



Fig. 42.1. Amino acid flux in sepsis and trauma. In sepsis and traumatic injury, glutamine and other amino acids are released from skeletal muscle for uptake by tissues involved in the immune response and tissue repair, such as macrophages, lymphocytes, fibroblasts, and the liver. Nitrogen excretion as urea and NH_4^+ results in negative nitrogen balance.

The body maintains a relatively large free amino acid pool in the blood, even during fasting. As a result, tissues have continuous access to individual amino acids for the synthesis of proteins and essential amino acid derivatives, such as neurotransmitters. The amino acid pool also provides the liver with **amino acid substrates** for **gluconeogenesis** and provides several other cell types with a source of **fuel**. The **free amino acid pool** is derived from **dietary amino acids** and the **turnover of proteins** in the body. During an **overnight fast** and during **hypercatabolic states**, **degradation** of labile **protein**, particularly that in **skeletal muscle**, is the major source of free amino acids.

The liver is the major site of amino acid metabolism in the body and the major site of **urea synthesis**. The liver is also the major site of amino acid degradation. Hepatocytes partially oxidize most amino acids, converting the carbon skeleton to glucose, ketone bodies, or CO_2 . Because ammonia is toxic, the liver converts most of the nitrogen from amino acid degradation to urea, which is excreted in the urine. The nitrogen derived from amino acid catabolism in other tissues is transported to the liver as **alanine** or **glutamine** and converted to urea.

The **branched-chain amino acids**, or BCAA (valine, isoleucine, and leucine) are oxidized principally in **skeletal muscle** and other tissues and not in the liver. In skeletal muscle, the carbon skeletons and some of the nitrogen are converted to glutamine, which is released into the blood. The remainder of the nitrogen is incorporated into alanine, which is taken up by the liver and converted to urea and glucose.

The formation and release of glutamine from skeletal muscle and other tissues serves several functions. In the kidney, the NH_4^+ carried by glutamine is excreted into the urine. This process removes protons formed during fuel oxidation and helps to maintain the body's pH, especially during metabolic acidosis. **Glutamine** also provides a **fuel** for the **kidney** and **gut**. In rapidly dividing cells (e.g., lymphocytes and macrophages), glutamine is required as a fuel, as a nitrogen donor for biosynthetic reactions, and as a substrate for protein synthesis.

During conditions of **sepsis** (the presence of various pathogenic organisms, or their toxins, in the blood or tissues), **trauma**, **injury**, or **burns**, the body enters a **catabolic state** characterized by a **negative nitrogen balance** (Fig. 42.1). Increased net protein degradation in skeletal muscle increases the availability of glutamine and other amino acids for cell division and protein synthesis in cells involved in the immune response and wound healing. In these conditions, an increased release of glucocorticoids from the adrenal cortex stimulates proteolysis.



THE WAITING ROOM

Katta Bolic, a 62-year-old homeless woman, was found by a neighborhood child who heard Katta's moans coming from an abandoned building. The child's mother called the police, who took Katta to the hospital emergency room. The patient was semicomatose, incontinent of urine, and her clothes were stained with vomitus. She had a fever of 103°F, was trembling uncontrollably, appeared to be severely dehydrated, and had marked muscle wasting. Her heart rate was very rapid, and her blood pressure was low (85/46 mm Hg). Her abdomen was distended and without bowel sounds. She responded to moderate pressure on her abdomen with moaning and grimacing.

Blood was sent for a broad laboratory profile, and cultures of her urine, stool, throat, and blood were taken. Intravenous glucose, saline, and parenteral broad-spectrum antibiotics were begun. X-rays performed after her vital signs were stabilized suggested a bowel perforation. These findings were compatible with a diagnosis of a ruptured viscus (e.g., an infected colonic diverticulum that perforated, allowing colonic bacteria to infect the tissues of the peritoneal cavity, causing peritonitis). Further studies confirmed that a diverticulum had ruptured, and appropriate surgery was performed. All of the arterial blood cultures grew out *Escherichia coli*, indicating that Katta also had a Gram-negative infection of her blood (septicemia) that had been seeded by the proliferating organisms in her peritoneal cavity. Intensive fluid and electrolyte therapy and antibiotic coverage were continued. The medical team (surgeons, internists, and nutritionists) began developing a complex therapeutic plan to reverse Katta's severely catabolic state.

I. MAINTENANCE OF THE FREE AMINO ACID POOL IN BLOOD

The body maintains a relatively large free amino acid pool in the blood, even in the absence of an intake of dietary protein. The large free amino acid pool ensures the continuous availability of individual amino acids to tissues for the synthesis of proteins, neurotransmitters, and other nitrogen-containing compounds (Fig. 42.2). In a normal, well-fed, healthy individual, approximately 300 to 600 g body protein is degraded per day. At the same time, roughly 100 g protein is consumed in the diet per day, which adds additional amino acids. From this pool, tissues use amino acids for the continuous synthesis of new proteins (300-600 g) to replace those degraded. The continuous turnover of proteins in the body makes the complete complement of amino acids available for the synthesis of new and different proteins, such as antibodies. Protein turnover allows shifts in the quantities of different proteins produced in tissues in response to changes in physiologic state and continuously removes modified or damaged proteins. It also provides a complete pool of specific amino acids that can be used as oxidizable substrates; precursors for gluconeogenesis and for heme, creatine phosphate, purine, pyrimidine, and neurotransmitter synthesis; for ammoniagenesis to maintain blood pH levels; and for numerous other functions.

A. Interorgan Flux of Amino Acids in the Postabsorptive State

The fasting state provides an example of the interorgan flux of amino acids necessary to maintain the free amino acid pool in the blood and supply tissues with their required amino acids (Fig. 42.3). During an overnight fast, protein synthesis in the liver and other tissues continues, but at a diminished rate compared with the

The concentration of free amino acids in the blood is not nearly as rigidly controlled as blood glucose levels. The free amino acid pool in the blood is only a small part (0.5%) of the total amino acid pool in whole body protein. Because of the large skeletal muscle mass, approximately 80% of the body's total protein is in skeletal muscle. Consequently, the concentration of individual amino acids in the blood is strongly affected by the rates of protein synthesis and degradation in skeletal muscle, as well as the rate of uptake and utilization of individual amino acids for metabolism in liver and other tissues. For the most part, changes in the rate of protein synthesis and degradation take place over a span of hours.



What changes in hormone levels and fuel metabolism occur during an overnight fast?

