-phosphate in the liver (Fig 3)
(1) Glucose entering the hepatocytes is phosphorylated by glucokinase to glucose 6-phosphate.
(2) Other dietary monosaccharides (fructose, galactose, and mannose) are also phosphorylated and rearranged to glucose 6-phosphate.
(3) Glycogenesis occurs primarily from gluconeogenic precursors delivered to the hepatocytes from peripheral tissues rather than through glucose directly.
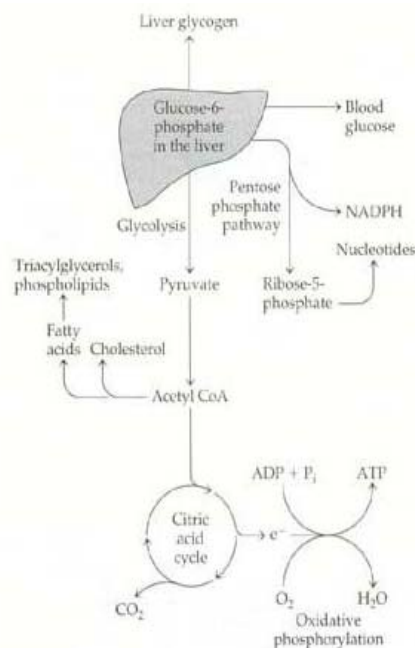

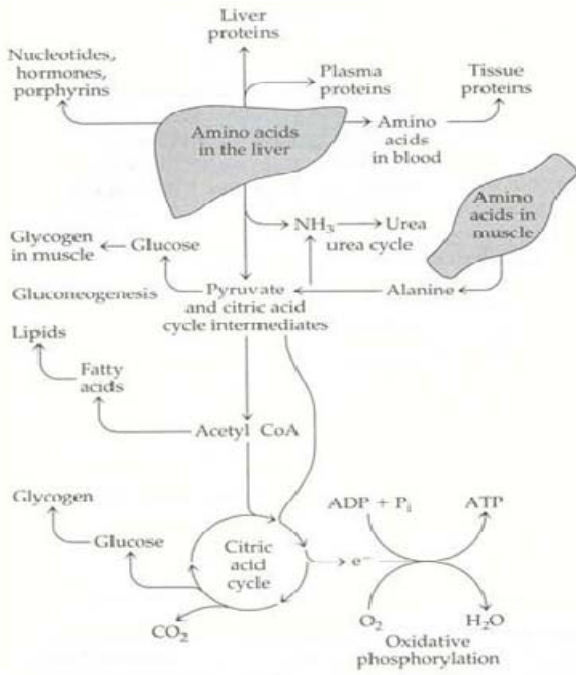Fig 2. Overview of lipid metabolism, emphasizing the central role of acetyl CoA.

Fig 3. Metabolic pathways for glucose 6-phosphate in the liver.

2. Pathways of amino acid metabolism in the liver (Fig 4)

1. Liver is site of synthesis of many different proteins (structural and plasma-borne) from amino acids.
2. Amino acids can also be converted into nonprotein products (nucleotides, hormones, and porphyrins).
3. Amino acids can be transaminated and degraded to acetyl CoA and other Krebs cycle intermediates, and these can in turn be oxidized for energy or converted to glucose or fat.
4. Glucose formed from gluconeogenesis can be transported to muscle for use by that tissue, and synthesized fatty acids can be mobilized to adipose tissue for storage or used as fuel by muscle.
5. Hepatocytes are exclusive site for formation of urea, the major excretory form of amino acid nitrogen.
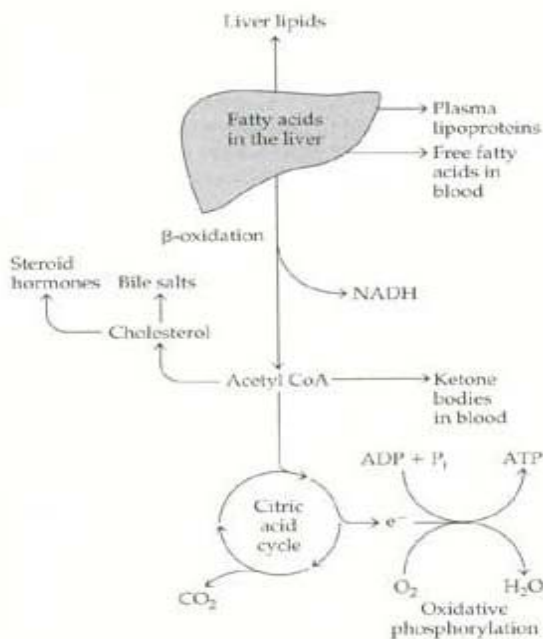

