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Item 1 of 40
Question Id: 1242

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Hemoglobin C (HbC) disease is due to a single amino acid substitution (glutamic acid → lysine) at position 6 in the beta globin chain of the hemoglobin molecule. Hemoglobin S (HbS) is similar to HbC in that it is also formed by an amino acid substitution at position 6 in the beta globin chain. However, patients homozygous for HbC have mild chronic hemolytic anemia, whereas those homozygous for HbS generally have a more severe anemia complicated by vasoocclusive pain episodes. Which of the following properties best accounts for the differing clinical severity between the two conditions?

A. HbS allows hydrophobic interaction among hemoglobin molecules
B. HbS decreases beta globin interaction with 2,3-bisphosphoglycerate
C. HbS impairs oxygen unloading from the heme moiety
D. HbS prevents proper folding of the alpha helix in the beta globin chain
E. HbS stabilizes the iron moiety in the ferric (Fe^{3+}) state

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Item 1 of 40
Question Id: 1242

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- ✔ A. HbS allows hydrophobic interaction among hemoglobin molecules [54%]
- B. HbS decreases beta globin interaction with 2,3-bisphosphoglycerate [6%]
- C. HbS impairs oxygen unloading from the heme moiety [8%]
- D. HbS prevents proper folding of the alpha helix in the beta globin chain [28%]
- E. HbS stabilizes the iron moiety in the ferric (Fe^{3+}) state [1%]

Omitted
Correct answer
A

54%
Answered correctly

19 Seconds
Time Spent

09/07/2018
Last Updated

Explanation

Globin chains in the hemoglobin tetramer are compactly folded due to nonpolar hydrophobic residues in the interior and charged polar residues on the surface. In **sickle cell disease**, the usual acidic (negatively charged) glutamic acid (glu) residue at the sixth position on the beta globin chain is replaced by a **nonpolar** (neutral charge) **valine** (val) residue, forming hemoglobin S (**HbS**). This single glu → val substitution leads to the

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

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In patients with hemoglobin C (**HbC**), glu is replaced by a basic **polar** (positively charged) **lysine** (lys) residue. Because lys is charged (although it has opposite polarity to glu), there is no hydrophobic interaction between hemoglobin molecules and no polymerization/sickling. However, the positive charge of lys causes HbC to have decreased mobility on electrophoresis.

(Choice B) HbS and HbC do not differ significantly from normal hemoglobin in affinity to 2,3-bisphosphoglycerate (2,3-BPG). In addition, weaker interaction with 2,3-BPG would lead to increased oxygen affinity (left shift of the **oxygen-hemoglobin dissociation curve**), which would help ameliorate sickling.

(Choice C) The ability of HbS to polymerize helps stabilize the deoxygenated form, causing a right shift of the oxygen-hemoglobin dissociation curve that facilitates oxygen unloading. In contrast, impaired oxygen unloading occurs with carboxyhemoglobin due to an allosteric change that increases the affinity of the remaining 3 oxygen-binding sites.

(Choice D) A glu → val substitution affects the 3-dimensional (tertiary) structure of hemoglobin, but it does not result in a significant change in the alpha helical (secondary) structure. Introducing proline into the primary structure could distort the alpha helix due to proline's rigid cyclic structure.

(Choice E) HbS and HbC mutations do not involve amino acids lining the heme pocket. Heme iron oxidation (ferrous [Fe^{2+}] → ferric [Fe^{3+}]) results in methemoglobin formation. Hemoglobin M disease is a congenital cause of methemoglobinemia due to a mutation in the heme-binding pocket.

Educational objective:

formation of a **hydrophobic pocket** on the beta globin surface that interacts with a complementary nonpolar residue on another hemoglobin molecule. The hydrophobic interaction causes **polymerization** of HbS molecules and subsequent **erythrocyte sickling**, leading to membrane damage and permanent distortion of red blood cells. Red cell sickling is promoted by low oxygen levels, increased acidity, and dehydration.

In patients with hemoglobin C (**HbC**), glu is replaced by a basic **polar** (positively charged) **lysine** (lys) residue. Because lys is charged (although it has opposite polarity to glu), there is no hydrophobic interaction between hemoglobin molecules and no polymerization/sickling. However, the positive charge of lys causes HbC to have decreased mobility on electrophoresis.

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Educational objective:
Hemoglobin S (HbS) contains valine in place of glutamic acid at the sixth amino acid position of the beta globin chain. This promotes hydrophobic interaction among Hb molecules and results in HbS polymerization and erythrocyte sickling.

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Item 2 of 40
Question Id: 1019

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An 8-year-old boy is evaluated for exercise intolerance. The patient experiences fatigue, muscle pain, and cramps during exercise as well as severe muscle stiffness following strenuous activity. Physical examination is unremarkable. A forearm ischemic exercise test is performed by applying a blood pressure cuff on the patient's exercising forearm and sampling blood lactate several minutes after the exercise. The patient's blood samples show no rise in lactate levels. Biochemical analysis of a muscle biopsy reveals absent lactate dehydrogenase activity. In this patient, strenuous exercise leads to inhibition of glycolysis in skeletal muscle due to intracellular depletion of which of the following substances?

A. AMP
B. Carnitine
C. Citrate
D. $FADH_2$
E. NAD^+
F. Pyruvate

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Item 2 of 40
Question Id: 1019

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- A. AMP [6%]
- B. Carnitine [3%]
- C. Citrate [3%]
- D. $FADH_2$ [2%]
- ✔ E. NAD^+ [64%]
- F. Pyruvate [18%]

Omitted
Correct answer
E

64%
Answered correctly

5 Seconds
Time Spent

09/20/2018
Last Updated

Explanation

In glycolysis, glucose is metabolized to pyruvate. Under aerobic conditions, pyruvate is converted to acetyl-CoA to enter the tricarboxylic acid

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Explanation

In glycolysis, glucose is metabolized to pyruvate. Under aerobic conditions, pyruvate is converted to acetyl-CoA to enter the tricarboxylic acid (TCA) cycle. When oxygen is depleted (eg, in exercising muscle), pyruvate is converted to lactate (**anaerobic glycolysis**).

During glycolysis, glyceraldehyde-3-phosphate (G3P) is converted to 1-3-bisphosphoglycerate (BPG) by the enzyme G3P dehydrogenase. This enzyme reduces NAD^+ to NADH. NAD^+ is present in limited amounts in most cells, and it must be regenerated from NADH for glycolysis to continue. Under aerobic conditions, NAD^+ is converted to NADH in the TCA cycle. NADH is then reconverted to NAD^+ in the electron transport chain as the energy in NADH is utilized to synthesize ATP.

In anaerobic glycolysis, **NAD+** is **regenerated** from NADH when pyruvate is converted to lactate via **lactate dehydrogenase**. In patients with lactate dehydrogenase deficiency, glycolysis is inhibited in strenuously exercising muscle as muscle cells cannot regenerate NAD^+. Consequently, high-intensity physical activity leads to muscle breakdown, pain, and fatigue as insufficient amounts of energy are being produced in the exercising muscle.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of glycogen phosphorylase, which activates this enzyme. Non-phosphorylation-dependent activation of glycogen phosphorylase can occur during muscle contraction via increased intracellular calcium concentrations and via AMP under extreme conditions.

(Choice B) Carnitine is an amino acid derivative responsible for transporting fatty acids into the mitochondria for beta-oxidation. Carnitine is synthesized from lysine and methionine; vitamin C is essential for this synthesis.

(Choice C) Citrate is formed from the condensation of acetyl CoA with oxaloacetate in the first step of the TCA cycle. Increased citrate concentrations decrease glycolysis as citrate is a powerful allosteric inhibitor of phosphofructokinase-1. In exercising muscles under anaerobic conditions, oxidative phosphorylation of glucose through the citric acid cycle is not a dominant pathway; therefore, excess citrate is not produced.

(Choice A) During muscle contraction, glycogen is broken down via glycogen phosphorylase for energy production by the glycolytic pathway. Epinephrine causes cyclic AMP-mediated phosphorylation of glycogen phosphorylase, which activates this enzyme. Non-phosphorylation-dependent activation of glycogen phosphorylase can occur during muscle contraction via increased intracellular calcium concentrations and via AMP under extreme conditions.

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(Choice D) $FADH_2$ is not produced in glycolysis. $FADH_2$ is produced from FAD during the conversion of succinate to fumarate in the TCA cycle by the enzyme succinate dehydrogenase.

(Choice F) In glycolysis, pyruvate is formed from phosphoenolpyruvate by a unidirectional enzyme called pyruvate kinase. In the absence of lactate dehydrogenase activity, pyruvate will accumulate in the cell under anaerobic conditions.

Educational objective:
Under anaerobic conditions, NADH transfers electrons to pyruvate to form lactate and regenerate NAD^+. NAD^+ is required to convert glyceraldehyde-3-phosphate to 1-3-bisphosphoglycerate in glycolysis.

References

- Lactate dehydrogenase M-subunit deficiencies: clinical features, metabolic background, and genetic heterogeneities.

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Item 3 of 40
Question Id: 2067

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A 6-month-old boy is brought to the office by his mother out of concern that he is not developing normally. He has been feeding regularly and has had no medical problems other than a mild respiratory infection a month earlier. However, the mother says, "he doesn't seem to be as interactive as my other children were at his age." Physical examination reveals delayed developmental milestones and hypotonia. Two years later, the child is found to have involuntary movements and demonstrates a tendency to aggressively bite his own lips and fingers. Laboratory analysis shows an elevated blood uric acid level. Activity of which of the following enzymes is most likely increased as a result of this patient's condition?

A. Aspartate carbamoyltransferase
B. Dihydroorotase
C. Hypoxanthine-guanine phosphoribosyltransferase
D. Phosphoribosyl pyrophosphate amidotransferase
E. Ribonucleotide reductase
F. Thymidylate synthase

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Item 3 of 40
Question Id: 2067

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- A. Aspartate carbamoyltransferase [4%]
- B. Dihydroorotase [3%]
- C. Hypoxanthine-guanine phosphoribosyltransferase [43%]
- ✔ D. Phosphoribosyl pyrophosphate amidotransferase [39%]
- E. Ribonucleotide reductase [4%]
- F. Thymidylate synthase [4%]

Omitted
Correct answer
D

39%
Answered correctly

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Time Spent

11/23/2018
Last Updated

Explanation

De novo purine synthesis

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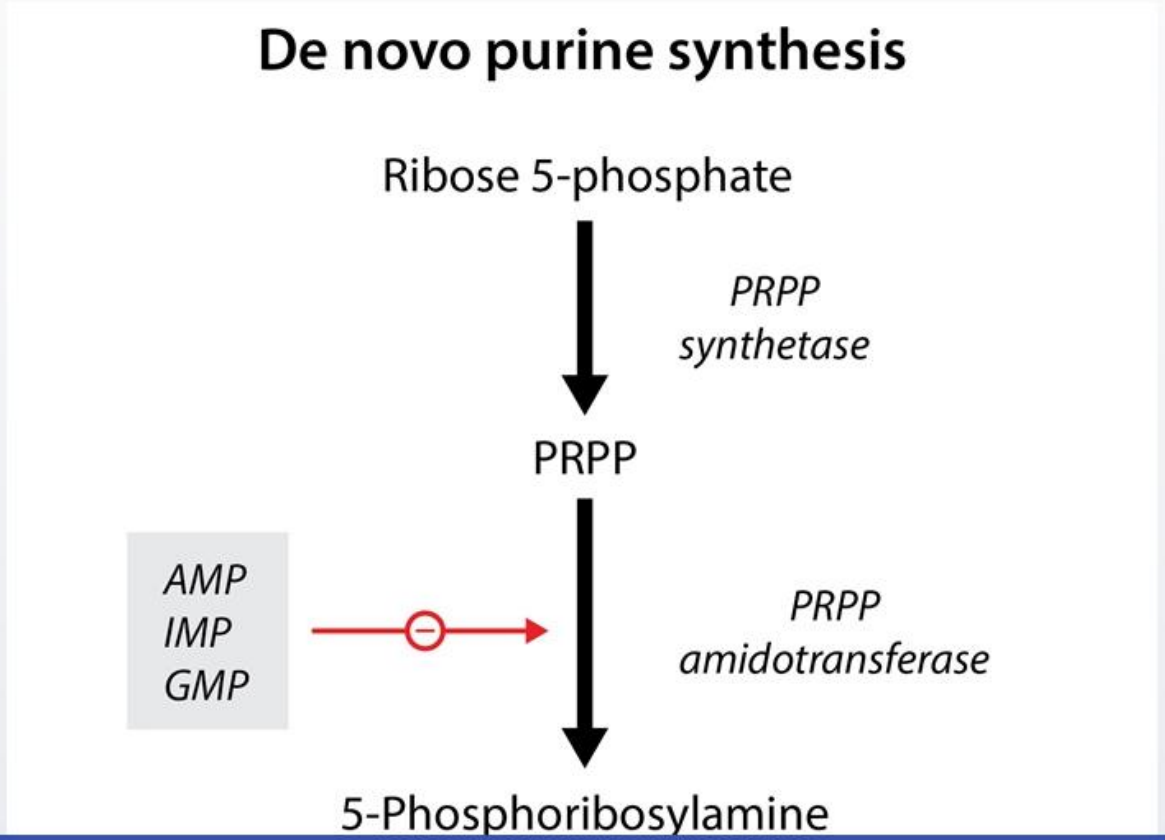
Explanation



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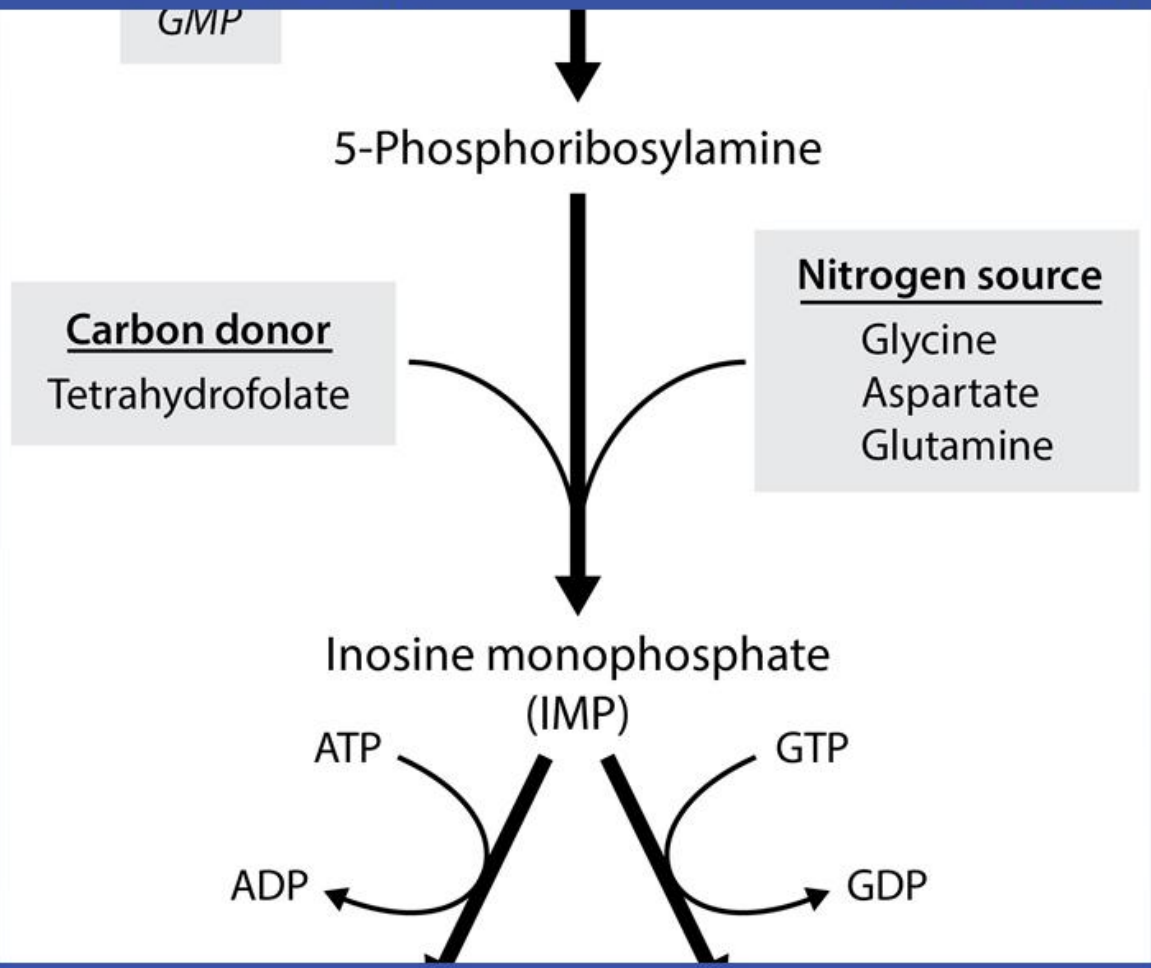

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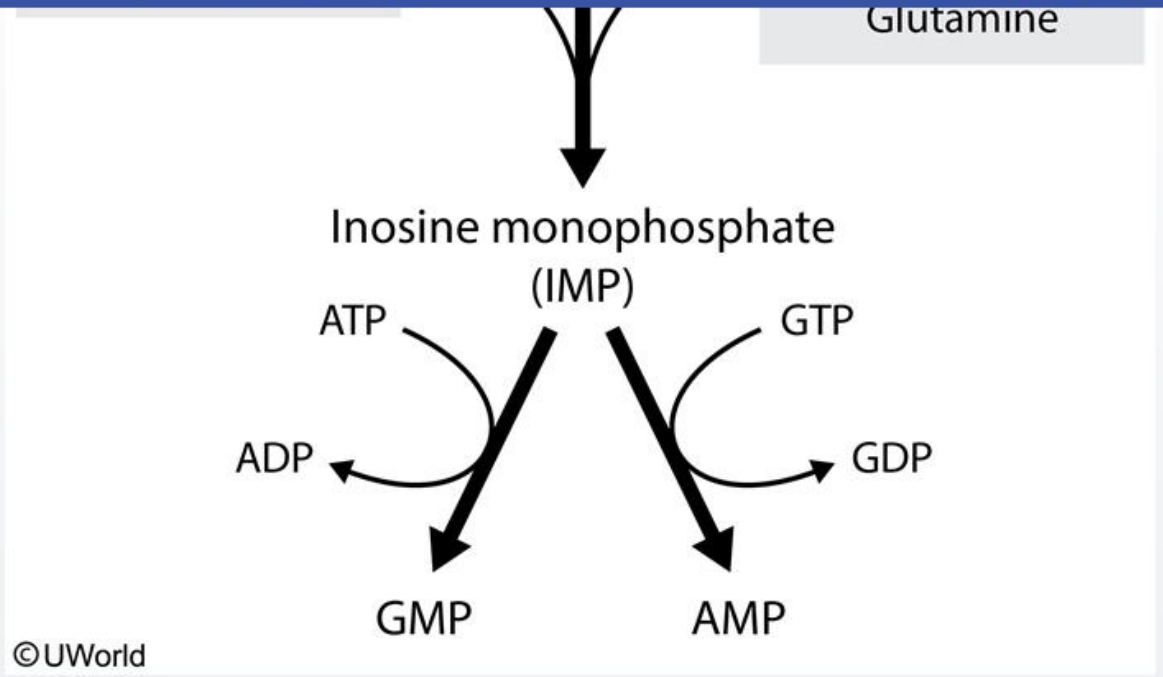

This patient has **Lesch-Nyhan syndrome**, an X-linked recessive disorder characterized by the development of dystonia, choreoathetosis, **self-mutilation**, and **hyperuricemia** within the first few years of life. The condition is caused by deficiency of **hypoxanthine-guanine phosphoribosyltransferase** (HGPRT), an enzyme that normally functions in the **purine salvage pathway** to convert hypoxanthine back to inosine monophosphate and guanine back into guanosine monophosphate. The absence of HGPRT results in increased degradation of guanine and hypoxanthine bases into uric acid, which increases the demand for de novo purine synthesis.

The first step of purine synthesis is the formation of phosphoribosyl pyrophosphate (PRPP) by PRPP synthetase. PRPP can be used by adenine phosphoribosyltransferase and HGPRT for purine salvage, or it can be converted to phosphoribosylamine by PRPP amidotransferase in the first

GMP AMP

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(Choices A, B, and F) These enzymes are involved in pyrimidine synthesis. Their activity would not be significantly altered in Lesch-Nyhan syndrome, which impairs purine salvage.

(Choice C) The activity of HGPRT is decreased (not increased) in Lesch-Nyhan syndrome.

(Choice E) Purine and pyrimidine nucleotides are initially synthesized as bases attached to a ribose sugar. The enzyme ribonucleotide reductase converts ribose sugars to their deoxyribose forms for use in DNA synthesis. This enzyme is negatively regulated by increased levels of deoxyribose nucleotides.

Educational objective:
Lesch-Nyhan syndrome is an X-linked recessive disorder caused by a defect in hypoxanthine-guanine phosphoribosyltransferase (HGPRT). This results in failure of the purine salvage pathway, leading to increased degradation of hypoxanthine and guanine to uric acid. De novo purine synthesis must increase to replace the lost bases, necessitating an increase in phosphoribosyl pyrophosphate (PRPP) amidotransferase activity.

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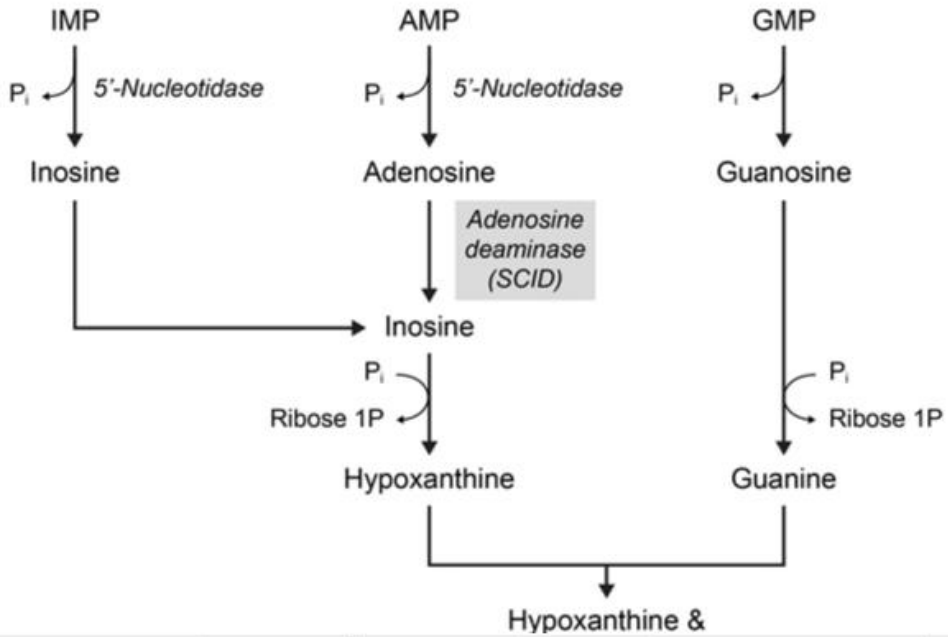
Exhibit Display

Purine degradation and salvage



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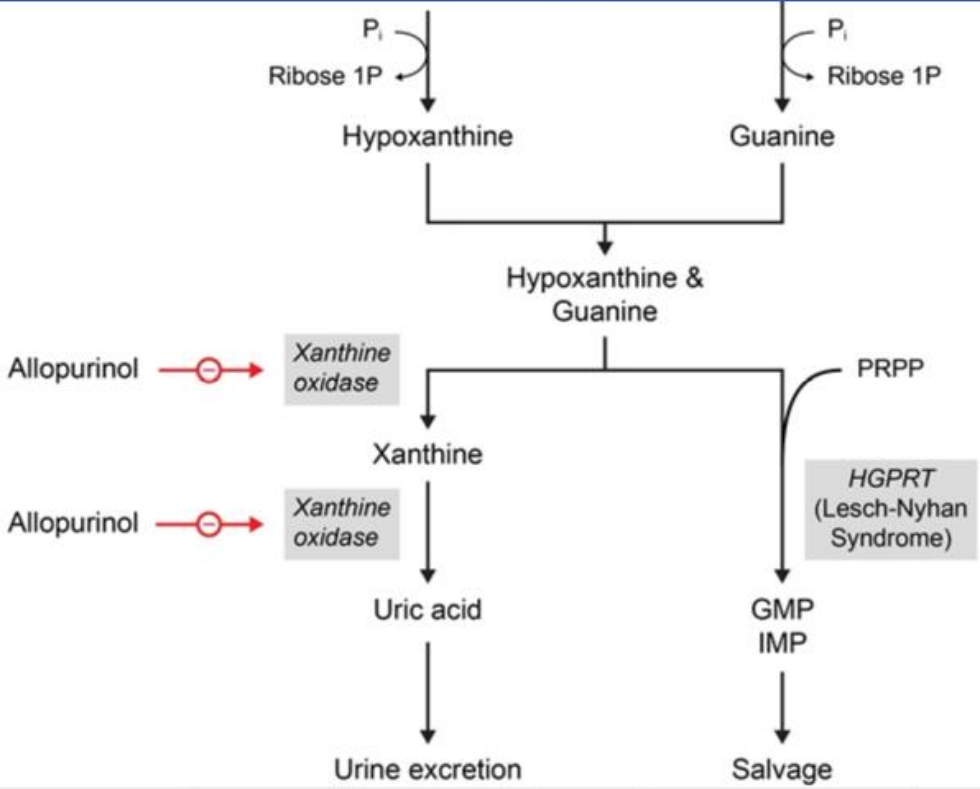

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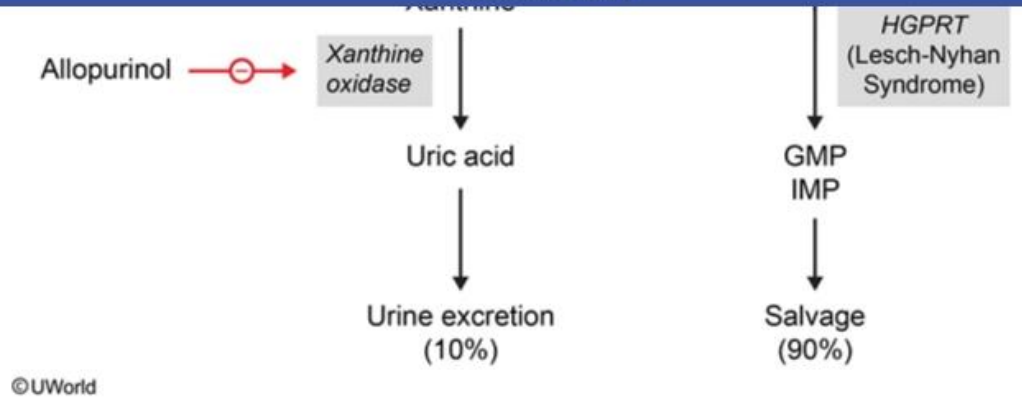

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Item 4 of 40
Question Id: 8578

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A 54-year-old man with a history of cirrhosis is brought to the emergency department by his wife, who found him agitated and confused. She reports that he was nauseous and vomited bright red blood several times yesterday. His cirrhosis is secondary to chronic hepatitis C infection, and he has received treatment for esophageal varices in the past. Physical examination reveals abdominal distension, decreased liver span, and testicular atrophy. A jerky, irregular flexion-extension tremor involving his hands is seen with wrist extension. Which of the following is most likely to be elevated in this patient's astrocytes?

A. α-ketoglutarate
B. Alanine
C. Aspartate
D. Carbamoyl phosphate
E. Glutamine

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Item 4 of 40
Question Id: 8578

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- A. α-ketoglutarate [17%]
- B. Alanine [13%]
- C. Aspartate [10%]
- D. Carbamoyl phosphate [14%]
- ✔ E. Glutamine [44%]

Omitted
Correct answer
E

44%
Answered correctly

4 Seconds
Time Spent

10/25/2018
Last Updated

Explanation

This patient has **hepatic encephalopathy**, likely due to his recent gastrointestinal bleeding causing a corresponding increase in nitrogen absorption by the gut. The pathogenesis of hepatic encephalopathy is related to increased circulatory levels of **ammonia** and other neurotoxins

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2/6/2019

Explanation

This patient has **hepatic encephalopathy**, likely due to his recent gastrointestinal bleeding causing a corresponding increase in nitrogen absorption by the gut. The pathogenesis of hepatic encephalopathy is related to increased circulatory levels of **ammonia** and other neurotoxins due to failure of the liver to metabolize waste products.

Under normal conditions, astrocytes regulate neurotransmission by taking up glutamate present in the synapse, preventing excessive neuronal excitation. Through the action of glutamine synthetase, glutamate undergoes a condensation reaction with ammonia to form glutamine (a non-neuroactive compound). Glutamine is then released by the astrocytes and taken up by neurons, where it is converted back to glutamate for use as a neurotransmitter (**glutamate-glutamine cycle**).

When **excess ammonia** is present in the blood, it crosses the blood-brain barrier and is taken up by astrocytes, **increasing glutamine production**. The presence of excess glutamine within astrocytes leads to increased intracellular osmolarity, causing astrocyte swelling and impaired glutamine release. Hyperammonemia consequently decreases the amount of glutamine available for conversion to glutamate in neurons, resulting in **disruption of excitatory neurotransmission**.

(Choice A) α-ketoglutarate functions as a key intermediate in the TCA cycle and as a nitrogen transporter in metabolic reactions. In the setting of hyperammonemia, ammonia is detoxified to glutamate via glutamate dehydrogenase, depleting α-ketoglutarate and impairing energy metabolism in the brain.

(Choice B) Alanine is an amino group transporter in the **glucose-alanine cycle** in liver and muscle tissue. This process allows tissues that use amino acids for fuel to shunt excess nitrogen back to the liver.

(Choice C) Aspartate is a nonessential amino acid that functions as a substrate in the urea cycle and as part of the malate-aspartate shuttle that transfers cytosolic-reducing equivalents into the mitochondrial matrix.

(Choice D) Carbamoyl phosphate is a urea cycle intermediate synthesized by carbamoyl phosphate synthetase I, which transfers an ammonia molecule from glutamine or glutamate to a phosphorylated bicarbonate. Carbamoyl phosphate production is decreased in patients with advanced liver disease.