The hormonal changes that occur during an overnight fast include a decrease of blood insulin levels and an increase of glucagon relative to levels after a high-carbohydrate meal. Glucocorticoid levels also increase in the blood. These hormones coordinate the changes of fat, carbohydrate, and amino acid metabolism. Fatty acids are released from adipose triacylglycerols and are used as the major fuel by heart, skeletal muscle, liver, and other tissues. The liver converts some of the fatty acids to ketone bodies. Liver glycogen stores are diminished and gluconeogenesis becomes the major support of blood glucose levels for glucose-dependent tissues. The major precursors of gluconeogenesis include amino acids released from skeletal muscle, lactate, and glycerol.



Fig. 42.2. Maintenance of the blood amino acid pool. Dietary protein (1) and degradation of endogenous protein (2) provide a source of essential amino acids (those that cannot be synthesized in the human). 3. The synthesis of new protein is the major use of amino acids from the free amino acid pool. 4. Compounds synthesized from amino acid precursors are essential for physiologic functions. Many of these compounds are degraded to N-containing urinary metabolites and do not return to the free amino acid pool. 5. In tissues, the nitrogen is removed from amino acids by transamination and deamination reactions. 6. The nitrogen from amino acid degradation appears in the urine primarily as urea or NH_4^+ , the ammonium ion. Ammonia excretion is necessary to maintain the pH of the blood. 7. Amino acids are used as fuels either directly or after being converted to glucose by gluconeogenesis. 8. Some amino acids can be synthesized in the human, provided that glucose and a nitrogen source are available.

postprandial state. Net degradation of labile protein occurs in skeletal muscle (which contains the body's largest protein mass) and other tissues.

1. RELEASE OF AMINO ACIDS FROM SKELETAL MUSCLE DURING FASTING

The efflux of amino acids from skeletal muscle supports the essential amino acid pool in the blood (see Fig. 42.3). Skeletal muscle oxidizes the BCAA (valine, leucine, isoleucine) to produce energy and glutamine. The amino groups of the BCAA, and of aspartate and glutamate, are transferred out of skeletal muscle in alanine and glutamine. Alanine and glutamine account for approximately 50% of the total α -amino nitrogen released by skeletal muscle (Fig. 42.4).

The release of amino acids from skeletal muscle is stimulated during an overnight fast by the decrease of insulin and increase of glucocorticoid levels in the blood (see Chapters 31 and 43). Insulin promotes the uptake of amino acids and the general synthesis of proteins. The mechanisms for the stimulation of protein synthesis in human skeletal muscle are not all known, but probably include an activation of the A system for amino acid transport (a modest effect), a general effect on initiation of translation, and an inhibition of lysosomal proteolysis. The fall of blood insulin levels during an overnight fast results in net proteolysis and release of amino acids. As glucocorticoid release from the adrenal cortex increases, an induction of ubiquitin synthesis and an increase of ubiquitin-dependent proteolysis also occur.

2. AMINO ACID METABOLISM IN LIVER DURING FASTING

The major site of alanine uptake is the liver, which disposes of the amino nitrogen by incorporating it into urea (see Fig. 42.3). The liver also extracts free amino acids,



Fig. 42.3. Interorgan amino acid exchange after an overnight fast. After an overnight fast (the postabsorptive state), the utilization of amino acids for protein synthesis, for fuels, and for the synthesis of essential functional compounds continues. The free amino acid pool is supported largely by net degradation of skeletal muscle protein. Glutamine and alanine serve as amino group carriers from skeletal muscle to other tissues. Glutamine brings NH_4^+ to the kidney for the excretion of protons and serves as a fuel for the kidney, gut, and cells of the immune system. Alanine transfers amino groups from skeletal muscle, the kidney, and the gut to the liver, where they are converted to urea for excretion. The brain continues to use amino acids for neurotransmitter synthesis.



Fig. 42.4. Amino acid release from skeletal muscle. The arteriovenous difference (concentration in arterial blood minus the concentration in venous blood) across the human forearm has been measured for many amino acids. This graph compares the amount of alanine, glutamine, and BCAA released with their composition in the average protein. Alanine and glutamine represent a much higher percentage of total nitrogen released than originally present in the degraded protein, evidence that they are being synthesized in the skeletal muscle. The BCAA (leucine, valine, and isoleucine) are released in much lower amounts than those present in the degraded protein, evidence that they are being catabolized. Aspartate and glutamate also contribute nitrogen to the formation of alanine and glutamine



Fig. 42.5. Hormonal regulation of hepatic amino acid metabolism in the postabsorptive state. Circled + = glucagon-mediated activation of enzymes or proteins; circled $\uparrow =$ induction of enzyme synthesis mediated by glucagon and glucocorticoids. Induction of urea cycle enzymes occurs both during fasting and after a high-protein meal. Because many individuals in the United States normally have a high-protein diet, the levels of urea cycle enzymes may not fluctuate to any great extent.

The body normally produces approximately 1 mmol of protons per kilogram of body weight per day. Nevertheless, the pH of the blood and extracellular fluid is normally maintained between 7.36 and 7.44. The narrow range is maintained principally by the bicarbonate (HCO₃⁻), phosphate (HPO₄⁻), and hemoglobin buffering systems, and by the excretion of an amount of acid equal to that produced. The excretion of protons by the kidney regenerates bicarbonate, which can be reclaimed from the glomerular filtrate.

The acids are produced from normal fuel metabolism. The major acid is carbonic acid, which is formed from water and CO_2 produced in the TCA cycle and other oxidative pathways. The oxidation of sulfur-containing amino acids (methionine and cysteine) ultimately produces sulfuric acid (H₂SO₄), which dissociates into 2H⁺ + SO₄²⁻, and the protons and sulfate are excreted. The hydrolysis of phosphate esters produces the equivalent of phosphoric acid. What other acids produced during metabolism appear in the blood?

 α -keto acids, and some glutamine from the blood. Alanine and other amino acids are oxidized and their carbon skeletons converted principally to glucose. Glucagon and glucocorticoids stimulate the uptake of amino acids into liver and increase gluconeogenesis and ureagenesis (Fig. 42.5). Alanine transport into the liver, in particular, is enhanced by glucagon. The induction of the synthesis of gluconeogenic enzymes by glucagon and glucocorticoids during the overnight fast correlates with an induction of many of the enzymes of amino acid degradation (e.g., tyrosine aminotransferase) and an induction of urea cycle enzymes (see Chapter 38). Urea synthesis also increases because of the increased supply of NH_4^+ from amino acid degradation in the liver.