Fig 4. Pathways of amino acid metabolism in the liver.

3. Pathways of fatty acid metabolism in the liver (Fig 5)

1. In humans, most fatty acid synthesis takes place in the liver rather than in adipocytes.
2. Fatty acids can be assembled into liver lipids or released into the circulation as plasma lipoproteins.
3. Adipocyte store triacylglycerols arriving from the liver primarily in the form of plasma VLDLs, and from the lipoprotein lipase action on chylomicrons.
4. Under most circumstances, fatty acids are the major oxidative fuel in the liver.
5. Acetyl CoA not used for energy can be used for formation of ketone bodies, which are very important fuels for certain peripheral tissues (brain and heart muscle), particularly during prolonged fasting
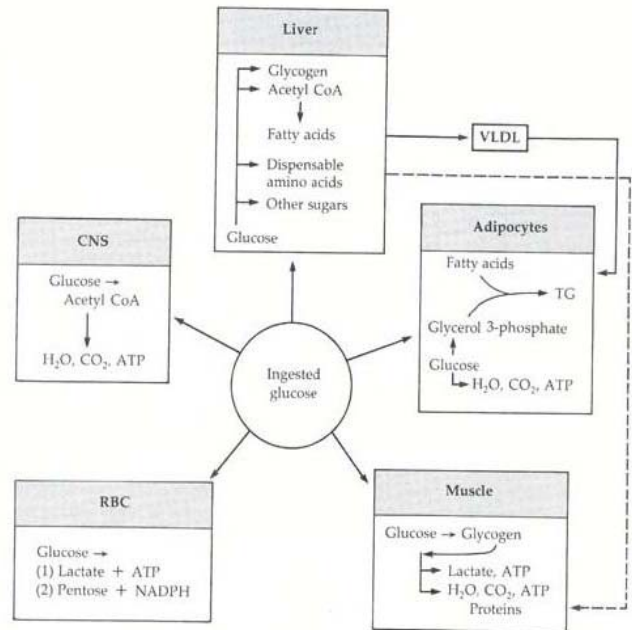

Fig 5. Pathways of fatty acid metabolism in the liver.

3. Tissue-specific metabolism during the feed-fast cycle

1. Carbohydrate and fat metabolism

* Feed-fast cycle

1. The fed state, lasting about 3 hours after the ingestion of a meal
2. The postabsorptive or early fasting state, occurring during a time span of from 3 to about 12 to 16 hours following the meal
3. The fasting state, lasting up to two days without additional intake of food
4. The starvation state, marked by prolonged food deprivation of several weeks¡¯ duration

1) The fed state (Fig 6)

1. The red blood cells (RBCs) and the central nervous system (CNS) have no metabolic mechanisms by which glucose can be converted into energy stores.
2. In the liver, some of the glucose can be converted to glycogen. However, most of the liver glycogen is synthesized indirectly from gluconeogenic precursors (pyruvate and lactate).
3. When available glucose or its glucogenic precursors exceed the glucose storage capacity of the liver, excess glucose can be metabolized in a variety of ways (conversion of glucose to fatty acids and dispensable amino acids) in the liver.

