Chapter 2
Normal Glucose Homeostasis

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Glucose: From Origins to Fates

Arterial plasma glucose values throughout a 24-h period average approximately 90 mg/dl, with a maximal concentration usually not exceeding 165 mg/dl such as after meal ingestion\(^1\) and remaining above 55 mg/dl such as after exercise\(^2\) or a moderate fast (60 h).\(^3\) This relative stability contrasts with the situation for other substrates such as glycerol, lactate, free fatty acids, and ketone bodies whose fluctuations are much wider (Table 2.1).\(^4\)

This narrow range defining normoglycemia is maintained through an intricate regulatory and counterregulatory neuro-hormonal system: A decrement in plasma glucose as little as 20 mg/dl (from 90 to 70 mg/dl) will suppress the release of insulin and will decrease glucose uptake in certain areas in the brain (e.g., hypothalamus where glucose sensors are located); this will activate the sympathetic nervous system and trigger the release of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone).\(^5\) All these changes will increase glucose release into plasma and decrease its removal so as to restore normoglycemia. On the other hand, a 10 mg/dl increment in plasma glucose will stimulate insulin release and suppress glucagon secretion to prevent further increments and restore normoglycemia.

Glucose in plasma either comes from dietary sources or is either the result of the breakdown of glycogen in liver (glycogenolysis) or the formation of glucose in liver and kidney from other carbons compounds (precursors) such as lactate, pyruvate, amino acids, and glycerol (gluconeogenesis).

In humans, glucose removed from plasma may have different fates in different tissues and under different conditions (e.g., postabsorptive vs. postprandial), but the pathways for its disposal are relatively limited. It (1) may be immediately stored as glycogen or (2) may undergo glycolysis, which can be non-oxidative producing pyruvate (which can be reduced to lactate or transaminated to form alanine) or oxidative through conversion to acetyl CoA which is further oxidized through the tricarboxylic acid cycle to form carbon dioxide and water. Non-oxidative glycolysis carbons undergo gluconeogenesis and the newly formed glucose is either stored as glycogen or released back into plasma (Fig. 2.1).

Importance of Glucose Homeostasis

Although free fatty acids are the main fuel for most organs, glucose is the obligate metabolic fuel for the brain under physiologic conditions. This occurs because of low circulating concentrations of other possible alternative substrates (e.g., ketone bodies) or because of limitations of transport across the blood-brain barriers (e.g., free fatty acids).\(^6\) After prolonged fasting, because of an increase in their circulating concentration, ketone bodies may be used by the brain to a significant extent.\(^7\)
Table 2.1  Circulating substrates and regulatory hormones after overnight, moderate, and prolonged fasting

<table>
<thead>
<tr>
<th>Substrates (mmol/l)</th>
<th>Overnight fast (12–16 h)</th>
<th>Moderate fast (30–60 h)</th>
<th>Prolonged fast (&gt;1 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>5.0</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>0.5</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.05</td>
<td>0.1</td>
<td>0.2</td>
</tr>
<tr>
<td>3-Hydroxybutyrate</td>
<td>0.02</td>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Lactate</td>
<td>0.8</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Glutamine</td>
<td>0.6</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Alanine</td>
<td>0.3</td>
<td>0.2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hormones</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin (pmol/l)</td>
<td>60</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Glucagon (ng/l)</td>
<td>100</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Cortisol (nmol/l)</td>
<td>0.3</td>
<td>0.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Growth hormone (ng/l)</td>
<td>&lt;2</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Triiodothyronine (nmol/l)</td>
<td>1.8</td>
<td>1.6</td>
<td>0.9</td>
</tr>
<tr>
<td>Epinephrine (nmol/l)</td>
<td>0.2</td>
<td>0.4</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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Brain cannot synthesize glucose or store as glycogen more than a few minutes supply. Thus brain is dependent on a continuous supply of glucose from plasma.

At plasma glucose concentrations 20 mg/dl below normal levels, glucose transport becomes rate-limiting for brain glucose utilization. Glucose plasma concentrations below 55 mg/dl impair cerebral function, whereas more severe and prolonged hypoglycemia causes convulsions, permanent brain damage, and even death. On the other hand, even mildly elevated plasma glucose concentrations which occur in patients with impaired glucose tolerance increase risk for cardiovascular morbidity.

**General Considerations**

**Relative Changes in Glucose Fluxes**

Plasma glucose concentrations are determined by the relative rates at which glucose enters and leaves the circulation. Thus, the plasma glucose will increase only if the rate of entry exceeds its rate of exit and, conversely, plasma glucose level will decrease only if rates of exit exceed the rates of entry. To maintain relatively stable plasma glucose concentrations, increases in rates of glucose delivery into the systemic circulation (e.g., when
meal is ingested) require a comparable increase in rates of glucose removal from the circulation. For example, during vigorous exercise, fever, or trauma when the body’s utilization of glucose increases, there is normally a compensatory increase in glucose delivery.

