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Control of glycaemia

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INTRODUCTION

Plasma glucose concentrations are normally maintained within a fairly narrow range despite wide fluctuations in the body's supply (e.g. meals) and demand (e.g. exercise) for nutrients. In adults, arterial values throughout a 24-h period average approximately 5 mmol/l, with maximal concentrations after meal ingestion, usually not exceeding 9 mmol/l (Rizza et al, 1980), and concentrations during exercise (Wahren et al, 1978) or a moderate fast (60 h) usually remaining above 3 mmol/l (Consoli et al, 1987). This relative stability contrasts with the situation for other substrates such as glycerol, lactate, free fatty acids and ketone bodies (β-hydroxybutyate and acetoacetate), whose fluctuations vary much more widely (Table 1). Why is glucose so different from the body's other substrates? Teleologically, the reasons for maintaining such a narrow range of glucose fluctuations may be inferred from the deleterious consequences of hypo- and hyperglycaemia. Mildly elevated plasma glucose concentrations such as occur in patients with impaired glucose tolerance are associated with increased cardiovascular

Table 1. Circulating substrates and regulatory hormones after overnight, moderate and prolonged fasting.

	Overnight fast (12–16 h)	Moderate fast (30–60 h)	Prolonged fast (> 1 week)
Substrates (mmol/l)			
Glucose	5.0	4.0	3.0
Free fatty acids	0.5	1.0	1.5
Glycerol	0.05	0.1	0.2
3-Hydroxybutyrate	0.02	0.5	1.0
Lactate	0.8	0.8	0.7
Glutamine	0.6	0.5	0.4
Alanine	0.3	0.2	0.2
Hormones			
Insulin (pmol/l)	60	40	20
Glucagon (ng/l)	100	150	150
Cortisol (mmol/l)	0.3	0.5	0.9
Growth hormone (ng/l)	<2	4	8
Triiodothyronine (nmol/l)	1.8	1.6	0.9
Epinephrine (nmol/l)	0.2	0.4	0.6

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morbidity (Jarrett and Kenn, 1976) and there is considerable evidence (Tchobroutsky, 1978) linking more severe hyperglycaemia with development of the long-term complication of diabetes. The main adverse effects of hypoglycaemia relate to its acute effects on the central nervous system.

Glucose is essentially the exclusive fuel used by the brain because of either low circulating concentrations of possible alternative substrates (e.g. ketone bodies) or limitations of transport across the blood–brain barrier (e.g. free fatty acids) (Siesjo, 1988). The brain does not produce glucose and can store only a few minutes' supply. It is, therefore, dependent on circulating glucose, the uptake of which depends on a gradient across the blood–brain barrier. At concentrations 1–2 mmol/l below normal circulating levels, uptake of glucose becomes rate-limiting for utilization (Siesjo, 1988). Concentrations of circulating glucose below 3.0 mmol/l impair cerebral function (Mitrakou et al, 1991b). More severe and prolonged hypoglycaemia can cause convulsions, permanent brain damage and even death.

Maintenance of relatively stable plasma glucose concentrations requires that changes in rates of glucose delivery into the systemic circulation be readily balanced by comparable changes in rates of glucose removal from the circulation, and conversely that alterations in removal of glucose from the circulation be balanced by appropriate changes in glucose delivery. For example, as described below in greater detail, when a meal is ingested, the increased delivery of glucose into the systemic circulation is ultimately balanced by increased removal of glucose from the circulation (Kelley et al, 1988). During vigorous exercise, fever or trauma when the body's utilization of glucose increases, there is normally a compensatory increase in glucose delivery (Wahren et al, 1978). This chapter reviews the mechanisms by which rates of glucose production and glucose utilization are regulated in normal humans and how changes in these rates are coordinated to maintain normoglycaemia. Before dealing with systemic or whole-body fluxes, the cellular basis for input and removal of glucose will be discussed.

CELLULAR MECHANISMS

Glucose production

Liver and kidney are the only tissues that contain significant amounts of the enzyme glucose-6-phosphatase; consequently, only these tissues can release glucose into the circulation. The liver is the sole source of circulating glucose except for two situations: (1) after a prolonged fast, when the kidney may provide up to 10% (Owen et al, 1969) and (2) after meals or administration of exogenous nutrients (e.g. intravenous infusions, parenteral nutrition).

The liver provides glucose to the circulation via two processes—glycogenolysis, the breakdown of glycogen, and gluconeogenesis, the formation of new glucose molecules from other substrates. For methodological reasons (Consoli et al, 1987), it has been difficult to establish the precise contribution of each of these processes in humans. Estimates based on serial

liver biopsies measuring the rate of decrease in liver glycogen (Nilsson and Hultman, 1973), those based on balance of gluconeogenic precursors across the splanchnic bed (Dietze et al, 1976) and those based on incorporation of isotopically labelled gluconeogenic precursors into circulating glucose (Consoli et al, 1987) have indicated that glycogenolysis accounts for 50–70% of overall hepatic glucose output. Recently, however, studies by Rothman et al (1991) employing nuclear magnetic resonance to measure depletion of hepatic glycogen stores suggest that glycogenolysis may account for only 30–40%. For the purposes of this review, it will be assumed that after an overnight fast glycogenolysis provides approximately 50%.

After a 12–14-h overnight fast, rates of glucose appearance into the circulation generally average about 10 μmol/kg body weight per minute (Gerich et al, 1990) (Table 2). The human liver contains about 80 g glycogen

Table 2. Summary of normal glucose homeostasis after overnight, moderate and prolonged fasting.

	Overnight fast (12–16 h)	Moderate fast (30–60 h)	Prolonged fast (> 1 week)
*Overall glucose production**	10(100)	7.5(100)	5.0(100)
Hepatic output	10(100)	7.1(95)	4.5(90)
Glycogenolysis	5.0(50)	0.4(15)	0(0)
Gluconeogenesis	5.0(50)	6.7(90)	4.5(90)
Renal gluconeogenesis	0(0)	0.3(5)	0.5(10)
*Overall glucose utilization**	10(100)	7.5(100)	5.0(100)
Brain	5.0(50)	4.4(60)	3.5(70)
Splanchnic tissues	1.5(15)	0.9(12)	0.3(6)
Muscle	1.5(15)	0.8(10)	0.3(6)
Blood cells, skin	1.0(10)	0.8(10)	0.6(12)
Renal medulla	0.5(5)	0.4(5)	0.2(4)
Adipose tissue	0.5(5)	0.2(3)	0.1(2)

* μmol/kg per min (percent of total).

before an overnight fast (Nilsson and Hultman, 1973; Rothman et al, 1991). If hepatic glucose output were to persist at overnight rates and if glycogenolysis were to continue to provide 50% of hepatic glucose output, liver glycogen stores would be completely depleted within 20 h. Instead, both tissue utilization of glucose and overall hepatic glucose output decrease during a fast so that not until after 48 h of fasting does gluconeogenesis become the overwhelmingly predominant process. Indeed, studies using serial liver biopsies (Nilsson and Hultman, 1973), nuclear magnetic resonance (Gerich et al, 1990) and isotopic dilution techniques (Consoli et al, 1987) all agree that after a 60-h fast gluconeogenesis accounts for virtually all of hepatic glucose output. Note that, although skeletal muscle as a whole contains about 5 times as much glycogen as liver (Wahren et al, 1978), when muscle glycogen is broken down the resultant carbons are either used within muscle or are released into the circulation as lactate and alanine.

Control of hepatic glycogen metabolism

Hepatic glycogen is composed of B particles (molecular output $\sim 10^7$) that are covalently linked to form larger A particles (molecular weight 2×10^9) (Mayes, 1985b). Each glycogen molecule represents a branching polymer of glucose (Figure 1). After formation of about ten 1,4 glycosidic linkages, the branching enzyme transfers part of the 1,4 chain to a neighbouring chain to form a 1,6 glycosidic linkage, thus establishing a branch point.

Following meal ingestion, hepatic glycogen stores are repleted via two pathways (Figure 2) (McGarry et al, 1987)—in the so-called direct pathway glucose is taken up, phosphorylated to glucose-6-P, mutated to glucose-1-P, converted UDP-glucose, and then incorporated into glycogen. The last reaction is catalysed by glycogen synthase and is considered to be the rate-limiting step.

The other pathway—the so-called indirect pathway—initially involves the metabolism of glucose to gluconeogenic precursors (mainly lactate and

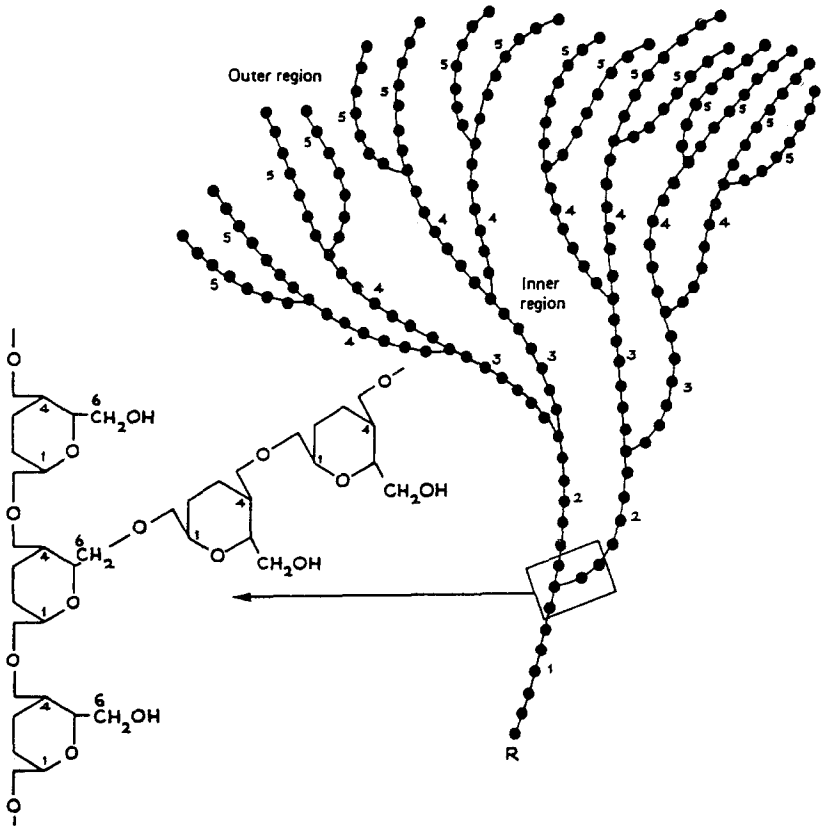

Figure 1. Branching nature of glycogen molecule. (From *Harper's Review of Biochemistry*, 20th edn, Lange Medical Publications, Los Altos, CA.)

alanine), which are subsequently converted to glucose-6-P in the liver and thence to glycogen by steps identical to those involved in the direct pathway. The exact proportions of glycogen formed via each pathway and the source of the gluconeogenic substrates used for the indirect pathway have not been precisely determined. The relative proportions depend on species, antecedent diet and duration of fast (Mitrakou et al, 1991a). In humans fasted overnight, it has been estimated that the direct pathway may account for 40–60% (Radziuk, 1982; Shulman et al, 1985; Consoli et al, 1989b).