4. Some exogenous glucose escapes the liver, and circulates to other tissues. Major users of glucose are CNS, RBCs, adipose tissue, and muscle.
5. Dietary fat, except for short-chain fatty acids, enters the bloodstream as chylomicrons releasing free fatty acids and glycerol. Chylomicron remnants are taken up by theliver, and their lipid contents transferred to VLDL fraction. The fatty acids are taken up by the adipocytes, re-esterified withglycerol to form triacylglycerols.
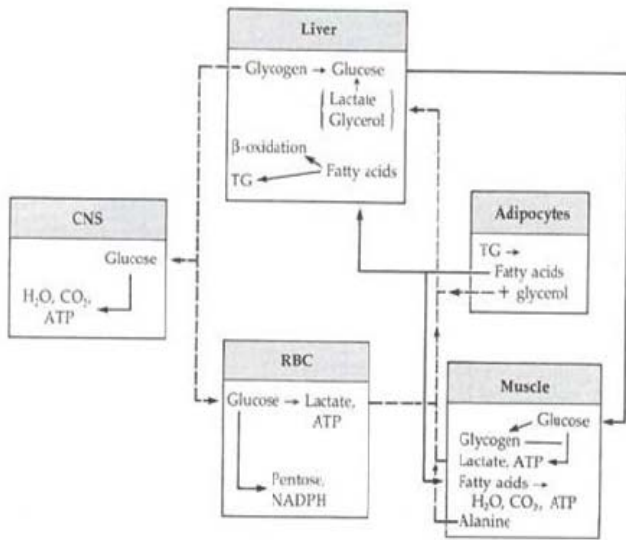

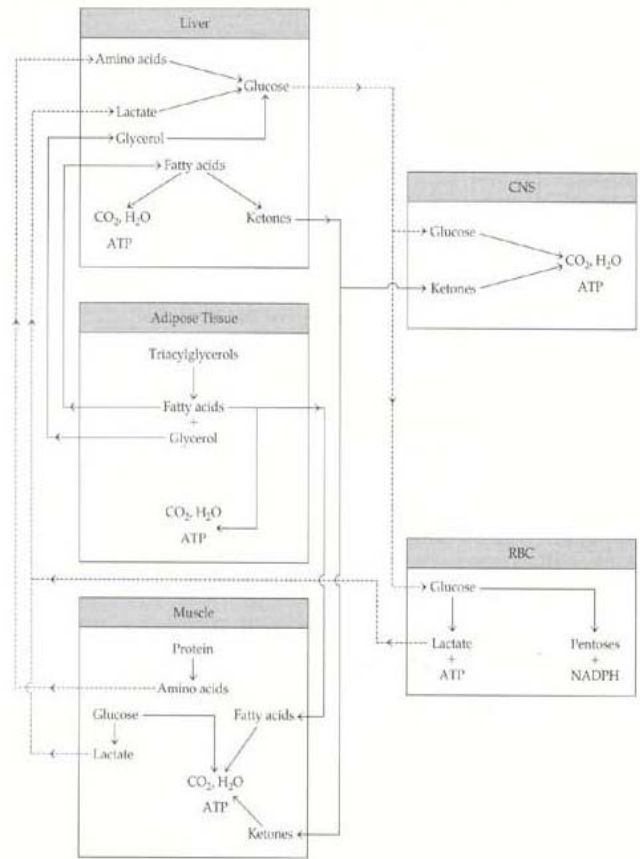Fig 6. Flow of substrates in the fed state between liver, CNS, adipose tissue, muscle, and erythrocytes.

Fig 7. The primary postabsorptive flow of substrates between the liver, CNS, adipose tissue, muscle, and erythrocytes.

