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Item 1 of 40
Question Id: 346

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

A 17-year-old girl comes to the office for follow-up on anemia. She has taken iron supplements regularly since being diagnosed with iron deficiency anemia 3 months ago. However, the patient still feels fatigued and does not think that the supplements have improved her symptoms. She has occasional gingival bleeding when brushing her teeth. Menses occur every 27-28 days and last 7-8 days with heavy flow, sometimes requiring her to change pads every hour. Platelet count is normal. Further evaluation reveals that the patient's platelets do not agglutinate appropriately in response to ristocetin. When normal plasma is added to the solution of patient platelets and ristocetin, appropriate platelet agglutination occurs. Which of the following is most likely deficient in this patient?

A. Glycoprotein Ib receptors
B. Glycoprotein IIb-IIIa receptors
C. Hageman factor
D. Thromboxane A2
E. Von Willebrand factor

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2/5/2019

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Item 1 of 40
Question Id: 346

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A 17-year-old girl comes to the office for follow-up on anemia. She has taken iron supplements regularly since being diagnosed with iron deficiency anemia 3 months ago. However, the patient still feels fatigued and does not think that the supplements have improved her symptoms. She has occasional gingival bleeding when brushing her teeth. Menses occur every 27-28 days and last 7-8 days with heavy flow, sometimes requiring her to change pads every hour. Platelet count is normal. Further evaluation reveals that the patient's platelets do not agglutinate appropriately in response to ristocetin. When normal plasma is added to the solution of patient platelets and ristocetin, appropriate platelet agglutination occurs. Which of the following is most likely deficient in this patient?

A. Glycoprotein Ib receptors [6%]
B. Glycoprotein IIb-IIIa receptors [13%]
C. Hageman factor [3%]
D. Thromboxane A2 [2%]
✔ E. Von Willebrand factor [73%]

Omitted
Correct answer
E

73%
Answered correctly

17 Seconds
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11/16/2018
Last Updated

Explanation

Platelet adhesion & activation via vWF

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Item 1 of 40
Question Id: 346

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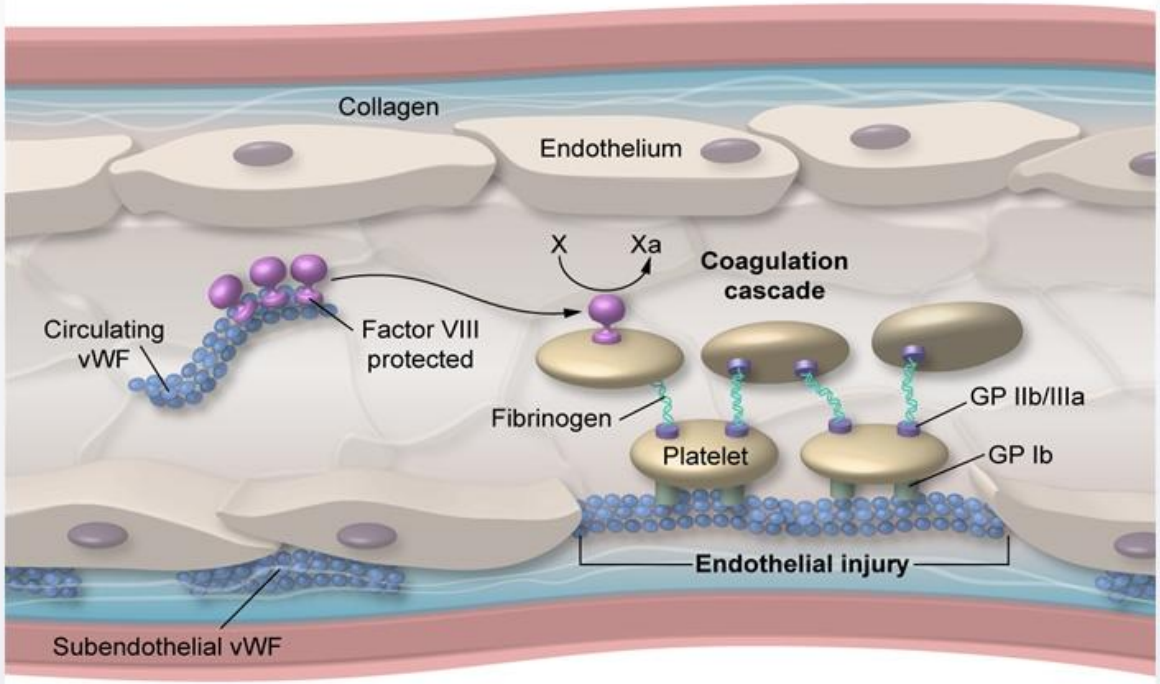
Platelet adhesion & activation via vWF



GP = glycoprotein; **vWF** = von Willebrand factor. ©UWorld

Von Willebrand factor (vWF) is an important hemostatic glycoprotein (GP) synthesized by endothelial cells and megakaryocytes. Following endothelial damage, vWF **binds GP Ib receptors** on the platelet membrane and mediates **platelet adhesion** to subendothelial collagen. Deficiency of vWF impairs platelet adhesion and can lead to easy bruising and **prolonged mucocutaneous bleeding** (eg, gingival bleeding,

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GP = glycoprotein; **vWF** = von Willebrand factor.

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Von Willebrand factor (vWF) is an important hemostatic glycoprotein (GP) synthesized by endothelial cells and megakaryocytes. Following endothelial damage, vWF **binds GP Ib receptors** on the platelet membrane and mediates **platelet adhesion** to subendothelial collagen. Deficiency of vWF impairs platelet adhesion and can lead to easy bruising and **prolonged mucocutaneous bleeding** (eg, gingival bleeding, heavy menses).

Laboratory workup in vWF deficiency reveals a normal platelet count and an **abnormal ristocetin cofactor assay**. The ristocetin cofactor assay measures in-vitro, vWF-dependent platelet agglutination (indicative of impaired platelet adhesion in-vivo). Ristocetin activates GP Ib receptors on platelets and makes them available for vWF binding; when the vWF level is decreased, there is **poor platelet agglutination in the presence of ristocetin**. When normal plasma that contains vWF is added, appropriate platelet agglutination occurs.

VWF also serves as a **carrier for factor VIII** to prolong its half-life, and vWF deficiency can lead to functional deficiency of factor VIII that further contributes to bleeding complications. PTT may be normal or prolonged depending on the degree of factor VIII impairment.

Combined oral contraceptives are often used for treatment of menorrhagia due to vWF deficiency. Patients can also be treated with desmopressin, which stimulates vWF release from endothelium.

(Choice A) Bernard-Soulier syndrome (hereditary deficiency of GP Ib receptors) is characterized by thrombocytopenia, enlarged platelets, and mucocutaneous bleeding. Platelet agglutination to ristocetin will be abnormal and, because the deficiency is with GP Ib receptors and not vWF, the addition of normal plasma will not correct the agglutination.

(Choice B) Hereditary deficiency of GP IIb/IIIa receptors occurs in Glanzmann thrombasthenia, which manifests with mucocutaneous bleeding. Platelet agglutination in response to ristocetin is normal because the levels of vWF and GP Ib receptors are normal.

(Choice C) Congenital deficiency of factor XII (Hageman) causes marked PTT prolongation; however, it does not cause clinical bleeding complications. Instead, patients may have a tendency for thromboembolic complications for unclear reasons.

(Choice D) Thromboxane A2 deficiency is associated with aspirin treatment due to irreversible inactivation of cyclooxygenase in platelets. The

contributes to bleeding complications. PTT may be normal or prolonged depending on the degree of factor VIII impairment.

Combined oral contraceptives are often used for treatment of menorrhagia due to vWF deficiency. Patients can also be treated with desmopressin, which stimulates vWF release from endothelium.

(Choice A) Bernard-Soulier syndrome (hereditary deficiency of GP Ib receptors) is characterized by thrombocytopenia, enlarged platelets, and mucocutaneous bleeding. Platelet agglutination to ristocetin will be abnormal and, because the deficiency is with GP Ib receptors and not vWF, the addition of normal plasma will not correct the agglutination.

(Choice B) Hereditary deficiency of GP IIb/IIIa receptors occurs in Glanzmann thrombasthenia, which manifests with mucocutaneous bleeding. Platelet agglutination in response to ristocetin is normal because the levels of vWF and GP Ib receptors are normal.

(Choice C) Congenital deficiency of factor XII (Hageman) causes marked PTT prolongation; however, it does not cause clinical bleeding complications. Instead, patients may have a tendency for thromboembolic complications for unclear reasons.

(Choice D) Thromboxane A2 deficiency is associated with aspirin treatment due to irreversible inactivation of cyclooxygenase in platelets. The major effect is on GP IIb/IIIa-mediated platelet aggregation rather than GP Ib-mediated platelet adhesion; therefore, platelet agglutination to ristocetin is normal.

Educational objective:
Following endothelial damage, von Willebrand factor (vWF) binds glycoprotein Ib receptors on platelets to mediate platelet adherence. The ristocetin cofactor assay measures platelet agglutination via binding of glycoprotein Ib receptors to vWF; it will be abnormal in vWF deficiency but will correct with the addition of normal (vWF-containing) plasma.

References

- Diagnosis and management of von Willebrand disease: guidelines for primary care.
- Of von Willebrand factor and platelets.

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Item 2 of 40
Question Id: 2037

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A series of experiments is being conducted to determine the structure and function of different types of bacterial RNA. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of 90 nucleotides is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

A. AUG
B. CCA
C. Methylguanosine triphosphate
D. Poly-A
E. TATA
F. UAG

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Item 2 of 40
Question Id: 2037

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

A series of experiments is being conducted to determine the structure and function of different types of bacterial RNA. Cultures of *Staphylococcus aureus* are exposed to chemicals that lyse the bacterial cells, and the RNA molecules are then extracted. A specific RNA consisting of 90 nucleotides is purified for further analysis. It is found to contain high amounts of chemically modified bases such as dihydrouridine, pseudouridine, and ribothymidine, and its secondary structure arises from base pairing within the chain. Which of the following is the most likely composition of the 3'-end of this molecule?

- A. AUG [5%]
- ✔ B. CCA [41%]
- C. Methylguanosine triphosphate [5%]
- D. Poly-A [30%]
- E. TATA [3%]
- F. UAG [12%]

Omitted
Correct answer
B

41%
Answered correctly

5 Seconds
Time Spent

08/17/2018
Last Updated

Explanation

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Explanation

Transfer RNA (tRNA) is a form of non-coding RNA composed of 74-93 nucleotides. Specific tRNAs transfer certain amino acid residues to the growing polypeptide during translation. tRNA functions by recognizing the 3 base codon on the mRNA being translated through its anticodon region, which contains complementary bases. The secondary structure of tRNA resembles a cloverleaf and contains the following regions:

- The **acceptor stem** is created through the base pairing of the 5'-terminal nucleotides with the 3'-terminal nucleotides. The CCA tail hangs off the 3' end, with the amino acid bound to the 3' terminal hydroxyl group. tRNA is "loaded" with the appropriate amino acid by aminoacyl tRNA synthetase. The acceptor stem helps mediate correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- A **3' CCA tail** is added to the 3' end of tRNA as a posttranscriptional modification in eukaryotes and most prokaryotes. Several enzymes utilize this tail to help recognize tRNA molecules.
- The **D loop** contains numerous dihydrouridine residues, which are modified bases often present in tRNA. The D loop (along with the acceptor stem and anticodon loop) facilitates correct tRNA recognition by the proper aminoacyl tRNA synthetase.
- The **anticodon loop** contains sequences that are complementary to the mRNA codon. During translation, the ribosome complex selects the proper tRNA based solely on its anticodon sequence.
- The **T loop** contains the TΨC sequence that is necessary for binding of tRNA to ribosomes. The TΨC sequence refers to the presence of ribothymidine, pseudouridine, and cytidine residues.

(Choices A and F) AUG and UAG are mRNA start and stop codons that initiate and terminate translation, respectively.

(Choices C and D) After transcription, eukaryotic pre-mRNA undergoes posttranscriptional modification, which includes the addition of a poly-A tail at the 3' end and methylguanosine cap at the 5' end, and the removal of introns.

(Choice E) A TATA box is an upstream promoter region associated with some genes in eukaryotic organisms. TATA binding protein binds to this promoter during transcription, unwinding the DNA and initiating separation of the strands.

utilize this tail to help recognize tRNA molecules.

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(Choice E) A TATA box is an upstream promoter region associated with some genes in eukaryotic organisms. TATA binding protein binds to this promoter during transcription, unwinding the DNA and initiating separation of the strands.

Educational objective:
Transfer RNA (tRNA) is a small, noncoding form of RNA that contains chemically modified bases (eg, dihydrouridine, ribothymidine, pseudouridine). tRNA has a CCA sequence at its 3'-end that is used as a recognition sequence by proteins. The 3' terminal hydroxyl group of the CCA tail serves as the amino acid binding site.

References

- CCA addition to tRNA: implications for tRNA quality control.

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Item 3 of 40
Question Id: 2038

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An 8-year-old boy of Ashkenazi Jewish ancestry is brought to the office after developing reduced sensitivity to pain, impaired tear formation, and orthostatic hypotension. Familial dysautonomia is suspected due to the patient's symptoms and heritage. This disorder is caused by loss of function of the IKAP protein, which is essential for development and survival of sensory and autonomic neurons. *IKAP* gene sequencing reveals a single nucleotide substitution that causes a guanine residue to be replaced by adenine at the highlighted position in the normal gene sequence shown below. Exon sequences are represented by capital letters and introns by lowercase letters.

Which of the following is the most likely effect of this mutation?

A. Decreased mRNA export to the cytosol
B. Impaired ribosomal attachment to mRNA
C. Incorrect splicing of pre-mRNA
D. Increased degradation of mRNA by 5' exonucleases
E. Translation of the 3'-untranslated region of mRNA

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Item 3 of 40
Question Id: 2038

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5'-GTACAAACATTGCTGCTGGGAAAGCCGCCGCCGCCACCATG
GGCTATGGGAGTGGTGGTAGCACTGGAGTTAACACCGAAATTG
GCAAGATCCGGGATGAAATGGTGG AACAGAACAGGAGAGAAC
ACCCCTTCAGCAAAAACTAGATGAATTTAAAGTCATCTCCCTTA
TTTGCATTGCAGGCTGGATCATAAATATTGGGCACTTCAATGAC
CCGGTTGATGGAGGGTCCTGGATCAGAGGTGCTATTTACTACT
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ACTGGTACACTTACAACAAACCAGATGTCAGTCTGCAGGC-3'

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Item 3 of 40
Question Id: 2038

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Which of the following is the most likely effect of this mutation?

A. Decreased mRNA export to the cytosol
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C. Incorrect splicing of pre-mRNA
D. Increased degradation of mRNA by 5' exonucleases
E. Translation of the 3'-untranslated region of mRNA

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Item 3 of 40
Question Id: 2038

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Which of the following is the most likely effect of this mutation?

- A. Decreased mRNA export to the cytosol [2%]
- B. Impaired ribosomal attachment to mRNA [4%]
- ✔ C. Incorrect splicing of pre-mRNA [86%]
- D. Increased degradation of mRNA by 5' exonucleases [3%]
- E. Translation of the 3'-untranslated region of mRNA [3%]

Omitted
Correct answer
C

86%
Answered correctly

5 Seconds
Time Spent

08/31/2018
Last Updated

Explanation

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Explanation

Following transcription, pre-mRNA is the initial transcript that contains both intron and exon sequences. Before leaving the nucleus, pre-mRNA must be processed to mature mRNA by 3 post-transcriptional modifications: 5' methylguanosine capping, addition of a 3' polyadenine (Poly A) tail, and splicing.

Splicing is performed by **spliceosomes**, which are complexes of small nuclear ribonucleoproteins (snRNPs) and other proteins that assemble on pre-mRNA. Spliceosomes **remove introns** containing **GU** at the **5' splice site** and **AG** at the **3' splice site**. Initially, the 5' end of intron 1 (splice donor site) is cleaved and joined 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. Mutations at splice sites may result in inappropriate removal of exons and retention of introns. This often leads to the formation of proteins with impaired structure and function as described in the case above.

(Choice A) Polyadenylation of the 3' end of mRNA is performed by the enzyme polyadenylate polymerase. This process stabilizes mRNA and helps it exit the nucleus.

(Choices B and D) In eukaryotes, translation is initiated when the small ribosomal subunit attaches to the 5' cap of mRNA and then scans for the AUG start codon within the Kozak consensus sequence. The 5' cap also protects against exonucleases and helps stabilize mRNA in the cytosol.

(Choice E) Termination of polypeptide synthesis occurs at the 3 stop codons (UAA, UAG, UGA) in mRNA. Mutations in stop codons (nonstop mutations) can result in continued and inappropriate translation of mRNA into the 3'-untranslated region, producing an extremely long, nonfunctional polypeptide.

Educational objective:
Splicing is performed by spliceosomes, which remove introns containing GU at the 5' splice site and AG at the 3' splice site. Splice site mutations may result in inappropriate removal of exons and retention of introns, leading to the formation of dysfunctional proteins.

References

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Item 4 of 40
Question Id: 1887

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A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower quadrant abdominal pain approximately 30 hours earlier but did not go to the hospital because she thought the pain would subside on its own. The patient had no food, only sips of water, during that time. Blood pressure is 115/72 mm Hg and pulse is 106/min. Mucous membranes are dry and there is tenderness in the right lower quadrant of the abdomen. Laboratory evaluation shows mild leukocytosis, normal serum electrolytes, borderline low serum glucose levels, and moderate ketones in the urine. Based on the evaluation, it is suspected that this patient is utilizing ketone bodies as a significant reserve of energy. Which of the following tissues cannot use this energy source?

A. Brain
B. Erythrocytes
C. Heart muscle
D. Renal cortex
E. Skeletal muscle

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Item 4 of 40
Question Id: 1887

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A 24-year-old woman is admitted to the hospital with a diagnosis of acute appendicitis. She started having right lower quadrant abdominal pain approximately 30 hours earlier but did not go to the hospital because she thought the pain would subside on its own. The patient had no food, only sips of water, during that time. Blood pressure is 115/72 mm Hg and pulse is 106/min. Mucous membranes are dry and there is tenderness in the right lower quadrant of the abdomen. Laboratory evaluation shows mild leukocytosis, normal serum electrolytes, borderline low serum glucose levels, and moderate ketones in the urine. Based on the evaluation, it is suspected that this patient is utilizing ketone bodies as a significant reserve of energy. Which of the following tissues cannot use this energy source?

- A. Brain [13%]
- ✔ B. Erythrocytes [79%]
- C. Heart muscle [1%]
- D. Renal cortex [1%]
- E. Skeletal muscle [4%]

Omitted
Correct answer
B

79%
Answered correctly

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01/10/2019
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Explanation

After about 12-18 hours of **fasting**, the body's glycogen stores are depleted and **gluconeogenesis** is required to maintain blood glucose levels

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Item 4 of 40
Question Id: 1887

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Omitted
Correct answer
B

79%
Answered correctly

5 Seconds
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Explanation

After about 12-18 hours of **fasting**, the body's glycogen stores are depleted and **gluconeogenesis** is required to maintain blood glucose levels. As fasting continues, the body limits its reliance on gluconeogenesis in an effort to conserve protein and resorts instead to **ketone body synthesis**. Ketone bodies are generated in the liver from fatty acids and yield energy when converted to acetyl CoA in the **mitochondria** of target cells.

The brain, kidneys, cardiac muscle, and skeletal muscle **(Choices A, C, D & E)** can all utilize ketones for energy. In the initial stages of fasting, the heart and skeletal muscle consume primarily ketone bodies to preserve glucose for the brain, but in prolonged starvation, even the brain will utilize ketone bodies for the majority of its energy needs. However, erythrocytes cannot use ketone bodies for energy because they lack mitochondria. The liver is also unable to utilize ketone bodies for energy because it lacks the enzyme succinyl CoA-acetoacetate CoA transferase (thiophorase), which is required to convert acetoacetate to acetoacetyl CoA.

Educational objective:
When glycogen stores are depleted during fasting, ketone bodies are produced in the liver and can be used as an energy source in the mitochondria of peripheral tissues. The brain preferentially uses glucose, but will utilize ketones for most of its energy needs during prolonged starvation. Erythrocytes lack mitochondria and are unable to use ketones.

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Item 5 of 40
Question Id: 1340

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A 7-day-old neonate born to a 28-year-old woman is brought to the office due to progressive lethargy, vomiting, and poor feeding. The mother reports an uneventful pregnancy and perinatal course. She exclusively breastfeeds the infant and has no medical problems in any of her other children. On examination, the infant is somnolent and dehydrated with decreased muscle tone. Laboratory studies reveal metabolic acidosis with an elevated anion gap, ketosis, and hypoglycemia. Further evaluation reveals a markedly elevated propionic acid level due to defective conversion of propionyl-CoA to methylmalonyl-CoA. This patient is most likely unable to use which of the following amino acids for energy production?

- A. Alanine
- B. Aspartate
- C. Glutamate
- D. Lysine
- E. Phenylalanine
- F. Valine

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Item 5 of 40
Question Id: 1340

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- A. Alanine [16%]
- B. Aspartate [9%]
- C. Glutamate [10%]
- D. Lysine [13%]
- E. Phenylalanine [15%]
- ✔ F. Valine [33%]

Omitted
Correct answer
F

33%
Answered correctly

4 Seconds
Time Spent

10/12/2018
Last Updated

Explanation

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2/5/2019

Omitted
Correct answer
F

33%
Answered correctly

4 Seconds
Time Spent

10/12/2018
Last Updated

Explanation

Catabolism of several essential amino acids (**valine**, **isoleucine**, **methionine**, and **threonine**) along with **odd-chain fatty acids** results in the generation of propionyl-CoA. Propionyl-CoA is subsequently converted to methylmalonyl-CoA in a reaction catalyzed by biotin-dependent propionyl-CoA carboxylase. Isomerization of methylmalonyl-CoA then generates succinyl-CoA, which enters the TCA cycle.

This patient's presentation is consistent with **propionic acidemia**, an autosomal recessive organic acidemia caused by congenital deficiency of propionyl-CoA carboxylase. This enzyme catalyzes the conversion of propionyl-CoA to methylmalonyl-CoA. In its absence, excess propionic acid accumulates in the bloodstream, causing **severe metabolic acidosis**. Hypoglycemia and ketosis frequently develop secondary to the acidosis. Affected patients present 1-2 weeks after birth with lethargy, poor feeding, vomiting, and hypotonia. Treatment involves starting a low-protein diet containing minimal amounts of valine, isoleucine, methionine, and threonine.

(Choice A) Alanine transaminase catalyzes the transfer of an amino group from alanine to α-ketoglutarate, generating pyruvate that can be used for gluconeogenesis.

(Choice B) Aspartate is a nonessential amino acid; it can be converted into oxaloacetate for use in the TCA cycle by aspartate transaminase.

(Choice C) Glutamate is deaminated by glutamate dehydrogenase to form the TCA cycle intermediate α-ketoglutarate.

(Choice D) Lysine and leucine are essential amino acids that are strictly ketogenic. They are metabolized into acetyl-CoA, which is a precursor for ketone bodies.

(Choice E) Phenylalanine is converted to tyrosine by the enzyme phenylalanine hydroxylase. Tyrosine is further converted into fumarate (TCA cycle intermediate) and acetoacetate (ketone body).

generation of propionyl-CoA. Propionyl-CoA is subsequently converted to methylmalonyl-CoA in a reaction catalyzed by biotin-dependent propionyl-CoA carboxylase. Isomerization of methylmalonyl-CoA then generates succinyl-CoA, which enters the TCA cycle.

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Educational objective:
Propionyl-CoA is derived from the metabolism of valine, isoleucine, methionine, threonine, and odd-chain fatty acids. Congenital deficiency of propionyl-CoA carboxylase, the enzyme responsible for the conversion of propionyl-CoA to methylmalonyl-CoA, leads to the development of propionic acidemia. The condition presents with lethargy, poor feeding, vomiting, and hypotonia 1-2 weeks after birth.

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Item 6 of 40
Question Id: 1074

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An 11-year-old girl is evaluated for blurry vision. The patient was adopted internationally at age 9. She has no history of head or eye trauma or exposure to ionizing radiation. Motor and cognitive milestones have been achieved at the appropriate age. She has a good appetite and does not follow any specific diet. The patient takes no medications and has no allergies. Vaccinations are up to date. Vital signs are normal. She is at the 40th percentile for height and weight. Other than bilateral lens opacities, the rest of her examination is normal. Urine is positive for reducing substances. Deficient activity of which of the following enzymes is the most likely cause of this patient's eye condition?

A. Aldolase B
B. Alpha-galactosidase A
C. Fructokinase
D. Galactokinase
E. Glucose-6-phosphatase
F. Hexosaminidase A
G. Sphingomyelinase

Submit

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2/5/2019

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Item 6 of 40
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Mark | Previous | Next | Tutorial | Lab Values | Notes | Calculator | Reverse Color | Text Zoom

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A. Aldolase B [20%]
B. Alpha-galactosidase A [6%]
C. Fructokinase [10%]
✔ D. Galactokinase [52%]
E. Glucose-6-phosphatase [2%]
F. Hexosaminidase A [4%]
G. Sphingomyelinase [2%]

Omitted
Correct answer
D

52%
Answered correctly

3 Seconds
Time Spent

11/28/2018
Last Updated

Explanation

Block Time Remaining: 00:00:48
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Explanation

Galactosemia results from deficiency of enzymes involved in galactose metabolism. First, lactose is broken down to galactose and glucose. Galactose is then phosphorylated to galactose-1-phosphate by the enzyme **galactokinase** (GALK). GALK deficiency causes galactose buildup and this excess is converted to **galactitol**, an osmotic agent that causes **cataracts**. Excess galactose also spills into the urine and causes it to test positive for a reducing substance. Serious systemic manifestations are not seen in GALK deficiency, and cataracts may be the only manifestation.

In contrast, deficiency of the enzyme galactose-1-phosphate uridyl transferase (GALT) results in a more serious form of galactosemia. This is related to the accumulation of galactose-1-phosphate, a toxic metabolite that causes hepatic and renal dysfunction. Consequently, patients with GALT deficiency present early, in the neonatal period, with vomiting, lethargy, and failure to thrive.

This patient's late presentation, normal growth, and the isolated presence of cataract are indicative of GALK deficiency. Infants born in the United States undergo **routine newborn screens** for detecting inborn errors of metabolism, such as galactosemia.

(Choice A) Patients with aldolase B deficiency (hereditary fructose intolerance) cannot metabolize fructose and develop hypoglycemia, hypophosphatemia, and failure to thrive. Although reducing substances can be positive in the urine, cataracts are not present.

(Choice B) Alpha-galactosidase A deficiency (X-linked recessive) results in Fabry disease, which can present with cataracts. However, neurological findings (eg, numbness, tingling, burning pain in the hands and feet) and **angiokeratomas** are also characteristic.

(Choice C) Fructokinase deficiency leads to essential fructosuria, a benign condition that can result in a positive test for reducing substance but not cataracts.

(Choice E) Glucose-6-phosphatase converts glucose-6-phosphate to glucose. Deficiency of glucose-6-phosphatase causes glycogen storage disease type 1 (von Gierke disease). The main clinical manifestations are hypoglycemia, lactic acidosis, hepatomegaly, and hypertriglyceridemia.

