SBCH321: UNIT 1

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Important notice

The questions and answers provided in this file are only for students' practice purposes. The intention of providing this information is purely to educate and make students aware of the correct way of answering the questions. All the sources used in the preparation of this material are properly cited at the end of this document. Students are requested not to regard this material as a reference, but as guidance on how to answer questions. However, ultimately the onus rests on the student to work hard and to read the books and other material on the topics listed in the module.

UNIT 1: Introduction to metabolic regulation

1. What is metabolism? List and describe the different types of metabolism.

Answer:

Metabolism is a term that is used to describe all chemical reactions involved in maintaining the living state of the cells and the organism.

Metabolism can be conveniently divided into two categories:

(i) Catabolism: The breakdown of molecules to obtain energy.

(ii) Anabolism: The synthesis of all compounds needed by the cells using the energy generated by catabolism.

2. What is a metabolic pathway? List and describe the different types of metabolic pathways.

Answer:

In biochemistry, a metabolic pathway is a linked series of chemical reactions occurring within a cell.

Metabolic pathways are usually classified into two different categories:

1. Anabolic pathway: Metabolic pathways that are characterized by their ability to synthesize molecules with the utilization of energy.

2. Catabolic pathway: Metabolic pathways that are characterized by their ability to break down complex molecules by releasing energy in the process.

3. List and describe the role of the five most important metabolic pathways in humans.

Answer:

Pathway	Role
Glycolysis	Glucose oxidation in order to obtain ATP
Citric acid cycle (Krebs' cycle)	Acetyl-CoA oxidation in order to obtain GTP and valuable intermediates
Oxidative phosphorylation (electron-transport chain)	Disposal of the electrons released by glycolysis and citric acid cycle. Much of the energy released in this process can be stored as ATP
Pentose phosphate pathway	Synthesis of pentoses and release of the reducing power needed for anabolic reactions
Urea cycle	Disposal of ammonia (NH_4^+) in less toxic forms
Fatty acid β-oxidation	Fatty acids breakdown into acetyl-CoA, to be used by the Krebs' cycle
Gluconeogenesis	Glucose synthesis from smaller precursors, to be used by the brain

4. List five advantages of metabolic regulation.

Answer:

(i) To maintain cell components in precise and correct amounts (metabolic balance)

(ii) To respond effectively to environmental changes

(iii) To conserve energy and material

(iv) To adjust the need of cell/organisms

(v) To maximize efficiency of operation by regulating the catabolic and anabolic pathways

5. List five different types of mechanisms of metabolic regulations present in humans.

Answer:

(i) Allosteric regulation

(ii) Covalent modification

(iii) Adjustment of enzyme levels

(iv) Compartmentation

(v) Metabolic specialization of organs

6. What is allosteric regulation? Describe the role of allosteric activators and inhibitors.

Answer:

Allosteric regulation (or allosteric control) is the regulation of an enzyme by binding an effector molecule at a site other than the enzyme's active site. The site to which the effector binds is termed the allosteric site. Allosteric sites allow effectors to bind to the protein, often resulting in a conformational change involving protein dynamics. Effectors that enhance the protein's activity are referred to as allosteric activators, whereas those that decrease the protein's activity are called allosteric inhibitors.

7. What is covalent modification?

Answer:

Regulatory enzymes also can be switched on and off by reversible covalent modification. Usually this occurs through the addition and removal of a particular group, one form of the enzyme being more active than the other. Phosphorylation and dephosphorylation are the most common but not the only means of covalent modification.

8. What is compartmentation in metabolism? Describe three advantages and the main disadvantage of compartmentation of metabolism.

Answer:

All reactions occurring in cells take place in certain spaces known as compartments, which are separated from other compartments by means of semi-permeable membranes.

Advantages:

(i) Compartmentation helps to separate even chemically quite heterogeneous environments and thus to optimize the course of chemical reactions.

(ii) Compartmentation provides optimal conditions for individual enzymatically catalysed reactions.

(iii) Compartmentation protects cell organelles from the activity of lytic enzymes.

(iv) Compartmentation helps in regulation of metabolic pathways, making them more accurate and targeted and less interfering with one another.

Disadvantage:

Despite its advantages, compartmentation puts greater demand on energy consumption. This arises from a frequent need to use ATP-dependent transporters, transporting substances across membranes against the concentration gradient and thus creating different environments in different compartments.

9. Match the cellular space, cytosol, mitochondrial matrix and the interplay of both spaces with the metabolic pathways: Glycolysis, fatty acid synthesis, gluconeogenesis, citric acid cycle, oxidative phosphorylation, beta-oxidation of fatty acids, ketone-body formation, pentose phosphate pathway and urea synthesis.

Answer:

Cytosol	Glycolysis, pentose phosphate pathway, fatty acid synthesis
Mitochondrial matrix	Citric acid cycle, oxidative phosphorylation, beta-oxidation of fatty acids, ketone-body formation
Interplay of above spaces	Gluconeogenesis, urea synthesis

10. In eukaryotic cells each organelle performs some major or specialized function. List eukaryotic organelles and their major functions.