2) Postabsorptive or early fasting state (Fig 7)
(1) With the onset of the postabsorptive state, tissues can no longer derive their energy directly fromingested glucose and other nutrients but must begin to depend on other sources of fuel.
(2) During the short period of time marking this phase (a few hours after eating), hepatic glycogenolysisis the major provider of glucose as fuel to other tissues. The do novo synthesis of glucose (gluconeogenesis) begin to help maintain blood glucose levels(lactate formed in and released by RBCs and muscle tissue; alanine from muscle cells).
(3) Glucose provided to the muscle by the liver comes primarily from the recycling of lactate and alanine, and to a lesser extent, from hepatic glycogenolysis. Muscle glycogenolysis provides glucose as fuel only for those muscle cells in which the glycogen is stored.
(4) The brain and other tissues of the CNS are extravagant consumers of glucose, oxidizing it forenergy and releasing no gluconeogenic precursors in return.
(5) In the of an overnight fast, nearly all reserves of liver glycogen and most of the muscle glycogen have been depleted.

3) The Fasting state (Fig 8, Fig 9)
(1) The postabsorptive state evolves into the fasting state after 48 hours of no food intake.
(2) Particularly notable in the liver is the de novo glucose synthesis (gluconeogenesis) occurring in the wake of glycogen depletion.
(3) Amino acids from muscle protein breakdown provide the chief substrate for gluconeogenesis, although the glycerol from lipolysis and the lactate from anaerobic metabolism of glucose also are used to some extent.
(4) The shift to gluconeogenesis during prolonged fasting is signaled by the secretion of the hormone glucagon and the glucocorticoid hormones in response to low levels of blood glucose.
(5) Ketogenic amino acids (leucine, lysine) released by muscle protein hydrolysis are converted into ketones and they allow the brain, heart, and skeletal muscle to adapt to the use of these substrates.
(6) The fasting state is accompanied by large daily losses of urinary nitrogen, in keeping with the high rate of gluconeogenic conversion of muscle protein to provide substrates for hepatic gluconeogenesis.
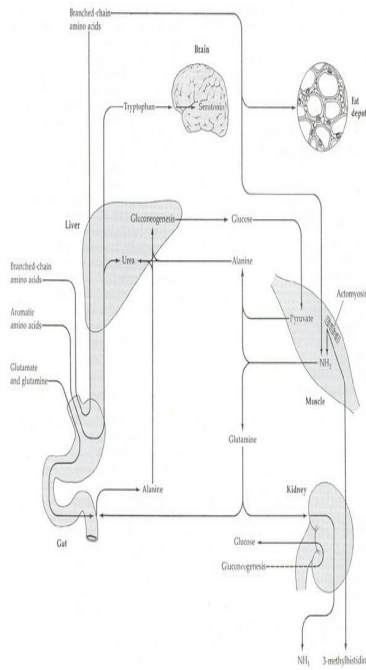
Fig 8. Flow of substrates among the liver, brain and CNS, adipose tissue, muscle, and RBC's during fasting and starvation states. Broken lines indicate major substrate flow during fasting of about two days' duration. Solid lines reflect predominant substrate flow during the starvation state.

4) The starvation state (Fig 8)

(1) If the fasting state persists, and progresses into a starvation state, a metabolic fuel shift occurs again in an effort to spare body protein.

(2) The protein-sparing shift at this point is from gluconeogenesis to lipolysis, as the fat stores become the major supplier of energy. The blood level of fatty acids increases sharply, and these replace glucose as the preferred fuel of heart, liver, and skeletal muscle tissue that oxidize them for energy.

(3) The brain cannot use fatty acids for energy because fat¼î acids cannot cross the blood-brain barrier. However, the shift to fat breakdown also releases a large amount of glycerol, which becomes the major gluconeogenic precursor, rather than amino acids. This assure a continued supply of glucose as fuel for the brain.

(4) Eventually, the use of Krebs cycle intermediates for gluconeogenesis depletes the supply of oxaloacetate. Low levels of oxaloacetate, coupled with the rapid production of acetyl CoA from fatty acid catabolism, causes acetyl CoA to accumulate, favoring the formation of acetoacetyl CoA and the ketone bodies. Ketone body concentration in the blood then rises (ketosis) as these fuels are exported from the liver to skeletal muscle, heart, and brain, which oxidize them instead of glucose.

