Splanchnic Regulation of Glucose Production

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Annu. Rev. Nutr. 2007. 27:329–45

First published online as a Review in Advance on April 27, 2007

The *Annual Review of Nutrition* is online at http://nutr.annualreviews.org

This article's doi: 10.1146/annurev.nutr.27.061406.093806

0199-9885/07/0821-0329$20.00

Key Words

glycogenolysis, gluconeogenesis, exercise, starvation, diabetes

Abstract

The liver plays a key role for the maintenance of blood glucose homeostasis under widely changing physiological conditions. In the overnight fasted state, breakdown of hepatic glycogen and synthesis of glucose from lactate, amino acids, glycerol, and pyruvate contribute about equally to hepatic glucose production. Postprandial glucose uptake by the liver is determined by the size of the glucose load reaching the liver, the rise in insulin concentration, and the route of glucose delivery. Hepatic glycogen stores are depleted within 36 to 48 hours of fasting, but gluconeogenesis continues to provide glucose for tissues with an obligatory glucose requirement. Glucose output from the liver increases during exercise; during short-term intensive exertion, hepatic glycogenolysis is the primary source of extra glucose for skeletal muscle, and during prolonged exercise, hepatic gluconeogenesis becomes gradually more important in keeping with falling insulin and rising glucagon levels. Type 1 diabetes is accompanied by diminished hepatic glycogen stores, augmented gluconeogenesis, and increased basal hepatic glucose production in proportion to the severity of the diabetic state. The hyperglycemia of type 2 diabetes is in part caused by an overproduction of glucose from the liver that is secondary to accelerated gluconeogenesis.

Contents

INTRODUCTION 330
BASAL SPLANCHNIC GLUCOSE PRODUCTION 330
Glycogenolysis 331
Gluconeogenesis 331
Regulatory Aspects 332
Extrahepatic Splanchnic Tissues ... 332
SPLANCHNIC GLUCOSE DISPOSAL 333
Hormonal Regulation of Hepatic Glucose Uptake 333
Route of Glucose Delivery 334
Hepatic Glucose Uptake in the Postexercise Period 334
SPLANCHNIC GLUCOSE OUTPUT DURING FASTING 335
Fasting for 12 to 60 Hours 335
Prolonged (Five to Six Weeks) Fasting 336
GLUCOSE PRODUCTION DURING PHYSICAL EXERCISE 336
Regulatory Aspects 337
SPLANCHNIC GLUCOSE PRODUCTION IN DIABETES 338
Type 1 Diabetes 338
Type 2 Diabetes 338

INTRODUCTION

The liver plays a key role in the maintenance of blood glucose homeostasis. It releases glucose in the fasted state and it takes up and stores some of the glucose ingested in meals. In so doing, the liver ensures an even and predictable supply of glucose to the extrahepatic tissues, primarily the brain. The liver is able to release glucose to the circulation from its glycogen stores and it has the capacity to take up the 3-carbon fragments lactate, pyruvate, glycerol, and amino acids and convert these to glucose. Hence, hepatic gluconeogenesis and glycogenolysis are the two processes responsible for hepatic glucose production. A dynamic equilibrium between the two serves to maintain blood glucose levels within a narrow range under widely changing physiological conditions.

The central role of the liver in blood glucose regulation was first identified by the French physiologist Claude Bernard, who documented that the liver is capable of producing glucose even in the absence of intestinal absorption. He discovered that carbohydrates could be stored in the liver as a polysaccharide, which he named "glycogen." He could also demonstrate that the liver continues to release glucose even after depletion of its glycogen stores, thus demonstrating that hepatic glucose production is possible via pathways other than the breakdown of glycogen. The experimental work was presented during the years 1848–1860 (96), but it took many decades before the significance of Bernard's observations was recognized.

Claude Bernard's studies were based on direct blood sampling from the hepatic blood vessels in dogs. Current development of techniques involving isotopic tracer dilution methods and nuclear magnetic resonance spectroscopy (NMRS) have made it possible to assess hepatic glucose and glycogen metabolism in animals and noninvasively in humans in a variety of physiological situations and in specific disorders, thereby providing improved insight into the metabolic regulation. This review summarizes recent findings on the regulation of splanchnic glucose exchange in the overnight and prolonged fasted state, during physical exercise, and in diabetes.

NMRS: nuclear magnetic resonance spectroscopy

BASAL SPLANCHNIC GLUCOSE PRODUCTION

In the morning, after an overnight fast absorption of nutrients from the intestine is completed, plasma insulin and glucagon concentrations have returned to their basal levels and body fuel consumption is matched by the release of endogenous substrates from storage

depots. The major source of energy is free fatty acids (FFAs), but the body continues to consume glucose at rates of 8–10 g/hour. The brain and the tissues with an obligatory need for glucose account for more than half of this amount (16). This rate of glucose consumption cannot be supported by the small pool of circulating glucose (4–5 g). The liver adapts to this situation by switching from postprandial glucose uptake and storage to postabsorptive production of glucose. In the overnight fasted state, the liver is the dominating source of glucose production, even though there is also a small contribution from the kidneys (36). Basal glucose output from the splanchnic area in healthy subjects amounts to approximately 0.8 mmol/min or 10 μmoles · min^{-1} · kg^{-1} (36, 108).

Glycogenolysis

Hepatic glycogenolysis contributes substantially to the liver's glucose output after an overnight fast. Even though the energy content of the hepatic glycogen stores is small in comparison with the body's daily energy requirements, it is evident that liver glycogen is essential for blood glucose homeostasis in the postabsorptive state. Thus, direct determinations of liver glycogen concentrations in biopsy material (81) and ^{13}C-NMRS measurements of hepatic glycogen during the postabsorptive phase (12–24 hours) show that liver glycogen decreases linearly at rates corresponding to approximately 40% of the simultaneous whole body glucose turnover (97). During continued fasting, hepatic glycogenolysis decreases gradually, and the glycogen stores are almost completely exhausted after 48 hours (**Figure 1**) (81, 97).

