دانشگاه کردستان
University of Kurdistan

Metabolism Regulation 5

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

Ref: Keith N. Frayn. Metabolic Regulation: A Human Perspective. 3rd Edition. Wiley Blackwell, 2010. Chapter 7.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.1 Carbohydrate Metabolism

❖ Glucose is always present in the blood. Although the concentration remains relatively constant, at close to 5 mM in humans (Figure 7.1).

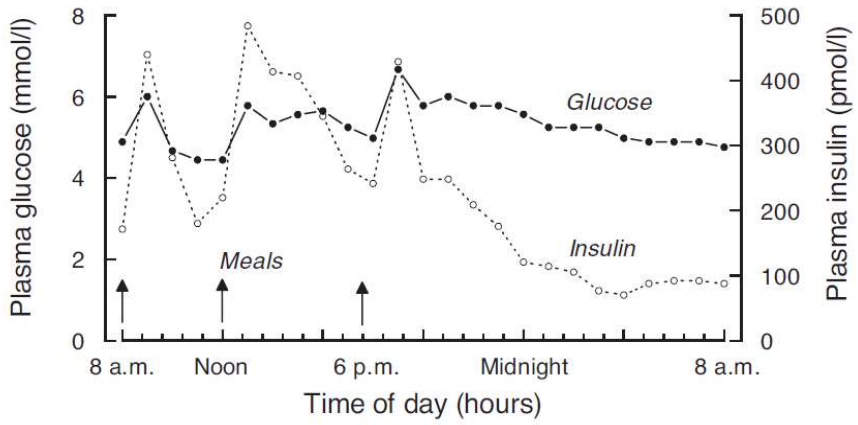

Figure 7.1 Relative constancy of blood glucose concentrations during a typical day, compared with the relative variability of plasma insulin concentrations. For a mechanical analogy, see Figure 7.2. Based on Reaven *et al.* (1988). From *Diabetes* by Reaven, G.M., Hollenbeck, C., Jeng, C.-Y., Wu, M.S., Chen, Y.-DI. Copyright © 1988 by American Diabetes Association. Reproduced with permission of American Diabetes Association.

- Among all the energy substrates circulating in the blood, the concentration of glucose is by far the most constant. Why?

One reason for this is that it is necessary to provide a constant source of energy for those tissues in which the rate of glucose utilization is regulated primarily by the extracellular glucose concentration. For instance, we have seen that in the brain the rate of glucose utilization is fairly constant over a range of glucose concentrations, but will decrease considerably – with adverse consequences – if the glucose concentration falls below about 3 mmol/l. Furthermore, consistently elevated concentrations of glucose in blood – above about 11 mmol/l – have harmful effects, although these may take a matter of years to develop

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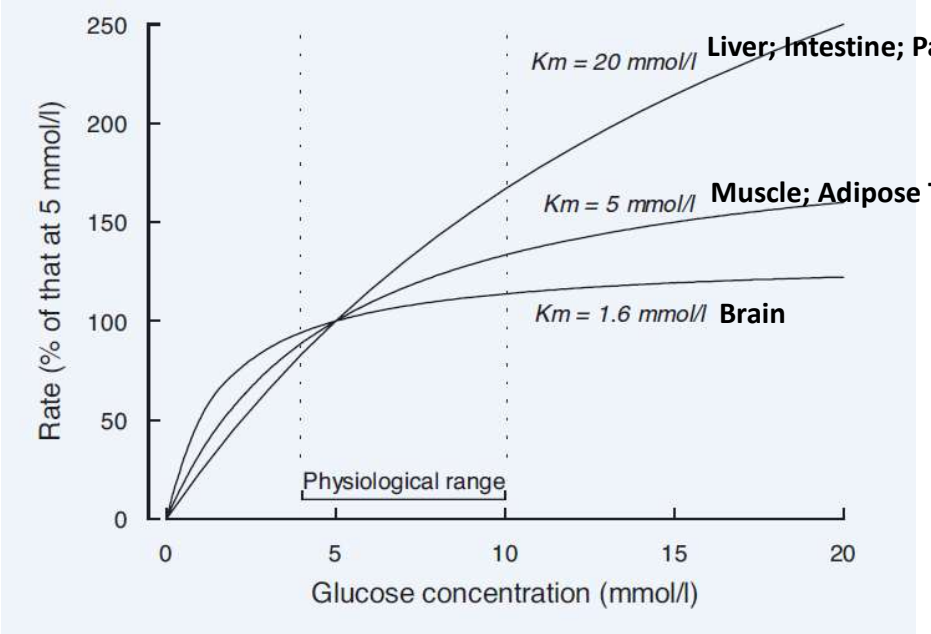
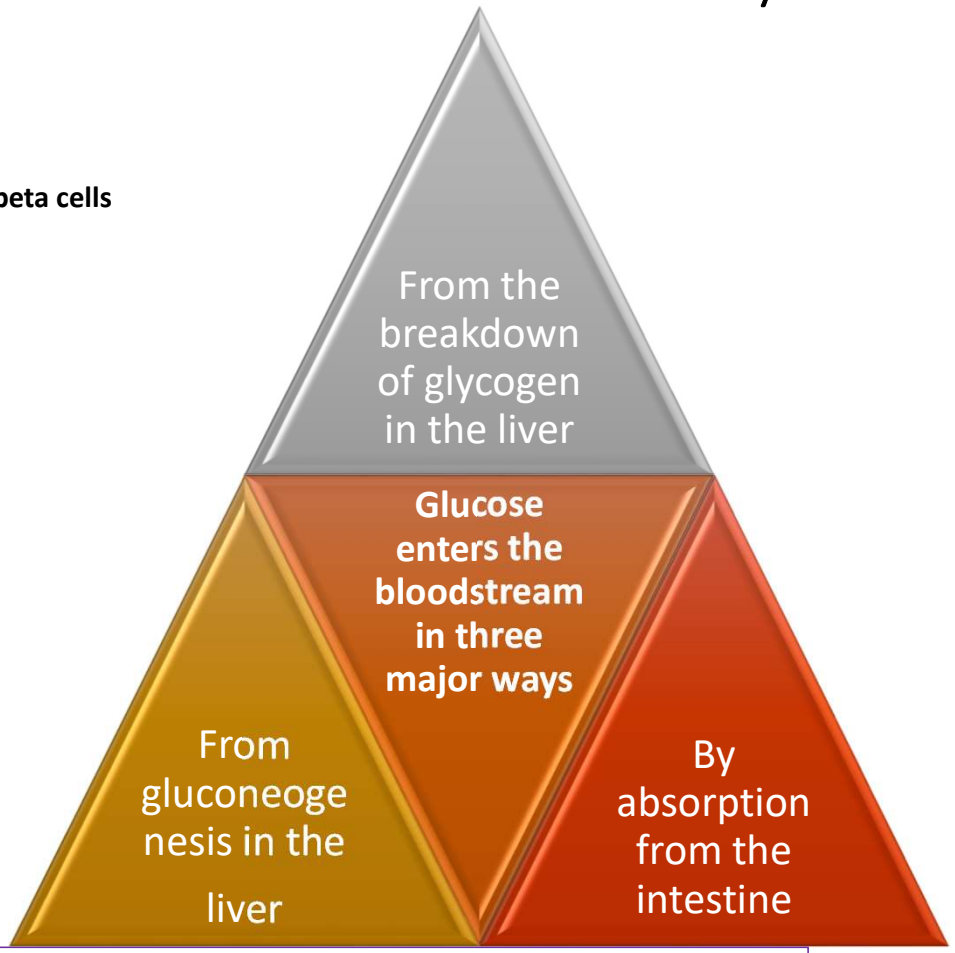
7.1 Carbohydrate Metabolism



The effect of the glucose transporter on the rate of glucose entry into cells



Remember that muscle glycogen breakdown does not liberate glucose into the blood, since muscle lacks glucose-6-phosphatase. Muscle glycogen can contribute to blood glucose indirectly, through glycolysis to lactate, released into the circulation, which can then be used by the liver for gluconeogenesis

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.1 Carbohydrate Metabolism

- The constancy of blood glucose concentration is brought about by coordinated control of various aspects of glucose metabolism. It will already be clear that insulin plays a major role in this coordination.
- The relationship between blood glucose and insulin concentrations is illustrated in Figure 7.1, which shows the relative constancy of glucose compared with the variability of insulin.

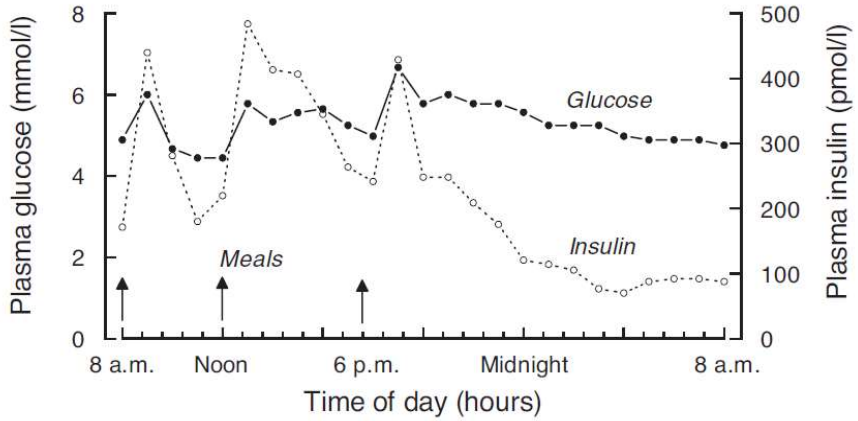


Figure 7.1 Relative constancy of blood glucose concentrations during a typical day, compared with the relative variability of plasma insulin concentrations. For a mechanical analogy, see Figure 7.2. Based on Reaven *et al.* (1988). From *Diabetes* by Reaven, G.M., Hollenbeck, C., Jeng, C.-Y., Wu, M.S., Chen, Y.-DI. Copyright © 1988 by American Diabetes Association. Reproduced with permission of American Diabetes Association.

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7.1 Carbohydrate Metabolism

- This is typical of many systems in which one component is varying in order to keep another constant. A useful analogy is with a thermostatically controlled water tank. At its simplest, a thermostat dips into the water. When the water temperature falls below a certain limit – for instance, 2◦ below the desired temperature or "set-point" – an electrical switch is triggered and the heating element is switched on. When the temperature reaches an upper limit – perhaps 2◦ above the set-point – the switch cuts out. The water temperature (the controlled variable) stays constant within quite narrow limits (4◦ in this case), whereas the electrical current through the switch and heater (the controlling variable) varies between wide extremes (Figure 7.2).

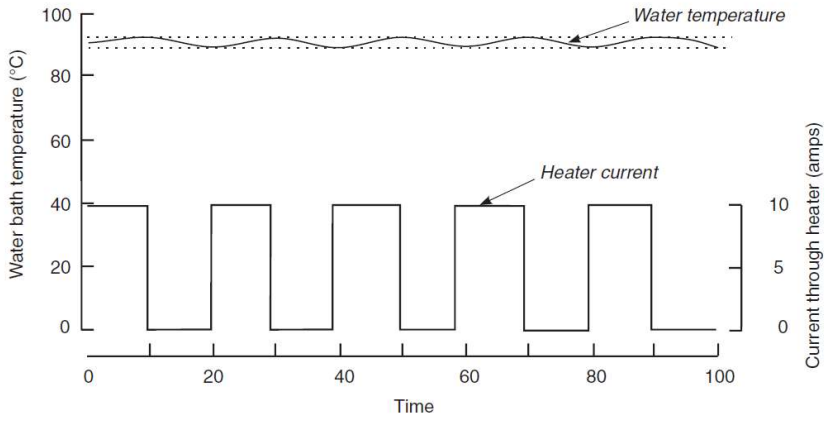

Figure 7.2 An analogy for metabolic regulation. The temperature in a thermostatically controlled water bath (the *controlled variable*) is relatively constant with only small variations around the *set-point* (the desired temperature), whereas the electrical current flowing through the heater (the *controlling variable*) varies between much wider extremes.