(5) Survival time in starvation depends on the quantity of fat stored before starvation. Stored triacylglycerols in the adipose tissue of an individual of normal weight and adiposity can provide enough fuel to sustain basal metabolism for about three months. When fat reserves are gone, the degradation of essential protein begins, leading to loss of liver and muscle function, and ultimately, to death.

2. Amino acid metabolism

(1) Organ interactions in amino acid metabolism, illustrated in Figure 10, are largely coordinated by the liver. The pathways shown undergo regulatory adjustments after consumption of a meal containing protein.

(2) In the fed state, absorbed amino acids pass into the liver, where the fate of most of them is determined in relation to needs of the body; amounts in excess of need are degraded.

(3) Only the branch-chain amino acids (BCAAs) are not regulated by the liver according to the body's need. Instead, the BCAAs pass to the periphery, going primarily to the muscles and adipose tissue, where they may be metabolized. These amino acids are usually much in excess of need for muscle protein synthesis.

(4) The liver is the site of urea synthesis, the primary mechanism for disposing of the excess nitrogen derived from amino acids used for energy or gluconeogenesis.

(5) The liver is the primary site for gluconeogenesis, where keto acids (amino acids from which the amine group has been removed) serve as the chief substrate. During fasting, gluconeogenesis becomes a very important metabolic pathway in the regulation of plasma glucose levels.

(6) Liver gluconeogenesis is supplemented by that occurring in the kidney during prolonged fasts. Kidney gluconeogenesis is accompanied by the formation and excretion of ammonia.

(7) The importance of the liver to the functioning of the muscle during the fasting state or very vigorous exercise is exemplified in the alanine-glucose cycle. Alanine, formed in the muscle, results primarily from pyruvate formed mainly from muscle glycogenolysis. Alanine returning to the liver is transaminated with ¥á-ketoglutarate, re-forming pyruvate. Pyruvate is converted once again to glucose through the gluconeogenic pathway. The glucose can then be returned to muscle for energy.

(8) Alanine can also be formed in intestinal mucosal cells by transamination involving pyruvate, thereby serving as a carrier of amino acid nitrogen from that site to the liver.

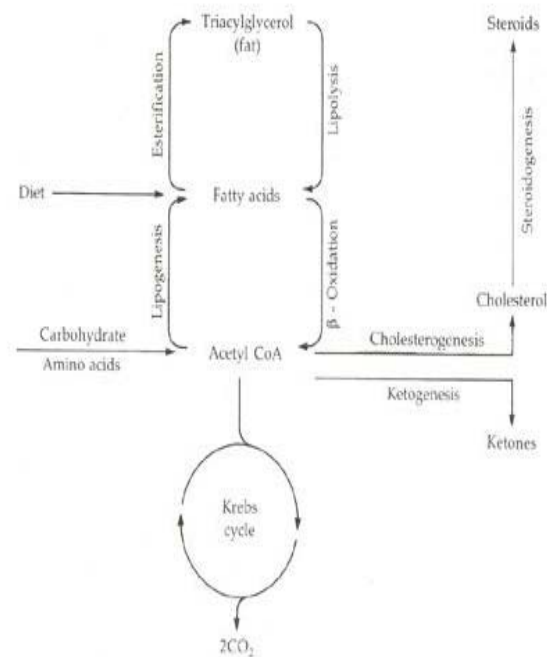(9) Glutamine also plays a central role in the transport and excretion of amino acid nitrogen.

Fig 9. Relative changes in metabolic parameters during the onset of starvation.

4. System integration and homeostasis

* The integration of metabolism at the cellular and the organ and tissue levels, which is essential for the survival of the entire organism.

* The three major systems that direct activities of the cells, tissues, and organs to ensure their harmony with the whole organism are the nervous, endocrine, and vascular systems.

1. Endocrine function in fed state

1) Most of endocrine organs are involved primarily with nutrient ingestion, that is, the gastrointestinal (GI) tract.