3. METABOLISM OF AMINO ACIDS IN OTHER TISSUES DURING FASTING

Glucose, produced by the liver, is used for energy by the brain and other glucosedependent tissues, such as erythrocytes. The muscle, under conditions of exercise, when the AMP-activated protein kinase is active, also oxidizes some of this glucose to pyruvate, which is used for the carbon skeleton of alanine (the glucose-alanine cycle; see Chapter 38).

Glutamine is generated in skeletal muscle from the oxidation of BCAA, and by the lungs and brain for the removal of NH_4^+ formed from amino acid catabolism or entering from the blood. The kidney, the gut, and cells with rapid turnover rates such as those of the immune system are the major sites of glutamine uptake (see Fig. 42.3). Glutamine serves as a fuel for these tissues, as a nitrogen donor for purine synthesis, and as a substrate for ammoniagenesis in the kidney. Much of the unused nitrogen from glutamine is transferred to pyruvate to form alanine in these tissues. Alanine then carries the unused nitrogen back to the liver.

The brain is glucose dependent, but, like many cells in the body, can use BCAA for energy. The BCAA also provide a source of nitrogen for neurotransmitter synthesis during fasting. Other amino acids released from skeletal muscle protein degradation also serve as precursors of neurotransmitters.

B. Principles Governing Amino Acid Flux between Tissues

The pattern of interorgan flux of amino acids is strongly affected by conditions that change the supply of fuels (for example, the overnight fast, a mixed meal, a high-protein meal) and by conditions that increase the demand for amino acids (metabolic acidosis, surgical stress, traumatic injury, burns, wound healing, and sepsis). The flux of amino acid carbon and nitrogen in these different conditions is dictated by several considerations:

1. Ammonia (NH₃) is toxic. Consequently, it is transported between tissues as alanine or glutamine. Alanine is the principal carrier of amino acid nitrogen from

Katta Bolic was in a severe stage of negative nitrogen balance on admission, which was caused by both her malnourished state and her intra-abdominal infection complicated by sepsis. The physiologic response to her advanced catabolic status includes a degradation of muscle protein with the release of amino acids into the blood. This release is coupled with an increased uptake of amino acids for "acute phase" protein synthesis by the liver (systemic response) and other cells involved in the immune response to general and severe infection.

The differences in amino acid metabolism between tissues are dictated by the types and amounts of different enzyme and transport proteins present in each tissue and the ability of each tissue to respond to different regulatory messages (hormones and neural signals).

other tissues back to the liver, where the nitrogen is converted to urea and subsequently excreted into the urine by the kidneys. The amount of urea synthesized is proportional to the amount of amino acid carbon that is being oxidized as a fuel.

- 2. The pool of glutamine in the blood serves several essential metabolic functions (Table 42.1). It provides ammonia for excretion of protons in the urine as NH₄⁺. It serves as a fuel for the gut, the kidney, and the cells of the immune system. Glutamine is also required by the cells of the immune system and other rapidly dividing cells in which its amide group serves as the source of nitrogen for biosynthetic reactions. In the brain, the formation of glutamine from glutamate and NH₄⁺ provides a means of removing ammonia and of transporting glutamate between different cell types within the brain. The utilization of the blood glutamine pool is prioritized. During metabolic acidosis, the kidney becomes the predominant site of glutamine uptake, at the expense of glutamine utilization in other tissues. Conversly, during sepsis, in the absence of acidosis, cells involved in the immune response (macrophages, hepatocytes) become the preferential sites of glutamine uptake.
- 3. The BCAA (valine, leucine, and isoleucine) form a significant portion of the composition of the average protein and can be converted to tricarboxylic acid (TCA) cycle intermediates and used as fuels by almost all tissues. They are also the major precursors of glutamine. Except for the BCAA and alanine, aspartate, and glutamate, the catabolism of amino acids occurs principally in the liver.
- 4. Amino acids are major gluconeogenic substrates, and most of the energy obtained from their oxidation is derived from oxidation of the glucose formed from their carbon skeletons. A much smaller percentage of amino acid carbon is converted to acetyl CoA or to ketone bodies and oxidized. The utilization of amino acids for glucose synthesis for the brain and other glucose-requiring tissues is subject to the hormonal regulatory mechanisms of glucose homeostasis (see Chapters 31 and 36).
- 5. The relative rates of protein synthesis and degradation (protein turnover) determine the size of the free amino acid pools available for the synthesis of new proteins and for other essential functions. For example, the synthesis of new proteins to mount an immune response is supported by the net degradation of other proteins in the body.

II. UTILIZATION OF AMINO ACIDS IN INDIVIDUAL TISSUES

Because tissues differ in their physiologic functions, they have different amino acid requirements and contribute differently to whole body nitrogen metabolism. However, all tissues share a common requirement for essential amino acids for protein synthesis, and protein turnover is an ongoing process in all cells.

A. Kidney

One of the primary roles of amino acid nitrogen is to provide ammonia in the kidney for the excretion of protons in the urine. NH_4^+ is released from glutamine by glutaminase and by glutamate dehydrogenase, resulting in the formation of α ketoglutarate (Fig. 42.6). α -Ketoglutarate is used as a fuel by the kidney and is oxidized to CO₂, converted to glucose for use in cells in the renal medulla, or converted to alanine to return ammonia to the liver for urea synthesis.

1. USE OF GLUTAMINE NITROGEN TO BUFFER URINE

The rate of glutamine uptake from the blood and its utilization by the kidney depends principally on the amount of acid that must be excreted to maintain a normal pH in the blood. During a metabolic acidosis, the excretion of NH_4^+ by the kidney increases severalfold (Table 42.2). Because glutamine nitrogen provides

Table 42.1. Functions of Glutamine

Protein synthesis Ammoniagenesis for proton excretion Nitrogen donor for synthesis of: Purines **Pvrimidines** NAD Amino sugars Asparagine Other compounds Glutamate donor for synthesis of: Glutathione GABA Ornithine Arginine Proline Other compounds

The ability to convert 4-carbon intermediates of the TCA cycle to pyruvate is required for oxidation of both BCAA and glutamine. This sequence of reactions requires PEP carboxykinase, or decarboxylating malate dehydrogenase (malic enzyme). Most tissues have one, or both, of these enzymes.



Lactic acid is produced from glucose and amino acid metabolism. The ketone bodies (acetoacetate and β-hydroxybutyrate) produced

during fatty acid oxidation are also acids. Many α -keto acids, formed from transamination reactions, are also found in the blood.



Fig. 42.6. Renal glutamine metabolism. Renal tubule cells preferentially oxidize glutamine. During metabolic acidosis, it is the major fuel for the kidney. Conversion of glutamine to α -ketoglutarate generates NH_4^+ . Ammonium ion excretion helps to buffer systemic acidemia.