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7.1 Carbohydrate Metabolism: The Postabsorptive State

- ***The phrase postabsorptive*** state implies that all of the last meal has been absorbed from the intestinal tract, but not much further time has elapsed or the beginnings of starvation would be apparent. In humans, it is typically represented by the state after an overnight fast before breakfast is consumed. *In the postabsorptive state the blood glucose concentration is usually a little under 5 mmol/l. The concentration of insulin* in plasma varies widely between individuals, but is typically *around 60 pmol/l*. *The concentration of glucagon* will be about *20–25 pmol/l*. (There are difficulties in giving typical glucagon concentrations. **Firstly**, the methods used to measure it in different laboratories tend to give varying results. **Secondly**, the point has already been made that glucagon exerts its metabolic effects mainly, if not entirely, in the liver, and the relevant concentration is that in the hepatic portal vein; this is not easy to measure in normal volunteers.)

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7.1 Carbohydrate Metabolism: The Post-absorptive State

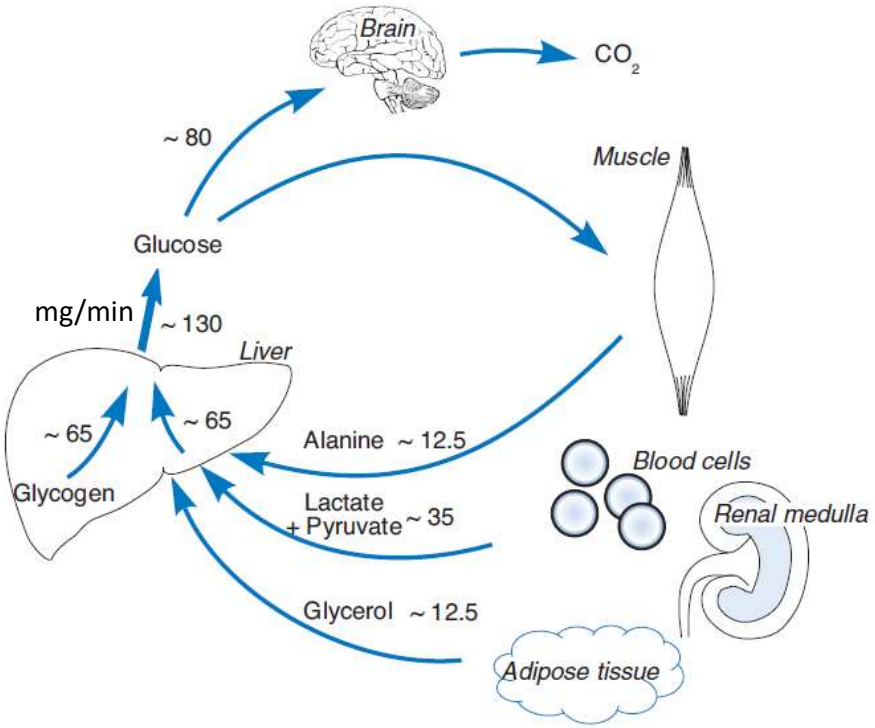

Figure 7.3 The pattern of glucose metabolism after an overnight fast. The numbers are approximations only, in mg per min, for a typical person of 65 kg body weight. *Much of the glucose delivered to peripheral tissues (muscle, adipose tissue, blood cells, etc.) is "recycled" as lactate, which returns to the liver as a substrate for gluconeogenesis.* However, a large proportion is oxidized, especially in the brain, and this constitutes an irreversible loss from the body's store of carbohydrate. Note that this picture shows only glucose metabolism: muscle and other tissues (e.g., renal cortex) will also be oxidizing non-esterified fatty acids from the plasma.

- Glucose enters the blood in the postabsorptive state almost exclusively from the liver, and of this a proportion arises from glycogen breakdown and a proportion from gluconeogenesis.

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7.1 Carbohydrate Metabolism: The Post-absorptive State

- *What are the substrates for this gluconeogenesis?* Lactate (with a smaller amount of pyruvate) will constitute a little over a half, and alanine (largely from muscle) and glycerol (from adipose tissue lipolysis) most of the remainder. The lactate arises from a variety of tissues. First, it comes from those tissues that use glucose almost entirely by anaerobic glycolysis, such as the red blood cells and renal medulla. Note that this constitutes a recycling of glucose; red blood cells, for example, use about 25 mg glucose/min and return that amount of lactate to the liver for synthesis of new glucose. Secondly, there will be some breakdown of muscle glycogen releasing lactate from anaerobic glycolysis. The stimulus for gluconeogenesis (again, comparing with the previous evening when it was suppressed after a meal) is again mainly the decreased insulin/glucagon ratio.
- On the disappearance side, the brain uses about 120 g glucose per day or about 80 mg/min, more than half of the total glucose utilization. The remainder is used by a number of tissues including red blood cells, skeletal muscle, renal medulla, and adipose tissue.

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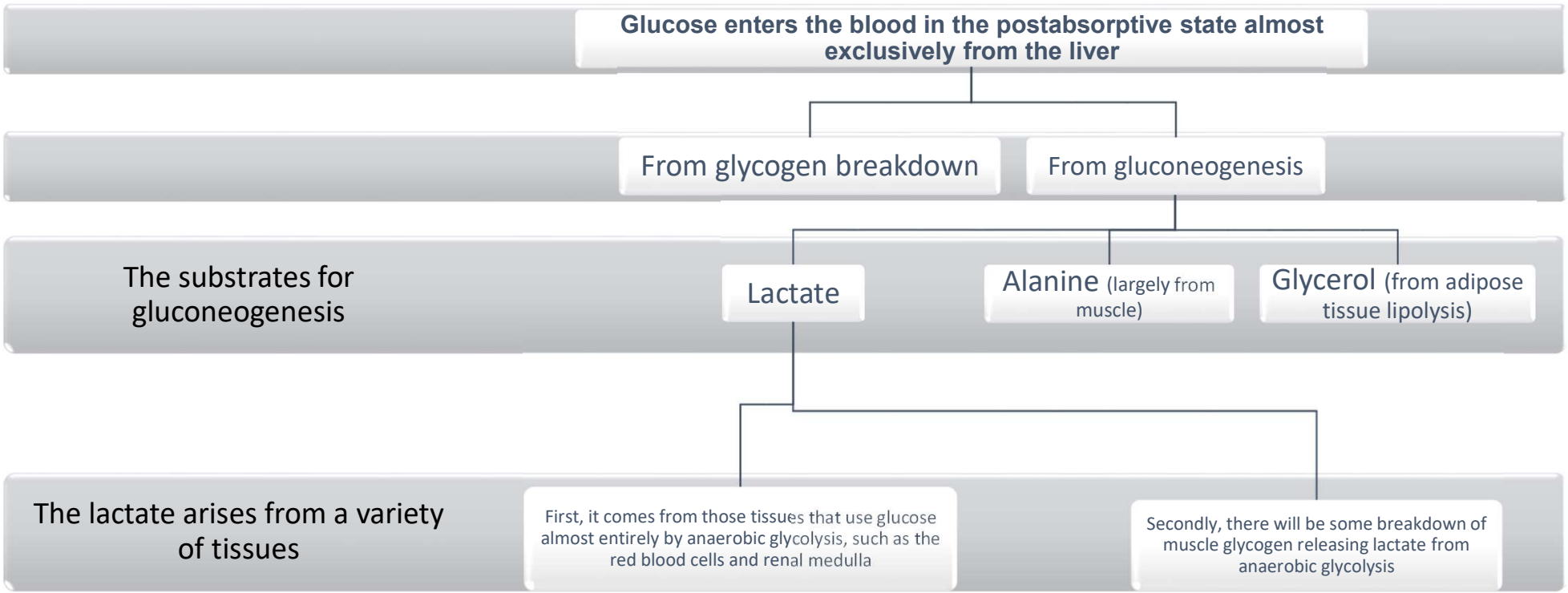
7.1 Carbohydrate Metabolism: The Post-absorptive State



Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.1 Carbohydrate Metabolism: Breakfast

- The postabsorptive state usually only lasts a few hours before it is interrupted by the arrival of a meal. The first meal of the day gives the most dramatic switch from “production” to “storage” mode and we will consider here how this comes about. For simplicity, we will consider *a breakfast containing mostly carbohydrate* – for instance, cereals and skimmed milk.
- The carbohydrate of the meal is digested and absorbed from the intestine. An increase in the concentration of glucose in the blood can be detected within about 15 minutes, and continues to a peak at around 30–60 minutes
- after a moderate breakfast (Figure 7.4).

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.1 Carbohydrate Metabolism: Breakfast

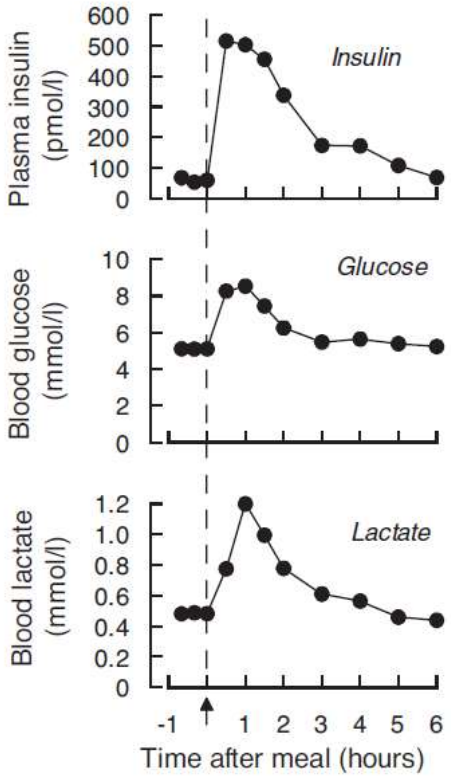


Figure 7.4 Concentrations of insulin, glucose, and lactate in blood after an overnight fast and following a single meal. The meal, shown by the arrow, contained 96 g carbohydrate and 33 g fat. Mean values for eight normal subjects are shown; based on data in Frayn *et al.* (1993).

An increase in the concentration of lactate in the blood after a breakfast ???

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.1 Carbohydrate Metabolism: Breakfast

After breakfast, the insulin/glucagon ratio in plasma rises. How does this affect metabolism in individual tissues?

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7.1 Carbohydrate Metabolism: Carbohydrate Metabolism in the Liver After Breakfast

- The liver receives the blood draining the small intestine in the hepatic portal vein, and so it sees the largest change in blood glucose concentration. This leads to an inflow of glucose into hepatocytes via the transporter GLUT2. The elevation of intracellular glucose concentration in hepatocytes, together with the change in insulin/glucagon ratio, leads to inactivation of glycogen phosphorylase and activation of glycogen synthetase, and thus a switch from glycogen breakdown to glycogen storage.
- We might expect that the pathway of gluconeogenesis would be inhibited by this hormonal switch, but this does not occur in practice. There is always an elevation of the blood lactate concentration after ingestion of carbohydrate (Figure 7.4). This probably represents the effect of a switch to partially anaerobic glucose metabolism in a number of tissues, including muscle and adipose tissue. The increase in blood lactate concentration is probably sufficient in itself to maintain the activity of the pathway of gluconeogenesis. The overall effect is that some of the glucose arriving in the blood is used by tissues, released into the blood as lactate, taken up by the liver and converted to glucose 6-phosphate and then glycogen – the “indirect pathway” of glycogen deposition. It is important to note, however, that unlike gluconeogenesis after an overnight fast, this gluconeogenic flux does not lead to release of glucose into the blood; the glucose 6-phosphate is instead mainly directed into glycogen synthesis (Some glucose release continues.). The direction of lactate into glycogen in the liver can all be seen as part of an intense drive to store as much as possible of the incoming glucose, even if it supplies some energy to other tissues first.