The significance of the direct versus indirect pathways and the source of substrates used for the indirect pathway lies in the potential influence of peripheral (extrahepatic) glucose metabolism on the liver. It was originally proposed that production of these precursors occurred in muscle (McGarry et al, 1987), a major tissue taking up glucose after meal ingestion (Kelley et al, 1988). However, limb balance studies directly examining the net release of lactate and alanine after glucose ingestion have demonstrated that skeletal muscle is not an important source in humans (Kelley et al, 1988). In dogs, balance studies indicate that neither the brain (Mitrakou et al, 1989) nor the gastrointestinal tract (Bergman et al, 1982; Mitrakou et al, 1991a) is a major source. This leaves skin, adipose tissue, erythrocytes and the liver itself as possible sites for generation of the gluconeogenesis precursors. Indeed, studies using a combination of balance and isotopic measurements

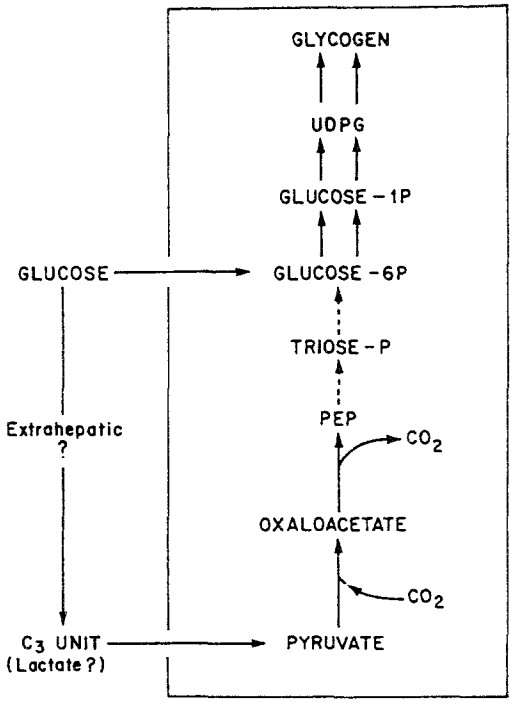

Figure 2. Direct and indirect pathways for hepatic glycogen formation.

across the liver in dogs indicate that hepatic uptake of gluconeogenic precursors cannot account for more than half of indirect pathway glycogen formation and that the liver itself produces lactate while taking it up and converting it to glycogen (simultaneous glycolysis and gluconeogenesis (Mitrakou et al, 1991a; Moore et al, 1991). These studies, therefore, suggest that in this species, and perhaps in man, the liver may be a major source of the gluconeogenic precursors used for indirect pathway glycogen synthesis.

The liver is freely permeable to glucose, and since the initial enzymatic steps of glucose metabolism are not acutely regulated, the rate-limiting step in the formation of glycogen is generally considered to be glycogen synthase rather than transport or phosphorylation. Breakdown of glycogen occurs as a result of the actions of several enzymes: (1) phosphorylase catalyses the hydrolysis of 1,4 glycosidic linkages; (2) the enzyme glucan transferase transfers the last three glycosyl units prior to an adjacent chain for further action by phosphorylase and (3) the debranching enzyme hydrolyses the 1,6 glycosidic branch point to permit further action by phosphorylase (Figure 3). As a consequence of its mode of formation and degradation, the most recent glycosidic residues formed are among the first to be hydrolysed.

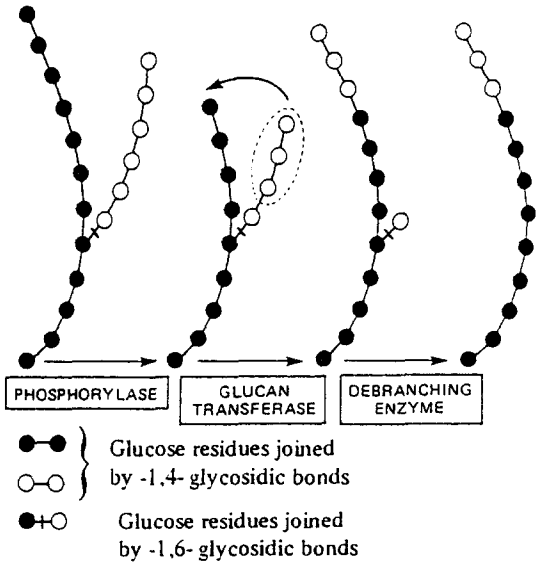

Figure 3. Steps in breakdown of hepatic glycogen molecules. (From *Harper's Review of Biochemistry*, 20th edn, Lange Medical Publications, Los Altos, CA.)

Glycogen metabolism is predominantly regulated by the activities of glycogen synthase and phosphorylase, which in turn are under substrate and hormonal control (Figure 4) (Stalmans, 1983). Phosphorylase A, the active enzyme, is formed by phosphorylation of phosphorylase B by a cAMP-dependent protein kinase; dephosphorylation of phosphorylase A by a hormone-sensitive protein phosphatase converts phosphorylase A to its

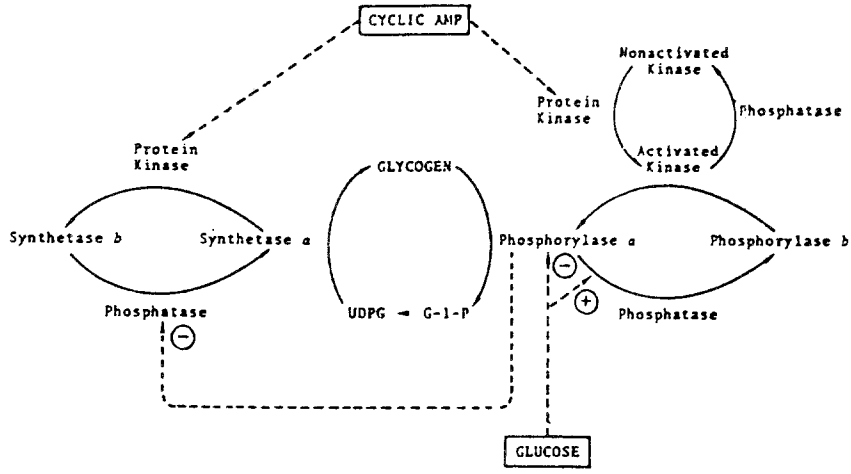

Figure 4. Hepatic phosphorylase and glycogen synthase interactions. (Reproduced with permission from Hers (1976) *Annual Review Biochemistry* **45:** 167–189; © Annual Reviews, Inc.)

inactive B form. The dephosphorylated form of glycogen synthase is the active enzyme, glycogen synthase A. Phosphorylation of glycogen synthase A by a cAMP-dependent protein kinase converts it to its inactive form. Thus, hormones that increase intrahepatic cAMP levels, such as glucagon and adrenaline, activate phosphorylase, inactivate glycogen synthase and stimulate glycogen breakdown. Insulin has the opposite effects on hepatic cAMP levels and glycogen breakdown. Glucose 6-phosphate is an allosteric activator of glycogen synthase B and reduces its K_m for UDP glucose. Glucose has a direct inhibitory effect on phosphorylase A. The level of phosphorylase is considered to be the major factor controlling glycogen metabolism since phosphorylase A inhibits glycogen synthase phosphatase, the enzyme that activates the synthase.

On a moment-to-moment basis, insulin and glucagon are the major hormonal factors regulating glycogen metabolism. After meal ingestion when plasma insulin concentrations are increased and plasma glucagon levels are suppressed, there is net glycogen formation and glycogenolysis is reduced. Conversely, as one proceeds from the fed into the fasted state, plasma insulin levels decrease, plasma glucagon levels increase, net glycogen formation ceases and glycogenolysis increases. Under stressful conditions, circulating adrenaline from the adrenal medulla and neurally released noradrenaline become involved and augment glycogen breakdown through β-adrenergic receptors (Rizza et al, 1979b; Clutter et al, 1988). Other hormones play more long-term permissive roles (Gerich and Cryer, 1991). Adrenocortical deficiency and thyroid hormone are associated with reduced hepatic glucagon stores (Cahill, 1971; Miller and Seitz, 1984). Moreover, the ability of glucagon and adrenaline to increase intrahepatic cAMP and mobilize glycogen is impaired by cortisol deficiency (Cahill, 1971).

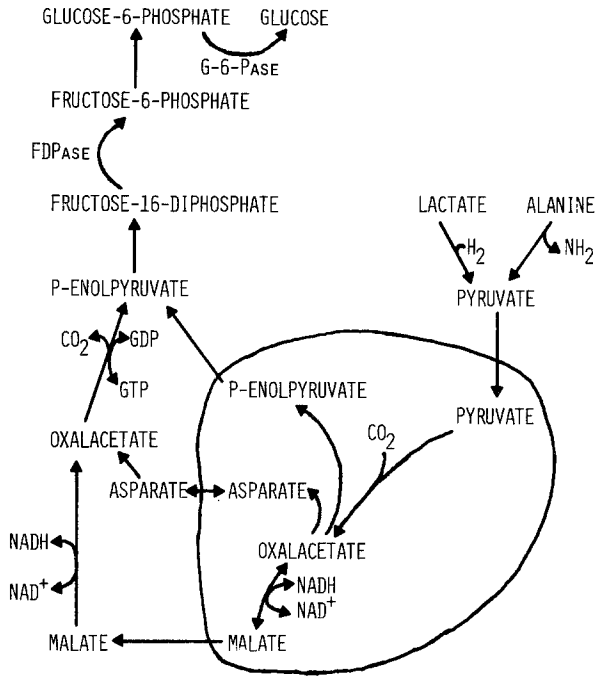

Figure 5. Gluconeogenic pathway. (From Gerich J (1984) Metabolism and energy mechanisms. In Frohlich, E. (ed.) *Pathophysiology. Altered Regulatory Mechanisms in Disease*, 3rd edn, pp 387–402, J.B. Lippincott.)

Control of hepatic gluconeogenesis

Flux through the gluconeogenic pathway (Figure 5) is regulated (1) by the provision of gluconeogenic substrates from peripheral tissues, (2) by the activities of certain key enzymes that in turn are influenced by substrates and hormones, and (3) by energetic and cofactor considerations. In vivo, rates of gluconeogenesis have generally been estimated by the incorporation of labelled precursors into plasma glucose. Except for glycerol, this approach generally underestimates substrate incorporation into glucose because of dilution of the labelled precursor in the Krebs cycle and the use of peripheral blood rather than intrahepatic specific activity of the precursor (Consoli et al, 1987). The latter probably results in a 15–30% error, whereas the former's error will vary considerably depending on the position of the label in the precursor used. In humans, it has been estimated that with [3-^{14}C]lactate or alanine the underestimation due to Krebs cycle carbon exchange is about 40%. The estimates presented in Table 3 are based on isotopic studies taking into consideration Krebs cycle carbon exchange and are probably accurate ±20%.