Gluconeogenesis

The rapid depletion of hepatic glycogen during the postabsorptive and early fasting period underscores the importance of gluconeogenesis from nonglucose precursors for the maintenance of blood glucose homeostasis. Our understanding of the quantitative contribution by gluconeogenesis to total glucose production has until recently been limited because of methodological problems. Early estimates of hepatic gluconeogenesis were based on arterial-hepatic venous catheterization and balance measurements in healthy subjects. These indicated a relative contribution of gluconeogenesis to splanchnic glucose output in the postabsorptive state of maximally 35% (**Figure 2**) (42, 108, 109). It should be recognized, however, that such estimates do not take into account splanchnic glucose utilization, nor extrahepatic splanchnic exchange or intrahepatic precursor supply (10). The balance technique estimates seem low in comparison with determinations of gluconeogenesis based on the difference between ^{13}C-NMRS-measured rates of hepatic glycogen breakdown and glucose turnover rates estimated by tracer dilution methodology, which indicate a gluconeogenic contribution of 50% to 65% (91, 97). Isotope tracing techniques using ^{14}C-lactate or ^{14}C-acetate have also been employed, but these are limited by inadequate labeling of the intracellular precursor pool or significant extrahepatic metabolism of the tracer (67, 99). Mass isotopomer distribution analysis (MIDA) using ^{13}C-glycerol has been employed for estimation of enrichment of the glucose precursor pool (52), but it now appears that this method is limited by hepatic heterogeneity in the metabolism of glycerol (64).

The above limitations in the determination of gluconeogenesis are avoided by the deuterated water technique (65, 66). With this method, the relative contribution of gluconeogenesis to whole-body glucose production can be estimated from the ratio of ^{2}H enrichment at carbon 5 over that at carbon 2 of plasma glucose after the ingestion of $^{2}H_2O$. This approach is based on the observation that all glucose molecules exchange hydrogens between body water and those at carbon 5 of glucose during gluconeogenesis and additional hydrogens at carbon 2 during both

FFAs: free fatty acid

MIDA: mass isotopomer distribution analysis

gluconeogenesis and glycogenolysis. This technique indicates a contribution of gluconeogenesis, including any renal component, to glucose turnover ranging from 47% to 53% at 12–16 hours of fasting in healthy subjects (**Figure 1**) (17, 66). Support for the validity of the deuterated water technique is obtained from the finding that after more than 42 hours of fasting, when the hepatic glycogen stores are almost completely exhausted, gluconeogenesis as estimated by this method accounts for 93 ± 6% of glucose turnover (17). In view of these findings, it is now widely believed that glycogenolysis and gluconeogenesis each contribute approximately 50% of glucose turnover in healthy subjects in the postabsorptive state.

Regulatory Aspects

Insulin is a primary regulator of hepatic glucose production, even though basal glucagon levels are required to support glucose output in the overnight fasted state (111). Insulin acts directly on the liver by binding to hepatic insulin receptors and activating insulin-signaling pathways. Small changes in portal insulin concentrations effectively modulate hepatic glycogenolysis as evident from studies in dogs (103) and in healthy subjects (40). Hepatic glycogenolysis and gluconeogenesis show differential sensitivities to changes in insulin concentration: even small increases effectively inhibit glycogenolysis (**Figure 3**), whereas substantial increments in insulin levels are required for inhibition of gluconeogenesis (21, 40). It has, however, been observed in obese subjects that suppression of glucose production in response to insulin infusion can occur even when the estimated portal insulin concentration does not increase (92), which suggests that insulin may inhibit glucose production also by indirect mechanisms. This may occur by insulin-induced inhibition of adipose tissue lipolysis that reduces both FFA levels and glycerol availability for gluconeogenesis. Likewise, insulin inhibits muscle proteolysis, resulting in further reduction of gluconeogenic precursor supply. Insulin also exerts inhibitory effects on pancreatic α-cells, resulting in reduced glucagon levels (57). Finally, studies in mice suggest that insulin action in the brain may play a role in the regulation of hepatic glucose output (82). A schematic representation of insulin's direct and indirect influence on hepatic glucose output is presented in **Figure 4**. It is now widely accepted that both direct and indirect effects of insulin are involved in the regulation of hepatic glucose output (1, 20), but the relative contributions of the two mechanisms have been controversial. Recent studies examining the effects of portal venous, systemic venous, and carotid arterial insulin infusion provide compelling evidence that the direct effects of insulin are dominant in overnight-fasted dogs and that indirect effects of insulin via the brain are of minor importance (35).

Extrahepatic Splanchnic Tissues

Besides the liver, only the kidney is recognized as being capable of gluconeogenesis. Recently, however, gluconeogenic capacity has been proposed also for the small intestine of the rat (77, 78). Gluconeogenic enzyme activities are expressed by the intestinal mucosa of rats and mice (95). Tracer dilution studies indicate ongoing simultaneous glucose production and utilization by the small intestine during starvation and diabetes (77). Attempts to identify the precursor for intestinal gluconeogenesis have indicated that glutamine and glycerol carbon may be incorporated into glucose by the intestine (26). The results from experiments in small rodents are not unequivocal and have recently been challenged (73). Studies using stable isotopes have failed to demonstrate the presence of measurable intestinal gluconeogenesis in fasting piglets (15). Moreover, arterial-portal venous concentration differences for glucose and gluconeogenic precursors in humans do not indicate net intestinal glucose synthesis (10). Thus, the interesting concept of intestinal

gluconeogenesis does not appear tenable on the basis of available evidence.

SPLANCHNIC GLUCOSE DISPOSAL

The liver's localization and its vascular anatomy make it ideally suited to regulate the flux of nutrients to the systemic circulation. It is also the only organ capable of both producing and assimilating substantial net amounts of glucose. Several studies have now established that the liver takes up approximately one third of an oral glucose load; muscle adipose tissue and the noninsulin-dependent tissues together account for the other two thirds (43, 76). Following ingestion of glucose, insulin and glucose levels rise, hepatic glucose output is suppressed, and net splanchnic glucose uptake can proceed at high rates (25–30 $\mu moles \cdot min^{-1} \cdot kg^{-1}$) (14, 43). Direct determinations of hepatic glycogen concentrations following ingestion of a glucose load using ^{13}C-NMRS confirm a marked increase in glycogen synthesis; hepatic glycogen deposition at 5 h after a glucose load accounts for 23% to 26% of the ingested glucose (7, 8). Studies of glycogen metabolism during infusion of ^{13}C-glucose in healthy subjects have revealed that hepatic synthesis and degradation of glycogen occur simultaneously under conditions of net glycogen breakdown (71). The observations indicate that glycogen may regulate its own rate of breakdown and that hepatic glycogen turnover may be a factor in limiting the accumulation of liver glycogen. Hepatic glycogen accumulation during normal eating behavior has also been examined. Liver glycogen was found to gradually increase following ingestion of three consecutive mixed meals with 5 h intervals, indicating that hepatic glycogenolysis may be limited during the daytime, with glucose absorbed from meals accounting for the dominating part of whole-body glucose turnover while net hepatic glycogenolysis contributes to glucose production primarily during the night (55).