Changes in glucose clearance, an index of efficiency of glucose removal from the circulation, by itself do not affect plasma glucose concentrations independent of changes in rates of glucose entry and exit.

**Factors Influencing Glucose Fluxes**

The most important factors on a moment to moment basis are the hormones (insulin, glucagon, and catecholamines), the sympathetic nervous system activity as well as the concentration of other substrates (FFA). On a more prolonged time basis (hours–days), other hormones (cortisol and growth hormone), nutritional factors (e.g., diet composition), exercise and physical fitness, along with concomitant changes in the sensitivity to hormones become important. Cortisol, growth hormone, and catecholamines affect glucose homeostasis by altering insulin sensitivity and also by changes in the availability of alternative substrates.

**Fasting vs. Postprandial States**

The mechanisms delivering glucose into the circulation (i.e., glycogenolysis vs. gluconeogenesis) and the sites for glucose disposal will vary depending on duration of fasting. For example, as fasting is prolonged, the proportion of gluconeogenesis increases and the contribution of hepatic glycogen stores decreases. Moreover, the relative contribution of the kidney increases. In regard to utilization, after an overnight fast, there is no net storage of glucose and all glucose taken up by tissues is either completely oxidized or converted to lactate.

**Actions of Key Regulatory Factors**

**Insulin**

Insulin regulates glucose metabolism by direct and indirect actions. Through binding to its receptors in the liver, kidney, muscle, and adipose tissue, insulin activates its signaling pathway which involves a complex cascade of protein kinases and regulatory proteins of which IRS-1 and IRS-2 are the most important (Table 2.2). This causes (1) suppression of glucose release from liver and kidney, (2) translocation of glucose transporters in muscle and adipose tissue to increase their glucose uptake, and (3) inhibition of release of FFA into the circulation due to suppression of the activity of hormone-sensitive lipase and a simultaneous increase in their clearance from the circulation. Although insulin does not increase glucose transport into liver, it promotes glycogen accumulation by inhibiting glucose-6-phosphatase and phosphorylase (glycogenolysis enzymes) while stimulating glycogen synthase.

The effect of insulin on circulating FFA levels indirectly reduces glucose release into circulation and promotes glucose removal since FFA stimulate gluconeogenesis and reduce glucose transport into cells.
Table 2.2  Mechanism of action of key metabolic regulators

<table>
<thead>
<tr>
<th></th>
<th>Glucose production</th>
<th>Glucose utilization</th>
<th>Lipolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Cortisol</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>FFA</td>
<td>↑</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

The main regulator of insulin secretion is the plasma glucose concentration: Increased plasma glucose after meal ingestion results in three-to fourfold increase in plasma insulin within 30–60 min whereas a decrease plasma glucose below 50 mg/dl will result in 80–90% reduction in plasma insulin levels. Acute increases in amino acids, and to a lesser extent, FFA also increase insulin secretion.4,16–18

After meal ingestion, intestinal factors called incretins (e.g., gastrointestinal-inhibitory peptide [GIP] and glucagon-like peptide [GLP-1]) augment insulin secretion. This is why plasma insulin concentrations increase to a greater extent after oral glucose load than after intravenous glucose despite identical plasma glucose concentrations.18,19

Metabolic processes vary in their sensitivity to insulin and their dose-response characteristics. At basal levels observed in the postabsorptive state (≈5–10 μU/ml), insulin is already inhibitng glucose and FFA release 30–50% (counteracting the effect of glucagon and the sympathetic nervous system) while having a trivial effect on tissue glucose uptake. Maximal suppression of glucose and FFA release normally is observed with plasma insulin concentrations seen postprandially (≈40–50 μU/ml), whereas maximal stimulation of tissue glucose uptake requires plasma insulin concentrations greater than 300 μU/ml levels not seen under normal physiological conditions except in extremely insulin resistant individuals in whom, of course, such level would not produce maximal effect.4,17,18,20

**Glucagon**

Glucagon, a hormone secreted from the α cells of the endocrine pancreas, is the major counterpart to insulin in the moment to moment regulation of plasma glucose. The control of its secretion is multifactorial.21 The main factors are direct effects of glucose and insulin. In humans, neural signals and substrates other than glucose, e.g., FFA and amino acids, play a minor role. Glucagon secretion is inhibited by hyperglycemia and stimulated by hypoglycemia.

