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Advanced article

Energy Balance, Obesity and Type-2 Diabetes

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Energy balance is determined by caloric intake versus caloric expenditure. Complex control systems promote energy storage (primarily as adipose tissue fat) during periods of food surplus and mobilization of energy stores when food is scarce. These regulatory systems operate both locally within cells and between different body tissues and are mediated by circulating hormones and direct neural connection from the central nervous system to peripheral tissues. In modern society where lifestyles have shifted towards the excessive consumption of palatable ‘high energy’ foods and a sedentary life, these control mechanisms can be circumvented and in so doing lead to obesity and its pathological consequences. Prominent among these consequences are insulin resistance, i.e. the inability of cells to respond normally to insulin, and Type-2 diabetes. Approximately 30% of the inhabitants of the United States meet the criteria for obesity.

Key concepts

- Animals possess complex control systems with which to regulate energy storage and expenditure.
- The concept of energy balance.
- How is blood glucose level regulated?
- How do changes in blood glucose level alter the secretion of hormones that regulate energy metabolism?
- What are the major physiological fuels that provide energy for different cell types and how do changes in hormone level affect fuel production and utilization?
- Nature of interplay between tissues/organs through the production and utilization of circulating physiological fuels.
- What is insulin resistance and what are its consequences?
- What constitutes the obese state and how does obesity lead to insulin resistance and Type-2 diabetes?
- how adipocytes develop from stem cells and the consequences of adipocyte hyperplasia.
- How does persistent obesity lead to failure of the insulin-secreting pancreatic β-cell and the diabetic state?

Introduction

All animals possess control systems to regulate energy storage and expenditure. These systems promote energy storage during periods of food surplus and mobilization when food is scarce (Cahill, 2006; Wolfgang and Lane, 2006, 2008; Wahren and Ekberg, 2007). They function locally within cells and globally via circulating hormones and neural projections from the central nervous system to peripheral tissues including the liver, muscle and adipose tissue. When food is abundant, nutrient metabolites are stored as glycogen and as fat. When food is scarce, these stores are mobilized to meet energy needs (Cahill, 2006). Although these control mechanisms evolved to survive ‘feast and famine’ situations,

in modern society lifestyle has shifted towards excessive consumption of high-energy foods and sedentary behaviour, which lead to obesity and its pathological consequences. Prominent among these outcomes are insulin resistance and Type-2 diabetes (Kahn, 1994; Muoio and Newgard, 2008). This article describes the systems that regulate energy balance and how, when overridden, result in obesity, insulin resistance and Type-2 diabetes.

Energy Content of Food Nutrients and Tissue Reserves

The major food nutrients – carbohydrate (CHO), protein and fat – differ widely in their caloric density and therefore, in their physiological fuel value (PFV). The PFVs of both CHO and protein are equivalent, ~4kcalg^{-1}, whereas that of fat is ~9kcalg^{-1} (**Table 1**). Thus, fat has a PFV more than twofold greater than that of CHO or protein. Moreover, since CHO and protein are hydrated in tissues, whereas fat is not, the mass of fat an animal must carry per calorie is far less than that for CHO or protein. It is not surprising, therefore, that during the course of animal evolution fat was 'selected' as the energy storage material of choice.

Table 1 Physiological fuel value (PFV) of food nutrients

CHO	4kcal/gram
Protein	4kcal/gram
Fat	9kcal/gram

The magnitude of the energy reserves of a 'typical' lean (154lb) versus an obese (400lb) human subject are compared in **Table 2**. Given a daily caloric expenditure of ~1800kCal for these individuals, both of which possess virtually the same level of nonadipose tissue mass, it can be calculated that the survival time of a lean versus obese individual in the starving state would be ~80 and ~180 days, respectively. These estimated differences in survival time

during starvation agree closely with those in clinical studies of George Cahill and colleagues in 1970 (Cahill, 2006, 1970). Although excessive fat accumulation may increase survival time during starvation, adiposity has an important downside. The accumulation of excessive body fat, particularly abdominal fat, is often a prelude to Type-2 diabetes. Numerous animal and human studies have shown that the obese state leads to insulin resistance, i.e. the inability of tissues to respond to insulin (Mauvais-Jarvis and Kahn, 2000). Therefore, despite adequate, often supra-normal levels of plasma insulin, insulin-activated glucose uptake and the suppression of hepatic glucose production by insulin are blunted. This cascade of events frequently leads to hyperglycaemia and the diabetic state.

Table 2 Tissue reserve fuels

	Normal[a]		Obese[b]	
Fuel/tissue	kg	kcal	kg	kcal
Fat	15	135 000	80	720 000
Protein	6	24 000	8	32 000
CHO (glycogen)				
Muscle	0.15	600	0.16	640
Liver	0.07	300	0.07	300
Circulating fuel	0.02	100	0.02	100
Total		160 000		753 000
Survival Time at 1800 kcal/day	~ 90 days		~ 420 days	

[a]70 kg (154 lb) human.
[b]82 kg (400 lb) obese human.