Answer:

Organelle	Major function
Mitochondria	Make energy out of food. Mitochondria are responsible for ATP production
Cytosol	A gel-like environment for the cell's organelles. The cytoplasm is the location for most cellular processes, including metabolism, protein folding, and internal transportation.
Lysosome	Garbage disposal - Enzymatic digestion of cell components and ingested matter
Nucleus	The nucleus houses the cell's DNA and directs the synthesis of proteins and ribosomes. DNA replication, transcription, and RNA processing.
Ribosomes	Responsible for protein synthesis
Golgi apparatus	Sorting of lipids and proteins takes place. Posttranslational processing of membrane and secretory proteins; formation of plasma membrane and secretory vesicles
Endoplasmic reticulum	Modifies proteins and synthesizes lipids
Vesicles	Storage and transport
Peroxisome	Carry out oxidation reactions that break down fatty acids and amino acids and detoxify poisons

11. What is metabolic specialization of organs? How many major organ systems are present in the body? List any five major organ systems and their organs and describe the function of the organ system.

Answer:

(i) In humans, each organ is specialized or evolved to perform a specific metabolic role in the body. This fact is known as metabolic specialization of organs.

(ii) There are ten major organ systems in the human body.

(iii) The table below lists the major organ systems, their organs and the role of the organ system in the human body.

Organs	System	Role
Heart, blood, blood vessels and lymphatics	Circulatory system	It is the body's delivery system, concerned with circulating blood to deliver oxygen and nutrients to every part of the body.
Mouth, stomach and intestines	Digestive system	The purpose of the digestive system is to turn the food one eats into something useful for the body. When one eats, one's body uses this system to digest food so one's cells can use it to make energy.
Collection of glands, including the pituitary and thyroid glands, as well as the ovaries and testes	Endocrine system	It regulates, coordinates, and controls a number of body functions by secreting chemicals into the bloodstream. These secretions help control moods, growth and development, and metabolism.
Skin, hair, nails and sweat glands	Integumentary system	Its main function is to act as a barrier to protect the body from the outside world. It also functions to retain body fluids and to protect against disease, eliminate waste products and regulate body temperature.
Muscle tissue	Muscular system	This system is made up of muscle tissue that helps move the body and move materials through the body. Quite simply, muscles move the body. Muscles are bundles of cells and fibers that work in a simple way: they tighten up and relax.
Brain, spinal cord, and nerves	Nervous system	The nervous system is the control center of the human body. It receives and interprets stimuli and transmits impulses to organs. One's brain uses the information it receives to coordinate all one's actions and reactions.
Uterus, penis, ovaries and testes	Reproductive system	The human reproductive system ensures that humans are able to reproduce and

		survive as a species.
Nose, larynx, trachea, diaphragm, bronchi and lungs	Respiratory system	The primary function of the respiratory system is to supply the blood with oxygen to enable the blood to deliver oxygen to all parts of the body. The respiratory system does this through breathing.
Bones, cartilage and joints	Skeletal system	The skeletal system provides the shape and form for human bodies in addition to supporting and protecting the bodies, allowing bodily movement, producing blood cells, and storing minerals.
Kidneys, ureters, urinary bladder, and urethra	Urinary system	The purpose of the urinary system is to filter out excess fluid and other substances from the bloodstream. Some fluid is reabsorbed by the body but most is expelled as urine.

12. Answer the below question on energy.

12.1. What is energy?

12.2. Why organisms need energy

Answers:

12.1. Energy is the capacity to do work.

12.2. Organisms need energy for (i) Growth (ii) Movement (iii) Reproduction (iv) Repair/maintenance

SOURCES

Berg, JM, Tymoczko JL and Stryer, L. Biochemistry, sixth edition, W.H. Freeman and Company, New York, 2002.

Voet, D, Voet, JG and Pratt CW. Principles of biochemistry, third edition, John Wiley & Sons, Inc, 2008.

Video 1: Living things need energy: https://www.youtube.com/watch?v=x99snLJBhts

Video 2: Why do living things need energy? https://www.youtube.com/watch?v=m-DykNG-lMg

Video 3: Metabolism: https://www.youtube.com/watch?v=0kZLQGByXN4

Video 4: Overview of metabolism: Anabolism and catabolism | Biomolecules | MCAT | Khan Academy

https://www.youtube.com/watch?v=ST1UWnenOo0

Video 5: Video on my website

Video 6: Metabolic Regulation: https://www.youtube.com/watch?v=GRkL2WToSCo

Video 6.1: Enzyme regulation: https://www.youtube.com/watch?v=hwMLhPSWIYs

Video 7: Enzymes, Feedback Inhibition, and Allosteric Regulation:
https://www.youtube.com/watch?v=LKiXfqaWNHI

Video 8: Enzymes -Allosteric Enzymes: https://www.youtube.com/watch?v=fyww37XOrXo

Video 9: Role of glycogen phosphorylase: https://www.youtube.com/watch?v=cWziKUftOc4

Video 10: 145-Regulation through Compartmentation:
https://www.youtube.com/watch?v=BUhdgFskWs4

Video 11: Biology: Cell Structure I Nucleus Medical Media :
https://www.youtube.com/watch?v=URUJD5NEXC8

Video 12: Human Body Systems and Functions: https://www.youtube.com/watch?v=qhajGKS5thQ

Useful video links:

Biochemistry introduction to metabolism tutorial by Prof. P M Bingham

https://www.youtube.com/watch?v=FgAuslfreKs

Basics of metabolism | MCAT | Khan Academy

https://www.youtube.com/watch?v=wQ1QGZ6gJ8w

A general overview of the major metabolic pathways by Prof. D. P. Silva

http://homepage.ufp.pt/pedros/bq/integration.htm

New allosteric regulation video: Allosteric Regulation of Enzymes by mena missa

https://www.youtube.com/watch?v=WAZXqhtduFw

SBCH321: UNIT 2 INFORMATION

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UNIT 2: Introduction to hormones and neurotransmitters

1. Hormones and neurotransmitters

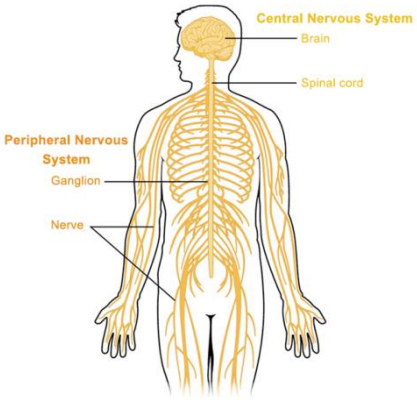
Hormones: A hormone is any member of a class of signaling molecules produced by glands in multicellular organisms that are transported by the circulatory system to target distant organs to regulate physiology and behaviour.

Neurotransmitters: Neurotransmitters, also known as chemical messengers, are endogenous chemicals that enable neurotransmission.

Or

Neurotransmitters are often referred to as the body's chemical messengers. They are the molecules used by the nervous system to transmit messages between neurons, or from neurons to muscles.

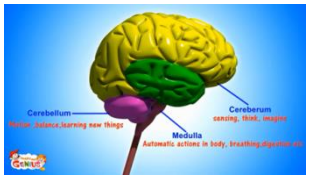
2. Nervous system



- Main function of nervous system is to controls all the actions of our body

Our nervous system is divided in two components:

- Central nervous system - brain and spinal cord
- Peripheral nervous system - which encompasses nerves outside the brain and spinal cord



Brian has 3 major parts

- Cereberum – sensing, thinking & imagination
- Cerebellum – motion, balance & learning new things
- Medulla – involuntary actions in the body (digestion, heart beat and breathing etc.,)

There are two different types of nerves in nervous system

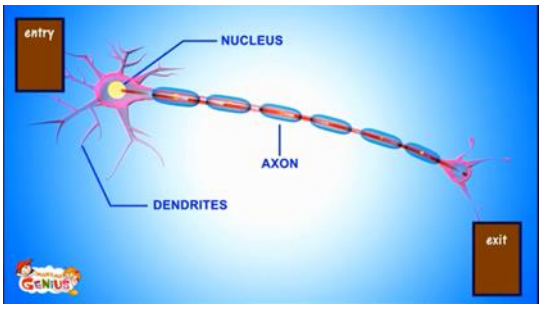
- Sensory nerves – carry messages from body (senses) to the brain
- Motor nerves - carry messages from brain to the body

2.1. Neurons

Neurons, also known as nerve cells, send and receive signals from your brain.

Neurons vary in size, shape, and structure depending on their role and location. However, nearly all neurons have three essential parts: a cell body, an axon, and dendrites.

Cell body



Also known as a soma, the cell body is the neuron's core. The cell body carries genetic information, maintains the neuron's structure, and provides energy to drive activities.

Like other cell bodies, a neuron's soma contains a nucleus and specialized organelles. It's enclosed by a membrane which both protects it and allows it to interact with its immediate surroundings.

Axon

An axon is a long, tail-like structure which joins the cell body at a specialized junction called the axon hillock. Many axons are insulated with a fatty substance called myelin. Myelin helps axons to conduct an electrical signal. Neurons generally have one main axon.

Dendrites

Dendrites are fibrous roots that branch out from the cell body. Like antennae, dendrites receive and process signals from the axons of other neurons. Neurons can have more than one set of dendrites, known as dendritic trees. How many they have generally depends on their role.

For instance, Purkinje cells are a special type of neuron found in the cerebellum. These cells have highly developed dendritic trees which allow them to receive thousands of signals.

In short

Neuron has three major parts

- Cell body – contains nucleus, maintain the neuron's structure and provide energy to drive activities
- Dendrites – receive stimulation and pass to cell body
- Axon – conducts electrical impulses away from nerve cell body

2.2. Some neurotransmitters and their functions.

Neurotransmitters	Major known function/diseases
Dopamine	• Critical for memory and motor skills. • Deficiency in dopamine production is associated with Parkinson's disease, a degenerative condition causing "shaking palsy"
Norepinephrine (also a hormone)	• Neuromodulator optimizes brain function. • As part of bodies fight or flight hormone. • Norepinephrine quickly provides an accurate assessment of danger or stressful situations.
Epinephrine	• Activates muscle adenylate cyclase, thereby stimulates glycogen breakdown. • Promotes lipolysis in adipose tissue. • Promotes Glycogenolysis and Gluconeogenesis in Liver.
Histamine	• Involved in allergic responses as well as in the control of acid secretion by the stomach
Serotonin	• It is popularly through to be a contributor to feelings of well-being and happiness. • Important factor in mood, depression, anxiety, sleep quality, emotions and regulation of appetite and body temperature. However, biological functional role of serotonin is not clear.
Acetylcholine	• Its basic functions involve the control of skeletal muscles via activation of the motor neurons as well as stimulating the muscles of the body
Gamma-aminobutyric acid or GABA	• The role of GABA is to inhibit or reduce the activity of the neurons or nerve cells. • People with too little GABA tend to suffer from anxiety disorders. • If GABA is lacking in certain parts of the brain, epilepsy results.
Glutamate	• Glutamate is the principal excitatory neurotransmitter in the brain.
Nitric oxide	• Plays a role in affecting smooth muscles, relaxing them to allow blood vessels to dilate and increase blood flow to certain areas of the body.