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(Choice F) Tay-Sachs disease results from hexosaminidase A deficiency. Affected infants have retinal cherry-red spots and loss of motor skills. Cataracts are not seen.

(Choice G) Sphingomyelinase deficiency is seen in Niemann-Pick disease and leads to accumulation of sphingomyelin. Characteristics include hepatosplenomegaly, motor neuropathy, anemia, and macular cherry-red spots but not cataracts.

Educational objective:
Lenticular accumulation of galactitol in the lenses of patients with galactosemia can cause osmotic damage and development of cataracts. Cataracts may be the only manifestation of galactokinase deficiency.

References

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Item 7 of 40
Question Id: 868

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A 2-day-old boy is being examined in the newborn nursery prior to discharge from the hospital. He was born at 38 weeks gestation by vaginal delivery. The pregnancy and delivery were uncomplicated, and the boy has been breastfeeding, stooling, and urinating normally. The patient's mother has beta-thalassemia trait, and his father has a normal hemoglobin electrophoresis. Vital signs and physical examination are normal. Which of the following hemoglobin compositions is most likely predominant in this infant?

A. $\alpha_2\beta_2$
B. $\alpha_2\gamma_2$
C. $\alpha_2\delta_2$
D. β_4
E. γ_4
F. $\zeta_2\varepsilon_2$
G. $\zeta_2\gamma_2$

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2/5/2019

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Item 7 of 40
Question Id: 868

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

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A. α2β2 [15%]
✔ B. α2γ2 [78%]
C. α2δ2 [4%]
D. β4 [0%]
E. γ4 [0%]
F. ζ2ε2 [0%]
G. ζ2γ2 [0%]

Omitted
Correct answer
B

78%
Answered correctly

3 Seconds
Time Spent

12/19/2018
Last Updated

Explanation

Block Time Remaining: 00:00:51
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2/5/2019

Hemoglobin		
Type	**Name**	**Components**
Embryonic	Gower 1	ζ2ε2
	Portland	ζ2γ2
	Gower 2	α2ε2
Fetal	F*	α2γ2
Adult	A	α2β2
	A2*	α2δ2
α-thalassemia intermedia	H	β4
α-thalassemia major	Barts	γ4

*Predominant in β-thalassemia.

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Hemoglobin is a **tetramer** that consists of 2 pairs of globin chains (total of 4 chains per molecule). During the first few weeks of embryogenesis,

*Predominant in β-thalassemia.

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Hemoglobin is a **tetramer** that consists of 2 pairs of globin chains (total of 4 chains per molecule). During the first few weeks of embryogenesis, hemoglobin is synthesized by the yolk sac and contains zeta or epsilon globin chains **(Choices G and F)**. Thereafter, one pair of the globin chains should always be alpha and the other should be non-alpha.

Fetal hemoglobin (Hb F) production begins around 8 weeks gestation and replaces all embryonic hemoglobin by 14 weeks gestation, when erythropoiesis in the fetal liver and spleen is established. Hb F consists of 2 alpha and 2 gamma protein subunits (**α2γ2**). Production declines at birth, and Hb F comprises ~60-80% of all hemoglobin in a term newborn. Hb F is gradually replaced by adult hemoglobin (Hb A, α2β2) **(Choice A)** during the first 6 months of life, after which Hb A composes the vast majority of adult hemoglobin.

Compared to red blood cells with Hb A, those with Hb F have a **high oxygen affinity** as Hb F **binds to 2,3-bisphosphoglycerate** poorly. The greater affinity of Hb F facilitates transplacental oxygen delivery from the maternal circulation to that of the fetus.

(Choice C) Hemoglobin A2 (α2δ2) is a normal hemoglobin variant that makes up 2%-3% of hemoglobin in a healthy adult and is functionally similar to Hb A. Patients with beta-thalassemia major have impaired beta globin production, resulting in an excess of alpha globin chains (eg, Hb A2, Hb F) and no Hb A.

(Choices D and E) Alpha-thalassemia results from a shortage of alpha globin chains. Hemoglobin H (β4) and hemoglobin Barts (γ4) have a very high oxygen affinity and cannot release oxygen, resulting in tissue hypoxia. Hemoglobin H disease manifests as chronic hemolytic anemia. Hemoglobin Barts is incompatible with life (eg, hydrops fetalis) as normal fetal and adult hemoglobin cannot be produced.

Educational objective:
Hemoglobin F (Hb F) is the predominant hemoglobin type in the second and third trimesters of pregnancy and during the first few months after birth. Hb F consists of 2 alpha and 2 gamma protein subunits (α2γ2) and has a high affinity for oxygen, which facilitates oxygen transport across the placenta to the fetus. Hb A (α2β2) is the major hemoglobin in adults.

References

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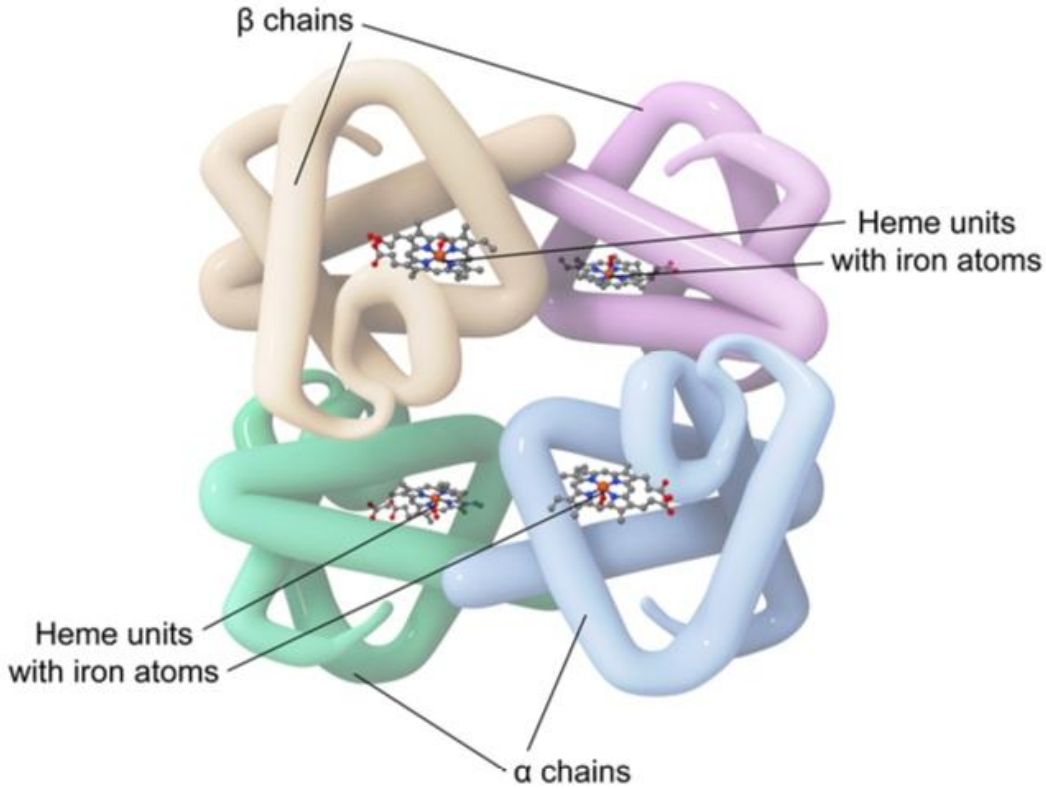

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References

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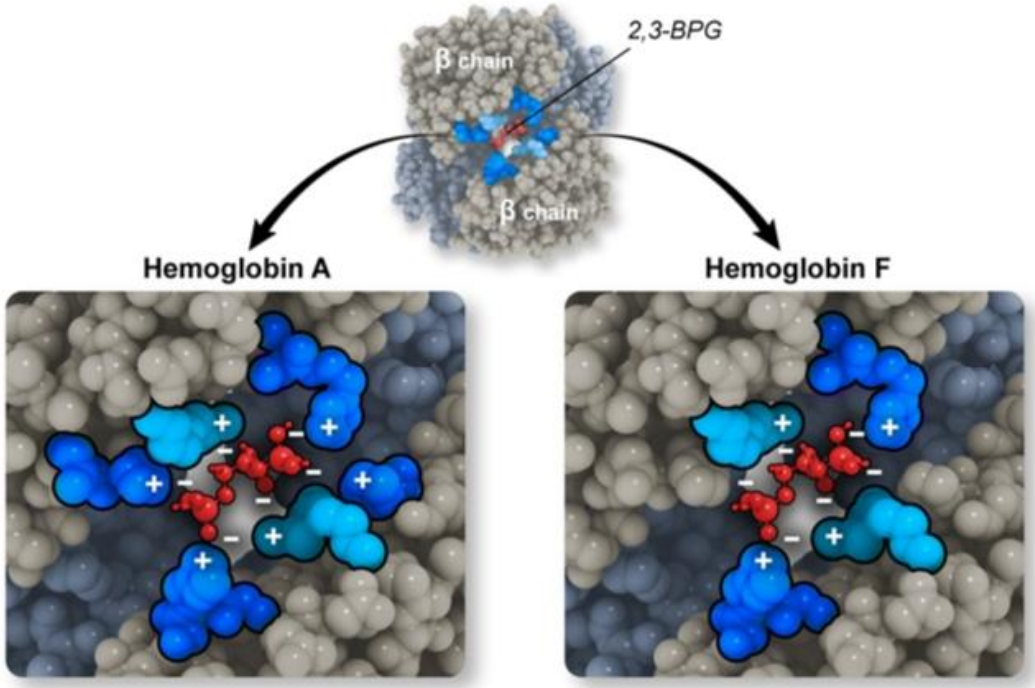
2,3-bisphosphoglycerate and hemoglobin binding



Positively charged histidine and lysine residues secure negatively charged

Replacement of histidine by serine in fetal hemoglobin reduces positive charge of the

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References

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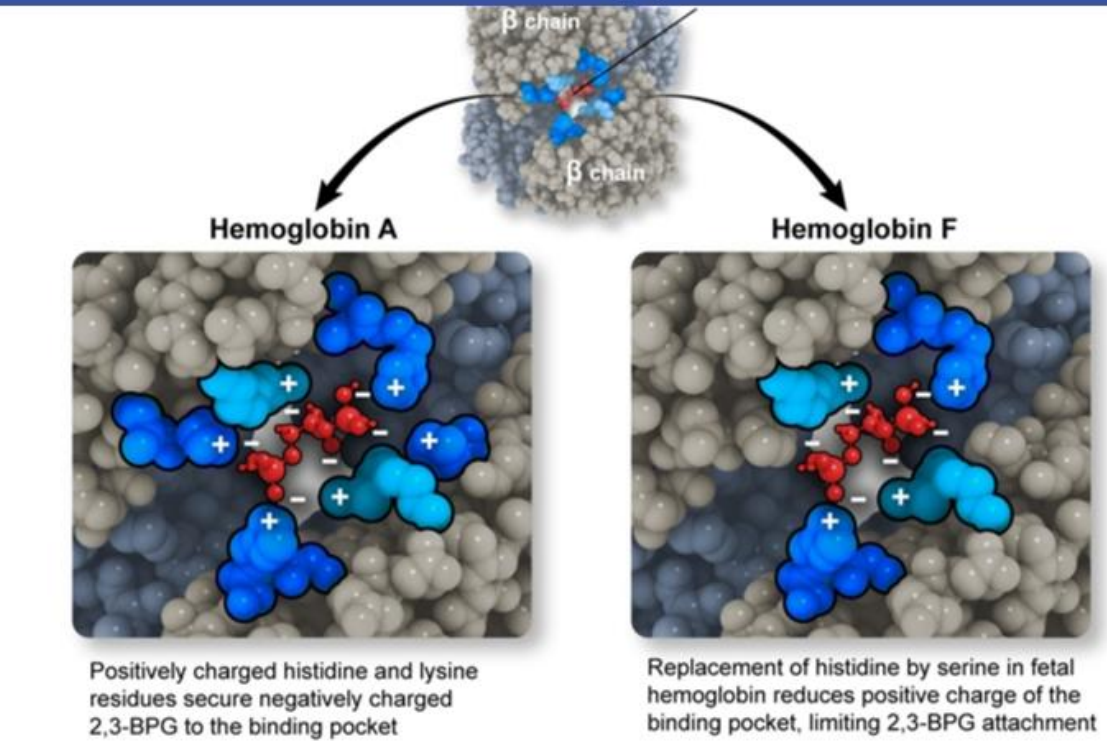

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References

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2/5/2019

A 34-year-old woman comes to the physician with abdominal pain and melena. She also complains of progressive fatigue and a 5 kg (11 lb) weight loss over the last 2 months. She has a strong family history of colon, endometrial, and ovarian cancer. Colonoscopy shows a protuberant, friable mass in the ascending colon, and biopsy is diagnostic for colon adenocarcinoma. Genetic analysis confirms a mutation consistent with Lynch syndrome (hereditary nonpolyposis colon cancer). Which of the following is most likely responsible for the development of colon cancer in this patient?

A. Nucleotide mismatches that escape repair
B. Covalent bonds between adjacent pyrimidines
C. Insertion of abnormal bases (eg, uracil) into DNA
D. Empty sugar-phosphate residues in the DNA molecule
E. Double-strand breaks in DNA

Submit

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- ✔ A. Nucleotide mismatches that escape repair [89%]
- B. Covalent bonds between adjacent pyrimidines [1%]
- C. Insertion of abnormal bases (eg, uracil) into DNA [3%]
- D. Empty sugar-phosphate residues in the DNA molecule [0%]
- E. Double-strand breaks in DNA [5%]

Omitted
Correct answer
A

89%
Answered correctly

5 Seconds
Time Spent

12/29/2018
Last Updated

Explanation

Lynch syndrome (hereditary nonpolyposis colon cancer) is an autosomal dominant disease caused by defective DNA mismatch repair. DNA replication occurs with a high degree of fidelity because mismatched nucleotides are repaired through the proofreading activity of DNA polymerases delta and epsilon. However, this proofreading functionality is not infallible; base substitutions and small insertion-deletion mismatches occur due to errors in base pairing every 10^6 bases on average. It is the function of the DNA mismatch repair system to fix these

polymerases delta and epsilon. However, this proofreading functionality is not infallible; base substitutions and small insertion-deletion mismatches occur due to errors in base pairing every 10^8 bases on average. It is the function of the DNA mismatch repair system to fix these errors shortly after the daughter strands are synthesized. The mismatch repair system involves several genes, including MSH2 and MLH1, which code for components of the human MutS and MutL homologs. Mutations in these 2 genes account for around 90% of cases of Lynch syndrome.

Mismatch repair begins with MutS homolog detecting a mismatch on the newly created daughter strand, which is distinguished from the parent strand by occasional nicks in the phosphodiester bonds. MutL homolog is then recruited, and the resulting complex slides along the DNA molecule until 1 of the daughter strand nicks is encountered. At this point, exonuclease 1 is loaded onto and activated by the repair complex. The daughter strand is then degraded backward past the initial mismatch point, leaving a variable gap of single-stranded DNA that is stabilized by ssDNA-binding protein. The complex then dissociates while DNA polymerase delta loads at the 3' end of the discontinuity and begins synthesizing a new daughter strand segment. Finally, DNA ligase I seals the remaining nick to complete the repair process.

(Choice B) Exposure to ultraviolet light can cause pyrimidine (usually thymine) dimers to form due to covalent joining of adjacent pyrimidines. Pyrimidine dimers interfere with DNA replication and are removed by nucleotide excision repair.

(Choices C and D) Several types of insults can alter the DNA bases. For example, nitrous acid can deaminate C, A, and G. There are also spontaneous changes, such as deamination of C to U and the constant low-level loss of purines via thermal disruption. Glycosylases are enzymes that detect and remove abnormal bases from DNA, creating an empty sugar-phosphate residue that is subsequently removed and replaced by the correct nucleotide (base excision repair).

(Choice E) Exposure to ionizing radiation causes double-stranded DNA breaks that are repaired by end-joining repair mechanisms. Non-homologous end joining, the main mechanism in primates, is more prone to cause mutations than homologous recombination.

Educational objective:
Lynch syndrome is an autosomal dominant disease caused by abnormal nucleotide mismatch repair. The mismatch repair system involves several genes, including MSH2 and MLH1, which code for components of the human MutS and MutL homologs. Mutations in these 2 genes account for around 90% of cases of Lynch syndrome.

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10:58 PM
2/5/2019

A 34-year-old woman comes to the office after her sister was diagnosed with breast cancer. She has no nipple discharge, breast lumps, or discomfort. Breast examination is normal. Her sister was found to have a multiple base pair insertion affecting exon 11 of the *BRCA1* gene that leads to a frameshift mutation. A screening test to evaluate for a similar insertion mutation in the patient's *BRCA1* gene is performed. The test uses polymerase chain reaction (PCR) to amplify the target exon and gel electrophoresis to assess the size of the exon compared to the wild-type allele. Which of the following must be known in order to perform the amplification part of this analysis?

A. Restriction enzyme susceptibility sites within the target exon
B. The amino acid sequence of the abnormal BRCA1 protein
C. The cDNA nucleotide sequence
D. The complete nucleotide sequence of the target exon
E. The nucleotide sequence of the regions flanking the target exon

Submit

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- A. Restriction enzyme susceptibility sites within the target exon [14%]
- B. The amino acid sequence of the abnormal BRCA1 protein [9%]
- C. The cDNA nucleotide sequence [10%]
- D. The complete nucleotide sequence of the target exon [10%]
- ✔ E. The nucleotide sequence of the regions flanking the target exon [54%]

Omitted
Correct answer
E

54%
Answered correctly

5 Seconds
Time Spent

01/08/2019
Last Updated

Explanation

Polymerase chain reaction (PCR) is used to **amplify** small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. Several elements are required for PCR. The first is a source **DNA template** that includes the target region to be amplified (eg, *BCRA1* exon 11) as well as flanking sequences adjacent to the target region. The oligonucleotide sequence of these flanking regions must be known in order to

Explanation

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1. **Denaturing**: Thermal separation of the DNA template is accomplished by exposing the sample to high temperatures
2. **Annealing**: Primers combine with the denatured, single-stranded flanking ends of the target region when the temperature is lowered
3. **Elongation**: DNA polymerase forms new daughter DNA strands in the 5' to 3' direction, starting from the 3' end of each primer

These steps are repeated to obtain millions of copies of the target DNA segment in a short period of time (exponential amplification).

(Choice A) Restriction sites are cleaved by specific endonucleases and can be used to identify polymorphisms within variant alleles on gel electrophoresis (restriction fragment length polymorphism analysis). However, knowing the restriction enzyme susceptibility sites within the target region is not necessary for PCR amplification.

(Choice B) In PCR, only DNA segments are amplified and studied; proteins are not involved. Proteins can be analyzed using Western blots, but even then, exact amino acid sequences do not need to be known.

(Choice C) Complementary DNA (cDNA) is produced by the reverse transcriptase enzyme using mRNA as a template in reverse transcriptase PCR; it is not used in regular PCR. cDNA can be used to express eukaryotic proteins in prokaryotes by transferring the cDNA into the genome of a recipient organism.

Educational objective:
Polymerase chain reaction is used to amplify small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. It requires primers that are complementary to the regions of DNA flanking the segment of interest. Thermostable DNA polymerase, deoxynucleotide

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Educational objective:
Polymerase chain reaction is used to amplify small fragments of DNA (eg, genes, exons, noncoding regions) by repeated replication. It requires primers that are complementary to the regions of DNA flanking the segment of interest. Thermostable DNA polymerase, deoxynucleotide triphosphates, and a source DNA template strand are also necessary.

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A 14-year-old boy is brought to the emergency department due to excessive urination and thirst. He has lost 4.5 kg (10 lb) in the last 3 weeks. The patient has no past medical problems. His father has type 1 diabetes mellitus. Physical examination shows dry mucous membranes. Laboratory studies reveal blood glucose of 455 mg/dL, normal anion gap, and hemoglobin A1c of 11.3%. The patient is diagnosed with type 1 diabetes, and treatment with insulin is initiated. In addition to lowering blood glucose, insulin increases glycogen synthesis in hepatocytes. Activation of which of the following molecules most likely promotes this metabolic effect?

A. Janus kinase (JAK)
B. Lipoxygenase
C. Phospholipase C
D. Protein kinase A
E. Protein phosphatase

Submit

10:59 PM
2/5/2019

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- A. Janus kinase (JAK) [23%]
- B. Lipoxygenase [1%]
- C. Phospholipase C [9%]
- D. Protein kinase A [27%]
- ✔ E. Protein phosphatase [38%]

Omitted
Correct answer
E

38%
Answered correctly

5 Seconds
Time Spent

09/23/2018
Last Updated

Explanation

Insulin decreases blood glucose levels by increasing glucose uptake into skeletal muscle and adipocytes. In addition to having glucose lowering effects, insulin is an anabolic hormone that promotes synthesis of glycogen, triglycerides, nucleic acids, and proteins. Furthermore, insulin inhibits glycogenolysis and gluconeogenesis.

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The surface receptor for insulin is a transmembrane protein with **intrinsic tyrosine kinase** activity in its cytoplasmic domain. Insulin binding activates tyrosine kinase, leading to phosphorylation of insulin receptor substrate 1 (IRS-1). IRS-1 then activates several intracellular pathways that induce the physiologic effects of insulin. Activation of the MAP kinase pathway promotes mitogenic functions such as DNA synthesis and cell growth. In contrast, activation of **phosphatidylinositol-3-kinase (PI3K)** stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, **glycogen synthesis**, and fat synthesis. PI3K promotes glycogen synthesis by activating **protein phosphatase**, an enzyme that dephosphorylates glycogen synthase, leading to its activation.

(Choice A) Janus kinase (JAK) is a component of the second messenger system for various peptide hormones (eg, growth hormone, prolactin) and cytokines (eg, interferon, interleukin). JAK has tyrosine kinase activity; however, it is a cytoplasmic enzyme that is not part of a cell surface receptor (non-receptor tyrosine kinase).

(Choice B) Lipoxygenase is an enzyme involved in arachidonic acid metabolism and is responsible for the arm of that pathway that synthesizes leukotrienes.

(Choice C) Phospholipase C is activated in the G-protein/inositol triphosphate (IP_3)/calcium second messenger system. Hormone-receptor binding activates a G-protein that in turn activates phospholipase C to degrade phospholipids into IP_3 and diacylglycerol. Both diacylglycerol and the increased intracellular calcium caused by IP_3 lead to protein kinase C activation.

(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:
Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and

growth. In contrast, activation of **phosphatidylinositol-3-kinase (PI3K)** stimulates metabolic functions such as translocation of GLUT-4 to the cell membrane, **glycogen synthesis**, and fat synthesis. PI3K promotes glycogen synthesis by activating **protein phosphatase**, an enzyme that dephosphorylates glycogen synthase, leading to its activation.

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(Choice D) Protein kinase A is the primary intracellular effector enzyme in the G-protein/adenylate cyclase second messenger system. Glucagon acts through this pathway to stimulate glycogen breakdown. Protein kinase A activates glycogen phosphorylase via activation of glycogen phosphorylase kinase.

Educational objective:
Insulin is an anabolic hormone that acts via receptor tyrosine kinase signaling to increase the synthesis of glycogen, proteins, fatty acids, and nucleic acids. Tyrosine kinase/phosphatidylinositol-3-kinase stimulation promotes glycogen synthesis by activating protein phosphatase, an enzyme that dephosphorylates (activates) glycogen synthase.

References

- Role of phosphatidylinositol 3-kinase activation on insulin action and its alteration in diabetic conditions.

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A 40-year-old woman comes to the office with a 3-month history of progressive limitation of physical activity due to fatigue. She says, "I could barely walk from my car to your office." Past medical history is significant for a positive tuberculin skin test 7 months ago with a normal chest radiograph. She has been compliant with the prescribed treatment despite its bitter taste. Physical examination shows a tired-appearing woman with conjunctival and palmar pallor. Results of complete blood count are as follows:

Hemoglobin	9 g/dL
Hematocrit	28%
Mean corpuscular volume	72 fL

Bone marrow aspirate revealed the following representative sample under Prussian blue stain.

Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

A. δ-aminolevulinate dehydratase
B. δ-aminolevulinate synthase
C. Cystathionine synthase
D. Glucose-6-phosphate dehydrogenase
E. Pyruvate kinase

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Item 11 of 40
Question Id: 11816

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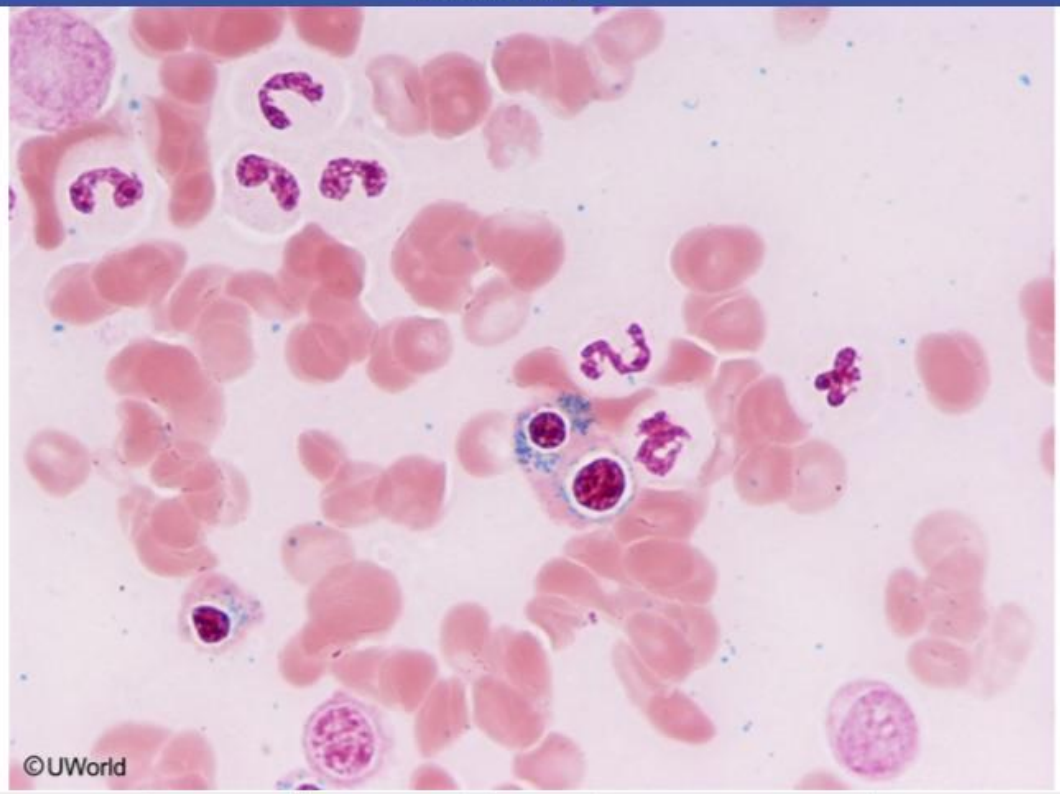

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2/9/2019

A 40-year-old woman comes to the office with a 3-month history of progressive limitation of physical activity due to fatigue. She says, "I could barely walk from my car to your office." Past medical history is significant for a positive tuberculin skin test 7 months ago with a normal chest radiograph. She has been compliant with the prescribed treatment despite its bitter taste. Physical examination shows a tired-appearing woman with conjunctival and palmar pallor. Results of complete blood count are as follows:

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Submit

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Hemoglobin	9 g/dL
Hematocrit	28%
Mean corpuscular volume	72 fL

Bone marrow aspirate revealed the following representative sample under Prussian blue stain.