The major gluconeogenic precursors after an overnight fast are lactate, glutamine and alanine, which together account for over 80% of gluconeogenesis. However, much of the lactate and alanine used for gluco-

Table 3. Formation of glucose from gluconeogenic precursors

Gluconeogenesis from	Overnight fast (12–16 h)	Moderate fast (30–60 h)	Prolonged fast (> 60 h)
Gluconeogenesis*	5.0	7.0	5.0
Lactate*	3.0(60)	2.5(35)	1.7(34)
Glutamine*	0.8(16)	1.4(20)	0.5(10)
Alanine*	0.7(14)	1.1(16)	0.5(10)
Other amino acids*	0.3(6)	1.1(16)	0.5(10)
Glycerol*	0.2(4)	0.9(12)	1.9(36)

*μmol/kg per min (percent of total).

neogenesis originate from plasma glucose and this merely represents recycling of carbon rather than addition of new carbons to the plasma glucose pool. It has been estimated that after an overnight fast as much as 80% of plasma lactate (Kreisberg, 1972) and 35% of plasma alanine (Waterhouse and Keilson, 1978) are derived from plasma glucose. If, therefore, we consider the relative importance of gluconeogenic precursors in terms of their addition of new carbons to the glucose pool, lactate would still be the most important, but glutamine would become the next most important precursor. During a moderate fast, as glucose utilization and the formation of lactate and alanine from glucose decrease, amino acids released from protein and glycerol become relatively more important. After a prolonged fast when there is markedly increased lipolysis, glycerol becomes a major precursor (Bortz et al, 1972).

The delivery of gluconeogenic precursors to the liver can be rate-limiting for gluconeogenesis. A decrease such as in maple syrup urine disease (Haymond et al, 1978) and renal insufficiency (Garber et al, 1976) can decrease gluconeogenesis and overall hepatic glucose output. However, an increase in the supply of gluconeogenic precursors, while it may increase the absolute rate of gluconeogenesis, may not necessarily increase overall hepatic glucose output (Jenssen et al, 1990). This implies that there is some autoregulatory process that compensates for an increase in gluconeogenesis to maintain stability of overall hepatic glucose output. The mechanism for this remains obscure but is clearly deranged in people with type II diabetes who have an increased supply of precursors, increased gluconeogenesis and increased hepatic glucose output (Consoli et al, 1989a).

Gluconeogenesis can be viewed as a reversal of glycolysis. However, it is more complicated since three steps of glycolysis are enzymatically irreversible, i.e. those catalysed by hexokinase, phosphofructokinase and pyruvate kinase. Therefore, for there to be net flux by the gluconeogenic pathway, additional enzymes must be present to circumvent these 'road blocks'. Moreover, there must be associated changes in additional enzymes to avoid futile cycles. The key regulatory enzymatic steps controlling net flux along the gluconeogenic pathway are currently considered to be (1) pyruvate dehydrogenase, (2) pyruvate carboxylase, (3) phosphoenolpyruvate carboxylkinase, (4) pyruvate kinase and (5) fructose-1,6-diphosphatase (Pilkis et al, 1985).

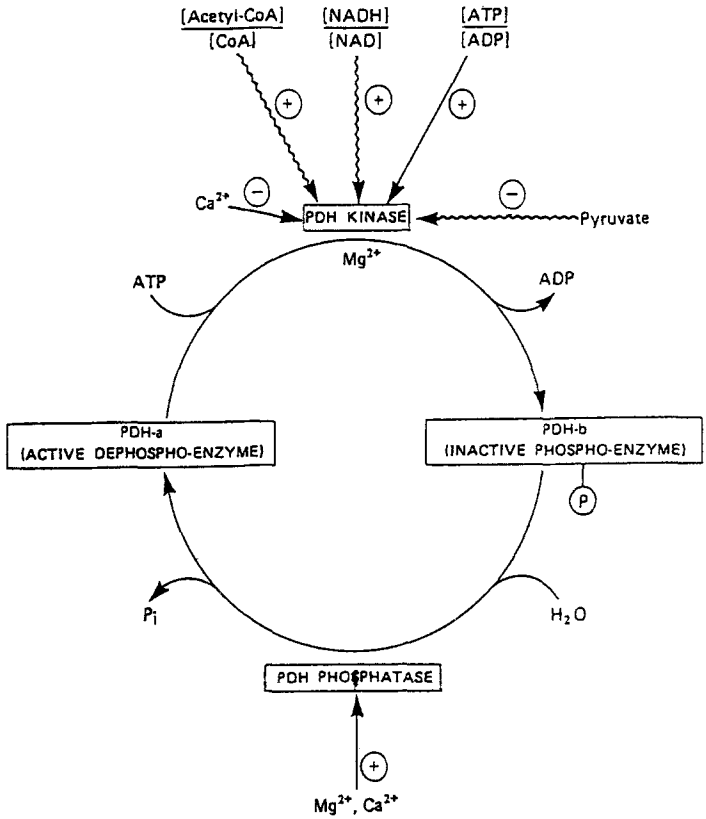

Figure 6. Regulation of pyruvate dehydrogenase. (From *Harper's Review of Biochemistry*, 20th edn, Lange Medical Publications, Los Altos, CA.)

Pyruvate dehydrogenase (PDH) is an enzyme complex that catalyses the conversion of pyruvate to acetyl-CoA. Its activity is decreased by phosphorylation and increased by dephosphorylation (Mayes, 1985a) (Figure 6). Its kinase is activated (i.e. the enzyme is inactivated) by increases in acetyl-CoA/CoA, the NADH/NAD^+ and ATP/ADP ratios and cAMP (Newsholme and Leech, 1986). The activity of PDH is decreased by glucagon and free fatty oxidation and is enhanced by insulin (Blumenthal, 1983; Pilkis et al, 1985). Inhibition of PDH would decrease the proportion of pyruvate oxidized and promote formation of oxaloacetate, which in turn could be converted to phosphoenolpyruvate.

Pyruvate kinase (PK) catalyses the conversion of phosphoenolpyruvate to pyruvate; it is inhibited by ATP, alanine, glucagon, cAMP and adrenaline (Mayes, 1985a; Newsholme and Leech, 1986). This inhibition would make more phosphoenolpyruvate available for gluconeogenesis.

Pyruvate carboxylase catalyses the conversion of pyruvate to oxaloacetate; it is activated by acetyl CoA, glucagon, and adrenaline and inhibited by insulin (Pilkis et al, 1985). Its activation would promote gluconeogenesis by

making more oxaloacetate available to be converted to phosphoenolpyruvate.

Phosphoenolpyruvate carboxylkinase catalyses the conversion of oxaloacetate to phosphoenolpyruvate. It is activated by glucagon (Pilkis et al, 1985). An increase in its activity in association with a decrease in PK and PDH activity would direct more phosphoenolpyruvate through the gluconeogenic pathway.

Another key enzyme is fructose-1,6-bisphosphatase, which catalyses the dephosphorylation of fructose 1,6-bisphosphate to fructose 6-phosphate. This enzyme is inhibited by fructose 2,6-bisphosphate which also activates phosphofructokinase, the enzyme that catalyses the reverse reaction. Fructose 2,6-bisphosphate thus controls both glycolysis and gluconeogenesis (Pilkis et al, 1990) (Figure 7). Formation of fructose 2,6-bisphosphate is

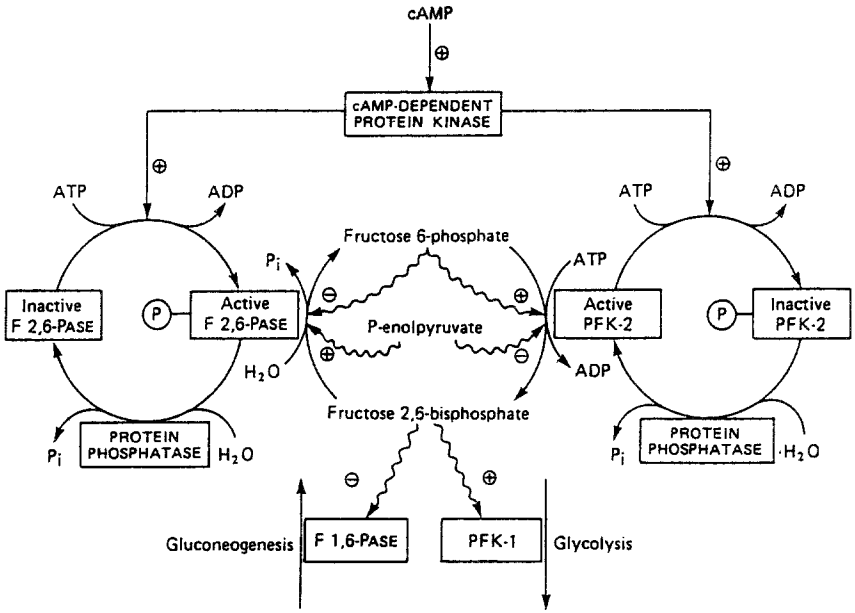

Figure 7. Fructose 2,6-bisphosphate as a regulator of glycolysis and gluconeogenesis. (From *Harper's Review of Biochemistry*, 20th edn, Lange Medical Publications, Los Altos, CA.)

inhibited by a cAMP-dependent kinase that is stimulated by glucagon and adrenaline. The resultant reduced intrahepatic fructose 2,6-bisphosphate level would inhibit glycolysis and promote gluconeogenesis. Insulin has the opposite effect. Intrahepatic levels of fructose 2,6-bisphosphate increases after meals and are reduced by fasting and in experimental forms of diabetes (Pilkis et al, 1990).

Glucagon and insulin are the key hormones regulating gluconeogenesis. At various enzymatic steps, glucagon has actions that would inhibit glycolysis while promoting gluconeogenesis, and insulin has opposite effects. Another important factor is the effect of alterations in lipid oxidation

(Blumenthal, 1983). Increased lipid oxidation increases the acetyl-CoA/CoA and NADH/NAD^+ ratios and the concentration of acetyl-CoA esters that lead to activation of gluconeogenic enzymes and inhibition of glycolytic enzymes. Increased lipid oxidation also makes more energy available to support gluconeogenesis. Recently, it has been demonstrated that increased free fatty acid availability (and thus presumably increased lipid oxidation) is associated with an increase in gluconeogenesis in humans (Clore et al, 1991; Nurjhan et al, 1992), and conversely suppression of lipolysis and lipid oxidation reduces gluconeogenesis (Fanelli et al, 1992a).