Varying results have been obtained in the estimation of the extent of suppression of hepatic glucose production following ingestion of an oral glucose load. Using tracer infusion and arterial-hepatic venous balance measurements in healthy subjects, suppression of hepatic glucose production has been estimated at 28% to 55% compared with basal levels (59, 75). The variability may partly be explained by the absence of steady state conditions after oral glucose ingestion, resulting in changes in glucose-specific activity. A new approach has been developed that is based on variable tracer infusion rates and results in relatively stable tracee/tracer ratios (105, 106). The findings using this technique indicate that 65% to 80% of the basal glucose production is suppressed at one hour after a mixed meal, which underscores the importance of this factor in the disposal of oral carbohydrates.

Hormonal Regulation of Hepatic Glucose Uptake

Glucose has the ability to modulate its own metabolism by the liver. Thus, there is a close relationship between the net balance of glucose across the liver and the ambient glucose concentration independent of any change in insulin concentration (101). When insulin and glucagon are at basal levels, hyperglycemia results in modest suppression of net release of glucose from the liver, and supraphysiological hyperglycemia (>12 mmol/L) is required to achieve a substantial rate of hepatic glucose uptake (29, 85, 104). This autoregulation by glucose is influenced by insulin, since the ability of the liver to respond to variations in glucose concentration is impaired in insulin-deficient states and ameliorated by insulin administration (27). Insulin stimulates glucose uptake by the liver, but physiological hyperinsulinemia by itself is relatively ineffective in promoting net hepatic glucose uptake. In healthy subjects, only modest rates of glucose uptake were evident in the presence of insulin levels greater than 500 pmol/L and euglycemia (29, 32). Similarly, pharmacological

concentrations of insulin (>12000 pmol/L) were required to achieve a substantial increase in net hepatic glucose uptake in the presence of euglycemia, as evident from studies in dogs (74). Glucagon concentrations tend to decrease following carbohydrate ingestion (76). Somatostatin-induced selective glucagon deficiency with simultaneous insulin replacement results in reduced basal hepatic glucose output but not in augmented hepatic glucose uptake after a glucose load (102). Likewise, lower-than-basal glucagon concentrations in dogs made hyperinsulinemic and hyperglycemic were not accompanied by increased hepatic glucose uptake compared with basal glucagon under the same conditions (53). Thus, there is no evidence to indicate that a decrease in glucagon concentrations is of importance for glucose uptake by the liver after oral glucose intake.

Route of Glucose Delivery

Oral ingestion of a carbohydrate load in comparison with systemic glucose infusion in healthy subjects results in substantially higher rates of hepatic glucose uptake (29). This increase is achieved by augmented splanchnic fractional extraction of glucose after oral compared with systemic glucose administration (44), a finding initially attributed to a gut-derived factor (31). Subsequent studies have demonstrated, however, that intraportal infusion of glucose in dogs elicits similar rates of hepatic glucose uptake, as observed after oral glucose administration (6, 56), rendering an incretin contribution unlikely. The enhancement of hepatic glucose uptake with portal infusion was found to be correlated to the arterial-portal venous concentration difference for glucose and has been referred to as the portal signal (2). In fact, the influence of this signal is such that if insulin concentrations and glucose load to the liver are maintained constant, portal as compared with systemic glucose administration results in a 2- to 2.5-fold greater hepatic glucose uptake (79, 85). Further studies have shown that the portal signal also affects nonhepatic tissues; it mediates suppression of glucose uptake by skeletal muscle (47) and stimulates insulin release from the pancreas (34), thereby further enhancing hepatic glycogen accumulation after an oral glucose load.

Much experimental work has been undertaken to elucidate the mechanism underlying the portal signal. Surgical denervation of the liver totally blocks the enhancement of hepatic glucose uptake following portal glucose delivery (3), indicating neural mediation of the portal signal. Glucose-sensitive neurons have been demonstrated in the portal vein, and their discharge rate is proportional to the portal vein glucose concentration (80), suggesting a role in mediating the portal glucose signal. Cooling of the vagus nerves, which interrupts the efferent parasympathetic firing, had no effect on hepatic glucose uptake in the presence of the portal signal (58), indicating that parasympathetic signaling is not involved in the transmission of the portal signal. Instead, recent evidence suggests that sympathetic efferents may be of importance in the regulation of hepatic glucose uptake by exerting a basal inhibitory influence that limits glucose uptake in response to systemic glucose administration (33). It may then be hypothesized that the portal signal leads to removal of a sympathetic inhibitory influence on the liver, which in turn allows hepatic glucose uptake to increase. Whether removal of sympathetic tone to the liver is accompanied by a stimulatory signal will require further evaluation.

Hepatic Glucose Uptake in the Postexercise Period

It is well known that muscle glucose uptake and glycogen synthesis are enhanced in the postexercise period. Important alterations in glucose metabolism occur also within the splanchnic area. Thus, the efficiency with which oral carbohydrate is made available to the systemic circulation is increased during the postexercise period as a consequence

of both accelerated intestinal absorption (88) and a shift in the partitioning of the absorbed glucose, resulting in a larger fraction escaping hepatic retention (51, 70). Nevertheless, net hepatic glucose uptake after exercise and oral ingestion of glucose is substantially increased (45). This phenomenon appears unrelated to any change in the portal signal, since its effectiveness in stimulating hepatic glucose uptake after portal glucose administration is similar in the basal and postexercise states (46). Exercise-induced changes in insulin and glucagon are not required for the postexercise enhancement of hepatic glucose uptake (87), and other, possibly intrinsic, hepatic mechanisms will have to be examined. However, irrespective of the exact mechanism involved, it is apparent that the above observations provide an additional physiological argument for advocating the benefits of physical exercise in individuals at risk of developing type 2 diabetes, particularly in view of the hepatic insulin resistance in this disorder (28, 89).

SPLANCHNIC GLUCOSE OUTPUT DURING FASTING

A series of well-coordinated hormonal and metabolic adjustments serve to ensure adequate supply of substrates to body tissues during periods of food deprivation. Blood glucose falls slightly when fasting extends beyond the first 12 hours after ingestion of a meal and reaches a new steady state level approximately 10% to 20% lower than before. This is accompanied by a reduction in insulin and rise in glucagon concentrations. Adipose tissue lipolysis is stimulated by the hormonal changes, resulting in increased availability and tissue utilization of FFA. As the period of fasting extends beyond 24–48 hours, there is augmented hepatic FFA uptake and acceleration of ketogenesis. The concentrations of betahydroxybutyrate and acetoacetate in plasma rise gradually and may in 2–3 weeks have risen as much as 100-fold above prefasting levels. The lipid-derived substrates FFA and ketoacids become the dominating fuels for most tissues, contributing substantially also to the supply of fuel for the brain. For a recent review of the metabolic adaptation to starvation, see (16).