3. Glands

- A gland is a just any structure that makes and secrets a hormone

3.1. Major glands and their hormones

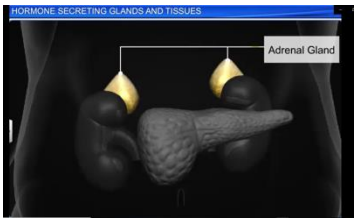
Gland	Hormone	Function
Hypothalamus	Releasing hormones (RH)	• Stimulate the Anterior Pituitary to secrete its hormones Example: 1. Gonadotrophin releasing hormone (GnRH) stimulates the release of Follicle Stimulating hormone (FSH) or Luteinizing hormones (LH) 2. Thyroid releasing hormone (TRH) stimulates the release of Thyroid stimulating hormone (TSH)
	Inhibiting hormones (IH)	Stop the Anterior Pituitary from secreting hormones Example: Somatostatin inhibits the release of Growth Hormone (GH)
	Antidiuretic Hormone (ADH)/Vasopressin	• Antidiuretic hormone conserves body water by reducing the loss of water in urine. • This hormone signals the collecting ducts of the kidneys to reabsorb more water and constrict blood vessels, which leads to higher blood pressure and thus counters the blood pressure drop caused by dehydration.
	Oxytocin	• Stimulates the smooth muscle of the uterus to contract, inducing labor. • Stimulates the myoepithelial cells of the breasts to contract which releases milk from breasts when nursing. • Stimulates maternal behavior. • In males it stimulates muscle contractions in the prostate gland to release semen during sexual activity

Pituitary gland parts	Hormones	Functions
Anterior pituitary gland	Growth hormone (GH) or Somatotropin	Regulates growth, metabolism and body composition
	Prolactin (PL)	Stimulates milk production
	Luteinizing hormone (LH) and Follicle Stimulating Hormone (FSH) (gonadotrophins)	Act on the ovaries or testes to stimulate sex hormone production, and egg and sperm maturity
	Adrenocorticotropic Hormone (ACTH) or Corticotropin	Stimulates the adrenal glands to secrete steroid hormones, principally cortisol
	Thyroid Stimulating Hormone (TSH) or Thryotropin	Travels to the thyroid gland (target cells) where it stimulates the release of thyroid hormones in response to low temperatures, stress, and pregnancy
Intermediate pituitary gland	Melanocyte-stimulating hormone (MSH)	Acts on cells in the skin to stimulate the production of melanin
Posterior pituitary	Anti-diuretic hormone (ADH) (also called vasopressin)	Controls water balance and blood pressure
	Oxytocin	Stimulates uterine contractions during labour and milk secretion during breastfeeding

Gland	Hormones	Functions/diseases
Thyroid	Triiodothyronine (T3) Thyroxine (T4)	• Help regulate tissue growth and development • Support the formation of red blood cells • Control the metabolism of proteins carbohydrates and fats • Maintain the water and electrolyte balance and

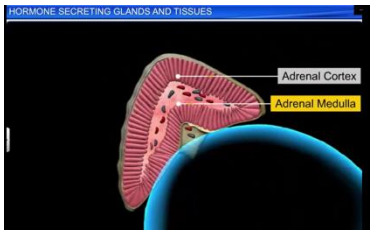
		regulate the basal metabolic rate (BMR)	
		Hyperthyroidism • High metabolic rate • Weight loss • Hyperactivity • Heat intolerance • Goiter	**Hypothyroidism** • Low metabolic rate • Weight gain • Sluggishness • Sensitivity to cold
	Calcitonin	• Regulate calcium concentration in body fluids. Calcitonin decreases the concentration of calcium in the blood where most of it is stored in the bones; it stimulates osteoblast activity and inhibits osteoclast activity, resulting in new bone matrix formation.	
Parathyroid	Parathyroid hormone (PTH)	•Regulator of calcium and phosphorus concentration in extracellular fluid. PTH has the opposite effect of calcitonin. •PTH stimulates osteoclasts which increases blood calcium levels. •PTH causes reabsorption of Ca^{+2} from kidneys so it is not excreted in the urine •PTH stimulates synthesis of calcitriol (hormone made in the kidney which the active form of Vitamin D which increases Ca+2 absorption from small intestine)	

Adrenal glands

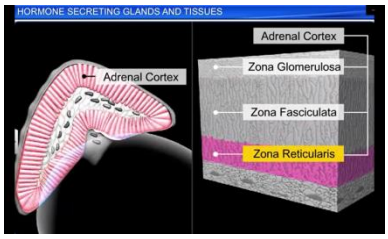


The yellowish triangular shaped glands are also called supra-renal glands because they are situated on the top of the anterior part of the kidneys. The adrenal glands are also known as 3F glands. The 3F's stands for fright, fight or flight. These glands also called 4S glands where the four S stands for sugar metabolism, salt metabolism, sex hormones and source of energy.