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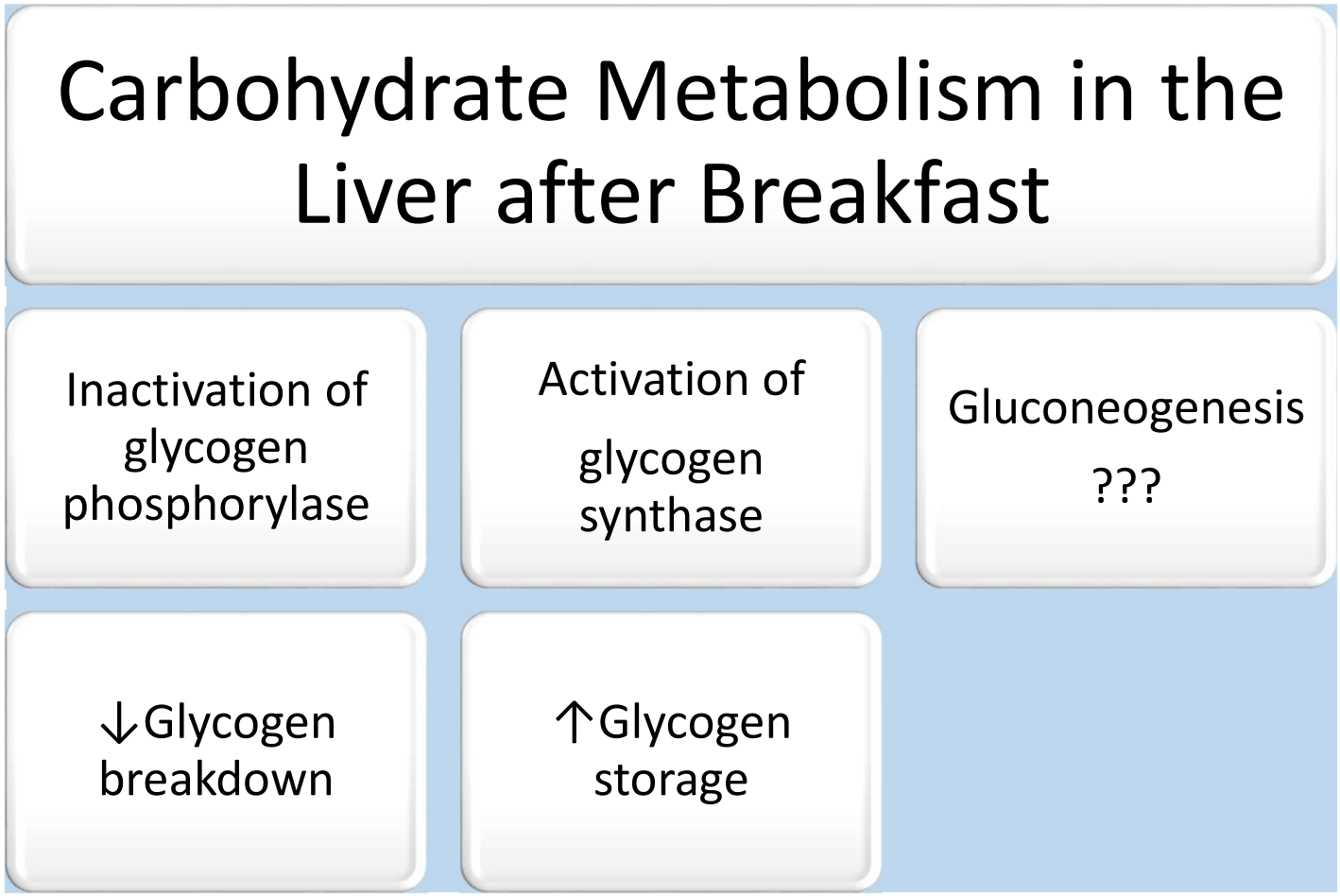
7.1 Carbohydrate Metabolism: Carbohydrate Metabolism in the Liver After Breakfast



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7.1 Carbohydrate Metabolism: Carbohydrate Metabolism in Other Tissues After Breakfast

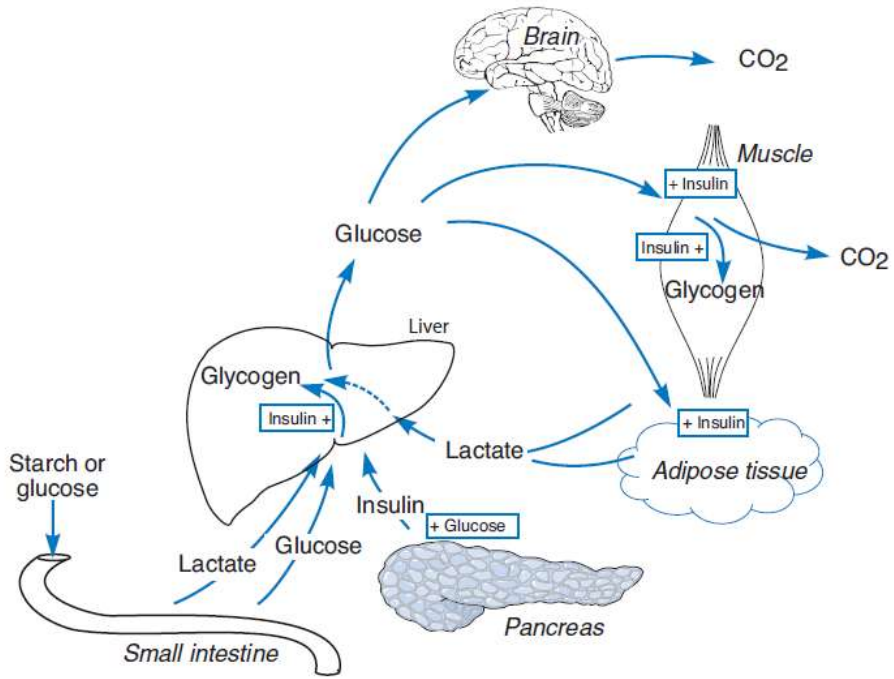

Figure 7.7 The pattern of glucose metabolism after a carbohydrate breakfast. The *direct pathway* of glycogen storage is shown (glucose from small intestine going to liver glycogen), as is the *indirect pathway* (glucose forming lactate in the small intestine or in peripheral tissues, lactate then being used for liver glycogen synthesis); Section 5.1.2.1.

- Other tissues respond to the increase in insulin concentration. *In skeletal muscle* and *adipose tissue*, glucose uptake will be stimulated by the rise in insulin through increased numbers of GLUT4 transporters at the cell membrane, and by increased disposal of glucose within the cell. At the same time, the plasma concentration of non-esterified fatty acids falls because fat mobilization in adipose tissue is suppressed. *Therefore, tissues such as skeletal muscle, which can use either fatty acids or glucose as their energy source, switch to utilization of glucose.* Not all the glucose taken up by muscle is oxidized under these conditions; insulin also activates muscle glycogen synthase and glycogen storage will replenish muscle glycogen stores (Figure 7.6). Thus, after a meal containing carbohydrate, there is a general switch in metabolism to the use of glucose rather than fatty acids, but there is also a major switch to the storage of glucose as glycogen. The pattern of postprandial glucose metabolism, and some important regulatory points, are illustrated in Figure 7.7.

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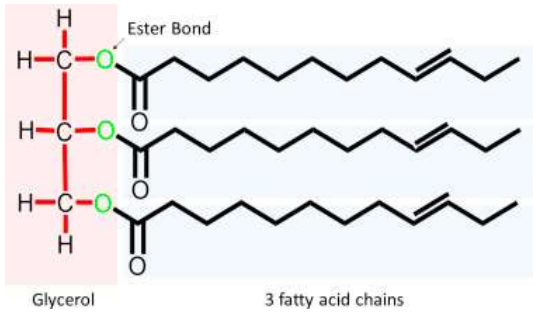
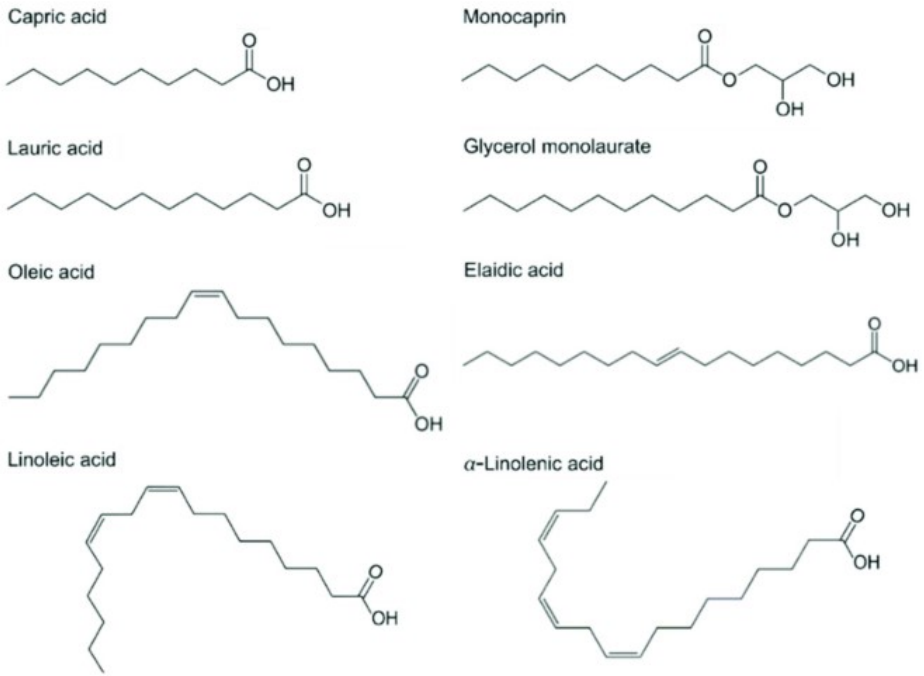
7.2 Fat Metabolism

- While there is one major form of carbohydrate (glucose) circulating in the blood, and its concentration is relatively constant, *there are various forms of fat and their concentrations may vary considerably throughout a normal day*.
- Both triacylglycerol and non-esterified fatty acids are always present in the plasma and, like glucose, they are constantly turning over – being used and replaced.





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7.2 Fat Metabolism: *Plasma Non-Esterified Fatty Acids*

- Non-esterified fatty acids enter the plasma only from *adipose tissue*.
- The process of fat mobilization is initiated by the enzyme adipose triglyceride lipase, but appears to be regulated primarily by the activity of the subsequent lipolysis step, catalyzed by hormone-sensitive lipase Thus, control of this enzyme, and of the opposing process of esterification of fatty acids in adipose tissue, has a major effect on the plasma concentration of non-esterified fatty acids.

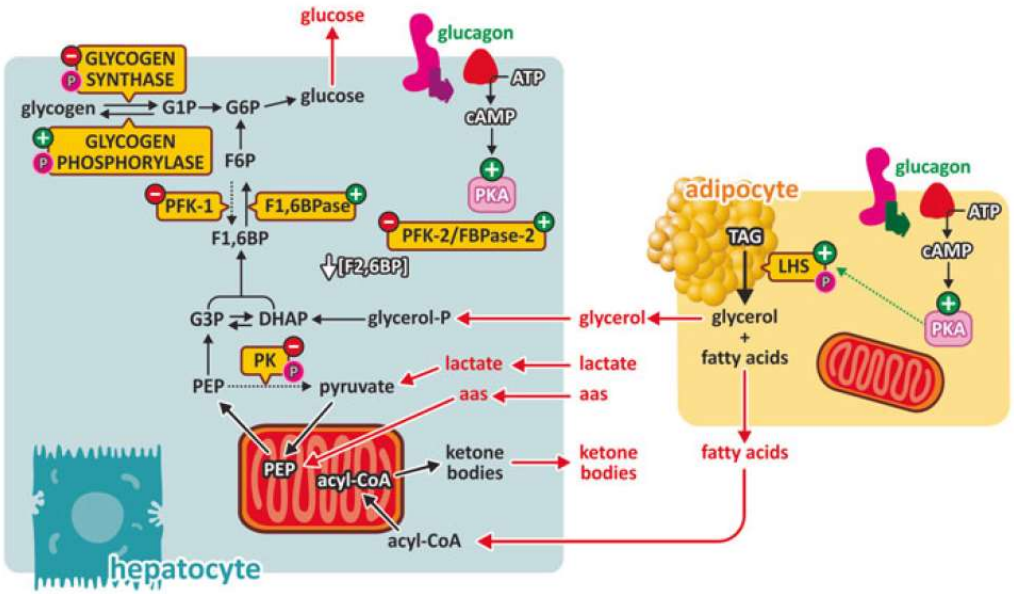
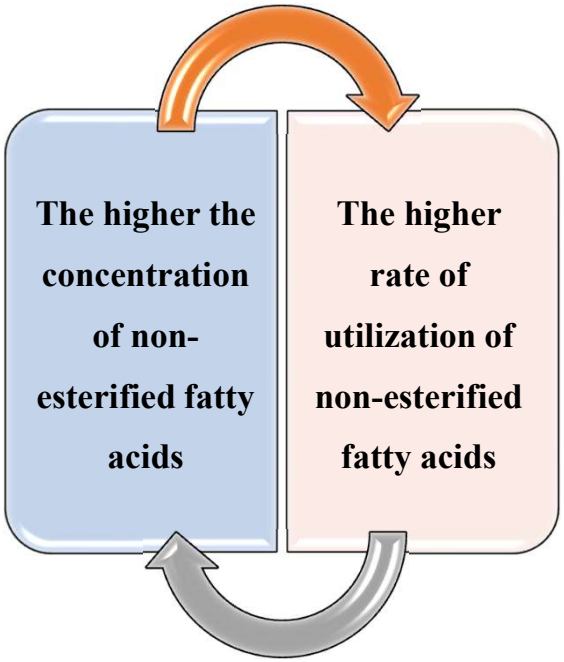


Fig. 9.18 Integration of the effects of glucagon on liver and adipose tissue, showing the enzymes and the metabolic pathway s regulated in each cell. The P in the pink circle represents the phosphate group introduced in the enzyme by PKA; + and − indicate the activated or inhibited states, respectively. The dashed lines represent inhibited reactions. PFK-1, phosphofructokinase-1; F1,6BPase, fructose -1,6- bisphosphatase ; PFK-2/F2,6BPase, phosphofructokinase-2/ fructose-2,6-bisphosphatase F2,6BP, fructose- 2,6- bisphosphate; LHS, hormone -sensitive lipase .