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Educational objective:
Hyperammonemia in advanced liver failure occurs as a direct result of the cirrhotic liver's inability to metabolize nitrogenous waste products. Ammonia crosses the blood-brain barrier and causes excess glutamine to accumulate within astrocytes. This decreases the amount of glutamine available for conversion to glutamate in the neurons, resulting in disruption of excitatory neurotransmission.

References

- Ammonium metabolism in humans.
- Roles of glutamine in neurotransmission.

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Question Id: 8578

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E. Glutamine [44%]

Omitted
Correct answer
E

Explanation

This patient has **hepatic encep**
absorption by the gut. The path
due to failure of the liver to met

Under normal conditions, astroc
excitation. Through the action
neuroactive compound). Glutat
as a neurotransmitter (**glutama**

When **excess ammonia** is pres
production. The presence of e
impaired glutamine release. Hy
neurons, resulting in **disruptio**

(Choice A) α-ketoglutarate functions as a key intermediate in the TCA cycle and as a nitrogen transporter in metabolic reactions. In the setting of hyperammonemia, ammonia is detoxified to glutamate via glutamate dehydrogenase, depleting α-ketoglutarate and impairing energy metabolism in the brain.

Exhibit Display

Hepatic encephalopathy	
Precipitating factors	• Drugs (eg, sedatives, narcotics) • Hypovolemia (eg, diarrhea) • Electrolyte changes (eg, hypokalemia) • ↑ Nitrogen load (eg, GI bleeding) • Infection (eg, pneumonia, UTI, SBP) • Portosystemic shunting (eg, TIPS)
Clinical presentation	• Sleep pattern changes • Altered mental status • Ataxia • Asterixis
Treatment	• Correct precipitating causes (eg, fluids, antibiotics) • ↓ Blood ammonia concentration (eg, lactulose, rifaximin)

GI = gastrointestinal; **SBP** = spontaneous bacterial peritonitis; **TIPS** = transjugular intrahepatic portosystemic shunt; **UTI** = urinary tract infection.

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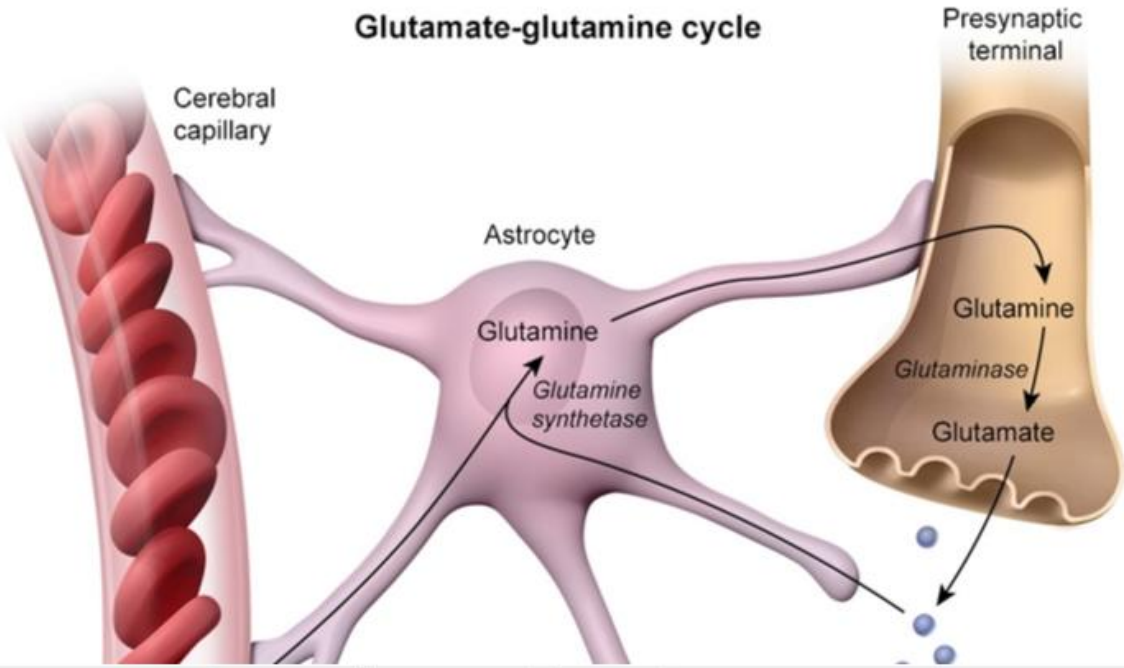
E. Glutamine [44%]

Exhibit Display



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E. Glutamine [44%]

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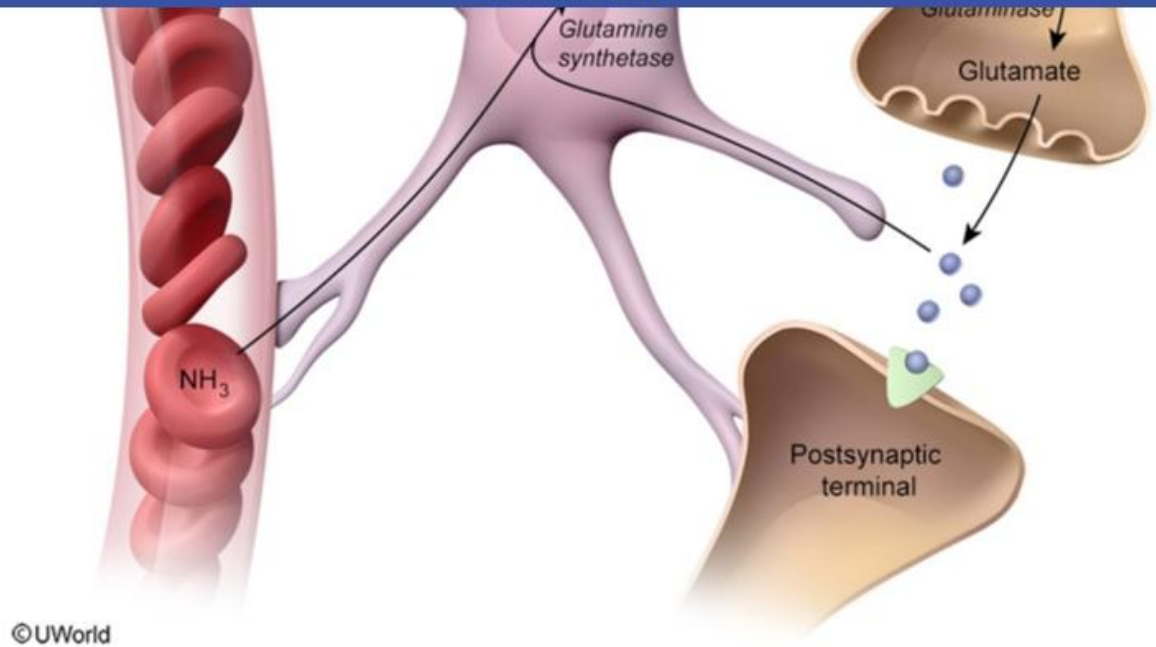

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E. Glutamine [44%]

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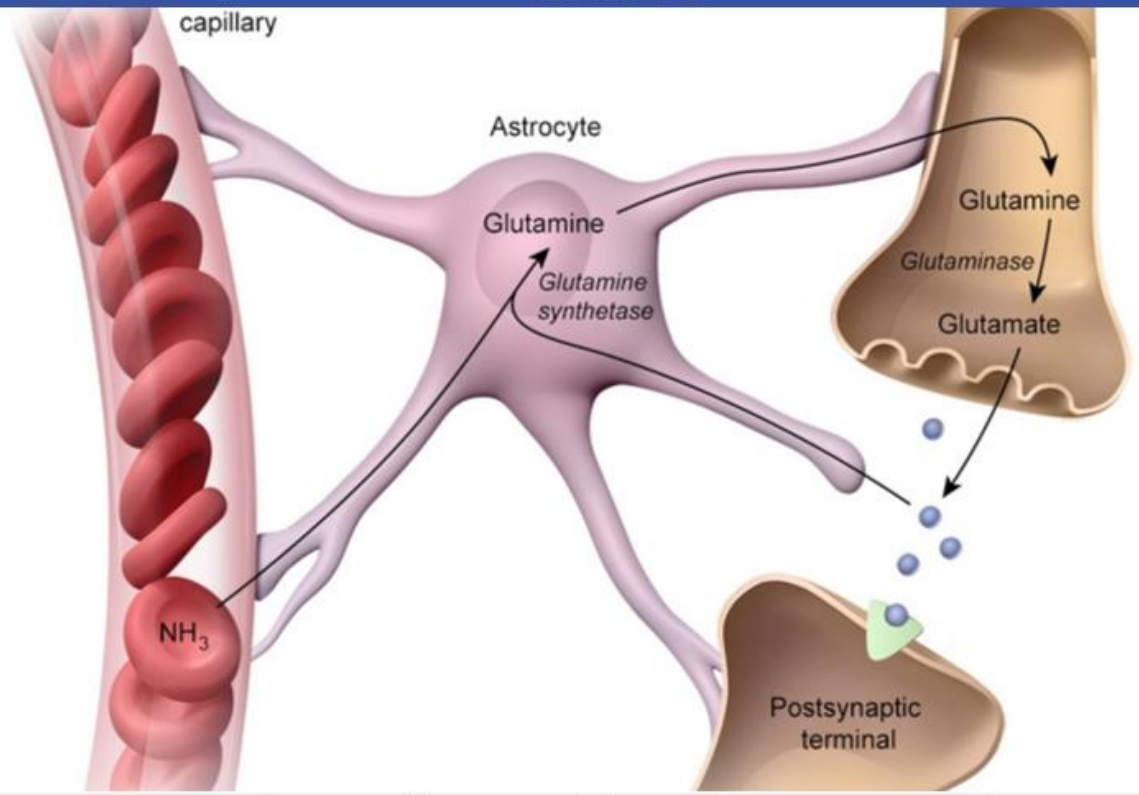

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Item 5 of 40
Question Id: 989

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A 69-year-old woman with Alzheimer disease is brought to the emergency department after her son found her wandering in a local park after being unable to contact her for the last day. The patient says that she got lost while taking a walk and has not eaten or drunk anything for over 24 hours. On examination, she is mildly confused and dehydrated. Laboratory studies show a blood glucose level within the normal range despite her prolonged fasting. Which of the following hormones contributes to this patient's laboratory findings by binding to an intracellular receptor?

- A. Cortisol
- B. Epinephrine
- C. Glucagon
- D. Growth hormone
- E. Insulin
- F. Norepinephrine

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Item 5 of 40
Question Id: 989

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- A. Cortisol [66%]
- B. Epinephrine [2%]
- C. Glucagon [26%]
- D. Growth hormone [2%]
- E. Insulin [1%]
- F. Norepinephrine [0%]

Omitted
Correct answer
A

66%
Answered correctly

4 Seconds
Time Spent

12/31/2018
Last Updated

Explanation

Blood glucose in normal subjects does not fall in the hypoglycemic range with fasting due to decreased insulin secretion and the protective actions of multiple **counterregulatory hormones**. Glucagon is the primary hormone secreted in response to a rapid drop in blood glucose levels, with

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Blood glucose in normal subjects does not fall in the hypoglycemic range with fasting due to decreased insulin secretion and the protective actions of multiple **counterregulatory hormones**. Glucagon is the primary hormone secreted in response to a rapid drop in blood glucose levels, with epinephrine acting as the major backup hormone. Cortisol and growth hormone contribute to glucose homeostasis during prolonged fasting by altering transcription of many key enzymes.

In the inactivated state, **cortisol receptors** are found **within the cytoplasm** in association with heat shock proteins. Binding of cortisol to the carboxy terminal portion of the receptor causes the release of the heat shock proteins and receptor dimerization. The activated homodimers are then **transported to the nucleus** where they control gene expression by binding to hormone-responsive DNA elements in the promoter region of target genes. Cortisol increases the **transcription** of enzymes involved in **gluconeogenesis** (formation of glucose from fat and protein substrates) as well as those involved in lipolysis and proteolysis.

(Choices B, C, and F) Epinephrine, norepinephrine, and glucagon exert their metabolic effects via **membrane-bound** G protein-coupled receptors that activate adenyl cyclase and increase cyclic AMP production. Glucagon increases hepatic glycogenolysis and gluconeogenesis. Epinephrine (and norepinephrine to a lesser extent) increases hepatic and renal glycogenolysis and gluconeogenesis; it also increases the release of gluconeogenic substrates from muscle and fat.

(Choice D) Growth hormone receptors are **membrane-bound** receptors that result in activation of the JAK-STAT pathway. Growth hormone antagonizes insulin action, increases gluconeogenesis, and promotes lipolysis (provides gluconeogenic substrates).

(Choice E) In addition to the production of counterregulatory hormones, inhibition of insulin release from pancreatic beta cells plays a primary role in preventing hypoglycemia during fasting. Insulin acts on a receptor tyrosine kinase present on the **cell surface**.

Educational objective:
Unlike the other counterregulatory (ie, insulin-opposing) hormone receptors, cortisol receptors are located within the cytoplasm and translocate to the nucleus after binding to their substrate. In the nucleus, the cortisol-receptor complex binds to hormone-responsive DNA elements, altering gene transcription to enhance hepatic glucose production and limit peripheral glucose utilization.

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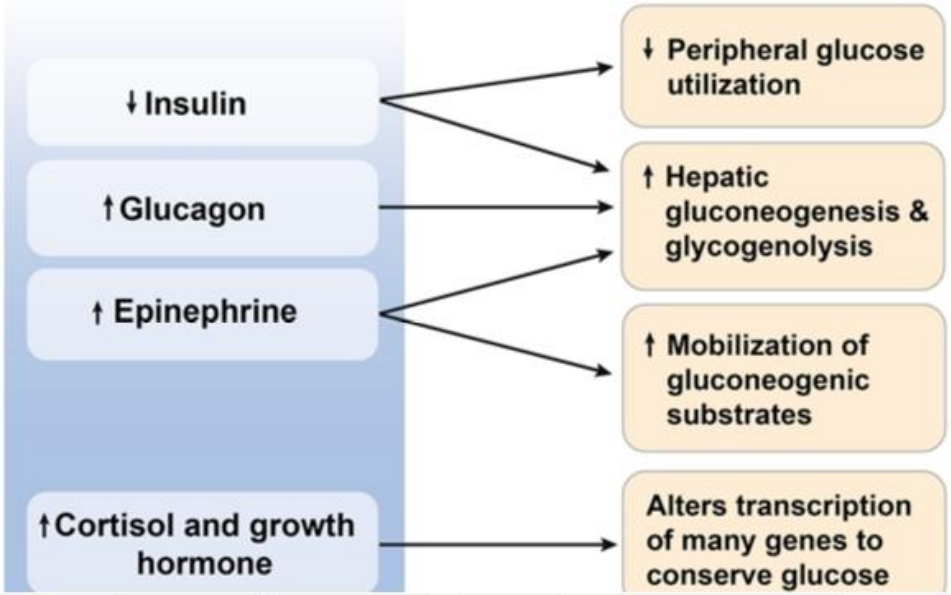
Exhibit Display

Physiologic defense against hypoglycemia



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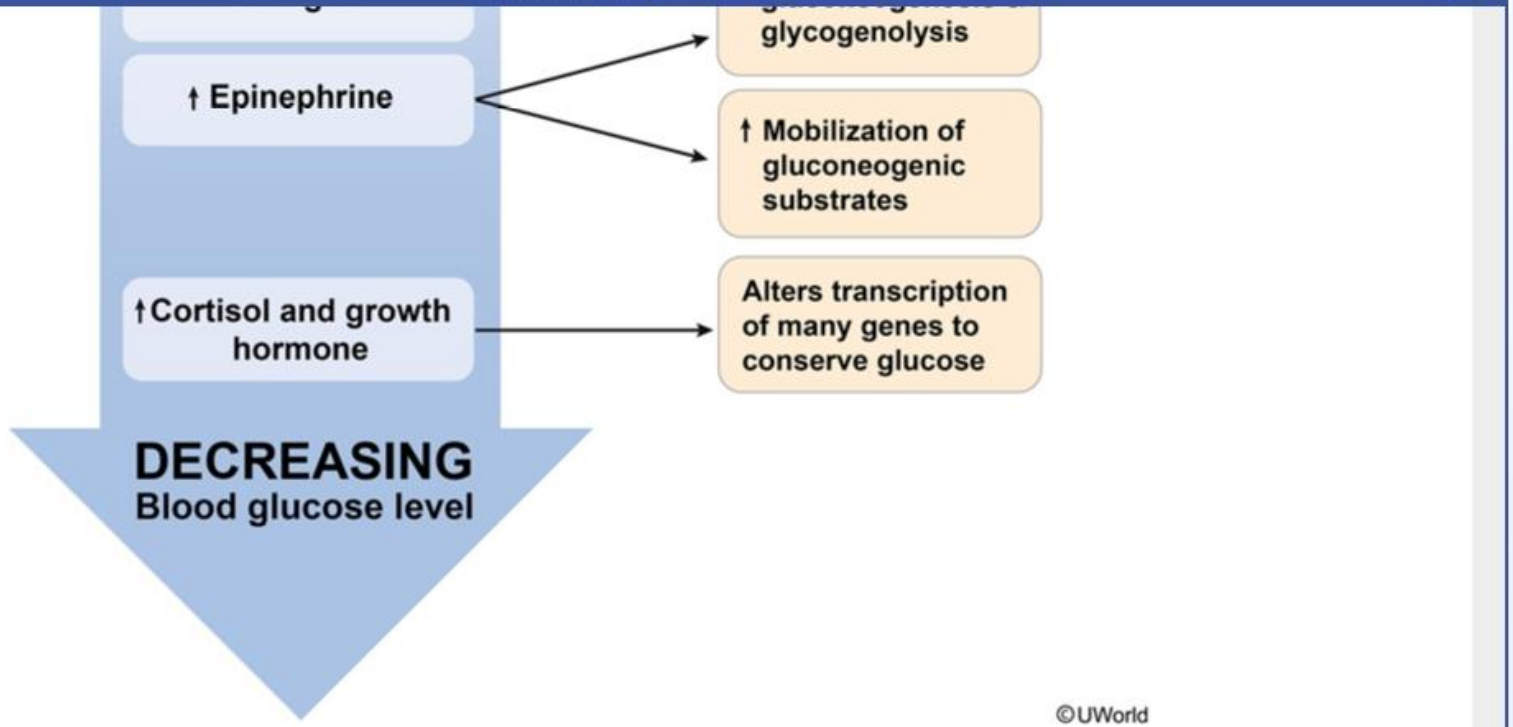

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Item 6 of 40
Question Id: 2036

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A 6-month-old boy is evaluated in the clinic due to delayed motor development. The mother reports that the boy is weaker than other children his age. He can barely lift his head up when prone and is unable to roll to the side. Physical examination shows generalized hypotonia and decreased deep tendon reflexes. Further evaluation reveals mutation of a protein involved in the assembly of small nuclear ribonucleoproteins (snRNPs) in motor neurons. This patient most likely has impaired function of which of the following cellular elements?

A. Nucleosomes
B. Peroxisomes
C. Proteasomes
D. Ribosomes
E. Spliceosomes

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Item 6 of 40
Question Id: 2036

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A 6-month-old boy is evaluated in the clinic due to delayed motor development. The mother reports that the boy is weaker than other children his age. He can barely lift his head up when prone and is unable to roll to the side. Physical examination shows generalized hypotonia and decreased deep tendon reflexes. Further evaluation reveals mutation of a protein involved in the assembly of small nuclear ribonucleoproteins (snRNPs) in motor neurons. This patient most likely has impaired function of which of the following cellular elements?

A. Nucleosomes [5%]
B. Peroxisomes [3%]
C. Proteasomes [4%]
D. Ribosomes [11%]
✔ E. Spliceosomes [75%]

Omitted
Correct answer
E

75%
Answered correctly

3 Seconds
Time Spent

08/10/2018
Last Updated

Explanation

This infant with delayed motor development and flaccid paralysis (eg, hypotonia, decreased deep tendon reflexes) likely has **spinal muscular atrophy**. This condition is caused by mutations in the **survival motor neuron (*SMN1*) gene**, which encodes a protein involved in assembly of **small nuclear ribonucleoproteins (snRNPs)** in lower motor neurons. Defective snRNP assembly results in impaired spliceosome function and

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This infant with delayed motor development and flaccid paralysis (eg, hypotonia, decreased deep tendon reflexes) likely has **spinal muscular atrophy**. This condition is caused by mutations in the **survival motor neuron (*SMN1*) gene**, which encodes a protein involved in assembly of **small nuclear ribonucleoproteins (snRNPs)** in lower motor neurons. Defective snRNP assembly results in impaired spliceosome function and degeneration of anterior horn cells in the spinal cord.

RNA molecules that carry out functions without first being translated into proteins are called non-coding RNAs. These include small nuclear RNA (snRNA), ribosomal RNA (rRNA), and transfer RNA (tRNA). snRNA is transcribed by RNA polymerase II and associates with specific proteins to form snRNPs. A collection of snRNPs and other proteins on pre-mRNA is referred to as a **spliceosome**. Spliceosomes **remove introns** from pre-mRNA by cleaving the 5' end of intron 1 (splice donor site) and joining that end to the branch point. The freed 3'-OH of exon 1 then forms a phosphodiester bond with the 5'-phosphate at the splice acceptor site, joining exons 1 and 2.

(Choice A) Eukaryotic chromatin is composed of repeated subunits called nucleosomes, which consist of double-stranded DNA wrapped around histone protein cores. Nucleosomes are important for the compact packaging of DNA into chromosomes with the aid of other packaging proteins.

(Choice B) Peroxisomes are cytoplasmic organelles containing oxidative enzymes (eg, catalase, D-amino acid oxidase, uric acid oxidase). These organelles are ubiquitous among eukaryotes and are most abundant in the liver and kidneys, where detoxification of ingested and environmental materials occurs. In the liver, peroxisomes also play a role in the breakdown of fatty acids.

(Choice C) Proteasomes and lysosomes are responsible for protein/polypeptide degradation. Proteasomes mainly degrade intracellular proteins, whereas lysosomes degrade extracellular proteins and worn-out organelles.

(Choice D) Ribosomes are present in the cytoplasm and are required for translation of mRNA into protein. Individual ribosomes are comprised of rRNA and ribosomal proteins. Within the cell, rRNA engages mRNA and facilitates tRNA entry during the formation of polypeptide chains.

Educational objective:
Small nuclear ribonucleoproteins (snRNPs) are important components of the spliceosome, a molecule which removes introns from pre-mRNA during processing within the nucleus. Spinal muscular atrophy is a disorder caused by mutations in the *SMN1* gene, resulting in impaired assembly of snRNPs in lower motor neurons. Infants often have flaccid paralysis due to degeneration of anterior horn cells in the spinal cord.

Settings

Item 7 of 40
Question Id: 790

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A 54-year-old woman is evaluated for progressive constipation, anorexia, and a 5.4-kg (12-lb) weight loss over the past several months. Physical examination is unremarkable. Stool guaiac test is positive, and a colonoscopy is performed. An exophytic mass is identified in the sigmoid colon. The patient undergoes a left hemicolectomy, and histopathology of the surgical specimen is positive for adenocarcinoma. Molecular testing of the cancer cells reveals a mutation in the *KRAS* gene that results in constitutive activation of the Ras protein. Under normal circumstances, this protein is only active when bound to which of the following substances?

- A. ATP
- B. Ca^{2+}
- C. cAMP
- D. GTP
- E. IP_3

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Item 7 of 40
Question Id: 790

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A. ATP [13%]
B. Ca^{2+} [7%]
C. cAMP [15%]
✔ D. GTP [55%]
E. IP_3 [8%]

Omitted
Correct answer
D

55%
Answered correctly

9 Seconds
Time Spent

09/29/2018
Last Updated

Explanation

RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras proteins exist in 2 different states: an **inactive GDP-bound state** and an **active GTP-bound state**. Ras becomes activated when a growth factor ligand binds to a **receptor**

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RAS genes code for a family of small G-proteins involved in signal transduction in the Ras-MAPK pathway. Ras proteins exist in 2 different states: an **inactive GDP-bound state** and an **active GTP-bound state**. Ras becomes activated when a growth factor ligand binds to a **receptor tyrosine kinase** located on the cell membrane, causing autophosphorylation of the receptor. This triggers binding of adaptor proteins that interact with Ras, promoting GDP removal and GTP binding. Activated Ras then begins a phosphorylation cascade that results in the activation of **mitogen-activated protein kinase (MAPK)**, which enters the nucleus to influence gene transcription.

Ras proteins have intrinsic GTPase activity that allows them to hydrolyze GTP; this mechanism prevents accumulation of active Ras (GTP-bound) in the absence of hormonal signaling. *RAS* gene mutations can lead to decreased intrinsic GTPase activity; this results in a constitutively activated Ras protein that causes constant and unregulated cell proliferation. *RAS* mutations are commonly identified in cancerous tumors, specifically colorectal and pancreatic malignancies.

(Choices A and C) ATP serves as a phosphate source for kinase-dependent phosphorylation reactions involved in numerous intracellular signaling pathways. It is also used as a substrate to produce cyclic AMP (cAMP) in the **cAMP** second messenger system.

(Choice B) Ca^{2+} is important for cell signaling as its intracellular presence alters the function of many proteins and enzymes. Ca^{2+} is required for many basic physiologic activities including apoptosis, muscular contraction, and neuronal transmission.

(Choice E) IP_3 is the water-soluble component of the **IP_3/DAG** second messenger system. IP_3 acts on the endoplasmic reticulum to cause intracellular Ca^{2+} release while DAG remains in the cell membrane and activates membrane-bound protein kinases.

Educational objective:
Regulation of the Ras-MAPK signal transduction pathway requires a balance between active (GTP-bound) and inactive (GDP-bound) Ras proteins. *RAS* gene mutations, which result in constitutively activated Ras proteins, are implicated in the development of malignant tumors.

References

- MEK inhibitors: a therapeutic approach to targeting the Ras-MAP kinase pathway in tumors.

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Item 8 of 40
Question Id: 1387

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A 15-year-old boy is found to have unexplained erythrocytosis on routine laboratory analysis. Evaluation of his immediate family shows that his father and sister also have elevated red cell levels. Genetic sequencing of the β-globin gene is performed in the affected family members. The results show a single base substitution at amino acid position 82 that replaces the normal lysine residue with methionine. Further analysis shows that this amino acid replacement impairs the ionic interaction between the β-subunit and 2,3-bisphosphoglycerate. As a result of this mutation, the patient's hemoglobin will be most similar to which of the following hemoglobin types?

A. Hemoglobin A_{1c}
B. Hemoglobin C
C. Hemoglobin F
D. Hemoglobin H
E. Hemoglobin S

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Item 8 of 40
Question Id: 1387

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A. Hemoglobin A_{1c} [2%]
B. Hemoglobin C [11%]
C. Hemoglobin F [70%] ✔
D. Hemoglobin H [3%]
E. Hemoglobin S [12%]

Omitted
Correct answer
C

70%
Answered correctly

3 Seconds
Time Spent

09/19/2018
Last Updated

Explanation

This patient most likely has **familial erythrocytosis** due to a β-globin mutation resulting in reduced binding of **2,3-bisphosphoglycerate** (2,3-BPG). 2,3-BPG is synthesized from glycolytic intermediates and binds strongly to deoxyhemoglobin in a pocket formed between the 2 beta

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Explanation

This patient most likely has **familial erythrocytosis** due to a β-globin mutation resulting in reduced binding of **2,3-bisphosphoglycerate** (2,3-BPG). 2,3-BPG is synthesized from glycolytic intermediates and binds strongly to deoxyhemoglobin in a pocket formed between the 2 beta chains. This binding reduces the oxygen affinity of hemoglobin, allowing more oxygen to diffuse into the peripheral tissues. The hemoglobin 2,3-BPG binding pocket contains positively charged amino acids (eg, histidine and lysine) that attract the negatively charged phosphate groups in 2,3-BPG. Mutations that decrease the positive charge of the binding site decrease 2,3-BPG binding and **increase hemoglobin oxygen affinity**.

Fetal hemoglobin (hemoglobin F) is synthesized primarily during fetal development (~8 weeks until term) and consists of the usual 2 alpha chains with 2 gamma chains in place of beta chains. The gamma chains do not bind effectively to 2,3-BPG due to replacement of a histidine residue with serine. As a result, fetal hemoglobin has significantly higher oxygen affinity than adult hemoglobin A. This allows fetal hemoglobin to extract more oxygen from the mother's adult hemoglobin in the placenta, providing the developing fetus with an adequate supply of oxygen.

(Choice A) Hemoglobin A_{1c} is formed by non-enzymatic glycosylation of hemoglobin A. Glycosylation can interfere with the binding of 2,3-BPG to hemoglobin by altering the physical structure of the binding pocket, which is compensated for by increased red cell 2,3-BPG levels in patients with diabetes. However, the reduced 2,3-BPG binding affinity of this patient's mutated hemoglobin more closely resembles that of hemoglobin F.

(Choice B) Hemoglobin C results from a mutation in the β-globin chain that causes glutamate to be replaced by lysine. Hemoglobin C forms hexagonal crystals and promotes red cell dehydration, causing a mild chronic hemolytic anemia. 2,3-BPG binding and tissue oxygen delivery are not significantly altered.

(Choice D) A defect in the synthesis of alpha chains results in varying degrees of alpha thalassemia, which is characterized by the formation of β-globin and γ-globin tetramers (hemoglobin H and Barts, respectively). These abnormal tetramers have extremely high oxygen affinity (resembling myoglobin) and are ineffective at delivering oxygen to tissues.

(Choice E) Hemoglobin S is the predominant form of hemoglobin in sickle cell disease and is caused by replacement of a glutamate by valine in the β-globin chain. This results in formation of hemoglobin polymers with reduced oxygen affinity.

BPG. Mutations that decrease the positive charge of the binding site decrease 2,3-BPG binding and **increase hemoglobin oxygen affinity**.

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(Choice E) Hemoglobin S is the predominant form of hemoglobin in sickle cell disease and is caused by replacement of a glutamate by valine in the β-globin chain. This results in formation of hemoglobin polymers with reduced oxygen affinity.