In summary, key factors affecting acute regulation of gluconeogenesis in humans include precursor supply, glucagon, insulin, and lipid oxidation by the liver. Catecholamines released under stressful conditions can directly increase gluconeogenesis but probably exert their main action via providing additional precursors (Sacca et al, 1983) (e.g. glycerol and amino acids) and increasing intrahepatic lipid oxidation (Blumenthal, 1983). Adrenocorticosteroids increase gluconeogenesis on a longer-term basis by increasing substrate supply and promoting increased synthesis of gluconeogenic enzyme (Cahill, 1971; Rizza et al, 1979b). Their effects are synergistic with those of glucagon and catecholamines. The role of growth hormone remains to be defined.

Glucose utilization

The primary determinants of glucose utilization in vivo are plasma glucose concentration, tissue requirements for glucose, and, for certain tissues, plasma insulin concentrations and the sensitivity of tissues to insulin; the latter can be affected by hormones such as cortisol, growth hormone and catecholamines and also by changes in the availability of alternative substrates (e.g. free fatty acids). Uptake of glucose by tissues occurs by facilitated diffusion, a process that is not energy-dependent and that follows Michaelis–Menten kinetics. In other words, glucose uptake will increase as plasma glucose concentrations increase but at proportionately decreasing rates as saturation of the transport process is approached (Gottesman et al, 1984) (Figure 8). Transport kinetics vary among tissues depending to a large extent on the characteristics of glucose transporters and whether the process is sensitive to insulin. Five homologous glucose transporter molecules have been identified whose distribution varies among tissues and whose dependency on insulin also varies (Mueckler, 1990). Insulin regulates the steady-state concentration of glucose transporters by promoting their synthesis but acutely accelerates uptake of glucose mainly by promoting mobilization of transporters to the cell membrane (Cushman and Wardzala, 1980); whether or not insulin causes activation of transporters as well is unclear (Gottesman et al, 1984). Normally, uptake (transport) of glucose is the rate-limiting step for its metabolism.

Glucose taken up by cells has basically three main fates: storage as glycogen or lipid, oxidation to CO_2, or conversion to lactate (or alanine) that is subsequently released into the circulation. The relative proportion in which glucose undergoes these fates varies between tissues and is dependent

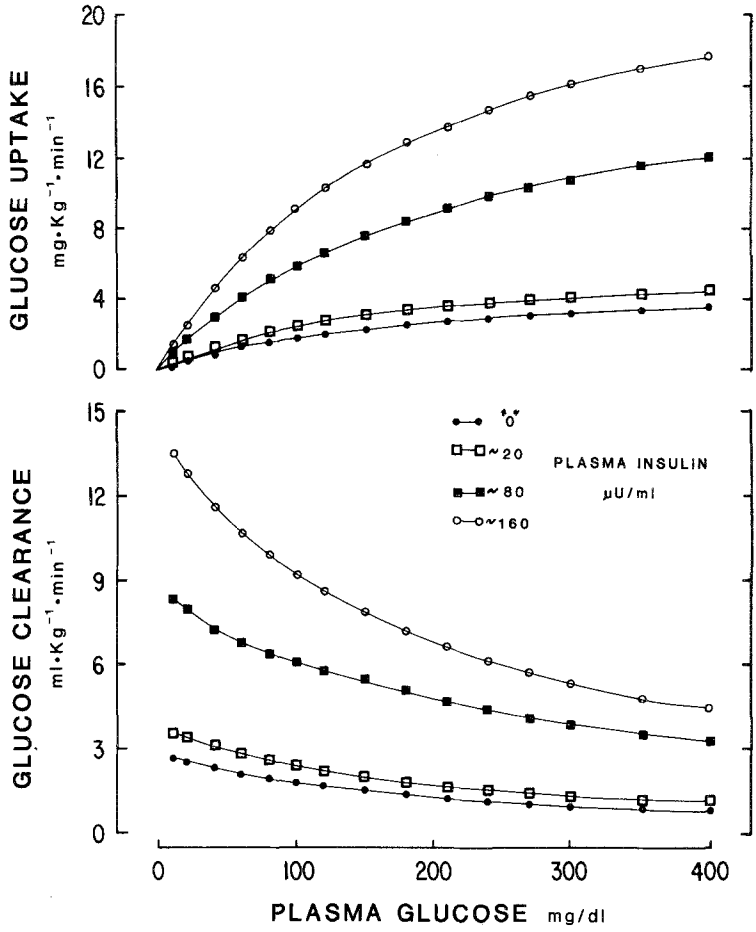

Figure 8. Whole-body rates of glucose uptake and efficiency of uptake (clearance) as a function of plasma glucose and insulin concentrations in humans (Reprinted with permission from Gottesman et al (1984) *Diabetes* **33:** 184–191. © 1984 American Diabetes Association, Inc.)

upon degree of fasting, the hormonal milieu and presence of alternative substrates, e.g. free fatty acids. For example, in the postabsorptive state, there is no net storage of glucose and therefore all of glucose taken up by tissues is either completely oxidized or converted to lactate (or alanine), which can be recycled back to the liver to be used for gluconeogenesis. The Cori (for lactate) and glucose–alanine cycles account for 25–35% of glucose uptake in the postabsorptive state (Felig, 1973; Randle et al, 1988). In brain, almost all of the glucose taken up is completely oxidized, whereas in muscle, blood cells, skin, kidney and gastrointestinal tract most of the glucose taken up probably only undergoes glycolysis and is recycled back to the liver as either lactate or alanine.

Control of glycolysis

Glycolysis (Figure 9) involves the anaerobic breakdown of glucose to pyruvate and lactate. When oxygen is not available, the reduced NADH, which is formed during glycolysis but cannot readily be oxidized by the respiratory chain, is oxidized by the lactate dehydrogenase (LDH) reaction, which catalyses the conversion of pyruvate to lactate, thereby allowing glycolysis to proceed.

After the uptake of glucose into cells, there are numerous potential control points for glycolysis. The first is the phosphorylation of glucose to form glucose 6-phosphate. In non-hepatic tissues, this reaction is catalysed by the enzyme hexokinase, which has a high affinity for glucose, thereby enabling cells to take up glucose and immediately convert it to glucose 6-phosphate even when the plasma glucose concentration is relatively low. The phosphorylation of glucose is important because it is an irreversible reaction, thus trapping the glucose inside the cell. Glucose-6-phosphatase,

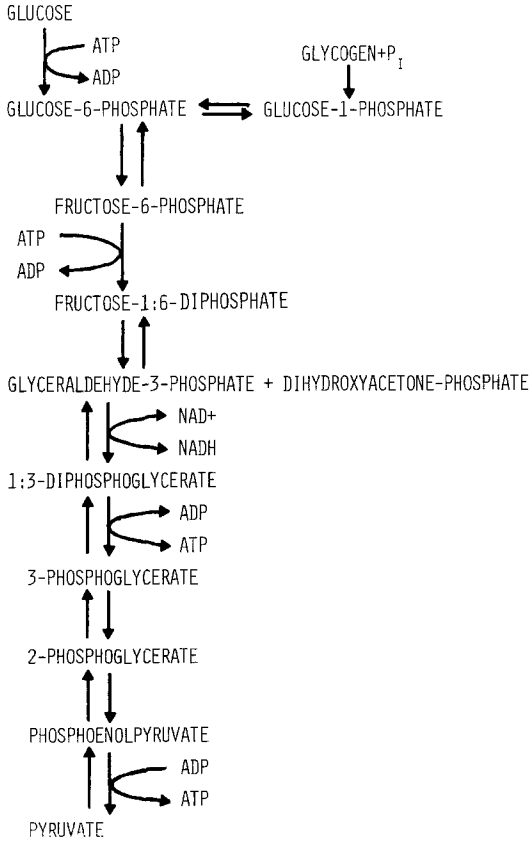

Figure 9. Glycolytic pathway. (From Gerich J (1984) In Frohlich E (ed.) *Pathophysiology. Altered Regulatory Mechanisms in Disease*, 3rd edn, pp 387–402. J.B. Lippincott.)

which catalyses the conversion of glucose 6-phosphate to free glucose is present only in liver and kidney; in other tissues, glucose taken up from plasma is rapidly converted to glucose 6-phosphate. Hexokinase is subject to product inhibition by glucose 6-phosphate but is probably not a major site of acute hormonal or nutritional regulation of glycolysis (Mayes, 1985a).

Glucose 6-phosphate formed within cells is either converted to glycogen (see above) or rapidly converted to fructose 6-phosphate by a reversible non-rate-limiting enzymatic step catalysed by phosphohexose isomerase. The next potential control point of glycolysis is the conversion of fructose 6-phosphate to fructose 1,6-diphosphate. This is catalysed by phosphofructokinase, an inducible enzyme whose activity is increased by AMP, fructose 6-phosphate, inorganic phosphate, fructose 2,6-bisphosphate and insulin and is decreased by citrate, ATP, cAMP, glucagon and catecholamines (Mayes, 1985a; Newsholme and Leech, 1986). Its activity increases following meal ingestion and is decreased after fasting and in experimental models of diabetes (Pilkis et al, 1990).

These next steps involving conversion of fructose 1,6-disphosphate to phosphoglyceric acid and glyceraldehyde-3(P) via aldolase, the conversion of these substrates to 1,3-diphosphoglycerate via glyceraldehyde-3-phosphate dehydrogenase, and the formation of phosphoenolpyruvate from 1,3-phosphoglycerate by enolase are not considered highly regulated reactions.

The last regulated step of glycolysis, the conversion of phosphoenolpyruvate to pyruvate, is catalysed by the enzyme pyruvate kinase, which, as indicated above, is highly regulated. Once pyruvate is formed, the redox state of the tissue and the activities of pyruvate dehydrogenase and pyruvate carboxylase determine the extent to which the pyruvate undergoes oxidation in mitochondria in the Krebs cycle or is reduced to lactate by lactate dehydrogenase. The regulation of pyruvate dehydrogenase and pyruvate carboxylase have been discussed above.

Control of glucose (pyruvate) oxidation

Pyruvate, which is formed in the cytoplasm, is transported in the mitochondria and, if adequate NAD^+ is available, is converted to acetyl-CoA and ultimately to CO_2 and H_2O by steps shown in Figure 10.