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *Plasma Non-Esterified Fatty Acids*

- *The overall rate of utilization of non-esterified fatty acids from the plasma depends almost entirely on their plasma concentration:* the higher the concentration of non-esterified fatty acids, the higher their rate of utilization.

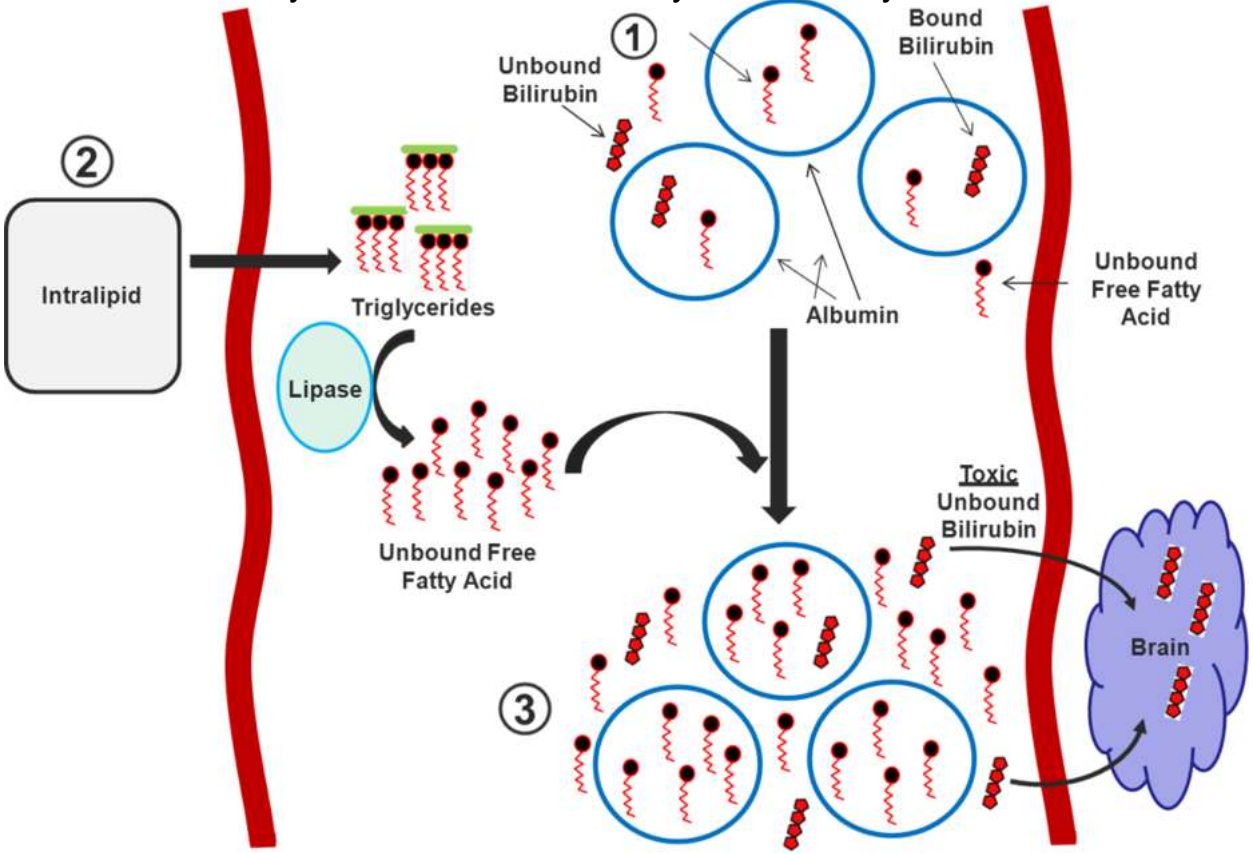


- Non-esterified fatty acids are not water soluble, and they are carried in plasma bound to the plasma protein albumin. The plasma concentration of albumin is around *40 g/l* and its M_r (relative molecular mass) is 66000, so the concentration is about *0.6 mmol/l*. Each molecule of albumin has *binding sites for around three fatty acid molecules*. (These *binding sites are not as specific* as, for instance, a hormone receptor binding a hormone. Albumin acts as a carrier for a number of hydrophobic substances including certain drugs and the amino acid tryptophan. Non-esterified fatty acids, tryptophan and drugs compete for binding, presumably to the same sites.) Thus, about 0.6×3, or say 2 mmol/l of non-esterified fatty acids can be comfortably accommodated.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *Plasma Non-Esterified Fatty Acids*

- There is always *an equilibrium between fatty acids bound to albumin and a very small concentration (less than 1 µmol/l) unbound, free in solution.* If the plasma concentration of non-esterified fatty acids rises above about 2 mmol/l the concentration of unbound fatty acids rises considerably and this may have adverse effects, particularly on the heart.



(1) Normally most Free Fatty Acids (FFA) and bilirubin are bound to albumin (the most common carrier protein in the blood). (2) Intralipid (an emulsion of triglycerides) is infused intravenously into the infant causing a large increase in triglycerides in the infant's blood. The triglycerides are broken down, by lipase, an enzyme in the blood, into unbound free fatty acids (FFAu). The FFAu are hydrophobic (they are repelled by water) and therefore want to be on the albumin. (3) Albumin has limited binding capacity for molecules including bilirubin. The large amount of FFA "out compete" and thereby displace bilirubin from its binding sites on albumin. The now unbound and therefore toxic bilirubin crosses the blood brain barrier and causes brain damage or death.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *Plasma Non-Esterified Fatty Acids*

- The plasma non-esterified fatty acid concentration during a normal day is an *inverse reflection* of the plasma glucose and insulin; when the body is relatively "starved" –for instance after overnight fast – the concentrations of glucose and insulin are at their lowest and the concentration of non-esterified fatty acids is at its highest. It can fall dramatically after a carbohydrate meal (Figure 7.8).

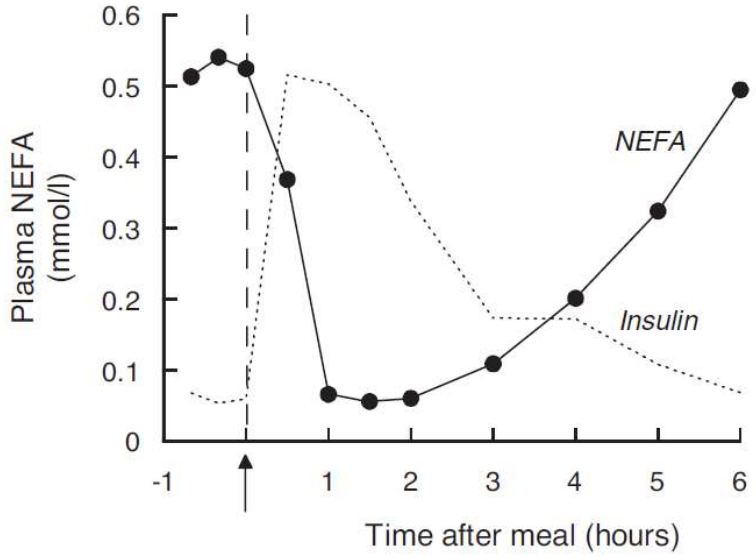


Figure 7.8 Plasma non-esterified fatty acid (NEFA) concentrations after an overnight fast and following a meal. The meal was the same as described in Figure 7.4. The plasma insulin concentration (expressed in nmol/l) is shown as a dotted line. Mean values for eight normal subjects are shown; data taken from Frayn *et al.* (1993).

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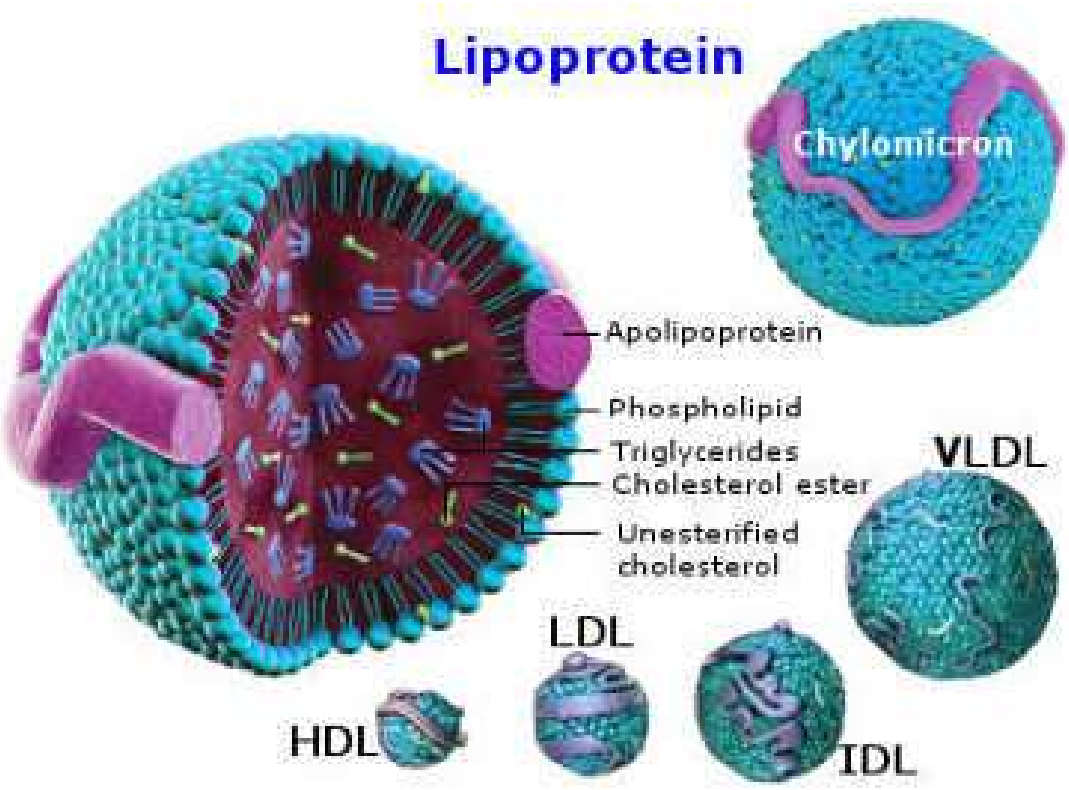
7.2 Fat Metabolism: *Plasma Triacylglycerol (TAG)*

Triacylglycerol is also water insoluble and is carried in the plasma in specialized particulate structures, the ***lipoproteins***.