Energy Balance

Whether the net energy balance of an adult animal is positive or negative will depend upon energy intake versus energy expenditure as illustrated below (in growing animals another component must be added to this equation to account the energy requirements for growth).

$$\text{Energy balance} = \text{energy intake} - \text{energy expenditure}$$
$$(\text{BMR} + \text{activity increment})\ (\text{adult})$$

The energy expenditure component consists of the basal metabolic rate (BMR) and activity increment components. The BMR for an adult (nongrowing) animal is constant and

proportional to lean body mass, i.e. the active metabolizing tissue. The activity increment component, however, is variable and depends on the level of physical (muscular) activity performed by the animal. When a growing animal reaches maturity, lean body mass tissue plateaus and is maintained at this level even during periods of excessive caloric intake and fat accumulation.

When energy intake exceeds expenditure, excess nutrient-derived metabolites are initially diverted into storage as CHO, i.e. glycogen, and then into fat (**Figure 1a**). The only form in which dietary CHO can be stored is in the form of glycogen, a starch-like polymer of glucose. Although quantitatively it contributes little to body's total energy reserve, liver glycogen is rapidly accessible and an immediate source of blood glucose. The liver is the only organ in which glycogen can be stored at substantial levels (up to ~5% of liver weight) and can be mobilized into the blood as glucose (although the kidney also contains the necessary enzymes, the amount of glycogen is relatively small). Only the hepatocyte (liver cell) possesses the necessary enzymatic machinery to convert glycogen into blood glucose during food deprivation (**Figure 1b**). The caloric equivalent of the entire glycogen reserve of the liver is only ~300kCal in an adult human, far less than the 1800kCal required daily for body maintenance. Although most other cell types, e.g. skeletal muscle, contain much lower levels of glycogen (<0.1% of tissue mass) for local use, only the liver (and to a minor extent the kidney) can produce blood glucose.