Educational objective:
2,3-bisphosphoglycerate (2,3-BPG) normally forms ionic bonds with the beta subunits of deoxygenated hemoglobin A, facilitating oxygen release in the peripheral tissues. Mutations that result in loss of the 2,3-BPG binding pocket's positive charge cause hemoglobin A to resemble fetal hemoglobin, which binds oxygen with a higher affinity due to its inability to interact with 2,3-BPG.

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Item 9 of 40
Question Id: 1998

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A 55-year-old farmer is brought to the emergency department after his daughter found him confused and disoriented in the tool shed at home. He has been otherwise healthy and does not take any medications. On physical examination, blood pressure is 110/70 mm Hg and pulse is 50/min. The patient's pupils are symmetric, 2 mm, and reactive to light. His eyes are tearing considerably. There are scattered wheezes bilaterally on lung auscultation. The patient's skin is clammy and he is sweating profusely. Impairment of which of the following steps at the neuromuscular junction is most likely responsible for his presentation?

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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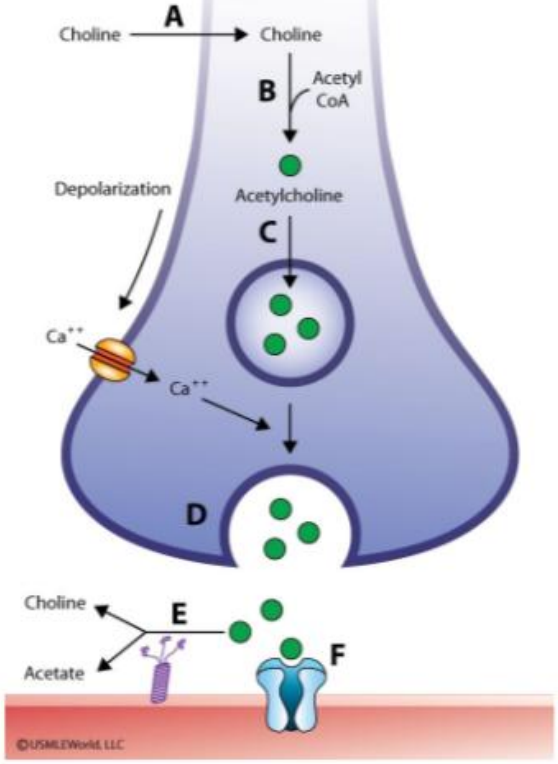

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Item 9 of 40
Question Id: 1998

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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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Question Id: 1998

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A 55-year-old farmer is brought to the emergency department after his daughter found him confused and disoriented in the tool shed at home. He has been otherwise healthy and does not take any medications. On physical examination, blood pressure is 110/70 mm Hg and pulse is 50/min. The patient's pupils are symmetric, 2 mm, and reactive to light. His eyes are tearing considerably. There are scattered wheezes bilaterally on lung auscultation. The patient's skin is clammy and he is sweating profusely. Impairment of which of the following steps at the neuromuscular junction is most likely responsible for his presentation?

- A. A [0%]
- B. B [1%]
- C. C [1%]
- D. D [5%]
- ✔ E. E [84%]
- F. F [6%]

Omitted
Correct answer
E

84%
Answered correctly

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Explanation

This patient's confusion, miosis and lacrimation, bradycardia, diaphoresis, and bronchospasm (bilateral wheezes) indicate a state of global

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Explanation

This patient's confusion, miosis and lacrimation, bradycardia, diaphoresis, and bronchospasm (bilateral wheezes) indicate a state of global muscarinic **cholinergic overstimulation**. This can be the result of a pharmacologic cholinomimetic (eg, carbachol, methacholine) or **cholinesterase inhibitor** (blocks breakdown of endogenous acetylcholine).

Organophosphates are cholinesterase inhibitors that are widely used as pesticides in agriculture. They are lipid soluble; rapidly absorbed via oral, cutaneous, and inhalational routes of exposure; and readily penetrate the blood brain barrier. Organophosphates are **irreversible** cholinesterase inhibitors; they elicit cholinergic stimulation that lasts until new cholinesterase enzymes are synthesized. Organophosphate poisoning is treated with muscarinic antagonists (eg, **atropine**) and **pralidoxime** (PAM), a drug that reactivates acetylcholinesterase by binding organophosphates and decoupling them from the enzyme.

(Choices A, B, and C) Blockade of neuronal choline uptake and inhibition of choline acetyltransferase would diminish acetylcholine synthesis. Blockade of acetylcholine uptake into axoplasmic vesicles would reduce acetylcholine release from presynaptic neurons. A decrease in acetylcholine synthesis or release would have effects opposite those observed in this patient.

(Choice D) Botulinum toxin inhibits acetylcholine release from presynaptic neurons. Botulinum toxicity (botulism) causes descending skeletal muscle paralysis, typically beginning with the cranial nerves.

(Choice F) Atropine is an anticholinergic agent used pharmacologically to block post-junctional acetylcholine receptors and is the antidote for organophosphate poisoning.

Educational objective:
Organophosphates are cholinesterase inhibitors that are widely used as pesticides in agriculture. They inhibit the breakdown of acetylcholine, leading to a state of cholinergic excess. Symptoms of organophosphate poisoning include salivation, lacrimation, diaphoresis, bradycardia, and bronchospasm.

References

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Item 10 of 40
Question Id: 8524

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An 8-month-old girl is brought to the office for evaluation of irritability and regression of motor skills. Her birth was unremarkable and she appeared to develop normally, but she can no longer sit or roll over. Her parents have also noticed that she startles easily with loud noises. Head circumference measurement is consistent with macrocephaly. Bilateral funduscopic evaluation shows a bright red fovea centralis that is surrounded by a contrasting white macula. Peripheral vision is decreased. Abdominal examination is normal. Accumulation of which of the following metabolites is most likely present in this patient's tissues?

- A. Galactocerebroside
- B. Globotriaosylceramide
- C. Glucocerebroside
- D. Glycogen
- E. GM_2 ganglioside
- F. Heparan sulfate
- G. Sphingomyelin

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Item 10 of 40
Question Id: 8524

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- A. Galactocerebroside [11%]
- B. Globotriaosylceramide [1%]
- C. Glucocerebroside [9%]
- D. Glycogen [1%]
- ✔ E. GM_2 ganglioside [56%]
- F. Heparan sulfate [2%]
- G. Sphingomyelin [17%]

Omitted
Correct answer
E

56%
Answered correctly

3 Seconds
Time Spent

08/23/2018
Last Updated

Explanation

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2/6/2019

Tay-Sachs disease is an autosomal recessive neurodegenerative disorder commonly seen in the Ashkenazi Jewish population. Tay-Sachs is caused by β-hexosaminidase A deficiency, which results in accumulation of the cell membrane glycolipid **GM2 ganglioside** within lysosomes.

Affected infants typically have normal development in the first few months of life, followed by progressive **neurologic deterioration** as glycolipids accumulate in the brain. Clinical consequences include weakness, hypotonia, developmental regression, seizures, blindness, and spasticity. Physical examination shows macrocephaly and an abnormal startle reflex with acoustic stimuli. In addition, the center of the fovea (blue arrow) appears bright red (**cherry-red macula spot**) as it is surrounded by white macula appearing as a **halo**. The halo results from a loss of retinal transparency due to ganglioside buildup in ganglion cells. The center of the fovea lacks ganglion cells, so the underlying choroid transmits its red color. Patients usually die by age 2-5 years.

(Choice A) Like Tay Sachs, Krabbe disease (galactocerebroside accumulation) causes progressive neurodegeneration. However, patients with Krabbe disease also have peripheral neuropathy and optic atrophy.

(Choice B) Fabry disease (globotriaosylceramide accumulation) causes angiokeratomas, peripheral neuropathy, and glomerulopathy that typically present in adulthood.

(Choices C and G) A similar cherry-red spot occurs in other lysosomal enzyme deficiencies, such as Gaucher disease and Niemann-Pick disease. Gaucher disease (β-glucocerebroside accumulation) and Niemann-Pick disease (sphingomyelin accumulation) are both unlikely due to this patient's normal abdominal examination (eg, no hepatosplenomegaly).

(Choice D) Glycogen storage diseases include von Gierke disease and Pompe disease. Infants with von Gierke disease (glucose-6-phosphatase deficiency) typically have hepatomegaly, hypoglycemia, seizures, and/or lactic acidosis. Pompe disease (lysosomal α-1,4-glucosidase deficiency) classically causes cardiomegaly and severe hypotonia.

(Choice F) Mucopolysaccharidosis (eg, Hurler syndrome, Hunter syndrome) are lysosomal storage disorders that cause buildup of glycosaminoglycans (GAGs) such as heparan and dermatan sulfate. GAG accumulation causes neurocognitive decline as well as coarse facial features and skeletal abnormalities.

(Choice A) Like Tay Sachs, Krabbe disease (galactocerebroside accumulation) causes progressive neurodegeneration. However, patients with Krabbe disease also have peripheral neuropathy and optic atrophy.

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Educational objective:
Tay-Sachs disease is an autosomal recessive disorder caused by β-hexosaminidase A deficiency, which results in GM_2 ganglioside accumulation. Key clinical features include progressive neurodegeneration and a cherry-red macular spot. In contrast to patients with Niemann-Pick disease, those with Tay Sachs disease have no hepatosplenomegaly.

References

- Lysosomal storage diseases as differential diagnosis of hepatosplenomegaly.
- Gangliosidoses

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Item 11 of 40
Question Id: 1807

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A 47-year-old homeless man comes to the emergency department due to a "pins-and-needles" sensation in his legs. He also has painful lesions on his lips and corners of his mouth. He has had no loss of consciousness, nausea, vomiting, or diplopia. The patient drinks alcohol heavily on a daily basis and has a history of intravenous heroin use. On physical examination, he appears unkempt and ill appearing. Temperature is 36.8 C (98.2 F), blood pressure is 146/90 mm Hg, and pulse is 106/min. He has glossitis and angular stomatitis. Abdominal examination reveals hepatomegaly. Laboratory evaluation shows very low urinary riboflavin excretion. Activity of which of the following enzymes is most likely directly impaired in this patient?

A. Fumarase
B. Glucose-6-phosphate dehydrogenase
C. HMG-CoA reductase
D. Isocitrate dehydrogenase
E. Malate dehydrogenase
F. Succinate dehydrogenase
G. Succinate thiokinase

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Item 11 of 40
Question Id: 1807

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A. Fumarase [7%]
B. Glucose-6-phosphate dehydrogenase [7%]
C. HMG-CoA reductase [6%]
D. Isocitrate dehydrogenase [14%]
E. Malate dehydrogenase [9%]
✔ F. Succinate dehydrogenase [50%]
G. Succinate thiokinase [4%]

Omitted
Correct answer
F

50%
Answered correctly

8 Seconds
Time Spent

01/23/2019
Last Updated

Explanation

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Explanation

This patient's low urinary riboflavin excretion suggests a significant deficiency in riboflavin intake. Symptomatic **riboflavin deficiency** is rare in the United States but can be seen in chronic alcoholics and the severely malnourished. Clinical manifestations include angular stomatitis, cheilitis, glossitis, seborrheic dermatitis, eye changes (eg, keratitis, corneal neovascularization), and anemia.

The **riboflavin** (vitamin B_2)-containing coenzymes are key constituents of the **electron transport chain**. Typically, riboflavin is first phosphorylated to become flavin mononucleotide (FMN), which can then be integrated into a coenzyme-flavin complex or further phosphorylated to flavin adenine dinucleotide (FAD). FMN and FAD participate as coenzymes in numerous reduction-oxidation reactions and are converted into reduced, energy-carrying states ($FMNH_2$ and $FADH_2$) through the acceptance of electrons.

FMN serves as a component of complex I, whereas FAD functions as a component of **succinate dehydrogenase** (complex II). Complex II participates in both the electron transport chain and tricarboxylic acid (TCA) cycle. During the TCA cycle, succinate dehydrogenase converts succinate to fumarate and transfers electrons to coenzyme Q (ubiquinone) via FAD. Complex II also accepts electrons from other sources of $FADH_2$, such as fatty acid oxidation.

(Choices A, D, E, and G) Isocitrate dehydrogenase, succinate thiokinase, malate dehydrogenase, and fumarase are enzymes that participate in the TCA cycle but do not use FAD or FMN as cofactors.

(Choice B) Reduced glutathione is an antioxidant that minimizes oxidative damage in many cells. Glutathione reductase regenerates reduced glutathione using nicotinamide adenine dinucleotide phosphate (NADPH) as an electron donor and FAD as a cofactor. Although glucose-6-phosphate dehydrogenase (G6PD) is the rate-limiting enzyme in the pentose phosphate pathway and supplies the necessary NADPH, it does not use FAD as a cofactor.

(Choice C) HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway. FMN and FAD are not used as cofactors.

Educational objective:
Riboflavin is a precursor of the coenzymes FMN and FAD. FAD participates in the tricarboxylic acid cycle and electron transport chain by acting as an electron acceptor for succinate dehydrogenase (complex II), which converts succinate into fumarate.

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(Choice C) HMG-CoA reductase is the rate-limiting enzyme in the cholesterol synthesis pathway. FMN and FAD are not used as cofactors.

Educational objective:
Riboflavin is a precursor of the coenzymes FMN and FAD. FAD participates in the tricarboxylic acid cycle and electron transport chain by acting as an electron acceptor for succinate dehydrogenase (complex II), which converts succinate into fumarate.

References

- Update on clinical aspects and treatment of selected vitamin-responsive disorders II (riboflavin and CoQ 10).

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Item 12 of 40
Question Id: 361

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A 24-year-old woman comes to the office due to a persistent facial rash. The patient easily develops "sunburns" after sun exposure and her fingers "turn blue" in cold weather. She has also felt more fatigued than usual. Physical examination shows a facial rash in a butterfly distribution that spares the nasolabial folds. Laboratory studies reveal several types of autoantibodies directed against components of the cell nucleus. One specific antibody targets proteins complexed with small nuclear ribonucleic acid. These protein-ribonucleic acid complexes are most likely involved in which of the following cellular functions?

A. Aiding mRNA in exiting the nucleus
B. Allowing proper functioning of DNA ligase
C. Charging tRNA with amino acids
D. Polyadenylation of RNA transcripts
E. Removal of introns from RNA transcripts
F. Synthesizing Okazaki fragments

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Item 12 of 40
Question Id: 361

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- A. Aiding mRNA in exiting the nucleus [12%]
- B. Allowing proper functioning of DNA ligase [5%]
- C. Charging tRNA with amino acids [8%]
- D. Polyadenylation of RNA transcripts [5%]
- ✔ E. Removal of introns from RNA transcripts [64%]
- F. Synthesizing Okazaki fragments [3%]

Omitted
Correct answer
E

64%
Answered correctly

3 Seconds
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02/01/2019
Last Updated

Explanation

This patient's constellation of symptoms (eg, malar rash, photosensitivity, Raynaud phenomenon ["blue fingers"], fatigue) is consistent with

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Explanation

This patient's constellation of symptoms (eg, malar rash, photosensitivity, Raynaud phenomenon ["blue fingers"], fatigue) is consistent with systemic lupus erythematosus, an autoimmune disease associated with anti-Smith antibodies (highly specific). Smith protein normally complexes with small nuclear RNA (snRNA) in the cytoplasm, forming small nuclear ribonucleoproteins (snRNPs).

Transcription occurs in the nucleus and is catalyzed by 3 types of RNA polymerases, leading to the formation of messenger RNA (mRNA), ribosomal RNA (rRNA), transport RNA (tRNA), and snRNA. **RNA polymerase II** synthesizes both mRNA and **snRNA**, the latter of which combines with specific proteins to form **snRNPs**. mRNA synthesis occurs in 2 stages. During the first, the DNA template is transcribed into a complementary strand of pre-mRNA. In the second, pre-mRNA is processed into mature mRNA through the following steps:

1. RNA capping: Addition of a methylated guanine nucleotide to the 5' end.
2. RNA polyadenylation: Addition of several adenine nucleotides to the 3' end (poly-A tail).
3. RNA splicing: **Removal of introns** (noncoding regions) by **spliceosomes**, which consist of snRNPs and other proteins.

Mature mRNA then transfers the genetic code to the cytoplasm and serves as a template for protein synthesis (translation).

(Choices A and D) Polyadenylation of RNA transcripts is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA, helping it exit the nucleus.

(Choices B and F) During eukaryotic DNA replication, DNA polymerase δ elongates Okazaki fragments of the lagging strand. These Okazaki fragments are later joined by the enzyme DNA ligase.

(Choice C) During translation, aminoacyl-tRNA synthetases catalyze the linkage of tRNAs to their corresponding amino acids. Each enzyme recognizes a specific amino acid and all of the tRNAs that match that amino acid.

Educational objective:
Small nuclear RNA (snRNA) is synthesized by RNA polymerase II in the nucleus and complexes with specific proteins to form small nuclear ribonucleoproteins (snRNPs). snRNPs are an essential component of spliceosomes, which remove introns from pre-mRNA to form mature

Transcription occurs in the nucleus and is catalyzed by 3 types of RNA polymerases, leading to the formation of messenger RNA (mRNA), ribosomal RNA (rRNA), transport RNA (tRNA), and snRNA. **RNA polymerase II** synthesizes both mRNA and **snRNA**, the latter of which combines with specific proteins to form **snRNPs**. mRNA synthesis occurs in 2 stages. During the first, the DNA template is transcribed into a complementary strand of pre-mRNA. In the second, pre-mRNA is processed into mature mRNA through the following steps:

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Educational objective:
Small nuclear RNA (snRNA) is synthesized by RNA polymerase II in the nucleus and complexes with specific proteins to form small nuclear ribonucleoproteins (snRNPs). snRNPs are an essential component of spliceosomes, which remove introns from pre-mRNA to form mature mRNA. Patients with systemic lupus erythematosus can have autoantibodies directed against snRNPs (eg, anti-Smith antibody).

References

- Spliceosome structure and function.
- Anti-Sm and anti-RNP antibodies

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Question Id: 361

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Exhibit Display

Synthesis & function of eukaryotic RNA

Synthesizing polymerase	Type of RNA produced	Function
RNA polymerase I	18S, 5.8S & 28S ribosomal RNA	Form essential ribosomal components
RNA polymerase II	Messenger RNA	Translated by ribosomes to form specific proteins
	Small nuclear RNA	Involved in mRNA splicing & transcription regulation
	Micro RNA	Cause gene silencing via translation arrest or mRNA degradation

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Question Id: 361

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Answered correctly | Time Spent | Last Updated

Exhibit Display

RNA polymerase II	Messenger RNA	Translated by ribosomes to form specific proteins
	Small nuclear RNA	Involved in mRNA splicing & transcription regulation
	Micro RNA	Cause gene silencing via translation arrest or mRNA degradation
RNA polymerase III	Transfer RNA	Adaptor molecule linking codons with specific amino acids
	5S ribosomal RNA	Essential component of 60S ribosomal subunit

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Item 13 of 40
Question Id: 1435

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A research scientist purifies DNA polymerase III from *Escherichia coli* extract. When the enzyme is incubated in a mixture containing DNA templates, RNA primer oligonucleotides, and tagged deoxynucleotides, she finds that the enzyme possesses 3' to 5' exonuclease activity. Which of the following enzymatic actions was most likely observed during the experiment?

A. Cleavage of DNA strands to remove supercoils
B. Excision of thymine dimers within DNA
C. Removal of mismatched base pairs during DNA replication
D. Removal of RNA primer nucleotides
E. Unwinding of the 2 strands of template DNA

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Item 13 of 40
Question Id: 1435

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A. Cleavage of DNA strands to remove supercoils [1%]
B. Excision of thymine dimers within DNA [4%]
✔ C. Removal of mismatched base pairs during DNA replication [70%]
D. Removal of RNA primer nucleotides [21%]
E. Unwinding of the 2 strands of template DNA [2%]

Omitted
Correct answer
C

70%
Answered correctly

4 Seconds
Time Spent

01/19/2019
Last Updated

Explanation

DNA replication is coordinated by the actions of multiple enzymes and proteins and requires a high degree of fidelity to ensure preservation of the genetic code in daughter cells.

DNA polymerases are the primary enzymes responsible for DNA synthesis. Prokaryotes such as *Escherichia coli* have 3 major types of DNA polymerase: I, II, and III. All 3 **prokaryotic DNA polymerases** are capable of removing mismatched nucleotides via their **3' to 5' exonuclease**

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(Choice A) In prokaryotes, topoisomerase II (DNA gyrase) temporarily cleaves both strands of the DNA double helix and introduces negative supercoils into the circular DNA to relieve tension created during strand unwinding.

(Choice B) One of the major methods of DNA damage by ultraviolet (UV) light is the dimerization of adjacent pyrimidine bases to form thymidine dimers. These dimers are routinely formed after exposure to sunlight but are usually removed via nucleotide excision repair by the enzyme UV-specific endonuclease.

(Choice E) Helicase promotes unwinding and dissociation of parent DNA strands at the replication fork.

Educational objective:
All 3 prokaryotic DNA polymerases can remove mismatched nucleotides via their 3' to 5' exonuclease ("proofreading") activity. Only DNA polymerase I has 5' to 3' exonuclease activity, which is used to remove the RNA primer synthesized by RNA primase.

References

- DNA replication fidelity in Escherichia coli: a multi-DNA polymerase affair.

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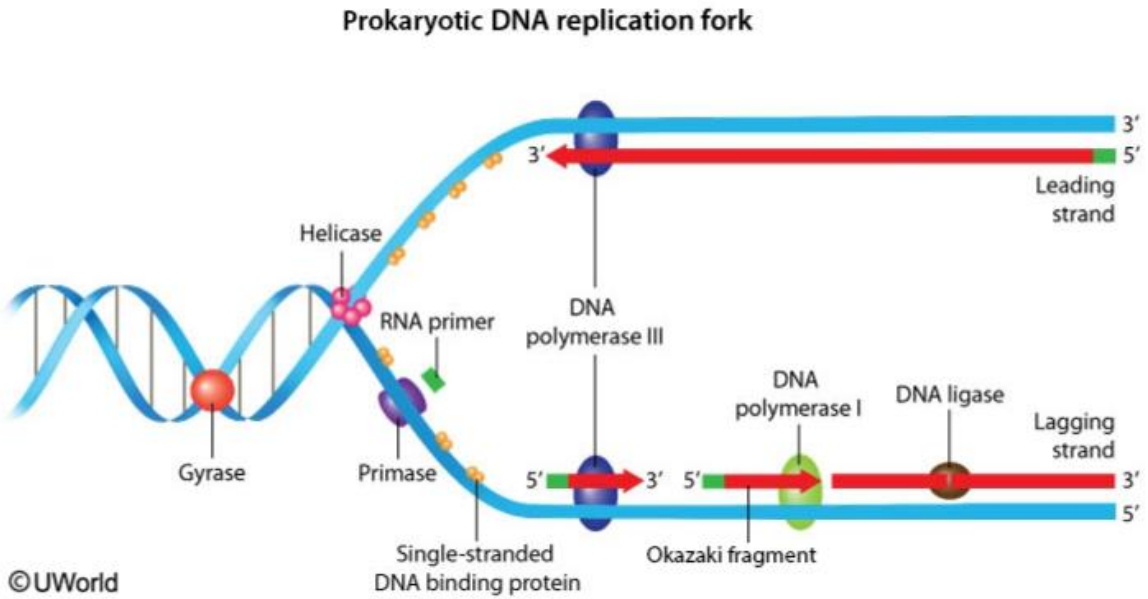

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Item 14 of 40
Question Id: 934

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 66-year-old man comes to the office due to progressive vision impairment over the last year that has begun to affect his ability to drive. He has difficulty reading road signs at night and reports excessive glare from the headlights of oncoming cars. The patient has a long history of hypertension and type 2 diabetes mellitus. Funduscopy reveals a diminished red reflex bilaterally with obscuration of retinal detail. It is determined that the patient's condition is in part due to intracellular accumulation of sorbitol. In healthy individuals, this sugar alcohol is normally metabolized into which of the following substances before being excreted from most cells?

- A. Fructose
- B. Galactitol
- C. Galactose
- D. Glucose
- E. Xylulose

Submit

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

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Feedback | Suspend | End Block

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Item 14 of 40
Question Id: 934

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 66-year-old man comes to the office due to progressive vision impairment over the last year that has begun to affect his ability to drive. He has difficulty reading road signs at night and reports excessive glare from the headlights of oncoming cars. The patient has a long history of hypertension and type 2 diabetes mellitus. Funduscopy reveals a diminished red reflex bilaterally with obscuration of retinal detail. It is determined that the patient's condition is in part due to intracellular accumulation of sorbitol. In healthy individuals, this sugar alcohol is normally metabolized into which of the following substances before being excreted from most cells?

- A. Fructose [48%]
- B. Galactitol [19%]
- C. Galactose [9%]
- D. Glucose [11%]
- E. Xylulose [10%]

Omitted
Correct answer
A

48%
Answered correctly

3 Seconds
Time Spent

01/18/2019
Last Updated

Explanation

This patient has **cataracts**, a vision-impairing opacification of the lens that causes loss of the **red reflex** with decreased visualization of retinal details on ophthalmoscopic evaluation. The incidence of cataracts increases with **age**; other risk factors include smoking, excessive sunlight

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This patient has **cataracts**, a vision-impairing opacification of the lens that causes loss of the **red reflex** with decreased visualization of retinal details on ophthalmoscopic evaluation. The incidence of cataracts increases with **age**; other risk factors include smoking, excessive sunlight exposure, **diabetes mellitus**, and glucocorticoid use. In this patient, long-term hyperglycemia most likely contributed to cataract formation by causing **oversaturation of the polyol pathway**.

The first step in the polyol pathway (an alternative route of glucose metabolism) is the conversion of glucose into sorbitol by aldose reductase. Sorbitol cannot readily cross cell membranes and is therefore trapped inside the cells where it forms. The second enzyme in the pathway, sorbitol dehydrogenase, is able to **convert sorbitol into fructose** at a sufficient rate to prevent accumulation when glucose levels are normal. However, the process is slow; in long-standing hyperglycemia, sorbitol accumulates in tissues with lower sorbitol dehydrogenase activity, such as the retina, lens, kidney, and peripheral nerves.

Sorbitol accumulation increases cellular **osmotic and oxidative stress** and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy. In lens cells, the increased stress leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

(Choices B and C) Another function of aldose reductase is the conversion of galactose into galactitol (ie, this enzyme converts sugars into their corresponding sugar alcohols). Galactitol production via this pathway is normally insignificant. In galactosemia (galactose-1-phosphate uridyltransferase deficiency), an increased amount of galactitol is produced, resulting in congenital cataracts.

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted and taken up by the liver to produce glucose and triglycerides.

(Choice E) Xylulose is an intermediate in the pentose phosphate pathway, which is used to generate NADPH (for cholesterol and fatty acid synthesis) and ribose 5-phosphate (for nucleotide synthesis).

Educational objective:
In the polyol pathway, aldose reductase converts glucose into sorbitol, which is slowly metabolized into fructose by sorbitol dehydrogenase.

dehydrogenase, is able to **convert sorbitol into fructose** at a sufficient rate to prevent accumulation when glucose levels are normal. However, the process is slow; in long-standing hyperglycemia, sorbitol accumulates in tissues with lower sorbitol dehydrogenase activity, such as the retina, lens, kidney, and peripheral nerves.

Sorbitol accumulation increases cellular **osmotic and oxidative stress** and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy. In lens cells, the increased stress leads to the development of hydropic lens fibers that degenerate, eventually resulting in lens opacification and cataract formation.

(Choices B and C) Another function of aldose reductase is the conversion of galactose into galactitol (ie, this enzyme converts sugars into their corresponding sugar alcohols). Galactitol production via this pathway is normally insignificant. In galactosemia (galactose-1-phosphate uridyltransferase deficiency), an increased amount of galactitol is produced, resulting in congenital cataracts.

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted and taken up by the liver to produce glucose and triglycerides.

(Choice E) Xylulose is an intermediate in the pentose phosphate pathway, which is used to generate NADPH (for cholesterol and fatty acid synthesis) and ribose 5-phosphate (for nucleotide synthesis).

Educational objective:
In the polyol pathway, aldose reductase converts glucose into sorbitol, which is slowly metabolized into fructose by sorbitol dehydrogenase. Chronic hyperglycemia overwhelms this pathway, causing intracellular sorbitol accumulation and increased osmotic/oxidative stress. This accelerates cataract development in patients with diabetes, and contributes to the pathogenesis of diabetic retinopathy, neuropathy, and nephropathy.