Fasting for 12 to 60 Hours

A continued supply of glucose during fasting is essential for the function of specific tissues. The brain requires glucose during the early phase of fasting, but as food deprivation continues and ketoacid availability increases, there is a gradual shift toward utilization of ketoacids, particularly betahydroxybutyrate by the brain, with a correspondingly diminished but not abolished need for glucose (84). Bone marrow, renal medulla, red blood cells, and peripheral nerves are all tissues with an obligatory requirement for glucose unable to utilize FFA or ketoacids. As a consequence, a minimum rate of glucose production has to be maintained throughout the period of fasting. This is achieved by continued hepatic glucose production supported by a gradually increasing component of renal gluconeogenesis. The contribution from hepatic glycogenolysis, accounting for 50% in the overnight fasted state, decreases progressively during the first 12–40 hours of fasting and then ceases altogether (**Figure 1**) (81, 97). Gluconeogenesis, primarily derived from the liver, continues during 12–40 hours of fasting at approximately the same rate as in the overnight fasted state (17, 19, 66) and shows a modest increase at 60 hours (36). Since glycogenolysis decreases during progressive fasting, it follows that the relative contribution by gluconeogenesis to total glucose production increases gradually and accounts for $93 \pm 2\%$ after 60 hours of fasting (36). Several factors contribute to the sustained or even augmented rates of gluconeogenesis during fasting. The arterial concentration and splanchnic uptake of glycerol increase, secondary to augmented lipolysis (9). Uptake of glucogenic amino acids tends to rise due to increased fractional extraction, which overrides the effect of falling arterial concentrations (36, 37). Finally, a distinct component of renal gluconeogenesis is detectable after

60 hours of fasting, accounting for 20% to 25% of whole-body glucose turnover (11, 36).

max VO_2: maximal pulmonary oxygen uptake

Prolonged (Five to Six Weeks) Fasting

The liver and the kidneys show further metabolic adjustments when fasting continues beyond 60 hours. In the prolonged fasted state, hepatic glucose output derived from gluconeogenesis is further decreased, as indicated by reduced net splanchnic glucose output and diminished urinary urea excretion (84). The attenuation of hepatic gluconeogenesis is an important step in the sparing of body protein during prolonged starvation, which is essential for survival. It results from diminished presentation of amino acids, primarily alanine, to the liver, while splanchnic fractional extraction is unchanged (39). The elevated levels of ketoacids during fasting have been suggested as an important regulating factor in the reduction of muscle proteolysis during fasting (100). Administration of exogenous alanine results in a prompt hyperglycemic response, suggesting that provision of gluconeogenic precursor substrate is the rate-limiting step in the control of hepatic gluconeogenesis in prolonged starvation (38). The increased levels of ketoacids are accompanied by a need to balance their urinary loss of ammonium cation excretion. Renal ammoniagenesis, accounting for approximately 40% of total nitrogen excretion in prolonged fasting, is tightly coupled to renal gluconeogenesis, which explains why renal gluconeogenesis may account for as much as 45% of total glucose production in prolonged fasting (83).

GLUCOSE PRODUCTION DURING PHYSICAL EXERCISE

It has been more than 100 years since it was demonstrated that glucose uptake increases by contracting muscle (18). The magnitude of the exercise-induced rise in glucose utilization during, for example, leg exercise, indicates that the turnover of the blood glucose pool must increase substantially. Since the arterial glucose concentration is maintained or even increased during heavy exercise, one can conclude that the augmented peripheral glucose utilization must be accompanied by continuous and matching repletion of the blood glucose pool. Although the kidney has the capacity to synthesize glucose, direct measurements show that there is very little or no renal glucose output during exercise (108). The liver is the only other tissue capable of significant glucose production, and it can be concluded that augmented hepatic glucose output is the primary source of the increased glucose available to exercising muscle.

It is primarily the intensity and duration of the exercise that determine the magnitude of the rise in glucose output and the relative contributions from glycogenolysis and gluconeogenesis (**Figure 5**). During light bicycle or treadmill exercise of short duration (20–30 minutes), glucose output rises by 50% to 100%; during moderate to heavy exercise it may increase 2 to 5 fold (108), as determined by either arterial-hepatic venous balance technique (108) or isotope tracer methods (5). Low- to moderate-intensity exercise [~30% maximal pulmonary oxygen uptake (max VO_2)] lasting several hours is accompanied by an initial rise in glucose output by 50% to 100% to a level that is sustained for several hours and then gradually decreases (4). During more strenuous (>60% max VO_2) and long-lasting exercise, glucose utilization by working muscle may outstrip glucose production, resulting in gradual development of hypoglycemia (**Figure 6**) (107).

Hepatic glycogenolysis accelerates in direct proportion to the intensity of the exercise during work of short to intermediate duration (<60 minutes) as estimated both from NMRS measurements (90) and arterial-hepatic venous balance measurements (108). Particularly during strenuous exercise, augmented hepatic glycogenolysis is the dominating source of increased glucose production

(108). With prolonged exercise, the contribution from glycogenolysis decreases gradually, in keeping with diminished hepatic glycogen stores, and the contribution from gluconeogenesis become greater. The rate of hepatic gluconeogenesis during exercise has been estimated primarily on the basis of splanchnic uptake of glucose precursors. Measurements show that splanchnic precursor uptake increases by 50% to 100% during mild to moderate exercise, mostly because of augmented availability and uptake of lactate (108), but total splanchnic glucose output rises more, so that the fractional contribution by gluconeogenesis becomes smaller than in the basal state. During prolonged exercise, splanchnic precursor uptake increases severalfold as a result of augmented precursor availability and splanchnic fractional extraction, resulting primarily in increased lactate and glycerol uptake (4). In addition, there is evidence to suggest that intrahepatic mechanisms more efficiently channel glucose precursors to glucose during exercise (113). Thus, during prolonged exercise, gluconeogenesis may account for as much as 30% to 40% of total glucose output (4).

It should be remembered, however, that estimates of hepatic gluconeogenesis based on precursor uptake during exercise are based on several assumptions; extrahepatic splanchnic metabolism of glucose and precursors is considered negligible and intrahepatic conversion of the gluconeogenic precursors is assumed to be fully efficient. Other methods for estimation of hepatic gluconeogenesis during exercise have been employed. The results using MIDA- and NMRS-based estimates support the contention that hepatic gluconeogenesis increases with exercise (90, 107), but quantitative interpretation of the data is complicated by the methodological difficulties discussed above. In summary, it may be concluded that both hepatic glycogenolysis and gluconeogenesis contribute importantly to the body's remarkable ability to maintain blood glucose homeostasis over a wide range of exercise intensities and durations.