Glucagon acts exclusively on the liver where it binds to its receptors and activates adenylate cyclase. As a result, intracellular cAMP level increases, enhancing glycogenolysis as a result of phosphorylase stimulation.22,23 This response wanes after several hours and is followed by an increase in gluconeogenesis due to a complex process involving both increased substrate uptake and enzyme activation.4,19–21,24 Thus, the main immediate action of glucagon to increase plasma glucose level is through stimulation of hepatic glycogenolysis.24

**Catecholamines**

Catecholamine release is mediated through changes in sympathetic nervous system, being increased during stress and hypoglycemia. Catecholamines inhibit insulin secretion while decreasing insulin action. Acting as both hormones (epinephrine) and neurotransmitters (norepinephrine), they are potent hyperglycemic factors whose actions, unlike those of glucagon, are sustained and affect both glucose release and glucose removal.20,25,26

For the most part, metabolic actions of catecholamines are mediated through beta 2 adrenergic receptors: At the liver, they directly increase glycogenolysis via cAMP activation of phosphorylase and, to a lesser extent, augment gluconeogenesis indirectly through increasing gluconeogenic substrate availability and plasma FFA.24,26
At the kidney level, they are potent stimulators of gluconeogenesis both directly and indirectly as in the liver and are actually more potent stimulators of renal glucose release than hepatic glucose release.\textsuperscript{27} In skeletal muscles, they reduce glucose uptake and stimulate glycogenolysis which results in an increase in release of lactate – the major gluconeogenic precursor. In adipose tissue, catecholamines stimulate lypolysis via activation of hormone-sensitive lipase which results in an increase in the release of FFA and glycerol, another key gluconeogenic precursor.\textsuperscript{24–26,28}

**Growth Hormone and Cortisol**

In contrast to glucagon and catecholamines which act almost immediately, the metabolic actions of growth hormone and cortisol generally take several hours to become evident. These can be summarized as being antagonistic to the action of insulin (i.e., they reduce the ability of insulin to suppress glucose release, stimulate glucose uptake, and inhibit lipolysis).\textsuperscript{25,29} Both hormones increase the synthesis of gluconeogenic enzymes and reduce glucose transport.\textsuperscript{29–31} In addition, cortisol can impair insulin secretion.\textsuperscript{31} Accordingly, the mechanisms for deterioration in glucose tolerance during immunosuppressive glucocorticoid treatment involve induction of insulin resistance and prevention of an appropriate compensatory increase in insulin secretion.\textsuperscript{31}

It is important to note that counterregulatory hormones work via different intracellular mechanisms which reinforce/synergize with one another. Simultaneously small increases in their plasma levels will have greater effect than large increases in plasma levels of only one hormone.\textsuperscript{8}

**FFA**

FFA are the predominant fuel used by most tissues of the body, the major exceptions being the brain, renal medulla, and blood cells.\textsuperscript{32–34} Increases in plasma FFA have many potentially important metabolic consequences:\textsuperscript{35,36} stimulation of hepatic and renal gluconeogenesis; inhibition of muscle glucose transport; and competition with glucose as an oxidative fuel. The major regulators of circulating FFA levels are the sympathetic nervous system and growth hormone\textsuperscript{32} (which increase plasma FFA levels), insulin (which reduces plasma FFA levels by suppressing lipolysis and increasing FFA clearance), and hyperglycemia. There is evidence for heterogeneity of adipose depots with visceral fat being more metabolically active than subcutaneous fat.\textsuperscript{32,36}

**Incretins: The Entero-insular Axis**

The concept that certain factors secreted from the intestinal mucosa in response to nutrients can stimulate the pancreas to release insulin was first introduced to explain the phenomenon of greater increase in plasma insulin levels in response to oral glucose load compared with the same load of glucose given intravenously (Table 2.3). The term incretin was used to denote these factors.\textsuperscript{37} The first incretin hormone identified, was called gastric inhibitory polypeptide (GIP) based on its ability to inhibit gastric acid secretion in dogs.\textsuperscript{37} Another peptide was discovered later and named glucagon-like peptide-1 based on its homology to glucagon.\textsuperscript{38} Both peptides are

<table>
<thead>
<tr>
<th>Effects on</th>
<th>GLP1</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreas</td>
<td>↑Insulin secretion</td>
<td>↑Insulin secretion</td>
</tr>
<tr>
<td></td>
<td>↓Glucagon secretion</td>
<td>–</td>
</tr>
<tr>
<td>Peripheral</td>
<td>↓Hepatic glucose release</td>
<td>–</td>
</tr>
<tr>
<td>Gastric</td>
<td>↑Muscle glucose uptake</td>
<td>–</td>
</tr>
<tr>
<td>CNS</td>
<td>↑Satiety, ↓appetite, ↓weight</td>
<td>–</td>
</tr>
</tbody>
</table>

Table 2.3 Effects of GLP1 and GIP on different tissues
secreted from intestinal endocrine mucosa (L and K cells) within minutes of nutrient ingestion and have short half-life (minutes) due to the rapid inactivation by a proteolytic enzyme called dipeptidyl peptidase-4 (DPP-4).