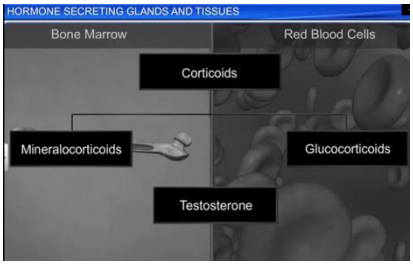
Each adrenal gland is formed of two types of tissues. The outer adrenal cortex and the inner or central adrenal medulla.



The adrenal cortex is formed of three layers of cells called Zona glomerulosa, which is the outer layer, Zona fasciculate, which the middle layer, and the Zona reticularis the inner layer.



The adrenal cortex secrets many hormones called corticoids. Based on the functions these corticoids are differentiated as mineralocorticoids and glucocorticoids. Apart from mineralocorticoids and glucocorticoids the adrenal cortex also secrets the small amount of androgenic hormone, Testosterone.



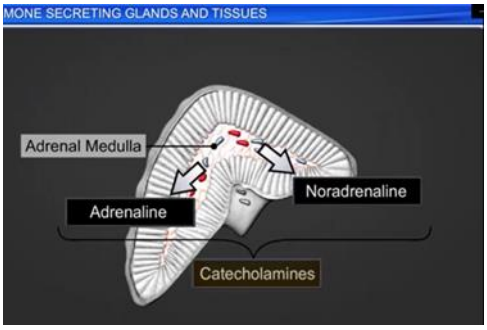
Adrenal cortex hormones and their functions

Mineralocorticoids		**The primary function of mineralocorticoids is to regulate the balance of water and electrolytes in our body.**
	Aldosterone	• Acts on the renal tubules on the kidneys and stimulates the reabsorption of sodium and water and the removal of potassium and phosphate ions. • also helps to maintain the body fluid volume, electrolytes, osmotic pressure and blood pressure

Glucocorticoids		• Involved in carbohydrate metabolism • Chief function is to stimulate Gluconeogenesis, Lipolysis and Proteolysis. • Also inhibit the utilization of amino acids and cellular uptake.
	Cortisol	• Provides anti-inflammatory reactions, helps to maintain the cardiovascular system and the functions of the kidneys • Cortisol stimulate red blood cell production and suppresses the immune response
Testosterone (male hormone)		• Stimulate the development of secondary sexual characters such as axial hair, pubic hair, facial hair and deepening of the voice.

Adrenal medulla which forms the central part of the glands also secrets hormones.

Adrenaline or epinephrine and noradrenaline or norepinephire are the two main hormones secreted by the adrenal medulla. These hormones are amine hormones and are derivatives of catechol and collectively called catecholamine's.



Catecholamine's	• **Increase the strength of heart contractions, heart beat and rate of respiration** • **Also increase alertness, sweating and papillary dilation** • **Stimulates the breakdown of glycogen, proteins and lipids** • **In short, catecholamine's are rapidly secreted in response to stress and emergency situations and or thus also called emergency hormones or hormones of flight or fight.**

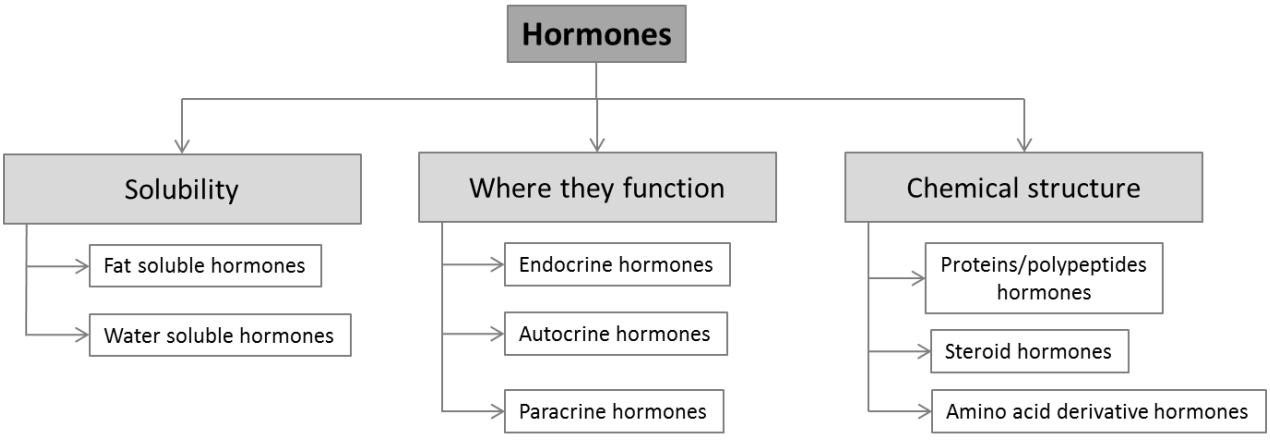
Pancreas

Please see my slides and recommended videos for information

Give an overview of three different types of hormone classifications and sub-classifications.

Answer:

Hormones can be classified into three different categories based on solubility; their function and based on their chemical structure as shown in the figure.



Based on their solubility, hormones are classified into two categories, fat-soluble hormones and water-soluble hormones.

Based on the site of function, hormones are classified into three different categories: endocrine hormones, autocrine hormones and paracrine hormones.