The key regulated enzymatic step determining pyruvate flux through the Krebs cycle is pyruvate dehydrogenase. Insulin activates PDH by reducing its phosphorylation and oxidation of free fatty acids by generating acetyl-CoA. Glucagon reduces its activity by increasing its phosphorylation. In most tissues, there is a competition between glucose and free fatty acids as oxidative fuels, and free fatty acids are the preferred substrate. The preferential utilization of free fatty acids can have a profound effect on glucose metabolism via a complex series of steps collectively referred to as the glucose–fatty acid cycle (Randle et al, 1963). First proposed by Randle and his colleagues (Randle et al, 1963), the concept has now received widespread experimental support and its basic operation in humans is generally accepted. According to this concept, the increased free fatty acid

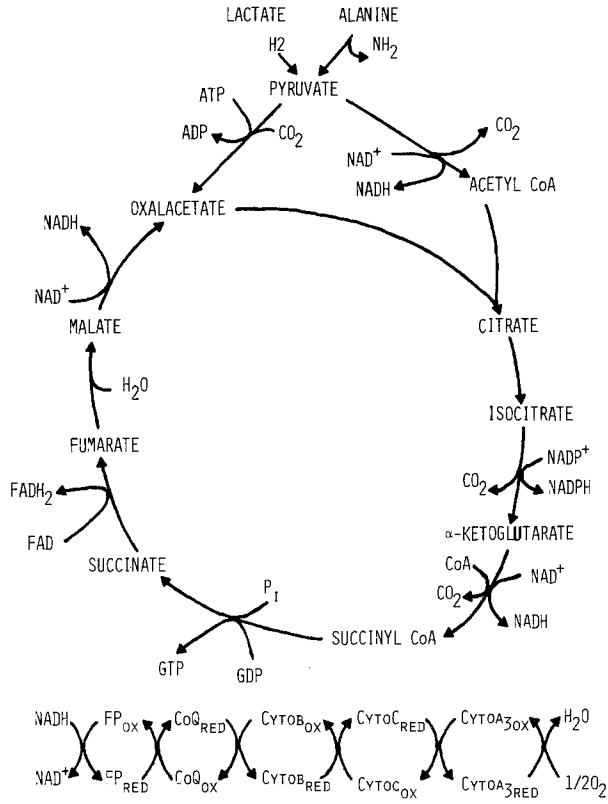

Figure 10. Steps in oxidation of pyruvate. (From Gerich J (1984) In Frohlich E (ed.) *Pathophysiology. Altered Regulatory Mechanisms in Disease*, 3rd edn, pp. 387–402. J.B. Lippincott Co.).

oxidation increases the mitochondrial acetyl-CoA/CoA ratio and cytosolic citrate levels. The increased acetyl-CoA/CoA ratio inhibits pyruvate dehydrogenase, reducing pyruvate formation and hence its oxidation. The increased intracellular citrate levels inhibit phosphofructokinase, which results in an increase in cytosolic glucose 6-phosphate, an inhibitor of hexokinase. Reduced activity of hexokinase via an increase in intracellular glucose will then reduce glucose transport (uptake) by tissues. This mechanism has been invoked to explain the reciprocal changes observed in glucose and lipid metabolism observed in a variety of physiological and pathological conditions (Randle et al, 1963). Thus, during starvation and diabetes when rates of fat oxidation are increased, there is impaired tissue glucose uptake and oxidation. Reduced suppression of lipid oxidation after meal ingestion may impair glycogen formation in diabetes because of impaired glucose uptake. Furthermore, increases in lipid oxidation also promote increased gluconeogenesis (Clore et al, 1991). Thus, alterations in lipid metabolism can affect both the production and utilization of glucose.

SYSTEMIC GLUCOSE HOMEOSTASIS

Having discussed basic mechanisms controlling the intracellular fate of glucose, this section will deal with (1) whole-body glucose homeostasis as it occurs normally immediately after meal ingestion and during various periods of food deprivation, (2) the mechanisms that normally protect against hypoglycaemia, and (3) derangements that occur in people with diabetes, the most common disorder affecting glucose homeostasis.

Postprandial state

Normal physiology

A hypothetical day may be divided into a so-called postabsorptive state constituting the 12–16-h period overnight after the last meal and postprandial periods each lasting 5–7 h during which the body assimilates ingested nutrients before returning to preprandial conditions.

Postprandial glycaemic excursions are dependent upon the form of carbohydrate ingested (Osei et al, 1988), the amount of accompanying protein and

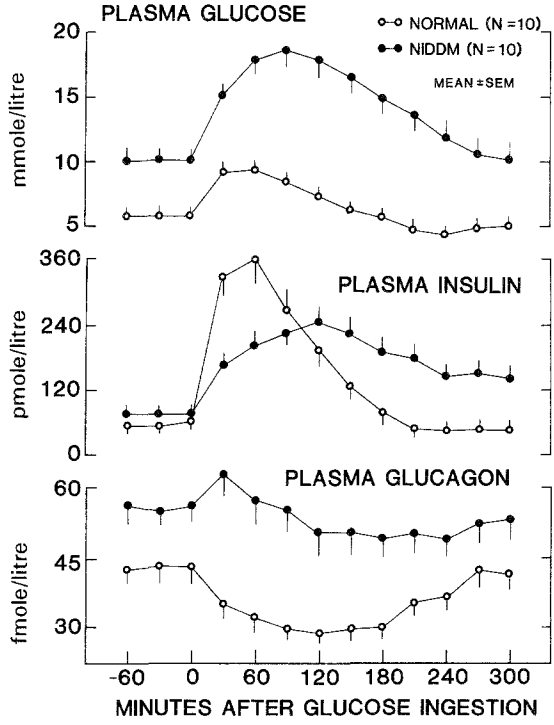

Figure 11. Changes in plasma glucose, insulin and glucagon after glucose ingestion in normal volunteers (o–o) and in people with type II diabetes (•–•). (Reprinted with permission from Mitrakou et al (1990) *Diabetes* **39:** 1381–1390. © 1990 American Diabetes Association, Inc.)

fat (Estrich et al, 1967; Gannon et al, 1988), the size of the meal (Serana et al, 1983) and the time of day (Serana et al, 1983). In general, complex carbohydrates are absorbed more slowly than simple sugars, and protein and fat delay absorption, both of which tend to reduce glycaemic excursions, while greater amounts of carbohydrates cause greater glycaemic excursions; and glucose tolerance is better in the morning than in the evening.

Following ingestion of a meal (Figure 11), plasma glucose levels increase within 15 min; this hyperglycaemia, in concert with neurogenic stimuli and release of gastrointestinal hormones, such as GIP and glucagon-related peptides, stimulate insulin secretion and suppress glucagon secretion. Plasma glucose concentrations peak between 45 and 90 min, at values generally below 9 mmol/l, returning to basal levels by 180 min. Plasma insulin follows the same pattern, whereas plasma glucagon decreases maximally between 45 and 90 min and begins to return to basal levels after 180 min. Sometimes 3–5 h after a meal, especially after a high-carbohydrate meal, plasma glucose levels may decrease below preprandial levels. In most

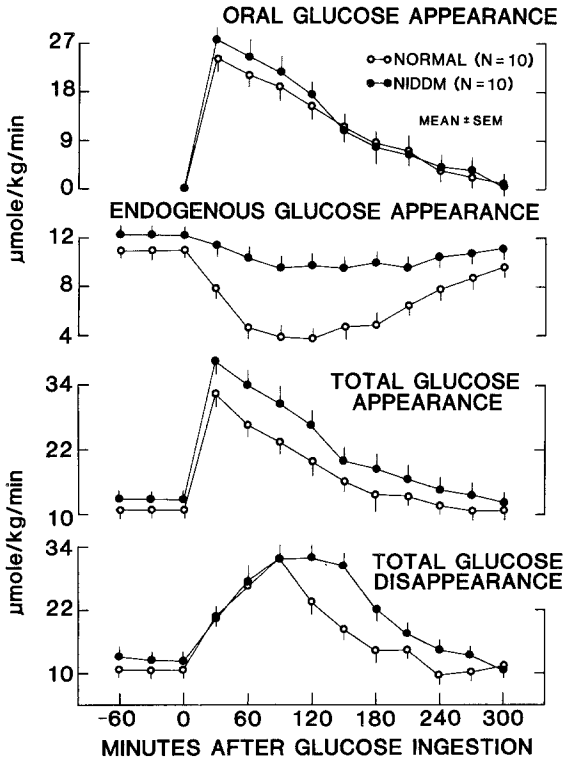

Figure 12. Changes in rates of total, exogenous and endogenous glucose appearance and disappearance of glucose from the circulation after glucose ingestion in normal volunteers (○–○) and in people with type II diabetes (●–●). (Reprinted with permission from Mitrakou et al (1990) *Diabetes* **39:** 1381–1390. © 1990 American Diabetes Association, Inc.)

instances, this is merely a normal variation without pathological significance and is generally asymptomatic.

Plasma glucose levels after meal ingestion are determined by the relative changes in rates of delivery and removal of glucose into the systemic circulation (Figure 12). Initially, both delivery and removal increase. For the first 60–90 min rates of glucose delivery exceed rates of glucose removal; afterward the situation is reversed. Delivery of glucose to the systemic circulation represents the sum of the ingested glucose escaping first past extraction by splanchnic tissues (liver and small intestines) and the residual release of endogenously produced glucose by the liver. Appearance of ingested glucose into the systemic circulation reaches peak values 30–60 min after meal ingestion and gradually decreases until absorption is complete at about 4–5 h. Early after meal ingestion there is a marked suppression of release of endogenously produced glucose from the liver. The magnitude of this is largely determined by early insulin and glucagon responses (Mitrakou et al, 1992). During the postprandial period, release of endogenously produced glucose is suppressed by 50–60%, resulting in approximately 25 g less of glucose being delivered into the systemic circulation (Ferrannini et al, 1985; Firth et al, 1986; Kelley et al, 1988; Mitrakou et al, 1990, 1992).

The major tissues responsible for removal of glucose from the systemic circulation are the liver, small intestine, brain, muscle and adipose tissue. Although reported estimates vary (Marin et al, 1987, 1992; Kelley et al, 1988), it seems (Figure 13) that muscle and splanchnic tissues (liver and gastrointestinal tract) probably each account for about 25–30%, brain about 15–20% and adipose tissue 5–10%. The magnitude of the glucose uptake by

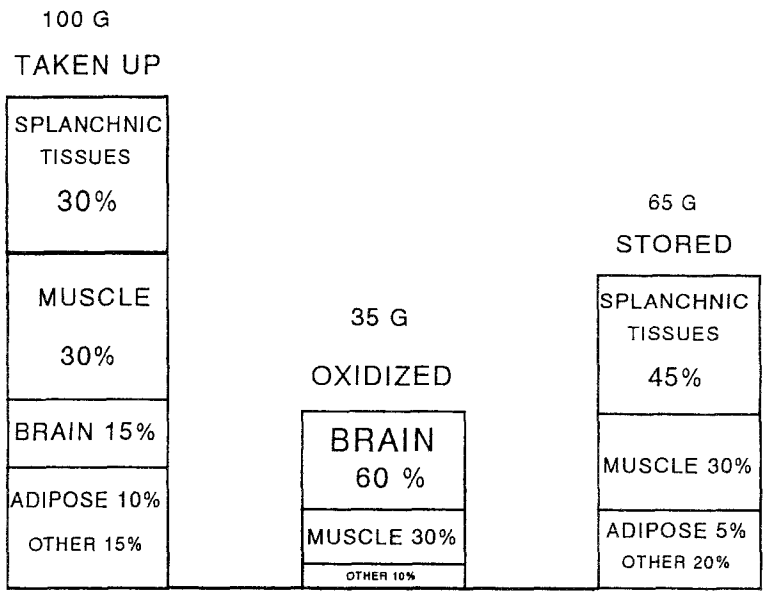

Figure 13. Overview of normal disposal of a 100-g oral glucose load.

the muscle, liver and adipose tissue is influenced by both plasma glucose and insulin concentrations, whereas uptake of glucose by brain and non-hepatic splanchnic tissue is largely determined by the plasma glucose concentration. During the postprandial period, lipolysis and lipid oxidation are suppressed (Kelley et al, 1988). Of glucose taken up by tissues during this period, approximately 60–70% is used to replenish glycogen stores, 30–40% is oxidized and 15–20% is released back into the circulation as lactate and alanine for probable uptake by the liver for indirect pathway glycogen formation (Marin et al, 1987; Kelley et al, 1988).