Decreased activity of which of the following enzymes most likely explains the anemia found in this patient?

- A. δ-aminolevulinate dehydratase [17%]
- ✔ B. δ-aminolevulinate synthase [57%]
- C. Cystathionine synthase [6%]
- D. Glucose-6-phosphate dehydrogenase [15%]
- E. Pyruvate kinase [3%]

Omitted
Correct answer
B

57%
Answered correctly

3 Seconds
Time Spent

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Last Updated

10:59 PM
2/5/2019

Explanation

This patient with latent tuberculosis has laboratory values and a bone marrow aspirate consistent with **sideroblastic anemia** due to isoniazid use. Sideroblastic anemia is diagnosed by bone-marrow examination with Prussian blue stain. Causes include X-linked sideroblastic anemia (due to an δ-aminolevulinate synthase mutation), myelodysplastic syndrome, alcohol abuse, copper deficiency, and certain medications (eg, isoniazid, chloramphenicol, linezolid).

Isoniazid directly inhibits the enzyme **pyridoxine phosphokinase**, which normally converts pyridoxine (vitamin B_6) to its active form, pyridoxal 5' phosphate. Pyridoxal 5' phosphate is a cofactor for **δ-aminolevulinic acid (ALA) synthase**, the enzyme that catalyzes the rate-limiting step in heme synthesis. Inhibition of this enzyme produces a **microcytic, hypochromic anemia**. Iron is transported to developing erythrocytes that cannot form heme, and its granules accumulate circumferentially around the nucleus, forming **ring sideroblasts**.

Because pyridoxal 5' phosphate is a cofactor for numerous enzymes, pyridoxine deficiency can also lead to dermatitis, stomatitis, neuropathy, and confusion. Therefore, pyridoxine is typically prescribed with isoniazid.

(Choice A) δ-aminolevulinate dehydratase is also involved in heme synthesis. Lead poisoning can cause anemia by directly inhibiting this enzyme.

(Choice C) Cystathionine synthase is a pyridoxine-dependent enzyme that catalyzes the formation of cystathionine from homocysteine. Cystathionine synthase deficiency results in homocystinuria, an autosomal recessive disorder characterized by a marfanoid body habitus and hypercoagulability.

(Choice D) Glucose-6-phosphate dehydrogenase (G6PD) deficiency results in increased red blood cell susceptibility to oxidative stress (eg, infection, medication, fava beans), which triggers hemolysis. This results in a normocytic normochromic anemia with increased reticulocyte count and decreased haptoglobin.

(Choice E) Pyruvate kinase deficiency, an autosomal recessive disorder, results in a hemolytic anemia characterized by a normocytic normochromic anemia, reticulocytosis, and elevated indirect bilirubin.

Educational objective:

heme synthesis. Inhibition of this enzyme produces a **microcytic, hypochromic anemia**. Iron is transported to developing erythrocytes that cannot form heme, and its granules accumulate circumferentially around the nucleus, forming **ring sideroblasts**.

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(Choice E) Pyruvate kinase deficiency, an autosomal recessive disorder, results in a hemolytic anemia characterized by a normocytic normochromic anemia, reticulocytosis, and elevated indirect bilirubin.

Educational objective:
Isoniazid inhibits pyridoxine phosphokinase, leading to pyridoxine (vitamin B_6) deficiency. Pyridoxine's active form is the cofactor for δ-aminolevulinate synthase, the enzyme that catalyzes the rate-limiting step of heme synthesis. Inhibition of this step can result in sideroblastic anemia.

References

- Sideroblastic anemia: diagnosis and management.
- Severe isoniazid related sideroblastic anemia.

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E. Pyruvate kinase [3%]

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E. Pyruvate kinase [3%]

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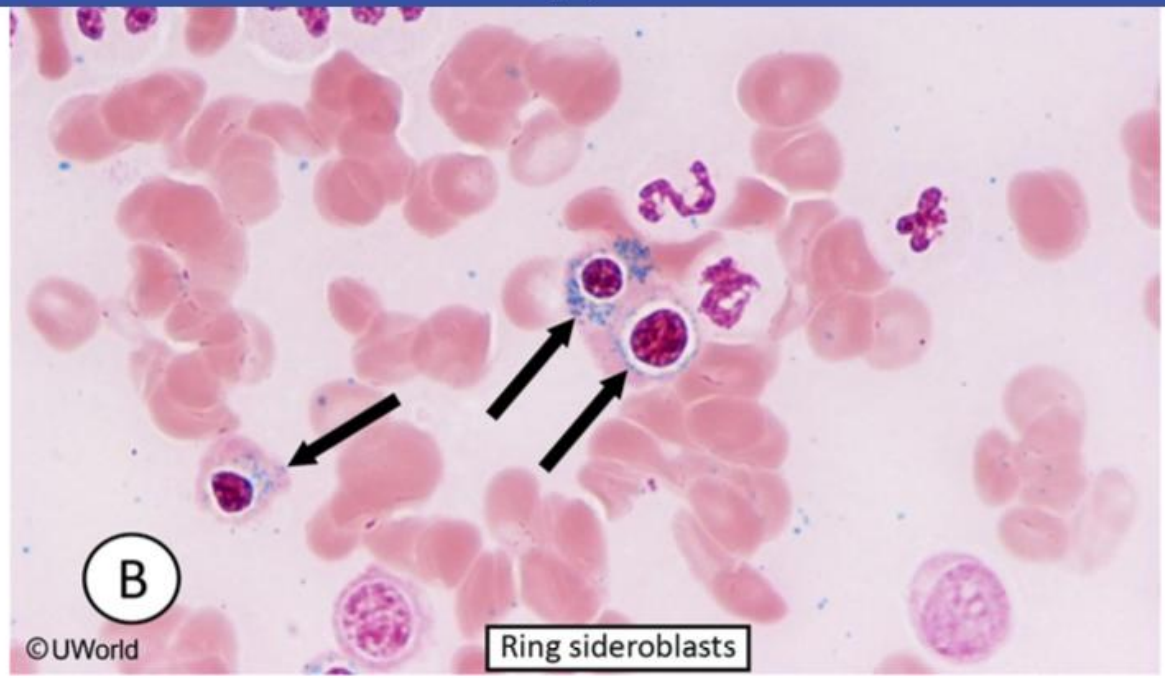

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2/5/2019

An 18-year-old man comes to the office due to a progressive skin rash over the past year. He also has a long-standing history of an intermittent burning sensation in his palms and soles that is exacerbated by stress and fatigue. The burning sensation is particularly severe after exercise, during which the patient notes that he sweats minimally. Skin examination shows clusters of non-blanching, red papules in the gluteal, inguinal, and umbilical areas. Laboratory evaluation reveals an undetectable level of α-galactosidase A. Which of the following conditions is this patient at greatest risk for developing?

- A. Ataxia
- B. Hepatomegaly
- C. Neurofibrosarcoma
- D. Optic atrophy
- E. Renal failure

Submit

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2/5/2019

An 18-year-old man comes to the office due to a progressive skin rash over the past year. He also has a long-standing history of an intermittent burning sensation in his palms and soles that is exacerbated by stress and fatigue. The burning sensation is particularly severe after exercise, during which the patient notes that he sweats minimally. Skin examination shows clusters of non-blanching, red papules in the gluteal, inguinal, and umbilical areas. Laboratory evaluation reveals an undetectable level of α-galactosidase A. Which of the following conditions is this patient at greatest risk for developing?

- A. Ataxia [13%]
- B. Hepatomegaly [24%]
- C. Neurofibrosarcoma [4%]
- D. Optic atrophy [17%]
- ✔ E. Renal failure [40%]

Omitted
Correct answer
E

40%
Answered correctly

3 Seconds
Time Spent

01/25/2019
Last Updated

Explanation

Fabry disease is an **X-linked recessive** **lipid storage disorder** characterized by **α-galactosidase A deficiency**. α-galactosidase A is a lysosomal enzyme responsible for the breakdown of **globotriaosylceramide (Gb3)**, a sphingolipid also known as ceramide trihexoside. Gb3 accumulation in vascular smooth muscle cells, glomerular/distal tubule cells, cardiac myocytes, and dorsal root and autonomic ganglia accounts

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The earliest symptoms present during adolescence and include **neuropathic pain** and **hypohidrosis** (decreased sweating). Small-fiber nerve involvement results in severe distal extremity pain and burning as well as distal loss of hot/cold temperature sensation. Exacerbating factors include exercise, stress, and fatigue. In late adolescence, **angiokeratomas** and **telangiectasias** develop on the skin. Angiokeratomas are dark red, non-blanching macules and papules that classically occur in clusters over the buttocks, groin, and umbilicus.

In early and mid-adulthood, **cerebrovascular** (eg, transient ischemic attack, stroke) and **cardiac** (eg, left ventricular hypertrophy) diseases develop and are the most common causes of death. In addition, Gb3 buildup in the **glomerulus and distal tubule** results in **proteinuria and polyuria**, respectively, and can progress to **renal failure** in the absence of enzyme replacement therapy.

(Choice A) Accumulation of cerebroside sulfate in metachromatic leukodystrophy (arylsulfatase A deficiency) causes progressive demyelination leading to ataxia, peripheral neuropathy, seizures, and hypotonia.

(Choice B) Hepatomegaly occurs in several lysosomal storage diseases. In Niemann-Pick disease, an accumulation of sphingomyelin also causes progressive neurodegeneration and cherry-red macular spots. In Hunter and Hurler syndromes, accumulation of heparan and dermatan sulfate results in developmental delay, skeletal abnormalities, and cardiac disease. In contrast, the liver is not typically affected in Fabry disease.

(Choice C) Neurofibrosarcomas are malignant peripheral nerve sheath tumors that arise from neurofibromas, which are soft, pink or flesh-colored, benign nerve sheath tumors often found on the trunk of patients with neurofibromatosis.

(Choice D) Optic atrophy, developmental regression, and seizures occur in Krabbe disease, a disorder characterized by galactocerebrosidase deficiency.

Educational objective:
In Fabry disease, α-galactosidase A deficiency causes accumulation of the sphingolipid globotriaosylceramide. The earliest manifestations of Fabry disease are neuropathic pain and angiokeratomas. Glomerular (eg, proteinuria, renal failure), cardiac (eg, left ventricular hypertrophy), and

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include exercise, stress, and fatigue. In late adolescence, **angiokeratomas** and **telangiectasias** develop on the skin. Angiokeratomas are dark red, non-blanching macules and papules that classically occur in clusters over the buttocks, groin, and umbilicus.

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(Choice D) Optic atrophy, developmental regression, and seizures occur in Krabbe disease, a disorder characterized by galactocerebrosidase deficiency.

Educational objective:
In Fabry disease, α-galactosidase A deficiency causes accumulation of the sphingolipid globotriaosylceramide. The earliest manifestations of Fabry disease are neuropathic pain and angiokeratomas. Glomerular (eg, proteinuria, renal failure), cardiac (eg, left ventricular hypertrophy), and cerebrovascular (eg, transient ischemic attack, stroke) complications develop in adulthood.

References

- Renal complications of Fabry disease in children.
- Fabry nephropathy: a review – how can we optimize the management of Fabry nephropathy?

Omitted

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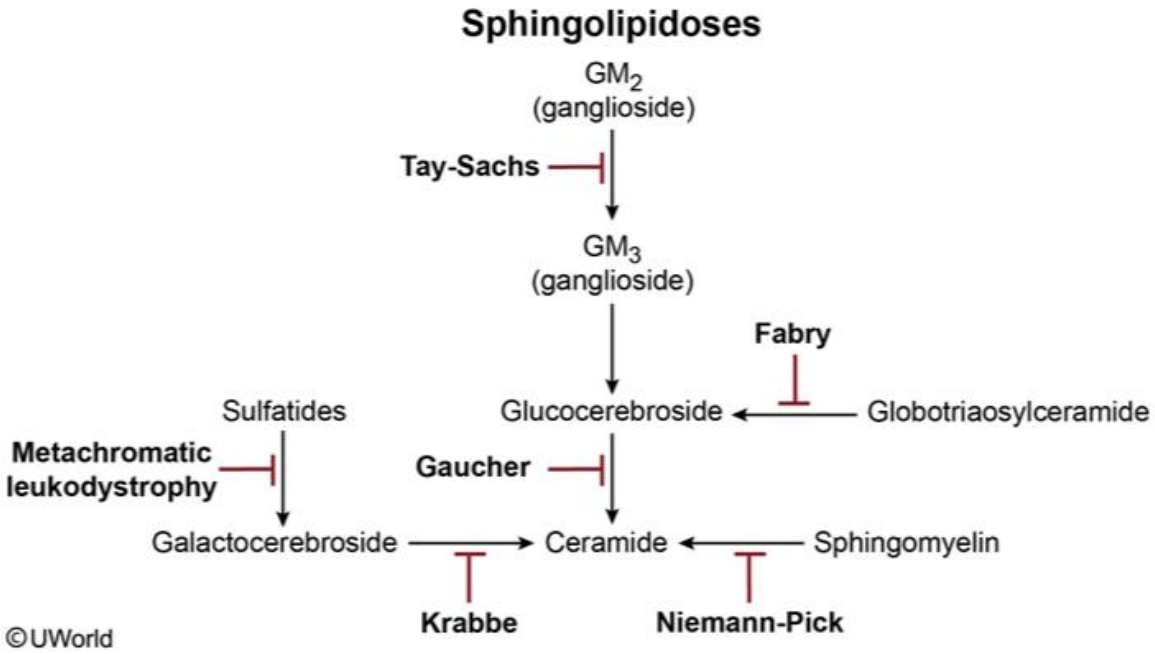

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(Choice C) Neurofibrosarcomas are malignant peripheral nerve sheath tumors that arise from neurofibromas, which are soft, pink or flesh-

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2/5/2019

A 54-year-old woman is evaluated in the clinic for exertional dyspnea and easy fatigability. The patient has no chest pain, cough, or wheezing. She does not use tobacco, alcohol, or illicit drugs. On physical examination, her gait is unstable when her eyes are closed and there is impaired vibratory sensation in the lower extremities. Marked pallor of the conjunctivae, nail beds, and palms is present. Which of the following laboratory tests would help confirm the most likely diagnosis in this patient?

A. Erythrocyte glucose-6-phosphate dehydrogenase activity
B. Erythrocyte glutathione reductase activity
C. Erythrocytic pyruvate kinase activity
D. Erythrocyte transketolase activity
E. Serum methylmalonic acid level
F. Serum protoporphyrin level

Submit

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2/5/2019

A 54-year-old woman is evaluated in the clinic for exertional dyspnea and easy fatigability. The patient has no chest pain, cough, or wheezing. She does not use tobacco, alcohol, or illicit drugs. On physical examination, her gait is unstable when her eyes are closed and there is impaired vibratory sensation in the lower extremities. Marked pallor of the conjunctivae, nail beds, and palms is present. Which of the following laboratory tests would help confirm the most likely diagnosis in this patient?

- A. Erythrocyte glucose-6-phosphate dehydrogenase activity [5%]
- B. Erythrocyte glutathione reductase activity [4%]
- C. Erythrocytic pyruvate kinase activity [3%]
- D. Erythrocyte transketolase activity [6%]
- ✔ E. Serum methylmalonic acid level [72%]
- F. Serum protoporphyrin level [7%]

Omitted
Correct answer
E

72%
Answered correctly

3 Seconds
Time Spent

01/31/2019
Last Updated

Explanation

This patient has features of anemia (eg, exertional dyspnea, fatigue, pallor) with associated neurologic deficits that are highly suggestive of **vitamin B_{12} deficiency**. The hematologic manifestations of B_{12} deficiency (eg, **megaloblastic anemia**, pancytopenia) are related to impaired DNA synthesis.

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Explanation

This patient has features of anemia (eg, exertional dyspnea, fatigue, pallor) with associated neurologic deficits that are highly suggestive of **vitamin B_{12} deficiency**. The hematologic manifestations of B_{12} deficiency (eg, **megaloblastic anemia**, pancytopenia) are related to impaired DNA synthesis.

Vitamin B_{12} (hydroxocobalamin) also serves as a cofactor for methylmalonyl-CoA mutase (converts methylmalonyl-CoA to succinyl-CoA) and methionine synthase (converts homocysteine and folic acid to methionine). B_{12} deficiency consequently results in **elevated** levels of **serum methylmalonic acid and homocysteine**. Increased methylmalonic acid levels can disrupt myelin synthesis and result in **subacute combined degeneration** of the dorsal columns (eg, loss of proprioception/vibration, Romberg sign) and lateral corticospinal tract (eg, spastic muscle weakness, hyperreflexia). Axonal degeneration of peripheral nerves can also be seen.

(Choice A) Glucose-6-phosphate dehydrogenase deficiency (G6PD) leads to acute hemolytic anemia in response to oxidative stress. Neurologic manifestations are not present in G6PD-associated anemia.

(Choice B) Erythrocyte glutathione reductase activity may be decreased in patients with vitamin B_2 (riboflavin) deficiency because glutathione reductase uses bound FAD (derived from vitamin B_2) and NADPH as cofactors to reduce disulfide bonds. Vitamin B_2 deficiency typically presents with normocytic anemia and inflammation of the lips (cheilosis), mouth (stomatitis), and/or tongue (glossitis).

(Choice C) Pyruvate kinase generates ATP through the conversion of phosphoenolpyruvate to pyruvate. Pyruvate kinase deficiency is an autosomal recessive condition that typically presents with congenital hemolytic anemia due to impaired glycolytic ATP generation.

(Choice D) Transketolase is an enzyme of the hexose monophosphate pathway that utilizes thiamine (vitamin B_1) as a coenzyme. Erythrocyte transketolase activity is decreased in thiamine deficiency, which causes Wernicke-Korsakoff syndrome and beriberi.

(Choice F) Serum protoporphyrin levels are increased in iron deficiency anemia, lead poisoning, and erythropoietic protoporphyria. Lead poisoning can cause sideroblastic anemia and peripheral neuropathy, but other characteristic features (eg, abdominal/musculoskeletal pain, cognitive impairment, nephropathy) are not evident in this patient.

Educational objective:

degeneration of the dorsal columns (eg, loss of proprioception/vibration, Romberg sign) and lateral corticospinal tract (eg, spastic muscle weakness, hyperreflexia). Axonal degeneration of peripheral nerves can also be seen.

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Educational objective:
Vitamin B_{12} deficiency often presents with megaloblastic anemia (impaired DNA synthesis) and neurologic deficits (impaired myelin synthesis). Characteristic neurologic findings include subacute combined degeneration of the dorsal columns and lateral corticospinal tract. Elevations in methylmalonic acid and homocysteine levels occur due to decreased metabolism of these molecules.

References

- Clinical practice. Vitamin B12 deficiency.

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A 1-day-old boy is diagnosed with hyperphenylalanemia by newborn screening. He is placed on a special phenylalanine-restricted diet with tyrosine supplementation. The parents are extensively counseled on the boy's condition and informed of the necessary dietary restrictions. They are also instructed to return to his physician for regular follow-up visits. Several months later, laboratory test results indicate that the infant has a normal serum phenylalanine level. Careful examination, however, reveals some neurological abnormalities, including axial hypotonia and microcephaly. Further workup is notable for elevated prolactin, and his physician suspects a cofactor deficiency. Which of the following enzymes is most likely deficient in this patient?

- A. Dihydrobiopterin reductase
- B. Dopamine β-hydroxylase
- C. Phenylalanine hydroxylase
- D. Phenylethanolamine N-methyltransferase
- E. Tyrosinase

Submit

A 1-day-old boy is diagnosed with hyperphenylalanemia by newborn screening. He is placed on a special phenylalanine-restricted diet with tyrosine supplementation. The parents are extensively counseled on the boy's condition and informed of the necessary dietary restrictions. They are also instructed to return to his physician for regular follow-up visits. Several months later, laboratory test results indicate that the infant has a normal serum phenylalanine level. Careful examination, however, reveals some neurological abnormalities, including axial hypotonia and microcephaly. Further workup is notable for elevated prolactin, and his physician suspects a cofactor deficiency. Which of the following enzymes is most likely deficient in this patient?

- A. Dihydrobiopterin reductase [53%]
- B. Dopamine β-hydroxylase [15%]
- C. Phenylalanine hydroxylase [14%]
- D. Phenylethanolamine N-methyltransferase [6%]
- E. Tyrosinase [9%]

Omitted
Correct answer
A

53%
Answered correctly

3 Seconds
Time Spent

08/09/2018
Last Updated

Explanation

This patient most likely has a **deficiency of dihydrobiopterin reductase** based on the combination of **hyperphenylalanemia** and **elevated prolactin**.

This patient most likely has a **deficiency of dihydrobiopterin reductase** based on the combination of **hyperphenylalanemia** and **elevated prolactin**.

Phenylalanine is converted to tyrosine by phenylalanine hydroxylase using **tetrahydrobiopterin** (BH_4) as a **cofactor**. Tyrosine is a nonessential amino acid that becomes essential in phenylketonuria (PKU). Tyrosine is converted to DOPA via the enzyme tyrosine hydroxylase, which also uses BH_4 as a cofactor. Once DOPA is synthesized, it is decarboxylated to dopamine by DOPA decarboxylase. Dopamine ultimately serves as the precursor molecule to the catecholamines epinephrine and norepinephrine.

In classic PKU, supplementation of tyrosine allows for normal catecholamine production due to intact function of tyrosine hydroxylase. Deficiency of dihydrobiopterin reductase, however, leads to hyperphenylalanemia from impaired phenylalanine hydroxylase activity and low dopamine levels from impaired tyrosine hydroxylase activity.

Disorders involving impaired BH_4 levels account for 2% of hyperphenylalanemia cases, and the most common cause is deficiency of dihydrobiopterin reductase, the enzyme responsible for reduction of dihydrobiopterin (BH_2) to BH_4. Although phenylalanine levels can be controlled by dietary restriction, downstream deficiencies of neurotransmitters (eg, dopamine, norepinephrine, epinephrine, serotonin) lead to progressive neurologic deterioration in these patients. Normally, **dopamine** from the tuberoinfundibular system **tonically inhibits prolactin release**. Decreased BH_4 causes lower levels of dopamine, which lead to increased prolactin levels. This pathophysiology is similar to the effects of bromocriptine, a dopamine agonist that is used to treat hyperprolactinemia.

(Choice B) The enzyme dopamine β-hydroxylase catalyzes the biosynthesis of norepinephrine from dopamine. It does not use BH_4 as a cofactor.

(Choice C) Phenylalanine hydroxylase deficiency is the most common cause of PKU. This patient's phenylalanine levels have normalized with dietary therapy, but he has low dopamine levels (as indicated by elevated prolactin). Patients with classic PKU or phenylalanine hydroxylase deficiency do not have any difficulty producing dopamine with adequate levels of dietary tyrosine.

(Choice D) Phenylethanolamine N-methyltransferase (PNMT) converts norepinephrine to epinephrine. It requires S-adenosyl-methionine (SAM) as a cofactor.

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(Choice D) Phenylethanolamine N-methyltransferase (PNMT) converts norepinephrine to epinephrine. It requires S-adenosyl-methionine (SAM) as a cofactor.

(Choice E) Tyrosinase deficiency causes albinism, characterized by a lack of pigment in skin and hair due to absent melanin production. Melanin is synthesized in melanocytes from tyrosine by tyrosinase.

Educational objective:
Disorders involving impaired tetrahydrobiopterin (BH_4) levels, the most common being dihydrobiopterin reductase deficiency, account for 2% of phenylketonuria cases. BH_4 is an important cofactor for both phenylalanine hydroxylase and tyrosine hydroxylase. Although phenylalanine levels can be corrected with dietary restriction, downstream deficiencies of dopamine, norepinephrine, epinephrine, and serotonin lead to progressive neurologic deterioration.

References

- Tyrosine, phenylalanine, and catecholamine synthesis and function in the brain.
- Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies

dihydrobiopterin reductase, the enzyme responsible for reduction of dihydrobiopterin (BH_2) to BH_4. Although phenylalanine levels can be

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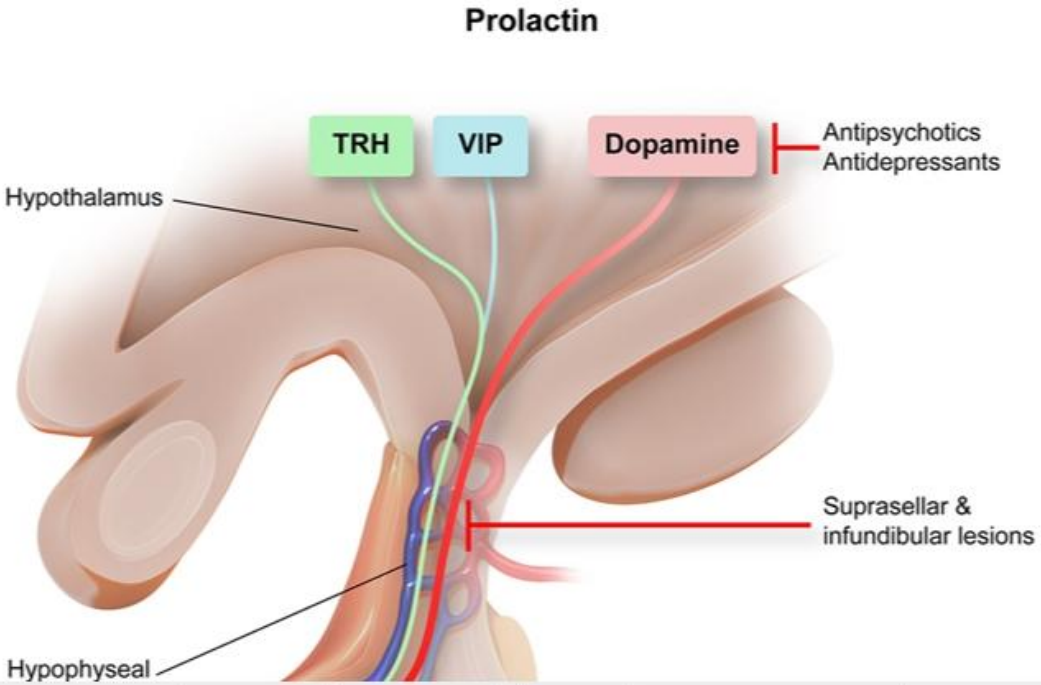

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Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies

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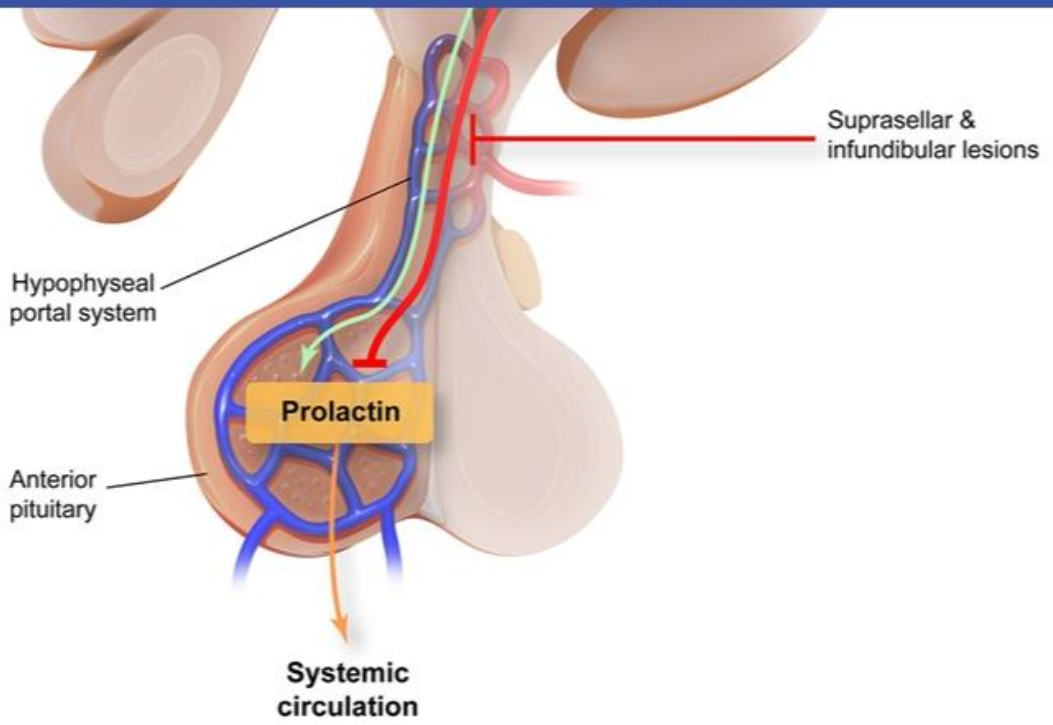

TRH = thyrotropin-releasing hormone; **VIP** = vasoactive intestinal peptide.