GLP-1 and GIP inhibit glucagon secretion, only GLP-1 delays gastric emptying and only GLP-1, possibly through a neural mechanism, promotes satiety, decreasing food intake and leading to weight loss.

Upper Gastrointestinal Function and Glycemic Homeostasis

Recent studies indicate that gastric emptying is a major physiologic determinant of postprandial glycemia by controlling the nutrient delivery into the small intestine: It accounts for $\sim 35\%$ of the variance in peak blood glucose concentrations after ingestion of oral glucose in healthy volunteers or patients with type 2 diabetes. It is delayed in acute hyperglycemia and accelerated during hypoglycemia.

Effect of Meal Composition on Glucose Metabolism

In healthy humans, adding protein or fat to oral glucose was found to lower postprandial glucose concentrations by slowing the gastric emptying and stimulating incretins. Protein also enhances non-glucose-dependent insulin release.

Glucose Transport Pathways

Due to its hydrophilic nature, glucose diffuses slowly across the lipid bilayer of the cell membrane and needs specific transporter proteins to facilitate its entry into cells. Glucose flux varies among tissues depending to a large extent on the characteristics of the transporters in that specific tissue and whether the process is sensitive to insulin or not. Insulin regulates the steady-state concentration of glucose transporters by promoting their synthesis and also acutely accelerates the uptake of glucose, promoting mobilization of the transporters to the cell membrane.

There are two distinct families of transport proteins. (1) Facilitative GLUT family: These transporters promote facilitated diffusion of glucose, a process that is not energy dependent and that follows Michaelis–Menten kinetics. The high-affinity transporters (GLUT 1, 3, 4) have a Michaelis–Menten constant ($K_m$) below the normal range of blood glucose concentrations and are capable of providing glucose transport under basal conditions for many cells. GLUT3 is the major neuronal transporter (lowest $K_m$) whereas GLUT4 mediates insulin-stimulated glucose uptake by skeletal muscle, heart, and adipose tissues. Insulin and exercise promote GLUT3 expression on cell surface. The low-affinity transporters (GLUT2) are present on ß-cells and in tissues exposed to large glucose fluxes, such as intestine, liver, and kidney. (2) SGLT family: These transporters utilize the electrochemical sodium gradient to transport glucose against concentration gradients and are prominent in intestine and kidney. SGLT1 is responsible for the dietary uptake of glucose from the small intestine lumen whereas SGLT2 plays a major role in glucose reabsorption from proximal renal tubule.

Glucose Production and Hepatorenal Glucose Reciprocity

A considerable body of evidence indicates that somehow release of glucose by the liver and kidney are interrelated so that a reduction in release by one organ is associated by an increase by the other to further maintain optimal glucose homeostasis. This relationship is referred to as hepatorenal glucose reciprocity.

Until recently, it was widely thought that the liver was the sole source of glucose except during acidosis and after prolonged fasting. During the past few years, numerous reports indicated that the kidney is responsible
on an average for about 20% of glucose released into the circulation in overnight fasted normal human volunteers. Moreover, a number of studies have shown that kidney increased its glucose release (gluconeogenesis) to compensate for restricted (physiologic) or impaired (pathologic) hepatic glucose release.53 Physiologic examples of the phenomena occur postprandially and after prolonged fasting. After meal ingestion, the hepatic glucose release is suppressed \( \sim 80\% \), while renal glucose release increases and actually exceeds hepatic glucose release (HGR) for several hours63 to allow for hepatic glycogen repletion.53 Also after prolonged fasting (60 h), renal glucose release increases fourfold while hepatic glucose release decreases by \( \sim 45\% \).59 Examples of renal compensation with pathologic process are the following: (1) Hepatic Diseases: Hypoglycemia is extremely uncommon in patients with severe liver disease in the absence of other factors (infection, heart failure). Studies using an animal model for liver failure have demonstrated that there is a compensatory increase in renal glucose release to compensate for the reduced hepatic glucose release.53,64–66 In humans, during the period of hepatic transplantation when patients have no functioning liver, hypoglycemia does not occur; overall glucose release into the circulation either decreases minimally or not at all, and there is an increase in renal glucose release.67,68 (2) Acidosis: Acidosis stimulates renal glucose release69 while inhibiting hepatic glucose release.70 In patients with respiratory acidosis, an increase in net renal glucose release has been demonstrated inversely proportional to blood pH.71 (3) Glucose Counterregulation in Diabetes: Patients with type 15 and prolonged type 272 diabetes lose their glucagon response and become dependent on catecholamine responses. Catecholamines are the major hormonal factor responsible for the increase in renal glucose release during hypoglycemia.73 Consequently, type 1 diabetic patients with both reduced glucagon and epinephrine responses have decreases in both hepatic and renal glucose release during hypoglycemia.74 In patients with type 2 diabetes, who have reduced plasma glucagon responses, compensatory increases in hepatic glucose release during recovery from hypoglycemia are reduced, whereas renal glucose release is increased.75