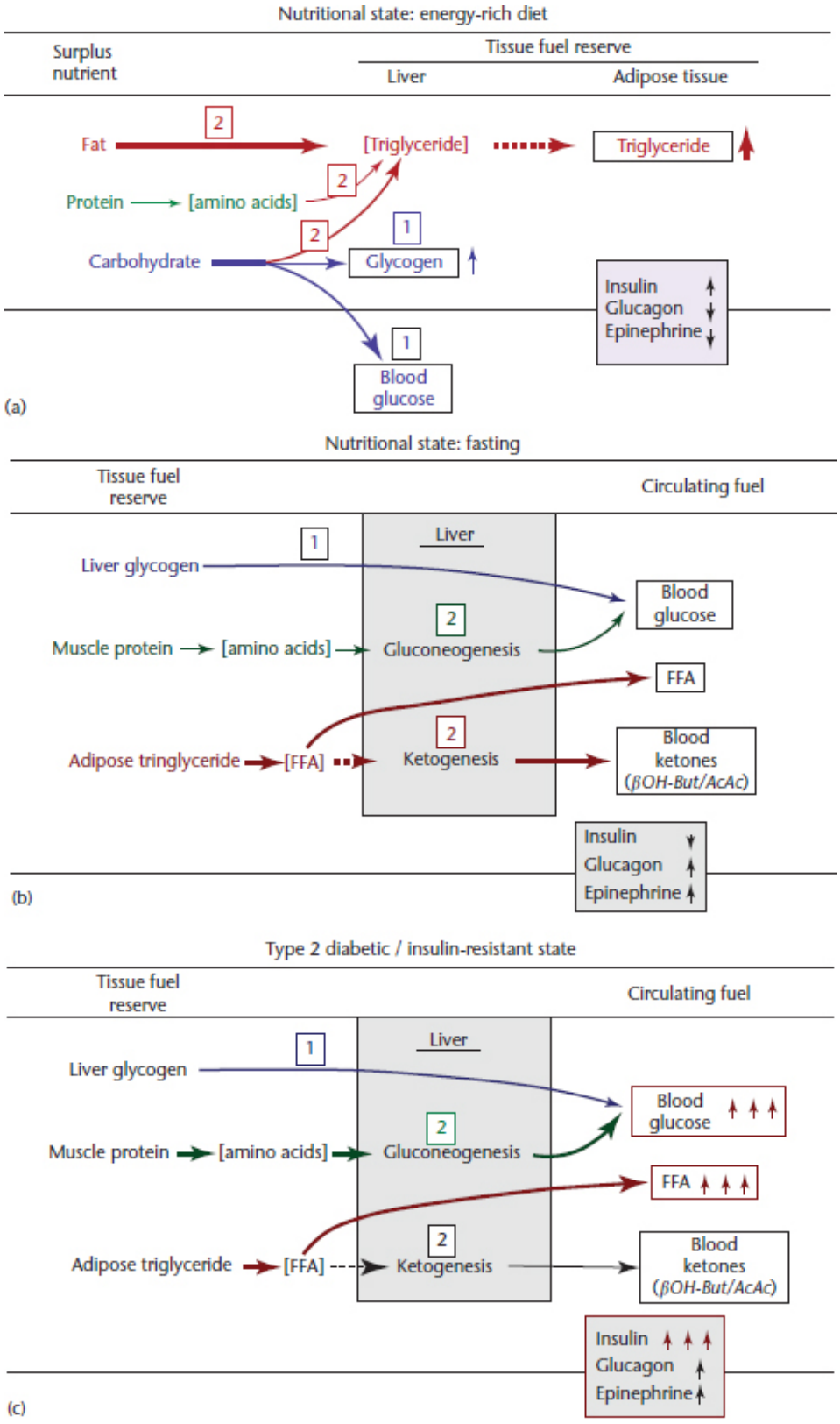


Figure 1 Effect of nutritional state (a and b) and Type-2 diabetes (c) on tissue fuel reserves and circulating physiological fuels. (a) When fed an energy-rich diet after fasting dietary CHO is first used to restore blood glucose level and replete liver glycogen reserves. Next excess dietary CHO and fat are diverted into triglyceride (fat) synthesis in the liver, which is transported to adipose tissue as very low-density lipoprotein to adipose tissue where fatty acids are released, resynthesized into triglyceride and stored. Under these circumstances the blood levels of insulin, glucagon and epinephrine change in the directions of the vertical arrows. (b) In the fasted state (food deprivation) liver glycogen is converted into glucose and is released into the blood stream. When this glycogen reserve is depleted, protein from tissues (primarily skeletal muscle) is mobilized as amino acids. The amino acids are transported in the blood to the liver where they are converted via gluconeogenesis into glucose, which is released into the blood stream. Concurrently, adipose tissue triglyceride is mobilized as fatty acids and released into the blood stream. The fatty acids are both used directly as fuels for many tissues (liver and muscle, but not brain) and also are taken up by the liver and converted into ketones (β-hydoxybutyrate and acetoacetate). The ketones are released into the blood stream and utilized as an alternative fuel for the brain (CNS neurons) and muscle. (c) In the pathological Type-2 diabetic state most cells become insulin resistant, which leads to hyperglycaemia and hyperlipidaemia (elevated blood fatty acid level) compounded by hyperinsulinaemia (see text for an explanation). The boxed numbers Cahill, 2006a and Wolfgang and Lane, 2006 indicate the sequence in which the transition occurs.

Once the hepatic glycogen reserve has been filled surplus nutrient-derived metabolites, whether from protein, CHO or fat, are diverted into fatty acid biosynthesis and deposited in

adipose tissue as fat. Although fat reserves increase in obesity and can become massive, body protein and bone mass in obese individuals do not increase significantly. Thus, adipose tissue fat constitutes the major energy reserve of higher animals.

When energy balance becomes negative, i.e. when energy expenditure exceeds intake, glycogen reserves are rapidly depleted and tissue protein (primarily muscle protein) is mobilized and the constituent amino acids become the major precursors for hepatic glucose production (gluconeogenesis) (**Figure 1b**). Concurrently, the fat reserves of adipose tissue are mobilized and released into the blood stream as free fatty acids and provide a physiological fuel that can be metabolize by most tissues. A substantial fraction of the fatty acids released are converted into ketones in the liver to provide an alternate fuel (to glucose) for the central nervous system (CNS). During prolonged food deprivation/starvation ketones become the predominant fuel for the brain/CNS replacing glucose as the major fuel.

Blood Glucose and the Control of Energy Balance

Energy balance in higher animals is regulated through complex interconnected endocrine and neuroendocrine systems. The primary physiological indicator of global energy status is blood glucose, the level of which is maintained within relatively narrow limits. Blood glucose levels in healthy individuals in the postabsorptive state range between 4 and 5mM (80–100mgdl^{-1}) normally decreasing to ~3mM during food deprivation and increasing to 6–7mM (120–140mgdl^{-1}) following a CHO-containing meal. In a diabetic individual these levels are much higher, often as high as 200–400mg/dl, and persist much longer after a meal. Deviations from the ‘normal’ blood glucose level are

controlled by the actions of hormones, largely those secreted by the pancreas, notably insulin and glucagon. Other hormone-secreting tissues come into play including the adrenal gland, which secretes both epinephrine and glucocorticoid, and neuroendocrine cells of the hypothalamus, which secrete neuropeptides, notably neuropeptide Y (NPY), Agouti-related protein (AgRP) and alpha melanocortin stimulating hormone (α-MSH), that elicit their effects in and through the CNS (Wolfgang *et al.*, 2007).