2) The primary action of GI hormones (GIP, CCK, gastrin, secretin), secreted in response to a mixed diet, is to amplify the response of the pancreatic islet ¥â-cells to glucose.
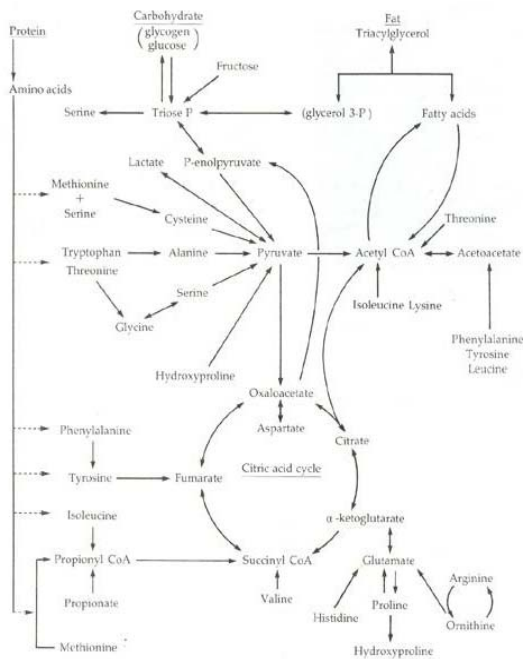

Fig 10. Interchanges of selected amino acids and their metabolites among body organs and tissues.

Insulin, secreted by the ¥â-cells, is the hormone primarily responsible for the direction of energy metabolism during the fed state.

(1) Very fast action of insulin, occurring in a matter of seconds: Membrane changes stimulated by insulin in specific cells where glucose entry depends on membrane transport.

(2) Fast action of insulin, occurring in minutes, involves the activation or inhibition of many enzymes, with anabolic actions being accentuated(glycogenesis, lipogenesis, and protein synthesis, Table 1).

(3) One slower action of insulin, occurring in minutes to several hours, involves a further regulation of enzyme activity through the selective induction (glucokinase) or repression of enzyme synthesis. Another slower action of insulin is its stimulation of cellular amino acid influx.

(4) The slowest action of insulin, only occurring after several hours or even days, is its promotion of growth through mitogenesis and cell replication.

2. Endocrine function in postabsorptive or fasting state

1) Metabolic adjustments that occur in response to food deprivation operate on two time scales: acutely, measured in minutes (such adjustments can be seen in a postabsorptive state), and chronically, measured in hours and days (adjustments occurring during fasting or starvation).

2) Fig 7 depicts the postabsorptive state wherein hepatic glycogenolysis is providing some glucose to the body, while increased use of fatty acids for energy is decreasing the glucose requirement of cells. Also, gluconeogenesis is being initiated, with lactate and glycerol serving as substrate.

3) Hepatic glycogenolysis is initiated through the action of glucagon, and of epinephrine and norepinephrine. Epinephrine is considerably more potent in this metabolic action than norepinephrine. The action of glucagon and the catecholamines is mediated through cAMP and protein kinase phosphorylation; glucose 6-phosphatase is activated and glycogen synthetase is inhibited.

4) In contrast, muscle glycogenolysis, stimulated by the catecholamines, provides glucose only for the muscles in which the glycogen has been stored. This is because muscle tissues lacks glucose 6-phosphatase and cannot release free glucose into the circulation.

5) Glycogenolysis can occur within minutes, and meets an acute need for raising the blood glucose level. However, because so little glycogen is stored in the liver (approximately 60 to 65 g), blood glucose cannot be maintained over a prolonged period.

(1) In prolonged glucose deprivation such as occurs during fasting, the liver employs another mechanism for supplying the body with glucose, namely gluconeogenesis.

(2) Although lactate and glycerol serve as substrates for gluconeogenesis, the primary substrates are the amino acids derived from protein tissues, principally from muscle mass.

(3) Gluconeogenesis is fostered by the same hormones that initiated glycogenolysis (glucagon and epinephrine), but the amino acids needed as substrate are made available through the action of the glucocorticoids.

(4) Alanine, generated in the muscle from other amino acids and from pyruvate by transamination, and serving as the principal gluconeogenic substrate, also acts as a stimulant of gluconeogenesis via its effect on the secretion of glucagon.