Component	g/24 hr	Nitrogen (mmol)
H ₂ O	1,000	_
$H_2O = SO_4^{-2} PO_4^{-2} K^+$	2–5	_
PO_4^{-2}	2–5	_
K ⁺	1–2	_
Urea	12–20	400–650
Creatinine	1–1.8	25–50
Uric acid	0.2–0.8	4–16
NH_4^+	0.2–1	11–55
·	(up to 10 in acidosis)	(up to 550 in acidosis)

approximately two thirds of the NH_4^+ excreted by the kidney, glutamine uptake by the kidney also increases. Renal glutamine utilization for proton excretion takes precedence over the requirements of other tissues for glutamine.

Ammonia increases proton excretion by providing a buffer for protons that are transported into the renal tubular fluid (which is transformed into urine as it passes through the tubules of the kidney) (Fig. 42.7). Specific transporters in the membranes of the renal tubular cells transport protons from these cells into the tubular lumen in exchange for Na⁺. The protons in the tubular fluid are buffered by



Fig. 42.7. Ammonia excretion by the kidney. Ammonia increases proton excretion by combining with a proton to form ammonium ion in the renal tubular fluid, which is transformed into urine as it passes through the tubules of the kidney. As blood is filtered in the capillary bed of the glomerulus, urea, sugars, amino acids, ions, and H_2O enter the renal tubular fluid (glomerular filtrate). As this fluid passes through a progression of tubules (the proximal convoluted tubule, the loop of Henle, the distal convoluted tubule, and the collecting duct) on its way to becoming urine, various components are reabsorbed or added to the filtrate by the epithelial cells lining the tubules. Specific transporters in the membranes of the renal tubule cells transport protons into the tubule lumen in exchange for Na⁺ so that the glomerular filtrate becomes more acidic as it is transformed into urine. The protons in the tubule fluid are buffered by phosphate, by bicarbonate, and by NH₃. The ammonia, which is uncharged, is able to diffuse through the membrane of the renal tubule cells into the urine. As it combines with a proton in the urine, it forms NH₄⁺, which cannot be transported back into the cells. The removal of protons as NH₄⁺ decreases the requirement for bicarbonate excretion to buffer the urine.

% of Total CO ₂ Formed in Different Physiologic States					
Fuel	Normal	Acidosis	Fasted		
Lactate	45	20	15		
Glucose ^a	25	20	0		
Fatty acids	15	20	60		
Glutamine	15	40	25		

Table 42.3. Major Fuel Sources for the Kidney

^aGlucose used in the renal medulla is produced in the renal cortex.

phosphate, by bicarbonate, and by ammonia. Ammonia (NH_3) , which is uncharged, enters the urine by free diffusion through the cell membrane. As it combines with a proton in the fluid, it forms ammonium ion (NH_4^+) , which cannot be transported back into the cells and is excreted in the urine.

2. GLUTAMINE AS A FUEL FOR THE KIDNEY

Glutamine is used as a fuel by the kidney in the normal fed state and, to a greater extent, during fasting and metabolic acidosis (Table 42.3). The carbon skeleton forms α -ketoglutarate, which is oxidized to CO₂, converted to glucose, or released as the carbon skeleton of serine or alanine (Fig. 42.8). α -Ketoglutarate can be converted to oxaloacetate by TCA cycle reactions, and oxaloacetate is converted to phosphoenolpyruvate (PEP) by PEP carboxykinase. PEP can then be converted to pyruvate and subsequently acetyl CoA, alanine, serine, or glucose. The glucose is used principally by the cells of the renal medulla, which have a relatively high dependence on anaerobic glycolysis because of their lower oxygen supply and mitochondrial capacity. The lactate released from anaerobic glycolysis in these cells is taken up and oxidized in the renal cortical cells, which have a higher mitochondrial capacity and a greater blood supply.



Fig. 42.8. Metabolism of glutamine and other fuels in the kidney. To completely oxidize glutamate carbon to CO_2 , it must enter the TCA cycle as acetyl CoA. Carbon entering the TCA cycle as α -Ketoglutarate (α -KG) exits as oxaloacetate and is converted to phosphoenolpyruvate (PEP) by PEP carboxykinase. PEP is converted to pyruvate, which may be oxidized to acetyl CoA. PEP also can be converted to serine, glucose, or alanine. GDH = glutamate dehydrogenase; PEPCK = phosphoenolpyruvate carboxykinase; TA = transaminase; OAA = oxaloacetate.

B. Skeletal Muscle

Skeletal muscle, because of its large mass, is a major site of protein synthesis and degradation in the human. After a high-protein meal, insulin promotes the uptake of certain amino acids and stimulates net protein synthesis. The insulin stimulation of protein synthesis is dependent on an adequate supply of amino acids to undergo protein synthesis. During fasting and other catabolic states, a net degradation of skeletal muscle protein and release of amino acids occur (see Fig. 42.3). The net degradation of protein affects functional proteins, such as myosin, which are sacrificed to meet more urgent demands for amino acids in other tissues. During sepsis, degradation of skeletal muscle protein is stimulated by the glucocorticoid cortisol. The effect of cortisol is exerted through the activation of ubiquitin-dependent proteolysis. During fasting, the decrease of blood insulin levels and the increase of blood cortisol levels increase net protein degradation.

Skeletal muscle is a major site of glutamine synthesis, thereby satisfying the demand for glutamine during the postabsorptive state, during metabolic acidosis, and during septic stress and trauma. The carbon skeleton and nitrogen of glutamine are derived principally from the metabolism of BCAA. Amino acid degradation in skeletal muscle is also accompanied by the formation of alanine, which transfers amino groups from skeletal muscle to the liver in the glucose-alanine cycle.

1. OXIDATION OF BRANCHED-CHAIN AMINO ACIDS IN SKELETAL MUSCLE

The BCAA play a special role in muscle and most other tissues because they are the major amino acids that can be oxidized in tissues other than the liver. However, all tissues can interconvert amino acids and TCA cycle intermediates through transaminase reactions, i.e., alanine \leftrightarrow pyruvate, aspartate \leftrightarrow oxaloacetate, and α -ketoglutarate \leftrightarrow glutamate. The first step of the pathway, transamination of the BCAA to α -keto acids, occurs principally in brain, heart, kidney, and skeletal muscles. These tissues have a high content of BCAA transaminase relative to the low levels in liver. The α -keto acids of the BCAA are then either released into the blood and taken up by liver, or oxidized to CO₂ or glutamine within the muscle or other tissue (Fig. 42.9). They can be oxidized by all tissues that contain mitochondria.