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Diagnosis, classification, and genetics of phenylketonuria and tetrahydrobiopterin (BH4) deficiencies

11:01 PM
2/5/2019

A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

A. Galactose-1-phosphate uridyl transferase
B. Aldolase B
C. Fructokinase
D. Galactokinase
E. Acid α-glucosidase

Submit

A 6-month-old boy is brought to the emergency department by his mother because of recent onset of vomiting, irritability, and jaundice. The infant was born at term and had been healthy until the onset of these symptoms. All of his vaccinations are up-to-date. He had been breast-fed exclusively until 1 week ago, when cereals and fruit juices were introduced into his diet. Further evaluation reveals hepatomegaly and abnormal liver function tests. Which of the following enzymes is most likely to be deficient in this patient?

- A. Galactose-1-phosphate uridyl transferase [9%]
- ✔ B. Aldolase B [64%]
- C. Fructokinase [20%]
- D. Galactokinase [3%]
- E. Acid α-glucosidase [2%]

Omitted
Correct answer
B

64%
Answered correctly

4 Seconds
Time Spent

12/29/2018
Last Updated

Explanation

Dietary fructose is obtained mainly from fruits, vegetables, honey, table sugar (sucrose), and processed foods. Fructose is rapidly absorbed in the proximal small bowel by the hexose transporter GLUT 5. Initial metabolism of fructose involves three enzymes: fructokinase, aldolase B, and triokinase. Fructose is phosphorylated on the first carbon by hepatic fructokinase, yielding fructose-1-phosphate. Metabolism of fructose-1-phosphate by aldolase B generates dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde is then phosphorylated to

proximal small bowel by the hexose transporter GLUT 5. Initial metabolism of fructose involves three enzymes: fructokinase, aldolase B, and triokinase. Fructose is phosphorylated on the first carbon by hepatic fructokinase, yielding fructose-1-phosphate. Metabolism of fructose-1-phosphate by aldolase B generates dihydroxyacetone phosphate (DHAP) and glyceraldehyde. Glyceraldehyde is then phosphorylated to glyceraldehyde-3-phosphate (G3P), an intermediate of glycolysis, by triose kinase. DHAP can also be converted to G3P by triose phosphate isomerase.

Aldolase B deficiency causes the potentially life-threatening disorder known as hereditary fructose intolerance. Patients typically present when fructose-containing foods are introduced into the diet. The primary manifestations are vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. Hypoglycemia results from intracellular accumulation of fructose-1-phosphate and depletion of inorganic phosphate, which inhibit glycogenolysis and gluconeogenesis. Failure to thrive, hepatomegaly, and jaundice can also occur. Undiagnosed individuals may eventually develop liver and renal failure. Elimination of dietary fructose is the mainstay of treatment and results in symptom improvement with a good long-term prognosis.

(Choices A and D) Galactose-1-phosphate uridyl transferase deficiency (classic galactosemia) is an autosomal recessive disorder characterized by vomiting, feeding intolerance, neonatal jaundice, hepatomegaly, and death if untreated. Symptoms start soon after breastfeeding is initiated. Galactokinase deficiency is a more benign disorder of galactose metabolism that results in the formation of neonatal cataracts.

(Choice C) Fructokinase deficiency causes essential fructosuria, a benign autosomal recessive disorder. Fructose from the diet is absorbed and secreted freely in the urine due to impairment of the first step in fructose metabolism.

(Choice E) Glycogenolysis is accomplished mainly by glycogen phosphorylase and debranching enzyme, but a small amount is also broken down by the lysosomal enzyme α-1,4-glucosidase. Alpha-glucosidase (or acid maltase) deficiency causes Pompe disease. This disease presents not with hypoglycemia, but with cardiomyopathy and hypotonia.

Educational objective:
Aldolase B deficiency causes hereditary fructose intolerance. This disease manifests after introduction of fructose into the diet with vomiting and hypoglycemia about 20-30 minutes after fructose ingestion. These infants can present with failure to thrive, jaundice, and hepatomegaly.

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A 4-day-old boy born to a 23-year-old woman is brought to the office for evaluation of poor feeding and vomiting. The pregnancy was uneventful and the mother had a normal delivery. Family history is noncontributory. The patient's temperature is 37.2 C (99 F), blood pressure is 60/30 mm Hg, pulse is 110/min, and respirations are 56/min. Physical examination reveals a lethargic newborn with exaggerated deep tendon reflexes and clonus. Further investigation reveals that the patient has an inherited condition that results in impaired transport of ornithine from the cytosol to the mitochondria. Nutritional restriction of which of the following substances can improve this patient's condition?

- A. Branched-chain amino acids
- B. Fructose
- C. Galactose
- D. Medium-chain triglycerides
- E. Phenylalanine
- F. Proteins
- G. Pyridoxine

Submit

11:01 PM
2/5/2019

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- A. Branched-chain amino acids [18%]
- B. Fructose [2%]
- C. Galactose [2%]
- D. Medium-chain triglycerides [14%]
- E. Phenylalanine [7%]
- ✔ F. Proteins [52%]
- G. Pyridoxine [3%]

Omitted
Correct answer
F

52%
Answered correctly

4 Seconds
Time Spent

01/07/2019
Last Updated

Explanation

Impaired transport of ornithine into the mitochondria can be caused by ornithine translocase deficiency, which results in a defect in the **hepatic urea cycle**. The urea cycle converts ammonia, which is generated from the **catabolism of amino acids**, into urea for excretion in urine. Urea cycle **defects** cause **ammonia to accumulate** in the blood, resulting in progressive lethargy, vomiting, seizures, and cerebral edema (may cause hyperreflexia and abnormal posturing when severe) in infancy and early childhood; milder defects caused by partial enzyme deficiencies may not manifest until adulthood.

Effective treatment of urea cycle disorders requires balancing dietary protein intake and metabolic requirements. **Protein restriction** is the main treatment for urea cycle disorders, such that the body receives the essential amino acids needed for growth and development but not in excess such that excessive ammonia is formed. Medications that provide an alternate pathway to excrete nitrogen (eg, phenylacetate) are also used to help remove ammonia from the blood.

(Choice A) Restriction of branched-chain amino acids (eg, valine, leucine, isoleucine) is used to treat maple syrup urine disease (branched-chain alpha-ketoacid dehydrogenase deficiency) and propionic acidemia (propionyl-CoA carboxylase).

(Choice B) Fructose and sucrose restriction is the treatment for fructose 1-phosphate aldolase (aldolase B) deficiency. This condition causes vomiting and hypoglycemia in infants after fruit or juice is introduced.

(Choice C) Galactose and lactose are excluded from the diet in patients with classic galactosemia (absent galactose-1-phosphate uridyltransferase). Galactosemia presents in neonates with jaundice, vomiting, poor feeding, lethargy, hypoglycemia, and galactose-1-phosphate accumulation.

(Choice D) Medium-chain triglycerides are restricted in medium-chain acyl-CoA dehydrogenase deficiency, a condition characterized by lethargy, seizures, and hypoketotic hypoglycemia following a period of fasting.

(Choice E) A phenylalanine-free diet is recommended in patients with phenylketonuria (phenylalanine hydroxylase deficiency). Failure to convert phenylalanine to tyrosine leads to accumulation of phenylalanine and intellectual disability if the condition is left untreated.

(Choice G) Pyridoxine (vitamin B_6) can be used to treat homocystinuria, which is caused by a defect in vitamin B_6-dependent cystathionine synthase. This condition is characterized by elevated homocysteine levels, ectopia lentis, intellectual disability, Marfanoid body habitus, and

alpha-ketoacid dehydrogenase deficiency) and propionic acidemia (propionyl-CoA carboxylase).

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Educational objective:
Ornithine transport into mitochondria is necessary for proper function of the urea cycle, which is the major disposal pathway for waste nitrogen generated by catabolism of amino acids. Urea cycle defects typically cause neurological damage due to the accumulation of ammonia. Protein restriction improves this condition by reducing the amount of amino acid turnover.

References

- The hyperornithinemia-hyperammonemia-homocitrullinuria syndrome.

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A 44-year-old man is evaluated due to progressive dyspnea over the past several years. The patient has no associated chest pain or palpitations. Physical examination shows a prolonged expiratory phase without wheezes or rhonchi. CT scan of the chest demonstrates bilateral lower lobe–predominant emphysema. Further testing reveals that the patient has a protease inhibitor deficiency, which has led to increased elastin fiber breakdown. Elastin fibers within alveolar walls normally allow the lung to stretch during active inspiration and recoil during passive expiration. Which of the following most likely contributes to this property of elastin?

A. Abundant interchain disulfide bridges
B. Chain assembly to form a triple helix
C. Heavy post-translational hydroxylation
D. High content of polar amino acids
E. Interchain cross-links involving lysine

Submit

11:02 PM
2/5/2019

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- A. Abundant interchain disulfide bridges [23%]
- B. Chain assembly to form a triple helix [14%]
- C. Heavy post-translational hydroxylation [8%]
- D. High content of polar amino acids [7%]
- ✔ E. Interchain cross-links involving lysine [45%]

Omitted
Correct answer
E

45%
Answered correctly

3 Seconds
Time Spent

01/28/2019
Last Updated

Explanation

This patient's emphysema is likely due to **alpha-1 antitrypsin deficiency**. Neutrophil-secreted elastase is an endogenous proteolytic enzyme that hydrolyzes elastin within alveolar walls. The liver synthesizes alpha-1 antitrypsin, a protein that inhibits neutrophil elastase and prevents alveolar wall degradation, particularly in the lower airways. Patients with alpha-1 antitrypsin deficiency consequently develop excessive alveolar **elastin**

Explanation

This patient's emphysema is likely due to **alpha-1 antitrypsin deficiency**. Neutrophil-secreted elastase is an endogenous proteolytic enzyme that hydrolyzes elastin within alveolar walls. The liver synthesizes alpha-1 antitrypsin, a protein that inhibits neutrophil elastase and prevents alveolar wall degradation, particularly in the lower airways. Patients with alpha-1 antitrypsin deficiency consequently develop excessive alveolar **elastin degradation**, which clinically manifests with **early-onset**, **lower lobe–predominant emphysema**.

Elastin is a fibrous connective tissue protein that provides elasticity to the skin, blood vessels, and pulmonary alveoli. The fibers can stretch to several times their length and recoil back to their original size once stretching forces are withdrawn. Elastin assembly is closely related to that of collagen. Similar to collagen, elastin is synthesized as a large polypeptide precursor (tropoelastin) composed of about 700, mostly nonpolar, amino acids (eg, glycine, alanine, valine) **(Choice D)**. Elastin also contains proline and lysine residues; however, in contrast to those found in collagen, few of these amino acids are hydroxylated **(Choice C)**.

After tropoelastin is formed, it is secreted into the extracellular space where it interacts with microfibrils (fibrillin) that function as a scaffold. Next, **lysyl oxidase**, a copper-dependent enzyme, oxidatively deaminates some of the lysine residues of tropoelastin, facilitating the formation of **desmosine cross-links** between neighboring polypeptides that hold the elastin molecules together. These cross-links, along with the high content of nonpolar (hydrophobic) amino acids, account for the **rubber-like properties** of elastin.

(Choices A and B) Disulfide bridges are formed during collagen, not elastin, synthesis. After post-translational hydroxylation and glycosylation of procollagen molecules, disulfide bond formation between the C-terminal propeptide regions of 3 alpha chains brings the chains into a favorable alignment for triple helix assembly.

Educational objective:
The rubber-like properties of elastin are due to high content of nonpolar (hydrophobic) amino acids and extensive cross-linking between elastin monomers facilitated by lysyl oxidase. Patients with alpha-1 antitrypsin deficiency can develop early-onset, lower lobe–predominant emphysema due to excessive alveolar elastin degradation.

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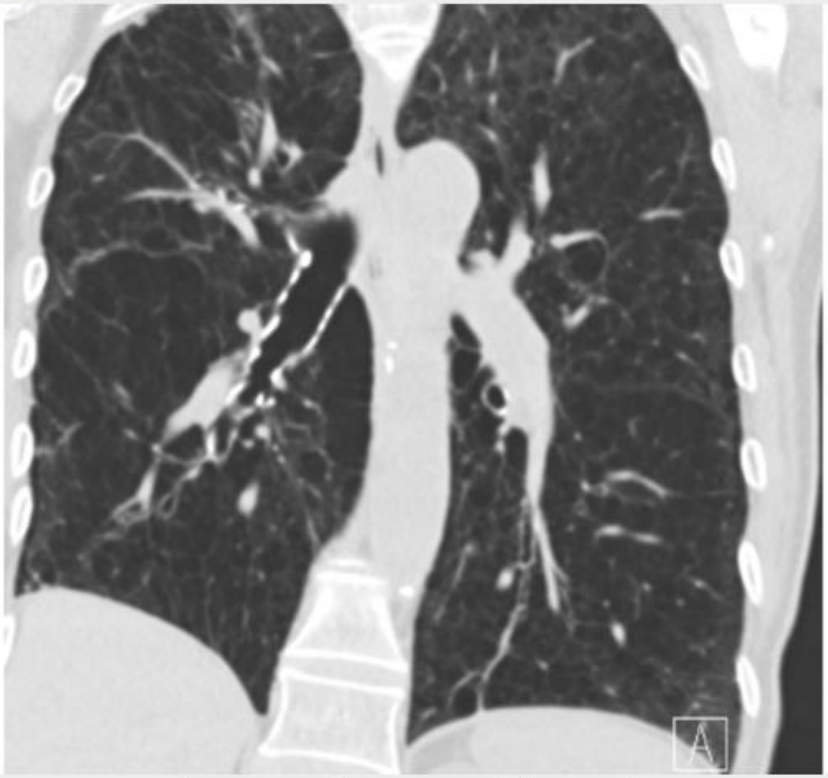
Explanation

Exhibit Display

Alpha-1-antitrypsin deficiency Alpha-1-antitrypsin deficiency



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11:02 PM
2/5/2019

A 45-year-old man is referred to an endocrinologist for newly diagnosed diabetes mellitus. A week ago, his primary care physician noted an elevated fasting serum glucose level. The endocrinologist discusses the different treatment options available, including oral and injectable medications. He recommends treatment with a medication that alters glucose metabolism within the liver by increasing the concentration of fructose 2,6-bisphosphate within hepatocytes. Which of the following conversions will be inhibited by high intracellular concentrations of this metabolite?

A. Acetyl CoA → fatty acids
B. Alanine → glucose
C. Fructose-6-phosphate → fructose-1,6-bisphosphate
D. Glucose → glycogen
E. NAD^+ → NADH

Submit

11:02 PM
2/5/2019

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- A. Acetyl CoA → fatty acids [3%]
- ✔ B. Alanine → glucose [37%]
- C. Fructose-6-phosphate → fructose-1,6-bisphosphate [43%]
- D. Glucose → glycogen [10%]
- E. NAD^+ → NADH [5%]

Omitted
Correct answer
B

37%
Answered correctly

5 Seconds
Time Spent

11/03/2018
Last Updated

Explanation

Fructose 2,6-bisphosphate helps control the balance between **gluconeogenesis** and **glycolysis** through inverse regulation of phosphofructokinase-1 (PFK-1) and fructose 1,6-bisphosphatase. Fructose 2,6-bisphosphate activates PFK-1, the main regulatory enzyme involved in glycolysis, which converts fructose 6-phosphate to fructose 1,6-bisphosphate. The opposite reaction (fructose 1,6-bisphosphate to

Fructose 2,6-bisphosphate helps control the balance between **gluconeogenesis** and **glycolysis** through inverse regulation of phosphofructokinase-1 (PFK-1) and fructose 1,6-bisphosphatase. Fructose 2,6-bisphosphate activates PFK-1, the main regulatory enzyme involved in glycolysis, which converts fructose 6-phosphate to fructose 1,6-bisphosphate. The opposite reaction (fructose 1,6-bisphosphate to fructose-6-phosphate) occurs in gluconeogenesis and is catalyzed by the enzyme fructose-1,6-bisphosphatase (inhibited by fructose 2,6-bisphosphate).

The interconversion of fructose-6-phosphate and fructose 2,6-bisphosphate is achieved by a bifunctional enzyme complex composed of PFK-2 (increases fructose 2,6-bisphosphate levels) and fructose 2,6-bisphosphophosphatase (decreases fructose 2,6-bisphosphate levels). **Insulin** causes activation of PFK-2, leading to **increased fructose 2,6-bisphosphate levels** and **augmented glycolysis**. High concentrations of fructose 2,6-bisphosphate also **inhibit gluconeogenesis**, leading to **decreased conversion of alanine** and other gluconeogenic substrates to glucose.

(Choice A) Fatty acid synthesis is upregulated by insulin and high citrate levels (which increase when acetyl-CoA is abundant, as with active glycolysis). Therefore, fatty acid synthesis is likely to be upregulated in metabolic states in which fructose 2,6-bisphosphate concentration is increased.

(Choice C) The conversion of fructose-6-phosphate to fructose-1,6-bisphosphate is catalyzed by the enzyme PFK-1. This enzyme is allosterically activated by high levels of fructose-2,6-bisphosphate, and so conversion would be increased.

(Choice D) Glycogen formation is stimulated by increased levels of insulin and glucose-6-phosphate. Because elevated insulin levels also increase fructose 2,6-bisphosphate formation, the rise of fructose 2,6-bisphosphate levels in hepatocytes is typically concurrent with increased glycogen synthesis.

(Choice E) The rise in fructose-2,6-bisphosphate accelerates glycolysis, leading to increased conversion of NAD^+ to NADH.

Educational objective:
Fructose 2,6-bisphosphate (F2,6BP) activates phosphofructokinase-1 (increasing glycolysis) and inhibits fructose 1,6-bisphosphatase (decreasing gluconeogenesis). F2,6BP concentration is regulated by a bifunctional enzyme complex: phosphofructokinase-2 increases F2,6BP levels in response to insulin, and fructose 2,6-bisphosphatase decreases F2,6BP levels in response to glucagon.

A 5-year-old girl is brought to the clinic due to several months of fatigue and difficulty walking. She ambulates normally at first but rapidly becomes weak and tired. The patient has not been ill recently and is usually happy and playful. She has a history of mild motor delays but is otherwise developmentally normal. Vital signs are within normal limits. Examination shows mildly decreased power in all extremities but no ataxia. Cardiac auscultation reveals a 1/6 systolic murmur and an S3 gallop. Laboratory results are as follows:

Serum chemistry

Glucose	37 mg/dL
Creatine kinase	304 U/L

Urinalysis

Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

A. Acetoacetate
B. Arachidonic acid
C. Glutathione
D. Homocysteine

Glucose	37 mg/dL
Creatine kinase	304 U/L

Urinalysis

Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

- A. Acetoacetate
- B. Arachidonic acid
- C. Glutathione
- D. Homocysteine
- E. Lactate
- F. Palmitate

Submit

11:03 PM
2/5/2019

Glucose	37 mg/dL
Creatine kinase	304 U/L

Urinalysis

Protein	none
Glucose	negative
Ketones	negative
Leukocyte esterase	negative
Nitrites	negative

Muscle biopsy shows a very low carnitine content. This patient most likely has deficient synthesis of which of the following substances?

- A. Acetoacetate [44%]
- B. Arachidonic acid [3%]
- C. Glutathione [6%]
- D. Homocysteine [8%]
- E. Lactate [8%]
- F. Palmitate [27%]

Omitted

44%

7 Seconds

09/12/2018

This patient's myopathy (eg, elevated creatine kinase, weakness), cardiomyopathy (eg, S3 gallop), and **hypoketotic hypoglycemia** (eg, absence of ketones in the urine) in the setting of **decreased muscle carnitine** content is consistent with **primary carnitine deficiency**. The condition is caused by a defect in the protein responsible for carnitine transport across the mitochondrial membrane. Without sufficient carnitine, fatty acids cannot be transported from the cytoplasm into the mitochondria as acyl-carnitine (carnitine shuttle). The mitochondria therefore cannot β-oxidize the fatty acids into acetyl CoA, the carbon substrate for the citric acid cycle. As a result, cardiac and skeletal myocytes cannot generate ATP from fatty acids (leading to muscle weakness, cardiomyopathy) and the liver is unable to synthesize **ketone bodies** (manifests as hypoketotic hypoglycemia).

Hypoketotic hypoglycemia is also seen in other fatty acid oxidation disorders (eg, acyl CoA dehydrogenase deficiency).

(Choice B) Arachidonic acid can be ingested or synthesized from phospholipids in the cell membrane. Its eicosanoid derivatives (eg, prostanoids, leukotrienes) are important modulators of inflammation. It is not affected by carnitine levels.

(Choice C) Glutathione is a tripeptide that can be synthesized from amino acids (glutamate, cysteine, and glycine). It is an important antioxidant and plays a role in DNA synthesis and repair.

(Choice D) Homocysteine is an amino acid that is synthesized from methionine. Using vitamin cofactors, it can be converted to cysteine (pyridoxine) or recycled into methionine (cobalamin).

(Choice E) Lactate is produced from pyruvate under anaerobic conditions. Patients with carnitine deficiency synthesize lactate normally but may produce increased lactate during times of catabolic stress due to inability to utilize fatty acids for energy production.

(Choice F) Palmitate is a fatty acid that can be ingested or synthesized from carbohydrates. Palmitate synthesis occurs in the cytosol and would not be affected by carnitine deficiency.

Educational objective:
Carnitine deficiency impairs fatty acid transport from the cytoplasm into mitochondria, preventing β-oxidation of fatty acids into acetyl CoA. This leads to cardiac and skeletal myocyte injury (lack of ATP from citric acid cycle) and impaired ketone body production by the liver during fasting periods.

A 4-day-old infant is brought to the emergency department with abnormal movements. The patient has had intermittent episodes of tonic posturing over the past 3 hours as well as poor feeding, vomiting, and irritability for the past 2 days. The mother also reports that his diapers smell like "caramelizing sugar." There are no known medical problems in the family, but the child's maternal aunt died "sometime in the first year" of life from unknown causes. Examination shows a lethargic infant with intermittent posturing episodes and increased generalized muscle tone. Laboratory studies of plasma and urine confirm the diagnosis. In addition to appropriate dietary restriction, supplementation with which of the following may improve this infant's condition?

- A. Arginine
- B. Cobalamin
- C. Pyridoxine
- D. Tetrahydrobiopterin
- E. Thiamine

Submit

11:03 PM
2/5/2019

A 4-day-old infant is brought to the emergency department with abnormal movements. The patient has had intermittent episodes of tonic posturing over the past 3 hours as well as poor feeding, vomiting, and irritability for the past 2 days. The mother also reports that his diapers smell like "caramelizing sugar." There are no known medical problems in the family, but the child's maternal aunt died "sometime in the first year" of life from unknown causes. Examination shows a lethargic infant with intermittent posturing episodes and increased generalized muscle tone. Laboratory studies of plasma and urine confirm the diagnosis. In addition to appropriate dietary restriction, supplementation with which of the following may improve this infant's condition?

- A. Arginine [15%]
- B. Cobalamin [5%]
- C. Pyridoxine [18%]
- D. Tetrahydrobiopterin [19%]
- ✔ E. Thiamine [41%]

Omitted
Correct answer
E

41%
Answered correctly

3 Seconds
Time Spent

11/07/2018
Last Updated

Explanation

This infant has symptoms typical of **maple syrup urine disease (MSUD)**, an autosomal recessive disorder characterized by the defective breakdown of branched-chain amino acids (**leucine**, **isoleucine**, and **valine**). Degradation of these 3 amino acids first involves transamination to

This infant has symptoms typical of **maple syrup urine disease (MSUD)**, an autosomal recessive disorder characterized by the defective breakdown of branched-chain amino acids (**leucine**, **isoleucine**, and **valine**). Degradation of these 3 amino acids first involves transamination to their respective α-ketoacids, which are subsequently metabolized by several enzymes referred to as the **branched-chain α-ketoacid dehydrogenase complex** (BCKDC).

Mutations in BCKDC result in accumulation of the branched-chain amino acids in serum and peripheral tissues, resulting in **neurotoxicity** that includes seizures, irritability, lethargy, and poor feeding. A metabolite of isoleucine gives the urine a distinctive **sweet odor**. MSUD can be life-threatening if untreated, as brain swelling may lead to death.

Branched-chain α-ketoacid dehydrogenase (in addition to pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) requires 5 cofactors: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with MSUD improve with high-dose **thiamine treatment**, but most still require lifelong dietary restrictions.

(Choice A) Most disorders of the **urea cycle** require arginine as an essential amino acid. When patients with urea cycle disorders develop hyperammonemia, arginine is administered for production of downstream water-soluble intermediates (eg, ornithine, citrulline) that lead to nitrogen disposal and decreased plasma ammonia levels.

(Choice B) Cobalamin (vitamin B_{12}) deficiency leads to megaloblastic anemia, neurologic changes including peripheral neuropathy, and elevated plasma levels of homocysteine (a prothrombotic substance). Supplementation of cobalamin is recommended to lower homocysteine levels in patients with hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism, as well as heme and neurotransmitter synthesis. Pyridoxine supplementation is also used in the treatment of hyperhomocysteinemia.

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria, as tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:
Branched-chain α-ketoacid dehydrogenase requires several coenzymes: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving

Branched-chain α-ketoacid dehydrogenase (in addition to pyruvate dehydrogenase and α-ketoglutarate dehydrogenase) requires 5 cofactors: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with MSUD improve with high-dose **thiamine treatment**, but most still require lifelong dietary restrictions.