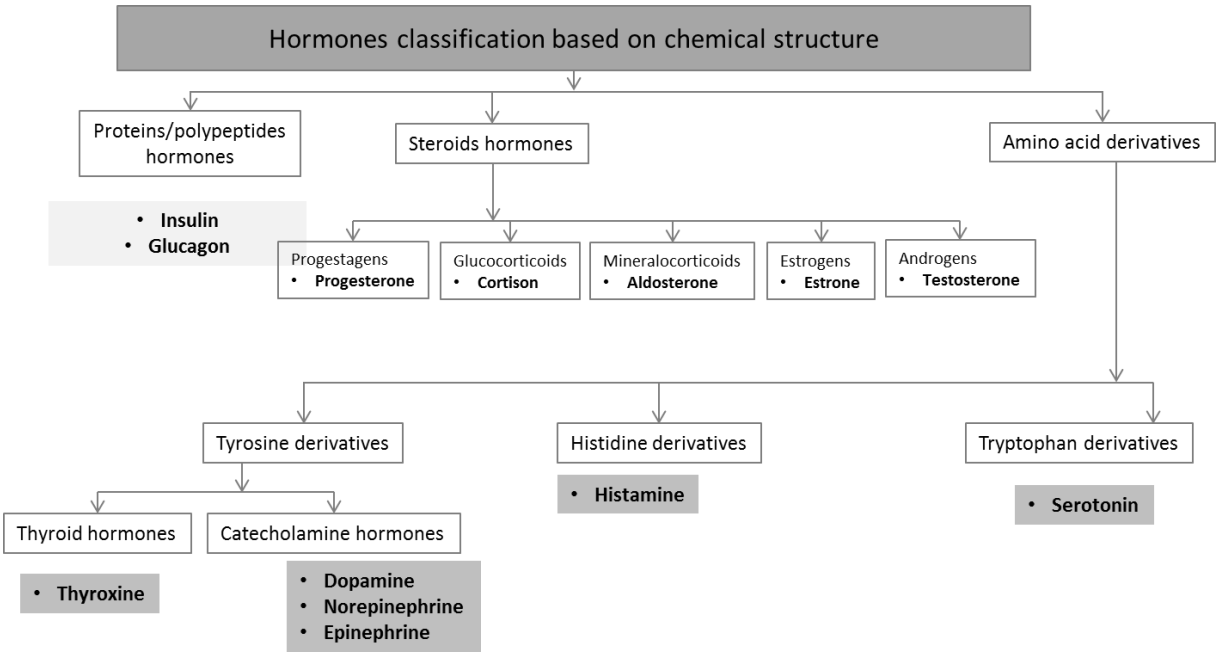
Based on chemical structure, hormones are classified into three different categories: proteins/polypeptide hormones, steroid hormones and amino acid derivative hormones.

Give a detailed classification of hormones based on their chemical structure. List the three main characteristic of the different categories of hormones. Provide one example of a hormone for each category.

Answer:

Based on chemical structure, hormones are classified into three different categories: Protein/polypeptide hormones, steroid hormones and amino acid derivative hormones. Steroid hormones are classified into five major classes based on the number of carbon, hydrogen and oxygen atoms: Progestagens, glucocorticoids, mineralocorticoids, androgens and estrogens. Amino acid derivative hormones are further classified into three different categories based on the type of amino acid: Tyrosine derivative hormones, histidine derivative hormones and tryptophan derivative hormones. The tyrosine derivative hormones, based on the mechanisms of signal transduction, are further classified into thyroid hormones and catecholamine hormones.

The diagram below shows the classification of hormones based on chemical structure and also shows an example of a hormone in each category/sub-category.



Characteristics of different categories of hormones:

Hormone	Characteristic
Protein/polypeptide hormones	(i) Made up of amino acids (≥ 3 amino acids) (ii) Water-soluble and charged (iii) Cannot cross the biological membrane (iv) Need receptors present in/on the cell surface to pass the signal
Steroid hormones	(i) Made up of lipids, mainly cholesterol (ii) Need carrier proteins to reach the target site (iii) Can cross the cell membrane (iv) Receptors inside the cell (cytoplasm or nucleus) (v) Affect transcription or translation
Amino acid derivative hormones	(i) Made up of a single amino acid (ii) Amino acid modified in the side chain (iii) Capable of dual signalizing as proteins/polypeptide hormones and steroid hormones