Glucose Homoeostasis

Although glucose can be metabolized by all mammalian cell types, certain cell types, notably erythrocytes and neurons of the CNS, have an absolute requirement for glucose. Therefore, blood glucose is supplied continuously and its concentration maintained within relatively narrow limits (3–5mM in humans). Not surprisingly, blood glucose serves as an indicator of global energy status to which the secretion of key regulatory hormones respond. Changes in blood glucose level are sensed by specific cell types within the Islets of Langerhans of the endocrine pancreas, which respond by secreting insulin and glucagon (Muoio and Newgard, 2008). Thus, insulin and glucagon secreted by islet β- and α-cells, respectively, exert counter-regulatory effects on the energy metabolism of peripheral tissues. The β-cell is exquisitely sensitive to changes in blood glucose concentration, in part, because of its unique glucose transport/kinase system (**Figure 2**). The glucose transporter, GLUT2, and glucokinase, which are expressed only by β-cells and hepatocytes, exhibit K_A/K_M values (concentration at which activation/catalysis is half-maximal) poised at the midpoint of the physiological dynamic range of blood glucose (~5mM). This ensures that changes in blood glucose level produce corresponding changes in the uptake and phosphorylation that alter the rate of glucose metabolism. Thus, the

downstream effects of glucose metabolism in β-cells produce a signal that activates insulin secretion (**Figure 2**). The catabolism of glucose gives rise to an increase in adenosine triphosphate (ATP) level, which in turn closes the plasma membrane ATP-dependent potassium (K^+) channel causing membrane depolarization. Depolarization of the membrane causes opening of the K^+-dependent Ca^{2+} channel and an influx of Ca^{2+}. Elevated intracellular calcium then triggers fusion of insulin-containing secretory vesicles with the plasma membrane resulting in insulin release and an increase in blood insulin level. This rise in blood insulin triggers a variety of metabolic changes in insulin-responsive cells/tissues that promote energy storage.

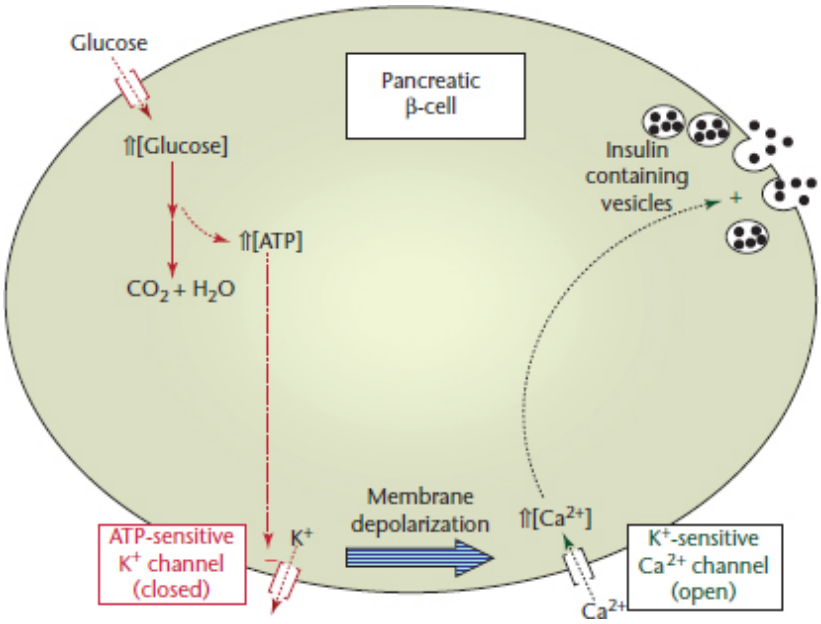


Figure 2 Glucose-activated insulin secretion by the pancreatic β-cell. When the blood glucose level rises the sequence of events lead to increased insulin (solid circles) secretion (see text for details). K^+ and Ca^{2+} refer to the potassium and calcium ions, respectively.