(Choice A) Most disorders of the **urea cycle** require arginine as an essential amino acid. When patients with urea cycle disorders develop hyperammonemia, arginine is administered for production of downstream water-soluble intermediates (eg, ornithine, citrulline) that lead to nitrogen disposal and decreased plasma ammonia levels.

(Choice B) Cobalamin (vitamin B_{12}) deficiency leads to megaloblastic anemia, neurologic changes including peripheral neuropathy, and elevated plasma levels of homocysteine (a prothrombotic substance). Supplementation of cobalamin is recommended to lower homocysteine levels in patients with hyperhomocysteinemia.

(Choice C) Pyridoxine (vitamin B_6) is involved in the transamination and decarboxylation steps in amino acid metabolism, as well as heme and neurotransmitter synthesis. Pyridoxine supplementation is also used in the treatment of hyperhomocysteinemia.

(Choice D) Tetrahydrobiopterin deficiency results in phenylketonuria, as tetrahydrobiopterin is a cofactor for phenylalanine hydroxylase. Phenylalanine levels can be reduced by tetrahydrobiopterin supplementation in patients with tetrahydrobiopterin deficiency.

Educational objective:
Branched-chain α-ketoacid dehydrogenase requires several coenzymes: **T**hiamine, **L**ipoate, **C**oenzyme A, **F**AD, **N**AD (mnemonic: **T**ender **L**oving **C**are **F**or **N**ancy). Some patients with maple syrup urine disease improve with high-dose thiamine treatment, but most require lifelong restriction of leucine, isoleucine, and valine.

References

- Branched-chain amino acid metabolism: From rare Mendelian diseases to more common disorders.
- Maple syrup urine disease.

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11:03 PM
2/5/2019

A 79-year-old woman comes to the office for evaluation of difficulty walking due to fatigue and bilateral leg pain. The pain started in her lower legs 3 weeks ago and progressed to involve the muscles of her thighs also. In addition, she has noted red spots on her legs. The patient has lived alone since her husband died 3 years ago and is largely homebound. Her diet consists mostly of bread and canned meat products. On examination, the gums are swollen and tender. The patient's skin findings are shown in the **exhibit**. Muscles of the lower limbs are tender to palpation. Imaging studies reveal a tibial subperiosteal hematoma. Which of the following nutrient deficiencies is most likely responsible for this patient's symptoms?

- A. Ascorbic acid
- B. Biotin
- C. Folic acid
- D. Linoleic acid
- E. Pyridoxine
- F. Riboflavin
- G. Thiamine
- H. Vitamin K
- I. Zinc

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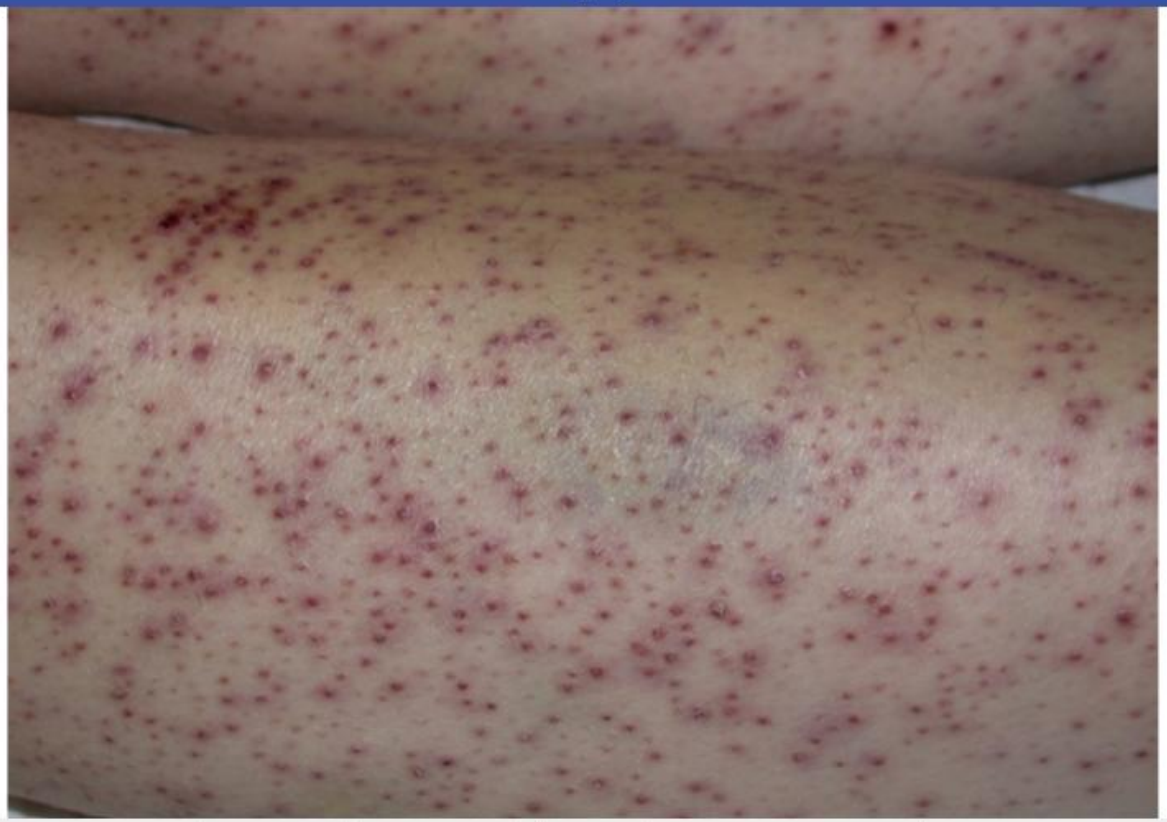

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11:04 PM
2/5/2019

A 79-year-old woman comes to the office for evaluation of difficulty walking due to fatigue and bilateral leg pain. The pain started in her lower legs 3 weeks ago and progressed to involve the muscles of her thighs also. In addition, she has noted red spots on her legs. The patient has lived alone since her husband died 3 years ago and is largely homebound. Her diet consists mostly of bread and canned meat products. On examination, the gums are swollen and tender. The patient's skin findings are shown in the **exhibit**. Muscles of the lower limbs are tender to palpation. Imaging studies reveal a tibial subperiosteal hematoma. Which of the following nutrient deficiencies is most likely responsible for this patient's symptoms?

- A. Ascorbic acid [77%] ✔
- B. Biotin [0%]
- C. Folic acid [2%]
- D. Linoleic acid [0%]
- E. Pyridoxine [1%]
- F. Riboflavin [1%]
- G. Thiamine [1%]
- H. Vitamin K [12%]
- I. Zinc [1%]

Omitted
Correct answer
A

77%
Answered correctly

28 Seconds
Time Spent

01/17/2019
Last Updated

Explanation

This patient with perifollicular hemorrhages, myalgias, subperiosteal hematoma, and gingivitis has typical features of **scurvy**. Scurvy, which is due to a deficiency of **ascorbic acid** (vitamin C), is uncommon in developed countries as this vitamin is widely available in fruits, vegetables, and a variety of other foods. However, it may occasionally be seen in patients with abnormal eating patterns, including the elderly, alcoholics, and persons who live alone. Other possible signs of scurvy include hemarthrosis, **petechial hemorrhages**, impaired wound healing, and weakened immune responses to local infections.

Ascorbic acid is a cofactor in a number of reactions but is especially important in the hydroxylation of proline and lysine residues. In particular, synthesis of **collagen** requires extensive formation of **hydroxyproline** in the procollagen polypeptide, and ascorbic acid deficiency leads to reduced production of collagen with lower tensile strength. Collagen defects in blood vessel walls lead to widespread microvascular bleeding.

(Choice B) Biotin plays a role in a number of carboxylation reactions. Deficiency is rare but can present with rash, hair loss, and neuropsychiatric defects.

(Choice C) Folic acid deficiency is characterized by megaloblastic anemia and fetal neural tube defects.

(Choice D) Linoleic acid is an essential fatty acid used in the synthesis of arachidonic acid. Deficiency is not well characterized, but reported features include growth deficiency and neurovisual defects.

(Choice E) Pyridoxine (vitamin B_6) deficiency is characterized by cheilosis, glossitis, dermatitis, and peripheral neuropathy.

(Choice F) Vitamin B_2 (riboflavin) deficiency is characterized by angular stomatitis, cheilitis, glossitis, seborrheic dermatitis, eye changes (eg, keratitis, corneal neovascularization), and anemia.

(Choice G) Vitamin B_1 (thiamine) deficiency causes beriberi (peripheral neuropathy, muscle wasting, and heart failure), Wernicke syndrome (nystagmus, ataxia, and ophthalmoplegia), and Korsakoff psychosis.

(Choice H) Vitamin K deficiency is characterized by a bleeding diathesis (but not painful gums).

(Choice I) Zinc deficiency is characterized by acrodermatitis enteropathica, growth retardation, and infertility.

11:04 PM
2/5/2019

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(Choice H) Vitamin K deficiency is characterized by a bleeding diathesis (but not painful gums).

(Choice I) Zinc deficiency is characterized by acrodermatitis enteropathica, growth retardation, and infertility.

Educational objective:
Ascorbic acid (vitamin C) is a cofactor in the hydroxylation of proline and lysine residues and is important in the synthesis of collagen. Deficiency (scurvy) is characterized by microvascular bleeding, gingivitis, and impaired wound healing.

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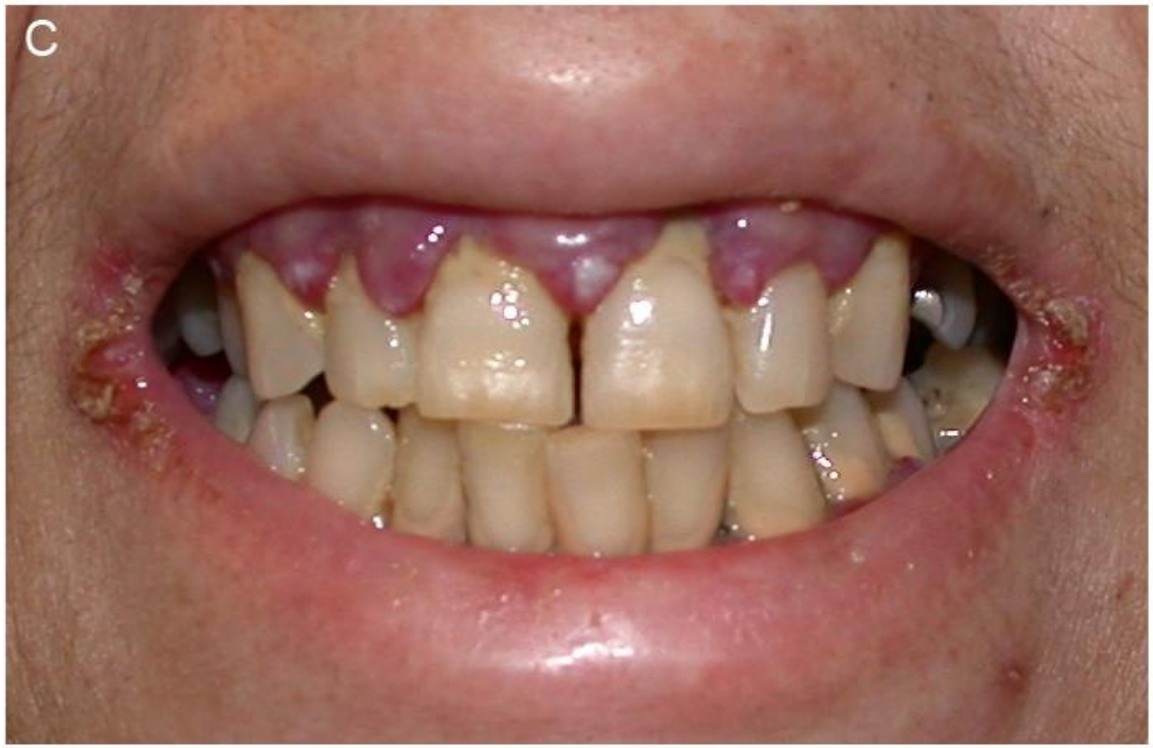
G. Thiamine [1%]

Exhibit Display



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(Choice D) Linoleic acid is an essential fatty acid used in the synthesis of arachidonic acid. Deficiency is not well characterized, but reported

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11:04 PM
2/5/2019

As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

- A. 3-Hydroxy-3-methylglutaryl-CoA lyase
- B. Ornithine transcarbamylase
- C. Pyruvate carboxylase
- D. Succinate dehydrogenase
- E. Transketolase

Submit

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2/5/2019

As part of a research study investigating enzymatic activity in both normal and diseased liver tissue, hepatocytes are isolated from biopsy samples obtained from patients undergoing routine care at a local tertiary referral center. The cells are homogenized and centrifuged to remove membrane components and organelles. Following subsequent rounds of centrifugation, the remaining supernatant contains only cytosol and cytosolic proteins. Activity of which of the following enzymes will most likely be detectable in the supernatant of healthy liver cells?

- A. 3-Hydroxy-3-methylglutaryl-CoA lyase [10%]
- B. Ornithine transcarbamylase [18%]
- C. Pyruvate carboxylase [26%]
- D. Succinate dehydrogenase [6%]
- ✔ E. Transketolase [37%]

Omitted
Correct answer
E

37%
Answered correctly

6 Seconds
Time Spent

10/27/2018
Last Updated

Explanation

Enzymes and the biochemical processes they catalyze often require distinct chemical environments for optimal function; small variations in temperature, molecular concentrations, and pH may render them ineffective. **Cellular compartmentalization** provides a means by which multiple heterogeneous environments can exist within a cell. Organelles such as the nucleus and mitochondria form distinct, membrane-bound regions with a chemical composition different from the cytosol. This allows multiple biochemical processes to occur simultaneously at maximum efficiency.

11:04 PM
2/5/2019

Enzymes and the biochemical processes they catalyze often require distinct chemical environments for optimal function; small variations in temperature, molecular concentrations, and pH may render them ineffective. **Cellular compartmentalization** provides a means by which multiple heterogeneous environments can exist within a cell. Organelles such as the nucleus and mitochondria form distinct, membrane-bound regions with a chemical composition different from the cytosol. This allows multiple biochemical processes to occur simultaneously at maximum efficiency.

The cytosol and mitochondria are the predominant sites of metabolism in the cell. Mitochondria are the site of beta-oxidation of fatty acids, the citric acid cycle, and the carboxylation of pyruvate (gluconeogenesis). The **cytosol** is home to enzymes necessary for glycolysis, fatty acid synthesis, and the **pentose phosphate pathway**. **Transketolase** is an enzyme of the pentose phosphate pathway that uses thiamine (vitamin B_1) as a cofactor to shuttle 2-carbon fragments between sugar molecules. Other processes such as heme synthesis, the urea cycle, and gluconeogenesis rely on a complex interplay between the mitochondria and cytosol to function optimally; enzymes present in both cellular compartments are required for these metabolic pathways.

(Choice A) 3-Hydroxy-3-methylglutaryl-CoA (HMG CoA) lyase is a mitochondrial enzyme necessary for ketogenesis. It is also responsible for metabolism of the ketogenic amino acid, leucine.

(Choice B) Ornithine transcarbamylase catalyzes the combination of ornithine and carbamoyl phosphate to form citrulline in the urea cycle. This reaction occurs within the mitochondria.

(Choice C) Pyruvate carboxylase catalyzes the initial step in gluconeogenesis by converting pyruvate to oxaloacetate. This enzyme requires biotin as a cofactor, and functions within the mitochondria.

(Choice D) Succinate dehydrogenase is a TCA cycle enzyme that converts succinate to fumarate. It is an inner mitochondrial membrane protein and functions as part of the electron transport chain.

Educational objective:
Cellular compartmentalization allows multiple biochemical processes to occur simultaneously at maximum efficiency. Beta-oxidation of fatty acids, the TCA cycle, and the carboxylation of pyruvate (gluconeogenesis) all occur within the mitochondria. The enzymes responsible for glycolysis, fatty acid synthesis, and the pentose phosphate pathway reside in the cytosol.

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A 22-year-old man comes to the office due to recurrent blistering on the back of his hands and forearms for the past several years. The patient usually develops small itchy spots but lately has had large blisters that heal with hyperpigmentation after rupturing. He has used over-the-counter topical hydrocortisone and emollients, but the symptoms have not improved. The patient works as a night security guard and has had no exposure to chemicals or animals. He drinks 2-3 cans of beer daily. Physical examination shows vesicles and erosions on the dorsum of both hands. Which of the following enzymes is most likely deficient in this patient?

- A. δ-Aminolevulinate dehydratase
- B. δ-Aminolevulinate synthase
- C. Bilirubin glucuronyl transferase
- D. Porphobilinogen deaminase
- E. Uroporphyrinogen decarboxylase

Submit

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- A. δ-Aminolevulinate dehydratase [7%]
- B. δ-Aminolevulinate synthase [11%]
- C. Bilirubin glucuronyl transferase [4%]
- D. Porphobilinogen deaminase [22%]
- ✔ E. Uroporphyrinogen decarboxylase [53%]

Omitted
Correct answer
E

53%
Answered correctly

3 Seconds
Time Spent

01/31/2019
Last Updated

Explanation

This patient most likely has **porphyria cutanea tarda (PCT)**, the most common disorder of porphyrin (eg, heme) synthesis. Enzyme deficiencies in the early steps in porphyrin synthesis cause abdominal pain and neuropsychiatric manifestations (due to metabolite buildup) without photosensitivity. **Late** step (ie, following porphobilinogen [PBG] conversion) derangements (eg, PCT) cause **photosensitivity**, which is thought to

This patient most likely has **porphyria cutanea tarda (PCT)**, the most common disorder of porphyrin (eg, heme) synthesis. Enzyme deficiencies in the early steps in porphyrin synthesis cause abdominal pain and neuropsychiatric manifestations (due to metabolite buildup) without photosensitivity. **Late** step (ie, following porphobilinogen [PBG] conversion) derangements (eg, PCT) cause **photosensitivity**, which is thought to be due to the accumulation of **porphyrinogens** that react with oxygen on excitation by ultraviolet (sun) light.

PCT is caused by **uroporphyrinogen decarboxylase (UROD)** deficiency, which is either inherited or (more commonly) acquired, manifesting in the presence of iron and of susceptibility factors (eg, alcohol [as in this patient], smoking, halogenated hydrocarbons, hepatitis C, HIV). Photosensitivity presents as vesicle and **blister** formation on sun-exposed areas as well as edema, pruritus, pain, and erythema. Deficiencies in coproporphyrinogen oxidase, protoporphyrinogen oxidase, or ferrochelatase can also result in photosensitivity.

(Choices A and D) Deficiencies in aminolevulinate (ALA) dehydratase and PBG deaminase do not result in photosensitivity because the metabolites that accumulate are not porphyrinogens or porphyrins. PBG deaminase deficiency is seen with acute intermittent porphyria (classically presenting with abdominal pain and neuropsychiatric manifestations).

(Choice B) Deficiency of ALA synthase will result in a decrease in formation of all porphyrins. This deficiency will not result in porphyria but will lead to a decrease in heme synthesis and concurrent hypochromic, microcytic anemia. Pyridoxal phosphate (vitamin B_6) is the cofactor required for activity of ALA synthase; therefore, pyridoxine deficiency can result in microcytic hypochromic anemia.

(Choice C) Bilirubin glucuronyl transferase is a hepatic enzyme responsible for the conjugation of bilirubin with glucuronide, improving solubility for biliary excretion. A decrease in glucuronyl transferase results in unconjugated hyperbilirubinemia.

Educational objective:
Enzyme deficiencies of the early steps in porphyrin synthesis cause neuropsychiatric manifestations without photosensitivity, whereas late step derangements lead to photosensitivity. Photosensitivity manifests as vesicle and blister formation on sun-exposed areas as well as edema, pruritus, pain, and erythema.

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E. coli colonies grown on a lactose-containing medium up-regulate the production of the enzymes β-galactosidase and galactoside permease. Which of the following best explains the synchronous production of both enzymes in response to lactose?

A. There are two activator binding sites for one activator protein
B. There are two operators for one repressor protein
C. There are two repressors for one inducer
D. There are two promoters in close proximity to each other
E. There is one mRNA coding for both enzymes

Submit

11:05 PM
2/5/2019

E. coli colonies grown on a lactose-containing medium up-regulate the production of the enzymes β-galactosidase and galactoside permease. Which of the following best explains the synchronous production of both enzymes in response to lactose?

A. There are two activator binding sites for one activator protein [11%]
B. There are two operators for one repressor protein [13%]
C. There are two repressors for one inducer [4%]
D. There are two promoters in close proximity to each other [14%]
✔ E. There is one mRNA coding for both enzymes [55%]

Omitted
Correct answer
E

55%
Answered correctly

3 Seconds
Time Spent

08/09/2018
Last Updated

Explanation

The *lac* operon is the sequence of the *E. coli* genome which is required for the metabolism of lactose. The *lac* operon consists of a regulatory gene (*i*), promoter region (*p*), operator region (*o*), and three structural genes (*z*, *y*, and *a*). The *z* gene codes for β-galactosidase (β-gal), which is primarily responsible for the hydrolysis of lactose to glucose and galactose. The *y* gene codes for permease, a transmembrane enzyme that increases the permeability of the cell to lactose. The *a* gene encodes a β-galactoside transacetylase, which transfers acetyl groups to β-galactosides and is unnecessary for lactose metabolism by *E. coli*.

In prokaryotes, one mRNA transcript contains the sequences for many proteins, and a single mRNA molecule can be translated into multiple

Explanation

The *lac* operon is the sequence of the *E. coli* genome which is required for the metabolism of lactose. The *lac* operon consists of a regulatory gene (*i*), promoter region (*p*), operator region (*o*), and three structural genes (*z, y,* and *a*). The *z* gene codes for β-galactosidase (β-gal), which is primarily responsible for the hydrolysis of lactose to glucose and galactose. The *y* gene codes for permease, a transmembrane enzyme that increases the permeability of the cell to lactose. The *a* gene encodes a β-galactoside transacetylase, which transfers acetyl groups to β-galactosides and is unnecessary for lactose metabolism by *E. coli*.

In prokaryotes, one mRNA transcript contains the sequences for many proteins, and a single mRNA molecule can be translated into multiple proteins or polypeptides. For instance, all three proteins of the *lac* operon (β-galactosidase, permease, and transacetylase) are synthesized from a single mRNA molecule containing the *z, y,* and *a* gene sequences, respectively. Transcription and translation of the genes of the *lac* operon is typically synchronous. Remember that a single mRNA molecule which codes for more than one protein is referred to as a polycistronic mRNA, and while most prokaryotic mRNA molecules are polycistronic, eukaryotic mRNA is rarely polycistronic.

(Choices A – D) The lac operon, which codes for all three aforementioned proteins, is regulated by a single operator, a promoter, and a single group of regulatory elements: an inducer, repressor, and catabolite activator protein. Modulation of the transcription of this operon through binding of the operator and action of the repressor or other regulatory elements will change the transcription of all three *lac*-operon structural genes (*z, y,* and *a*). On the other hand, there are no operators, repressors, or inducers that can desynchronize the transcription of lac-operon structural genes.

Educational Objective:
Bacterial mRNA can be polycistronic, meaning that one mRNA codes for several proteins. An example of polycistronic mRNA is the bacterial lac operon, which codes for the proteins necessary for lactose metabolism by *E. coli*; the transcription and translation of these bacterial proteins is regulated by a single promoter, operator, and set of regulatory elements.

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A research scientist studying the metabolic pathways that contribute to obesity feeds experimental animals a high-carbohydrate, high-protein diet for a prolonged period. A sample of liver tissue is then obtained from the animals, and the activity of various enzymes involved in fatty acid metabolism is measured and recorded. It is determined that beta-oxidation of fatty acids is inhibited within these cells as a result of the diet. An increase in which of the following substances is most likely responsible for the observed effect?

A. Acetoacetate
B. Carnitine
C. Citrate
D. Malonyl-CoA
E. NADPH

Submit

11:05 PM
2/5/2019

A research scientist studying the metabolic pathways that contribute to obesity feeds experimental animals a high-carbohydrate, high-protein diet for a prolonged period. A sample of liver tissue is then obtained from the animals, and the activity of various enzymes involved in fatty acid metabolism is measured and recorded. It is determined that beta-oxidation of fatty acids is inhibited within these cells as a result of the diet. An increase in which of the following substances is most likely responsible for the observed effect?

A. Acetoacetate [10%]
B. Carnitine [18%]
C. Citrate [18%]
✔ D. Malonyl-CoA [38%]
E. NADPH [13%]

Omitted
Correct answer
D

38%
Answered correctly

3 Seconds
Time Spent

10/30/2018
Last Updated

Explanation

In the **well-fed state**, the abundance of ATP in hepatocytes inhibits isocitrate dehydrogenase, leading to high levels of citrate in the mitochondria. Citrate is transferred to the cytosol via the citrate shuttle and cleaved by ATP citrate lyase to form acetyl-CoA. High citrate levels (in addition to elevated insulin caused by high carbohydrate intake) causes upregulation of **Acetyl-CoA carboxylase**. This cytosolic enzyme catalyzes the conversion of acetyl-CoA to malonyl-CoA in the rate-limiting step of de novo **fatty acid synthesis**. Fatty acid synthase then catalyzes the condensation of malonyl-CoA with acetyl-CoA to create a 4-carbon molecule that will undergo subsequent condensation reactions to form a 16-

In the **well-fed state**, the abundance of ATP in hepatocytes inhibits isocitrate dehydrogenase, leading to high levels of citrate in the mitochondria. Citrate is transferred to the cytosol via the citrate shuttle and cleaved by ATP citrate lyase to form acetyl-CoA. High citrate levels (in addition to elevated insulin caused by high carbohydrate intake) causes upregulation of **Acetyl-CoA carboxylase**. This cytosolic enzyme catalyzes the conversion of acetyl-CoA to malonyl-CoA in the rate-limiting step of de novo **fatty acid synthesis**. Fatty acid synthase then catalyzes the condensation of malonyl-CoA with acetyl-CoA to create a 4-carbon molecule that will undergo subsequent condensation reactions to form a 16-carbon fatty acid.

Beta-oxidation of fatty acids takes place primarily within the **mitochondrial matrix**. Mitochondrial membranes are impermeable to fatty acids due to their negative charge, so a specialized membrane carrier (**carnitine**) must be used to shuttle them into the matrix. **Malonyl-CoA inhibits carnitine acyltransferase**, preventing the transfer of acyl groups into the mitochondria. This inhibitory action functions to prevent the breakdown of newly synthesized fatty acids.

(Choice A) Ketone bodies (eg, acetoacetate) are a major source of fuel for muscle, brain, and cardiac tissue that are produced during times of starvation or fasting when oxaloacetate is in short supply and acetyl-CoA is in excess.

(Choice B) Carnitine is an amino acid that is essential for the transport of fatty acids through the mitochondrial membrane. It is a necessary component of fatty acid oxidation.

(Choice C) Citrate is an intermediate in the TCA cycle. It can be exported out of the mitochondrial matrix and into the cytosol, where it is broken down into acetyl-CoA for use in de novo fatty acid synthesis.