The Postabsorptive State

The period after 14–16 h overnight fast is commonly referred to as the postabsorptive state. During this time plasma glucose concentrations average about 85 mg/dl (70–100 mg/dl) and are relatively stable since rates of glucose release into the circulation approximate the rates of glucose exit from the circulation (\( \sim 10 \mu g/kg/min \)).4

Glucose Production

The liver is responsible for approximately 80% of glucose release into the circulation in the postabsorptive state.76 Under these conditions, \( \sim 50\% \) of the glucose entering the circulation is due to glycogenolysis and the reminder (\( \sim 5.0 \mu mol/kg/min \)) to gluconeogenesis77 (Table 2.4). The proportion owing to gluconeogenesis rapidly increases with the duration of fasting, as glycogen stores become depleted; by 24 h from the last meal, gluconeogenesis accounts for about 70% of all glucose released into the circulation, and by 48 h, it accounts for over 90% of all glucose released into the circulation.3,77

The kidney normally contains little glycogen and renal cells that could make glycogen lack glucose-6-phosphatase. Consequently, virtually all the glucose released by the kidney is the result of gluconeogenesis.76 Although the liver releases about four times as much as the kidney under postabsorptive conditions, both organs release about the same amount (2.5–3.0 \( \mu mol/kg/min \)) from gluconeogenesis and the proportion of overall glucose release owing to renal gluconeogenesis increases even further with prolonged fasting 60

The liver releases glucose both by glycogenolysis and gluconeogenesis and can be considered to be the sole source of glucose due to glycogenolysis. In overnight fasted people, the liver contains about 75 g of glycogen.78 Thus, if it releases glycogen at a rate of 63 mg/min (5 \( \mu mol/kg/min \)), glycogen stores would be totally depleted in about 20 h and the sole source of glucose released into the circulation at this point would be gluconeogenesis.4
Table 2.4 Summary of postabsorptive glucose release

<table>
<thead>
<tr>
<th></th>
<th>Rate (μmol/kg/min)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Glucose release</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. Hepatic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Glycogenolysis</td>
<td>5.0</td>
<td>50</td>
</tr>
<tr>
<td>2. Gluconeogenesis</td>
<td>3.0</td>
<td>30</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.3</td>
<td>13</td>
</tr>
<tr>
<td>Alanine</td>
<td>0.8</td>
<td>8</td>
</tr>
<tr>
<td>Other amino acids</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>Glycogenolysis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gluconeogenesis</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>B. Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Glycogenolysis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2. Gluconeogenesis</td>
<td>2.0</td>
<td>20</td>
</tr>
<tr>
<td>Lactate</td>
<td>1.2</td>
<td>12</td>
</tr>
<tr>
<td>Glutamine</td>
<td>0.4</td>
<td>4</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.2</td>
<td>2</td>
</tr>
<tr>
<td>Other amino acids</td>
<td>0.1</td>
<td>1</td>
</tr>
<tr>
<td>Alanine</td>
<td>0.1</td>
<td>1</td>
</tr>
</tbody>
</table>

Regulation of Glucose Production: Hepatic vs. Renal

Glucose release by the liver and kidney are regulated differently. Insulin suppresses glucose release by both organs (1) directly by affecting enzyme activation/deactivation and (2) indirectly through gluconeogenic substrate availability and gluconeogenic activators (e.g., suppression of FFA and glucagon).\(^\text{13}\)

Glucagon, which increases both glycogenolysis and gluconeogenesis in the liver, however, has no effect on the kidney.\(^\text{55}\) Epinephrine, which can directly activate hepatic glycogenolysis, appears to increase glucose release, predominantly by directly stimulating renal gluconeogenesis and, to a lesser extent, by increasing availability of gluconeogenic precursors/activators (e.g., glycerol and FFA).\(^\text{27,56}\)