Movement of Physiological Fuels Between Tissues

Whole body energy metabolism involves the flux of blood-borne physiological fuels (glucose, FFA and ketones) between remotely located tissues (Wahren and Ekberg, 2007). To understand how the movement of these circulating fuels is directed within and between tissues, it is instructive to compare their origins and fates in different physiological states, in particular the fed/energy-rich, fasted and diabetic states (**Figure 1a**, **b** and **c**). The liver occupies a central position in orchestrating this metabolite flow and serves as the switching point for the uptake, modification and distribution of physiological fuel molecules for transport in the blood to their ultimate tissue site of metabolism. The movement of physiological fuels between tissues is under direct hormonal control. Insulin promotes the movement of these fuels into energy storage pathways, whereas glucagon initiates the mobilization and catabolism of the stored energy reserves (liver glycogen, adipose tissue fat and muscle protein). Insulin activates glucose uptake and glycogen and fat synthesis and suppresses energy mobilization (**Figure 1a** and **1b**, **Figure 3** and **Figure 4**). Glucagon, however, counterbalances the effects of insulin by causing the mobilization of stored glycogen and fat and inhibiting energy storage pathways.

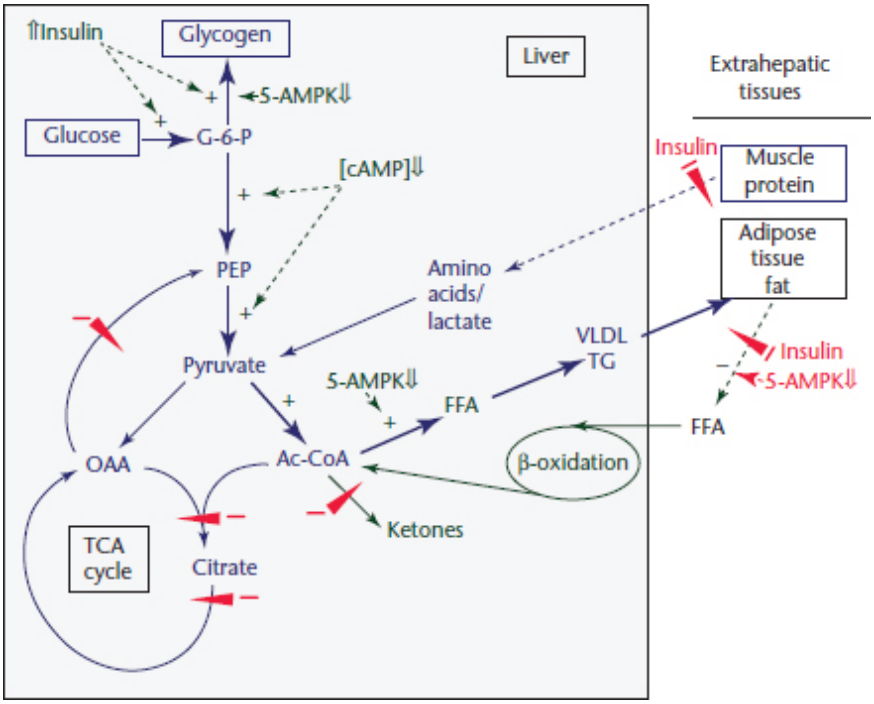


Figure 3 Regulation of hepatic energy metabolism in the 'fed' state. Under the physiological conditions described in **Figure 1a** the pathways illustrated by the broad arrows dominate over those represented by thin arrows. The control features shown by + and − illustrate the basis for the changes in flux through the pathways. Changes in the regulatory factors that cause these changes are described in the text. TCA, tricarboxylic cycle; Ac-CoA, acetyl-CoA; VLDL, very low-density lipoprotein; PEP, phosphoenolpyruvate; cAMP, cyclicAMP.