(Choice E) NADPH is a reducing molecule necessary for the synthesis of fatty acids. In contrast, beta-oxidation of fats produces $FADH_2$ and NADH-reducing equivalents.

Educational objective:
Cytosolic acetyl-CoA carboxylase converts acetyl-CoA to malonyl-CoA during the rate-limiting step of de novo fatty acid synthesis. Malonyl-CoA also inhibits the action of mitochondrial carnitine acyltransferase, thereby inhibiting beta-oxidation of newly formed fatty acids.

References

A 39-year-old woman comes to the emergency department due to several episodes of severe upper abdominal pain. Her pain is triggered by fatty foods and resolves spontaneously. The symptoms first began a few months earlier after an uncomplicated pregnancy. Past medical history is notable for hypertension, for which the patient takes a calcium channel blocker, and hypertriglyceridemia, which is treated with a fibrate. Temperature is 37.2 C (98.9 F) and blood pressure is 143/76 mm Hg. The patient weighs 95 kg (210 lb) and is 173 cm (5 ft 8 in) tall. Ultrasound reveals thickening of the gallbladder wall, with tenderness elicited by the ultrasound probe directly over the gallbladder. She undergoes a laparoscopic cholecystectomy, with multiple stones noted in the contents of the gallbladder. Decreased activity of which of the following enzymes would most likely have contributed to this patient's condition?

- A. Aromatase
- B. β-glucuronidase
- C. Cholesterol 7α-hydroxylase
- D. HMG-CoA reductase
- E. Thiolase

Submit

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- A. Aromatase [3%]
- B. β-glucuronidase [14%]
- ✔ C. Cholesterol 7α-hydroxylase [65%]
- D. HMG-CoA reductase [14%]
- E. Thiolase [2%]

Omitted
Correct answer
C

65%
Answered correctly

3 Seconds
Time Spent

01/31/2019
Last Updated

Explanation

This patient, with recurring abdominal pain, a positive "sonographic Murphy sign," and multiple cholesterol **gallstones**, has acute cholecystitis.

11:05 PM
2/5/2019

This patient, with recurring abdominal pain, a positive "sonographic Murphy sign," and multiple cholesterol **gallstones**, has acute cholecystitis. Water-insoluble **cholesterol** is secreted in bile, where it is solubilized by detergent-like bile salts and phosphatidylcholine. If there is more cholesterol than can be dissolved by the bile salts, it will **precipitate** into insoluble crystals, leading to formation of gallstones. Risk factors for gallstone formation include obesity or rapid weight loss, female sex, glucose intolerance, and hypomotility of the gallbladder (eg, pregnancy, prolonged fasting).

Fibrate medications (eg, fenofibrate, gemfibrozil) upregulate lipoprotein lipase, resulting in increased oxidation of fatty acids. In addition, fibrates inhibit **cholesterol 7α-hydroxylase**, which catalyzes the rate-limiting step in the synthesis of bile acids. The reduced bile acid production results in decreased cholesterol solubility in bile and favors the formation of cholesterol stones.

(Choice A) Estrogens increase the biosynthesis of cholesterol by upregulating hepatic HMG-CoA reductase activity. Estrogenic medications (eg, estrogen replacement therapy, combined oral contraceptives) increase the amount of cholesterol secreted in bile and contribute to formation of gallstones. Aromatase catalyzes the conversion of androgens to estrogen; inhibition would lead to reduced gallstone formation.

(Choice B) β-glucuronidase is released by damaged hepatocytes and bacteria in infected bile. It deconjugates bilirubin, and the resulting free bilirubin precipitates with calcium in the bile to form pigmented gallstones. Decreased activity of this enzyme would reduce the formation of pigmented stones but would not affect the formation of cholesterol gallstones.

(Choices D and E) The first step in cholesterol synthesis is the condensation of 2 molecules of acetyl-CoA by acetyl-CoA acetyl transferase (thiolase) to form acetoacetyl-CoA. Condensation with a third molecule of acetyl-CoA yields β-hydroxy-β-methylglutaryl-CoA (HMG-CoA). HMG-CoA reductase then catalyzes the conversion of HMG-CoA to mevalonate, the rate-limiting step in cholesterol synthesis. Decreased activity of these enzymes would reduce cholesterol synthesis and the amount of cholesterol secreted in bile, discouraging cholesterol stone formation.

Educational objective:
Fibrate medications (eg, fenofibrate, gemfibrozil) inhibit cholesterol 7α-hydroxylase, which catalyzes the rate-limiting step in the synthesis of bile acids. The reduced bile acid production results in decreased cholesterol solubility in bile and favors the formation of cholesterol gallstones.

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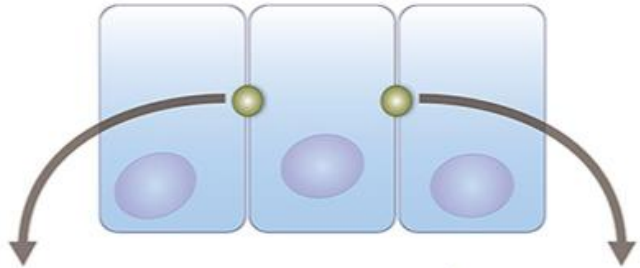
Exhibit Display

Pathogenesis of cholesterol gallstones



Normal levels of cholesterol, bile salts, and phosphatidylcholine

↓

Biliary micelles and vesicles remain unsaturated with cholesterol

↑ Cholesterol
↓ Bile acids
↓ Phosphatidylcholine

↓

Bile becomes supersaturated with cholesterol

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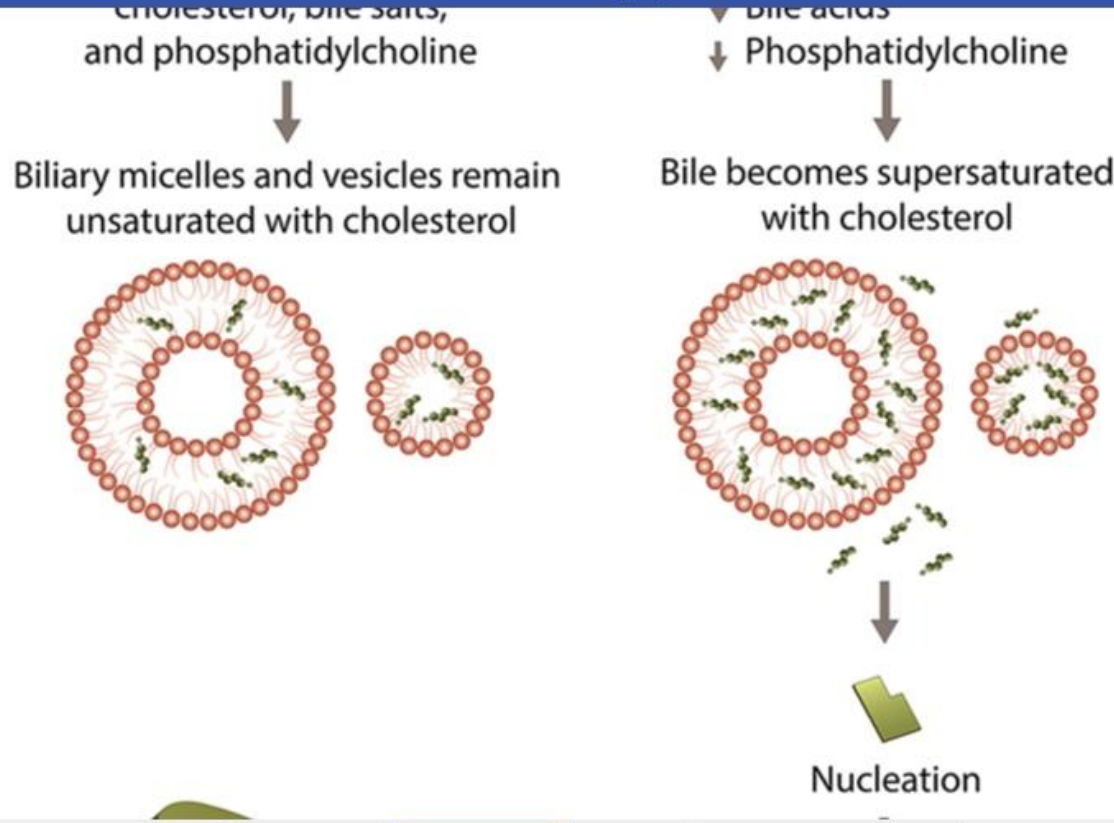

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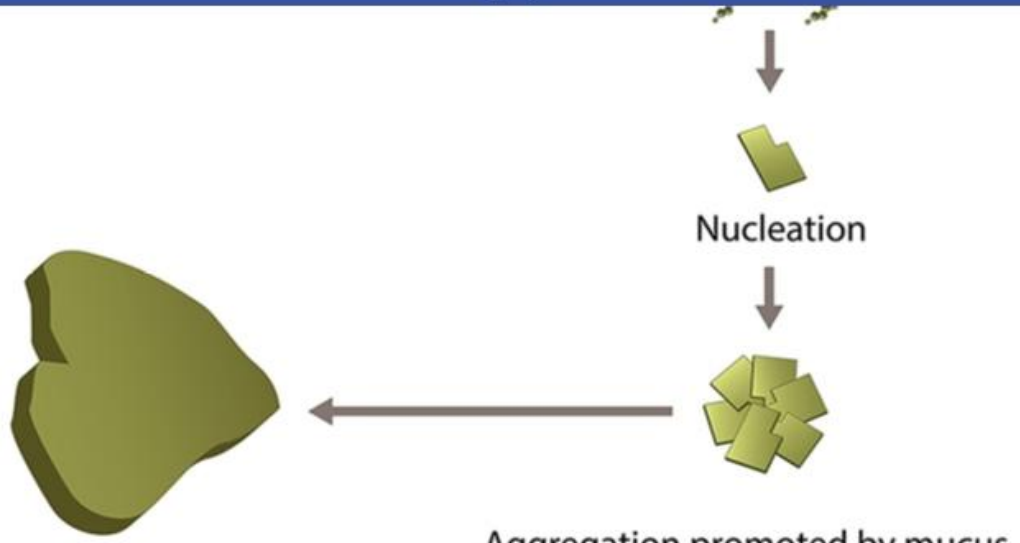

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A pharmaceutical corporation is investigating new therapeutic agents for treatment of Burkitt lymphoma. A double-stranded RNA molecule consisting of 21 base pairs is created that is complementary to a region of mRNA encoding c-Myc. Introduction of this molecule into tumor cells results in a significant reduction in cell growth. Western blot analysis of equivalent numbers of treated and untreated cells is shown below.

Which of the following processes was most likely directly interrupted by the treatment?

- A. DNA replication
- B. DNA transcription
- C. mRNA translation
- D. Proteasome activity
- E. Splicing

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Question Id: 11595

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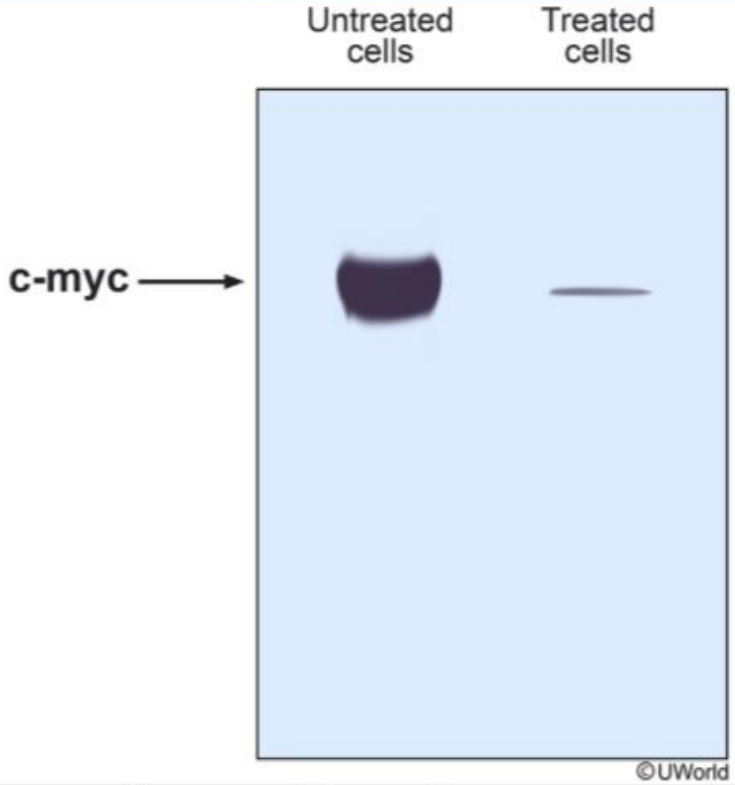

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A pharmaceutical corporation is investigating new therapeutic agents for treatment of Burkitt lymphoma. A double-stranded RNA molecule consisting of 21 base pairs is created that is complementary to a region of mRNA encoding c-Myc. Introduction of this molecule into tumor cells results in a significant reduction in cell growth. Western blot analysis of equivalent numbers of treated and untreated cells is shown below.

Which of the following processes was most likely directly interrupted by the treatment?

- A. DNA replication
- B. DNA transcription
- C. mRNA translation
- D. Proteasome activity
- E. Splicing

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2/5/2019

A pharmaceutical corporation is investigating new therapeutic agents for treatment of Burkitt lymphoma. A double-stranded RNA molecule consisting of 21 base pairs is created that is complementary to a region of mRNA encoding c-Myc. Introduction of this molecule into tumor cells results in a significant reduction in cell growth. Western blot analysis of equivalent numbers of treated and untreated cells is shown below.

Which of the following processes was most likely directly interrupted by the treatment?

- A. DNA replication [11%]
- B. DNA transcription [23%]
- ✔ C. mRNA translation [58%]
- D. Proteasome activity [2%]
- E. Splicing [3%]

Omitted
Correct answer
C

58%
Answered correctly

7 Seconds
Time Spent

08/16/2018
Last Updated

Explanation

RNA interference is an important mechanism by which short (20-30 base pair) non-coding RNA sequences induce **posttranscriptional gene silencing**. Types of silencing RNA include **small interfering RNA** (siRNA) and **microRNA** (miRNA). The human genome encodes over 1000 miRNA genes, each one capable of repressing hundreds of target genes. Altered expression of even a few miRNA genes can lead to cellular dysregulation and has been implicated in the development of many diseases, including hematologic and solid malignancies. In addition, synthetic

RNA interference is an important mechanism by which short (20-30 base pair) non-coding RNA sequences induce **posttranscriptional gene silencing**. Types of silencing RNA include **small interfering RNA** (siRNA) and **microRNA** (miRNA). The human genome encodes over 1000 miRNA genes, each one capable of repressing hundreds of target genes. Altered expression of even a few miRNA genes can lead to cellular dysregulation and has been implicated in the development of many diseases, including hematologic and solid malignancies. In addition, synthetic siRNA sequences can be introduced into cells to silence specific pathogenic genes (eg, c-Myc oncogene) and are being explored as possible **therapeutic agents**.

After being transcribed, miRNA undergoes processing in the nucleus to form a **double-stranded** precursor that is then exported into the cytoplasm. There, the precursor is cleaved into a short RNA helix by a ribonuclease protein called **dicer**. The individual strands are then separated and incorporated into **RNA-induced silencing complex** (RISC). This multiprotein complex uses its associated miRNA as a template to bind to complementary sequences found on target mRNAs. An exact match generally results in mRNA degradation, but a partial match also causes translational repression by preventing ribosome and transcription factor binding.

(Choice A) DNA polymerase requires a short nucleic acid sequence primer for initiation of DNA synthesis. During DNA replication, these primers are formed from RNA bases by the enzyme DNA primase.

(Choice B) DNA transcription is the process in which RNA is transcribed from a DNA template by an RNA polymerase enzyme. Although certain miRNA sequences can cause transcriptional inhibition, posttranscriptional silencing is the predominant means of RNA interference.

(Choice D) Degradation of proteins and polypeptides occurs in proteasomes and lysosomes. Proteasomes mainly degrade nuclear and cytoplasmic proteins; lysosomes degrade cellular organelles and extracellular proteins.

(Choice E) Small nuclear RNA (snRNA) molecules bind to specific proteins to form small nuclear ribonucleoproteins (snRNPs). These snRNPs associate with pre-mRNA to form spliceosomes, which function to remove introns from pre-mRNA during processing within the nucleus.

Educational objective:
Short non-coding RNA sequences (eg, microRNA and small interfering RNA) induce posttranscriptional gene silencing by base-pairing with complementary sequences within target mRNA molecules.

A 32-year-old man is recovering from extensive burns. Fibroblasts near the site of injury actively synthesize precursor mRNA to be used as templates for protein synthesis. After transcription, extensive processing of the precursor RNA occurs to form the finalized mRNA sequence. The finalized mRNA then exits the nucleus and undergoes translation by ribosome complexes before being degraded. Which of the following steps involving the processing and handling of mRNA occurs only within the cytoplasm of cells?

- A. 5'-terminal guanosine triphosphate addition
- B. Methylation of the 5'-terminal guanine
- C. Multiple adenine nucleotide attachment to the 3'-end
- D. Interaction with snRNP
- E. Removal of intervening sequences
- F. Interaction with P bodies

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- A. 5'-terminal guanosine triphosphate addition [6%]
- B. Methylation of the 5'-terminal guanine [13%]
- C. Multiple adenine nucleotide attachment to the 3'-end [11%]
- D. Interaction with snRNP [14%]
- E. Removal of intervening sequences [8%]
- ✔ F. Interaction with P bodies [44%]

Omitted
Correct answer
F

44%
Answered correctly

3 Seconds
Time Spent

02/05/2019
Last Updated

Explanation

After transcription, the preliminary, unprocessed mRNA is known as precursor mRNA, or heterogeneous nuclear RNA (hnRNA). Eukaryotic pre-mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

mRNA undergoes significant posttranscriptional processing before leaving the nucleus, including 5'-capping, poly A tail addition, and intron splicing.

Once mRNA is finalized, it leaves the nucleus bound to specific packaging proteins. Upon entering the cytoplasm, these mRNA complexes often associate with ribosomes to undergo translation. However, certain mRNA sequences instead associate with proteins that are found in P bodies. P bodies are distinct foci found within eukaryotic cells that are involved in mRNA regulation and turnover. They play a fundamental role in translation repression and mRNA decay, and contain numerous proteins including RNA exonucleases, mRNA decapping enzymes, and constituents involved in mRNA quality control and microRNA-induced mRNA silencing. P bodies also seem to function as a form of mRNA storage, as certain mRNAs are incorporated into P bodies only to be later released and utilized for protein translation.

(Choices A and B) The 5' end of all mRNA is capped with a 7-methylguanosine residue by a unique 5' to 5' linkage, which occurs in two stages. The first step is the addition of guanine triphosphate to the 5' end of mRNA in a reaction catalyzed by guanylyltransferase. Methylation of the guanosine cap is then catalyzed by guanine-7-methyltransferase. Capping of the precursor RNA occurs in the nucleus as the RNA is being transcribed. This methylated cap protects mRNA from degradation by cellular exonucleases, and allows it to exit the nucleus.

(Choice C) mRNA is polyadenylated at the 3' end by the polyadenylate polymerase complex, which recognizes a specific sequence (AAUAAA), cleaves the pre-mRNA molecule a few residues downstream from this sequence, and then adds a stretch of 20 - 250 adenine residues called the poly A tail. The addition of the poly A tail occurs before the mRNA exits the nucleus. In the cytosol, the poly A tail is gradually shortened, eventually leading to mRNA degradation.

(Choices D and E) Since pre-mRNA contains both introns and exons, and only exons code for proteins, introns must be excised before translation through a process known as splicing. Splicing of pre-mRNA occurs within the nucleus and is facilitated by the interaction of pre-mRNA with small ribonucleoprotein particles called snRNPs (or "snurps" for short).

Educational objective:
When mRNA is first transcribed from DNA, it is in an unprocessed form called pre-mRNA or heterogeneous nuclear mRNA (hnRNA). Several processing steps are required before finalized mRNA molecules can leave the nucleus, including 5'-capping, poly A tail addition, and intron splicing. Cytoplasmic P bodies play an important role in mRNA translation regulation and mRNA degradation.

A 6-year-old African American male is brought to your office for a routine check-up. His mother remarks that he often seems uninterested in playing with his peers and appears to "run out of breath quickly." His medical records reveal that he has missed several pediatric vaccinations and has been hospitalized twice, once with a "chest infection" and once with abdominal pain. The patient mentions to you that occasionally his "bones hurt." Which of the following protein changes most likely accounts for this patient's condition?

A. Phenylalanine deletion
B. Valine substitution for glutamic acid
C. Phenylalanine substitution for proline
D. Valine substitution for lysine
E. Early termination of polypeptide synthesis

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A 6-year-old African American male is brought to your office for a routine check-up. His mother remarks that he often seems uninterested in playing with his peers and appears to "run out of breath quickly." His medical records reveal that he has missed several pediatric vaccinations and has been hospitalized twice, once with a "chest infection" and once with abdominal pain. The patient mentions to you that occasionally his "bones hurt." Which of the following protein changes most likely accounts for this patient's condition?

- A. Phenylalanine deletion [2%]
- ✔ B. Valine substitution for glutamic acid [82%]
- C. Phenylalanine substitution for proline [3%]
- D. Valine substitution for lysine [9%]
- E. Early termination of polypeptide synthesis [2%]

Omitted
Correct answer
B

82%
Answered correctly

3 Seconds
Time Spent

08/09/2018
Last Updated

Explanation

This patient is exhibiting signs and symptoms of sickle cell anemia. Sickle cell anemia is a hemoglobinopathy that typically affects patients of African ancestry. A point mutation in the 6th codon of the beta-globin gene, which causes the substitution of valine (hydrophobic) for glutamic acid (hydrophilic), is responsible. The incorporation of this abnormal beta-globin protein into hemoglobin results in the formation of hemoglobin S (HbS). HbS polymerizes at low oxygen tension, causing sickling and hemolysis of erythrocytes and resultant vascular occlusion. This patient's

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E. Early termination of polypeptide synthesis [2%]

Omitted
Correct answer
B

82%
Answered correctly

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08/09/2018
Last Updated

Explanation

This patient is exhibiting signs and symptoms of sickle cell anemia. Sickle cell anemia is a hemoglobinopathy that typically affects patients of African ancestry. A point mutation in the 6th codon of the beta-globin gene, which causes the substitution of valine (hydrophobic) for glutamic acid (hydrophilic), is responsible. The incorporation of this abnormal beta-globin protein into hemoglobin results in the formation of hemoglobin S (HbS). HbS polymerizes at low oxygen tension, causing sickling and hemolysis of erythrocytes and resultant vascular occlusion. This patient's poor exercise tolerance and exertional dyspnea are due to anemia. His history of acute chest syndrome, abdominal pain, and bone pain are due to vaso-occlusive events in the lungs, spleen and bone, respectively.

(Choice A) A phenylalanine deletion (ΔF508) is the most common cause of cystic fibrosis, the most common fatal genetic disease of Caucasians.

(Choice E) Early termination of polypeptide synthesis (nonsense mutation) will produce a truncated protein.

Educational Objective:
Exertional dyspnea, pneumonia resulting in life-threatening acute chest syndrome, and recurrent abdominal and bone pain are clinical features of sickle cell anemia. Sickle cell anemia results from a point mutation that causes valine to substitute for glutamic acid in the sixth position of the b-globin chain of hemoglobin.

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2/5/2019

A 46-year-old man comes to the emergency department due to recurrent nosebleeds. When interviewed for additional history, he becomes belligerent and uncooperative. The patient has a history of alcohol abuse and chronic mental illness. He has been placed in homeless shelters on multiple occasions but has not remained there for any prolonged periods. Physical examination shows swollen gums, scattered ecchymoses, and hyperkeratosis. He also has a chronic ulcer on the left lower extremity that does not appear to be infected. Which of the following mechanisms accounts for this patient's examination findings?

- A. Abnormal oxidative decarboxylation of ketoacids
- B. Abnormal proline hydroxylation
- C. Abnormal transamination
- D. Deficient methionine synthesis
- E. Diminished synthesis of purines

Submit

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2/5/2019

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- A. Abnormal oxidative decarboxylation of ketoacids [4%]
- ✔ B. Abnormal proline hydroxylation [80%]
- C. Abnormal transamination [4%]
- D. Deficient methionine synthesis [5%]
- E. Diminished synthesis of purines [4%]

Omitted
Correct answer
B

80%
Answered correctly

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01/28/2019
Last Updated

Explanation

In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug abusers). Symptoms of vitamin C deficiency are the result of decreased connective tissue strength. The capillary walls are especially fragile, leading to **easy bruising**, mucosal bleeding, and perifollicular petechial hemorrhages. Patients may also suffer from **periodontal disease** (gum

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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug abusers). Symptoms of vitamin C deficiency are the result of decreased connective tissue strength. The capillary walls are especially fragile, leading to **easy bruising**, mucosal bleeding, and perifollicular petechial hemorrhages. Patients may also suffer from **periodontal disease** (gum swelling, loosening of the teeth, and infection) and **poor wound healing**, and have **hyperkeratotic follicles** with corkscrew hairs. Scurvy is even more severe in children and manifests with hemorrhages, bony deformities, and subperiosteal and joint hematomas.

Vitamin C is necessary for the **hydroxylation of proline and lysine** residues during **collagen synthesis**. This reaction is executed by prolyl and lysyl hydroxylases, with vitamin C serving as a reducing agent. Hydroxyproline and hydroxylysine are essential for cross-linking collagen molecules. In scurvy, collagen cross-linking is compromised, thereby greatly reducing its tensile strength.

(Choice A) Thiamine (vitamin B_1) serves as a coenzyme in the decarboxylation reactions mediated by several dehydrogenase enzymes. It is necessary for the conversions of pyruvate to acetyl-CoA and of alpha-ketoglutarate to succinyl-CoA in the citric acid cycle. Vitamin B_1 deficiency can cause peripheral neuropathy, heart failure, and central nervous system dysfunction (Wernicke-Korsakoff syndrome).

(Choice C) Vitamin B_6 (pyridoxine) serves as a cofactor in many reactions that involve amino acids (eg, transamination, decarboxylation, deamination). Pyridoxine deficiency manifests with seborrheic dermatitis, glossitis, and peripheral neuropathy.

(Choice D) Vitamin B_{12} is necessary for the synthesis of methionine from homocysteine and for the synthesis of succinyl-CoA from methylmalonyl-CoA. Deficiency of vitamin B_{12} causes megaloblastic anemia and subacute combined degeneration of the spinal cord.

(Choice E) Purine and thymidine synthesis is diminished in patients with folate deficiency. The resultant decreased ability of erythropoietic cells to form DNA causes megaloblastic anemia.

Educational objective:
Vitamin C is necessary for the hydroxylation of proline and lysine residues in pro-collagen. Vitamin C deficiency (scurvy) is most often seen in severely malnourished individuals and leads to capillary bleeding, poor wound healing, and periodontal disease. In children, bony deformities and subperiosteal hemorrhages are also characteristic.