The oxidative pathways of the BCAA convert the carbon skeleton to either succinyl CoA or acetyl CoA (see Chapter 39 and Fig. 42.9). The pathways generate NADH and FAD(2H) for ATP synthesis before the conversion of carbon into intermediates of the TCA cycle, thus providing the muscle with energy without loss of carbon as CO₂. Leucine is "ketogenic" in that it is converted to acetyl CoA and acetoacetate. Skeletal muscle, adipocytes, and most other tissues are able to use these products and, therefore, directly oxidize leucine to CO₂. The portion of isoleucine converted to acetyl CoA is also oxidized directly to CO₂. For the portion of valine and isoleucine that enters the TCA cycle as succinyl CoA to be completely oxidized to CO₂, it must first be converted to acetyl CoA. To form acetyl CoA, succinyl CoA is oxidized to malate in the TCA cycle, and malate is then converted to pyruvate by malic enzyme (malate + NADP⁺ \rightarrow pyruvate + NADPH + H⁺) (see Fig. 42.9). Pyruvate can then be oxidized to acetyl CoA. Alternatively, pyruvate can form alanine or lactate.

2. CONVERSION OF BRANCHED-CHAIN AMINO ACIDS TO GLUTAMINE

The major route of valine and isoleucine catabolism in skeletal muscle is to enter the TCA cycle as succinyl CoA and exit as α -ketoglutarate to provide the carbon skeleton for glutamine formation (see Fig. 42.9). Some of the glutamine and CO₂ that is formed from net protein degradation in skeletal muscle may also arise from

When the carbon skeleton of alanine is derived from glucose, the efflux of alanine from skeletal muscle and its uptake by liver provide no net transfer of amino acid carbon to the liver for gluconeogenesis. However, some of the alanine carbon is derived from sources other than glucose. Which amino acids can provide carbon for alanine formation? (Hint: See Fig. 42.9.)



Fig. 42.9. Metabolism of the carbon skeletons of BCAA in skeletal muscle. 1. The first step in the metabolism of BCAA is transamination (TA). 2. Carbon from valine and isoleucine enters the TCA cycle as succinyl CoA and is converted to pyruvate by decarboxylating malate dehydrogenase (malic enzyme). 3. The oxidative pathways generate NADH and FAD(2H) even before the carbon skeleton enters the TCA cycle. The rate-limiting enzyme in the oxidative pathways is the α -keto acid dehydrogenase complex. The carbon skeleton also can be converted to glutamate and alanine, shown in blue.

the carbon skeletons of aspartate and glutamate. These amino acids are transaminated and become part of the pool of 4-carbon intermediates of the TCA cycle.

Glutamine nitrogen is derived principally from the BCAA (Fig. 42.10). The α -amino group arises from transamination reactions that form glutamate from α -ketoglutarate, and the amide nitrogen is formed from the addition of free ammonia to glutamate by glutamine synthetase. Free ammonia in skeletal muscle arises principally from the deamination of glutamate by glutamate dehydrogenase or from the purine nucleotide cycle.

In the purine nucleotide cycle (Fig. 42.11), the deamination of AMP to IMP releases NH_4^+ . AMP is resynthesized with amino groups provided from aspartate. The aspartate amino groups can arise from the BCAA through transamination reactions. The fumarate can be used to replenish TCA cycle intermediates.

3. GLUCOSE-ALANINE CYCLE

The nitrogen arising from the oxidation of BCAA in skeletal muscle can also be transferred back to the liver as alanine in the glucose-alanine cycle (Fig. 42.12, see also Fig. 41.13). The amino group of the BCAA is first transferred to α -ketoglutarate

Some of the alanine released from skeletal muscle is derived directly from protein degradation. The carbon skeletons of valine, isoleucine, aspartate, and glutamate, which are converted to malate and oxaloacetate in the TCA cycle, can be converted to pyruvate and subsequently transaminated to alanine. The extent to which these amino acids contribute carbon to alanine efflux differs between different types of muscles in the human. These amino acids also may contribute to alanine efflux from the gut.

The purine nucleotide cycle is found in skeletal muscle and brain but is absent in liver and many other tissues. One of its functions in skeletal muscle is to respond to the rapid utilization of ATP during exercise. During exercise, the rapid hydrolysis of ATP increases AMP levels, resulting in an activation of AMP deaminase (see Fig. 42.11). As a consequence, the cellular concentration of IMP increases and ammonia is generated. IMP, like AMP, activates muscle glycogen phosphorylase during exercise (see Chapter 22). The ammonia that is generated may help to buffer the increased lactic acid production occurring in skeletal muscles during strenuous exercise.



Fig. 42.10. Formation of glutamine from the amino groups of BCAA. The BCAA are first transaminated with α -ketoglutarate to form glutamate and the branched chain α -keto acids. The glutamate nitrogen can then follow either of two paths leading to glutamine formation. TA = transamination; OAA = oxaloacetate; α -KG = α -ketoglutarate.

to form glutamate and then transferred to pyruvate to form alanine by sequential transamination reactions. The pyruvate arises principally from glucose via the glycolytic pathway. The alanine released from skeletal muscle is taken up principally by the liver, where the amino group is incorporated into urea, and the carbon skeleton can be converted back to glucose through gluconeogenesis. Although the amount of alanine formed varies with dietary intake and physiologic state, the transport of nitrogen from skeletal muscle to liver as alanine occurs almost continuously throughout our daily fasting–feeding cycle.

C. Gut

Amino acids are an important fuel for the intestinal mucosal cells after a protein-containing meal and in catabolic states such as fasting or surgical trauma (Fig. 42.13). During fasting, glutamine is one of the major amino acids used by the gut. The principal fates of glutamine carbon in the gut are oxidation to CO_2 and conversion to the carbon



Fig. 42.12. Glucose-alanine cycle. The pathway for transfer of the amino groups from BCAA in skeletal muscle to urea in the liver is shown in blue.



Fig. 42.11. Purine nucleotide cycle. In skeletal muscle, the purine nucleotide cycle can convert the amino groups of the BCAA to NH_3 , which is incorporated into glutamine. The compounds containing the amino group released in the purine nucleotide cycle are shown in blue.