6) Low levels of circulating insulin not only decrease the use of glucose but also promote lipolysis and a rise in free fatty acids.

(1) Contributing to this effect is the increase in glucagon during the fasting period. Glucagon raises the level of cyclic AMP in adipose cells, and the cyclic AMP than activates a lipase that hydrolyzes stored triacylglycerols.

(2) The muscles, inhibited by the catecholamines from taking up glucose, now begin to use fatty acids as the primary source of energy. This increased use of fatty acids by the muscles represents an important adaptation fasting.

(3) Growth hormone and the glucocorticoids foster this adaptation because they, like the catecholamines, inhibit in some manner the use of glucose by the muscles.

7) As starvation is prolonged, less and less glucose is used, thereby reducing the amount of protein thatmust be catabolized to provide substrate for gluconeogenesis.

(1) As glucose use decreases, hepatic ketogenesis increases and the brain adapts to the use of ketones (primarily hydroxybutyrate) as a partial source of energy.
(2) Under conditions of continued carbohydrate shortage, ketones are oxidized by the muscle in preference not only to glucose but also to fatty acids. During starvation, the use of ketones by the muscles as the preferred source of energy spares protein, thereby prolonging life.
(3) The duration of starvation compatible with life depends to large degree on depot fat status.

Conclusions

The recent large increase in the prevalence of obesity has been mostly caused by our modern urban societies in which demand for physical activity is extremely reduced, and highly palatable and relatively cheap food is ubiquitously available. However, in this 'obesogenic' environment, there are still many people who are protected against obesity. As reviewed above, high levels of fat oxidation, metabolic rate, spontaneous physical activity and sympathetic activity are all protective factors against weight gain. It is, however, not clear how these factors are altering the balance between intake and expenditure of energy. For instance, subjects with low fat oxidation have increased carbohydrate oxidation to sustain the ATP demand, and therefore have decreased carbohydrate stores. A low carbohydrate reserve has been associated with increased weight gain, probably mediated through small but significant changes in energy intake. The mechanisms underlying the genetic variability in substrate oxidation are not known, but may explain why there is such a wide interindividual variability in weight gain in our modern 'westernized' lifestyle. Of course, factors such as cognition, emotion and reward all affect food intake behaviors and may explain why some individuals are resistant to large weight gains.

Additionally, differences in energy efficiency of growth and/or of weight maintenance are most likely to play a role in the susceptibly to weight gain in our present environment. Unlike measurements of food intake, we have reasonably accurate and precise methods to measure energy metabolism in humans. Whether the precision is sufficient to detect the necessary small chronic imbalances leading to obesity is debatable, especially with a lack of means to measure food intake. Uncovering the mechanisms underlying intersubject variability in energy metabolism (expenditure and fuel partitioning) will probably enhance our ability to identify people at risk for weight gain. As an example, recent investigations have provided evidence about differences in skeletal muscle efficiency to generate ATP as a function of training status or in response to weight perturbation. More research is needed to confirm these preliminary findings and to assess its impact on whole-body energy efficiency and body weight regulation. Perhaps, the evidence showing that low whole-body metabolic rate, low sympathetic activity and low spontaneous physical activity are predictors of weight gain will converge on new discoveries regarding the energy efficiency of the maintenance of tissues and organs. But, we absolutely need accurate and precise novel creative methods to measure energy intake from fat, carbohydrate and protein in free-living conditions.

Conversely, one must acknowledge that remarkable progress has been made in the past two decades regarding our understanding of both the complex disease called obesity and the regulation of body weight. Now, we need to translate this new knowledge into the prevention of obesity by establishing innovative public health policies and redesigning our built environment. Even if we do not have the reliable technology to identify those subjects at risk for obesity, one can expect new health policies to curb the present pandemic of obesity and its future cost to health care systems. However, we will need major technological break-throughs to identify the susceptibility of individuals to obesity even though they may live in a less 'obesogenic' environment.

Acknowledgements

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