Regulatory Aspects

Several hormonal changes that accompany the onset of physical exercise serve to regulate splanchnic release of glucose. The plasma insulin concentration, which decreases with light exercise, decreases even more so during heavy work (108), thereby increasing the liver's sensitivity to the effects of glucagon (68). Glucagon levels are largely unchanged during mild to moderate exercise but rise in response to either strenuous or prolonged work (4, 41), particularly if a degree of hypoglycemia ensues. It should be recognized that the liver is exposed to more marked changes in glucagon concentration during exercise—because of the portal venous drainage of the pancreas—than is reflected by the systemic concentrations of the hormone. In addition, hepatic blood flow is known to decrease during exercise. Thus, if hepatic blood flow decreases by 50% during exercise (108), then a doubling of the glucagon concentration in the portal vein would be expected even if secretion rates did not change. Research in humans and dogs involving clamp studies, pharmacological blockage, and replacement infusions of insulin and glucagon have demonstrated that the exercise-induced reciprocal changes in the two glucoregulatory hormones account for a major proportion of the increase in hepatic glucose output by augmenting glycogenolysis and stimulating both glucose precursor extraction and their intrahepatic conversion to glucose (22, 111, 114).

Factors other than altered levels of insulin and glucagon have also been suggested to be of importance for the exercise-induced rise in glucose production (24). Plasma concentrations of adrenaline and noradrenalin markedly increase during exercise (60, 98). Yet, despite a close relationship between exercise-induced changes in glucose output and catecholamine levels, several studies using a variety of experimental techniques have failed to establish causality (23, 25, 54). Likewise, neither pharmacological blockade of the sympathetic innervation of the liver and the adrenals nor

surgical denervation of the liver, as in humans with a liver transplant, result in marked effects on the exercise-induced increment in glucose output (61, 62, 112). Thus, it appears that although glucagon and insulin are of primary importance for the accurate regulation of hepatic glucose production during exercise, other and yet undetermined factors may also contribute.

SPLANCHNIC GLUCOSE PRODUCTION IN DIABETES

Type 1 Diabetes

The metabolic alterations observed in type 1 diabetes primarily reflect the degree to which there is an absolute or relative deficiency of insulin. Mild insulin deficiency can be expected to result in diminished ability to replenish the stores of carbohydrates and other fuels. With major insulin deficiency, not only is postprandial carbohydrate accumulation hampered, but excessive mobilization of endogenous substrates also occurs, resulting in hyperglycemia, hyperaminoacidemia, and elevated FFA levels. In keeping with these considerations, net splanchnic glucose production in patients with type 1 diabetes, who were studied after an overnight fast and without having received their morning dose of insulin, was similar or slightly augmented compared with controls (109, 110). Splanchnic uptake of gluconeogenic precursors was increased as a consequence of augmented fractional extraction in the case of lactate and amino acids. Hepatic gluconeogenesis, estimated from splanchnic precursor uptake, was 60% greater in the patients compared with controls (109). Direct determinations of hepatic glycogen using ^{13}C-NMRS in mildly insulin-deficient type 1 patients have indicated reduced glycogen levels and diminished rates of glycogenolysis (8, 90). Both defects of glycogen metabolism improved substantially after restoration of near-normal levels of insulin and blood glucose (7). In agreement with these observations, gluconeogenesis determined by the deuterated water technique has been found to be in the normal range in well-controlled type 1 patients (13). Hepatic glucose uptake and glycogen repletion after carbohydrate ingestion is reduced in type 1 diabetes (8, 55), resulting in excessive entry of glucose into the systemic circulation, in part caused by insufficient suppression of hepatic glucose output (86). Again, intensive insulin therapy and achievement of good blood glucose control restored normal postprandial suppression of hepatic glucose production (86) and net hepatic glucose assimilation after glucose ingestion (7). These observations emphasize that optimal metabolic control in type 1 diabetes ensures adequate postprandial hepatic glycogen accumulation despite systemic, as distinct from portal, delivery of insulin.

Type 2 Diabetes

The abnormal glucose homeostasis in type 2 diabetes is a consequence of several metabolic alterations: defective insulin secretion, insulin resistance involving muscle, liver, and adipose tissue, and abnormal splanchnic glucose metabolism. Only the latter factor is discussed here. The potential role of augmented basal glucose production from the liver in the pathogenesis of hyperglycemia in type 2 diabetes has been much discussed, and measurements of glucose production have yielded varying results [for a review see (93)]. When the diversity of the patient population, the experimental conditions, and techniques of measurement are carefully considered, the combined evidence supports the view that there is a direct relationship between hepatic glucose production in type 2 diabetes patients and fasting blood glucose levels (30, 94). An excessive rate of glucose production may thus be an important factor contributing to the elevated fasting glucose levels in patients with poor metabolic control (30).

The augmented flux of glucose from the liver in type 2 diabetes can derive from accelerated glycogenolysis, gluconeogenesis, or

both. The hepatic glycogen store and rates of glycogenolysis have been estimated using ^{13}C-NMRS techniques and were found to be reduced in type 2 patients with relatively poor metabolic control (72) and similar to that of healthy subjects in type 2 patients with good metabolic control (49). Hepatic gluconeogenesis, on the other hand, is reported to be increased in proportion to the severity of the diabetic state and the reduction in hepatic glycogen stores, both in absolute and relative terms (12, 49, 72). In this context, it is noted that an important component of the therapeutic effect of peroxisome proliferator-activated receptor-γ activating agents, such as thiazolidinediones, on the fasting blood glucose level is exerted by reducing the gluconeogenic flux in type 2 diabetic subjects (48).

Elevated plasma insulin levels after an overnight fast together with varying degrees of hyperglycemia are characteristic features in subjects with type 2 diabetes. Since hyperinsulinemia together with elevated levels of glucose are potent inhibitors of hepatic glucose output in healthy subjects (**Figure 3**) (40, 103), it can be concluded that there is hepatic resistance to the action of both insulin and glucose in type 2 patients (28) and that this defect becomes more pronounced with increasing severity of the diabetic state (50). Consequently, ingestion of glucose or a mixed meal leads to excessive and prolonged hyperglycemia in type 2 diabetes, which in part can be attributed to diminished net hepatic glucose uptake and failure to adequately suppress glucose production (63, 105). Thus, a reduced efficiency of the splanchnic tissues to take up glucose after oral ingestion is an important contributing factor in the impaired glucose tolerance of type 2 diabetes.