The major precursors for gluconeogenesis are lactate, glycerol, glutamine, and alanine.\(^4\) Most amino acids released from skeletal muscle protein are converted to alanine and glutamine for transport through plasma to liver and kidney: alanine being selectively used by liver, glutamine being preferentially used in the kidney, while lactate and glycerol used to roughly comparable extent by both organs. In the resting postabsorptive state, lactate is the major gluconeogenic precursor, accounting for about half of all gluconeogenesis.\(^4\)

Glucose Utilization

Although the postabsorptive state is often considered to represent a steady state, it is actually a pseudo-steady state, since rates of glucose removal slightly, and undetectably, exceed rates of glucose release so that if fasting is prolonged, plasma glucose levels gradually decrease; by 20–24 h of fasting they may be 15–20% lower (Fig. 2.2). However, even after 72 h of fasting, they are usually maintained above 50 mg/dl.\(^5\)

In the postabsorptive state, there is no net storage of glucose; consequently, glucose taken up by tissues is either completely oxidized to CO\(_2\) or released back into the circulation as lactate, alanine, and glutamine\(^79\) for reincorporation into glucose via gluconeogenesis (Table 2.5).

Most glucose used by the body can be accounted for by six tissues: the brain (45–60%), skeletal muscle (15–20%), kidney (10–15%), blood cells (5–10%), splanchnic organs (3–6%), and adipose tissue (2–4%).\(^4\)

Glucose taken up by the brain is completely oxidized whereas that taken up by the kidney, blood cells, splanchnic tissues, and muscle mainly undergoes glycolysis. Recall that most of the body energy requirements are met by oxidation of FFA which compete with glucose as the fuel of choice in certain organs (e.g., skeletal muscles, heart, and possibly kidney).\(^35\)
Glucose uptake by brain, blood cells, renal medulla, and splanchnic tissue occurs largely independent of insulin, and plasma insulin concentrations are low in the postabsorptive state (<10 μU/ml). Under these conditions, amount of glucose removed from the circulation is determined almost exclusively by tissue demands, the mass action effect of the plasma glucose concentration per se, and the number and characteristics of the glucose transporters in specific tissue rather than by insulin. Insulin may be viewed as playing a permissive role, while counterregulatory hormones that antagonize the action of insulin (e.g., cortisol, growth hormone, epinephrine, and thyroid hormones) can be viewed as modulating the sensitivity of tissue to the effect of insulin on tissue glucose uptake and utilization.4,8

### Prolonged Fasting

With prolongation of fasting, plasma insulin levels decrease while those of glucagon, catecholamines, growth hormone, and cortisol increase (Table 2.6). Consequently, plasma FFA, glycerol, and the ketone bodies – products of FFA oxidation (beta hydroxybutyrate) – increase. Since hepatic glycogen stores become depleted by 60 h, virtually all of the glucose release at this time is due to gluconeogenesis. Initially, hepatic gluconeogenesis decreases while renal gluconeogenesis increases, with an overall result of a decrease in overall glucose release
Table 2.6  Glucose release and disposal after prolonged fasting (~60 h)

<table>
<thead>
<tr>
<th>Tissues</th>
<th>Glucose disposala</th>
<th>Glucose releasea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.0</td>
<td>Overall</td>
</tr>
<tr>
<td>Oxidation</td>
<td>4.8</td>
<td>Gluconeogenesis</td>
</tr>
<tr>
<td>Glycolysis</td>
<td>1.2</td>
<td>Glycogenolysis</td>
</tr>
<tr>
<td>Tissues</td>
<td></td>
<td>Tissues</td>
</tr>
<tr>
<td>Brain</td>
<td>3.5</td>
<td>Liver</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>1.0</td>
<td>Kidney</td>
</tr>
<tr>
<td>Splanchnic organs</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Adipose tissue</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Blood cells</td>
<td>0.4</td>
<td></td>
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a \( \mu \text{mol/kg/min.} \)

and a slight increase in gluconeogenesis. With more prolonged fasting, there is a further decrease in glucose release as gluconeogenesis decreases.\(^{59}\)

Although more glycerol is available for gluconeogenesis, less lactate is available due to decreased production by glycolysis, and less amino acids are available because muscle proteolysis decreases. These changes limit gluconeogenesis despite increase in plasma FFA and counterregulatory hormones which promote gluconeogenesis.