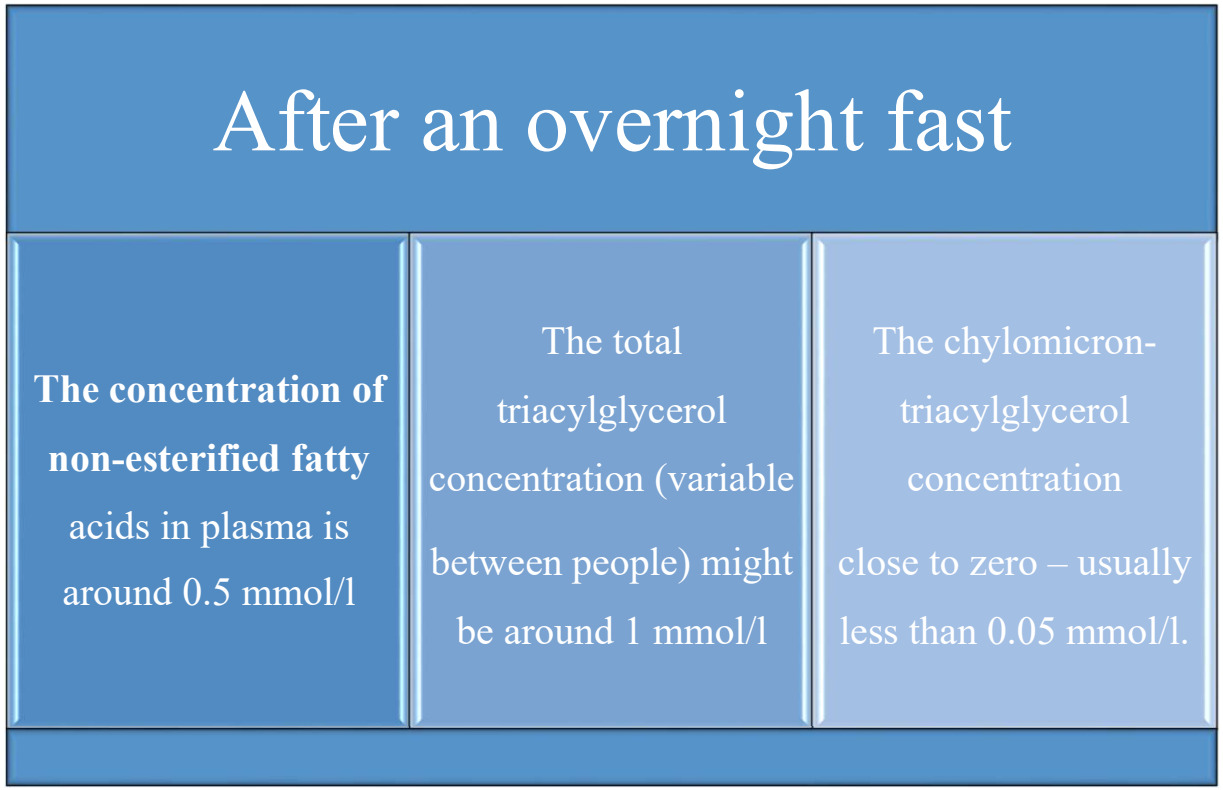


- *The total concentration of triacylglycerol in plasma* varies widely between different people (even apparently quite healthy people), depending greatly upon fitness, body build, and genetic influences.
- *The concentration of chylomicron-triacylglycerol* also varies widely between people, but it is close to zero in the overnight-fasted state, and rises after meals to (typically) 0.4–0.6 mmol/l.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *Post-absorpative state*

- After an overnight fast, the concentration of non-esterified fatty acids in plasma is around 0.5 mmol/l. As noted above, the total triacylglycerol concentration (variable between people) might be around 1 mmol/l and the chylomicron-triacylglycerol concentration close to zero – usually less than 0.05 mmol/l.



Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *Post-absorpative state*

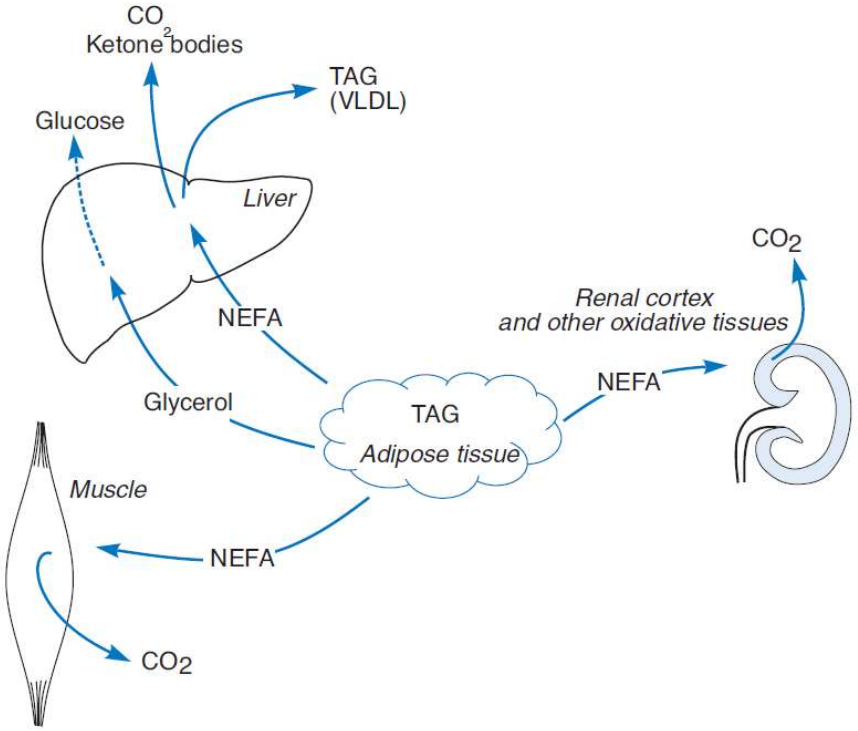


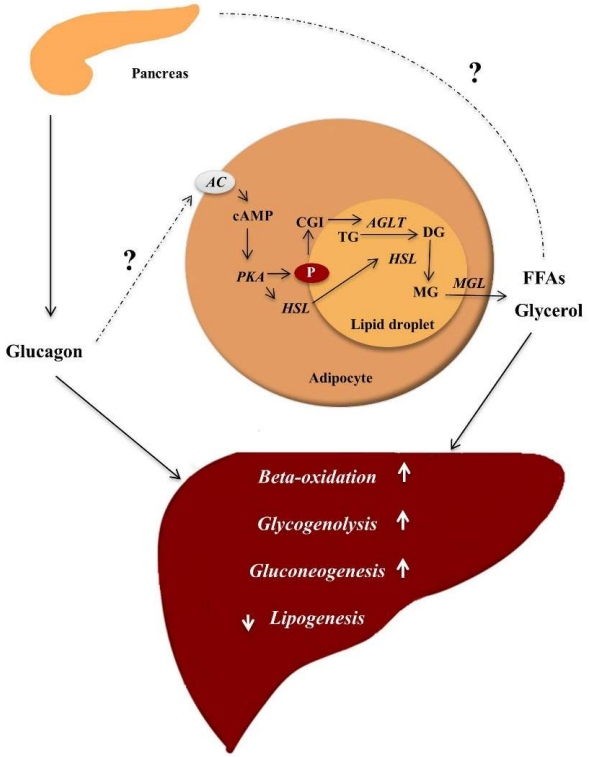
Figure 7.9 The pattern of non-esterified fatty acid (NEFA) metabolism after an overnight fast. Fatty acids are released by lipolysis of the triacylglycerol (TAG) stores in adipose tissue. VLDL: very-low-density lipoprotein.

- The turnover of non-esterified fatty acids in the postabsorptive state involves their liberation from adipose tissue and their uptake by a number of tissues, predominantly skeletal muscle and liver (Figure 7.9).

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *Post-absorpative state*

The total amount of non-esterified fatty acid in the plasma is influenced from:
1- The rate of non-esterified fatty acid release from adipose tissue → Index of Hormone sensitive lipase activity (HSL)
2- The process of fatty acid re-esterification within the fat tissue → Require glycerol 3-phosphate



- The rate of non-esterified fatty acid release from adipose tissue is also regulated by the process of fatty acid re-esterification within the tissue (Figure 5.18).
- However, the process of re-esterification requires glycerol 3-phosphate produced from glycolysis, and this will be occurring at a relatively low rate, so most of the fatty acids will escape from the adipocyte. The best estimates available suggest that around 10% of the fatty acids released by intracellular lipolysis in the adipocyte is retained by re-esterification in the overnight-fasted state, but this figure falls to near zero if the fast extends another few hours.

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7.2 Fat Metabolism: *Non-Esterified Fatty Acid Metabolism After Breakfast*

- As the meal is absorbed, so the rising glucose concentration stimulates insulin secretion and the concentration of insulin in the plasma rises. This has a direct suppressive effect on lipolysis in *adipose tissue*.
- The fall in plasma non-esterified fatty acid concentration affects the metabolism of tissues that use fatty acids as an oxidative fuel after the overnight fast. Skeletal muscle is a good example.

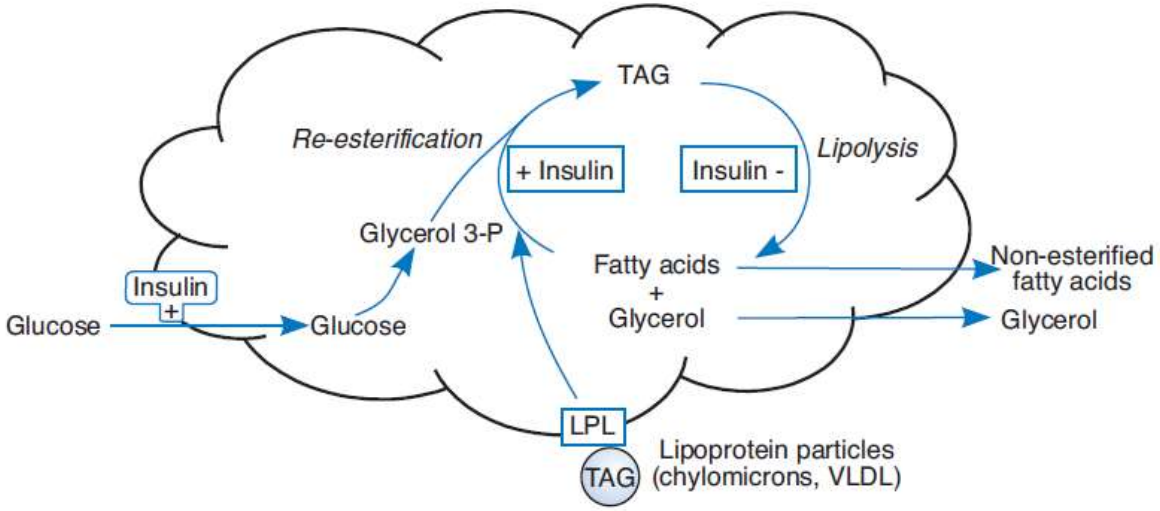


Figure 5.18 Suppression of fat mobilization by insulin. Insulin restrains fat mobilization by two mechanisms: suppression of lipolysis (mechanisms are described in the text), and stimulation of the re-esterification of fatty acids within the adipocytes. Note that the same process of esterification will also be simultaneously incorporating fatty acids from circulating triacylglycerol, released by lipoprotein lipase (LPL), into stored triacylglycerol.

- The rate of uptake of non-esterified fatty acids by *muscle* is a function primarily of fatty acid delivery – that is, plasma concentration and blood flow. On the other hand, when glucose becomes available in the plasma after a meal, its utilization is stimulated by the rise in insulin concentration.
- Along with the reduction in plasma non-esterified fatty acid concentration, there is a switch in *liver metabolism*, also brought about by the increased insulin/glucagon ratio, leading to a reduction in the rate of ketone body formation and release.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *TAG Metabolism After Breakfast*

- The absorption of TAG in the small intestine *is much slower than the absorption of glucose or amino acids*, so that the peak in plasma triacylglycerol concentration after a fatty meal does not occur until 3–5 hours after the meal. As chylomicron-triacylglycerol enters the plasma, the large, triacylglycerol-rich particles give the plasma a "milky" appearance (Figure 7.10).
- In fact, most of the triacylglycerol is removed from chylomicrons in tissues outside the liver, particularly adipose tissue, skeletal muscle, and heart. Adipose tissue contains the enzyme *lipoprotein lipase* in its capillaries and this is the enzyme responsible for hydrolysis of the chylomicron-triacylglycerol (Figure 5.17, p. 132). *The activity of lipoprotein lipase is stimulated by insulin and exercise.*

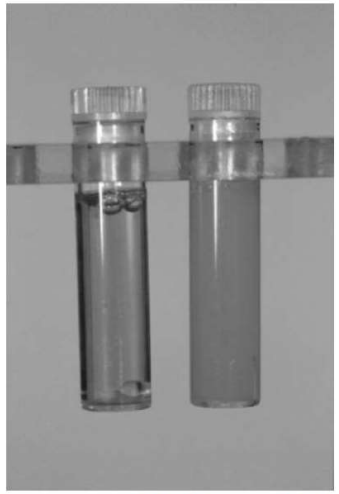


Figure 7.10 The milky appearance of blood plasma (right) after a fatty meal, compared with its clear appearance in the fasted state (left). The turbidity is caused by the presence of the large chylomicron particles. [Please see color plate 4 to see this figure in color.]