Finally, although Claude Bernard was unable to identify the pathogenic mechanisms underlying the development of diabetes, primarily due to lack of knowledge of the existence of insulin, much of his original work applies to normal physiology and to the forms of diabetes that we now distinguish as type 1 and type 2 (69). Bernard's fundamental contributions in the middle of the nineteenth century proved a rational basis for subsequent discoveries to build on.

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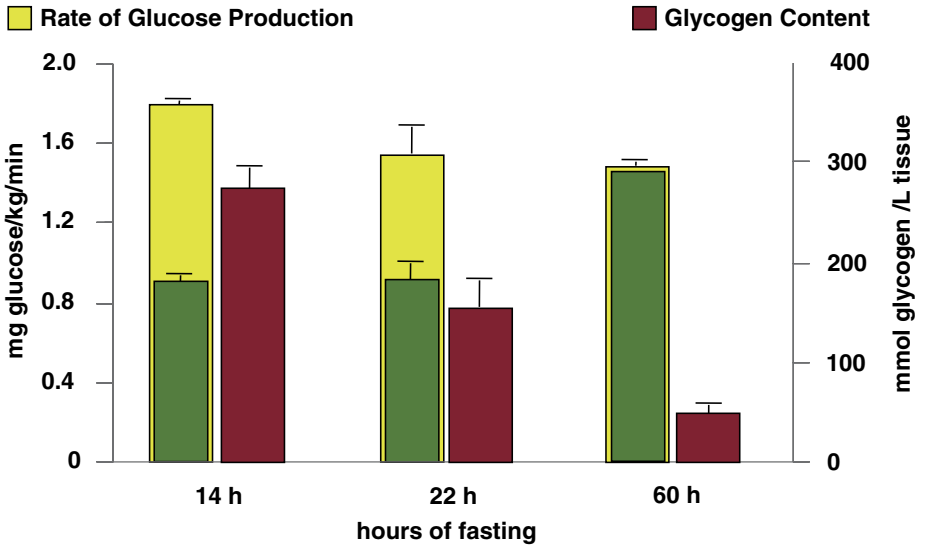

Figure 1

Rates of whole-body glucose production (*yellow*) and gluconeogenesis (*green*) as well as hepatic glycogen content (*red*) after 14, 22, and 60 hours of fasting. Adapted from (17, 66, 97).

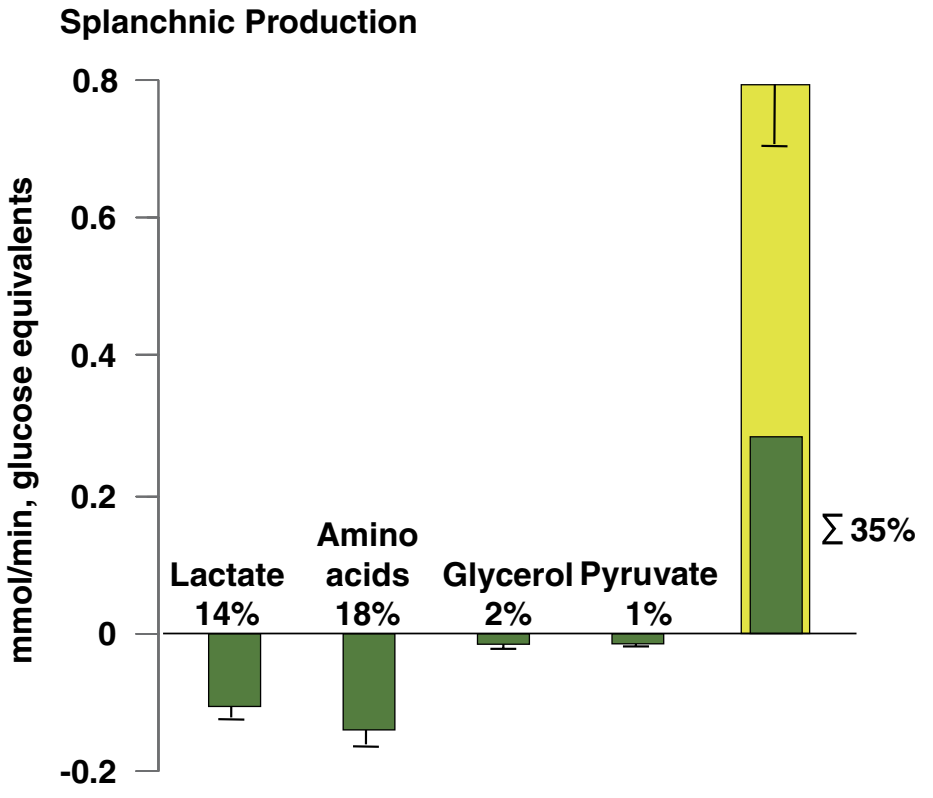

Figure 2

Rates of splanchnic glucose production (*yellow*) and gluconeogenic precursor uptake (*green*) in the overnight fasted state in healthy subjects. Adapted from (4, 42, 108, 109).