Initially during the course of the fast, decreases in glucose release are slightly greater than decreases in glucose uptake so that plasma glucose levels decrease slowly. However, eventually, the rates of uptake and release approximate one another so that a new pseudo-steady state is established after 60–70 h with plasma glucose levels usually averaging 55–65 mg/dl.\(^{59}\)

These changes during prolonged fasting are relevant to changes seen in chronically ill patients who often are anorexic, malnourished, and miss meals in hospital because of diagnostic or therapeutic procedures. Because of the limitations on gluconeogenesis, such patients, i.e., those with chronic renal failure, severe liver disease, or heart failure, are prone to develop hypoglycemia during infections or other situations which increase the body’s glucose utilization.\(^{4,59}\)

Suppression of insulin secretion with prolonged fasting forms the basis for the 72 h fast for the diagnosis of insulinoma. In such patients, insulin secretion is not appropriately reduced and this leads to the development of hypoglycemia (i.e., plasma glucose levels <45 mg/dl).\(^{4}\)

The Postprandial State

Complete assimilation of the constituents of a mixed meal containing fat, protein, and carbohydrate and restoration of the postabsorptive state takes at least 6 h,\(^{80}\) whereas assimilation of a pure carbohydrate load is generally complete within 4–5 h. Despite these time differences, there is little evidence that the fate of ingested carbohydrate differs markedly under the two conditions.\(^{80}\) Because people usually eat at least three times a day, the majority of the day is spent in the postprandial state.

Various factors can affect the extent of circulating glucose excursions after meal ingestion. These include the time and the degree of physical activity since the last meal; the composition and form (liquid vs. solid); rate of gastric emptying; digestion within the lumen of the small intestine; absorption into the portal vein; extraction by the liver; suppression of endogenous glucose release; and finally the uptake, storage, oxidation, and glycolysis of glucose in posthepatic tissues.\(^{81}\)

From a practical point of view, however, the major factors influencing postprandial glucose homeostasis are those that affect suppression of endogenous glucose release and those that affect hepatic and posthepatic tissue glucose uptake.
Glucose taken up by tissues postprandially can be either immediately stored or undergoes glycolysis. Therefore, initial direct storage of glucose (glucose to glucose-6-phosphate to glycogen) can be calculated as the difference between whole body glucose uptake and whole body glycolysis. Since postprandial de novo lipogenesis and adipose tissue glucose storage are negligible in humans, virtually all of this storage should represent glycogen formation.\(^{30,82}\)

Of the glucose undergoing glycolysis, some will be oxidized; the remainder will undergo non-oxidative glycolysis leading to the formation of pyruvate, lactate, and alanine. These 3-carbon compounds will then be available to undergo gluconeogenesis and either be stored in glycogen via the indirect pathway or be released into plasma as glucose.\(^{18}\)

Figure 2.3 depicts the pathways for disposal of a mixed meal containing 78 g of glucose.\(^{18}\) During the 6-h postprandial period, a total of \(~98\) g of glucose were disposed of. This was more than the glucose contained in the meal due to persistent endogenous glucose release (\(~21\) g): Splanchnic tissues initially took up \(~23\) g, and an additional \(~75\) g were removed from the systemic circulation. Direct glucose storage accounted for \(~32\) g and glycolysis \(~66\) g (oxidative \(~43\) g and non-oxidative \(~23\) g). About 11 g of glucose appeared in plasma as a result of gluconeogenesis. This indicates that glycolysis is the main initial postprandial fate of glucose, accounting for \(~66\)% of overall disposal. Oxidation and storage each account for about 45%. The majority of glycogen is formed via the direct pathway (\(~73\)%).

**Fig. 2.3** Summary of sites and routes of postprandial glucose disposal. From Woerle et al.\(^{18}\). Copyright © 2003. The American Physiological Society. Used with permission

**Changes in Plasma Hormone and Substrate Concentration**

After ingestion of 75 g glucose, plasma glucose levels increase to a peak in 30–60 min, usually not exceeding 160 mg/dl and gradually return to or slightly below postabsorptive values by 3–4 h (Fig. 2.4). Although plasma glucose levels have returned to postabsorptive levels, glucose fluxes and organ glucose exchange have not. Plasma insulin concentrations follow a similar profile to those of plasma glucose and average only about three- to fourfold basal values during this period.