SOURCES

- Berg, JM, Tymoczko JL and Stryer, L. Biochemistry, sixth edition, W.H. Freeman and Company, New York, 2002.
- Voet, D, Voet, JG and Pratt CW. Principles of biochemistry, third edition, John Wiley & Sons, Inc, 2008.
- Video 1: The Nervous System Functions and Facts -Animation video: https://www.youtube.com/watch?v=NALZwb-_YO4
- Video 2:Neurotransmitters - What Are Neurotransmitters And What Do They Do In The Body? : https://www.youtube.com/watch?v=Mz3PIvyu3ew
- Video 3:CBSE Class 11 Biology, Chemical Coordination and integration – 1, Human Endocrine System https://www.youtube.com/watch?v=OECzHqH_mGA
- Video 4: CBSE Class 11 Biology, Chemical Coordination and integration– 2, Hypothalamus, Pituitary Gland & Pineal gland: https://www.youtube.com/watch?v=qMCWQ2LnLsg
- Video 5: CBSE Class 11 Biology, Chemical Coordination and integration – 3, Thyroid and Parathyroid Glands: https://www.youtube.com/watch?v=3BWUp5XwrQI
- Video 6: CBSE Class 11 Biology, Chemical Coordination and integration – 4, Hormone Secreting Glands & Tissues: https://www.youtube.com/watch?v=aQc_e4R1L2s (from 0:58 to 6:29)
- Video 7: CBSE Class 11 Biology, Chemical Coordination and integration – 5, Heterocrine Glands Pancreas: https://www.youtube.com/watch?v=PF_VKS4D4qM (from 0:28 to 1:30)
- Video 8: Endocrine pancreas | Gastrointestinal system physiology | NCLEX-RN | Khan Academy: https://www.youtube.com/watch?v=xNf--q0YMq8
- Video 9: Types of hormones/overview of cell signaling: https://www.youtube.com/watch?v=FQFBygnIONU
- Video 10: Types of hormones | Endocrine system physiology | NCLEX-RN | Khan Academy https://www.youtube.com/watch?v=KSclrkk_Ako
- Endocrine gland hormone review | Endocrine system physiology | NCLEX-RN | Khan Academy: https://www.youtube.com/watch?v=ER49EweKwW8
- Hormones and the endocrine systems: https://www.youtube.com/watch?v=WMVEGAVdEoc
- Good videos: http://www.austincc.edu/apreview/NursingPics/NursingAnimationsWebPage.html
- Textual information: http://www.austincc.edu/apreview/PhysText/Endocrine.html

SBCH321: Unit 3 Information

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Important notice

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Unit 3: Signal transduction

1. **What is signal transduction? Provide an overview on the five components of the signal transduction pathway. List the component names, describe each component and give an example of the component in human body**.

Molecular events or pathways whereby intercellular signals are converted (transduced) to intracellular signals are known as "signal transduction".

Or

Signal transduction is the process by which a chemical or physical signal is transmitted through a cell as a series of molecular events, most commonly protein phosphorylation catalyzed by protein kinases, which ultimately results in cellular response.

Each component (or node) of a signaling pathway is classified according to its role.

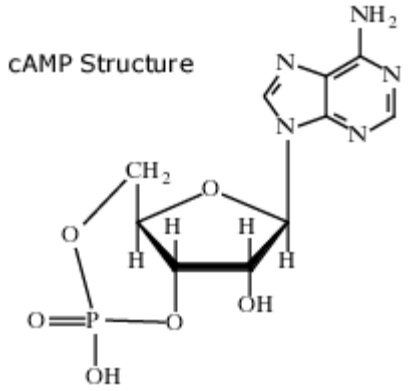
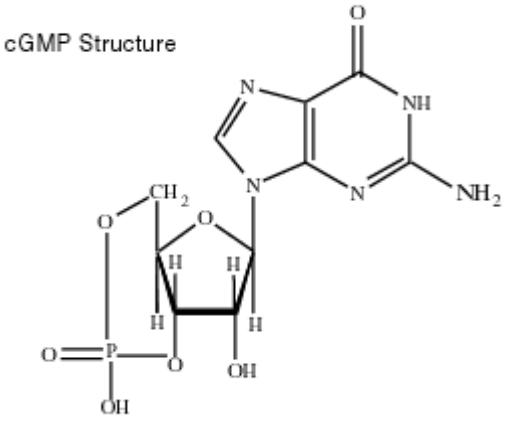
Component	Description	Example
Ligands	Ligands are first messengers that are released in response to stimuli by specialized glands. Ligands can be classified roughly into two categories based on permeability across the cellular membrane: permeable and non-permeable	Hormones including neurotransmitters. Permeable hormones: steroid hormones Non-permeable hormones: proteins/polypeptide hormones
Receptor	Proteins that bind to the ligands are known to be receptors. Thus, receptors act as signal transducers as they transfer the information that the ligand has bound to the cell's interior. The binding of a ligand with a receptor causes a change in the structure of the receptor, known as receptor activation. Receptors can be roughly divided into two major classes: Extracellular and intracellular	Extracellular receptors: G protein-coupled receptors (GPCR) Intracellular receptors: cytoplasmic (NOD-like receptors) and nuclear receptors (retinoic acid receptors)
Primary effector	The activated receptor interacts and activates another component of the signal transduction pathway, which is known as a primary effector. Primary effectors are linked to the generation of second messengers.	Adenylate cyclase and phospholipase C
Second messenger	An intracellular substance that mediates cell activity by relaying a signal from an extracellular molecule (as of a hormone or neurotransmitter) bound to the cell's surface. Second messengers further activate secondary effectors.	Cyclic AMP (cAMP) Cyclic GMP (cGMP) Calcium ion (Ca2+) Inositol 1,4,5-triphosphate (IP3) Diacylglycerol (DAG) Nitric oxide (NO)
Secondary effector	Components of signal transduction pathways activated by second messengers are known as secondary effectors. Secondary effectors are	Protein kinases, phosphatases and calmodulin

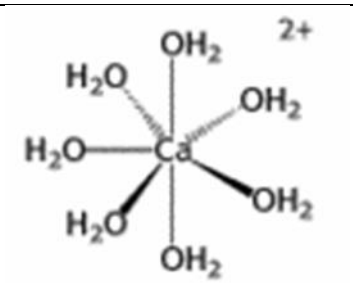
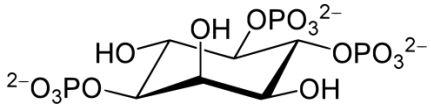
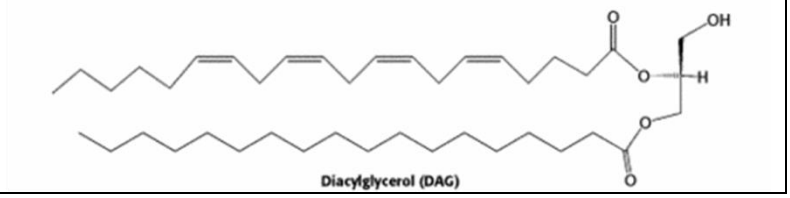
	responsible for activating different genes/proteins and thus generating the cellular response.	