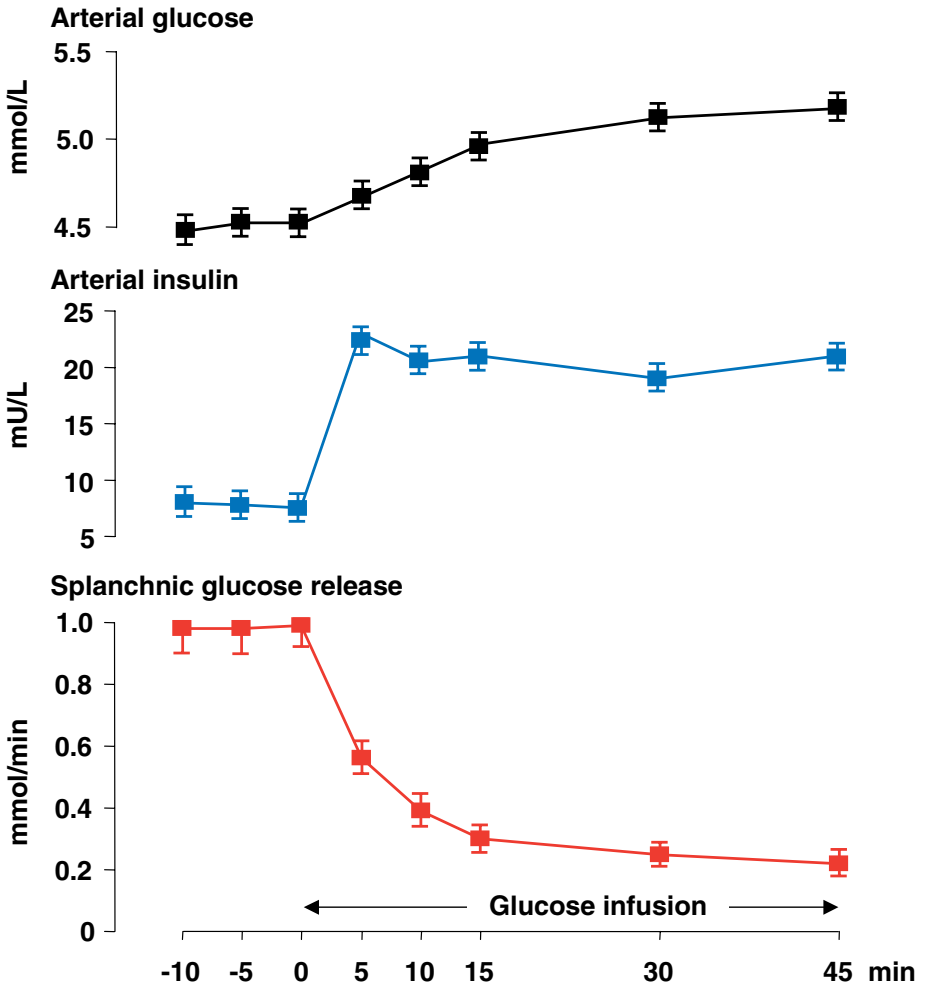

Figure 3

Arterial glucose and insulin concentrations and splanchnic glucose output in the basal state and during intravenous glucose administration (0.8 mmol/min) in healthy subjects. Data from (40).

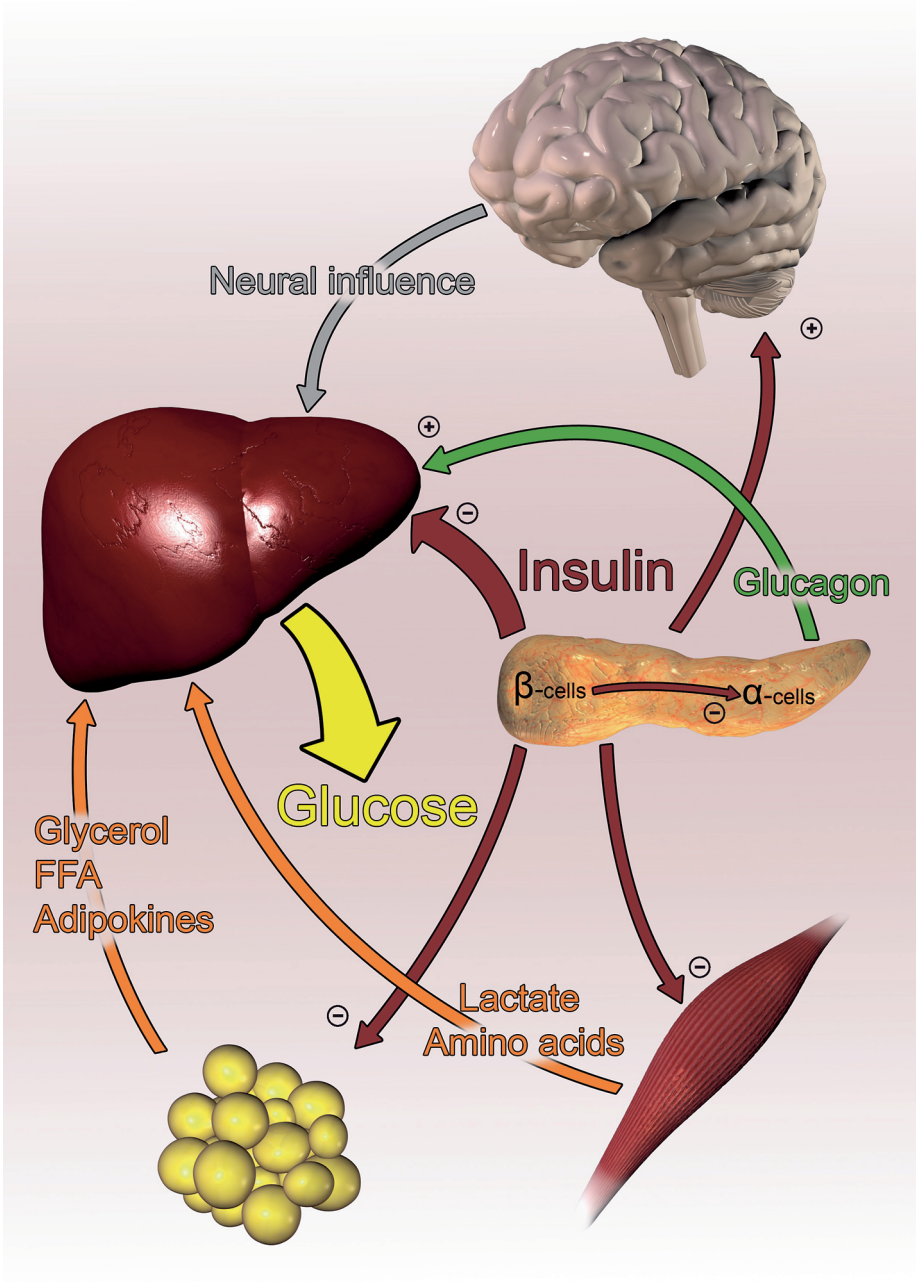

Figure 4

Schematic presentation of insulin's direct and indirect inhibitory effects on hepatic glucose production.