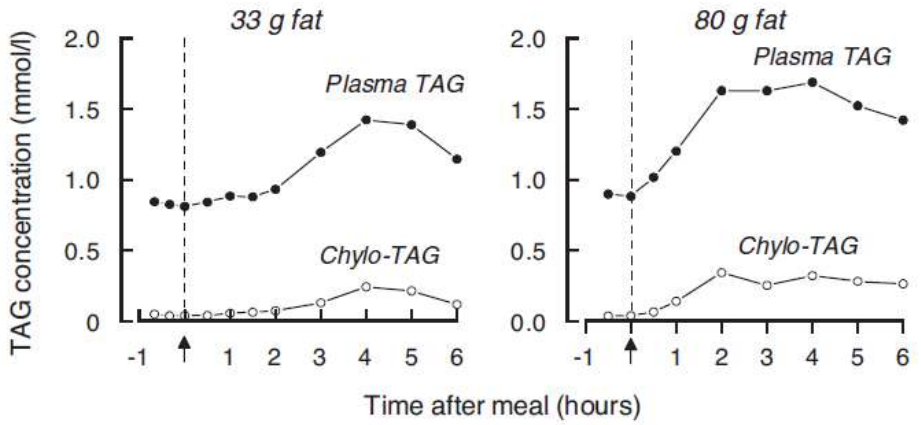


Figure 7.11 Concentrations of triacylglycerol (TAG) in whole plasma (solid circles) and in chylomicrons (open circles) after overnight fast and after meals (shown by the arrows) containing either 33 g fat (a typical mixed meal) or 80 g fat (a high-fat meal) in groups of normal subjects. Data from Griffiths *et al.* (1994) and Coppack *et al.* (1990).

- Adipose tissue is not the only tissue that expresses lipoprotein lipase.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.2 Fat Metabolism: *TAG Metabolism After Breakfast*

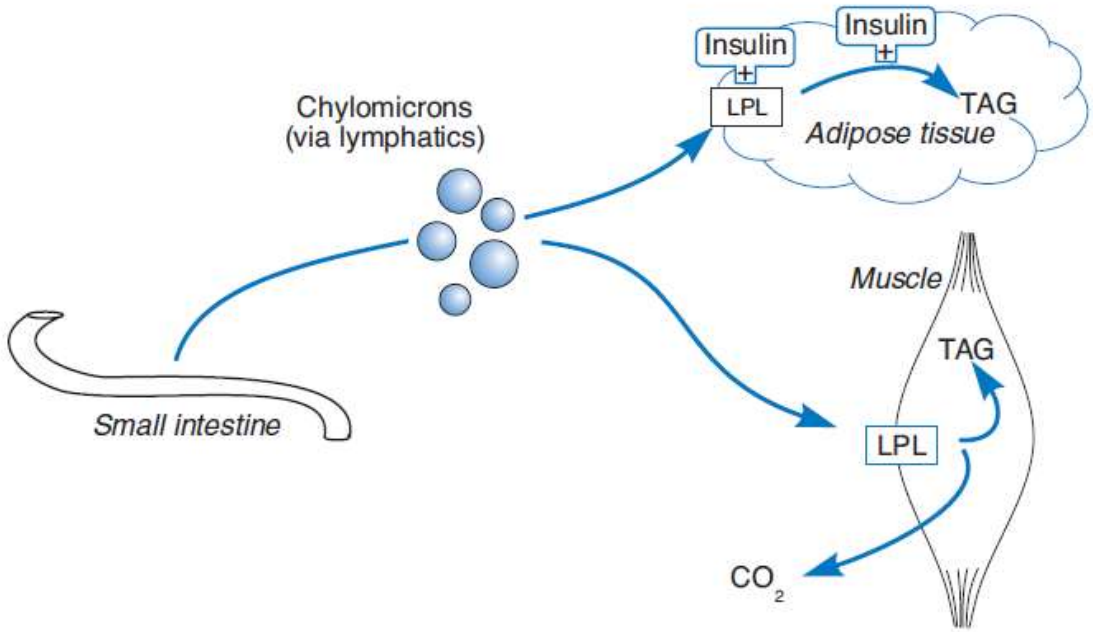


Figure 7.12 The pattern of plasma triacylglycerol metabolism after a breakfast containing both fat and carbohydrate. Triacylglycerol (TAG) enters the circulation in the form of chylomicron particles and is hydrolyzed by the enzyme lipoprotein lipase (LPL) in the capillaries of tissues (see Figure 5.17 for more details of this process).

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism

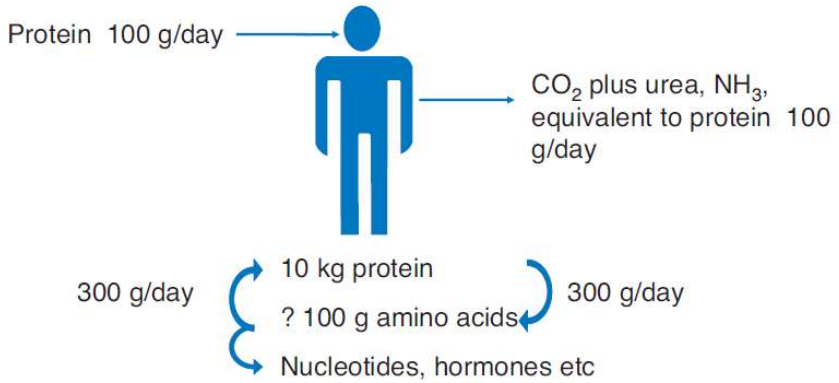


Figure 7.13 Overview of protein and amino acid turnover in the body. We eat (very approximately) 100 g protein per day and therefore (unless we are growing) must dispose of an equal amount, mainly by oxidation of amino acids with generation of CO_2, H_2O, urea, and some NH_3. Of the (approximately) 10 kg of protein in the body, there is continuous synthesis and breakdown of (about) 300 g/day (i.e., a 3% "turnover"), although this varies greatly from tissue to tissue (Table 7.1). Some of the amino acid pool is used for synthesis of purines, pyrimidines, and hormones. This may also be put in terms of nitrogen balance. Each 6.25 g protein contains about 1 g nitrogen. Therefore, (in round figures) we take in about 16 g N per day. Each day, around 2 g is lost in feces, 0.5 g in shed skin cells, and so on, and the remainder of the 16 g as urea and NH_3 in urine. Reproduced from Frayn (2003), from *Oxford Textbook of Medicine* edited by Warrell, Cox, Firth, and Benz (1995) with permission from Oxford University Press. www.oup.com.

- Each *6.25 g protein* contains about *1 g nitrogen*. Therefore, (in round figures) we take in about 16 g N per day. Each day, around 2 g is lost in *feces*, 0.5 g in *shed skin cells*, and so on, and the remainder of the 13.5 g as urea and NH3 in *urine*.

6.25 g protein	1g N_2	
100g protein	X	→X=16g N_2

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism

- One important *difference between amino acids and carbohydrates and fatty acids*, however, is that (in mammals) *amino acids are not stored simply for energy production*: all proteins have some biological function apart from storage. For this reason, body protein is largely preserved during normal conditions; *the amount does not fluctuate like the glycogen* store, for instance. However, *unlike fatty acids, amino acids can be converted into glucose*.
- Protein is a constituent of all tissues, but *some tissues play a more important role than others in amino acid metabolism*. *Skeletal muscle*, in particular, is important mainly because of its bulk – about 40% of body weight. The *liver* is important for a number of reasons: because it is the first organ through which amino acids pass after absorption from the intestine; because some important links between amino acid and carbohydrate metabolism occur there; and because it is the organ where urea synthesis takes place.
- *Free amino acids* (i.e., those not bound in proteins) are found both in *tissues* and in the *blood*. They are taken up into tissues by *specific active transport mechanisms* and their concentrations inside tissues may be many times those in blood.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism

- *The amount of free amino acid within the body* reflects the balance between a number of processes: *input into the pool from the intestine* (i.e., amino acids from food), *from the breakdown of proteins* and *by synthesis of new amino acids*; and *loss by incorporation into protein*, *oxidation and conversion to other metabolites*.
- There is some general control of the rates of protein synthesis and breakdown in particular tissues, and some regulation of the rates of interconversions of amino acids and conversion to non-amino acid metabolites, but ***little*** active control of amino acid oxidation.

Proteins ↔ Amino Acids ↔ α-keto acids + $NH4^+$

This is because the enzymes for degradation and oxidation of amino acids almost exclusively have *high Km values* and, thus, when amino acids are in excess, they will be degraded and oxidized in proportion to the extent of their concentration.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism

Proteins ↔ Amino Acids ↔ α-keto acids + $NH4^+$

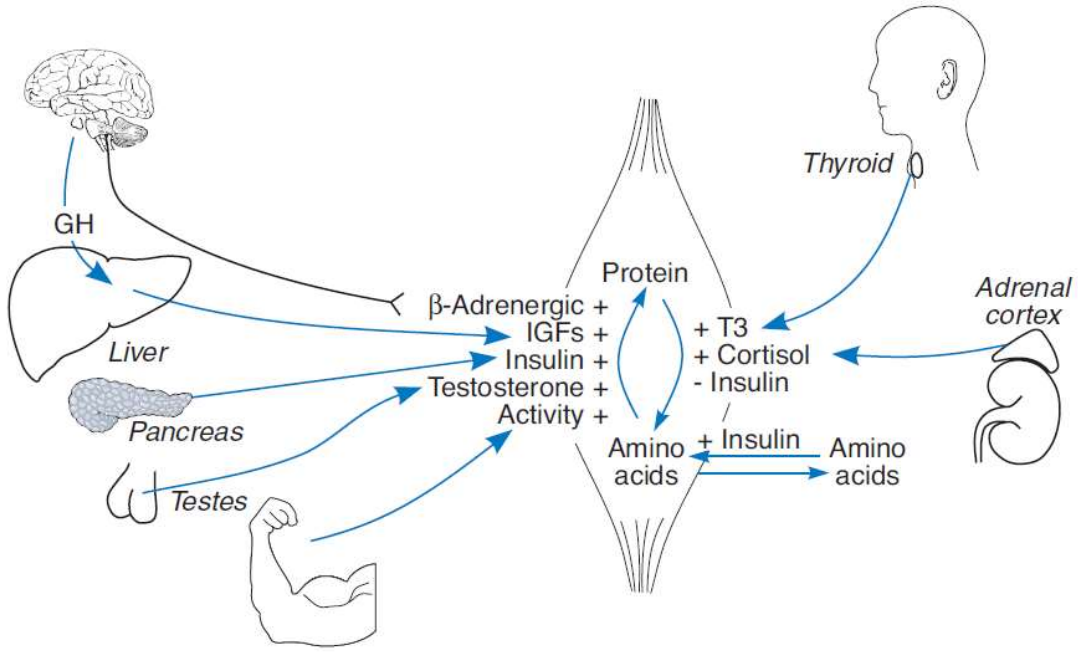


Figure 7.18 Overall control of protein synthesis and breakdown in muscle (and other tissues). Some of the stimuli here are tissue specific (especially physical activity, testosterone, and β-adrenergic stimulation); more details are given in the text. *IGF*s are the insulin-like growth factors (IGF-1 and -2), generated in the liver in response to growth hormone (GH). *β-adrenergic* represents activation of β-adrenergic receptors, either by noradrenaline released at sympathetic nerve terminals or by adrenaline in the plasma.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

Branched-Chain Amino Acids and Muscle Amino Acid Metabolism

- The branched-chain amino acids (leucine, isoleucine, and valine) are preferentially taken up by skeletal muscle after a meal. Their uptake is not directly stimulated by insulin and increases because the blood concentration rises.
- Muscle possesses a specific branched-chain 2-oxoacid dehydrogenase, which is a large complex related, and similar in many ways, to pyruvate dehydrogenase (also a 2-oxoacid dehydrogenase). Thus, branched-chain amino acids in muscle may be transaminated and oxidized, providing a source of energy for the muscle. The amino group is transferred to a 2-oxoacid. It may then be "passed around" between recipients, but usually the ultimate acceptor 2-oxoacid is either pyruvate (forming alanine) or 2-oxoglutarate (forming glutamate). In addition, amino groups may form ammonia (strictly, ammonium ions, NH_4^+) through the action of glutamate dehydrogenase, which removes the amino group from glutamate as NH_4^+, producing 2-oxoglutarate again, which may again participate in transamination reactions. Glutamate and ammonia may also combine to form glutamine through the action of glutamine synthase (or synthetase) (Figure 7.15). Thus, catabolism of branched chain and other amino acids leads predominantly to the release of glutamine and alanine.