References

- The sorbitol pathway in the human lens: aldose reductase and polyol dehydrogenase.
- Osmotic stress induced oxidative damage: possible mechanism of cataract formation in diabetes

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Item 14 of 40
Question Id: 934

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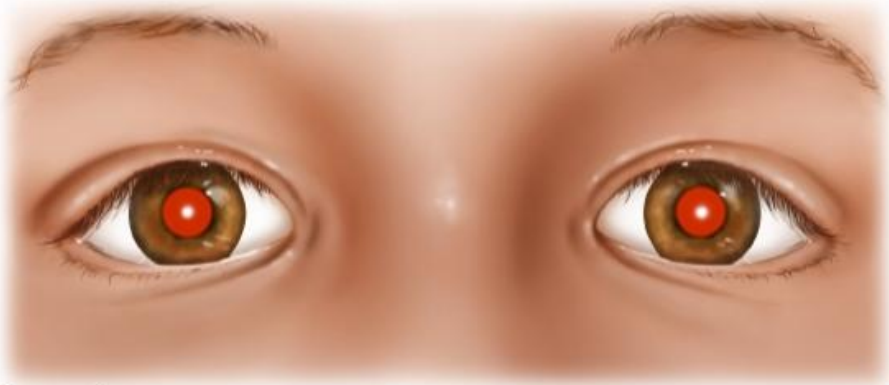
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Exhibit Display

Normal eyes & white reflex



Normal eyes

Red reflexes & corneal light reflexes are equal

Zoom In | Zoom Out | Reset | Add To Flash Card

(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted and taken up by the liver to

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Question Id: 934

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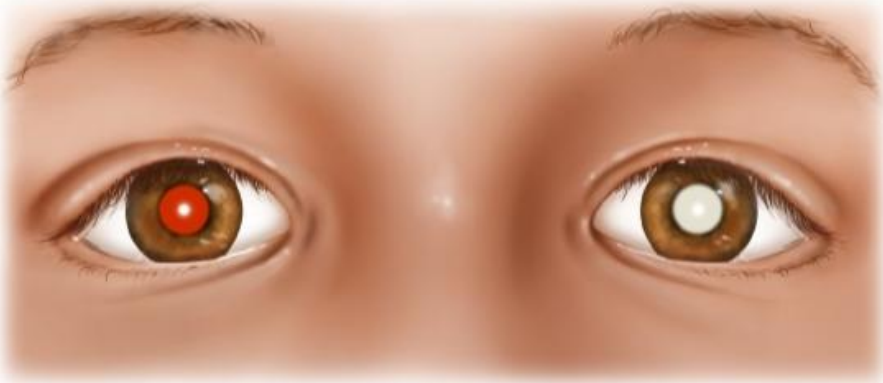
Exhibit Display

Normal eyes

Red reflexes & corneal light reflexes are equal



Absent reflex

White reflex on abnormal eye can result from opacities of the lens (eg, cataract) or tumor (eg, retinoblastoma)

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(Choice D) The end product of sorbitol metabolism in most cells is fructose (not glucose), which is then excreted and taken up by the liver to

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Item 15 of 40
Question Id: 11939

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A 68-year-old man comes to the emergency department due to abdominal pain and nausea for the past 2 days. He has a history of atherosclerotic cardiovascular disease and underwent coronary artery bypass surgery 2 years ago. Blood pressure is 105/65 mm Hg and heart rate is 120/min and irregular. Abdominal examination reveals mild diffuse tenderness and decreased bowel sounds. Laboratory studies are as follows:

Serum chemistry	
Sodium	142 mEq/L
Chloride	104 mEq/L
Bicarbonate	12 mEq/L
Creatinine	0.8 mg/dL
Arterial blood gases	
pH	7.25
$PaCO_2$	29 mm Hg
Lactic acid, venous blood	5.6 mmol/L (normal: 0.5 - 2.0 mmol/L)

ECG shows absent P waves and an irregular rate and rhythm. CT scan of the abdomen reveals colonic wall thickening and no enhancement with intravenous contrast. Urinalysis shows acidic urine. Renal metabolism of which of the following amino acids is most important for maximizing acid excretion in this patient?

A. Alanine
B. Arginine

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Chloride	104 mEq/L
Bicarbonate	12 mEq/L
Creatinine	0.8 mg/dL
Arterial blood gases	
pH	7.25
$PaCO_2$	29 mm Hg
Lactic acid, venous blood	5.6 mmol/L (normal: 0.5 - 2.0 mmol/L)

ECG shows absent P waves and an irregular rate and rhythm. CT scan of the abdomen reveals colonic wall thickening and no enhancement with intravenous contrast. Urinalysis shows acidic urine. Renal metabolism of which of the following amino acids is most important for maximizing acid excretion in this patient?

- A. Alanine
- B. Arginine
- C. Aspartate
- D. Glutamine
- E. Histidine

Submit

Chloride	104 mEq/L
Bicarbonate	12 mEq/L
Creatinine	0.8 mg/dL
Arterial blood gases	
pH	7.25
$PaCO_2$	29 mm Hg
Lactic acid, venous blood	5.6 mmol/L (normal: 0.5 - 2.0 mmol/L)

ECG shows absent P waves and an irregular rate and rhythm. CT scan of the abdomen reveals colonic wall thickening and no enhancement with intravenous contrast. Urinalysis shows acidic urine. Renal metabolism of which of the following amino acids is most important for maximizing acid excretion in this patient?

- A. Alanine [10%]
- B. Arginine [22%]
- C. Aspartate [22%]
- ✔ D. Glutamine [36%]
- E. Histidine [6%]

Omitted
Correct answer

36%
Answered correctly

140 Seconds
Time Spent

12/01/2018
Last Updated

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

This patient has **acute ischemic colitis**, which is most likely due to embolic disease related to his atrial fibrillation. The ischemic bowel undergoes anaerobic metabolism, causing **lactate accumulation** in the blood that leads to an anion gap metabolic acidosis. Acidosis stimulates **renal ammoniagenesis**, a process by which renal epithelial cells metabolize **glutamine**, generating ammonium and bicarbonate. Ammonium ions are transported into the tubular fluid and excreted in the urine while peritubular capillaries absorb bicarbonate, which functions to buffer acids in the blood.

Under normal physiologic conditions, about half of the total amount of acid secreted in the urine is in the form of ammonium, and the remainder is excreted primarily as titratable acids, particularly inorganic phosphate. However, **increased ammonium production** is almost entirely responsible for the increase in renal acid excretion seen with **chronic acidosis**.

(Choices A and C) Alanine and aspartate are glucogenic amino acids. Alanine is metabolized in the liver to produce pyruvate and aspartate can be readily interconverted with oxaloacetate.

(Choice B) Arginine is a urea cycle intermediate that helps to remove nitrogenous waste products (eg, ammonium) from the blood. Hepatic metabolism of arginine results in the production of urea and ornithine.

(Choice E) Histidine, an essential amino acid, is converted to histamine by histidine decarboxylase. Histamine is involved in the acute inflammatory response and gastric acid secretion; it also functions as a neurotransmitter.

Educational objective:
Acidosis stimulates renal ammoniagenesis, a process by which renal tubular epithelial cells metabolize glutamine to glutamate, generating ammonium that is excreted in the urine and bicarbonate that is absorbed into the blood. This process is responsible for the vast majority of renal acid excretion in chronic acidotic states.

References

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Item 16 of 40
Question Id: 1010

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A 24-year-old woman is diagnosed with gestational diabetes mellitus during her first pregnancy. Although her glycemic status improves markedly after delivery, her fasting glucose levels remain modestly elevated. The patient's past medical history is otherwise unremarkable, but her mother and younger sister had "high blood sugars" during pregnancy. If this patient's gestational hyperglycemia is genetically predisposed, she is most likely to have decreased activity in which of the following enzymes?

A. Aldolase
B. Enolase
C. Glucokinase
D. Lactate dehydrogenase
E. Phosphofructokinase
F. Pyruvate carboxylase
G. Pyruvate kinase

Submit

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11:43 AM
2/6/2019

Settings

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Item 16 of 40
Question Id: 1010

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A 24-year-old woman is diagnosed with gestational diabetes mellitus during her first pregnancy. Although her glycemic status improves markedly after delivery, her fasting glucose levels remain modestly elevated. The patient's past medical history is otherwise unremarkable, but her mother and younger sister had "high blood sugars" during pregnancy. If this patient's gestational hyperglycemia is genetically predisposed, she is most likely to have decreased activity in which of the following enzymes?

- A. Aldolase [3%]
- B. Enolase [1%]
- ✔ C. Glucokinase [56%]
- D. Lactate dehydrogenase [3%]
- E. Phosphofructokinase [21%]
- F. Pyruvate carboxylase [7%]
- G. Pyruvate kinase [6%]

Omitted
Correct answer
C

56%
Answered correctly

3 Seconds
Time Spent

09/13/2018
Last Updated

Explanation

Block Time Remaining: 00:03:47
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11:43 AM
2/6/2019

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

Glucose is the major stimulant of insulin secretion. Glucose-induced insulin release from the beta cells requires the following steps:

1. Glucose enters the beta cell through glucose transporter type 2 (GLUT-2).
2. Glucose is metabolized by glucokinase to glucose-6-phosphate
3. Glucose-6-phosphate is further metabolized by glycolysis and the Krebs cycle to produce ATP
4. A high ATP to ADP ratio within the beta cell results in the closure of ATP-sensitive potassium (K_{ATP}) channels
5. Depolarization of beta cells results in opening of voltage-dependent calcium channels
6. High intracellular calcium causes insulin release

Glucokinase has a lower glucose affinity than other hexokinases. This allows it to function as a glucose sensor in beta cells by varying the rate of glucose entry into the glycolytic pathway based on blood glucose levels. Heterozygous mutations of the glucokinase gene cause a decrease in beta cell metabolism of glucose, less ATP formation, and diminished insulin secretion. This produces a type of **maturity-onset diabetes of the young**, which is characterized by mild, nonprogressive hyperglycemia that often worsens with pregnancy-induced insulin resistance. Homozygous mutations lead to fetal growth retardation and severe hyperglycemia at birth.

(Choices A, B, E, and G) Glycolytic enzyme deficiencies (eg, aldolase A, enolase, phosphofructokinase, pyruvate kinase) generally present with hemolytic anemia, as red blood cells rely completely on anaerobic glycolysis for energy production.

(Choice D) Lactate dehydrogenase is present in most cells and catalyzes conversion of pyruvate to lactate during anaerobic glycolysis. Deficiency can cause decreased exercise tolerance and muscle stiffness.

(Choice F) Pyruvate carboxylase, one of the gluconeogenetic pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

Educational objective:
Insulin release by pancreatic beta cells is stimulated by increased ATP production. Glucokinase functions as a glucose sensor in pancreatic beta

5. Depolarization of beta cells results in opening of voltage-dependent calcium channels
6. High intracellular calcium causes insulin release

Glucokinase has a lower glucose affinity than other hexokinases. This allows it to function as a glucose sensor in beta cells by varying the rate of glucose entry into the glycolytic pathway based on blood glucose levels. Heterozygous mutations of the glucokinase gene cause a decrease in beta cell metabolism of glucose, less ATP formation, and diminished insulin secretion. This produces a type of **maturity-onset diabetes of the young**, which is characterized by mild, nonprogressive hyperglycemia that often worsens with pregnancy-induced insulin resistance. Homozygous mutations lead to fetal growth retardation and severe hyperglycemia at birth.

(Choices A, B, E, and G) Glycolytic enzyme deficiencies (eg, aldolase A, enolase, phosphofructokinase, pyruvate kinase) generally present with hemolytic anemia, as red blood cells rely completely on anaerobic glycolysis for energy production.

(Choice D) Lactate dehydrogenase is present in most cells and catalyzes conversion of pyruvate to lactate during anaerobic glycolysis. Deficiency can cause decreased exercise tolerance and muscle stiffness.

(Choice F) Pyruvate carboxylase, one of the gluconeogenetic pathway enzymes in the mitochondria, catalyzes the conversion of pyruvate to oxaloacetate. Deficiency of pyruvate carboxylase causes lactic acidosis and fasting hypoglycemia.

Educational objective:
Insulin release by pancreatic beta cells is stimulated by increased ATP production. Glucokinase functions as a glucose sensor in pancreatic beta cells by controlling the rate of glucose entry into the glycolytic pathway. Mutations in the glucokinase gene are a cause of maturity-onset diabetes of the young.

References

- Glucokinase MODY and implications for treatment goals of common forms of diabetes.

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Item 17 of 40
Question Id: 1240

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A 48-year-old woman comes to the emergency department with headache, dizziness, and nausea for the past several hours. She has no fever, nasal congestion, or cough but reports that her husband has also been complaining of headache. The patient has been burning wood in the fireplace to warm her house after losing electricity during a snowstorm. Her temperature is 37 C (98.6 F), blood pressure is 135/70 mm Hg, and pulse is 94/min and regular. Physical examination is unremarkable. The substance responsible for this patient's condition most likely impairs hemoglobin function through which of the following mechanisms?

A. Alteration of the partial pressure of oxygen
B. Competitive binding to heme
C. Deactivation of a reductase enzyme
D. Denaturation of the globin chains
E. Irreversible linking to heme
F. Oxidation of the porphyrin ring

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11:43 AM
2/6/2019

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Item 17 of 40
Question Id: 1240

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 48-year-old woman comes to the emergency department with headache, dizziness, and nausea for the past several hours. She has no fever, nasal congestion, or cough but reports that her husband has also been complaining of headache. The patient has been burning wood in the fireplace to warm her house after losing electricity during a snowstorm. Her temperature is 37 C (98.6 F), blood pressure is 135/70 mm Hg, and pulse is 94/min and regular. Physical examination is unremarkable. The substance responsible for this patient's condition most likely impairs hemoglobin function through which of the following mechanisms?

- A. Alteration of the partial pressure of oxygen [1%]
- ✔ B. Competitive binding to heme [86%]
- C. Deactivation of a reductase enzyme [1%]
- D. Denaturation of the globin chains [0%]
- E. Irreversible linking to heme [9%]
- F. Oxidation of the porphyrin ring [0%]

Omitted
Correct answer
B

86%
Answered correctly

3 Seconds
Time Spent

10/31/2018
Last Updated

Explanation

This patient most likely has **carbon monoxide (CO) poisoning**, a condition that presents with nonspecific findings ranging from headache and

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11:43 AM
2/6/2019

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

B

Explanation

This patient most likely has **carbon monoxide (CO) poisoning**, a condition that presents with nonspecific findings ranging from headache and dizziness to convulsions and respiratory arrest depending on concentration and exposure. CO is a colorless, odorless, tasteless gas that is a byproduct of incomplete hydrocarbon combustion. CO poisoning is most often caused by smoke inhalation from a fire or the burning of fuel sources such as wood, coal, or natural gas in poorly ventilated environments.

CO toxicity occurs because of CO's ability to competitively bind iron present in heme proteins. The gas binds to heme iron with a much higher affinity than oxygen, forming **carboxyhemoglobin**. Even if only 1 of the 4 heme sites is affected, the remaining 3 heme groups have **increased oxygen affinity** (leftward shift of the oxygen dissociation curve), impeding oxygen delivery to tissues. CO is also capable of binding cardiac myoglobin with high affinity, disrupting the heart's ability to use oxygen and thereby decreasing cardiac output. At a cellular level, CO binds to cytochrome oxidase, inhibiting aerobic metabolism and exacerbating tissue hypoxia.

Treatment for CO poisoning is administration of **high-flow or hyperbaric oxygen** therapy as this hastens the dissociation of CO from carboxyhemoglobin.

(Choice A) The partial pressure of oxygen (pO_2) is a measure of dissolved oxygen in the plasma, the amount of which does not change in CO poisoning.

(Choice C) NADH methemoglobin reductase reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), regenerating hemoglobin from methemoglobin. Enzyme deficiency results in congenital methemoglobinemia.

(Choice D) Globin chain denaturation occurs in G6PD-deficient red blood cells when oxidant stressors cause sulfhydryl group cross-linking.

(Choice E) CO reversibly binds hemoglobin at its heme moieties.

myoglobin with high affinity, disrupting the heart's ability to use oxygen and thereby decreasing cardiac output. At a cellular level, CO binds to cytochrome oxidase, inhibiting aerobic metabolism and exacerbating tissue hypoxia.

Treatment for CO poisoning is administration of **high-flow or hyperbaric oxygen** therapy as this hastens the dissociation of CO from carboxyhemoglobin.

(Choice A) The partial pressure of oxygen (pO_2) is a measure of dissolved oxygen in the plasma, the amount of which does not change in CO poisoning.

(Choice C) NADH methemoglobin reductase reduces ferric iron (Fe^{3+}) to ferrous iron (Fe^{2+}), regenerating hemoglobin from methemoglobin. Enzyme deficiency results in congenital methemoglobinemia.

(Choice D) Globin chain denaturation occurs in G6PD-deficient red blood cells when oxidant stressors cause sulfhydryl group cross-linking.

(Choice E) CO reversibly binds hemoglobin at its heme moieties.

(Choice F) Heme consists of an iron bound to protoporphyrin IX. CO binds to iron in metalloproteins but does not cause oxidation of the porphyrin component.

Educational objective:
Carbon monoxide binds heme iron in hemoglobin with an affinity much greater than oxygen, generating carboxyhemoglobin. Remaining binding sites on carboxyhemoglobin have an increased affinity for oxygen that causes the oxygen dissociation curve to shift to the left, impeding oxygen delivery to tissues.

References

- Carbon monoxide intoxication.

Settings

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Item 18 of 40
Question Id: 1888

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An 8-year-old boy is brought to the emergency department due to vomiting and lethargy. The patient had been on an overnight hiking trip with his family. During the trip, the family lost their food pack while canoeing and had to hike back to their car. The child became weak and was carried for the last mile. None of the family has eaten for approximately 24 hours. On examination, the patient appears listless. Mild hepatomegaly is noted. Laboratory results are as follows:

Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

A. Acetyl-CoA carboxylase
B. Acid alpha-glucosidase
C. Acyl-CoA dehydrogenase
D. Glucose 6-phosphatase
E. Glycogen phosphorylase

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11:43 AM
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Item 18 of 40
Question Id: 1888

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An 8-year-old boy is brought to the emergency department due to vomiting and lethargy. The patient had been on an overnight hiking trip with his family. During the trip, the family lost their food pack while canoeing and had to hike back to their car. The child became weak and was carried for the last mile. None of the family has eaten for approximately 24 hours. On examination, the patient appears listless. Mild hepatomegaly is noted. Laboratory results are as follows:

Glucose	22 mg/dL
Acetoacetate	not detected
Aspartate aminotransferase	47 U/L
Alanine aminotransferase	53 U/L

The patient begins seizing shortly after arriving at the emergency department. Which of the following enzymes is most likely deficient in this patient?

A. Acetyl-CoA carboxylase [15%]
B. Acid alpha-glucosidase [3%]
✔ C. Acyl-CoA dehydrogenase [34%]
D. Glucose 6-phosphatase [25%]
E. Glycogen phosphorylase [21%]

Omitted
Correct answer

34%

4 Seconds

09/12/2018

Block Time Remaining: 00:03:54
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11:43 AM
2/6/2019

This patient developed **hypoketotic hypoglycemia** after fasting, which is consistent with a **defect in fatty acid beta-oxidation** in the mitochondria. Beta-oxidation of fatty acids yields $FADH_2$ and NADH for ATP production and generates acetyl-CoA for use in the citric acid cycle or ketone body production. **Ketone bodies** are an important energy source during periods of fasting; adults generally require more than 1-2 days of fasting before ketone use becomes substantial, whereas children have limited glucose reserves and begin using ketone bodies after as little as 8-10 hours.

Impaired beta-oxidation can be caused by a variety of enzymatic defects, the most common of which is **medium chain acyl-CoA dehydrogenase deficiency**. Affected individuals may remain asymptomatic for long periods until they experience a **significant fast**, during which they are unable to oxidize fatty acids to maintain glucose and ketone body production. Classic manifestations include hypoketotic hypoglycemia (eg, undetectable acetoacetate level), mild hepatomegaly, and liver dysfunction. Because the resulting metabolic crisis can have severe consequences (eg, seizures, sudden infant death), fatty acid oxidation disorders are part of standard newborn screening.

Treatment of acyl-CoA dehydrogenase deficiency consists of prevention of fat catabolism. This means avoiding prolonged fasting as well as promptly supplying **glucose** during periods of illness.

(Choice A) Acetyl-CoA carboxylase is the rate-limiting enzyme that catalyzes the first step in fatty acid synthesis. Acetyl-CoA carboxylase is normally suppressed during prolonged fasting.

(Choices B, D, and E) Acid alpha-glucosidase, glucose 6-phosphatase, and glycogen phosphorylase are involved in **glycogenolysis**. Deficiency of any of these enzymes can lead to glycogen storage disease. However, patients with glycogen storage disease have normal fatty acid oxidation and produce ketones during periods of fasting.

Educational objective:
Impaired beta-oxidation of fatty acids causes hypoglycemia after prolonged fasting and insufficient levels of ketone bodies. Acyl-CoA dehydrogenase catalyzes the first step in the beta-oxidation pathway and is the most commonly deficient enzyme.

References

Succinate dehydrogenase (SDH) is an enzyme complex located within the inner mitochondrial membrane that catalyzes the oxidation of succinate to fumarate. An experiment is conducted to determine if malate alters the rate of SDH activity. Reaction velocity is measured with and without a fixed quantity of malate as succinate concentration is gradually increased. Obtained results are shown below.

Succinate concentration (mM)	Rate of reaction without malate (µmol/L/sec)	Rate of reaction with malate (µmol/L/sec)
2	80	40
8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction
B. It binds the enzyme at a different site than succinate
C. It covalently binds the enzyme
D. It decreases affinity of the enzyme for succinate
E. It is a competitive inhibitor of the enzyme

fixed quantity of malate as succinate concentration is gradually increased. Obtained results are shown below.

Succinate concentration (mM)	Rate of reaction without malate (µmol/L/sec)	Rate of reaction with malate (µmol/L/sec)
2	80	40
8	200	120
16	280	200
64	400	400
128	400	400

Which of the following is the most accurate statement about malate in this experiment?

A. It alters the maximal velocity of the reaction [3%]
B. It binds the enzyme at a different site than succinate [8%]
C. It covalently binds the enzyme [1%]
D. It decreases affinity of the enzyme for succinate [10%]
E. It is a competitive inhibitor of the enzyme [76%]

Omitted
Correct answer

76%
Answered correctly

6 Seconds
Time Spent

09/29/2018
Last Updated

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

The **Michaelis-Menten model** describes the behavior of enzyme-driven reactions by comparing the rate of reaction (V) to the concentration of the substrate (S). Maximal velocity (V_{max}) represents the speed at which the reaction occurs when the enzyme's active sites are completely saturated with substrate. The Michaelis constant (K_m) defines the substrate concentration at which half of the enzyme's binding sites are occupied by substrate (½ V_{max}). Substrates with high affinity for the enzyme typically have a low K_m.

Competitive inhibition occurs when an inhibitor binds to an enzyme and prevents it from binding the substrate. Most competitive inhibitors (including malate) **bind at the active site** (substrate-binding pocket) and physically impede substrate binding. Because these inhibitors compete with the substrate for binding to the active site, additional substrate is required to reach ½ V_{max}, thereby **increasing apparent K_m**. Competitive inhibitors have no effect on enzyme function, and therefore **V_{max} is unchanged**.

In this example, V_{max} remains constant (at 400 µmol/L/sec) while K_m increases (from 8 to 16 mM) in the presence of malate. Therefore, malate is a competitive inhibitor of succinate dehydrogenase for succinate.

(Choice A) V_{max} depends on how fast an enzyme can catalyze a reaction when there are enough substrate molecules to fully saturate its active sites. Competitive inhibitors do not affect V_{max}, as higher substrate concentrations are able to overcome the inhibition.

(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). **Noncompetitive inhibition** does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

(Choice C) Irreversible inhibitors bind to enzymes through strong covalent bonds; this typically renders the enzyme permanently ineffective, decreasing the V_{max}.

(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the substrate remains unchanged.

substrate (½ V_{max}). Substrates with high affinity for the enzyme typically have a low K_m.

Competitive inhibition occurs when an inhibitor binds to an enzyme and prevents it from binding the substrate. Most competitive inhibitors (including malate) **bind at the active site** (substrate-binding pocket) and physically impede substrate binding. Because these inhibitors compete with the substrate for binding to the active site, additional substrate is required to reach ½ V_{max}, thereby **increasing apparent K_m**. Competitive inhibitors have no effect on enzyme function, and therefore **V_{max} is unchanged**.

In this example, V_{max} remains constant (at 400 µmol/L/sec) while K_m increases (from 8 to 16 mM) in the presence of malate. Therefore, malate is a competitive inhibitor of succinate dehydrogenase for succinate.

(Choice A) V_{max} depends on how fast an enzyme can catalyze a reaction when there are enough substrate molecules to fully saturate its active sites. Competitive inhibitors do not affect V_{max}, as higher substrate concentrations are able to overcome the inhibition.

(Choice B) Most competitive inhibitors, such as malate, bind in the substrate-binding pocket. In contrast, most noncompetitive inhibitors bind at allosteric sites, resulting in a conformational change of the enzyme that decreases enzymatic activity and slows the rate of reaction (V_{max}). Noncompetitive inhibition does not change the apparent K_m and cannot be overcome with higher substrate concentrations.

(Choice C) Irreversible inhibitors bind to enzymes through strong covalent bonds; this typically renders the enzyme permanently ineffective, decreasing the V_{max}.

(Choice D) Competitive inhibitors interfere with substrate binding due to the inhibitor's own high affinity for the enzyme's active site. This causes the measured K_m value to increase; however, the actual enzyme affinity for the substrate remains unchanged.

Educational objective:
Competitive inhibitors compete with substrate for active binding sites on enzymes. Additional substrate is required to achieve the same rate of reaction, increasing the measured value of the Michaelis constant (K_m). Competitive inhibitors do not affect enzyme function; therefore, maximal velocity (V_{max}) is unchanged in their presence.

Settings

Item 19 of 40
Question Id: 12066

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A. It alters the maximal velocity of the reaction [3%]

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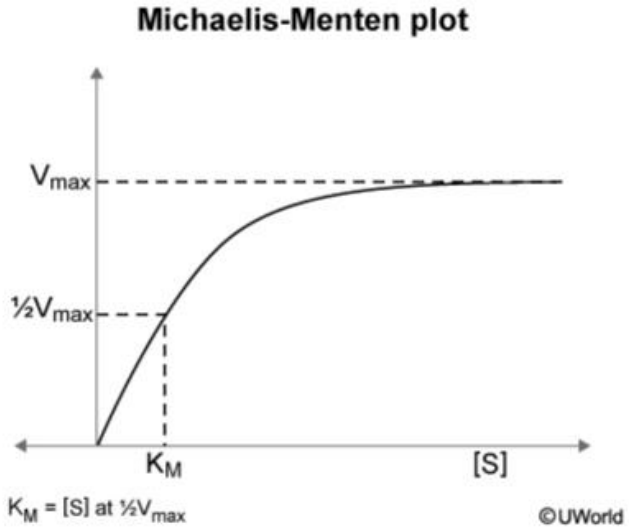

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Item 20 of 40
Question Id: 11930

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A 2-year-old boy is being evaluated for failure to thrive and developmental delay. His past medical history is significant for recurrent ear infections since age 6 months. Physical examination shows coarse facial features, corneal clouding, hepatosplenomegaly, and restricted joint mobility. Mass spectrometry analysis is performed on cultured fibroblasts and reveals deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. Normally, these proteins are most likely to be transported to which of the following cellular locations?

A. Extracellular space
B. Lysosome
C. Mitochondria
D. Nucleus
E. Plasma membrane

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Item 20 of 40
Question Id: 11930

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 2-year-old boy is being evaluated for failure to thrive and developmental delay. His past medical history is significant for recurrent ear infections since age 6 months. Physical examination shows coarse facial features, corneal clouding, hepatosplenomegaly, and restricted joint mobility. Mass spectrometry analysis is performed on cultured fibroblasts and reveals deficient phosphorylation of mannose residues on certain glycoproteins in the Golgi apparatus. Normally, these proteins are most likely to be transported to which of the following cellular locations?

- A. Extracellular space [8%]
- ✔ B. Lysosome [77%]
- C. Mitochondria [2%]
- D. Nucleus [0%]
- E. Plasma membrane [11%]

Omitted
Correct answer
B

77%
Answered correctly

3 Seconds
Time Spent

09/21/2018
Last Updated

Explanation

This patient has **inclusion cell (I-cell) disease**, an autosomal recessive lysosomal storage disorder. I-cell disease occurs due to defects in **protein targeting**, a process by which proteins are transported to their appropriate intra- or extracellular location. Post-translational modifications (eg, folding, glycosylation, and phosphorylation) often function as markers that help guide the protein to its final destination.

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protein targeting, a process by which proteins are transported to their appropriate intra- or extracellular location. Post-translational modifications (eg, folding, glycosylation, and phosphorylation) often function as markers that help guide the protein to its final destination.

Proteins targeted for **lysosomes** are modified differently than those destined for extracellular secretion. A Golgi body **phosphotransferase enzyme** catalyzes the **phosphorylation of mannose residues** on lysosome-bound proteins, allowing them to traverse the Golgi network and ultimately be transported to the lysosome, where they serve as catalysts for degradation of cellular components.

A defective phosphotransferase enzyme causes extracellular secretion of these proteins and accumulation of cellular debris in the lysosome, forming the characteristic inclusion bodies seen in I-cell disease. Patients with this disorder typically present with failure to thrive and cognitive deficits in the first year of life along with characteristic physical features (eg, coarse facial features, corneal clouding). I-cell disease is typically fatal in childhood.

(Choice A) Following translation in the endoplasmic reticulum, secretory proteins traverse the Golgi apparatus and are packaged into vesicles that ultimately fuse with the plasma membrane, facilitating extracellular protein secretion.

(Choice C) Most mitochondrial proteins are synthesized in the cytosol and contain specific mitochondrial targeting sequences. Translocases detect these sequences and shuttle the proteins into and between the different mitochondrial compartments.

(Choice D) In order for nuclear proteins to be imported into the nucleus, they must first present a nuclear localization signal to nuclear pore complexes located on the nuclear envelope. A different nuclear export signal is required for proteins to leave the nucleus.

(Choice E) Peripheral membrane proteins may be modified through a lipidation process in which a hydrophobic lipid anchor is covalently attached to the protein. This process facilitates protein interaction with the cell membrane.

Educational objective:
Protein targeting is the process by which proteins with different intra- and extracellular fates reach their destination. Proteins destined for the lysosome require phosphorylation of specific mannose residues to ensure proper transit through the Golgi apparatus.

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The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

As part of a long-term cohort study, members of a large extended family undergo periodic analysis of multiple serum markers. Many male participants are found to have abnormal laboratory results despite no obvious signs of disease. Further analysis shows that these men have an X-linked mutation affecting the phosphoribosyl pyrophosphate (PRPP) synthetase gene, resulting in greatly increased substrate conversion.

Item 1 of 2

Which of the following organs is most likely to develop pathology secondary to this mutation?

- A. Aorta
- B. Heart
- C. Joints
- D. Liver
- E. Pancreas

Submit

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 21 of 40
Question Id: 2090

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

The following vignette applies to the next **2** items. The items in the set must be answered in sequential order. Once you click **Proceed to Next Item**, you will not be able to add or change an answer.

As part of a long-term cohort study, members of a large extended family undergo periodic analysis of multiple serum markers. Many male participants are found to have abnormal laboratory results despite no obvious signs of disease. Further analysis shows that these men have an X-linked mutation affecting the phosphoribosyl pyrophosphate (PRPP) synthetase gene, resulting in greatly increased substrate conversion.

Item 1 of 2

Which of the following organs is most likely to develop pathology secondary to this mutation?