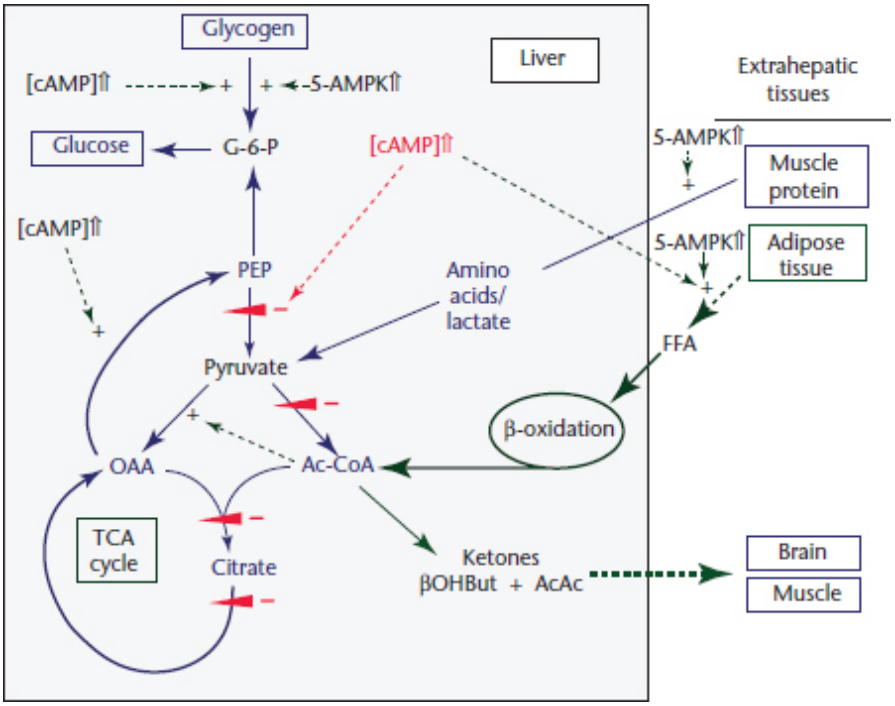


Figure 4 Regulation of hepatic energy metabolism in the 'food deprived' (fated) state. Under the physiological conditions described in **Figure 1b** the pathways illustrated by the broad arrows dominate over those represented by thin arrows. The control features shown by + and − illustrate the basis for the changes in flux through the pathways. Changes in the regulatory factors that cause these changes are described in the text. Abbreviations are as in the legend to **Figure 3** and 5′3-AMPK refers to 5′-AMP kinase.

Control of Energy Balance

Energy balance, which ultimately governs the movement of physiological fuels between tissues, is regulated at several levels − locally within cells and tissues, via the circulation by hormones and by direct neural connection from the central nervous system to peripheral tissues.

Tissue/cellular control

ATP is the primary energy currency used by cells to drive energy-requiring processes. Two kinases found in most cell

types, the 5′-adenine monophosphate (AMP) kinase (AMPK) (Kahn *et al.*, 2005) and the cyclic AMP (cAMP)-dependent kinase (A kinase) are utilized to transmit signals in response to changes in 'ATP status'. These kinases act as intracellular intermediaries of systems that monitor both cellular and whole body energy status. AMPK responds to fluctuations in the cellular level of 5′-AMP, an activator of AMPK, which inversely reflects ATP level via a reaction catalysed by the ubiquitous enzyme, adenylate kinase (AK) as illustrated below:

$$\mathrm{ATP} + 5'\text{-AMP} \underset{\mathrm{AK}}{\rightleftarrows} \mathrm{ADP} + \mathrm{ADP}$$

Since total adenine nucleotide concentration is constant and the K_{eq} for the reaction is ~1.0, it follows that as ATP level falls, the level of 5′-AMP rises. Thus, as the 'energy charge' of a cell decreases due to ATP depletion, AMPK is activated. Many key regulatory enzymes of energy metabolism (e.g. acetyl-coenzyme A (CoA) carboxylase, glycogen synthase and hormones-sensitive lipase) are substrate targets of AMPK that undergo phosphorylation provoking either inhibition or activation depending on whether the enzyme is involved in energy storage or mobilization (**Figure 3** and **Figure 4**). In general, pivotal enzymes that control biosynthetic pathways are inhibited by AMPK as the ATP level falls, while enzymes that control mobilization of energy reserves to replenish ATP are activated. As described below this mechanism also functions in the hypothalamic sensing system of the CNS that regulates appetite and peripheral energy metabolism.

The intracellular cAMP second-messenger system responds to external hormonal stimuli. Key peptide hormones that regulate global energy metabolism including glucagon, epinephrine and insulin, act by binding to their respective cell-surface receptors on responsive cells and transmitting a signal across the plasma membrane to the cell's interior. Binding of the hormone to its specific receptor induces a

conformational signal that activates (or inhibits) adenyl cyclase, which catalyses the formation of cAMP. Although all three of these hormones alter intracellular cAMP levels, they do so by different mechanisms. Glucagon and epinephrine increase, whereas insulin decreases, the level of cAMP. cAMP binds to and activates the cAMP-dependent protein kinase (A-kinase) which, like AMPK, targets and activates enzymes (e.g. glycogen phosphorylase and hormone-sensitive lipase) that mobilize physiological fuels, e.g. the conversion of liver glycogen → glucose and adipose tissue triglyceride (fat) (TG) → FFA. Once hepatic glycogen reserves have been depleted, A-kinase activates hepatic gluconeogenesis to produce glucose via an alternative route, largely from non-CHO sources such as protein-derived amino acids. In contrast, insulin exerts inverse effects by blocking energy mobilization and gluconeogenesis. The effects of perturbing nutritional state and of Type-2 diabetes on the levels of circulating insulin, glucagons and epinephrine are summarized in **Figure 1a**, **b** and **c**, and the effects of these perturbations on hepatic energy metabolism are illustrated in **Figure 3** and **Figure 4**.