Plasma glucagon concentrations change reciprocally to those of insulin and are generally suppressed by about 50%. Early insulin release (i.e., that accruing within 30–60 min) plays a critical role in maintaining normal postprandial glucose homeostasis.\(^{81}\)

Plasma FFA and glycerol levels decrease due to inhibition of lipolysis while plasma lactate concentrations increase as a result of increased glycolysis in liver, muscle, adipose tissue, and kidney. After ingestion of a mixed meal containing protein, the circulating concentrations of several amino acids increase.\(^{18}\)
**Fig. 2.4** Changes in plasma glucose, insulin, and glucagon after ingestion of a 75 g oral glucose load in normal volunteers

**Changes in Rates of Glucose Entry into and Exit from Plasma**

Rates of glucose appearance in plasma represent the sum of orally ingested glucose escaping first pass splanchnic (hepatic) extraction and the residual release of endogenous glucose by liver and kidney (Figs. 2.5 and 2.6). Appearance of ingested glucose in the systemic circulation is detected as early as 15 min. Glucose concentration reaches a peak at 60–80 min and gradually decreases thereafter.18

On average during a 4–5 h postprandial period about 75% of the glucose molecules in plasma represent those from the meal. Endogenous glucose release by the liver decreases rapidly and is suppressed nearly 80% during the 5 h postprandial period. As a result, nearly 25 g less glucose due to endogenous production reaches the systemic circulation during this interval. In contrast to the liver, recent studies indicate that endogenous renal glucose release is not suppressed and actually increases during this period so that it exceeds hepatic glucose release.83 This increase in renal glucose release would permit more complete suppression of hepatic glucose release and facilitate more efficient hepatic glycogen replenishment.83

**Fig. 2.5** Changes in rates of glucose entry into and removal from plasma after ingestion of a 75 g oral glucose load in normal volunteers
**Normal Glucose Homeostasis**

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**Tissues Responsible for Disposal of Ingested Glucose**

Based on a survey of published studies, a consensus view of the disposal of a hypothetical meal containing 100 g carbohydrate is depicted in Fig. 2.7. About 30% of the ingested glucose (∼33 g) is initially extracted by splanchnic tissues. Most is taken up by the liver and immediately incorporated into glycogen via “direct pathway” to hepatic glycogen. A significant portion of glucose taken up by the liver probably undergoes glycolysis and is released as lactate which is eventually taken up by the liver where it undergoes gluconeogenesis and is subsequently incorporated into glycogen via “indirect pathway.” Inhibition of glucose-6-phosphatase causes the glucose-6-phosphate made from this lactate to enter glycogen rather than being released into the circulation as free glucose.

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**Gut**

**Liver**

**Kidney**

**Muscle**

**Brain**

**Adipose Tissue**

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**Fig. 2.7** Postprandial glucose disposal. Of 100 g glucose ingested 30% is taken up by the liver and 70% is released into the systemic circulation. Of this 70 g, 15 g (∼20%) is extracted by the liver, 15 g (∼20%) is taken up by the brain, 27 g (∼40%) is taken up by skeletal muscle, and the remaining 20% is taken up by kidney, adipose tissue, skin, and blood cells.

Of the remaining 70 g glucose, which enters the systemic circulation, 25–30 g is taken up by skeletal muscle, initially to be oxidized in place of FFA and later (after 2–3 h) to be stored as glycogen. Relatively little of the glucose taken up by muscle is released into the circulation as lactate and alanine.

About 15 g (∼20% of the ingested glucose entering the circulation) is taken up by brain as a substitute for the endogenously produced glucose that normally would have been taken up during this period. Recall that endogenous release of glucose from the liver is markedly reduced postprandially.
Another 15 g is extracted from the systemic circulation by the liver either as intact glucose (direct pathway) or as lactate, alanine, and glutamine, whose carbon backbone originated from ingested glucose, for further glycolysis (indirect pathway). Thus, ultimately splanchnic tissues dispose of nearly half of the ingested glucose. The kidney may take up as much as 8 g (~10% of the ingested glucose entering the circulation). This would leave 5–10 g (7–15%) of the ingested glucose reaching the systemic circulation to be taken up by adipose and other tissues.

**Summary**

For both the fasting and postprandial states, factors which affect the rate of entry of glucose into the circulation are more important for maintaining normal glucose homeostasis than those which affect the rate of removal of glucose from the circulation. In the postabsorptive state gluconeogenesis and glycogenolysis contribute equally to glucose release. The liver is responsible for all of glycogenolysis and half of gluconeogenesis. In the postprandial state almost all endogenous glucose release is via gluconeogenesis.

The regulation of glucose entry into the circulation is complex, being influenced by hormones, the sympathetic nervous system, and substrates (i.e., free fatty acid concentrations and availability of gluconeogenic precursors). Of these, insulin and glucagon are most important both in the fasting and in the postprandial state. In the latter, incretins which form the entero-insular axis contribute by altering gastric emptying and insulin and glucagon secretion. Finally, recent studies have provided evidence for hepatorenal reciprocity, meaning that, under a variety of conditions, reciprocal changes occur in hepatic and renal glucose release so as to maintain overall glucose release relatively constant.

**References**


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