Branched-Chain Amino Acids Are Not Degraded in the Liver

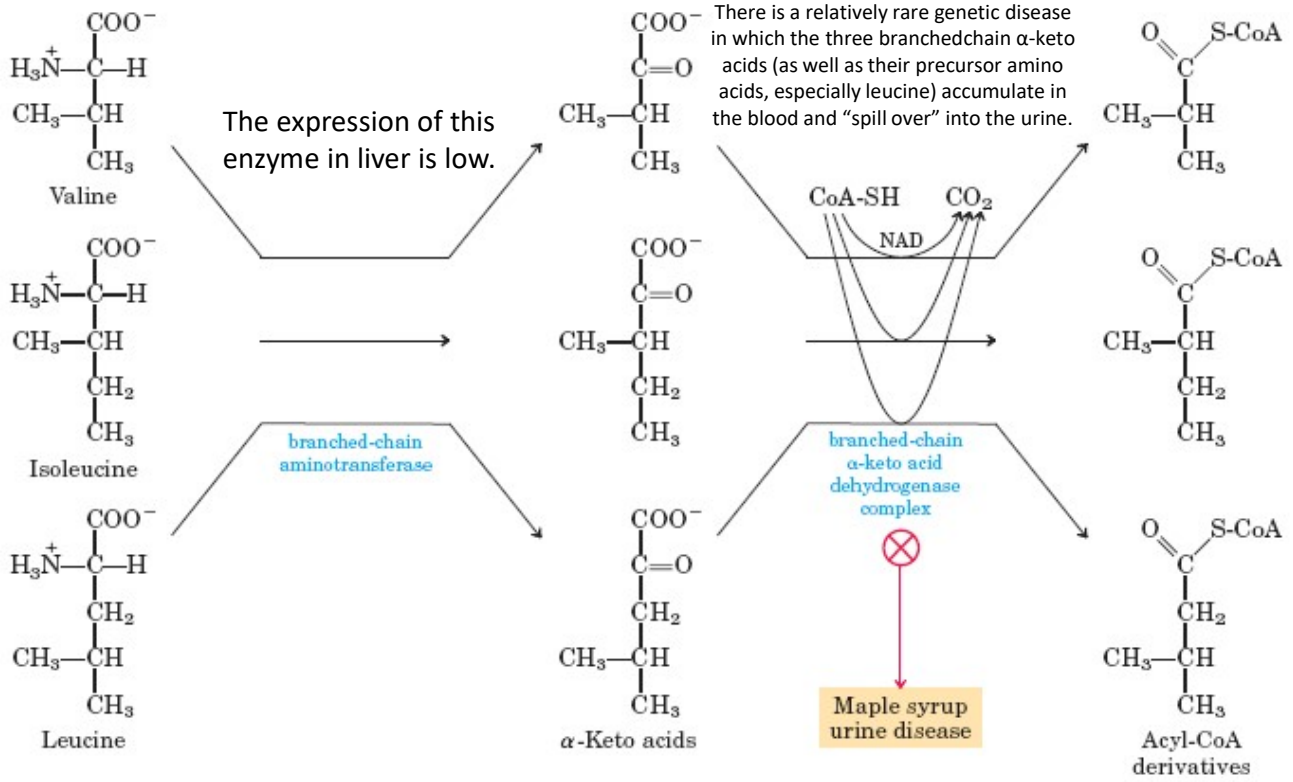


FIGURE 18–28 Catabolic pathways for the three branched-chain amino acids: valine, isoleucine, and leucine. The three pathways, which occur in extrahepatic tissues, share the first two enzymes, as shown here. The branched-chain α-keto acid dehydrogenase complex is analogous to the pyruvate and α-ketoglutarate dehydrogenase complexes and requires the same five cofactors (some not shown here). This enzyme is defective in people with maple syrup urine disease.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

Alanine and Glutamine

- Ala and Gln have a special place in a discussion of energy metabolism, as they provide links between amino acid and carbohydrate metabolism.
- Alanine and glutamine predominate among the amino acids leaving muscle. This is also true of other "peripheral tissues," including adipose tissue and brain. Since glutamine carries two nitrogen atoms (in its amino group and its amide group), it is usually a larger transporter of nitrogen than is alanine. The preponderance of alanine and glutamine is much greater than would be expected if the amino acids leaving muscle simply reflected the composition of proteins being degraded (Figure 7.14). Therefore, they must be synthesized in the tissues. We will consider their formation a little more deeply. The amino groups for alanine and glutamine, and the amide group of glutamine, may arise from the amino groups of other amino acids as discussed above. What, then, is the origin of their "carbon skeletons" (i.e., the corresponding 2-oxoacids)?

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

- Alanine and Glutamine

- For glutamine, the 2-oxoacid is 2-oxoglutarate, an intermediate in the tricarboxylic acid cycle. It is rather more possible that the carbon skeletons of other amino acids may contribute to glutamine than to alanine, since any amino acid whose breakdown leads to acetyl-CoA may do so. However, an intermediate of the tricarboxylic acid cycle cannot be "tapped off" indefinitely without some topping up of cycle intermediates – or, since it is a cycle, it will stop. It may be that pairs of amino acids contribute to this process; for instance, catabolism of leucine leads to acetyl-CoA and catabolism of valine leads to succinyl-CoA, another intermediate in the tricarboxylic acid cycle. Thus, these two amino acids together may replace the 2-oxoglutarate used in glutamine formation.
- Alanine is taken up avidly by the liver, particularly under conditions of active gluconeogenesis, when its uptake is stimulated by glucagon. Within the liver, which has very active transaminases, alanine readily passes its amino group to 2-oxoglutarate, leaving its carbon skeleton as pyruvate, a substrate for gluconeogenesis.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

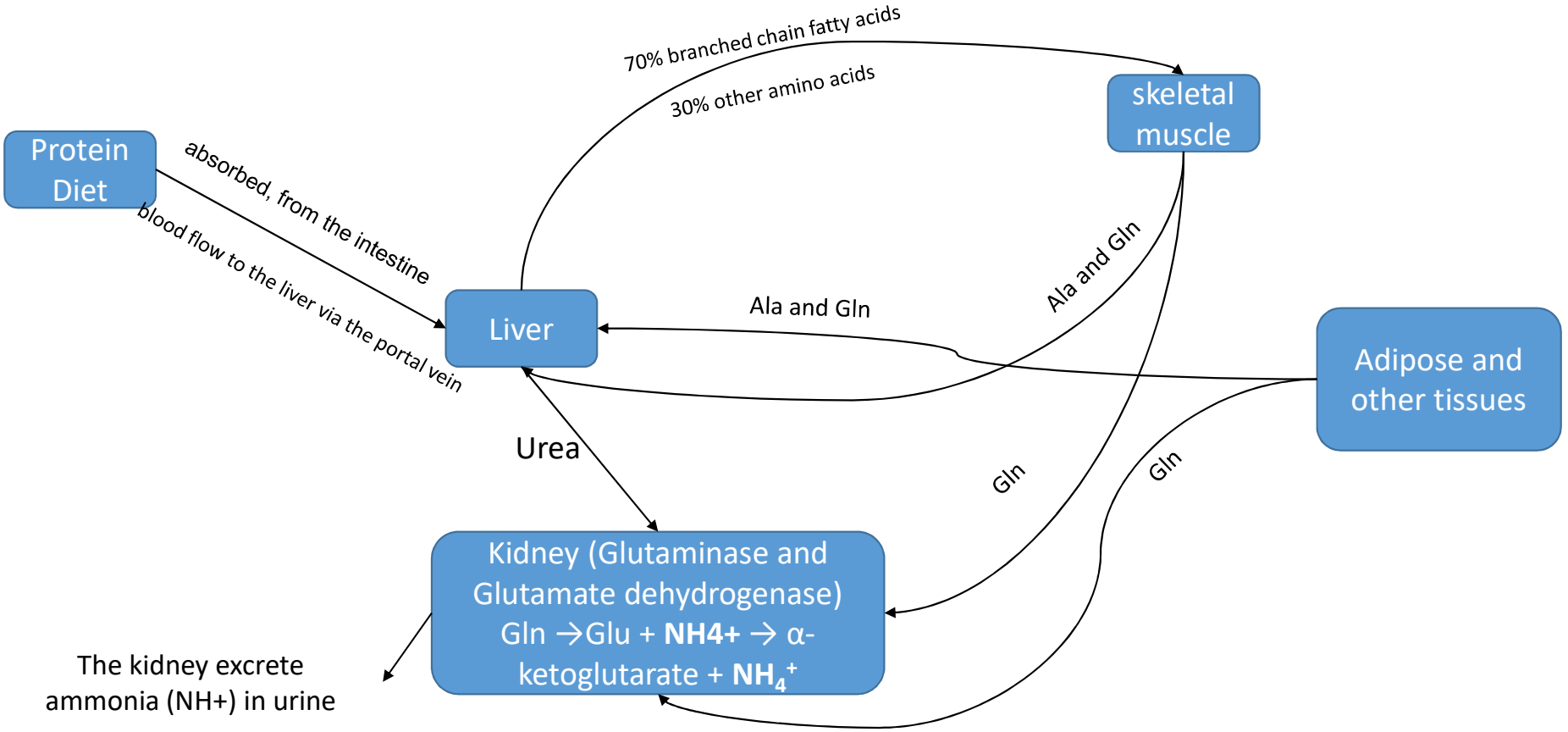
- Alanine and Glutamine

- Glutamine is not as good a substrate for hepatic uptake, but is removed particularly by the kidney and by the intestinal mucosal cells. In the kidney, the action of glutaminase (Figure 7.15) removes the amide group (forming ammonia) and leaves glutamate; glutamate can be converted to 2-oxoglutarate by the action of glutamine dehydrogenase, again forming ammonia. It is generally believed that this ammonia is a route for urinary excretion of protons (H+ ions), especially in conditions of excessive acidity in the body. This point is controversial, however, and will not be further discussed here. In the intestinal cells, glutamine is an important metabolic fuel (Section 5.7.2). The pathway of metabolism leads to production of alanine, which leaves in the portal vein and thus reaches the liver, again as a substrate for conversion to pyruvate and hence glucose. Glutamine is also an important fuel for other rapidly dividing cells.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

❑ Alanine and Glutamine



Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

- Branched-Chain Amino Acids and Muscle Amino Acid Metabolism
- Alanine and Glutamine

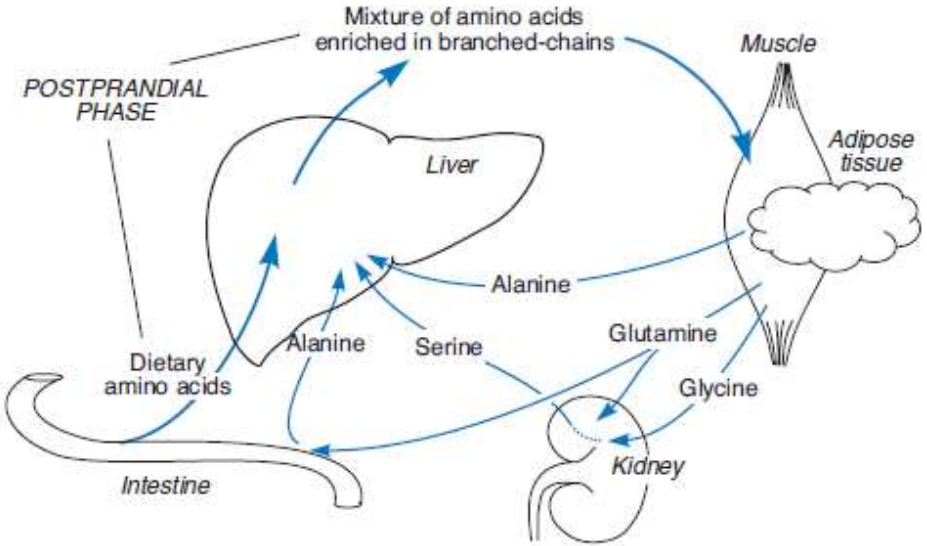


Figure 7.17 Major pathways for amino acid flow between tissues. The pathways are discussed in the text, with the exception of serine release by the kidney. The precursor for this is probably glycine (released from peripheral tissues). In the liver, serine may be converted to D-2-phosphoglycerate (or pyruvate in some species) and, thus, enter the hepatic pool of gluconeogenic precursors. Based loosely on Felig (1975) and Christensen (1982); for discussion of serine metabolism see Snell (1986), Snell and Fell (1990).