Diabetes mellitus

The ingestion of carbohydrate results in a prolonged excessive increase in plasma glucose in patients with type I and type II diabetes and, to a lesser extent, in those with glucose intolerance (Pehling et al, 1984; Firth et al, 1986; Ferrannini et al, 1988; Mitrakou et al, 1990, 1992; Dinneen et al, 1992). In all three conditions, the underlying defect is impaired insulin secretion coupled with impaired suppression of glucagon release (Dinneen et al, 1992). This is illustrated in Figure 7 in the case of patients with type II diabetes. In this condition (Mitrakou et al, 1990) and in people with impaired glucose tolerance (Mitrakou et al, 1992), a delayed initial β-cell response leads to prolonged hyperglycaemia that eventually results in late hyperinsulinaemia. In poorly controlled diabetic patients, insulin resistance also contributes to the hyperglycaemia (Dinneen et al, 1992). The role of insulin resistance in people with impaired glucose tolerance remains to be fully elucidated.

Mechanistically, excessive postprandial hyperglycaemia in people with diabetes occurs because rates of glucose appearance into the systemic circulation markedly exceed rates of glucose removal. Since rates of glucose removal in an absolute sense (Figure 12) are normal or even increased (Mitrakou et al, 1990; Dinneen et al, 1992) in people with diabetes, the primary abnormality must be excessive appearance of glucose. The latter has been consistently shown to be the result of impaired suppression of endogenous hepatic glucose output, whereas appearance in the circulation of ingested glucose is generally normal (Dinneen et al, 1992).

Several mechanisms may contribute to this impaired suppression of postprandial hepatic glucose release. The increased incorporation of labelled carbon dioxide into glucose suggests accelerated postprandial gluconeogenesis (Dinneen et al, 1992). Insulin secretion is delayed and decreased relative to the prevailing plasma glucose concentration; furthermore, the suppression of glucagon secretion is impaired. Hepatic insulin resistance may also be involved. The delay in insulin secretion may be particularly important, since the dynamics of insulin availability appear to have as great an effect on carbohydrate metabolism as the absolute amount of insulin released (Bruce et al, 1988; Mitrakou et al, 1992).

It should be pointed out that apparently normal postprandial glucose removal from the circulation is inappropriate in the presence of hyperglycaemia. Moreover, the metabolic fate of the glucose taken up by tissues is

also abnormal. Glucose oxidation is either low or inappropriately normal despite hyperglycaemia (Boden et al, 1983; Firth et al, 1986; Mitrakou et al, 1990, 1992), the amount of glucose stored as glycogen is reduced (Boden et al, 1983; Firth et al, 1986; Mitrakou et al, 1990, 1992), and the amount released as lactate and alanine is increased (Mitrakou et al, 1990). The decrease in postprandial glycogen synthesis in type II diabetes appears to be due at least in part to impaired stimulation of muscle glycogen synthetase (Wright et al, 1988). The extent to which these abnormalities are due to abnormal insulin secretion or insulin resistance is a matter of controversy.

Postabsorptive state

Normal physiology

The postabsorptive state refers to the 8–16-h period after a meal during which transition from the postprandial to the fasting state occurs. During the overnight period, glucose turnover, plasma glucose and insulin secretion (as assessed from changes in plasma c-peptide) decrease to a nadir at approximately 03:00 after which all increase in parallel (Figure 14) (Bolli and

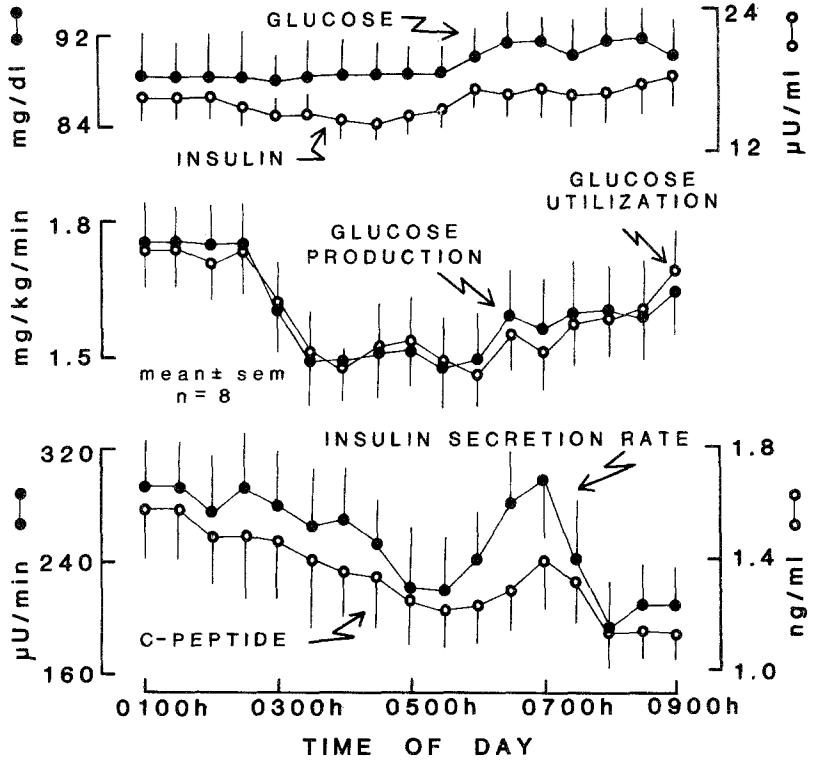

Figure 14. Overnight changes in plasma glucose, insulin and c-peptide concentrations and rates of glucose production, glucose utilization, and insulin secretion. (Reproduced with permission from Bolli et al (1984) *Diabetes* **33:** 1150–1153. © 1984 American Diabetes Association, Inc.)

Gerich, 1984). In normal individuals, when rates of glucose production and utilization are well matched, little or no change is observed in the plasma glucose concentration. However, in people with type I and type II diabetes who do not increase their insulin secretion appropriately, plasma glucose levels can increase appreciably (Campbell et al, 1985a). The phenomenon, now referred to as the dawn phenomenon (Schmidt et al, 1981), was long known to occur in people with diabetes (Hatlehol, 1924) but only recently was it recognized also to occur in people without diabetes (Bolli et al, 1984a; Schmidt et al, 1984). Experiments using various inhibitors of hormonal secretion and action (Campbell et al, 1985b) have provided strong evidence that the phenomenon is caused by nocturnal surges of growth hormone secretion that occur shortly after the onset of sleep. It is a metabolic curiosity in normal individuals but in people with diabetes it can present a problem in maintaining glycaemic control (Bolli and Gerich, 1984; Perriello et al, 1991).

After an overnight fast, a quasi-steady state exists such that rates of glucose production equal rates of glucose utilization and plasma glucose concentrations are stable. Under these conditions, glucose turnover (production and utilization) is about 10 μmol/kg per min, and glycogenolysis and gluconeogenesis make approximately similar contributions to overall hepatic glucose output (Table 2). As there is no net storage of glucose in the fasting state, glucose taken up by tissues is either oxidized completely or merely undergoes glycolysis. Approximately 30% is cycled back to the liver (mainly as lactate (Cori cycle) but also as alanine) and the rest is oxidized. About 80% of glucose utilization occurs independently of insulin, in brain, blood cells, skin, gastrointestinal tissues and kidney, with brain alone accounting for 50%.

The key factors normally regulating glucose homeostasis under these conditions are (1) tissue requirements for glucose, (2) availability of gluconeogenic precursors and alternative sources of fuel, (3) glucagon, which supports appropriate output of glucose by the liver, and (4) insulin, which restrains the effects of glucagon on the liver and prevents accelerated lipolysis and proteolysis while permitting a limited amount of glucose uptake in insulin-sensitive tissues. The liver is the main site of hormonal regulation. Counterregulatory hormones such as growth hormone, cortisol, adrenaline and thyroid hormone play permissive roles in setting tissue sensitivity to glucagon and insulin, while the autonomic nervous system under such basal conditions probably exerts its major effect in supporting lipolysis. Thus, hypoglycaemia is distinctly uncommon in individuals with isolated growth hormone or cortisol deficiency (Gerich and Campbell, 1988) and infusion of α- or β-adrenergic receptor antagonists has no detectable effect on glucose turnover (Clutter et al, 1988).

As a period of food deprivation lengthens into a moderate fast, utilization of glucose by tissues decreases, while utilization of lipid (FFA and ketone bodies) increases (Owen and Reichard, 1971; Havel, 1972). A reduction in hepatic glucose output slightly greater than the decrease in glucose utilization causes plasma glucose concentrations to decrease about 20%. Associated with this is a decrease in plasma insulin concentrations.

The decrease in hepatic glucose output is accounted for by a decreased glycogenolysis, since gluconeogenesis increases (Consoli et al, 1987). The latter is the consequence of several factors: increased secretion of glucagon and other counterregulatory hormones, reduced insulin secretion changes secondary to increase intrahepatic lipid oxidation, and greater availability of gluconeogenic precursors in the form of glycerol, provided by increased lipolysis, and amino acids, provided by increased proteolysis (Tables 1 to 3).

The key initiating factors in these changes remain to be identified, but one could envision the following scenario. An early decrease in plasma glucose concentration could decrease insulin secretion and increase sympathetic nervous tone (Misbin et al, 1970); the increase in sympathetic tone in turn would further reduce insulin secretion while increasing lipolysis and glucagon secretion. The reduction in insulin secretion would reduce glucose utilization in insulin-sensitive tissues and would also permit lipolysis and proteolysis to increase. Increases in lipid oxidation as a result of increased lipolysis would further reduce glucose utilization in both non-insulin-sensitive and insulin-sensitive tissues via the glucose–fatty cycle and would also promote increased gluconeogenesis. During more prolonged fasting (more than 3 days), there is a further reduction in glucose turnover and an increase in utilization of lipid (Havel, 1972). As circulating ketone body levels increase as a result of increased fatty acid oxidation, they become an important alternative fuel for the brain, and its utilization of glucose decreases (Owen et al, 1967). Plasma glucose and insulin concentration decrease to about 3 mmol/l and 20 pmol/l, respectively and remain at these levels despite further fasting. Decreases in thyroid hormone levels (due to conversion of thyroxine to reverse triiodothyronine rather than to triiodothyronine) lead to an overall reduction in energy consumption. Additionally, despite the appearance of insulin resistance and persistent elevations of circulating cortisol and growth hormone levels, proteolysis decreases so that gluconeogenesis is primarily supported by recycled lactate and glycerol provided by ongoing lipolysis (Cahill, 1970). The mechanism responsible for the reduction in proteolysis is not completely understood but may involve the combined effects of elevated circulating concentrations of growth hormone, branched-chain amino acids (leucine, isoleucine and valine) and ketone bodies (Sherwin et al, 1975; Sherwin, 1978; Salomon et al, 1989).