Hormonal control

Endocrine cells of the pancreas and adrenal gland respond to changes in blood glucose, the primary indicator of global energy status (Wahren and Ekberg, 2007). Four hormones, insulin, glucagon, epinephrine and glucocorticoid play primary roles in regulating energy metabolism. As illustrated in **Figure 1a** and **b** changes in physiological state cause changes in blood glucose level, which provoke changes in the circulating levels of these hormones. Thus, when an animal is deprived of food and blood glucose level falls, glucose sensors within β- and α-cells of the pancreas (see above) and endocrine cells of the adrenal medulla and cortex alter secretion of epinephrine and glucocorticoid. All of these hormones have effects on the liver and peripheral tissues as

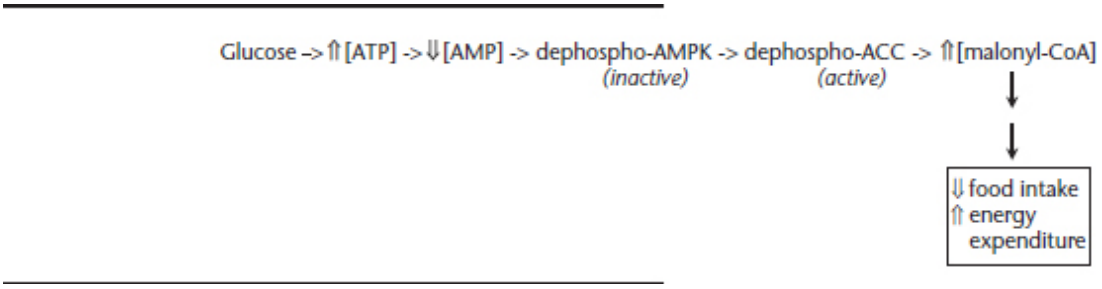
illustrated in **Figure 3** and **Figure 4**. Insulin suppresses energy storing enzymes while glucagon (secreted by α-cells of the pancreas) and epinephrine (secreted by the adrenal medulla) and glucocorticoid (secreted by the adrenal cortex) activate the energy-mobilizing enzymes. Hence, in the state of food deprivation a decrease of blood insulin causes an immediate cessation of energy-storage pathways. The concomitant rise in blood glucagon, epinephrine and glucocorticoid leads to the activation of energy-mobilizing pathways. Among these hormones, glucocorticoid is unique in that it interacts with an intracellular nuclear hormone receptor, which translocates to the nucleus where it activates transcription of genes involved in the mobilization of energy reserves and hepatic gluconogenesis and has the opposing effect on genes of energy storage.

Central nervous system/hypothalamic control

The hypothalamus, a small region of the ventral midbrain, contains neuronal nuclei that receive and process hormonal and other afferent signals that reflect the energy status of the animal (Schwartz *et al.*, 2000; Schwartz and Porte, 2005). These signals are integrated and alter the expression and secretion of orexigenic or anorexigenic neuropeptides that alter food intake and energy expenditure. Most notable among these neuropeptides are the orexigens, NPY and AgRP, and the anorexigens, α-MSH and cocaine-amphetamine-regulated transcript (CART). These neuropeptides are expressed by neurons in the medial and ventral regions of the hypothalamus, most notably the arcuate nucleus (Arc). Second-order neurons from these sites project to higher brain centres, where this information is processed and behavioural responses are formulated. Among the hormonal inputs to the hypothalamus are insulin, leptin and the gut-derived peptides, ghrelin and peptide YY (PYY). Insulin, leptin and PYY, which are produced by pancreatic β-cells, adipocytes and the small intestine, respectively, are

anorexigenic, whereas ghrelin, which is produced by the stomach, is orexigenic.

Glucose, an indicator of global energy status and a primary physiological fuel for the brain, is another important input to the hypothalamus (Wolfgang *et al.*, 2007). Glucose rapidly activates hypothalamic neuronal firing and inhibits food intake. Although the molecular mechanism by which hypothalamic glucose suppresses food intake is still under investigation, it has been established that AMPK and acetyl-CoA carboxylase (ACC) activity function in transmitting its signal. Thus, increased glucose flux into the hypothalamus/CNS leads to the dephosphorylation and thereby, inactivation of AMPK, which in turn activates ACC increasing the level of malonyl-CoA, its reaction product. An increase in hypothalamic malonyl-CoA suppresses food intake and increases energy expenditure (Wolfgang *et al.*, 2007). This sequence of events is depicted below:



Mechanism of Action of Insulin and its Metabolic Effects

All actions of insulin are initiated by its interaction with specific receptors on the cell surface of many types of cell types including muscle cells, adipocytes, hepatocytes and neurons of the CNS (White and Kahn, 1994). Upon binding of insulin to its receptors, which spans the plasma membrane, an allosteric signal is transmitted across the membrane to the cell's interior. The signal is amplified and initiates a variety of intracellular responses that promote energy storage and inhibit mobilization of energy reserves. Thus,

insulin activates glucose uptake by muscle cells and adipocytes, hepatic glycogen and fat synthesis (**Figure 3**). Concurrently, insulin suppresses hepatic gluconeogenesis and glycogenolysis, as well as adipocyte lipolysis (**Figure 3**). However, when blood glucose levels rise following refeeding a high CHO diet, this pattern is reversed.