A. Aorta [2%]
B. Heart [5%]
✔ C. Joints [55%]
D. Liver [33%]
E. Pancreas [4%]

Omitted
Correct answer
C

55%
Answered correctly

4 Seconds
Time Spent

12/26/2018
Last Updated

Explanation

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Item 21 of 40
Question Id: 2090

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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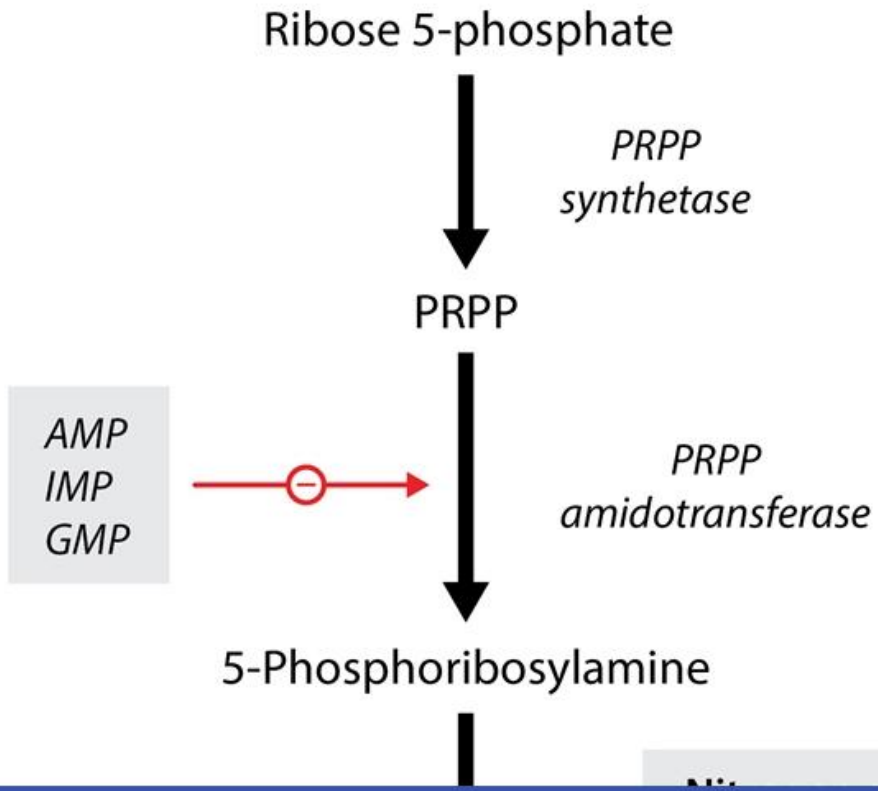
De novo purine synthesis



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Item 21 of 40
Question Id: 2090

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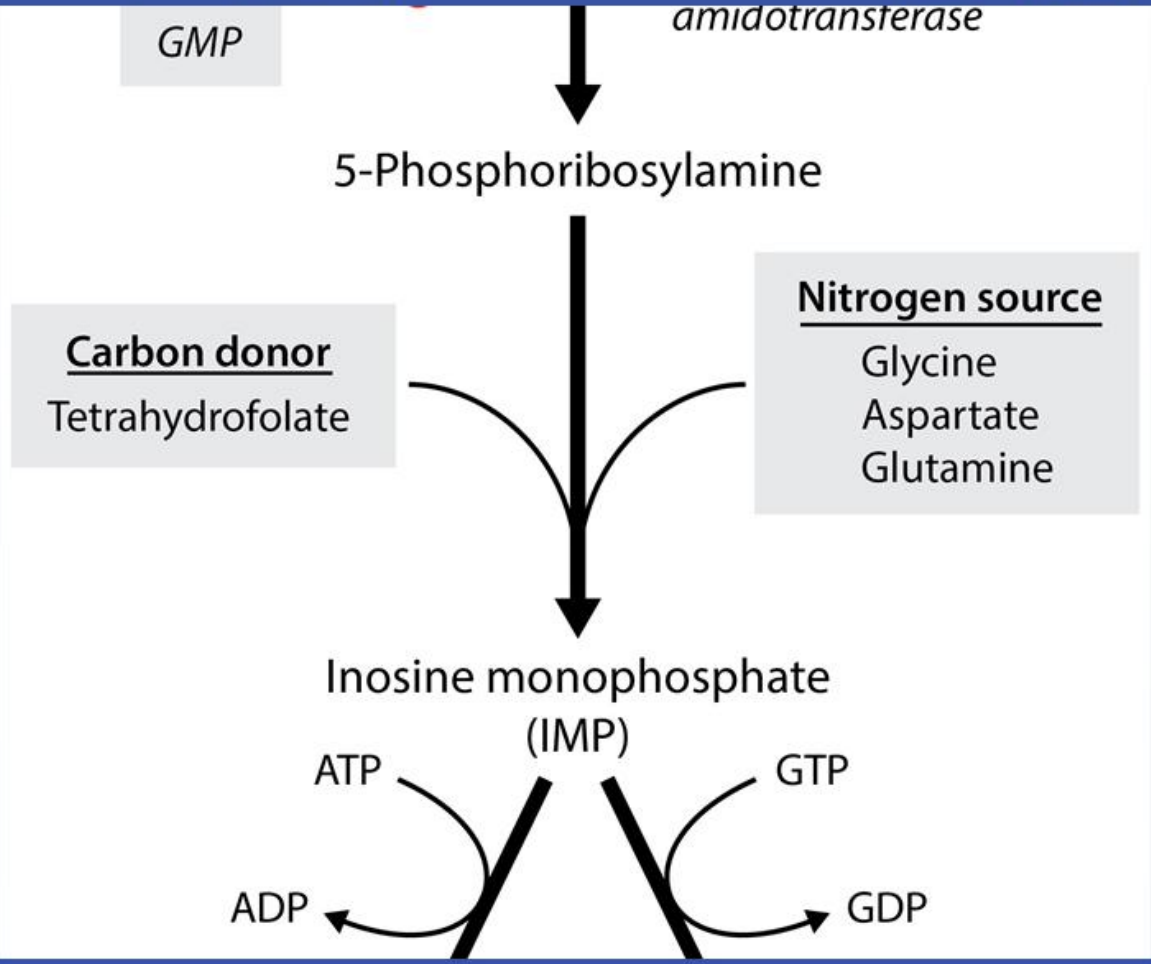

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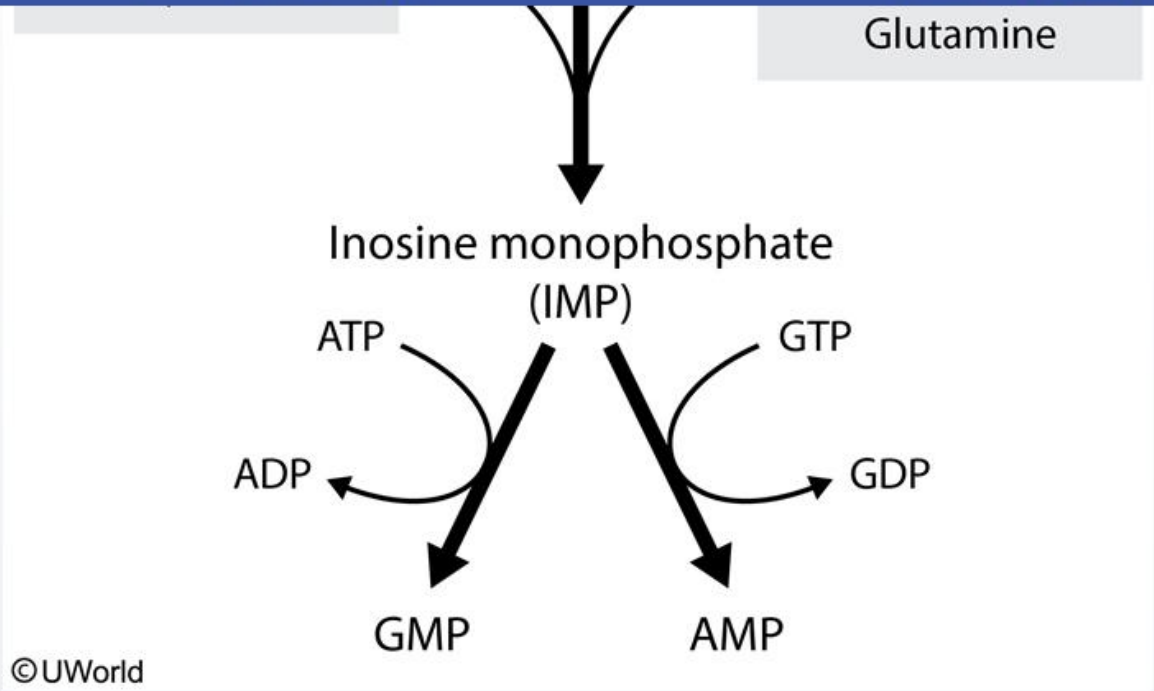

Gout is a disease caused by tissue deposition of monosodium urate crystals. Elevated uric acid levels are a known risk factor for gout and increased purine metabolism is one possible cause of hyperuricemia. Phosphoribosyl pyrophosphate (PRPP) synthetase is the enzyme responsible for the production of the activated ribose necessary for de novo synthesis of purine and pyrimidine nucleotides. The mutation described in the question stem will cause increased production of purines due to feed-forward activation of the purine synthesis pathway. As a result, more purine molecules will undergo degradation, resulting in hyperuricemia and an increased risk of gout.

(Choice A) The aorta can develop aneurysms in patients with Marfan syndrome, which results from defects in fibrillin-1.

Gout is a disease caused by tissue deposition of monosodium urate crystals. Elevated uric acid levels are a known risk factor for gout and increased purine metabolism is one possible cause of hyperuricemia. Phosphoribosyl pyrophosphate (PRPP) synthetase is the enzyme responsible for the production of the activated ribose necessary for de novo synthesis of purine and pyrimidine nucleotides. The mutation described in the question stem will cause increased production of purines due to feed-forward activation of the purine synthesis pathway. As a result, more purine molecules will undergo degradation, resulting in hyperuricemia and an increased risk of gout.

(Choice A) The aorta can develop aneurysms in patients with Marfan syndrome, which results from defects in fibrillin-1.

(Choices B and D) The heart and liver can be affected by glycogen storage diseases resulting from a variety of enzyme deficiencies such as glucose-6-phosphatase deficiency (von Gierke disease) and acid maltase deficiency (Pompe disease).

(Choice E) The pancreas is affected in patients with cystic fibrosis, which results from a mutation in the cystic fibrosis transmembrane conductance regulator gene. Common sequelae include pancreatitis, pancreatic insufficiency, and destruction of islet cells.

Educational objective:
Gout occurs with increased frequency in patients with activating mutations involving phosphoribosyl pyrophosphate synthetase due to increased production and degradation of purines.

References

- Inherited superactivity of phosphoribosylpyrophosphate synthetase: association of uric acid overproduction and sensorineural deafness.

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Item 22 of 40
Question Id: 2091

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Item 2 of 2

Incidentally, one of the male patients followed in the study is hospitalized with right knee pain and swelling. A sample of his synovial fluid shows negatively birefringent crystals under polarized light microscopy. To achieve rapid improvement in this patient's symptoms, therapy should be directed toward inhibiting which of the following types of cells?

A. Eosinophils
B. Lymphocytes
C. Neutrophils
D. Synovial cells
E. Mast cells

Submit

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Item 22 of 40
Question Id: 2091

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

Item 2 of 2

Incidentally, one of the male patients followed in the study is hospitalized with right knee pain and swelling. A sample of his synovial fluid shows negatively birefringent crystals under polarized light microscopy. To achieve rapid improvement in this patient's symptoms, therapy should be directed toward inhibiting which of the following types of cells?

- A. Eosinophils [2%]
- B. Lymphocytes [14%]
- ✔ C. Neutrophils [70%]
- D. Synovial cells [6%]
- E. Mast cells [5%]

Omitted
Correct answer
C

70%
Answered correctly

3 Seconds
Time Spent

12/26/2018
Last Updated

Explanation

This patient's synovial fluid analysis shows negatively birefringent crystals (ie, monosodium urate crystals) under polarized light, which is diagnostic for gouty arthritis. Neutrophils are the primary cells responsible for the intense inflammatory response seen in patients with gout. Phagocytosis of urate crystals by neutrophils causes the release of various cytokines and inflammatory mediators that lead to further neutrophil

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Explanation

This patient's synovial fluid analysis shows negatively birefringent crystals (ie, monosodium urate crystals) under polarized light, which is diagnostic for gouty arthritis. Neutrophils are the primary cells responsible for the intense inflammatory response seen in patients with gout. Phagocytosis of urate crystals by neutrophils causes the release of various cytokines and inflammatory mediators that lead to further neutrophil activation and chemotaxis, resulting in a positive feedback loop that amplifies the inflammatory response.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for treating acute gouty arthritis. They inhibit prostanoid biosynthesis (eg, prostaglandins, prostacyclin, thromboxanes), exerting a broad anti-inflammatory effect that includes inhibition of neutrophils. Patients with contraindications to NSAIDs (eg, peptic ulcer disease, renal impairment) are often treated with colchicine, which impairs neutrophil migration and phagocytosis by interfering with microtubule formation. Colchicine also decreases tyrosine phosphorylation in response to monosodium urate crystals, resulting in decreased neutrophil activation.

(Choice A) Eosinophils function in defense against parasitic infections and are also pathogenic in patients with asthma, allergy, hypereosinophilic syndromes, and vasculitides such as Churg-Strauss syndrome.

(Choice B) Lymphocytes produce delayed-type hypersensitivity reactions that do not play a role in gout.

(Choice D) Synovial cells and macrophages play a role in initiating the inflammatory response in gouty arthritis. However, targeting these cells would not eliminate the inflammatory amplification caused by neutrophils, which is the central mechanism involved in precipitating an acute gouty attack.

(Choice E) Mast cell degranulation can be inhibited by medications such as cromolyn sodium, which is used in conditions such as asthma and allergic rhinitis.

Educational objective:
Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for treating acute gouty arthritis. They inhibit cyclooxygenase and exert a

crystals, resulting in decreased neutrophil activation.

(Choice A) Eosinophils function in defense against parasitic infections and are also pathogenic in patients with asthma, allergy, hypereosinophilic syndromes, and vasculitides such as Churg-Strauss syndrome.

(Choice B) Lymphocytes produce delayed-type hypersensitivity reactions that do not play a role in gout.

(Choice D) Synovial cells and macrophages play a role in initiating the inflammatory response in gouty arthritis. However, targeting these cells would not eliminate the inflammatory amplification caused by neutrophils, which is the central mechanism involved in precipitating an acute gouty attack.

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Educational objective:
Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line therapy for treating acute gouty arthritis. They inhibit cyclooxygenase and exert a broad anti-inflammatory effect that includes inhibition of neutrophils. When NSAIDs are contraindicated (eg, peptic ulcer disease, renal impairment), colchicine is useful in the acute management of gout as it inhibits neutrophil chemotaxis and phagocytosis by preventing microtubule formation.

References

- Crystal-induced neutrophil activation. III. Inflammatory microcrystals induce a distinct pattern of tyrosine phosphorylation in human neutrophils.
- Prevention of neutrophil apoptosis by monosodium urate crystals.
- Colchicine: its mechanism of action and efficacy in crystal-induced inflammation.

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Item 23 of 40
Question Id: 1122

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein- dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

A. Ca^{2+}
B. cAMP
C. cGMP
D. Cl^-
E. mRNA
F. NO

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Item 23 of 40
Question Id: 1122

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Molecular biologists studying signal transduction apply an agent to human cells that activates G-protein- dependent phospholipase C. Which of the following intracellular substances is most likely to increase immediately after exposure to this agent?

- A. Ca^{2+} [77%]
- B. cAMP [10%]
- C. cGMP [9%]
- D. Cl^- [0%]
- E. mRNA [0%]
- F. NO [1%]

Omitted
Correct answer
A

77%
Answered correctly

3 Seconds
Time Spent

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Last Updated

Explanation

A variety of hormone receptors are known to exert their intracellular effects via the **phosphoinositol system**. Examples include α_1-adrenergic, M_1 and M_3 cholinergic, V_1 (vasopressin), H_1 (histamine), oxytocin, angiotensin II, TRH, and GnRH receptors. This signal transduction pathway proceeds through the following steps:

1. Binding of a ligand to its cell surface receptor causes the exchange of GDP for GTP on the α subunit of a G protein associated with the

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Explanation

A variety of hormone receptors are known to exert their intracellular effects via the **phosphoinositol system**. Examples include α_1-adrenergic, M_1 and M_3 cholinergic, V_1 (vasopressin), H_1 (histamine), oxytocin, angiotensin II, TRH, and GnRH receptors. This signal transduction pathway proceeds through the following steps:

1. Binding of a ligand to its cell surface receptor causes the **exchange of GDP for GTP** on the α-subunit of a **G_q-protein** associated with the receptor. The activated α-subunit undergoes a conformational change and exposes a **phospholipase C** (PLC) activating site.
2. After activation, PLC hydrolyzes **phosphatidyl inositol bisphosphate** (PIP_2) into **diacylglycerol** (DAG) and **inositol triphosphate** (IP_3).
3. DAG is able to directly stimulate **protein kinase C** (PKC), but the major activator of PKC is **increased intracellular Ca^{2+}** that occurs due to IP_3 mediated-release of intracellular Ca^{2+} stores from the endoplasmic reticulum. PKC is the major effector molecule in this pathway; it directly modulates the activity of other proteins via phosphorylation.

(Choices B and C) Intracellular cAMP and cGMP concentrations increase during activation of adenylate or guanylate cyclase second messenger systems, respectively. Levels can also increase following cyclic nucleotide phosphodiesterase inhibition, as seen on exposure to sildenafil, which selectively inhibits cGMP phosphodiesterease and results in smooth muscle relaxation in blood vessels.

(Choice D) Intracellular Cl^- concentration increases slightly after inhibitory neurotransmitters (eg, GABA, glycine) act on the neuron to increase Cl^- membrane conductance (hyperpolarization).

(Choice E) The intracellular concentration of mRNA increases during cellular states of elevated protein synthesis (eg, during cell division).

(Choice F) Nitric oxide (NO) is a paracrine signaling molecule with a lifetime of a few seconds. It can freely cross cell membranes and functions as a critical component of endothelium-mediated vasodilation. NO is synthesized from arginine and O_2 by the enzyme NO-synthase.

Educational objective:

The phosphoinositol second messenger system begins with ligand-receptor binding and G-protein activation leading to activation of

proceeds through the following steps:

1. Binding of a ligand to its cell surface receptor causes the **exchange of GDP for GTP** on the α-subunit of a **G_q-protein** associated with the receptor. The activated α-subunit undergoes a conformational change and exposes a **phospholipase C** (PLC) activating site.
2. After activation, PLC hydrolyzes **phosphatidyl inositol bisphosphate** (PIP_2) into **diacylglycerol** (DAG) and **inositol triphosphate** (IP_3).
3. DAG is able to directly stimulate **protein kinase C** (PKC), but the major activator of PKC is **increased intracellular Ca^{2+}** that occurs due to IP_3 mediated-release of intracellular Ca^{2+} stores from the endoplasmic reticulum. PKC is the major effector molecule in this pathway; it directly modulates the activity of other proteins via phosphorylation.

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Educational objective:
The phosphoinositol second messenger system begins with ligand-receptor binding and G_q-protein activation leading to activation of phospholipase C (PLC). PLC then hydrolyzes phosphatidyl inositol bisphosphate and forms diacylglycerol and inositol triphosphate (IP_3). Finally, IP_3 activates protein kinase C via an increase in intracellular Ca^{2+}.

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Item 24 of 40
Question Id: 1424

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A researcher develops 2 functional mRNA sequences composed of CUC and CUU trinucleotide repeats, respectively. He subsequently incubates these mRNAs in a solution containing functional ribosomes and tRNAs charged with the appropriate amino acids. After several hours, it is found that both mRNA sequences produce polypeptide chains containing leucine repeats. This observed finding is due to which of the following genetic principles?

A. Ambiguity
B. No punctuation
C. Transition
D. Universality
E. Wobble

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Item 24 of 40
Question Id: 1424

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A researcher develops 2 functional mRNA sequences composed of CUC and CUU trinucleotide repeats, respectively. He subsequently incubates these mRNAs in a solution containing functional ribosomes and tRNAs charged with the appropriate amino acids. After several hours, it is found that both mRNA sequences produce polypeptide chains containing leucine repeats. This observed finding is due to which of the following genetic principles?

- A. Ambiguity [11%]
- B. No punctuation [0%]
- C. Transition [2%]
- D. Universality [7%]
- ✔ E. Wobble [78%]

Omitted
Correct answer
E

78%
Answered correctly

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Last Updated

Explanation

There are 61 codons that code for amino acids, but only 20 amino acids are used in protein synthesis. The **genetic code** is therefore considered **"degenerate"** because more than 1 codon can code for a particular amino acid. For instance, the codons CUC and CUU both code for the amino acid leucine.

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

There are 61 codons that code for amino acids, but only 20 amino acids are used in protein synthesis. The **genetic code** is therefore considered **"degenerate"** because more than 1 codon can code for a particular amino acid. For instance, the codons CUC and CUU both code for the amino acid leucine.

Individual tRNA molecules are specific for certain amino acids and recognize the mRNA codons associated with those amino acids. Certain tRNA molecules can recognize **multiple different codons** coding for the **same amino acid**, a phenomenon explained by the **wobble hypothesis**. This hypothesis states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing with their complementary nucleotides on tRNA, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing. In the case of leucine, for example, 1 tRNA molecule recognizes 2 codons (CUC and CUU) because only the first 2 nucleotide positions (CU in the codon) form traditional bonds.

(Choice A) The genetic code is not ambiguous as each codon is associated with only a single amino acid.

(Choice B) The genetic code is read sequentially from a starting point and has no internal punctuation as each codon is adjacent to the next without spacer nucleotides in between.

(Choice C) Genetic transition refers to a point mutation that results in replacement of a purine nucleotide for another purine or a pyrimidine nucleotide for another pyrimidine. In contrast, transversion refers to a point mutation that results in the replacement of a purine nucleotide for a pyrimidine or a pyrimidine nucleotide for a purine.

(Choice D) The genetic code is almost universal as amino acid codons are nearly identical across species; however, mitochondria and some bacteria and single-celled eukaryotes deviate from the standard genetic code.

Educational objective:
The genetic code is considered "degenerate" because more than 1 codon can code for a particular amino acid. Some of this degeneracy is explained by the wobble hypothesis, which states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base

Individual tRNA molecules are specific for certain amino acids and recognize the mRNA codons associated with those amino acids. Certain tRNA molecules can recognize **multiple different codons** coding for the **same amino acid**, a phenomenon explained by the **wobble hypothesis**. This hypothesis states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing with their complementary nucleotides on tRNA, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing. In the case of leucine, for example, 1 tRNA molecule recognizes 2 codons (CUC and CUU) because only the first 2 nucleotide positions (CU in the codon) form traditional bonds.

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Educational objective:
The genetic code is considered "degenerate" because more than 1 codon can code for a particular amino acid. Some of this degeneracy is explained by the wobble hypothesis, which states that the first 2 nucleotide positions on the mRNA codon require traditional (Watson-Crick) base pairing, whereas the third "wobble" nucleotide position may undergo less stringent (nontraditional) base pairing.

References

- tRNA's wobble decoding of the genome: 40 years of modification.

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 25 of 40
Question Id: 2032

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In an experiment, erythrocyte precursor cells are incubated in a medium containing radiolabeled cysteine. These radiolabeled cysteine residues are attached to their appropriate tRNAs by the enzyme aminoacyl-tRNA synthetase. The bound cysteine residues are then chemically modified to form alanine. The end product of this reaction is a tRNA molecule that contains the cysteine anticodon but is mischarged with alanine. Which of the following is most likely to occur to this alanine residue during polypeptide synthesis of alpha-hemoglobin?

A. It will be incorporated into the polypeptide chain at a site requiring alanine
B. It will be incorporated into the polypeptide chain at a site requiring cysteine
C. It will be randomly incorporated into the polypeptide chain, halting chain elongation
D. It will be rapidly cleaved off tRNA by the enzyme glycosylase
E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA

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Settings

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Item 25 of 40
Question Id: 2032

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- A. It will be incorporated into the polypeptide chain at a site requiring alanine [5%]
- ✔ B. It will be incorporated into the polypeptide chain at a site requiring cysteine [69%]
- C. It will be randomly incorporated into the polypeptide chain, halting chain elongation [5%]
- D. It will be rapidly cleaved off tRNA by the enzyme glycosylase [13%]
- E. It will never be incorporated into the polypeptide chain and will remain attached to tRNA [6%]

Omitted
Correct answer
B

69%
Answered correctly

3 Seconds
Time Spent

09/14/2018
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Explanation

Amino acid activation and attachment to the 3' end of tRNA are catalyzed by **aminoacyl-tRNA synthetases** (AA-tRNA synthetases). Each amino acid/tRNA pair has a specific AA-tRNA synthetase that links them together. These enzymes are responsible for ensuring that each amino acid binds to the tRNA with the proper anticodon. AA-tRNA synthetase activation and binding sites are **highly specific** for their correct amino acids and tRNA molecules. In addition, some AA-tRNA synthetases can **"proofread"** their specific tRNA molecules and hydrolyze the amino acid bond

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Amino acid activation and attachment to the 3' end of tRNA are catalyzed by **aminoacyl-tRNA synthetases** (AA-tRNA synthetases). Each amino acid/tRNA pair has a specific AA-tRNA synthetase that links them together. These enzymes are responsible for ensuring that each amino acid binds to the tRNA with the proper anticodon. AA-tRNA synthetase activation and binding sites are **highly specific** for their correct amino acids and tRNA molecules. In addition, some AA-tRNA synthetases can **"proofread"** their specific tRNA molecules and hydrolyze the amino acid bond when their tRNAs are incorrectly charged. The error rate for AA-tRNA synthetases is therefore very low, with less than 1 error per 10^4 charges.

During protein synthesis, tRNA acts as an adaptor molecule between the codons found on mRNA and the amino acids being incorporated into the polypeptide chain. The amino acid sequence in a polypeptide chain is dictated by the binding of a tRNA anticodon to its complementary codon on the mRNA molecule being translated. **Erroneous amino acid/tRNA coupling** by AA-tRNA synthetase causes the **wrong amino acid** to be **incorporated** into the growing polypeptide chain **(Choice E)**.

For example, under normal circumstances, when the ribosome encounters a cysteine codon (eg, UGU) on mRNA, the complementary tRNA anticodon (eg, ACA) binds. If this tRNA is improperly charged with alanine, as described in the experiment above, alanine will be incorrectly incorporated into the growing polypeptide chain in place of cysteine **(Choice A)**.

(Choice C) During polypeptide chain elongation, ribosomes move from codon to codon on mRNA in the 5' to 3' direction, sequentially adding amino acids from aminoacyl-tRNA to the peptide chain. This continues until the ribosome encounters a stop codon (ie, UAA, UAG, or UGA). Releasing factors then assist in polypeptide chain termination.

(Choice D) DNA glycosylases are enzymes involved in DNA base excision repair.

Educational objective:
The sequence of amino acids in a growing polypeptide chain is dictated by the interaction of the mRNA codon with the tRNA anticodon. tRNA that is mischarged with the incorrect amino acid (and not corrected by aminoacyl-tRNA synthetase proofreading) will incorporate the wrong amino acid into the growing polypeptide chain.

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Item 26 of 40
Question Id: 12276

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A 52-year-old man is being evaluated in the emergency department for abdominal pain associated with watery diarrhea. His symptoms have been progressive over the last month. He says that he is depressed and often has difficulty remembering things. The patient has a 20-year history of alcohol abuse. On examination, he appears disheveled. A pigmented scaly skin rash is present in the malar distribution of his face, neck, and back of his hands. The rash has been present for several months and worsens on exposure to sunlight. It is determined that the patient's symptoms are secondary to lack of a specific nutrient. Activity of which of the following enzymes is most likely decreased in the patient as a result of this deficiency?

A. Citrate synthase
B. Hexokinase
C. Isocitrate dehydrogenase
D. Phosphoglycerate kinase
E. Succinate dehydrogenase

Submit

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Item 26 of 40
Question Id: 12276

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- A. Citrate synthase [7%]
- B. Hexokinase [5%]
- ✔ C. Isocitrate dehydrogenase [46%]
- D. Phosphoglycerate kinase [8%]
- E. Succinate dehydrogenase [31%]

Omitted
Correct answer
C

46%
Answered correctly

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Time Spent

09/04/2018
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Explanation

This patient likely has **pellagra**, a disease characterized by **photosensitive dermatitis**, diarrhea, and dementia occurring secondary to **vitamin**

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28

Explanation

This patient likely has **pellagra**, a disease characterized by **photosensitive dermatitis**, diarrhea, and dementia occurring secondary to **vitamin B_3 (niacin) deficiency**. In the United States, pellagra is seen predominantly in malnourished populations (eg, patients with alcoholism or GI malabsorption).

Niacin is a precursor for nicotinamide adenine dinucleotide (**NAD**) and nicotinamide adenine dinucleotide phosphate (**NADP**), two important **cofactors** for many **dehydrogenase** and **reductase enzymes**. NAD is required for catabolic reactions (eg, glycolysis, beta-oxidation) as well as cell signaling and DNA repair, whereas NADP is necessary for many anabolic reactions such as fatty acid and cholesterol synthesis. NAD is a key constituent of the citric acid cycle; it serves as a cofactor for isocitrate dehydrogenase, alpha-ketoglutarate dehydrogenase, and malate dehydrogenase.

(Choice A) Citrate synthase is an enzyme of the citric acid cycle; it does not require NAD or NADP as a cofactor.

(Choices B and D) Hexokinase and phosphoglycerate kinase are enzymes used in glycolysis; they do not require NAD or NADP as cofactors.

(Choice E) Succinate dehydrogenase is an enzyme of the citric acid cycle; it catalyzes the conversion of succinate to fumarate using flavin adenine dinucleotide (FAD) as a cofactor.

Educational objective:
Niacin is a precursor for nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), two important cofactors for many dehydrogenase and reductase enzymes. Niacin deficiency results in pellagra (ie, diarrhea, dementia, and dermatitis).

References

- Pellagra: a non-eradicated old disease.