Diabetes mellitus

In both type I and type II diabetes, rates of glucose production and utilization are increased in the postabsorptive state (Dinneen et al, 1992) and are directly correlated with fasting plasma glucose concentrations (Figure 15). Studies examining the metabolic events that occur during development of hyperglycaemia after withdrawal of insulin in patients with type I and type II diabetes (Miles et al, 1980; Korytkowski et al, 1992) indicate that the primary factor is an increase in hepatic glucose output. Because plasma glucose levels will increase until rates of glucose disappearance from the circulation equal rates of glucose delivery into the circulation (i.e. hepatic

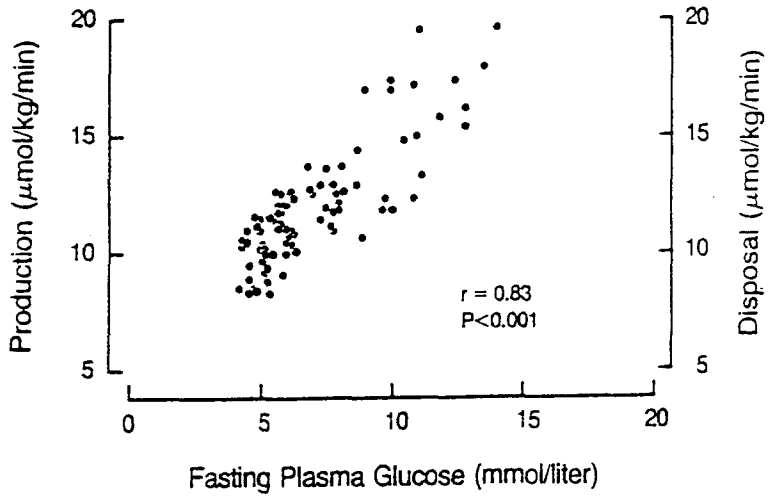

Figure 15. Correlation between fasting plasma glucose concentrations, hepatic glucose output and glucose disposal. (Reproduced with permission from Dineen et al (1992) *New England Journal of Medicine* **327**: 707–713).

glucose output), reduced efficiency of glucose removal from the circulation due to both resistance to insulin and an inadequate release of insulin in response to the increasing plasma glucose concentration participates in determining the magnitude of the steady-state hyperglycaemia ultimately achieved. Glucose removal from the circulation in a hyperglycaemic diabetic person includes glycosuria and more than a normal amount of non-insulin-mediated tissue uptake simply due to the mass action effects of the hyperglycaemia (Dinneen et al, 1992).

Increased gluconeogenesis rather than increased glycogenolysis appears to be the predominant process responsible for the increased postabsorptive rates of hepatic glucose output in type II diabetes (Consoli et al, 1989a; Magnusson et al, 1992). Increased gluconeogenesis from lactate (Consoli et al, 1990), alanine (Consoli et al, 1990) and glycerol (Nurjhan et al, 1992; Puhakainen et al, 1992) have been found in patients with this condition. Although fluxes of these precursors are generally greater than normal, increased intrahepatic conversion rather than increased substrate availability is the major abnormality (Consoli et al, 1989a, 1990; Nurjhan et al, 1992; Puhakainen et al, 1992). Several factors have been proposed as being responsible at least in part for this. These include hyperglucagonaemia, insulin resistance, relative insulin deficiency, and increased hepatic free fatty acid oxidation consequent to increased lipolysis (Consoli et al, 1989a). Recently Acipimox, a nicotinic acid derivative that inhibits lipolysis, has been shown to reduce hepatic glucose output in patients with type II diabetes (Ratheiser et al, 1991).

The mechanism responsible for the impaired glucose uptake is poorly understood but is probably heterogenous and multifactorial. Rare instances

of genetic mutations of the insulin receptor have been found (Flier, 1992). There is evidence for operation of the glucose fatty acid cycle (Vaag et al, 1991), abnormal glucose transport activity and impairment in their mobilization from intracellular sites to the plasma membrane (Garvey et al, 1988), and deleterious effects due to chronic hyperglycaemia (Yki-Jarvinen, 1990), but their relative importance is unclear. Except for the abnormal glucokinase found in certain families with maturity-onset diabetes of the young (Permutt et al, 1992), the so-called MODY form of type II diabetes, no consistent primary enzymatic defects have been identified in pathways for glucose utilization.

GLUCOSE COUNTERREGULATION

Insulin-induced hypoglycaemia

The above-described gradual changes that occur during food deprivation contrast sharply with changes that occur following acute reductions in plasma glucose concentrations. The term glucose counterregulation refers to all of the processes by which the body defends itself against hypoglycaemia. Insulin-induced hypoglycaemia has been used as a model to study counterregulation. A characteristic hierarchy of responses is observed (Mitrakou et al, 1991b). First, as the plasma glucose concentration decreases to about 4 mmol/l, there is an increase in the secretion of counterregulatory hormones (glucagon, adrenaline, growth hormone, cortisol) and activation of the autonomic nervous system. If this action response is not sufficient to prevent a further decrease in plasma glucose, by the time levels reach about 3.2 mmol/l, the increase in autonomic nervous system activity is of such a magnitude as to initiate warning signs and symptoms (i.e. tremor, anxiety, sweating, hunger, palpitations). A further decrease in plasma glucose to approximately 2.7 mmol/l causes neuroglycopenic symptoms and signs of cognitive dysfunction.

With insulin-induced hypoglycaemia, initially there is both suppression of hepatic glucose output and stimulation of glucose uptake. Reversal of these changes is needed for recovery. The most important event is an early increase in hepatic glucose output (Rizza et al, 1979a), initially due to glycogenolysis, later mostly due to gluconeogenesis (Lecavalier et al, 1989). When insulin is administered as an intravenous or subcutaneous injection, hepatic glucose output increases until it exceeds increased rates of glucose utilization (Rizza et al, 1979a; Bolli et al, 1984d). As the effect of insulin dissipates, glucose utilization decreases; plasma glucose concentrations increase towards normal and counterregulatory hormone secretion diminishes (Figure 16). When insulin is administered as an infusion sufficient to raise circulating levels about 2–3-fold, plasma glucose levels generally remain below normal at a new steady state where glucose utilization, hepatic glucose output and counterregulatory hormone secretion remain increased (DeFeo et al, 1987) (Figure 17).

The physiological mechanisms involved in acute counterregulation in which insulin is administered as an intravenous bolus causes hypoglycaemia in human beings have been clarified from studies using somatostatin employed to inhibit glucagon and growth hormone secretion, adrenergic antagonists, and adrenalectomy (adrenaline and cortisol deficiency) (Rizza et al, 1979a; Cryer and Gerich, 1985). First of all, the prevention or correction of hypoglycaemia is due to dissipation of insulin coupled with activation of glucose counterregulatory systems. Secondly, there are several glucose counterregulatory factors and a hierarchy among them. Glucagon has a primary role in protecting against rapid decrements in plasma glucose; adrenaline is not normally critical, but it becomes important when glucagon is deficient. Thus, the process is affected little, if at all, when adrenaline

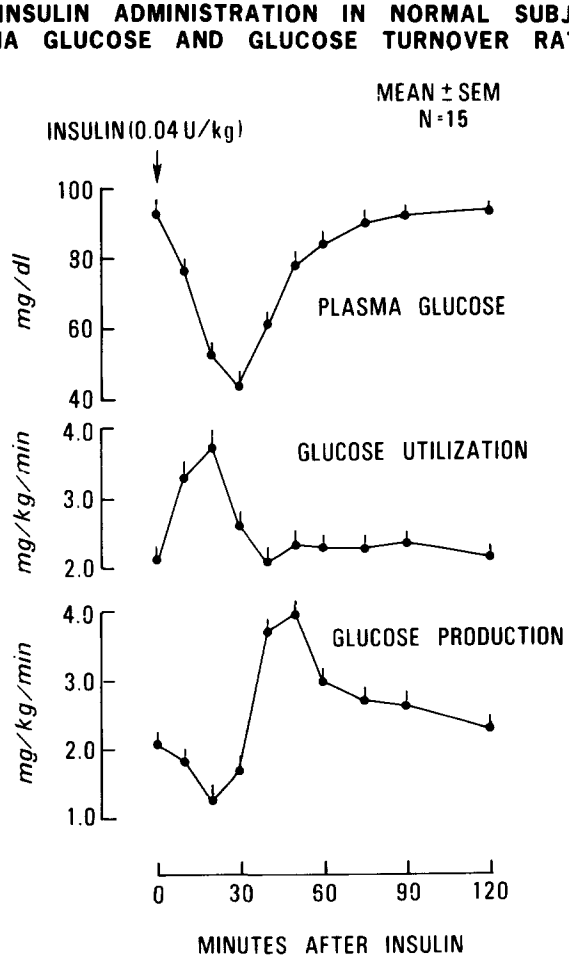

Figure 16. Changes in plasma glucose concentrations and rates of glucose, production and utilization in normal volunteers after intravenous injection of insulin.

secretion or action alone is deficient and is only partially impaired in the absence of glucagon secretion alone. However, glucose counterregulation fails and progressive hypoglycaemia occurs when both glucagon and adrenaline are deficient. Although other hormones, neural mechanisms or substrate effects, including glucose autoregulation, may well be involved in glucose counterregulation they are not sufficiently potent to prevent or correct hypoglycaemia when both of the key counterregulatory hormones, glucagon and adrenaline, are deficient and insulin is present.

Studies using similar tools but involving gradual induction of prolonged hypoglycaemia produced by infusion of insulin have reaffirmed the primarity of glucagon but have revealed more important roles of catecholamines, growth hormone and cortisol (DeFeo et al 1986, 1989a,b, 1991a,b) (Figure 17). Indeed, in this model, recent evidence indicates that a major portion of the effect of catecholamines on hepatic glucose output and glucose utilization is indirect, being mediated by increased lipolysis (Fanelli et al, 1992b). The resultant increase in lipid oxidation promotes increased gluconeogenesis and suppresses glucose utilization.