Fig. 42.13. Amino acid metabolism in the gut. The pathways of glutamine metabolism in the gut are the same whether it is supplied by the diet (postprandial state) or from the blood (postabsorptive state). Cells of the gut also metabolize aspartate, glutamate, and BCAA. Glucose is converted principally to the carbon skeleton of alanine. α -KG = α -ketoglutarate; GDH = glutamate dehydrogenase; TA = transaminase.

skeletons of lactate, citrulline, and ornithine. The gut also oxidizes BCAA. Nitrogen derived from amino acid degradation is converted to citrulline, alanine, NH_4^+ , and other compounds that are released into the blood and taken up by the liver. Although most of the carbon in this alanine is derived from glucose, the oxidation of glucose to CO_2 is not a major fuel pathway for the gut. Fatty acids are also not a significant source of fuel for the intestinal mucosal cells, although they do use ketone bodies.

After a protein meal, dietary glutamine is a major fuel for the gut, and the products of glutamine metabolism are similar to those seen in the postabsorptive state. The gut also uses dietary aspartate and glutamate, which enter the TCA cycle. Colonocytes (the cells of the colon) also use short-chain fatty acids, derived from bacterial action in the lumen.

The importance of the gut in whole body nitrogen metabolism arises from the high rate of division and death of intestinal mucosal cells and the need to continuously provide these cells with amino acids to sustain the high rates of protein synthesis required for cellular division. Not only are these cells important for the uptake of nutrients, but they maintain a barrier against invading bacteria from the gut lumen and are, therefore, part of our passive defense system. As a result of these important functions, the intestinal mucosal cells are supplied with the amino acids required for protein synthesis and fuel oxidation at the expense of the more expendable skeletal muscle protein.

D. Liver

The liver is the major site of amino acid metabolism. It is the major site of amino acid catabolism and converts most of the carbon in amino acids to intermediates of the TCA cycle or the glycolytic pathway (which can be converted to glucose or oxidized to CO_2), or to acetyl CoA and ketone bodies. The liver is also the major site for urea synthesis. It can take up both glutamine and alanine and convert the

The intestine contains the enzymes for the urea cycle, but the V_{max} for argininosuccinate synthetase and argininosuccinate lyase are very low, suggesting that the primary role of the urea cycle enzymes in the gut is to produce citrulline from the carbons of glutamine (glutamine \rightarrow glutamate \rightarrow glutamate semialdehyde \rightarrow ornithine \rightarrow citrulline). The citrulline is released in the circulation for use by the liver.

Glutamine utilization by the gut is diminished by a metabolic acidosis compared with the postabsorptive or postprandial states. During metabolic acidosis, the uptake of glutamine by the kidney is increased, and blood glutamine levels decrease. As a consequence, the gut takes up less glutamine. nitrogen to urea for disposal (see Chapter 38). Other pathways in the liver provide it with an unusually high amino acid requirement. The liver synthesizes plasma proteins, such as serum albumin, transferrin, and the proteins of the blood coagulation cascade. It is a major site for the synthesis of nonessential amino acids, the conjugation of xenobiotic compounds with glycine, the synthesis of heme and purine nucleotides, and the synthesis of glutathione.

E. Brain and Nervous Tissue

1. AMINO ACID POOL AND NEUROTRANSMITTER SYNTHESIS

A major function of amino acid metabolism in neural tissue is the synthesis of neurotransmitters. More than 40 compounds are believed to function as neurotransmitters, and all of these contain nitrogen derived from precursor amino acids. They include amino acids, which are themselves neurotransmitters (e.g., glutamate, glycine), the catecholamines derived from tyrosine (dopamine and norepinephrine), serotonin (derived from tryptophan), GABA (derived from glutamate), acetyl-choline (derived from choline synthesized in the liver and acetyl CoA), and many peptides. In general, neurotransmitters are formed in the presynaptic terminals of axons and stored in vesicles until released by a transient change in electrochemical potential along the axon. Subsequent catabolism of some of the neurotransmitter results in the formation of a urinary excretion product. The rapid metabolism of neurotransmitters requires the continuous availability of a precursor pool of amino acids for de novo neurotransmitter synthesis (see Chapter 47).

2. METABOLISM OF GLUTAMINE IN THE BRAIN

The brain is a net glutamine producer owing principally to the presence of glutamine synthetase in astroglial cells (see Chapter 47). Glutamate and aspartate are synthesized in these cells, using amino groups donated by the BCAA (principally valine) and TCA cycle intermediates formed from glucose and from the carbon skeletons of BCAA (Fig. 42.14) The glutamate is converted to glutamine by glutamine synthetase, which incorporates NH_4^+ released from deamination of amino acids and deamination of AMP in the purine nucleotide cycle in the brain. This glutamine may efflux from the brain, carrying excess NH_4^+ into the blood, or serve as a precursor of glutamate in neuronal cells.



Fig. 42.14. Role of glutamine in the brain. Glutamine serves as a nitrogen transporter in the brain for the synthesis of many different neurotransmitters. Different neurons convert glutamine to γ -aminobutyric acid (GABA) or to glutamate. Glutamine also transports excess NH₄⁺ from the brain into the blood. BCKA = branched-chain keto acids; α -KG = α -ketoglutarate.

Glutamine synthesized in the astroglial cells is a precursor of glutamate (an excitatory neurotransmitter) and GABA (an inhibitory neurotransmitter) in the neuronal cells (see Fig. 42.14). It is converted to glutamate by a neuronal glutaminase isozyme. In GABAergic neurons, glutamate is then decarboxylated to GABA, which is released during excitation of the neuron. GABA is one of the neurotransmitters that is recycled; a transaminase converts it to succinaldehyde, which is then oxidized to succinate. Succinate enters the TCA cycle.

III. CHANGES IN AMINO ACID METABOLISM WITH DIETARY AND PHYSIOLOGIC STATE

The rate and pattern of amino acid utilization by different tissues change with dietary and physiologic state. Two such states, the postprandial period following a high-protein meal and the hypercatabolic state produced by sepsis or surgical trauma, differ from the postabsorptive state with respect to the availability of amino acids and other fuels and the levels of different hormones in the blood. As a result, the pattern of amino acid utilization is somewhat different.

A. A High-Protein Meal

After the ingestion of a high-protein meal, the gut and the liver use most of the absorbed amino acids (Fig. 42.15). Glutamate and aspartate are used as fuels by the gut, and very little enters the portal vein. The gut also may use some BCAA. The liver takes up 60 to 70% of the amino acids present in the portal vein. These amino acids, for the most part, are converted to glucose in the gluconeogenic pathway.