References

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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug

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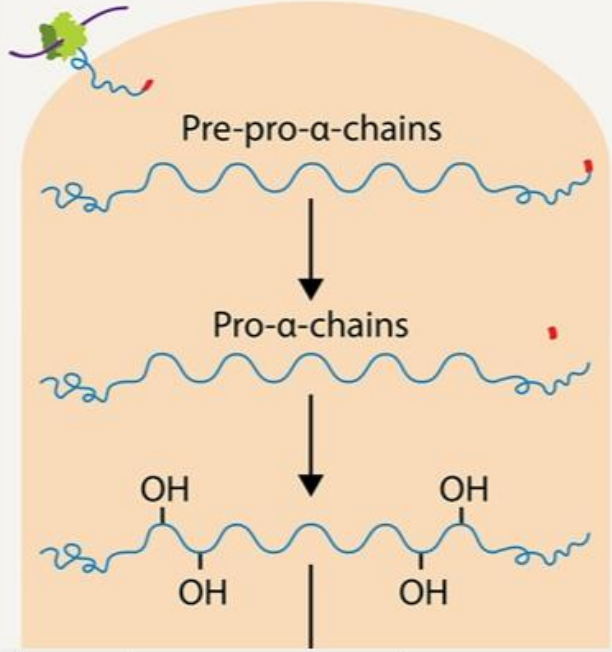
Collagen synthesis

Signal sequence directs growing polypeptide chain into endoplasmic reticulum

Signal sequence is cleaved

Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**



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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug

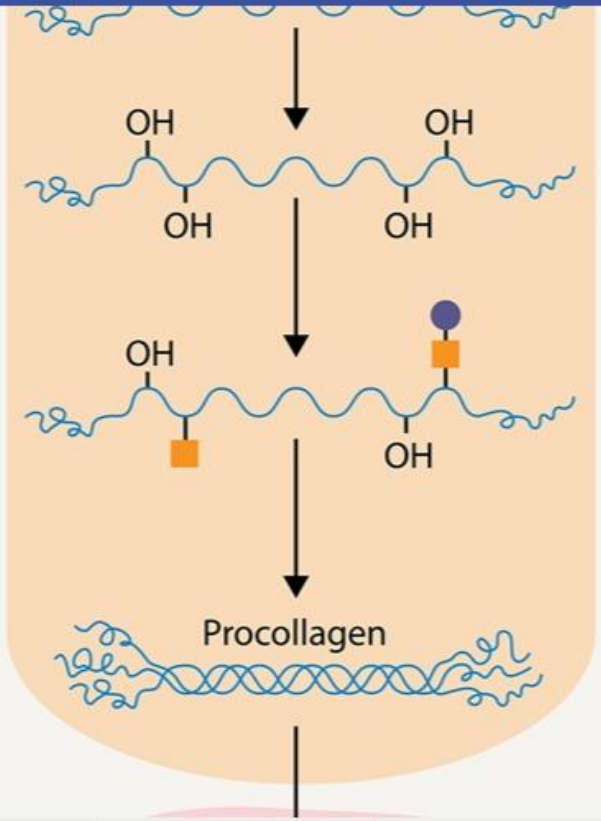
Exhibit Display

Hydroxylation of selected proline & lysine residues **(vitamin C dependent)**

Glycosylation of selected hydroxylysine residues

Galactose
Glucose

Assembly of pro-α-chains into **procollagen triple helix**



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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug

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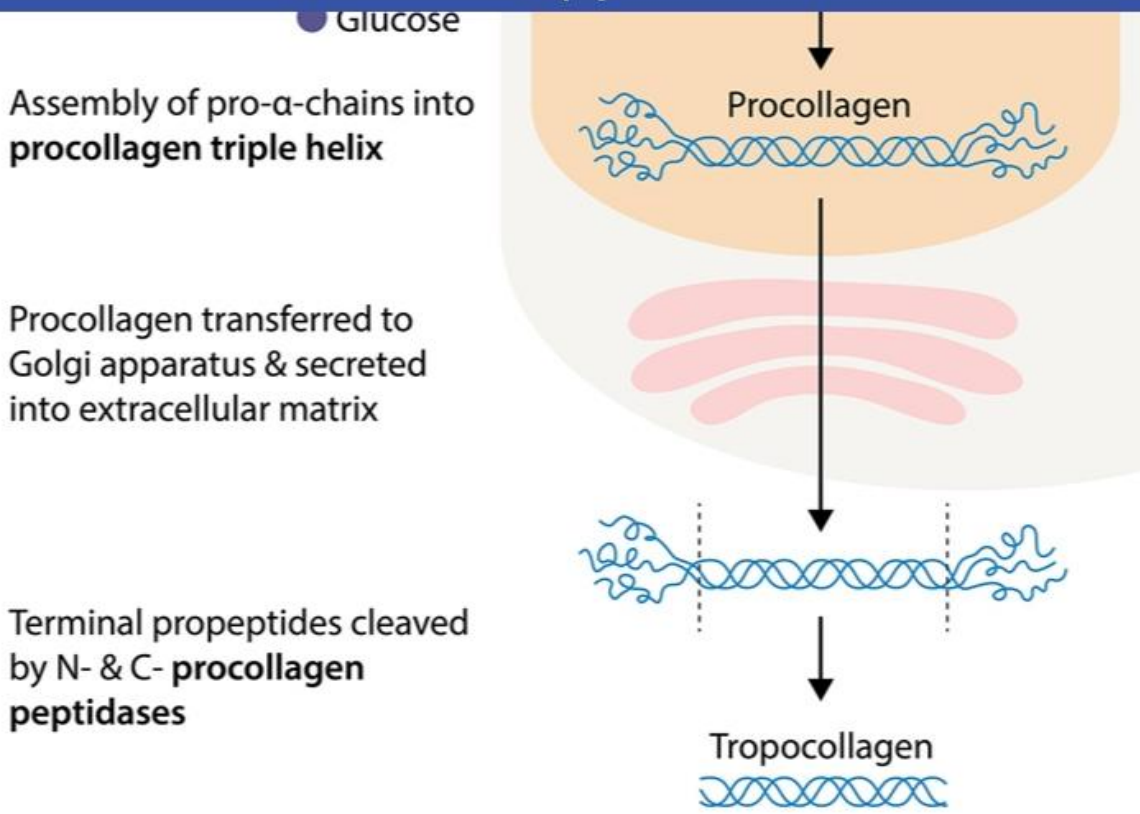

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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug

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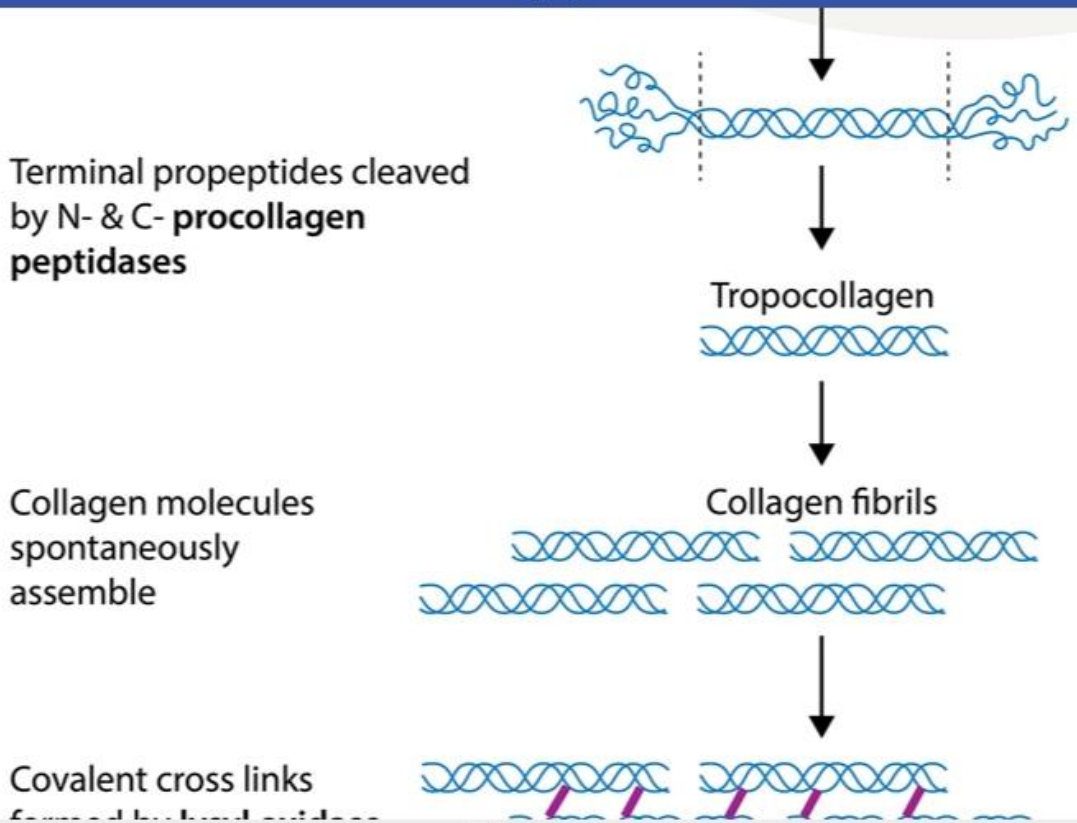

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In the United States, **vitamin C deficiency (scurvy)** is most often seen in severely malnourished individuals (eg, homeless, alcohol or drug

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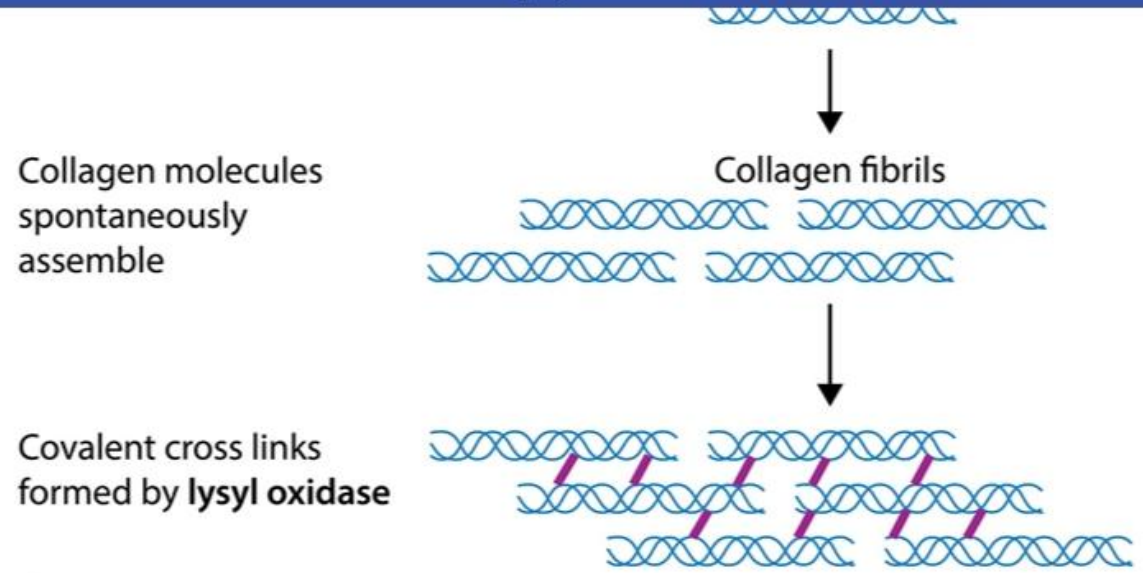

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2/5/2019

A 44-year-old homeless man is brought to the emergency department after police officers found him agitated and confused. During transport to the hospital, he is started on intravenous fluids with dextrose. On arrival, the patient is disoriented but cooperative. Physical examination shows bruises on his forehead, forearms, and shins. Extraocular findings include bilateral horizontal nystagmus and decreased lateral eye movements. He also has an unsteady gait with widely-spaced legs and short steps. The ambulance personnel state that the patient's extraocular movements were intact when they picked him up. A review of the medical record shows that the patient has been admitted to the hospital with alcohol intoxication several times before. Which of the following reactions is likely to be the most impaired in this patient?

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

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Item 31 of 40
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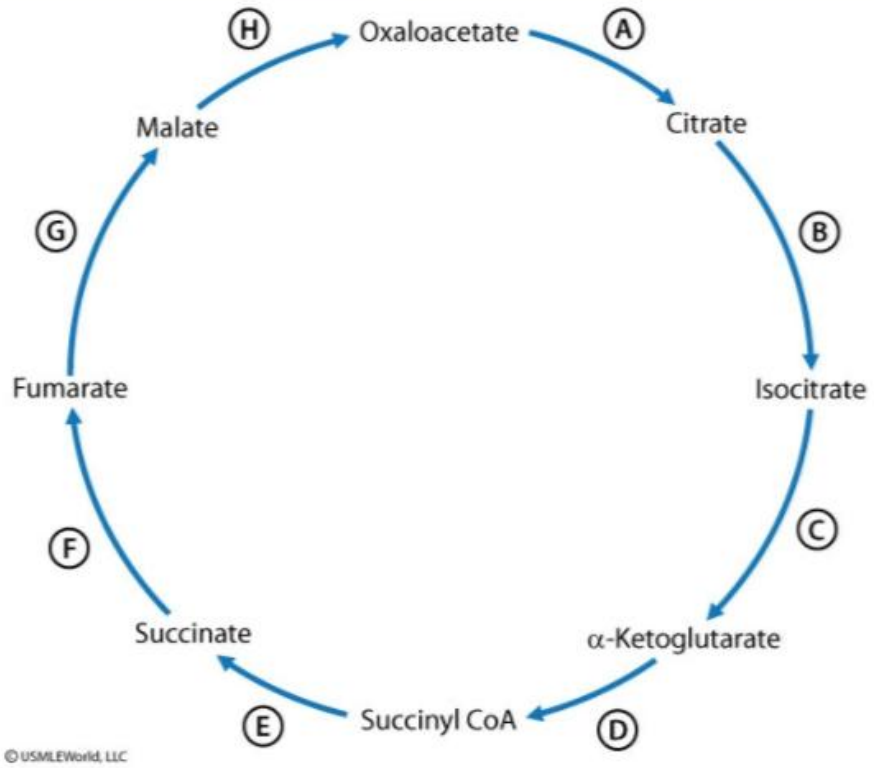

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12:24 PM
2/9/2019

A 44-year-old homeless man is brought to the emergency department after police officers found him agitated and confused. During transport to the hospital, he is started on intravenous fluids with dextrose. On arrival, the patient is disoriented but cooperative. Physical examination shows bruises on his forehead, forearms, and shins. Extraocular findings include bilateral horizontal nystagmus and decreased lateral eye movements. He also has an unsteady gait with widely-spaced legs and short steps. The ambulance personnel state that the patient's extraocular movements were intact when they picked him up. A review of the medical record shows that the patient has been admitted to the hospital with alcohol intoxication several times before. Which of the following reactions is likely to be the most impaired in this patient?

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11:08 PM
2/5/2019

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- A. A [10%]
- B. B [2%]
- C. C [12%]
- ✔ D. D [57%]
- E. E [5%]
- F. F [3%]
- G. G [1%]
- H. H [7%]

Omitted
Correct answer
D

57%
Answered correctly

4 Seconds
Time Spent

11/08/2018
Last Updated

11:08 PM
2/5/2019

Omitted
Correct answer
D

57%
Answered correctly

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11/08/2018
Last Updated

Explanation

Patients with **chronic alcoholism** are frequently deficient in **thiamine**, a necessary cofactor for **pyruvate dehydrogenase, α-ketoglutarate dehydrogenase**, and transketolase. Administration of glucose to thiamine-deficient patients can cause rapid depletion of the small amount of thiamine remaining in the circulation. This can result in neuronal injury within highly metabolic brain regions, leading to acute **Wernicke encephalopathy**.

The metabolism of ethanol by alcohol dehydrogenase and aldehyde dehydrogenase consumes NAD^+ and increases the **NADH to NAD^+ ratio**. This skewed ratio inhibits all pathways requiring NAD^+; as a result, the entire citric acid cycle is inhibited. However, in the setting of Wernicke encephalopathy, thiamine-dependent enzymes are especially affected due to the lack of NAD^+ and thiamine **(Choices A, B, C, E, F, G, and H)**.

Educational objective:
Pyruvate dehydrogenase and α-ketoglutarate dehydrogenase require thiamine as a cofactor. Administration of glucose to thiamine-deficient patients (eg, alcoholics) can result in Wernicke encephalopathy (eg, acute confusion, ophthalmoplegia, and ataxia) due to increased thiamine demand.

References

- Thiamine pyrophosphate-requiring enzymes are altered during pyrithiamine-induced thiamine deficiency in cultured human lymphoblasts.
- Dietary thiamin level influences levels of its diphosphate form and thiamin-dependent enzymic activities of rat liver.

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11:08 PM
2/5/2019

Omitted
Correct answer
D

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11/08/2018

Explanation

Patients with **chronic alcoholi** **dehydrogenase**, and transketo thiamine remaining in the circul **encephalopathy**.

The metabolism of ethanol by a This skewed ratio inhibits all pa encephalopathy, thiamine-depe

Educational objective:
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References

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Exhibit Display

Wernicke encephalopathy	
Associated conditions	• Chronic alcoholism (most common) • Malnutrition (eg, anorexia nervosa) • Hyperemesis gravidarum
Pathophysiology	• Thiamine deficiency
Clinical features	• **Encephalopathy** • **Oculomotor dysfunction** (eg, horizontal nystagmus, bilateral abducens palsy) • Postural & gait **ataxia**
Treatment	• Intravenous thiamine followed by glucose infusion

Add To Flash Card

11:08 PM
2/5/2019

A 31-year-old man comes to the office for a routine checkup. He has no significant medical problems and does not take any medications. The patient works as a fitness trainer and lifts weights recreationally. He has been consuming carbohydrate-rich food prior to his weightlifting sessions and claims that it increases muscle strength. A literature review shows that the rate of glycogenolysis within myocytes increases several hundredfold during active skeletal muscle contraction. Which of the following substances is most likely responsible for increasing the reaction rate during active contraction?

- A. ATP
- B. Ca^{2+}
- C. cAMP
- D. Glucose-6-phosphate
- E. Lactate

Submit

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11:08 PM
2/5/2019

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- A. ATP [15%]
- ✔ B. Ca^{2+} [38%]
- C. cAMP [22%]
- D. Glucose-6-phosphate [6%]
- E. Lactate [16%]

Omitted
Correct answer
B

38%
Answered correctly

3 Seconds
Time Spent

11/03/2018
Last Updated

Explanation

Glycogen is broken down by the enzyme **glycogen phosphorylase**, which is regulated through phosphorylation (active state) and dephosphorylation (inactive state). **Phosphorylase kinase (PK)** is the enzyme responsible for the phosphorylation of glycogen phosphorylase, whereas **phosphoprotein phosphatase** catalyzes its dephosphorylation.

11:08 PM
2/5/2019

Glycogen is broken down by the enzyme **glycogen phosphorylase**, which is regulated through phosphorylation (active state) and dephosphorylation (inactive state). **Phosphorylase kinase (PK)** is the enzyme responsible for the phosphorylation of glycogen phosphorylase, whereas **phosphoprotein phosphatase** catalyzes its dephosphorylation.

PK is regulated differently in liver than in muscles. Glycogen stored in the **liver** is used to maintain blood glucose levels during the fasting state, whereas glycogen in the muscles is used to provide energy for muscle contraction. In the liver, PK is activated primarily through the binding of **epinephrine and glucagon** to G_s protein-coupled receptors, which **increases cAMP concentrations** and causes phosphorylation of PK (via protein kinase A).

Skeletal muscle lacks glucagon receptors, but muscle PK can still be phosphorylated in response to an epinephrine-induced increase in cAMP concentrations. However, increased **intracellular calcium** is a more powerful activator of muscle PK. Release of sarcoplasmic calcium stores following neuromuscular acetylcholine stimulation allows for **synchronization** of skeletal muscle contraction and glycogen breakdown, providing the energy necessary for anaerobic muscle contraction.

(Choices A and D) Phosphorylated glycogen phosphorylase (active form) is allosterically inhibited by ATP and glucose-6-phosphate in both liver and muscle cells. Increased intracellular ATP levels help to decrease the rate of glycogenolysis upon cessation of active muscle contraction.

(Choice C) Although increased cAMP stimulates muscle glycogen breakdown via the action of epinephrine on beta-1 adrenergic receptors, it is not responsible for synchronization of active muscle contraction and glycogen breakdown.

(Choice E) Lactate is produced in tissues during anaerobic glycolysis, such as in muscles during strenuous exercise as a result of relatively hypoxic conditions. The lactate produced by the muscles can be converted to glucose in the liver via gluconeogenesis.

Educational objective:
Synchronization of glycogen degradation with skeletal muscle contraction occurs due to release of sarcoplasmic calcium following neuromuscular stimulation. Increased intracellular calcium causes activation of phosphorylase kinase, stimulating glycogen phosphorylase to increase glycogenolysis.

11:08 PM
2/5/2019

A 62-year-old man comes to the emergency department due to severe colicky upper abdominal pain, nausea, and vomiting. He reports several episodes of similar abdominal discomfort in the past. The patient does not use tobacco, alcohol, or illicit drugs. He immigrated to the United States from East Asia several years ago. Physical examination shows right upper quadrant abdominal tenderness. An imaging study shows several gallstones in the common bile duct and gallbladder. The stones are removed from the duct endoscopically, and a cholecystectomy is also performed. The gallstones are dark brown, soft, and composed primarily of calcium bilirubinate with variable amounts of cholesterol. Which of the following enzymes most likely played an important role in the pathogenesis of this patient's condition?

A. 7-alpha-hydroxylase
B. Aromatase
C. Beta-glucuronidase
D. Desmolase
E. HMG-CoA reductase

Submit

11:09 PM
2/5/2019

A 62-year-old man comes to the emergency department due to severe colicky upper abdominal pain, nausea, and vomiting. He reports several episodes of similar abdominal discomfort in the past. The patient does not use tobacco, alcohol, or illicit drugs. He immigrated to the United States from East Asia several years ago. Physical examination shows right upper quadrant abdominal tenderness. An imaging study shows several gallstones in the common bile duct and gallbladder. The stones are removed from the duct endoscopically, and a cholecystectomy is also performed. The gallstones are dark brown, soft, and composed primarily of calcium bilirubinate with variable amounts of cholesterol. Which of the following enzymes most likely played an important role in the pathogenesis of this patient's condition?

- A. 7-alpha-hydroxylase [27%]
- B. Aromatase [1%]
- ✔ C. Beta-glucuronidase [45%]
- D. Desmolase [3%]
- E. HMG-CoA reductase [22%]

Omitted
Correct answer
C

45%
Answered correctly

3 Seconds
Time Spent

09/07/2018
Last Updated

Explanation

Gallstones can be categorized as cholesterol, pigment, or mixed stones. Cholesterol stones are formed when the ability of bile salts to solubilize cholesterol is overwhelmed by high concentrations of cholesterol in bile. Cholesterol stones are yellow to pale gray and hard. By contrast,

Gallstones can be categorized as cholesterol, pigment, or mixed stones. Cholesterol stones are formed when the ability of bile salts to solubilize cholesterol is overwhelmed by high concentrations of cholesterol in bile. Cholesterol stones are yellow to pale gray and hard. By contrast, **pigment gallstones** are composed of calcium salts of **unconjugated bilirubin**, are comparatively soft, and are dark brown to black.

Brown pigment stones typically arise secondary to bacterial (eg, *Escherichia coli*) or helminthic (eg, *Ascaris lumbricoides, Clonorchis sinensis*) **infection of the biliary tract**, which results in the release of **beta-glucuronidase** by injured hepatocytes and bacteria. This enzyme hydrolyzes bilirubin glucuronides and increases the amount of unconjugated bilirubin. The liver fluke *C sinensis* is a common cause of pigmented stones in East Asian countries and can have a prolonged quiescent phase before inducing symptoms.

Pigment stones may also occur in the absence of infection when excess bilirubin is excreted, such as with chronic **hemolytic anemia**. A small amount of conjugated bilirubin normally becomes deconjugated by endogenous beta-glucuronidase in the biliary tract. When large amounts of conjugated bilirubin are excreted into the bile, enough becomes deconjugated to promote black pigment stone formation.

(Choice A) Inhibition of 7-alpha-hydroxylase (eg, fibrates) reduces the conversion of cholesterol to bile acids and increases the risk of cholesterol stones. However, this patient's gallstones are composed primarily of unconjugated bilirubin, not cholesterol.

(Choices B and E) Aromatase catalyzes the conversion of androgens to estrogen, which increases hepatic cholesterol uptake. In addition, estrogens upregulate HMG Co-A reductase, which increases cholesterol synthesis. This increases biliary excretion of cholesterol, favoring formation of cholesterol stones, not pigment stones.

(Choice D) Desmolase (cholesterol side-chain cleavage enzyme) catalyzes the conversion of cholesterol to pregnenolone, which is the first step in the synthesis of steroid hormones.

Educational objective:
Brown pigment gallstones are composed of calcium salts of unconjugated bilirubin and arise secondary to bacterial or helminthic infection of the biliary tract. Beta-glucuronidase released by injured hepatocytes and bacteria hydrolyzes bilirubin glucuronides to unconjugated bilirubin. The liver fluke *Clonorchis sinensis* has a high prevalence in East Asian countries and is a common cause of pigment stones.

11:09 PM
2/5/2019

An 18-month-old boy is brought to the office due to language regression. He said several words at his 1-year appointment but now no longer speaks any words at all. His moods have also become more unpredictable over the past 4 months with frequent tantrums. The parents tried to bring him in sooner for evaluation, but they live in an impoverished part of the city and experienced financial difficulties with transportation to the office. On physical examination, the boy is quiet and maintains appropriate eye contact throughout the visit. Hemoglobin is 9 g/dL. Which of the following enzymes is most likely inhibited in this patient?

- A. δ-Aminolevulinate dehydratase
- B. Bilirubin glucuronyl transferase
- C. Porphobilinogen deaminase
- D. Pyruvate kinase
- E. Uroporphyrinogen decarboxylase

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11:09 PM
2/5/2019

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- A. δ-Aminolevulinate dehydratase [61%]
- B. Bilirubin glucuronyl transferase [5%]
- C. Porphobilinogen deaminase [15%]
- D. Pyruvate kinase [7%]
- E. Uroporphyrinogen decarboxylase [9%]

Omitted
Correct answer
A

61%
Answered correctly

3 Seconds
Time Spent

01/11/2019
Last Updated

Explanation

This child's language regression and anemia are most likely due to lead poisoning. **Lead toxicity** is most prevalent among **impoverished children** residing in deteriorating urban **housing built before 1978**. Young children are particularly susceptible to lead poisoning via inhalation and ingestion of lead-based paint dust or chips due to normal crawling and mouthing behaviors. The incomplete blood-brain-barrier in children is

This child's language regression and anemia are most likely due to lead poisoning. **Lead toxicity** is most prevalent among **impoverished children** residing in deteriorating urban **housing built before 1978**. Young children are particularly susceptible to lead poisoning via inhalation and ingestion of lead-based paint dust or chips due to normal crawling and mouthing behaviors. The incomplete blood-brain-barrier in children is vulnerable to the **neurotoxic** effects of lead, which include long-standing behavioral problems and developmental delay or regression.