The Diabetic State

Diabetes mellitus is characterized either by fasting hyperglycaemia or a persisting high level of glucose that exceeds defined limits during a glucose tolerance test (Muoio and Newgard, 2008). Diabetes is a consequence either of the absence of insulin or the resistance to insulin. Type-1 diabetes is caused by destruction of the insulin-producing pancreatic β-cell, most often in children due to autoimmunity directed against specific cell-surface proteins of the insulin-producing pancreatic β-cell. Type-2 diabetes is the result of insulin resistance, i.e. failure of peripheral cells to respond to insulin, and most frequently a consequence of obesity. Of the estimated ~20 million diagnosed and undiagnosed cases in the USA, about 90% are Type-2 diabetics and 10% Type-1 diabetics.

The Adipocyte and Obesity

The mature adipocyte contains a single large fat droplet, which occupies most of the cell's volume, and is surrounded by a thin rim of cytoplasm that lies between the droplet and the plasma membrane. The primary function of the adipocyte is to store energy in the form of TG during periods of energy surplus and to mobilize this stored lipid as fatty acid when energy is required (Otto and Lane, 2005). Fatty acids are released into the blood stream and supply peripheral tissues, especially skeletal muscle and the liver, as an energy-rich fuel.

Additionally, adipocytes function as an endocrine tissue that plays a major role in the control of metabolism through secretion of hormones and cytokines. Certain of these hormones act locally as paracrine factors and others such as leptin and adiponectin, which have long-range effects and act on feeding centres in the brain. Leptin is anorexigenic and is produced in proportion to adipose tissue mass and acts to limit energy storage when adipose tissue reserves have been filled. It does so by interacting with specific receptors in the hypothalamus to reduce food intake. In the obese state, however, resistance to leptin sets in limiting its effectiveness.

Adipose tissue contains the largest energy reserve in the body in the form of TG (**Table 2**). To understand the role of adipocytes – the major cell type in adipose tissue – it is instructive to understand the origin of this lineage. The adipose lineage develops from pluripotent stem cells of mesodermal (or mesenchymal) origin. This stem cell population has the capacity to undergo commitment into several lineages including the adipose, muscle, bone or cartilage lineages (Otto and Lane, 2005). Increasing evidence indicates that commitment to the adipose lineage is triggered by morphogenetic factors and other cytokines that activate expression of genes/proteins, which direct entry of the lineage-specific development programme.

These pluripotent stem cells reside in the vascular stroma of adipose tissue, as well as in the bone marrow, and when appropriately triggered undergo a multi-step process of commitment in which the progenitor cells become restricted to the preadipocyte lineage. Recruitment of stem cells to the adipocyte lineage gives rise to large numbers of new cell type, i.e. preadipocytes. Preadipocytes themselves undergo multiple rounds of mitosis then differentiate into adipocytes, which express genes that characterize the adipocyte phenotype. Cytokines, notably bone morphogenetic protein-4 (BMP-4) that induce commitment of stem cells to the

adipocyte lineage, are secreted by the surrounding vascular stromal cells of adipocyte tissue (Tang *et al.*, 2004; Otto and Lane, 2005; Bowers and Lane, 2007). The characterization of these secretory proteins has provided insight into the pathway and mechanisms by which pluripotent progenitors undergo commitment to the adipose lineage.

It has been established that the increase in adipose tissue mass in obesity is the result of both an increase in the number (hyperplasia) and size (hypertrophy) of fat-laden adipocytes (Otto and Lane, 2005). Although the hypertrophy of adipocytes is rapidly reduced by food deprivation, i.e. fasting, hyperplasia is resistant to change. Therefore, once an individual has experienced the obese state, the 'new' adipocytes acquired persist and are quickly refilled if energy intake exceeds expenditure.

Measurement of Adiposity

Although imperfect the most generally used measure of adiposity in the United States is *body mass index* (BMI). BMI is defined as

$$\text{BMI} = \text{kg/m}^2$$

(body mass in kilograms/height in meters^2)

Individuals with a BMI of more than 25 are considered overweight and those with a BMI of >30 are considered to be obese. With heavily muscular individuals this measure greatly overestimates adiposity. Nevertheless, this measurement is easily made and therefore, is widely used.

Obesity, Insulin Resistance and β-cell Failure

Insulin resistance is a physiological/pathological state associated with obesity in which normally insulin-responsive cells fail to respond appropriately to insulin (**Figure 1c**). Thus, skeletal muscle and adipocytes lose their ability to take up glucose in response to insulin. Likewise, glucose