After a pure protein meal, the increased levels of dietary amino acids reaching the pancreas stimulate the release of glucagon above fasting levels, thereby increasing amino acid uptake into liver and stimulating gluconeogenesis. Insulin release is also stimulated, but not nearly to the levels found after a high-carbohydrate meal. During hyperammonemia, ammonia (NH₃) can diffuse into the brain from the blood. The ammonia is able to inhibit the neural isozyme of glutaminase, thereby decreasing additional ammonia formation in the brain and inhibiting the formation of glutamate and its subsequent metabolism to GABA. This effect of ammonia might contribute to the lethargy associated with the hyperammonemia found in patients with hepatic disease.

The levels of transthyretin (binds to vitamin A and thyroid hormones in the blood) and serum albumin in the blood may be used as indicators of the degree of protein malnutrition. In the absence of hepatic disease, decreased levels of these proteins in the blood indicate insufficient availability of amino acids to the liver for synthesis of serum proteins.

In what ways does liver metabolism after a high-protein meal resemble liver metabolism in the fasting state?



Fig. 42.15. Flux of amino acids after a high-protein meal.



Both of these dietary states are characterized by an elevation of glucagon. Glucagon stimulates amino acid transport into the liver, stimulates gluconeogenesis through decreasing

levels of fructose 2,6-bisphosphate, and induces the synthesis of enzymes in the urea cycle, the gluconeogenic pathway, and the pathways for degradation of some of the amino acids.



The Atkins high-protein diet is based on the premise that ingesting high-protein, low-carbohydrate

meals will keep circulating insulin levels low, such that energy storage is not induced, and glucagon release will point the insulin/glucagon ratio to energy mobilization, particularly fatty acid release from the adipocyte and oxidation by the tissues. The lack of energy storage, coupled with the loss of fat, leads to weight loss.

In general, the insulin released after a high-protein meal is sufficiently high that the uptake of BCAA into skeletal muscle and net protein synthesis is stimulated, but gluconeogenesis in the liver is not inhibited. The higher the carbohydrate content of the meal, the higher the insulin/glucagon ratio and the greater the shift of amino acids away from gluconeogenesis into biosynthetic pathways in the liver such as the synthesis of plasma proteins.

Most of the amino acid nitrogen entering the peripheral circulation after a highprotein meal or a mixed meal is present as the BCAA. Because the liver has low levels of transaminases for these amino acids, it cannot oxidize them to a significant extent, and they enter the systemic circulation. The BCAA are slowly taken up by skeletal muscle and other tissues. These peripheral nonhepatic tissues use the amino acids derived from the diet principally for net protein synthesis.

B. Hypercatabolic States

Surgery, trauma, burns, and septic stress are examples of hypercatabolic states characterized by increased fuel utilization and a negative nitrogen balance (Fig. 42.16). The mobilization of body protein, fat, and carbohydrate stores serves to maintain normal tissue function in the presence of a limited dietary intake, as well as to support the energy and amino acid requirements for the immune response and wound healing. The negative nitrogen balance that occurs in these hypercatabolic states



Fig. 42.16. Negative nitrogen balance during infection. The effects of experimentally induced infections on nitrogen balance were determined in human volunteers. After inoculation with sandfly fever, increased amino acid catabolism produced a negative nitrogen balance. A few days after exposure, the daily nitrogen balance became positive until the volunteers returned to their original state. Experiments with patients exposed to tularemia showed that the negative nitrogen balance was much larger than could be expected from a decreased appetite alone. Volunteers who ate the same amount of food as the infected individuals (pairfed nonexposed controls) had a much smaller cumulative negative nitrogen balance than the infected volunteers. From Beisel WR. Am J Clin Nutr 1977;30:1236–1247. © 1977 American Society for Clinical Nutrition.

results from an accelerated protein turnover and an increased rate of net protein degradation, primarily in skeletal muscle.

The catabolic state of sepsis (acute, generalized, febrile infection) is one of enhanced mobilization of fuels and amino acids to provide the energy and precursors required by cells of the immune system, host defense mechanisms, and wound healing. The amino acids must provide the substrates for new protein synthesis and cell division. Glucose synthesis and release are enhanced to provide fuel for these cells, and the patient may become mildly hyperglycemic.

In these hypercatabolic states, skeletal muscle protein synthesis decreases, and protein degradation increases. Oxidation of BCAA is increased and glutamine production enhanced. Amino acid uptake is diminished. Cortisol is the major hormonal mediator of these responses, although certain cytokines may also have direct effects on skeletal muscle metabolism. As occurs during fasting and metabolic acidosis, increased levels of cortisol stimulate ubiquitin-mediated proteolysis, induce the synthesis of glutamine synthetase, and enhance release of amino acids and glutamine from the muscle cells.

The amino acids released from skeletal muscle during periods of hypercatabolic stress are used in a prioritized manner, with the cellular components of the immune system receiving top priority. For example, the uptake of amino acids by the liver for the synthesis of acute phase proteins, which are part of the immune system, is greatly increased. Conversly, during the early phase of the acute response, the synthesis of other plasma proteins (e.g., albumin) is decreased. The increased availability of amino acids and the increased cortisol levels also stimulate gluconeogenesis, thereby providing fuel for the glucose-dependent cells of the immune system (e.g., lymphocytes). An increase of urea synthesis accompanies the acceleration of amino acid degradation.

The increased efflux of glutamine from skeletal muscle during sepsis serves several functions (see Fig. 42.1). It provides the rapidly dividing cells of the immune system with an energy source. Glutamine is available as a nitrogen donor for purine synthesis, for NAD⁺ synthesis, and for other biosynthetic functions essential to growth and division of the cells. An increased production of metabolic acids may accompany stress such as sepsis, so there is an increased utilization of glutamine by the kidney.

Under the influence of elevated levels of glucocorticoids, epinephrine, and glucagon, fatty acids are mobilized from adipose tissue to provide alternate fuels for other tissues and spare glucose. Under these conditions, fatty acids are the major energy source for skeletal muscle, and glucose uptake is decreased. These changes may lead to a mild hyperglycemia.

CLINICAL COMMENTS

The clinician can determine whether a patient such as **Katta Bolic** is mounting an acute phase response to some insult, however subtle, by determining whether several unique acute phase proteins are being secreted by the liver. C-reactive protein, so named because of its ability to interact with the Cpolysaccharide of pneumococci, and serum amyloid A protein, a precursor of the amyloid fibril found in secondary amyloidosis, are elevated in patients undergoing the acute phase response and as compared with healthy individuals. Other proteins normally found in the blood of healthy individuals are present in increased concentrations in patients undergoing an acute phase response. These include haptoglobin, certain protease inhibitors, complement components, ceruloplasmin, and fibrinogen. The elevated concentration of these proteins in the blood increases the erythrocyte sedimentation rate (ESR), another laboratory measure of the presence of an acute phase response.