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *Some Particular Aspects of Amino Acid Metabolism*

- Alanine and Glutamine

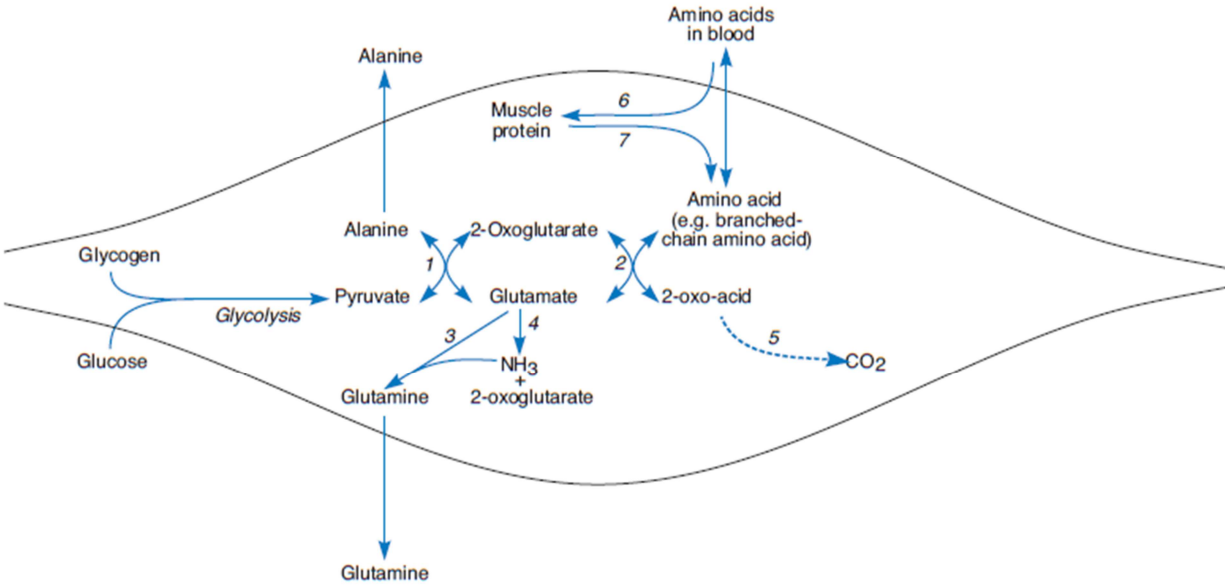


Figure 7.16 Major amino acids interconversions in muscle. (Adipose tissue and brain may be similar.) *1*, alanine aminotransferase (also called glutamate-pyruvate transaminase); *2*, leucine, valine or other aminotransferase; *3*, glutamine synthetase; *4*, glutamate dehydrogenase; *5*, branched-chain 2-oxoacid dehydrogenase and further catabolism; *6*, muscle protein synthesis; *7*, muscle protein breakdown (*proteolysis*). For simplicity, ionization states are not shown (e.g., NH_3 would be in the form of NH_4^+ at physiological pH).

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *The Overall Control of Protein Synthesis and Breakdown*

- There are some generalizations that can be made about the regulation of protein synthesis and breakdown (summarized in Figure 7.18). Two hormones have a general anabolic role (stimulating net protein synthesis) in the body: insulin and growth hormone. In people with a deficiency of insulin (insulin-dependent diabetes mellitus;), there is marked loss of protein from the body – the "melting of flesh into urine." Treatment with insulin restores body protein. Growth hormone acts through the insulin-like growth factors IGF-1 and IGF-2 and has an important role during development. In the adult this is not of major importance; adults whose pituitaries have been removed do not need growth hormone to be replaced to lead fairly normal lives. However, growth hormone is beneficial in stimulating protein anabolism in patients who have lost protein through severe illness. The male sex hormone, testosterone (a steroid hormone produced in the testes), also has a role in promoting protein synthesis, particularly in muscle. This was first realized because of the difference in average muscle strength between men and women. It became clear that this was a function of testosterone. Since that time, synthetic steroids have been developed which have increased anabolic tendencies and less androgenic (masculinizing) tendencies – these are the anabolic steroids. In individual tissues, there are other specific controlling factors. In skeletal muscle, the level of physical activity is an obvious one. The various factors generally work in concert; the effects of exercise and anabolic steroids, for instance, are greater than either alone. Skeletal muscle protein mass is also regulated by adrenergic influences.

Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *The Overall Control of Protein Synthesis and Breakdown*

- It has long been known that if a muscle is denervated – has its nerve supply cut –then it wastes away (atrophies). It has been assumed that this is because it no longer contracts and, therefore, there is no "training stimulus" to growth – so-called disuse atrophy. Now it appears that loss of an adrenergic stimulus may also be important. Administration of adrenergic β-stimulating drugs can increase muscle bulk. It is still not clear whether these act through one of the "classical" β-adrenergic receptors or whether some new type of receptor is involved. One such agent is clenbuterol, which has been used in agriculture to increase muscle bulk in cows, and misused in the sports world. Skeletal muscle protein synthesis is also stimulated, independently of hormonal effects, by increased supply of amino acids, as would occur after a meal.
- Some endocrine glands are stimulated to growth by their own trophic (or tropic) (hormone-releasing) factors. A good example is the stimulation of the thyroid gland by thyroid-stimulating hormone (TSH) from the anterior pituitary. TSH increases thyroid size as well as stimulating thyroid hormone secretion. However, this is not of significance for the overall protein metabolism of the body.

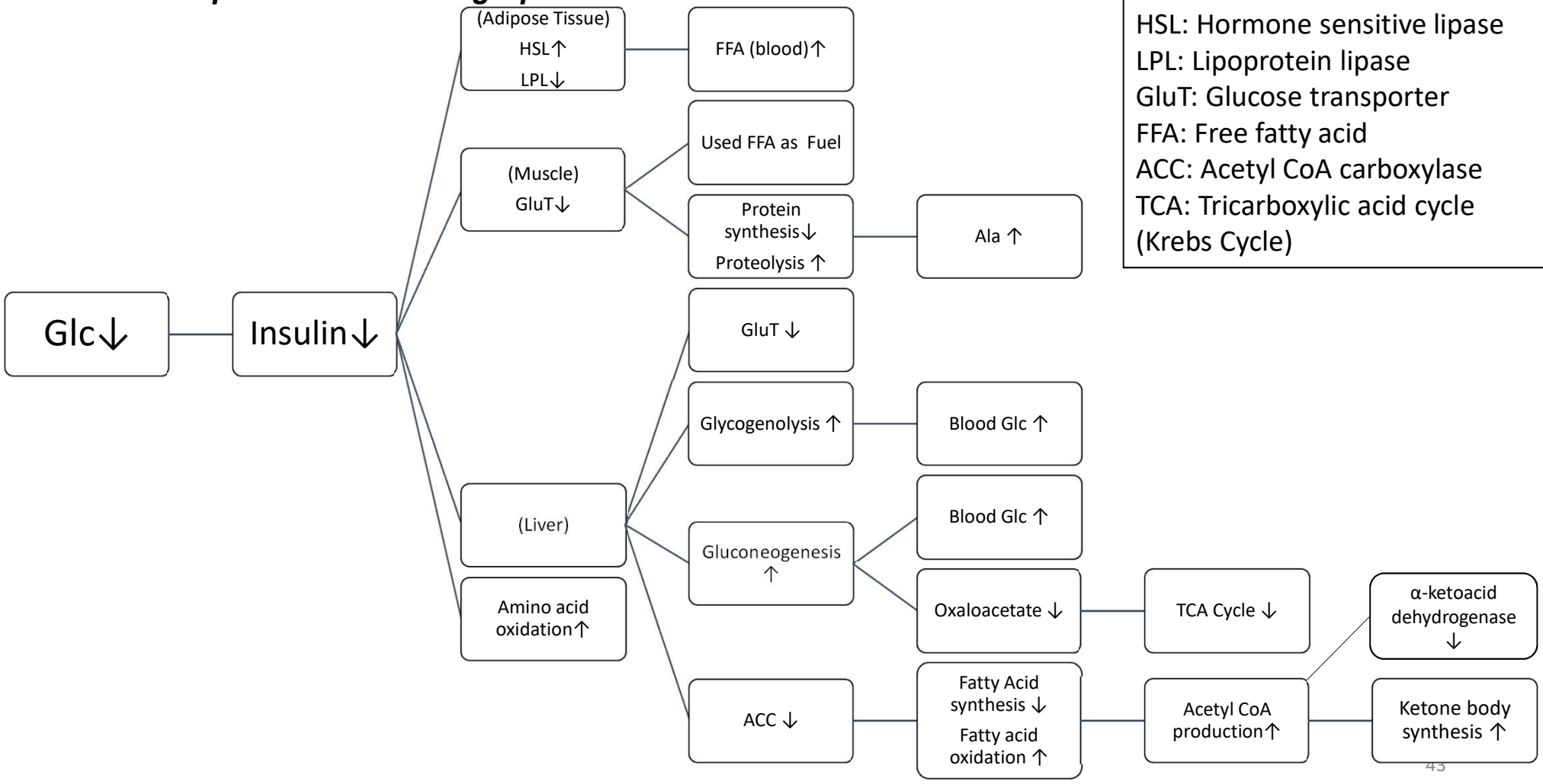
Integration of Carbohydrate, Fat, and Protein Metabolism in Normal Daily Life

7.3 Amino Acid and Protein Metabolism: *The Overall Control of Protein Synthesis and Breakdown*

- The overall rate of protein breakdown to amino acids is also under hormonal control. Insulin itself may act more by restraining protein breakdown than by stimulating protein synthesis. Since there is continual turnover of protein, the net effect is the same. In addition, two hormones are regarded as having particularly catabolic effects: cortisol and the thyroid hormone triiodothyronine (T3).
- The protein catabolic effect of cortisol does not affect all tissues equally. This is clearly seen in Cushing's syndrome, the disease caused by overproduction of cortisol from the adrenal cortex. In this condition there is loss of protein from both muscle and bone, and one of the consequences is a liability to bone fractures. The wasting of muscle is, however, somewhat selective and affects the so-called proximal muscles – those nearer the trunk rather than on the lower limbs. It also affects primarily the Type II, fast-twitch muscle fibers. Loss of body mass, including muscle mass, is one of the features of thyroid excess and it is clear that the thyroid hormones have a net degradative effect on muscle protein. In experimental models, T3 may also increase the rate of protein synthesis, but less than it increases protein degradation, so the net result is accelerated protein turnover and net loss of protein.

Links Between Carbohydrate, Fat, and Amino Acid Metabolism

The Post-absorptive State: Waking Up



Glc: Glucose
HSL: Hormone sensitive lipase
LPL: Lipoprotein lipase
GluT: Glucose transporter
FFA: Free fatty acid
ACC: Acetyl CoA carboxylase
TCA: Tricarboxylic acid cycle (Krebs Cycle)