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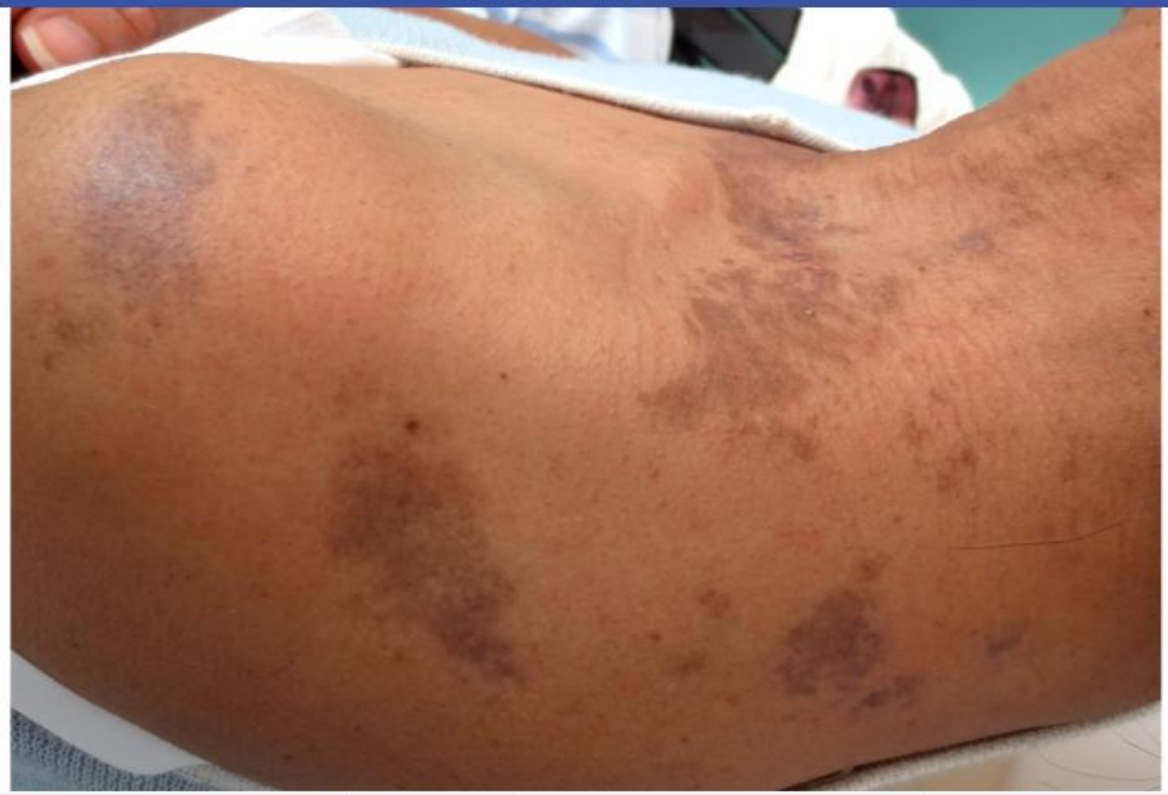
Exhibit Display



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Item 27 of 40
Question Id: 755

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A 46-year-old obese man is referred to a dietitian for evaluation of his food intake. He has been trying to lose weight but has been unsuccessful. The patient is 172.7 cm (5 ft 8 in) tall and weighs 113 kg (250 lb). Analysis of his food intake shows that he is consuming 3600 Calories a day. The dietitian recommends increasing physical activity and implementing a dietary plan. In the first phase, the patient is advised to reduce his daily dietary intake to 3,000 Calories, with 30% coming from protein. How much protein per day will this patient consume on the new dietary plan?

- A. 130 g
- B. 160 g
- C. 180 g
- D. 225 g
- E. 250 g

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Item 27 of 40
Question Id: 755

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- A. 130 g [8%]
- B. 160 g [6%]
- C. 180 g [17%]
- ✔ D. 225 g [58%]
- E. 250 g [8%]

Omitted
Correct answer
D

58%
Answered correctly

3 Seconds
Time Spent

09/20/2018
Last Updated

Explanation

Dietary energy comes predominantly from protein, carbohydrate, and fat. Metabolism yields 4 Calories (Cal) per gram of protein or carbohydrate and 9 Cal per gram of fat. Ethanol yields 7 Cal per gram.

This patient is instructed to consume 3000 Cal per day, 900 (30%) of which are to be from protein. Because 1 g of protein yields 4 Cal of energy,

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Item 27 of 40
Question Id: 755

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- A. 130 g [8%]
- B. 160 g [6%]
- C. 180 g [17%]
- ✔ D. 225 g [58%]
- E. 250 g [8%]

Omitted
Correct answer
D

58%
Answered correctly

3 Seconds
Time Spent

09/20/2018
Last Updated

Explanation

Dietary energy comes predominantly from protein, carbohydrate, and fat. Metabolism yields 4 Calories (Cal) per gram of protein or carbohydrate and 9 Cal per gram of fat. Ethanol yields 7 Cal per gram.

This patient is instructed to consume 3000 Cal per day, 900 (30%) of which are to be from protein. Because 1 g of protein yields 4 Cal of energy, this patient should consume (900 Cal /4 Cal) = 225 g/day of protein.

Educational objective:
Metabolism of 1 g of protein or carbohydrate produces 4 Calories of energy; metabolism of 1 g of fat produces 9 Calories.

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Question Id: 1035

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Erythroblasts isolated from a bone marrow biopsy sample of a patient with neonatal jaundice are incubated in a medium containing radiolabeled glucose. The cells are unable to generate NADPH from glucose metabolism but are able to convert fructose-6-phosphate to ribose-5-phosphate, which is required for nucleic acid synthesis. Which of the following enzymes is essential for the latter conversion?

A. Aconitase
B. Enolase
C. Glucose-6-phosphate dehydrogenase
D. Glutathione reductase
E. Transketolase

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Question Id: 1035

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A. Aconitase
B. Enolase
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D. Glutathione reductase
E. Transketolase

Submit

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Submit

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- A. Aconitase [3%]
- B. Enolase [11%]
- C. Glucose-6-phosphate dehydrogenase [18%]
- D. Glutathione reductase [7%]
- ✔ E. Transketolase [59%]

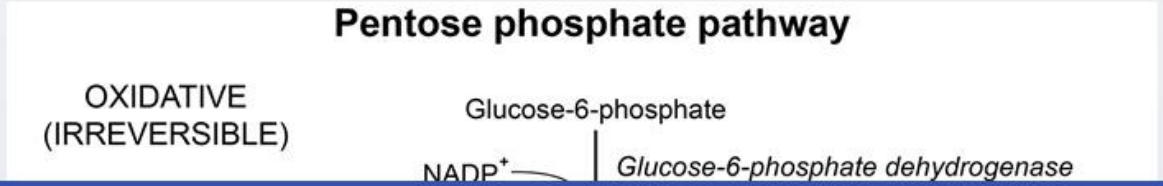
Omitted
Correct answer
E

59%
Answered correctly

6 Seconds
Time Spent

11/15/2018
Last Updated

Explanation



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Item 28 of 40
Question Id: 1035

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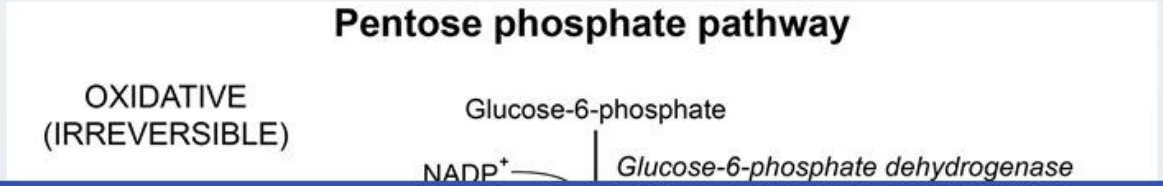
Omitted
Correct answer
E

59%
Answered correctly

6 Seconds
Time Spent

11/15/2018
Last Updated

Explanation



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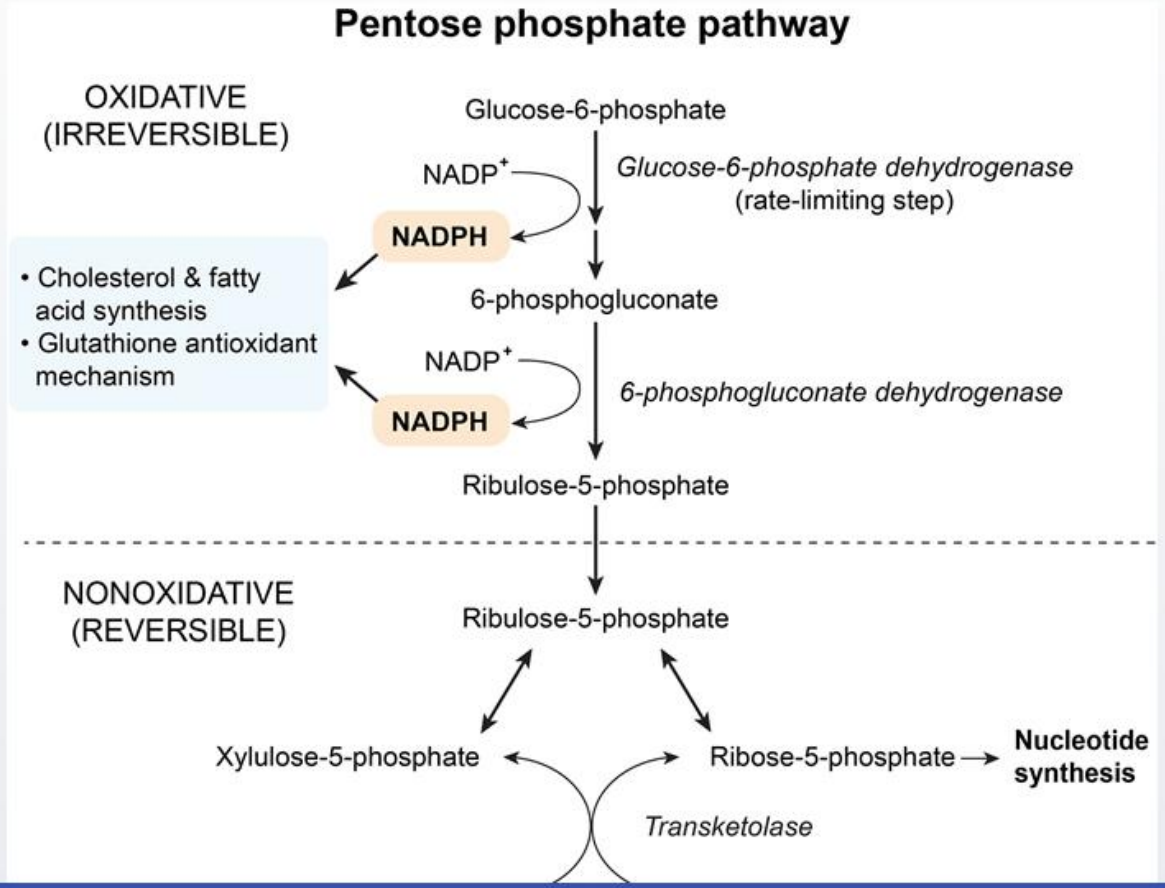

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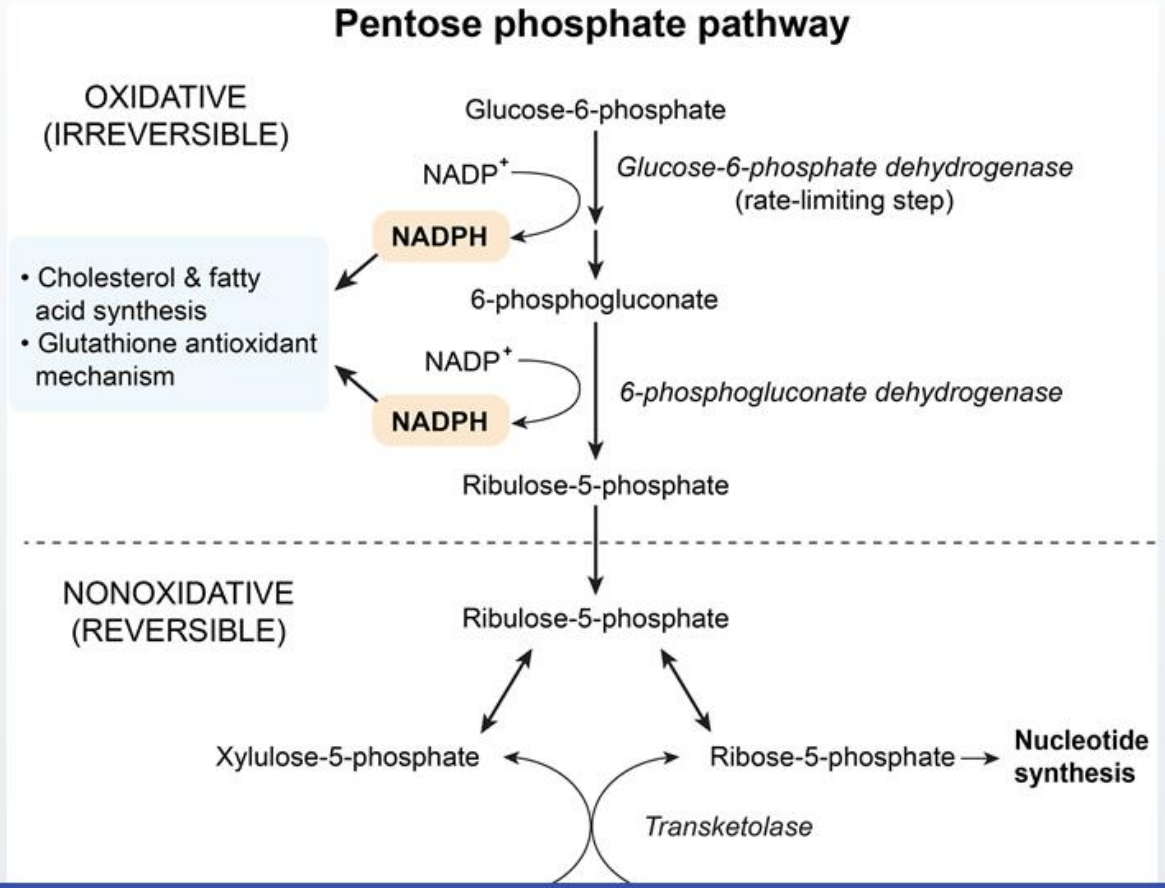
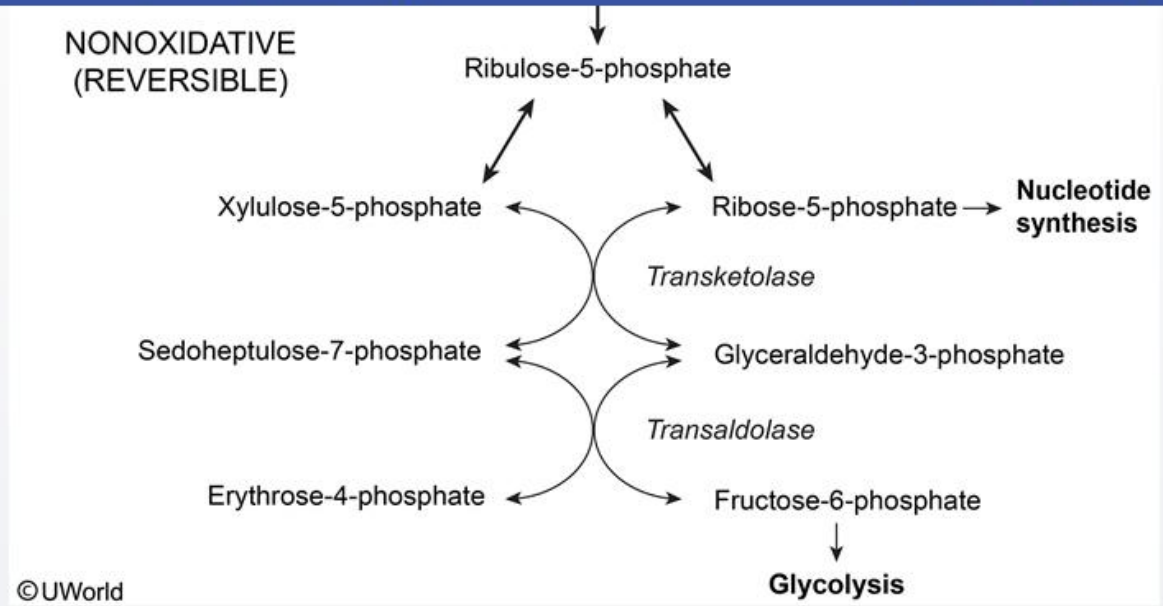
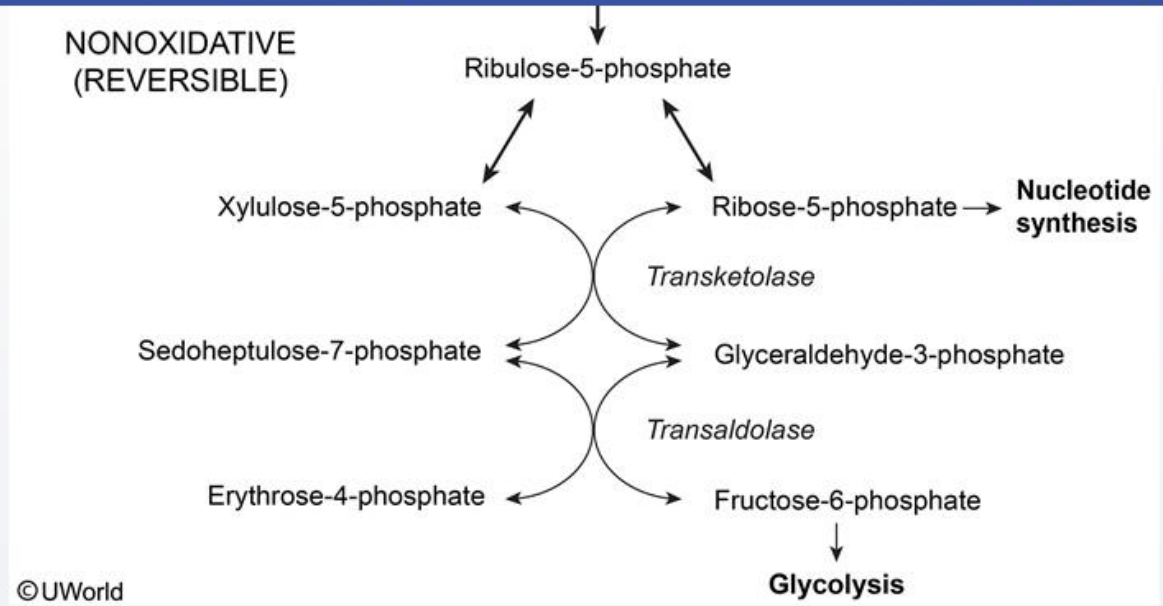




The **pentose phosphate pathway** (HMP shunt) generates **NADPH** for use in reductive reactions and **ribose-5-phosphate**, a precursor for the synthesis of nucleotides. The pathway consists of 2 types of reactions, oxidative (irreversible) and nonoxidative (reversible), both of which can function independently depending on cellular requirements.

Activity of the nonoxidative reactions is governed by the cellular demand for ribose-5-phosphate. When ribose-5-phosphate is produced in excess, transketolase and transaldolase can produce the **glycolytic intermediates** glyceraldehyde-3-phosphate and fructose-6-phosphate for ATP generation. When ribose-5-phosphate demand exceeds the production capabilities of the oxidative pathway, the nonoxidative pathway functions in **reverse** and transketolase and transaldolase catalyze the conversion of fructose-6-phosphate and glycerldehyde-3-phosphate to ribose-5-phosphate.



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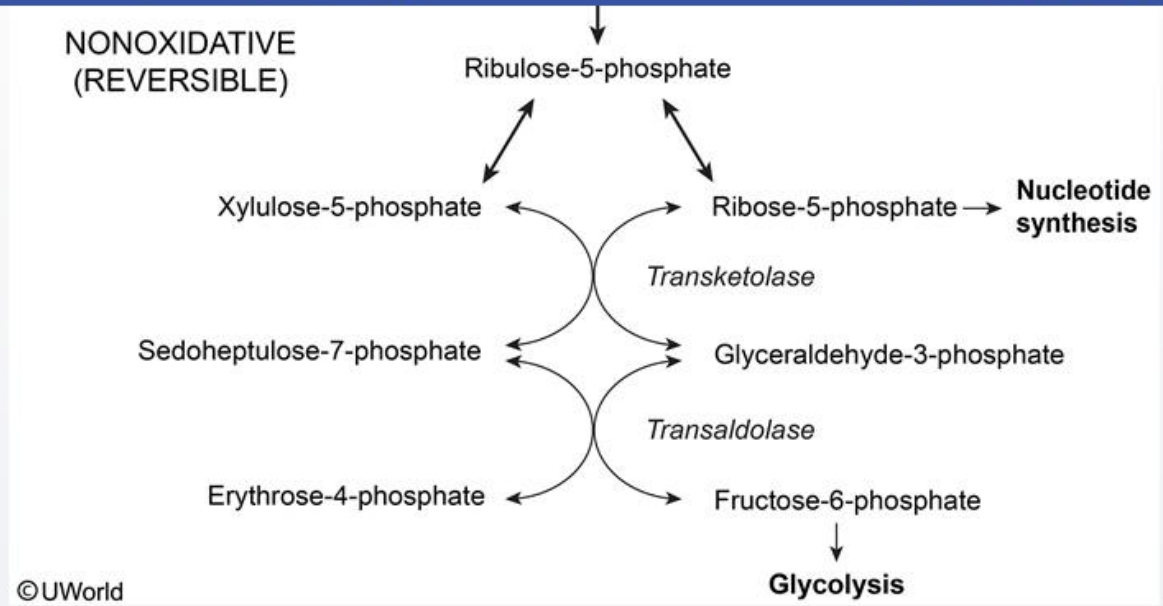

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(Choice A) Aconitase catalyzes the isomerization of citrate to isocitrate in the citric acid cycle.

(Choice B) Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate in glycolysis.

(Choice C) Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway. Deficiency of this enzyme results in hemolytic anemia due to the inability to generate NADPH in the oxidative portion of the pathway. However, nonoxidative reactions are responsible for conversion of fructose-6-phosphate to ribose-5-phosphate.

(Choice D) Glutathione reductase catalyzes the reduction of glutathione disulfide to glutathione using NADPH. Glutathione aids red blood cells in resisting oxidative stress.

Educational objective:
The pentose phosphate pathway consists of an oxidative (irreversible) branch and a nonoxidative (reversible) branch, and each can function independently based on cellular requirements. Transketolase, an enzyme of the nonoxidative branch, is responsible in part for the interconversion of ribose-5-phosphate (nucleotide precursor) and fructose-6-phosphate (glycolytic intermediate).

References

- The pentose phosphate pathway and cancer.

synthesis of nucleotides. The pathway consists of 2 types of reactions, oxidative (irreversible) and nonoxidative (reversible), both of which can function independently depending on cellular requirements.

Activity of the nonoxidative reactions is governed by the cellular demand for ribose-5-phosphate. When ribose-5-phosphate is produced in excess, transketolase and transaldolase can produce the **glycolytic intermediates** glyceraldehyde-3-phosphate and fructose-6-phosphate for ATP generation. When ribose-5-phosphate demand exceeds the production capabilities of the oxidative pathway, the nonoxidative pathway functions in **reverse** and transketolase and transaldolase catalyze the conversion of fructose-6-phosphate and glycerldehyde-3-phosphate to ribose-5-phosphate.

(Choice A) Aconitase catalyzes the isomerization of citrate to isocitrate in the citric acid cycle.

(Choice B) Enolase catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate in glycolysis.

(Choice C) Glucose-6-phosphate dehydrogenase catalyzes the initial and rate-limiting step of the pentose phosphate pathway. Deficiency of this enzyme results in hemolytic anemia due to the inability to generate NADPH in the oxidative portion of the pathway. However, nonoxidative reactions are responsible for conversion of fructose-6-phosphate to ribose-5-phosphate.

(Choice D) Glutathione reductase catalyzes the reduction of glutathione disulfide to glutathione using NADPH. Glutathione aids red blood cells in resisting oxidative stress.

Educational objective:
The pentose phosphate pathway consists of an oxidative (irreversible) branch and a nonoxidative (reversible) branch, and each can function independently based on cellular requirements. Transketolase, an enzyme of the nonoxidative branch, is responsible in part for the interconversion of ribose-5-phosphate (nucleotide precursor) and fructose-6-phosphate (glycolytic intermediate).

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References

- The pentose phosphate pathway and cancer.

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Item 29 of 40
Question Id: 1032

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A 15-year-old boy is being evaluated for poor exercise endurance. He recently started weightlifting with some of his friends and is disappointed that he is "the weakest one by far." He says he tries as hard as possible, but his "arms feel like jelly after just a few repetitions." The patient also says he sometimes experiences severe muscle cramping and urine discoloration after periods of intense straining. Further evaluation reveals that his exercise tolerance can be greatly improved by drinking an oral glucose solution before beginning a strenuous activity. This patient is most likely deficient in an enzyme that catalyzes which of the following conversions?

- A. A
- B. B
- C. C
- D. D
- E. E

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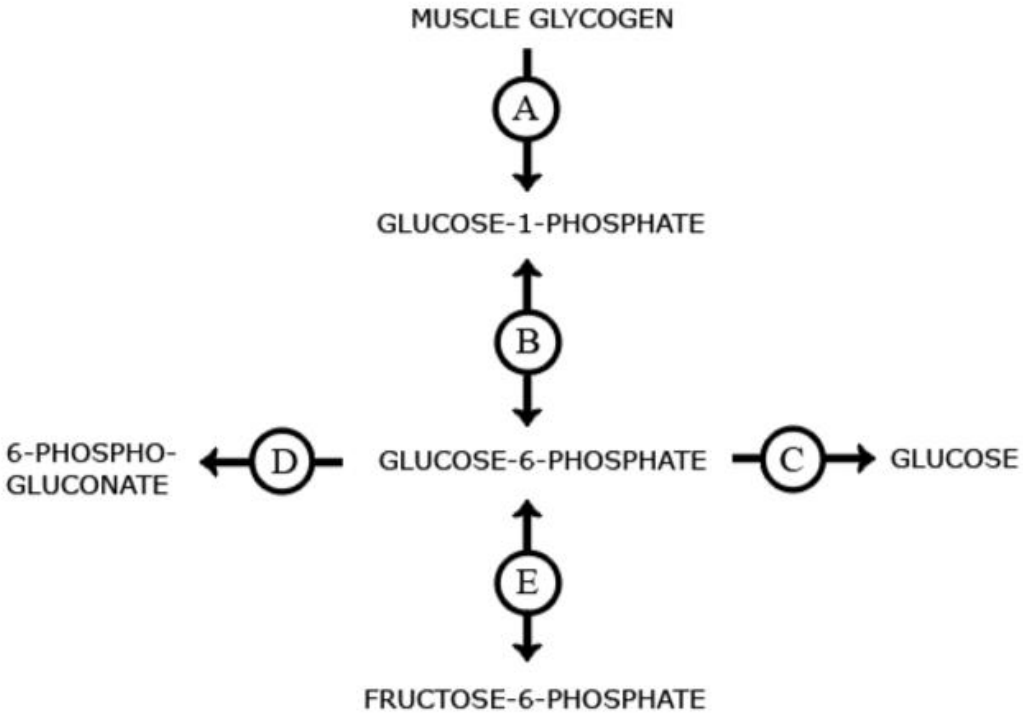

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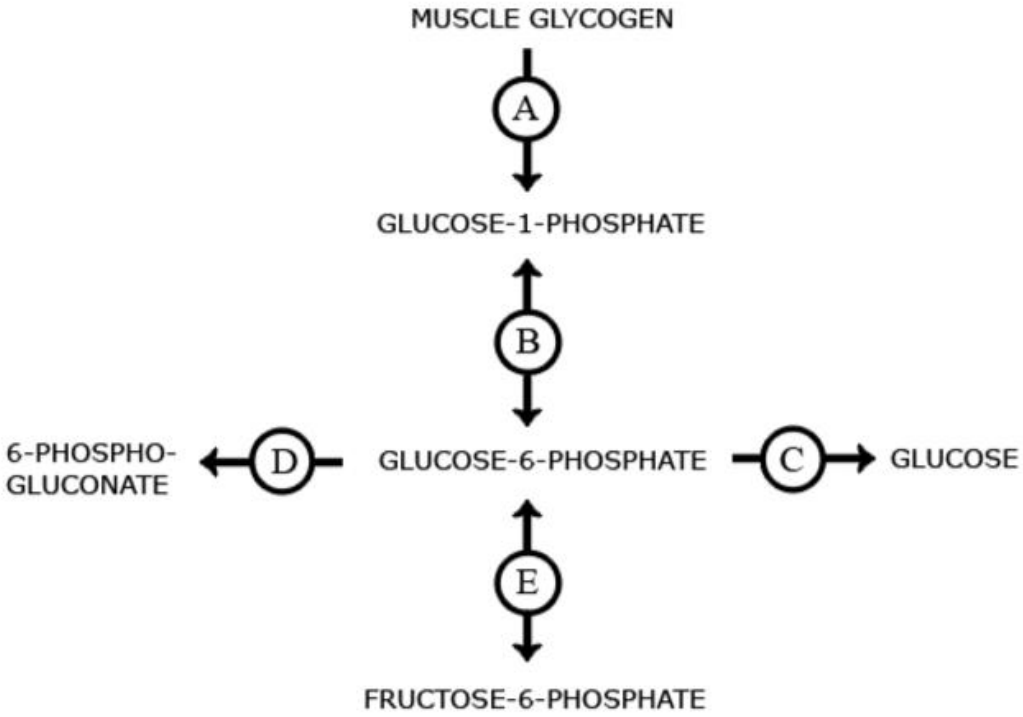

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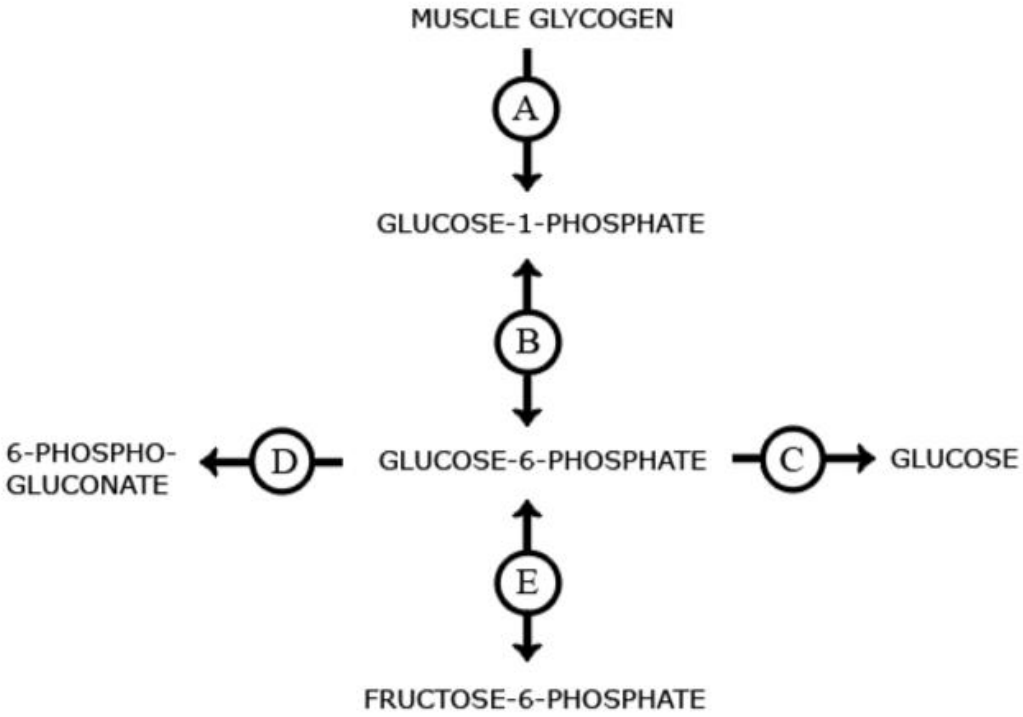

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- A. A [67%] ✔
- B. B [9%]
- C. C [18%]
- D. D [1%]
- E. E [1%]

Omitted
Correct answer
A

67%
Answered correctly

3 Seconds
Time Spent

11/15/2018
Last Updated

Explanation

This patient most likely has **McArdle disease** (glycogen storage disease type V). This condition is caused by deficiency of **myophosphorylase**, an isoenzyme of glycogen phosphorylase present in muscle tissue. Deficiency of this enzyme leads to decreased breakdown of glycogen during

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Omitted
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Explanation

This patient most likely has **McArdle disease** (glycogen storage disease type V). This condition is caused by deficiency of **myophosphorylase**, an isoenzyme of glycogen phosphorylase present in muscle tissue. Deficiency of this enzyme leads to decreased breakdown of glycogen during exercise, resulting in **poor exercise tolerance**, **muscle cramps**, and **rhabdomyolysis**. The prognosis is generally good and symptoms can be improved by consuming simple sugars before beginning physical activity.