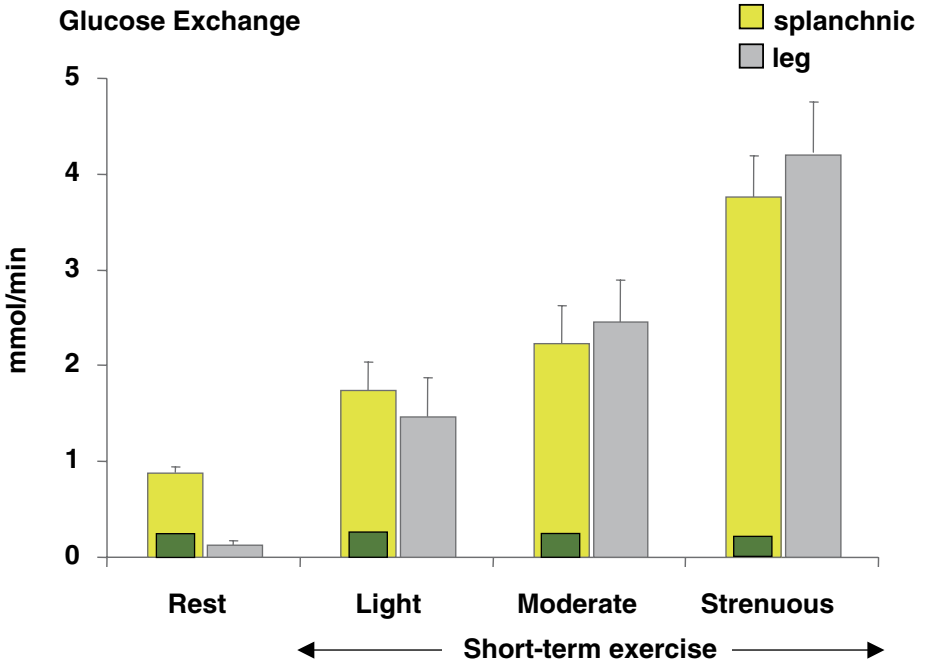

Figure 5

Splanchnic (*yellow*) and leg (*gray*) glucose exchange during short-term exercise of varying intensity in healthy subjects. Gluconeogenesis, evaluated as the sum of gluconeogenic precursor uptake by the splanchnic area, is indicated in green. Data from (108).

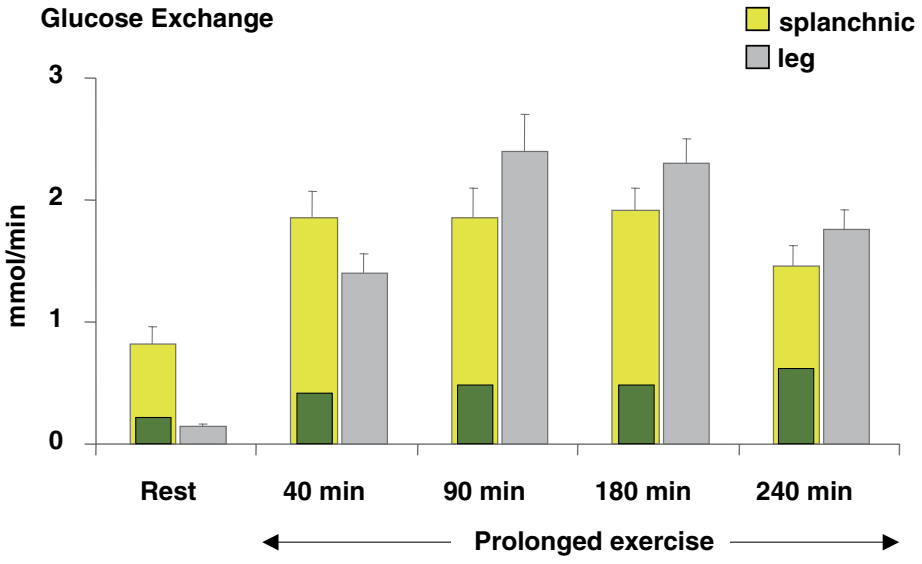

Figure 6

Splanchnic (*yellow*) and leg (*gray*) glucose exchange during prolonged exercise. Gluconeogenesis, evaluated as the sum of gluconeogenic precursor uptake by the splanchnic area, is indicated in green. Data from (4).

Annual Review of Nutrition
Volume 27, 2007

Contents

Fifty-Five-Year Personal Experience With Human Nutrition Worldwide
Nevin S. Scrimshaw 1

Protein Turnover Via Autophagy: Implications for Metabolism
Noboru Mizushima and Daniel J. Klionsky 19

Metabolic Regulation and Function of Glutathione Peroxidase-1
Xin Gen Lei, Wen-Hsing Cheng, and James P. McClung 41

Mechanisms of Food Intake Repression in Indispensable Amino Acid Deficiency
Dorothy W. Gietzen, Shuzhen Hao, and Tracy G. Anthony 63

Regulation of Lipolysis in Adipocytes
Robin E. Duncan, Maryam Ahmadian, Kathy Jaworski, Eszter Sarkadi-Nagy, and Hei Sook Sul 79

Association of Maternal Obesity Before Conception with Poor Lactation Performance
Kathleen Maher Rasmussen 103

Evolution of Infant and Young Child Feeding: Implications for Contemporary Public Health
Daniel W. Sellen 123

Regional Fat Deposition as a Factor in FFA Metabolism
Susanne B. Votruba and Michael D. Jensen 149

Trace Element Transport in the Mammary Gland
Bo Lönnerdal 165

ChREBP, A Transcriptional Regulator of Glucose and Lipid Metabolism
Catherine Postic, Renaud Dentin, Pierre-Damien Denechaud, and Jean Girard 179

Conserved and Tissue-Specific Genic and Physiologic Responses to Caloric Restriction and Altered IGFI Signaling in Mitotic and Postmitotic Tissues
Stephen R. Spindler and Joseph M. Dhahbi 193

The Clockwork of Metabolism
Kathryn Moynihan Ramsey, Biliana Marcheva, Akira Kohsaka and Joseph Bass 219

Creatine: Endogenous Metabolite, Dietary, and Therapeutic Supplement
John T. Brosnan and Margaret E. Brosnan 241

The Genetics of Anorexia Nervosa
Cynthia M. Bulik, Margarita C.T. Slof-Op't Landt, Eric F. van Furth, and Patrick F. Sullivan 263

Energy Metabolism During Human Pregnancy
Elisabet Forsum and Marie Löf 277

Role of Dietary Proteins and Amino Acids in the Pathogenesis of Insulin Resistance
Frédéric Tremblay, Charles Lavigne, Hélène Jacques, and André Marette 293

Effects of Brain Evolution on Human Nutrition and Metabolism
William R. Leonard, J. Josh Snodgrass, and Marcia L. Robertson 311

Splanchnic Regulation of Glucose Production
John Wahren and Karin Ekberg 329

Vitamin E Regulatory Mechanisms
Maret G. Traber 347

Epigenetic Epidemiology of the Developmental Origins Hypothesis
Robert A. Waterland and Karin B. Michels 363

Taste Receptor Genes
Alexander A. Bachmanov and Gary K. Beauchamp 389

The Ketogenic Diet and Brain Metabolism of Amino Acids: Relationship to the Anticonvulsant Effect
Marc Yudkoff, Vevgeny Daikhin, Torun Margareta Melø, Ilana Nissim, Ursula Sonnewald, and Itzhak Nissim 415

Indexes

Cumulative Index of Contributing Authors, Volumes 23–27 431

Cumulative Index of Chapter Titles, Volumes 23–27 434

Errata

An online log of corrections to *Annual Review of Nutrition* chapters (if any, 1997 to the present) may be found at http://nutr.annualreviews.org/errata.shtml