Clinical situations associated with hypoglycaemia are discussed elsewhere in this volume. One of the most common is diabetes mellitus (Bolli et al, 1983, 1984b,e; Cryer and Gerich, 1985). Patients with type I diabetes, for reasons as yet unclear, lose their glucagon response shortly after onset of the

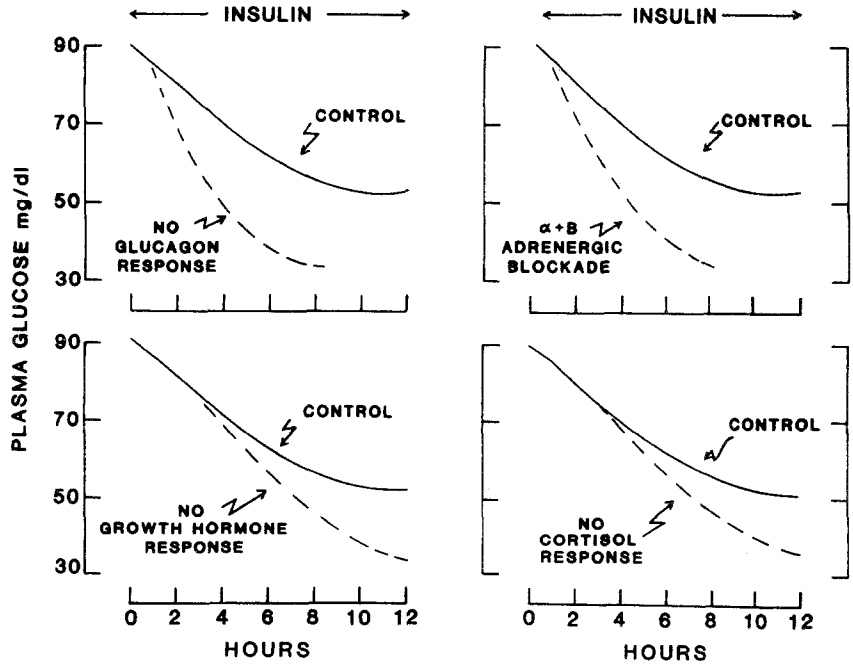

Figure 17. Effects of individual counterregulatory hormonal deficiencies on plasma glucose concentrations during intravenous infusion of insulin in normal volunteers.

disorder, placing them at risk for more frequent and more severe hypoglycaemia. As time progresses, the catecholamine response is also lost. In some cases this may simply be the result of autonomic neuropathy, but in other instances, perhaps the majority, this appears to be the result of recurrent hypoglycaemia (Cryer, 1992). As mentioned earlier, when glucagon and catecholamine responses are deficient there is almost complete paralysis of counterregulation to acute reductions in plasma glucose concentrations. In this situation, patients are less aware of the hypoglycaemia and often do not take appropriate action to prevent development of more severe hypoglycaemia. Finally, in patients with type I diabetes there is often a rebound of plasma glucose levels from hypoglycaemia to hyperglycaemia, the so-called Somogyi phenomenon, which can adversely affect glycaemic control (Figure 18) (Bolli et al, 1984c; Perriello et al, 1988).

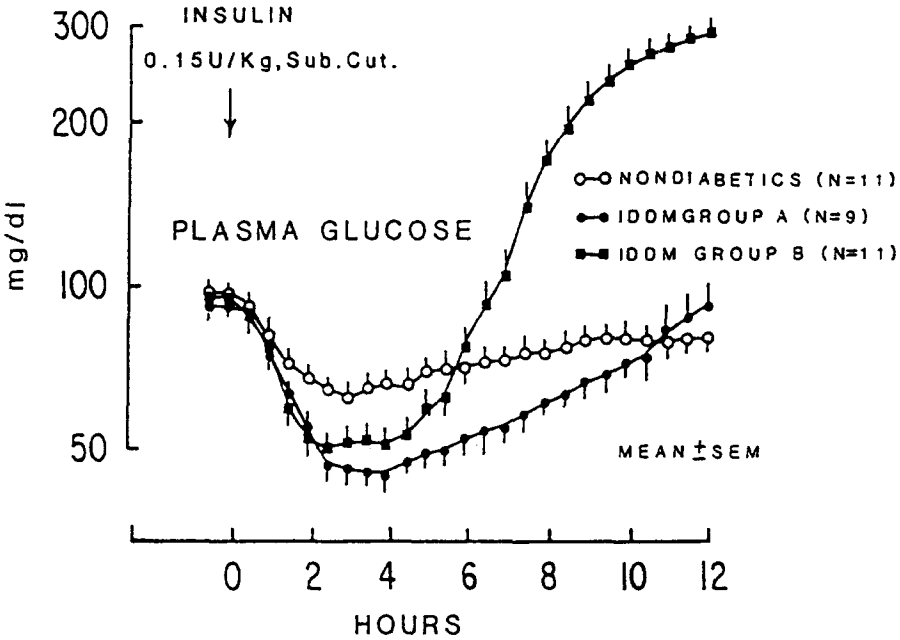

Figure 18. Example of rebound hyperglycaemia (Somogyi phenomenon) in patients with type I diabetes mellitus. (Reproduced with permission from Bolli et al (1984) *New England Journal of Medicine* **310:** 1706–1711.)

Physical activity and exercise

Many of the changes involved in counterregulation of insulin-induced hypoglycaemia are also involved during physical activity and exercise, except that this is a situation characterized by increased hepatic glucose output, increased glucose utilization and reduced circulating insulin levels (Wahren et al, 1978; Hirsch et al, 1991; Marker et al, 1991; Wasserman and Cherrington, 1991).

The metabolic response to exercise depends on its intensity and duration. Initially during modest exercise (e.g. cycling), muscle glycogen is the primary fuel for the active muscle. Beyond 10–15 min, circulating glucose and free fatty acids become increasingly important. Despite marked increases in glucose uptake by muscle, plasma glucose levels decrease by not more than 15–30% in healthy individuals. This occurs because the increased utilization of glucose is more or less approximated by increases in hepatic glucose output, initially mainly by glycogenolysis, later mainly by gluconeogenesis.

The factors involved in this have not been as clearly delineated as during counterregulation of insulin-induced hypoglycaemia. During exercise, secretion of glucagon, catecholamines, growth hormone and cortisol are increased, while insulin secretion diminishes. The latter is probably the result of neural input to the β-cell or the effect of circulating catecholamines, since it is observed even when plasma glucose concentrations do not change. Glucagon is the principal hormone responsible for the increased hepatic glucose output (Hirsch et al, 1991; Wasserman and Cherrington, 1991). The reduction in insulin secretion and increase in catecholamine release are probably the main factors responsible for the increase in lipolysis observed during exercise. Muscle takes up and utilizes free fatty acids primarily as a function of their circulating levels (Hagenfeldt and Wahren, 1968). Utilization of lipid by muscle would have a glucose-sparing effect via the glucose–fatty acid cycle described earlier. Moreover, increased hepatic lipid oxidation would promote increased gluconeogenesis, especially in a setting where there is reduced insulin secretion and increased glucagon and catecholamine secretion.

Except for marathon runners, severe hypoglycaemia is uncommon during exercise in healthy individuals. However, in patients with type I diabetes, exercise or strenuous exercise can produce either marked exaggeration of pre-existing hyperglycaemia or severe hypoglycaemia (Wahren et al, 1978). The latter appears to be the result of relative hyperinsulinaemia rather than deficient counterregulatory hormone responses. In non-diabetic individuals, insulin availability decreases during exercise because insulin secretion is suppressed. This cannot happen in a person whose insulin availability has been determined by prior injection. Moreover, increased blood flow to exercising limbs can increase absorption of insulin injected into limbs. Increases in hyperglycaemia generally occur only in ketotic diabetics and appear to be the result of both increased hepatic glucose output (mainly gluconeogenesis) and reduced glucose utilization.

Trauma and infection

Limitations of space do not permit a detailed discussion of this clinically important area. The reader is therefore referred to papers by Wolfe et al (1977a,b, 1979), Goschke et al (1978) and Wolfe and Durkot (1982), and reviews by Barton (1985), Frayn (1985), Wilmore and Aulick (1978), Lund and Williamson (1985), Buckingham (1985) and Evans et al (1989) which will be summarized here.

Trauma and infection are generally hypermetabolic states characterized

by increased energy expenditure, increased mobilization of endogenous fuels and massive release of counterregulatory neuroendocrine factors and various cytokines. Hepatic glucose output is increased mainly due to gluconeogenesis. Although there may be more glucose oxidation, a greater portion of the glucose taken up by cells is cycled back to the liver as lactate. Insulin resistance is readily understandable from the marked elevations of circulating levels of glucagon, growth hormone, cortisol and catecholamines. Thus, despite hyperinsulinaemia, there is enhanced proteolysis and lipolysis, both of which would provide substrate necessary to support increased gluconeogenesis. Also, the resultant increased fat oxidation would enhance hepatic glucose production while decreasing glucose utilization in peripheral tissues.

What one generally sees, therefore, is a catabolic state in which glucose is shunted away from its normal sites of utilization and redirected to other sites, presumably to assist in wound repair or overcoming infection. The situation resembles severe diabetic ketoacidosis except that substrates such as the overproduced glucose and ketone bodies are not lost in the urine but are utilized internally.

SUMMARY

Maintenance of plasma glucose concentrations within a narrow range despite wide fluctuations in the demand (e.g. vigorous exercise) and supply (e.g. large carbohydrate meals) of glucose results from coordination of factors that regulate glucose release into and removal from the circulation. On a moment-to-moment basis these processes are controlled mainly by insulin and glucagon, whose secretion is reciprocally influenced by the plasma glucose concentration. In the resting postabsorptive state, release of glucose from the liver (equally via glycogenolysis and gluconeogenesis) is the key regulated process. Glycogenolysis depends on the relative activities of glycogen synthase and phosphorylase, the latter being the more important. The activities of fructose-1,6-diphosphatase, phosphoenolpyruvate carboxylkinase and pyruvate dehydrogenase regulate gluconeogenesis, whose main precursors are lactate, glutamine and alanine. In the postprandial state, suppression of liver glucose output and stimulation of skeletal muscle glucose uptake are the most important factors. Glucose disposal by insulin-sensitive tissues is regulated initially at the transport step and then mainly by glycogen synthase, phosphofructokinase and pyruvate dehydrogenase. Hormonally induced changes in intracellular fructose 2,6-bisphosphate concentrations play a key role in muscle glycolytic flux and both glycolytic and gluconeogenic flux in the liver. Under stressful conditions (e.g. hypoglycaemia, trauma, vigorous exercise), increased secretion of other hormones such as adrenaline, cortisol and growth hormone, and increased activity of the sympathetic nervous system, come into play; their actions to increase hepatic glucose output and to suppress tissue glucose uptake are partly mediated by increases in tissue fatty acid oxidation. In

diabetes, the most common disorder of glucose homeostasis, fasting hyperglycaemia, results primarily from excessive release of glucose by the liver due to increased gluconeogenesis; postprandial hyperglycaemia results from both impaired suppression of hepatic glucose release and impaired skeletal muscle glucose uptake. These abnormalities are usually due to the combination of impaired insulin secretion and tissue resistance to insulin, the causes of which remain to be determined.

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