During glycogenolysis, **glycogen phosphorylase** shortens glycogen chains by cleaving α-1,4-glycosidic linkages between glucose residues, liberating glucose 1-phosphate in the process. This occurs until 4 residues remain before a branch point (the "limit" dextrin). At this point, the debranching enzyme performs 2 enzymatic functions:

1. Glucosyltransferase cleaves the 3 outer glucose residues of the 4 that are left by glycogen phosphorylase and transfers them to a nearby branch
2. The enzyme α-1,6-glucosidase removes the single remaining branch residue, producing free glucose and a linear glycogen chain that can be further shortened by glycogen phosphorylase

(Choice B) The glucose 1-phosphate generated by glycogenolysis is converted by phosphoglucomutase to glucose 6-phosphate, which can then undergo glycolysis.

(Choice C) Within the liver and kidney, glucose 6-phosphatase converts glucose 6-phosphate to glucose to help maintain blood glucose levels during periods of fasting. However, muscles lack glucose 6-phosphatase and so must utilize glucose 6-phosphate for glycolysis during muscle contraction.

(Choice D) The first step in the pentose phosphate pathway (hexose monophosphate pathway) is conversion of glucose 6-phosphate to 6-phosphogluconate by glucose-6-phosphate dehydrogenase. This pathway maintains cellular NADPH levels and produces pentose sugars for nucleotide synthesis.

(Choice E) Glucose 6-phosphate is converted into fructose 6-phosphate by glucose 6-phosphate isomerase during the second step of glycolysis.

Explanation

This patient most likely has **McArdle disease** (glycogen storage disease type V). This condition is caused by deficiency of **myophosphorylase**, an isoenzyme of glycogen phosphorylase present in muscle tissue. Deficiency of this enzyme leads to decreased breakdown of glycogen during exercise, resulting in **poor exercise tolerance**, **muscle cramps**, and **rhabdomyolysis**. The prognosis is generally good and symptoms can be improved by consuming simple sugars before beginning physical activity.

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Educational objective:
Glycogen serves as a source of glucose during fasting and as an energy store that can be mobilized quickly during strenuous muscle contraction. Myophosphorylase deficiency (McArdle disease or glycogen storage disease type V) causes failure of muscle glycogenolysis, resulting in decreased exercise tolerance, muscle pain and cramping, and myoglobinuria with physical activity.

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Question Id: 8385

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A 42-year-old woman comes to the neurologist for enrollment in a research study. She has a 15-year history of resting tremor, bradykinesia, and cogwheel rigidity consistent with Parkinson's disease. One of her siblings recently started having similar symptoms. Genetic analysis is performed on the patient and her affected sibling. The results show a loss-of-function mutation in a gene that leads to an accumulation of misfolded proteins. Which of the following biochemical processes is most likely defective in this patient?

- A. Acetylation
- B. Gamma-carboxylation
- C. Glucuronidation
- D. Phosphorylation
- E. Ubiquitination

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Question Id: 8385

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- A. Acetylation [7%]
- B. Gamma-carboxylation [5%]
- C. Glucuronidation [2%]
- D. Phosphorylation [6%]
- ✔ E. Ubiquitination [78%]

Omitted
Correct answer
E

78%
Answered correctly

3 Seconds
Time Spent

01/12/2019
Last Updated

Explanation

Ubiquitin is a protein found in all eukaryotic cells that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. The proteasome then recognizes these ubiquinated proteins and uses ATP energy to drive them through its tubular structure, degrading them into small peptides in the process. Attachment of 4 or more ubiquitin monomers is required before most proteins are allowed entry into the

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Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Failure of the system to properly degrade abnormal proteins causes protein misfolding, aggregation, and eventual obstruction of intracellular molecular traffic, leading to cell death. Together, the Parkin, PINK1, and DJ-1 genes code for a protein complex that promotes the degradation of misfolded proteins via the ubiquitin-proteasome system. Mutations in Parkin, PINK1, and DJ-1 are each associated with autosomal recessive forms of Parkinson's disease that have an early age of onset (< 50 years).

(Choice A) Heterochromatin is condensed and methylated DNA that has a low level of transcriptional activity. In contrast to heterochromatin, euchromatin (loosely arranged chromatin) has very high levels of transcriptional activity. Histone acetylation promotes the formation of euchromatin.

(Choice B) Vitamin K-dependent gamma-carboxylation is critical for the functioning of clotting factors II, VII, IX, and X, and of the anticoagulative proteins C and S. Warfarin inhibits carboxylation of these proteins.

(Choice C) The hepatic processing of bilirubin is accomplished in three key steps: carrier-mediated passive uptake of bilirubin at the sinusoidal membrane; conjugation of bilirubin with glucuronic acid in the endoplasmic reticulum; and active biliary excretion of the water-soluble, nontoxic bilirubin-glucuronides. Disruption of this process occurs in Crigler-Najjar syndrome, a condition in which patients lack the enzyme needed to catalyze bilirubin glucuronidation.

(Choice D) Phosphorylation is the addition of a phosphate group (PO_4^{3-}) to a protein or other organic molecule. Phosphorylation is commonly involved in the regulation of enzymatic activity.

Educational objective:

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Educational objective:
Ubiquitin is a protein that undergoes ATP-dependent attachment to other proteins, labeling them for degradation. These modified proteins enter the proteasome and are degraded into small peptides. Impairment of the ubiquitin-proteasome system can contribute to the development of neurodegenerative disorders, including Parkinson's and Alzheimer's diseases.

References

- Parkin and defective ubiquitination in Parkinson's disease.
- Parkin, PINK1, and DJ-1 form a ubiquitin E3 ligase complex promoting unfolded protein degradation.

Settings

Item 31 of 40
Question Id: 846

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A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

A. Galactitol to tagatose
B. Galactose to galactitol
C. Glucose to sorbitol
D. Glucose-6-phosphate to 6-phosphogluconolactone
E. Pyruvate to lactate

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Item 31 of 40
Question Id: 846

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 56-year-old man is evaluated for progressive visual impairment. The patient works as part of the grounds crew at an airport, and says he has trouble identifying aircraft at a distance and with filling out paperwork at the end of his shift. His medical history includes poorly controlled diabetes mellitus, hypertension, and gout. A year ago, the patient underwent an uncomplicated repair of a right inguinal hernia. Physical examination shows bilateral clouding of the lens. The remainder of the examination is unremarkable. Which of the following metabolic conversions is most likely contributing to this patient's current condition?

- A. Galactitol to tagatose [0%]
- B. Galactose to galactitol [12%]
- ✔ C. Glucose to sorbitol [83%]
- D. Glucose-6-phosphate to 6-phosphogluconolactone [1%]
- E. Pyruvate to lactate [1%]

Omitted
Correct answer
C

83%
Answered correctly

3 Seconds
Time Spent

01/18/2019
Last Updated

Explanation

This patient has **cataracts**, an opacification of the lens of the eye that can lead to blindness, likely a result of long-standing **hyperglycemia** due to poorly controlled diabetes mellitus. Certain cells (eg, retinal, endothelial, lens, renal mesangial, Schwann) are more vulnerable to hyperglycemia-

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2/6/2019

This patient has **cataracts**, an opacification of the lens of the eye that can lead to blindness, likely a result of long-standing **hyperglycemia** due to poorly controlled diabetes mellitus. Certain cells (eg, retinal, endothelial, lens, renal mesangial, Schwann) are more vulnerable to hyperglycemia-induced damage because they are unable to regulate glucose transport when circulating levels are high.

Multiple metabolic pathways are involved in the pathogenesis of hyperglycemia-induced tissue damage:

- **Advanced glycosylation end-products (AGEs):** Glucose can nonenzymatically attach to proteins and lipids, forming reversible glycosylation products that slowly stabilize into irreversible products. Under hyperglycemic conditions, AGEs accumulate and facilitate deposition of LDL in blood vessel walls and inflammatory cell invasion that causes atherosclerosis and microangiopathic complications. High glucose levels in the aqueous humor may also induce nonenzymatic glycation of lens proteins, which contributes to cataract formation.
- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

(Choices A and B) Aldose reductase also catalyzes the conversion of galactose (obtained from dietary lactose) to galactitol, but sorbitol dehydrogenase is incapable of oxidizing galactitol to its corresponding keto sugar (tagatose, a food sweetener). In galactosemia (galactose 1-phosphate uridyltransferase deficiency), excess galactitol is produced, which causes cataracts in newborns.

(Choice D) In the hexose monophosphate shunt, glucose-6-phosphate is converted to 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase (G6PD), generating the reducing equivalent NADPH. G6PD deficiency results in hemolytic anemia during times of increased oxidative stress.

(Choice E) Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate under anaerobic conditions. Excess lactate forms in hypoxic states, causing metabolic acidosis.

- **Polyol pathway overactivity:** The enzyme aldose reductase converts **glucose to sorbitol**, which is then oxidized to fructose by the enzyme sorbitol dehydrogenase. With hyperglycemia, formation of sorbitol occurs faster than its metabolism to fructose, resulting in its accumulation. Sorbitol increases the osmotic pressure in tissues and stimulates the influx of water, leading to **osmotic cellular injury**. In addition, **oxidative stress** resulting from the depletion of NADPH (aldose reductase consumes NADPH) also contributes to cataract formation and other diabetic complications such as retinopathy, peripheral neuropathy, and nephropathy.

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(Choice D) In the hexose monophosphate shunt, glucose-6-phosphate is converted to 6-phosphogluconolactone by the enzyme glucose-6-phosphate dehydrogenase (G6PD), generating the reducing equivalent NADPH. G6PD deficiency results in hemolytic anemia during times of increased oxidative stress.

(Choice E) Lactate dehydrogenase catalyzes the conversion of pyruvate to lactate under anaerobic conditions. Excess lactate forms in hypoxic states, causing metabolic acidosis.

Educational objective:
In hyperglycemic states, aldose reductase converts glucose to sorbitol at a rate faster than sorbitol can be metabolized. Sorbitol accumulates in certain cells such as lens cells, causing an influx of water and resulting in osmotic cellular injury. Depletion of NADPH by aldose reductase also increases oxidative stress, which accelerates development of cataracts and diabetic microvascular complications (eg, neuropathy, retinopathy).

References

- The pathobiology of diabetic complications: a unifying mechanism.

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Item 32 of 40
Question Id: 1385

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A group of investigators is researching the changes in oxygen-hemoglobin binding that occur under various clinical conditions. They are especially interested in situations that alter the shape and position of the oxygen-hemoglobin dissociation curve. Which of the following processes would most likely cause a shift from the blue curve to the red curve in the graph below?

A. Chronic high-altitude adaptation
B. Hypothermia
C. Hypoventilation
D. Severe anemia
E. Strenuous exercise

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Item 32 of 40
Question Id: 1385

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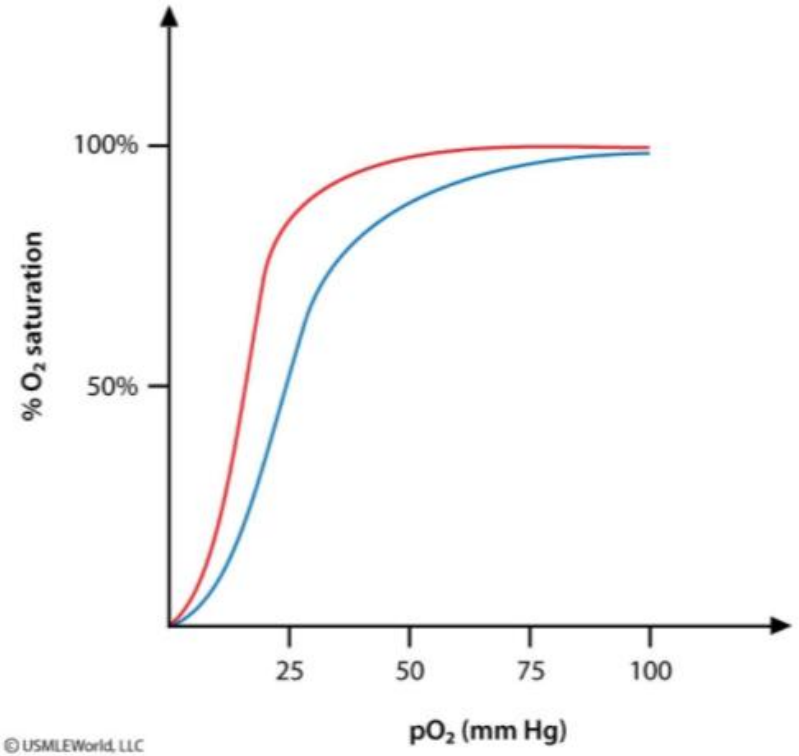

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Item 32 of 40
Question Id: 1385

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A group of investigators is researching the changes in oxygen-hemoglobin binding that occur under various clinical conditions. They are especially interested in situations that alter the shape and position of the oxygen-hemoglobin dissociation curve. Which of the following processes would most likely cause a shift from the blue curve to the red curve in the graph below?

A. Chronic high-altitude adaptation
B. Hypothermia
C. Hypoventilation
D. Severe anemia
E. Strenuous exercise

Submit

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Item 32 of 40
Question Id: 1385

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A group of investigators is researching the changes in oxygen-hemoglobin binding that occur under various clinical conditions. They are especially interested in situations that alter the shape and position of the oxygen-hemoglobin dissociation curve. Which of the following processes would most likely cause a shift from the blue curve to the red curve in the graph below?

- A. Chronic high-altitude adaptation [19%]
- ✔ B. Hypothermia [64%]
- C. Hypoventilation [4%]
- D. Severe anemia [4%]
- E. Strenuous exercise [6%]

Omitted
Correct answer
B

64%
Answered correctly

3 Seconds
Time Spent

10/21/2018
Last Updated

Explanation

The oxygen-hemoglobin dissociation curve describes the relationship between the partial pressure of oxygen (x-axis) and the hemoglobin oxygen saturation (y-axis). Oxygen saturation increases in a sigmoidal fashion as the pO_2 increases because of the increase in oxygen-binding affinity that occurs after the first oxygen molecule binds to hemoglobin. As more oxygen molecules bind to hemoglobin, the number of available binding sites decreases and the curve eventually flattens out.

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2/6/2019

The oxygen-hemoglobin dissociation curve describes the relationship between the partial pressure of oxygen (x-axis) and the hemoglobin oxygen saturation (y-axis). Oxygen saturation increases in a sigmoidal fashion as the pO_2 increases because of the increase in oxygen-binding affinity that occurs after the first oxygen molecule binds to hemoglobin. As more oxygen molecules bind to hemoglobin, the number of available binding sites decreases and the curve eventually flattens out.

The partial pressure of oxygen in the blood at which hemoglobin is 50% saturated is known as the P_{50} (dotted black line in diagram above); this value is a standard measure of hemoglobin's affinity for oxygen and is about 26 mm Hg in normal individuals. A leftward shift of the oxygen-hemoglobin dissociation curve occurs when hemoglobin has increased affinity for oxygen (ie, a lower P_{50}). Because decreased temperatures help to stabilize the bonds between oxygen and hemoglobin, hypothermia increases hemoglobin's oxygen affinity and shifts the dissociation curve to the left.

(Choice A) 2,3-bisphosphoglycerate (2,3-BPG) is an organophosphate created in erythrocytes during glycolysis. The production of 2,3-BPG is increased when oxygen availability is reduced, as occurs in chronic lung disease, heart failure, and chronic exposure to high altitudes. Elevated levels of 2,3-BPG decrease hemoglobin O_2 affinity, allowing the release of more O_2 in the peripheral tissues.

(Choices C and D) Anemia severe enough to cause lactic acidosis will result in lower blood pH, shifting the hemoglobin curve to the right. Similarly, hypoventilation causes increased CO_2 retention and respiratory acidosis that shifts the curve to the right.

(Choice E) Strenuous exercise will cause increased tissue oxidative phosphorylation, increased tissue CO_2 levels, and decreased tissue pH. This results in a shift of the dissociation curve to the right and decreased hemoglobin O_2 affinity.

Educational objective:
A left shift of the hemoglobin oxygen dissociation curve indicates increased hemoglobin O_2 affinity and can be caused by increased pH, decreased 2,3-bisphosphoglycerate, and decreased temperature. A leftward shift of the oxygen-dissociation curve means that O_2 is relatively less available to tissues.

Settings

Item 33 of 40
Question Id: 1475

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A 56-year-old man comes to the office due to difficulty swallowing for the past several months. He has the most trouble with solid foods and says, "They seem to get stuck in my throat if I don't chew a lot." The patient has no chest pain or heartburn and has lost 4.5 kg (10 lb) in the last 3 months. He has been an avid hunter for many years and frequently cures the meat he eats with sodium nitrite. Physical examination is unremarkable. Endoscopy shows an ulcerated mass in the distal third of the esophagus, and biopsy samples are obtained from the mass and adjacent normal mucosa. Analysis of the samples shows accelerated cytosine deamination of chromosomal DNA in both normal and malignant epithelial cells. This damage is most likely to be repaired through which of the following enzymatic sequences?

A. Endonuclease, polymerase, glycosylase, lyase, ligase
B. Endonuclease, polymerase, lyase, glycosylase, ligase
C. Glycosylase, endonuclease, lyase, polymerase, ligase
D. Glycosylase, ligase, lyase, endonuclease, polymerase
E. Lyase, endonuclease, glycosylase, polymerase, ligase

Submit

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Item 33 of 40
Question Id: 1475

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A 56-year-old man comes to the office due to difficulty swallowing for the past several months. He has the most trouble with solid foods and says, "They seem to get stuck in my throat if I don't chew a lot." The patient has no chest pain or heartburn and has lost 4.5 kg (10 lb) in the last 3 months. He has been an avid hunter for many years and frequently cures the meat he eats with sodium nitrite. Physical examination is unremarkable. Endoscopy shows an ulcerated mass in the distal third of the esophagus, and biopsy samples are obtained from the mass and adjacent normal mucosa. Analysis of the samples shows accelerated cytosine deamination of chromosomal DNA in both normal and malignant epithelial cells. This damage is most likely to be repaired through which of the following enzymatic sequences?

- A. Endonuclease, polymerase, glycosylase, lyase, ligase [15%]
- B. Endonuclease, polymerase, lyase, glycosylase, ligase [23%]
- ✔ C. Glycosylase, endonuclease, lyase, polymerase, ligase [44%]
- D. Glycosylase, ligase, lyase, endonuclease, polymerase [1%]
- E. Lyase, endonuclease, glycosylase, polymerase, ligase [14%]

Omitted
Correct answer
C

44%
Answered correctly

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Time Spent

09/14/2018
Last Updated

Explanation

Base excision repair is responsible for repairing various non-bulky DNA base alterations, including depurination, alkylation, oxidation, and

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2/6/2019

C

Explanation

Base excision repair is responsible for repairing various non-bulky DNA base alterations, including depurination, alkylation, oxidation, and deamination. Excessive consumption of **dietary nitrites** can promote the deamination of cytosine, adenine, and guanine to form uracil, hypoxanthine, and xanthine, respectively. If these abnormal bases are not removed and replaced with the correct base, DNA mutations and **carcinogenesis** may result.

Base excision repair (not to be confused with nucleotide excision repair or mismatch repair) begins with recognition of abnormal bases by specific **glycosylases**. These cleave the altered DNA bases from the parent DNA molecule, leaving an empty sugar-phosphate site called an apurinic/apyrimidinic site (AP). An **endonuclease** then cleaves the 5' end of the AP site before a **lyase** (or phosphodiesterase) enzyme subsequently completes extraction of the AP site from the DNA molecule by removing the remaining sugar-phosphate group. **DNA polymerase** then fills the gap with the correct sugar-phosphate base, and the final nick is sealed by **ligase**.

Educational objective:
Base excision repair is used to correct single-base DNA defects induced spontaneously or by exogenous chemicals. In this process, glycosylases remove the defective base, and the corresponding empty sugar-phosphate site is cleaved and removed by the action of endonuclease and lyase. DNA polymerase then replaces the missing nucleotide, and ligase seals the final remaining nick.

References

- Overview of base excision repair biochemistry.

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A 64-year-old man comes to the emergency department due to severe abdominal pain, nausea, and vomiting. He has a history of hypertension, myocardial infarction, and systolic heart failure. His blood pressure is 100/60 mm Hg, pulse is 116/min and irregular, and respirations are 24/min. Examination shows a soft, mildly distended, and tender abdomen. Laboratory results are as follows:

Serum chemistry

Sodium	136 mEq/L
Chloride	96 mEq/L
Bicarbonate	12 mEq/L

Arterial blood gases

pH	7.20	
$PaCO_2$	26 mm Hg	
Lactic acid	6.2 mmol/L	(normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

A. Enolase
B. Lactate dehydrogenase
C. Pyruvate carboxylase

Chloride	96 mEq/L
Bicarbonate	12 mEq/L

Arterial blood gases

pH	7.20
$PaCO_2$	26 mm Hg

Lactic acid 6.2 mmol/L (normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

- A. Enolase
- B. Lactate dehydrogenase
- C. Pyruvate carboxylase
- D. Pyruvate dehydrogenase
- E. Pyruvate kinase

Submit

Chloride	96 mEq/L
Bicarbonate	12 mEq/L

Arterial blood gases

pH	7.20
$PaCO_2$	26 mm Hg

Lactic acid 6.2 mmol/L (normal: 0.5-2.2 mmol/L)

CT scan of the abdomen reveals distal ileal wall thickening and lack of enhancement with intravenous contrast. Decreased activity of which of the following enzymes best explains the acid-base disorder in this patient?

- A. Enolase [1%]
- B. Lactate dehydrogenase [25%]
- C. Pyruvate carboxylase [8%]
- ✔ D. Pyruvate dehydrogenase [57%]
- E. Pyruvate kinase [7%]

Omitted
Correct answer

57%
Answered correctly

6 Seconds
Time Spent

08/24/2018
Last Updated

Explanation

This patient has **acute mesenteric ischemia**, with inadequate delivery of oxygen to intestinal tissues. During glycolysis, the concentration of oxygen in the tissues affects the metabolic fate of pyruvate. In the presence of oxygen, pyruvate is preferentially converted to acetyl coenzyme A by pyruvate dehydrogenase in the mitochondrial matrix. Acetyl coenzyme A then undergoes oxidation in the citric acid (TCA) cycle. However, under **hypoxic conditions**, intracellular accumulation of NADH **inhibits pyruvate dehydrogenase**. As a result, increased amounts of **pyruvate** are converted to **lactate** by lactate dehydrogenase **(Choice B)**, which regenerates NAD^+ from NADH (allowing for limited ATP production via anaerobic glycolysis). With significant tissue ischemia, lactate begins to accumulate in the circulation and can lead to **lactic acidosis**. Patients with lactic (or other metabolic) acidosis will typically hyperventilate to eliminate CO_2 and induce a compensatory respiratory alkalosis.

(Choices A and E) 2-phosphoglycerate is converted to phosphoenolpyruvate by the enzyme enolase. Phosphoenolpyruvate is subsequently metabolized to pyruvate by pyruvate kinase. These reactions are performed under both aerobic and anaerobic conditions.

(Choice C) Pyruvate can also be converted to oxaloacetate by pyruvate carboxylase. This enzyme is involved in regeneration of glucose from pyruvate by the process of gluconeogenesis.

Educational objective:
In the presence of oxygen, pyruvate produced during glycolysis is converted by pyruvate dehydrogenase to acetyl coenzyme A, which is subsequently metabolized by oxidative phosphorylation. However, if inadequate oxygen is present in the tissues, pyruvate is converted to lactate by lactate dehydrogenase, leading to lactic acidosis.

References

- Clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department.

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Item 35 of 40
Question Id: 1369

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As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

- A. α-Ketoglutarate
- B. L-citrulline
- C. Malate
- D. Citrate
- E. Oxaloacetate

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Item 35 of 40
Question Id: 1369

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As part of an experiment, healthy volunteers undergo a 12-hour fast and then drink a solution containing radiolabeled alanine. Consecutive blood samples are drawn every 15 minutes for the next 3 hours. Initial blood samples detect the radiolabeled alanine, but analysis of later samples shows that the radiotracer is present in blood primarily in the form of glucose. Before alanine can be converted to glucose, its amino group is transferred to which of the following?

- A. α-Ketoglutarate [61%]
- B. L-citrulline [5%]
- C. Malate [7%]
- D. Citrate [5%]
- E. Oxaloacetate [19%]

Omitted
Correct answer
A

61%
Answered correctly

3 Seconds
Time Spent

08/17/2018
Last Updated

Explanation

Alanine and glutamine play an important role in transporting nitrogen throughout the body. Glutamine is produced by most body tissues and is catabolized primarily by the gut and kidney for maintenance of cellular metabolism and acid-base regulation, respectively. A significant portion of the glutamine used by these tissues is converted to alanine and released into the circulation. Alanine is also released by skeletal muscle tissue

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Explanation

Alanine and glutamine play an important role in transporting nitrogen throughout the body. Glutamine is produced by most body tissues and is catabolized primarily by the gut and kidney for maintenance of cellular metabolism and acid-base regulation, respectively. A significant portion of the glutamine used by these tissues is converted to alanine and released into the circulation. Alanine is also released by skeletal muscle tissue during protein catabolism as part of the **glucose-alanine cycle** that helps remove excess nitrogen. Alanine is then transported to the liver, where it serves as a vehicle for nitrogen disposal and as a source of carbon skeletons for gluconeogenesis.

In the liver, alanine is transaminated by alanine aminotransferase to pyruvate with the amino group being transferred to α-ketoglutarate to form glutamate. Almost all aminotransferase enzymes use α-ketoglutarate as the amino group acceptor. Thus, amino groups are funneled into glutamate during protein catabolism. Glutamate is further metabolized by the enzyme glutamate dehydrogenase, which liberates free ammonia and regenerates α-ketoglutarate. Ammonia then enters the urea cycle to form urea, the primary disposal form of nitrogen in humans. Urea subsequently enters the blood and is excreted in the urine.

(Choices C, D, and E) Malate, citrate, and oxaloacetate are all intermediates of the tricarboxylic acid cycle.

(Choice B) L-citrulline is an amino acid produced as an intermediate in the conversion of ornithine to argininosuccinate during the hepatic urea cycle.

Educational objective:
Alanine is the major amino acid responsible for transferring nitrogen to the liver for disposal. During the catabolism of proteins, amino groups are transferred to α-ketoglutarate to form glutamate. Glutamate is then processed in the liver to form urea, the primary disposal form of nitrogen in humans. Free ammonia is also excreted into the urine by the kidney for regulation of acid-base status.