The degree of the body's hypercatabolic response depends on the severity and duration of the trauma

or stress. After an uncomplicated surgical procedure in an otherwise healthy patient, the net negative nitrogen balance may be limited to about 1 week. The mild nitrogen losses are usually reversed by dietary protein supplementation as the patient recovers. With more severe traumatic injury or septic stress, the body may catabolize body protein and adipose tissue lipids for a prolonged period, and the negative nitrogen balance may not be corrected for weeks.

Katta Bolic's severe negative nitrogen balance was caused by both her malnourished state and her intra-abdominal infection complicated by sepsis. The systemic and diverse responses the body makes to insults such as an acute febrile illness are termed the "acute phase response." An early event in this response is the stimulation of phagocytic activity (see Fig. 42.17). Stimulated macrophages release cytokines, which are regulatory proteins that stimulate the release of cortisol, insulin, and growth hormone. Cytokines also directly mediate the acute phase response of the liver and skeletal muscle to sepsis.

To determine the ESR, the patients' blood is placed vertically in a small-bore glass tube. The speed with which the red blood cells sediment toward the bottom of the tube depends on what percentage of the red blood cells clump together and, thereby, become more dense. The degree of clumping is directly correlated with the presence of one or more of the first-phase proteins listed previously. These proteins interfere with what is known as the zeta-potential of the red blood cells, which normally prevents the red blood cells from clumping. Because many different proteins can individually alter the zeta-potential, the ESR is a nonspecific test for the presence of acute inflammation.

The weight loss often noted in septic patients is primarily caused by a loss of appetite resulting from the effect of certain cytokines on the medullary appetite center. Other causes include increased energy expenditure from fever and enhanced muscle proteolysis.

BIOCHEMICAL COMMENTS

After a catabolic insult such as injury, trauma, infection, or cancer, the interorgan flow of glutamine and fuels is dramatically altered. Teleologically, the changes in metabolism that occur give first priority to cells that are part of the immune system. Evidence suggests that the changes in glutamine and



Fig. 42.17. Cytokines and hormones mediate amino acid flux during sepsis. Bacterial products act on macrophages to stimulate the release of cytokines and on the brain to stimulate the sympathoadrenal response. The result is a stimulation of the release of the insulin counterregulatory hormones, epinephrine, glucagon, and glucocorticoids. The glucocorticoid cortisol may be the principal mediator of net muscle protein degradation during sepsis. Hepatic protein synthesis, particularly that of acute phase proteins, is stimulated both by cortisol and cytokines. Amino acid metabolism in the gut is also probably affected by glucocorticoids and cytokines. Because of the release of the counterregulatory hormones, muscle and other tissues become resistant to insulin action, as indicated by the bar on the figure. Adapted with permission from Fisher J. Am J Surg 1991;161:270.

fuel metabolism are mediated by the insulin counterregulatory hormones, such as cortisol and epinephrine, and several different cytokines (see Chapter 11 for a review of cytokines). Cytokines appear to play a more important role than hormones during sepsis, although they exert their effects, in part, through hormones (Fig. 42.17). Although cytokines can be released from a variety of cells, macrophages are the principal source during trauma and sepsis.

Two cytokines that are important in sepsis are interleukin-1 (IL-1) and tumor necrosis factor (TNF). IL-1 and TNF affect amino acid metabolism both through regulation of the release of glucocorticoids and through direct effects on tissues. Although cytokines are generally considered to be paracrine, with their effects being exerted over cells in the immediate vicinity, TNF and IL-1 increase in the blood during sepsis. Other cytokines, such as IL-6, also may be involved.

During sepsis, TNF, IL-1, and possibly other cytokines, bacterial products, or mediators act on the brain to stimulate the release of glucocorticoids from the adrenal cortex (a process mediated by adrenocorticotropic hormone [ACTH]), epinephrine from the adrenal medulla, and both insulin and glucagon from the pancreas. Although insulin is elevated during sepsis, the tissues exhibit an insulin resistance that is similar to that of the non-insulin-dependent diabetes mellitus patient, possibly resulting from the elevated levels of the insulin counterregulatory hormones (glucocorticoids, epinephrine, and glucagon). Changes in the rate of acute phase protein synthesis are mediated, at least in part, by effects of TNF, IL-1, and IL-6 on the synthesis of groups of proteins in the liver.

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REVIEW QUESTIONS—CHAPTER 42

1. Which of the profiles indicated below would occur within 2 hours after eating a meal very high in protein and low in carbohydrates?

	Blood glucagon	Liver	BCAA oxidation in
	levels	gluconeogenesis	muscle
(A)	\downarrow	\downarrow	1
(B)	\uparrow	\downarrow	1
(C)	\downarrow	\uparrow	1
(D)	\uparrow	\uparrow	\uparrow
(E)	\downarrow	\downarrow	\downarrow
(F)	\uparrow	\downarrow	\downarrow
(G)	\downarrow	\uparrow	\downarrow
(H)	\uparrow	\uparrow	\downarrow

Hypercatabolic states may be accompanied by varying degrees of insulin resistance caused, in part, by the release of counterregulatory hormones into the blood. Thus, patients with diabetes mellitus may require higher levels of exogenous insulin during sepsis.

- 2. The gut uses glutamine as an energy source, but can also secrete citrulline, synthesized from the carbons of glutamine. Which of the following compounds is an obligatory intermediate in this conversion (consider only the carbon atoms of glutamine while answering this question)?
 - (A) Aspartate
 - (B) Succinyl CoA
 - (C) Glutamate
 - (D) Serine
 - (E) Fumarate
- 3. The signal that indicates to muscle that protein degradation needs to be initiated is which of the following?
 - (A) Insulin
 - (B) Glucagon
 - (C) Epinephrine
 - (D) Cortisol
 - (E) Glucose
- 4. The skeletal muscles convert BCAA carbons to glutamine for export to the rest of the body. An obligatory intermediate, which carries carbons originally from the BCAA, in the conversion of BCAA to glutamine, is which of the following?
 - (A) Urea
 - (B) Pyruvate
 - (C) Lactate
 - (D) Isocitrate
 - (E) Phosphoenolpyruvate
- 5. An individual in sepsis would display which of the following metabolic patterns?

	Nitrogen balance	Gluconeogenesis	Fatty acid oxidation
(A)	Positive	\uparrow	\uparrow
(B)	Negative	\uparrow	\uparrow
(C)	Positive	\uparrow	\downarrow
(D)	Negative	\uparrow	\downarrow
(E)	Positive	\downarrow	\uparrow
(F)	Negative	\downarrow	\downarrow