Anemia in lead poisoning results from inhibition of **ferrochelatase** and **δ-aminolevulinic acid (ALA) dehydratase** in the heme biosynthesis pathway. Because protoporphyrin IX cannot combine with iron (Fe^{2+}) to form heme due to ferrochelatase inhibition, it instead incorporates a zinc ion, leading to **elevated zinc protoporphyrin levels**. In addition, ALA levels are increased. Lead poisoning also commonly coexists with iron deficiency anemia, and severe lead poisoning can also induce hemolytic anemia.

(Choice B) Glucuronyl transferase (uridine 5'-diphospho-glucuronosyltransferase) is necessary for hepatic bilirubin conjugation. Gilbert syndrome, a condition marked by jaundice (elevated unconjugated bilirubin levels) during times of stress, results from mutations in the gene encoding glucuronyl transferase.

(Choice C) Defects in porphobilinogen deaminase result in acute intermittent porphyria (AIP), a disorder characterized by acute attacks of abdominal pain, neuropsychiatric symptoms, and **red or brown urine**. The chronicity of symptoms, lack of abdominal pain, and anemia make AIP unlikely in this patient.

(Choice D) Pyruvate kinase deficiency is typically inherited in an autosomal recessive pattern and leads to hemolytic anemia. Pyruvate kinase deficiency can present with pallor, scleral icterus, and splenomegaly, but it does not present with behavioral regression or language difficulties.

(Choice E) Defects in uroporphyrinogen decarboxylase cause porphyria cutanea tarda (PCT), the most common form of porphyria. Patients with PCT exhibit chronic **photosensitivity** with blistering in areas of sun exposure and elevated levels of uroporphyrinogen in the urine.

Educational objective:
Young children who reside in homes built before 1978 are at significant risk for lead toxicity. Lead directly inhibits ferrochelatase and δ-aminolevulinic acid (ALA) dehydratase, resulting in anemia, ALA accumulation, and elevated zinc protoporphyrin levels. Neurotoxicity is also a significant long-term complication.

11:09 PM
2/5/2019

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References

- Lead toxicity, a review of the literature. Part 1: Exposure, evaluation, and treatment.
- A study on the ALAD gene polymorphisms associated with lead exposure.
- The important health impact of where a child lives: neighborhood characteristics and the burden of lead poisoning.

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11:09 PM
2/5/2019

A 35-year-old female is hospitalized with headaches and vomiting. She has a long history of psychiatric illness and is known to practice eccentric dietary habits. Physical findings include papilledema, dry skin and hepatosplenomegaly. Head CT scan is ordered immediately but is negative for intracranial mass. Which of the following is a likely cause of this patient's condition?

A. Thiamine deficiency
B. Niacin deficiency
C. Vitamin B_{12} deficiency
D. Riboflavin deficiency
E. Vitamin C overuse
F. Vitamin E overuse
G. Vitamin A overuse

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11:09 PM
2/5/2019

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- A. Thiamine deficiency [8%]
- B. Niacin deficiency [11%]
- C. Vitamin B_{12} deficiency [5%]
- D. Riboflavin deficiency [4%]
- E. Vitamin C overuse [2%]
- F. Vitamin E overuse [5%]
- ✔ G. Vitamin A overuse [61%]

Omitted
Correct answer
G

61%
Answered correctly

3 Seconds
Time Spent

08/09/2018
Last Updated

Explanation

Individuals who consume more than 10 times the Daily Value (Recommended Dietary Allowance) of vitamin A are prone to developing toxicity and may suffer hepatic injury so severe as to cause cirrhosis.

Explanation

Individuals who consume more than 10 times the Daily Value (Recommended Dietary Allowance) of vitamin A are prone to developing toxicity and may suffer hepatic injury so severe as to cause cirrhosis.

Vitamin A toxicity has been subdivided into three syndromes: acute, chronic, and teratogenic. The signs and symptoms of acute toxicity occur after the ingestion of a single high dose of vitamin A and include nausea, vomiting, vertigo, and blurred vision. The signs and symptoms of chronic toxicity occur after the long-term ingestion of high doses of vitamin A, and include alopecia, dry skin, hyperlipidemia, hepatotoxicity, hepatosplenomegaly, and visual difficulties. Papilledema, when present, is suggestive of cerebral edema in the setting of benign intracranial hypertension (pseudotumor cerebri). Teratogenic effects of excessive vitamin A ingestion include microcephaly, cardiac anomalies, and fetal death (especially in the first trimester of pregnancy).

(Choice A) Thiamine deficiency is associated with infantile and adult beriberi, as well as Wernicke-Korsakoff syndrome in alcoholics.

(Choice B) Niacin deficiency is characterized by the 3 D's of pellagra: (dementia, dermatitis, and diarrhea).

(Choice C) Vitamin B_{12} (cobalamin) deficiency is frequently associated with pernicious anemia. The classic presentation of pernicious anemia is an older, mentally slow woman of northern European descent who is "lemon colored" (anemic and icteric), has a smooth, shiny tongue indicative of atrophic glossitis, and demonstrates a shuffling broad-based gait.

(Choice D) Vitamin B2 (riboflavin) deficiency is characterized by cheilosis, stomatitis, glossitis, dermatitis, corneal vascularization, and ariboflavinosis.

(Choice E) Large doses of vitamin C can give false negative stool guaiac results and are associated with diarrhea and abdominal bloating. Some studies suggest an association between high doses of vitamin C and calcium oxalate nephrolithiasis, though this remains controversial.

(Choice F) Large doses of vitamin E have been associated with higher mortality rates due to hemorrhagic stroke in adults and higher rates of necrotizing enterocolitis in infants.

Educational Objective:
Vitamin A overuse can result in intracranial hypertension, skin changes and hepatosplenomegaly.

may suffer hepatic injury so severe as to cause cirrhosis.

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(Choice F) Large doses of vitamin E have been associated with higher mortality rates due to hemorrhagic stroke in adults and higher rates of necrotizing enterocolitis in infants.

Educational Objective:
Vitamin A overuse can result in intracranial hypertension, skin changes and hepatosplenomegaly.

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11:09 PM
2/5/2019

A 72-year-old woman is brought to the emergency department after lying on the floor in her home for the past 2 days. The patient's neighbor called police after phone calls were not answered and no one opened the door. She was found awake on the bathroom floor lying in feces and urine. The patient says she fell and injured her right hip and was unable to get up to call for help. She did not eat or drink anything during that time. On examination, the patient appears dehydrated and has right hip tenderness. Laboratory studies show serum glucose of 72 mg/dL and positive urine ketones. Radiographs of the right hip show a right femoral neck fracture. Increased activity of which of the following enzymes is most likely contributing to both the serum and urine laboratory findings?

- A. Glycogen phosphorylase
- B. Hormone-sensitive lipase
- C. Lipoprotein lipase
- D. Mitochondrial HMG CoA synthase
- E. Phosphofructokinase-1

Submit

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11:09 PM
2/5/2019

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- A. Glycogen phosphorylase [17%]
- ✔ B. Hormone-sensitive lipase [40%]
- C. Lipoprotein lipase [11%]
- D. Mitochondrial HMG CoA synthase [20%]
- E. Phosphofructokinase-1 [10%]

Omitted
Correct answer
B

40%
Answered correctly

3 Seconds
Time Spent

12/19/2018
Last Updated

Explanation

This patient's laboratory studies show the presence of ketones in the urine and maintenance of fasting blood glucose values in the low-normal range despite prolonged fasting.

11:09 PM
2/5/2019

This patient's laboratory studies show the presence of ketones in the urine and maintenance of fasting blood glucose values in the low-normal range despite prolonged fasting.

Hormone-sensitive lipase (HSL) is an enzyme found in adipose tissue that catalyzes the mobilization of stored triglycerides into **free fatty acids** (FFAs) and **glycerol**. HSL is activated in response to stress hormones (eg, catecholamines, glucagon, ACTH), whereas it is inhibited by the release of insulin. The stress hormones stimulate Gs protein-coupled receptors on adipocytes, leading to increased cAMP production and activation of protein kinase A (PKA). Finally, PKA phosphorylates and activates HSL, stimulating lipolysis.

FFAs and glycerol released into the circulation can be taken up by the liver, where the glycerol is used primarily as a carbon source for **gluconeogenesis**. The liver oxidizes the FFAs to acetyl-coA, which can then be further metabolized to **ketone bodies** (eg, acetoacetate, beta-hydroxybutyrate) or shunted into the TCA cycle to generate energy for gluconeogenesis. During starvation, most tissues utilize a combination of FFAs and ketones for their energy needs. Important exceptions include the brain (FFAs do not cross the blood-brain barrier, so only ketone bodies/glucose can be used) and erythrocytes (can use only glucose due to lack of mitochondria).

(Choice A) Glycogen phosphorylase is the rate-limiting enzyme in glycogenolysis, a process that frees glucose-1-phosphate from stored glycogen chains. Glycogenolysis increases blood glucose levels during the first several hours of fasting but has no effect on fatty acid oxidation.

(Choice C) Lipoprotein lipase is an enzyme found on endothelial cells that functions to degrade triglycerides found in chylomicrons and VLDL. Although it is functionally similar to HSL, it works in the bloodstream to form FFAs that are then transported into adipocytes storage or used by tissues (eg, heart/skeletal muscle) for energy production.

(Choice D) Mitochondrial HMG-CoA synthase plays a role in the production of ketones. Although it could be responsible for the presence of urinary ketone bodies in this patient, it would not account for the maintenance of blood glucose levels.

(Choice E) Phosphofructokinase-1 catalyzes the major rate-limiting step in glycolysis by converting fructose-6-phosphate to fructose-1,6-bisphosphate. It is not involved in gluconeogenesis or ketone production.

Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates for hepatic gluconeogenesis and ketone body formation.

11:09 PM
2/5/2019

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Educational objective:
Hormone-sensitive lipase is found in adipose tissue, where it functions to drive the breakdown of stored triglycerides into free fatty acids and glycerol. During times of starvation, this enzyme provides substrates for hepatic gluconeogenesis and ketone body formation.

References

- Lipolysis: more than just a lipase.

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11:09 PM
2/5/2019

A 4-day-old girl is brought to the office for a routine newborn visit. She was born at 39 weeks gestation via normal spontaneous vaginal delivery to a gravida 5 para 4 woman. The patient has been breastfed exclusively but has had increasing difficulty feeding over the past 24 hours. Her parents say that she is "too sleepy to feed" and has been vomiting. The infant has 3 healthy, living siblings and a brother who died in infancy from "low sugar in his blood." Physical examination shows tachypnea and signs of dehydration. The patient is responsive to painful stimuli only. After acute treatment and stabilization, urine testing reveals significantly elevated levels of methylmalonic acid. Which of the following sets of laboratory values would most likely result from this patient's condition?

	Urine propionic acid	Serum glucose	Urine ketones	Serum ammonia
A.	Normal	↓	↑	Normal
B.	↑	↓	↑	↑
C.	Normal	↓	Negative	↑
D.	Normal	Normal	Negative	↑
E.	Normal	↓	↑	↓

Submit

11:09 PM
2/5/2019

A 4-day-old girl is brought to the office for a routine newborn visit. She was born at 39 weeks gestation via normal spontaneous vaginal delivery to a gravida 5 para 4 woman. The patient has been breastfed exclusively but has had increasing difficulty feeding over the past 24 hours. Her parents say that she is "too sleepy to feed" and has been vomiting. The infant has 3 healthy, living siblings and a brother who died in infancy from "low sugar in his blood." Physical examination shows tachypnea and signs of dehydration. The patient is responsive to painful stimuli only. After acute treatment and stabilization, urine testing reveals significantly elevated levels of methylmalonic acid. Which of the following sets of laboratory values would most likely result from this patient's condition?

	Urine propionic acid	Serum glucose	Urine ketones	Serum ammonia
A. [15%]	Normal	↓	↑	Normal
✔ B. [47%]	↑	↓	↑	↑
C. [26%]	Normal	↓	Negative	↑
D. [3%]	Normal	Normal	Negative	↑
E. [7%]	Normal	↓	↑	↓

Omitted
Correct answer
B

47%
Answered correctly

3 Seconds
Time Spent

02/02/2019
Last Updated

11:10 PM
2/5/2019

Explanation

This patient's presentation is consistent with methylmalonic acidemia, an **autosomal recessive organic acidemia** resulting from complete or partial deficiency of the enzyme **methylmalonyl-CoA mutase**.

Catabolism of isoleucine, valine, threonine, methionine, and odd-chain fatty acids normally leads to formation of propionyl CoA, which is then converted to methylmalonyl CoA by biotin-dependent carboxylation. Isomerization of methylmalonyl CoA through a vitamin B12-dependent reaction forms succinyl CoA, which subsequently enters the TCA cycle. Mutations in methylmalonyl-CoA mutase result in buildup of methylmalonic acid and propionic acid, leading to a **metabolic acidosis**. **Hypoglycemia** results from overall increased metabolic rate leading to increased glucose utilization and direct toxic inhibition of gluconeogenesis by the organic acids. The presence of hypoglycemia leads to increased free fatty acid metabolism that produces **ketones**, resulting in a further anion gap metabolic acidosis. Finally, organic acids also directly inhibit the urea cycle, leading to **hyperammonemia**.

Complete deficiency of methylmalonyl-CoA mutase results in an anion gap metabolic acidosis, hypoglycemia, ketosis, and hyperammonemia. These metabolic derangements manifest as hypotonia, lethargy, vomiting, and respiratory distress (tachypnea due to acidosis) in the neonatal period. Diagnosis is confirmed by the presence of **elevated urine methylmalonic acid and propionic acid**.

Propionic acidemia, a deficiency in propionyl-CoA carboxylase, also results in hyperammonemia, hypoglycemia, and metabolic acidosis, although it does not display elevated levels of urine methylmalonic acid.

(Choice A) Production of ketones in the presence of hypoglycemia is an appropriate response in the fasting state, as ketones provide fuel for the brain. In this patient, the notable family history and elevated serum methylmalonic acid level make methylmalonic acidemia more likely than simple fasting or dehydration.

(Choice C) Fatty acid oxidation disorders, such as medium-chain acyl-CoA dehydrogenase (MCAD) deficiency, can present with hypoglycemia, hyperammonemia, and metabolic acidosis, but these disorders lack an appropriate ketosis.

(Choice D) Urea cycle defects typically present with hyperammonemia without hypoglycemia or ketosis.

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(Choice D) Urea cycle defects typically present with hyperammonemia without hypoglycemia or ketosis.

(Choice E) Propionic acid levels are elevated in patients with methylmalonic acidemia due to downstream enzymatic deficiency of methylmalonyl-CoA mutase.

Educational objective:
Methylmalonic acidemia is an organic acidemia due to complete or partial deficiency of methylmalonyl-CoA mutase. Complete deficiency classically presents with lethargy, vomiting, and tachypnea in a newborn. Laboratory testing shows hyperammonemia, ketotic hypoglycemia, and metabolic acidosis. The diagnosis is confirmed by elevated urine methylmalonic acid and propionic acid.

References

- Proposed guidelines for the diagnosis and management of methylmalonic and propionic acidemia.

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11:10 PM
2/5/2019

Researchers are investigating the relationship between glucose transporters and insulin concentration in various cells and tissues. Data are collected and plotted on the graph below. The graph shows the number of glucose transporters found on the surface of 2 types of cells (circles versus triangles) compared to serum insulin concentration.

Which of the following cell types are most likely represented by the circles and triangles, respectively?

A. Adipocytes and skeletal muscle cells
B. Hepatocytes and cortical pyramidal cells
C. Hepatocytes and renal tubular cells
D. Pancreatic β cells and intestinal epithelial cells
E. Skeletal muscle cells and renal tubular cells

Submit

11:10 PM
2/5/2019

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Item 38 of 40
Question Id: 847

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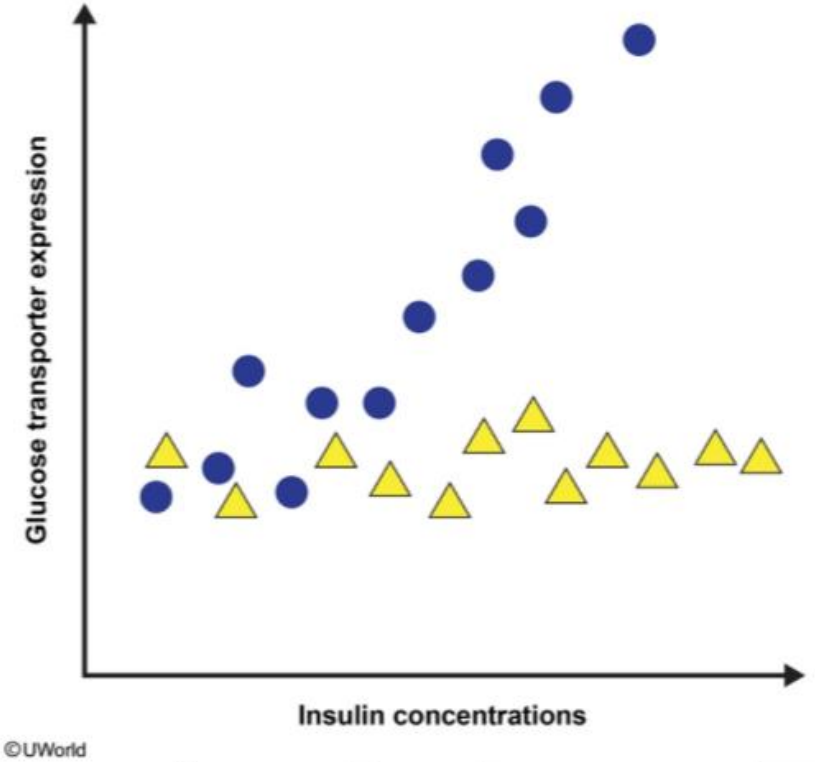

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12:24 PM
2/9/2019

Researchers are investigating the relationship between glucose transporters and insulin concentration in various cells and tissues. Data are collected and plotted on the graph below. The graph shows the number of glucose transporters found on the surface of 2 types of cells (circles versus triangles) compared to serum insulin concentration.

Which of the following cell types are most likely represented by the circles and triangles, respectively?

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Submit

11:10 PM
2/5/2019

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Which of the following cell types are most likely represented by the circles and triangles, respectively?

- A. Adipocytes and skeletal muscle cells [13%]
- B. Hepatocytes and cortical pyramidal cells [12%]
- C. Hepatocytes and renal tubular cells [10%]
- D. Pancreatic β cells and intestinal epithelial cells [7%]
- ✔ E. Skeletal muscle cells and renal tubular cells [55%]

Omitted
Correct answer
E

55%
Answered correctly

3 Seconds
Time Spent

08/09/2018
Last Updated

Explanation

Of the 5 major transmembrane glucose transport proteins (GLUTs), **only GLUT-4 is responsive to insulin**. GLUT-4 is expressed predominantly in **skeletal muscle cells** and **adipocytes**. In the absence of insulin, GLUT-4 is sequestered in the cytoplasm and the cells are impermeable to glucose. However, as insulin concentrations rise, the receptors translocate to the plasma membrane, facilitating glucose transport into the cell.

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2/5/2019

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Of the remaining glucose transporter subtypes,

- GLUT-1 contributes to basal glucose transport in erythrocytes and at the blood-brain barrier.
- GLUT-2 is present in hepatocytes, pancreatic β cells, and at the basolateral membrane of renal tubules and small intestinal mucosa. It plays a role in absorption of dietary glucose, reabsorption of glucose from renal tubules, hepatic glucose regulation, and sensitivity of β cells to circulating glucose.
- GLUT-3 is involved in placental and neuronal glucose transport.
- GLUT-5 is a fructose transporter found in spermatocytes and the gastrointestinal tract.

In contrast to GLUT-4, **GLUT-1, 2, 3, and 5** are always present on the plasma membrane, regardless of insulin levels, and constitutively transport glucose (**insulin-independent**).

(Choice A) Adipocytes and skeletal muscle cells have insulin-responsive GLUT-4 transporters. The corresponding **graph** would show increasing GLUT expression on both cells with rising insulin concentrations.

(Choices B, C, and D) Hepatocytes, pyramidal neurons, renal tubular cells, pancreatic β cells, and intestinal epithelial cells all express insulin-independent GLUTs. The corresponding **graph** would show unchanging GLUT expression on both cells with rising insulin concentrations.

Educational objective:
Glucose transport protein (GLUT)-4 is an insulin-sensitive glucose transporter expressed in skeletal muscle cells and adipocytes. In the absence of insulin, it is sequestered in the cytoplasm. However, as insulin concentrations rise, the receptors translocate to the plasma membrane, facilitating glucose transport into the cell.

References

A pharmaceutical researcher is studying a target protein involved in the signal transduction and cellular response to TSH. The protein is isolated and purified from thyroid follicular cells. Further analysis reveals that the protein contains multiple alpha-helical regions. Each of these regions is composed of approximately 20 amino acid residues consisting primarily of valine, alanine, and isoleucine. This particular region of the protein most likely performs which of the following functions?

A. Anchoring to the cell membrane
B. Binding to an extracellular ligand
C. Binding to intranuclear DNA
D. Interacting with metal ions in transporting proteins
E. Phosphorylating tyrosine residues

Submit

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- ✔ A. Anchoring to the cell membrane [48%]
- B. Binding to an extracellular ligand [15%]
- C. Binding to intranuclear DNA [17%]
- D. Interacting with metal ions in transporting proteins [8%]
- E. Phosphorylating tyrosine residues [10%]

Omitted
Correct answer
A

48%
Answered correctly

3 Seconds
Time Spent

01/12/2019
Last Updated

Explanation

G protein-coupled receptors that bind glycoprotein hormones (eg, TSH, LH, FSH) contain 3 major domains: an extracellular domain responsible for ligand binding, a transmembrane domain, and an intracellular domain coupled with heterotrimeric G proteins.

The **transmembrane domain** is made up of **nonpolar, hydrophobic amino acids** (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These amino acids are arranged in an alpha-helical fashion and project their hydrophobic R groups

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2/5/2019

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The **transmembrane domain** is made up of **nonpolar, hydrophobic amino acids** (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These amino acids are arranged in an alpha-helical fashion and project their hydrophobic R groups outwardly, **anchoring** the transmembrane region of the protein to the hydrophobic core of the **phospholipid bilayer**. The transmembrane domain may also play an important role in cellular signaling and transport.

(Choice B) Binding of a ligand to the extracellular domain of a transmembrane receptor can result in activation of the cAMP or phosphatidylinositol second messenger system, activation of receptor tyrosine kinases, opening of ion channels, and activation of the calcium-calmodulin system. The extracellular domain of these receptors is typically composed of hydrophilic amino acids.

(Choice C) Activation of G protein-coupled receptors utilizing the cAMP second messenger system results in increased synthesis of intracellular cAMP and subsequent activation of protein kinase A. Protein kinase A then phosphorylates cytosolic proteins that translocate into the nucleus and bind to DNA promotor regions to modulate transcription.

(Choice D) Intracellular iron-containing proteins (hemeproteins) include hemoglobin, myoglobin, and cytochrome oxidase. Heme is a complex of protoporphyrin IX and iron. Hemoglobin A, the most common hemoglobin in adults, consists of 2 alpha and 2 beta globin chains held together by noncovalent interactions. Each subunit contains stretches of alpha helices that form a heme-binding pocket lined by nonpolar amino acids.

(Choice E) Insulin and IGF-1 bind to receptors that possess tyrosine kinase on their intracellular domain (receptor tyrosine kinases). These receptors dimerizes on ligand binding to the extracellular domain, which subsequently activates tyrosine kinase. Tyrosine kinase phosphorylates tyrosine residues, triggering a downstream cellular response.

Educational objective:
Integral membrane proteins contain transmembrane domains composed of alpha helices with hydrophobic amino acid residues (eg, alanine, valine, leucine, isoleucine, phenylalanine, tryptophan, methionine, proline, glycine). These transmembrane domains help anchor the protein to the phospholipid bilayer of the cell membrane.

A 31-year-old previously healthy man comes to the office due to myalgias, anorexia, and skin rash. He does not use tobacco, alcohol, or illicit drugs. The patient works as a personal trainer and is a bodybuilding enthusiast. He denies using anabolic steroids but has been consuming large amounts of raw egg whites for the past several months. Physical examination shows macular dermatitis of the extremities. A water-soluble vitamin deficiency is suspected as the cause of his condition. Which of the following biochemical conversions most likely uses the deficient vitamin as a cofactor?

- A. Glucose to ribose-5-phosphate
- B. Pyruvate to acetyl-CoA
- C. Pyruvate to alanine
- D. Pyruvate to oxaloacetate
- E. Succinate to oxaloacetate

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11:10 PM
2/5/2019

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- A. Glucose to ribose-5-phosphate [6%]
- B. Pyruvate to acetyl-CoA [24%]
- C. Pyruvate to alanine [8%]
- ✔ D. Pyruvate to oxaloacetate [50%]
- E. Succinate to oxaloacetate [9%]

Omitted
Correct answer
D

50%
Answered correctly

6 Seconds
Time Spent

10/05/2018
Last Updated

Explanation

Biotin (vitamin B_7) is an important cofactor for several **carboxylase** enzymes. It functions as a CO_2 carrier and plays an essential role in carbohydrate, lipid, and amino acid metabolism. In the liver, the conversion of **pyruvate to oxaloacetate** for gluconeogenesis requires pyruvate carboxylase and biotin.

11:10 PM
2/5/2019

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Biotin deficiency is rare but can occur secondary to poor diet, excessive raw egg white consumption (due to high levels of **biotin-binding avidin** in egg whites), and congenital disorders of biotin metabolism. Patients with biotin deficiency present with nonspecific symptoms, including changes in mental status, myalgias, anorexia, and chronic **dermatologic changes** such as macular dermatitis. Biotin-deficient individuals can also develop **metabolic acidosis** as a result of increased conversion of pyruvate to lactic acid.

(Choice A) Niacin (vitamin B_3), in the form of $NADP^+$, is used to oxidize glucose-6-phosphate in the pentose phosphate pathway, generating ribose-5-phosphate and NADPH in the process.

(Choice B) Thiamine (vitamin B_1), riboflavin (vitamin B_2), niacin (vitamin B_3), pantothenic acid (vitamin B_5), and lipoic acid are the 5 cofactors required by the mitochondrial enzyme complex **pyruvate dehydrogenase**. In their absence, the metabolism of pyruvate to acetyl-CoA is not possible.

(Choice C) Pyridoxal phosphate (vitamin B_6) acts as a cofactor for **alanine transaminase**, which catalyzes the reversible reaction between pyruvate and glutamate to alanine and alpha-ketoglutarate in the liver and muscle tissue.

(Choice E) Production of oxaloacetate from succinate in the TCA cycle requires 2 enzymes (succinate dehydrogenase and malate dehydrogenase), along with riboflavin (vitamin B_2) and niacin (vitamin B_3) in the forms of cofactors FAD^+ and NAD^+, respectively.

Educational objective:
Biotin acts as a CO_2 carrier on the surface of carboxylase enzymes and is an essential cofactor for numerous reactions, including the conversion of pyruvate to oxaloacetate and fatty acid metabolism. Excess ingestion of avidin, found in egg whites, has been associated with biotin deficiency. This condition presents with mental status changes, myalgias, anorexia, macular dermatitis, and lactic acidosis.

11:10 PM
2/5/2019

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