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Question Id: 1369

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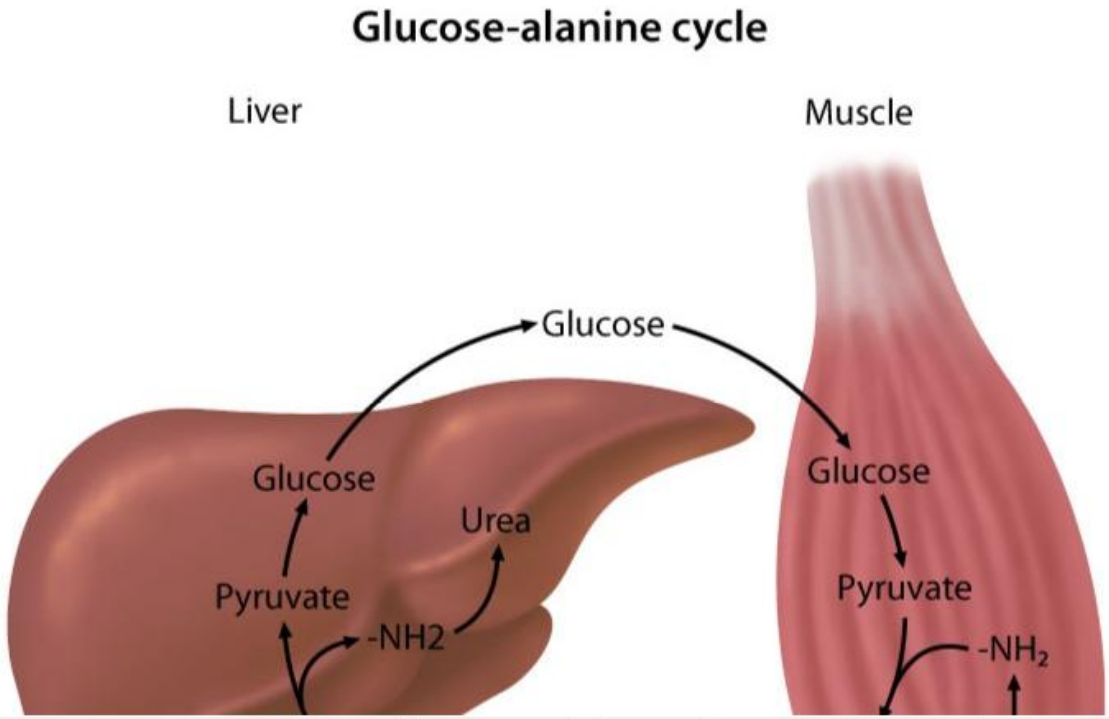

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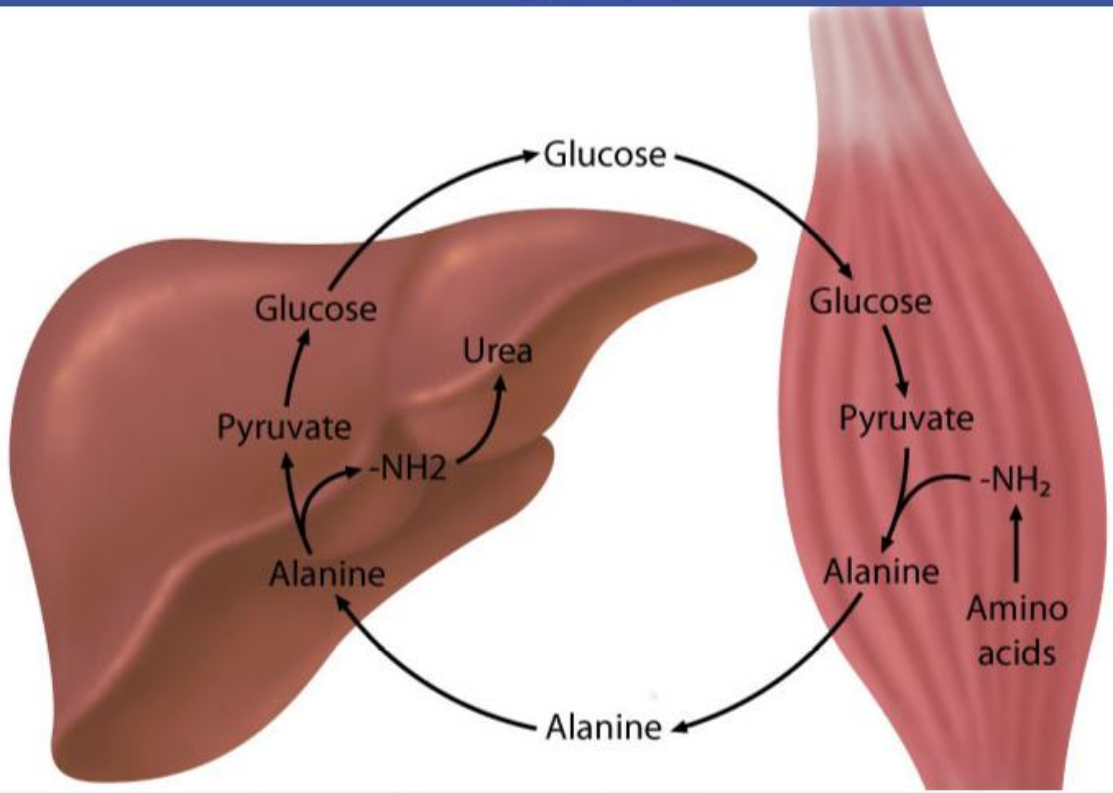
Exhibit Display



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Item 36 of 40
Question Id: 1500

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A 5-month-old boy is brought to the office by his parents who are concerned that he has developmental delay. He has 3 older siblings, and the parents report that his siblings were much more active and interactive at the boy's age. The family has just moved to the United States from South America and did not have consistent primary care previously. Physical examination shows that the boy is unable to roll from front to back or back to front and does not seem to recognize his parents. Comprehensive laboratory evaluation reveals impaired tetrahydrobiopterin synthesis. Which of the following is most likely deficient in this patient?

A. Acetylcholine
B. Gamma-aminobutyric acid
C. Glutamate
D. Phenylalanine
E. Serotonin

Submit

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2/6/2019

Settings

Item 36 of 40
Question Id: 1500

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 5-month-old boy is brought to the office by his parents who are concerned that he has developmental delay. He has 3 older siblings, and the parents report that his siblings were much more active and interactive at the boy's age. The family has just moved to the United States from South America and did not have consistent primary care previously. Physical examination shows that the boy is unable to roll from front to back or back to front and does not seem to recognize his parents. Comprehensive laboratory evaluation reveals impaired tetrahydrobiopterin synthesis. Which of the following is most likely deficient in this patient?

- A. Acetylcholine [6%]
- B. Gamma-aminobutyric acid [10%]
- C. Glutamate [14%]
- D. Phenylalanine [30%]
- ✔ E. Serotonin [37%]

Omitted
Correct answer
E

37%
Answered correctly

3 Seconds
Time Spent

09/12/2018
Last Updated

Explanation

Tetrahydrobiopterin (BH_4) is a cofactor in the synthesis of serotonin (a major neurotransmitter), tyrosine (a precursor of DOPA), and DOPA (the antecedent of the neurotransmitters dopamine, norepinephrine and epinephrine). Dihydropteridine reductase enzymatically reduces

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Explanation

Tetrahydrobiopterin (BH_4) is a cofactor in the synthesis of serotonin (a major neurotransmitter), tyrosine (a precursor of DOPA), and DOPA (the antecedent of the neurotransmitters dopamine, norepinephrine and epinephrine). Dihydropteridine reductase enzymatically reduces dihydrobiopterin (BH_2) to tetrahydrobiopterin (BH_4). Serotonin (5-hydroxytryptamine, or 5HT) is formed through hydroxylation and decarboxylation of the amino acid tryptophan.

Most cases of **phenylketonuria** are due to phenylalanine hydroxylase deficiency. Less commonly, the etiology is due to **BH_4 deficiency** secondary to **dihydropteridine reductase deficiency**. The consequences of defective phenylalanine and tryptophan metabolism are phenylalanine accumulation **(Choice D)** and **low levels of serotonin and other neurotransmitters**, respectively.

The combination of high phenylalanine levels, which may disrupt neuronal and glial development, and low serotonin and other neurotransmitters results in progressive **neurologic deterioration** in untreated patients. Manifestations include developmental delay, hypotonia, dystonia, and seizures. Treatment includes both a **low phenylalanine diet** and **BH_4 supplementation**.

(Choice A) Acetylcholine is a neuromuscular junction neurotransmitter synthesized from choline and acetyl-CoA by choline acetyltransferase. In myasthenia gravis, production of antibodies against acetylcholine receptors leads to muscle weakness.

(Choice B) Gamma-aminobutyric acid (GABA) is an inhibitor of presynaptic transmission in the central nervous system that is formed by glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase. Phenobarbital, an antiepileptic medication, potentiates GABA activity to decrease or cease seizure activity.

(Choice C) Glutamate is an excitatory neurotransmitter that is synthesized from glutamine by the enzyme glutaminase. Ketamine is an N-methyl-D-aspartate (NMDA) receptor noncompetitive antagonist that blocks glutamate, which can result in anesthesia, sedation, and memory loss.

Educational objective:
Tetrahydrobiopterin (BH_4) is a cofactor used by hydroxylase enzymes in the synthesis of tyrosine, dopamine, and serotonin. Phenylketonuria can result from BH_4 deficiency due to dihydropteridine reductase deficiency. Intellectual disability is the hallmark of this condition and results in neurotransmitter (eg, serotonin) deficiency and hyperphenylalanemia. Treatment involves a low phenylalanine diet and BH_4 supplementation.

phenylalanine accumulation **(Choice D)** and **low levels of serotonin and other neurotransmitters**, respectively.

The combination of high phenylalanine levels, which may disrupt neuronal and glial development, and low serotonin and other neurotransmitters results in progressive **neurologic deterioration** in untreated patients. Manifestations include developmental delay, hypotonia, dystonia, and seizures. Treatment includes both a **low phenylalanine diet** and **BH_4 supplementation**.

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(Choice B) Gamma-aminobutyric acid (GABA) is an inhibitor of presynaptic transmission in the central nervous system that is formed by glutamate decarboxylation, a reaction catalyzed by glutamate decarboxylase. Phenobarbital, an antiepileptic medication, potentiates GABA activity to decrease or cease seizure activity.

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Educational objective:
Tetrahydrobiopterin (BH_4) is a cofactor used by hydroxylase enzymes in the synthesis of tyrosine, dopamine, and serotonin. Phenylketonuria can result from BH_4 deficiency due to dihydropteridine reductase deficiency. Intellectual disability is the hallmark of this condition and results in neurotransmitter (eg, serotonin) deficiency and hyperphenylalanemia. Treatment involves a low phenylalanine diet and BH_4 supplementation.

References

- Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies.
- Disorders of Tetrahydrobiopterin Metabolism and their Treatment

Settings

Item 37 of 40
Question Id: 1419

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the emergency department due to profound fevers and malaise. After initial evaluation, she is hospitalized for septicemia. Blood cultures plated on lactose-containing media grow rapidly dividing gram-negative bacteria. Replication of these microbial cells requires synthesis of two daughter strands of DNA using the parent strands as templates. Which of the following processes will differ the most between the 2 daughter strands formed at each replication fork?

A. Enzymatic function of DNA helicase
B. Interaction with single-stranded DNA-binding proteins
C. Joining of DNA fragments by ligase
D. Proofreading of the newly synthesized DNA
E. Relief of supercoils by topoisomerase

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Settings

Item 37 of 40
Question Id: 1419

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 65-year-old woman with chronic obstructive pulmonary disease and type II diabetes mellitus comes to the emergency department due to profound fevers and malaise. After initial evaluation, she is hospitalized for septicemia. Blood cultures plated on lactose-containing media grow rapidly dividing gram-negative bacteria. Replication of these microbial cells requires synthesis of two daughter strands of DNA using the parent strands as templates. Which of the following processes will differ the most between the 2 daughter strands formed at each replication fork?

- A. Enzymatic function of DNA helicase [2%]
- B. Interaction with single-stranded DNA-binding proteins [8%]
- ✔ C. Joining of DNA fragments by ligase [65%]
- D. Proofreading of the newly synthesized DNA [19%]
- E. Relief of supercoils by topoisomerase [3%]

Omitted
Correct answer
C

65%
Answered correctly

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08/18/2018
Last Updated

Explanation

DNA replication is similar in prokaryotes and eukaryotes, with DNA polymerases I and III being the main polymerase enzymes involved in prokaryotic DNA replication. For DNA replication to begin, DNA helicase must first unwind the DNA double helix and separate the parent strands **(Choice A)**. The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA-binding proteins to prevent spontaneous

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DNA replication is similar in prokaryotes and eukaryotes, with DNA polymerases I and III being the main polymerase enzymes involved in prokaryotic DNA replication. For DNA replication to begin, DNA helicase must first unwind the DNA double helix and separate the parent strands **(Choice A)**. The unwound single-stranded DNA is stabilized by the binding of single-stranded DNA-binding proteins to prevent spontaneous reannealing **(Choice B)**.

Synthesis of the daughter strands occurs simultaneously from both parent strands. Because **DNA synthesis can occur only in the 5'→3' direction**, one daughter strand is synthesized continuously toward the replication fork (leading strand). However, the other strand must be synthesized **discontinuously** in a direction away from the replication fork (lagging strand), with more and more segments being added as the replication fork moves across the DNA double helix. This results in the formation of **Okazaki fragments**, short stretches of newly synthesized DNA that are separated by RNA primers. These primers are removed and replaced with DNA, and the Okazaki fragments are subsequently joined together by DNA ligase. Because of the discontinuous nature of DNA synthesis on the lagging strand, **DNA ligase** acts many more times on the lagging strand than on the leading strand.

(Choice D) DNA polymerases I and III have proofreading ability (ie, 3'→5' exonuclease activity), and the proofreading function of these polymerases is not restricted to either the leading or lagging strand.

(Choice E) Topoisomerase II produces negative supercoiling in the DNA helix ahead of the replication fork to reduce the strain produced by unwinding, which causes positive supercoiling.

Educational objective:
DNA replication occurs in the 5'→3' direction on both strands. In contrast to the continuous synthesis of the leading strand, lagging strand synthesis occurs discontinuously and is composed of short stretches of RNA primer plus newly synthesized DNA segments (Okazaki fragments). As a result, lagging strand synthesis requires the repetitive action of DNA primase and DNA ligase.

References

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Item 38 of 40
Question Id: 1455

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A 54-year-old man with a history of chronic kidney disease due to hypertension develops anemia. Evaluation reveals that the cause of anemia is erythropoietin deficiency. Erythropoietin increases the numbers of erythroid precursor cells in the bone marrow and induces heme production in erythrocyte precursors. In this patient, mature erythrocytes are found that are unable to synthesize heme even though they contain detectable levels of cytoplasmic enzymes involved in heme synthesis. Lack of which of the following cellular organelles best explains this phenomenon?

- A. Endoplasmic reticulum
- B. Golgi apparatus
- C. Mitochondria
- D. Nucleus
- E. Peroxisomes
- F. Proteasomes

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Item 38 of 40
Question Id: 1455

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 54-year-old man with a history of chronic kidney disease due to hypertension develops anemia. Evaluation reveals that the cause of anemia is erythropoietin deficiency. Erythropoietin increases the numbers of erythroid precursor cells in the bone marrow and induces heme production in erythrocyte precursors. In this patient, mature erythrocytes are found that are unable to synthesize heme even though they contain detectable levels of cytoplasmic enzymes involved in heme synthesis. Lack of which of the following cellular organelles best explains this phenomenon?

- A. Endoplasmic reticulum [14%]
- B. Golgi apparatus [5%]
- ✔ C. Mitochondria [64%]
- D. Nucleus [10%]
- E. Peroxisomes [3%]
- F. Proteasomes [1%]

Omitted
Correct answer
C

64%
Answered correctly

3 Seconds
Time Spent

09/07/2018
Last Updated

Explanation

Heme synthesis occurs partly in the mitochondria and partly in the cytoplasm of erythrocytes. **Mitochondria** are necessary for the first and the final 3 steps. Erythrocyte precursors divide a number of times before finally losing their nuclei and mitochondria and forming mature red blood

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Omitted
Correct answer
C

64%
Answered correctly

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09/07/2018
Last Updated

Explanation

Heme synthesis occurs partly in the mitochondria and partly in the cytoplasm of erythrocytes. **Mitochondria** are necessary for the first and the final 3 steps. Erythrocyte precursors divide a number of times before finally losing their nuclei and mitochondria and forming mature red blood cells that survive for about 120 days (4 months). When erythrocytes lose their mitochondria, they lose the ability to generate heme and therefore hemoglobin.

Heme is synthesized in virtually every organ, but the principal sites of synthesis are erythrocyte precursor cells (located in the bone marrow) and hepatocytes (use heme in microsomal cytochrome P450 system).

(Choices A, B, and D) Although mature erythrocytes do not contain a nucleus, a Golgi apparatus, or an endoplasmic reticulum, their cytoplasm still contains residual amounts of the enzymes necessary for heme synthesis. Therefore, the lack of mitochondria (and their associated heme biosynthetic enzymes) is a better explanation for the lack of heme synthesis.

(Choices E and F) Proteasomes are involved in protein recycling and peroxisomes are involved in fatty acid catabolism. These organelles typically disappear during erythrocyte development.

Educational objective:
Maturing erythrocytes lose their ability to synthesize heme when they lose their mitochondria, which are necessary for the first and final 3 steps of heme synthesis.

Settings

Item 39 of 40
Question Id: 1022

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A 43-year-old man prospecting for gold in Arizona becomes stuck in the desert after his truck breaks down. He brought a large supply of water with him but only a few granola bars as food. After 3 days, he is able to flag down a passing vehicle and obtain transportation to the nearest settlement. During this ordeal, his liver begins to synthesize large quantities of glucose from source molecules such as alanine, lactate, and glycerol. As part of this process, phosphoenolpyruvate is formed from oxaloacetate in a reaction that requires a specific nucleoside triphosphate as a cofactor. Which of the following reactions directly synthesizes this cofactor?

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F
- G. G
- H. H

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Item 39 of 40
Question Id: 1022

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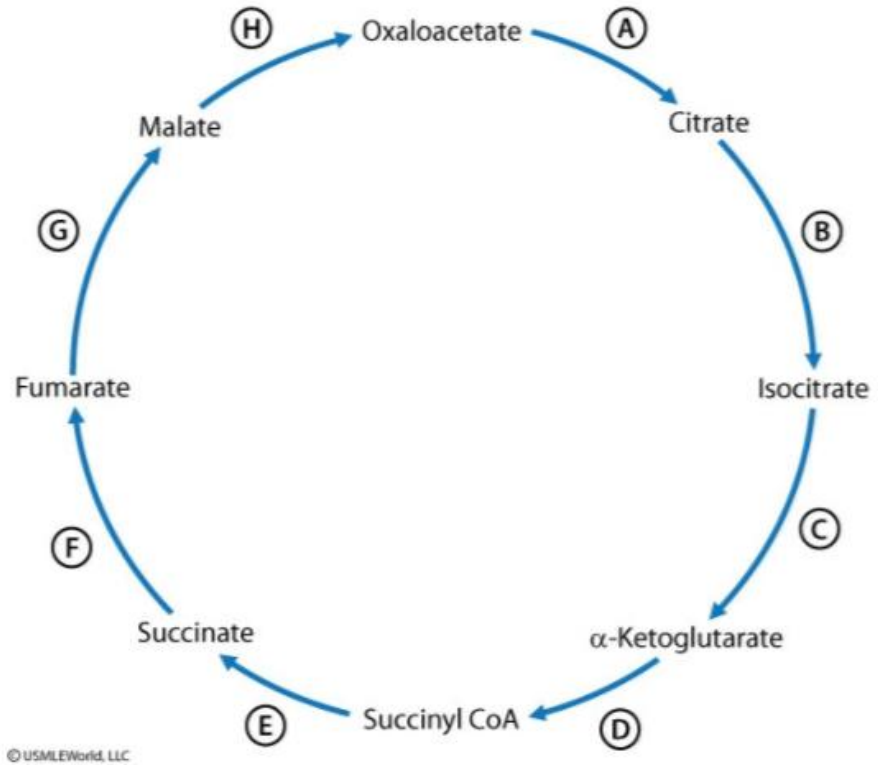

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Settings

Item 39 of 40
Question Id: 1022

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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- A. A
- B. B
- C. C
- D. D
- E. E
- F. F
- G. G
- H. H

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Settings

Item 39 of 40
Question Id: 1022

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A 43-year-old man prospecting for gold in Arizona becomes stuck in the desert after his truck breaks down. He brought a large supply of water with him but only a few granola bars as food. After 3 days, he is able to flag down a passing vehicle and obtain transportation to the nearest settlement. During this ordeal, his liver begins to synthesize large quantities of glucose from source molecules such as alanine, lactate, and glycerol. As part of this process, phosphoenolpyruvate is formed from oxaloacetate in a reaction that requires a specific nucleoside triphosphate as a cofactor. Which of the following reactions directly synthesizes this cofactor?

- A. A [3%]
- B. B [3%]
- C. C [10%]
- D. D [20%]
- ✔ E. E [39%]
- F. F [11%]
- G. G [4%]
- H. H [5%]

Omitted
Correct answer
E

39%
Answered correctly

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Time Spent

11/08/2018
Last Updated

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2/6/2019

H. H [5%]

Omitted
Correct answer
E

39%
Answered correctly

3 Seconds
Time Spent

11/08/2018
Last Updated

Explanation

The majority of ATP used for cellular processes is generated by the oxidation of acetate in the tricarboxylic acid (TCA) cycle. The enzymes of the TCA cycle are located in the mitochondria and generate reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide ($FADH_2$) **(Choices C, D, F, and H)**. These molecules drive the process of oxidative phosphorylation, which converts their reducing potential into high-energy ATP via the electron transport chain.

ATP can also be generated by **substrate-level phosphorylation**, which involves the direct transfer of a phosphate group from a reactive intermediate to a nucleotide diphosphate (eg, ADP, GDP). **Succinyl-CoA synthetase** converts succinyl-CoA to succinate and uses the high-energy thioester present in succinyl-CoA to drive **GTP synthesis**. This GTP can then be used to transphosphorylate ADP to ATP, or it may be utilized by specific GTP-hydrolyzing enzymes, such as **phosphoenolpyruvate carboxykinase** (converts oxaloacetate to phosphoenolpyruvate during gluconeogenesis).

Educational objective:
GTP is synthesized by succinyl-CoA synthetase during the conversion of succinyl-CoA to succinate in the citric acid cycle. During gluconeogenesis, phosphoenolpyruvate carboxykinase uses GTP to synthesize phosphoenolpyruvate from oxaloacetate.

Settings

Item 40 of 40
Question Id: 2066

Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

A 14-month-old boy is evaluated for failure to thrive and developmental delay. His mother reports that at 12 months he could barely lift his head and had difficulty sitting unsupported. The toddler has not started babbling or forming words. He is at the 10th percentile for height and 5th percentile for weight. Laboratory results are as follows:

Hemoglobin	8.6 g/dL
Mean corpuscular volume	114 fL
Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

A. Ascorbic acid
B. Folic acid
C. Guanine
D. Iron
E. Pyridoxine
F. Uridine

Submit

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Hemoglobin	8.6 g/dL
Mean corpuscular volume	114 fL
Reticulocytes	1%
Ammonia, plasma	42 µg/dL normal: 40-80 µg/dL

Urine specimens contain large amounts of orotic acid crystals. Supplementation with which of the following substances would most likely benefit this patient?

- A. Ascorbic acid [2%]
- B. Folic acid [26%]
- C. Guanine [5%]
- D. Iron [1%]
- E. Pyridoxine [23%]
- ✔ F. Uridine [40%]

Omitted

Settings

Item 40 of 40
Question Id: 2066

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Correct answer
F

40%
Answered correctly

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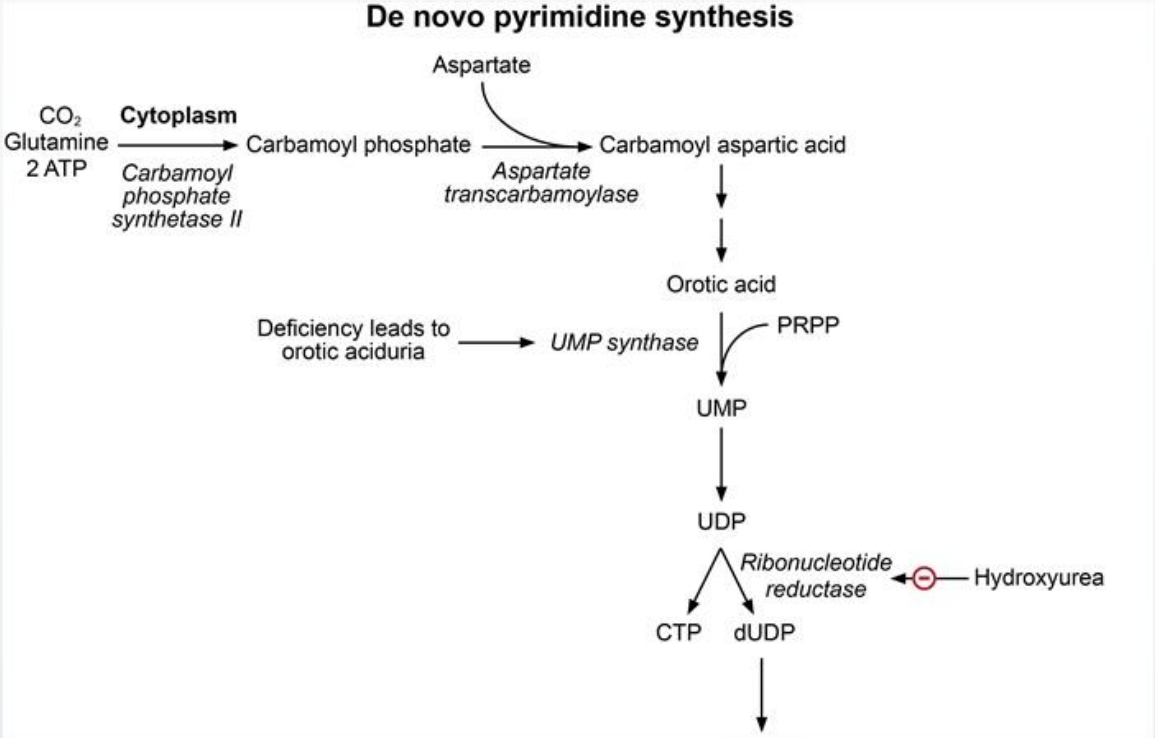
12/25/2018
Last Updated

Explanation



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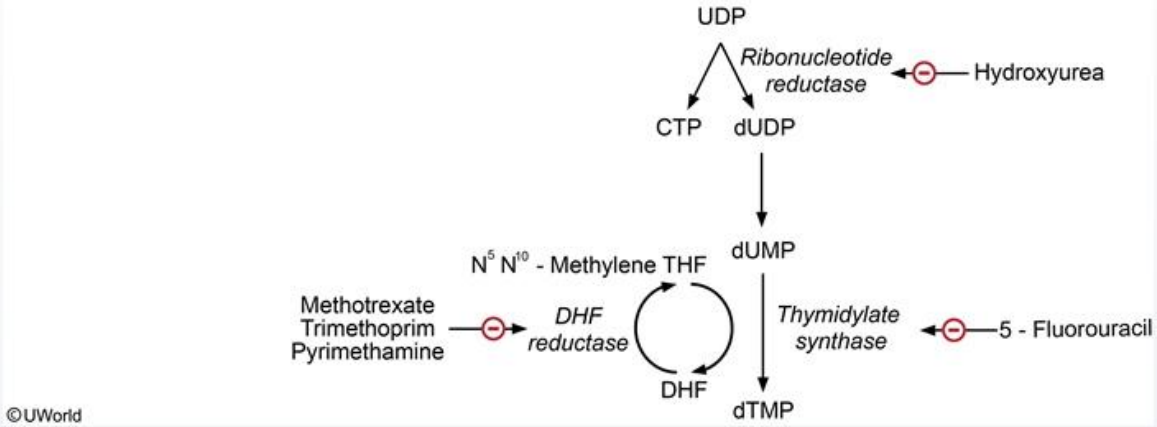

This patient likely has **hereditary orotic aciduria**, a rare autosomal recessive disorder of de novo pyrimidine synthesis that results in **physical and mental retardation** (eg, low height/weight, delayed developmental milestones), **megaloblastic anemia** (eg, elevated mean corpuscular volume, low reticulocyte count), and **elevated urinary orotic acid** levels. Increased urinary orotic acid may also be seen in ornithine transcarbamylase deficiency; however, patients with this condition classically have failure to thrive and hyperammonemic encephalopathy within the first few weeks of life (due to impaired urea synthesis).

Hereditary orotic aciduria occurs due to a **defect** in **uridine 5'-monophosphate (UMP) synthase**, a polypeptide containing 2 enzymatic domains (orotate phosphoribosyltransferase and OMP decarboxylase) that catalyze the final conversion of orotic acid to UMP. Impaired conversion of orotic acid to UMP results in the excretion of large amounts of orotic acid in the urine and the clinical features described above. **Uridine supplementation** can bypass this enzymatic defect and improve symptoms as uridine is converted to UMP via nucleoside kinases.

(Choice A) Ascorbic acid (vitamin C) is required for hydroxylation of proline and lysine residues in collagen synthesis; therefore, it plays an important role in connective tissue maintenance and wound healing.

(Choice B) Folate participates in single carbon transfer reactions, as in the de novo synthesis of purines and thymidine. Folate supplements will

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(Choice A) Ascorbic acid (vitamin C) is required for hydroxylation of proline and lysine residues in collagen synthesis; therefore, it plays an important role in connective tissue maintenance and wound healing.

(Choice B) Folate participates in single carbon transfer reactions, as in the de novo synthesis of purines and thymidine. Folate supplements will improve megaloblastic anemia resulting from folate deficiency but will not improve the anemia in orotic aciduria.

(Choice C) Guanine and adenine are purine bases present in DNA and RNA. Orotic aciduria is a defect in the synthesis of pyrimidine bases, so supplementation with purines would not affect orate synthesis.

(Choice D) Iron supplementation improves iron deficiency anemia, classically a microcytic hypochromic anemia.

(Choice E) Pyridoxine (vitamin B_6) supplementation is indicated during treatment with isoniazid. Pyridoxine is a cofactor in transamination, deamination, decarboxylation, and condensation reactions.

Educational objective:
Orotic aciduria is a rare autosomal recessive disorder of de novo pyrimidine synthesis that occurs due to a defect in uridine 5'-monophosphate (UMP) synthase. Children typically present with physical and mental retardation, megaloblastic anemia, and large amounts of urinary orotic acid. Uridine supplementation can improve symptoms as uridine is converted to UMP via nucleoside kinases.

References

- Orotic aciduria and uridine monophosphate synthase: a reappraisal.
- Inborn errors of pyrimidine metabolism: clinical update and therapy.

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