2. What is a second messenger in the signal transduction process? List any five second messengers with their chemical structure. Describe three advantages of second messengers.

An intracellular substance that mediates cell activity by relaying a signal from an extracellular molecule (as of a hormone or neurotransmitter) bound to the cell's surface.

Five second messengers and their chemical structures:

Second messenger	Chemical structure
Cyclic AMP (cAMP)	
Cyclic GMP (cGMP)	

Calcium ion (Ca2+)	
Inositol 1,4,5-triphosphate (IP3)	
Diacylglycerol (DAG)	

Advantages of second messengers:

(i) The signal may be amplified significantly in the generation of second messengers. Only a small number of receptor molecules may be activated by the direct binding of signal molecules, but each activated receptor molecule can lead to the generation of many second messengers. Thus, a low concentration of signal in the environment, even as little as a single molecule, can yield a large intracellular signal and response.

(ii) Second messengers are often free to diffuse to other cellular compartments where they can influence processes throughout the cell.

(iii) The use of common second messengers in multiple signaling pathways creates both opportunities and potential problems. Input from several signaling pathways, often called cross-talk, may alter the concentration of a common second messenger. Cross-talk permits more finely tuned regulation of cell activity than the action of individual independent pathways would. However, inappropriate cross-talk can cause changes in second-messenger concentration to be misinterpreted.

3. What is a G-protein signaling pathway and why is it named a G-protein signaling pathway?

Answer:

A G-protein signaling pathway is one of the most important signaling pathways across the cells of the human body. G-protein is an intracellular signaling protein attached to the inner part of the cell membrane. It is named for its ability to bind to the guanosine triphosphate (GTP) molecule and has GTPase activity as well.

4. Describe the composition of G-proteins and what makes each G-proteins unique.

Answer:

The family of heterotrimeric or large G-proteins consists of three non-identical subunits, alpha (α), beta (β) and gama (γ). The alpha subunit carries a guanosine diphosphate (GDP) molecule when inactive and it has different forms, resulting in different types of G-proteins.

5. Describe three types of alpha subunits of G-protein and their importance in signal transduction pathways.

Answer:

Different signal transduction pathways use different alpha subunits of G-protein. Thus, according to the type of alpha subunit of G protein the signal takes a different path, since the activated alpha proteins interact with different effector proteins. The table below summarizes three different alpha subunits and their importance in the signal transduction pathway.

Alpha subunit	G-protein	Importance
S-type (stimulatory)	Gs-protein	Stimulates adenylate cyclase
I-type (inhibitor)	Gi-protein	Inhibits adenylate cyclase
q-type	Gq-protein	Stimulates phospholipase C

6. What are GPCR? Describe their structure.

GPCR are G-protein coupled receptors that bind to ligands. They are transmembrane proteins with seven membranes spanning regions or helices. Upon binding of the ligand, it undergoes a conformational change and binds to the target G-protein.

7. **Write an over-view in ten points on the G-protein signaling pathway from initiation to biological response to inactivation of the pathway. Also present the G-protein signaling pathway events as a schematic diagram.**

Point 1: G-protein signaling pathway is one of the most important signaling pathways across the cells of the human body. G-protein is an intracellular signaling protein attached to the inner part of the cell membrane. It is named for its ability to bind to the guanosine triphosphate (GTP) molecule and has GTPase activity as well.

Point 2: The family of heterotrimeric or large G-proteins consists of three non-identical subunits, alpha (α), beta (β) and gama (γ). The alpha subunit carries a guanosine diphosphate (GDP) molecule when inactive and it has different forms, resulting in different types of G-proteins.

Point 3: The signaling process is initiated by a ligand-like hormone or neurotransmitter binding to a receptor linked to the G-protein and hence called a G-protein coupled receptor (GPCR). The GPCR is a transmembrane protein with seven membranes spanning regions or helices. Upon activation the GPCR undergoes a conformational change, making it able to interact with the G-protein.

Point 4: In response to the receptor binding to the G-protein, the alpha subunit undergoes another conformational change leading to the release of the GDP molecule and binding of a GTP molecule instead. The G-protein is now active and the alpha subunit dissociates from the beta and gama subunits, resulting in an activated alpha-submit and an activated beta and gama heterodimer.

Point 5: The activated alpha subunit then regulates an enzyme that is membrane-bound. This enzyme catalyzes a reaction that produces a second messenger. This second messenger acts like an amplifier to the first signal sent to the cell by the ligand and this occurs in many cases by activation of protein kinases, which are enzymes that phosphorylate certain target proteins many, of which are enzymes too.

Point 6: Changes in the phosphorylation status of such proteins alter their activity, carrying out the biological response of the cell to the hormone or the neurotransmitter.

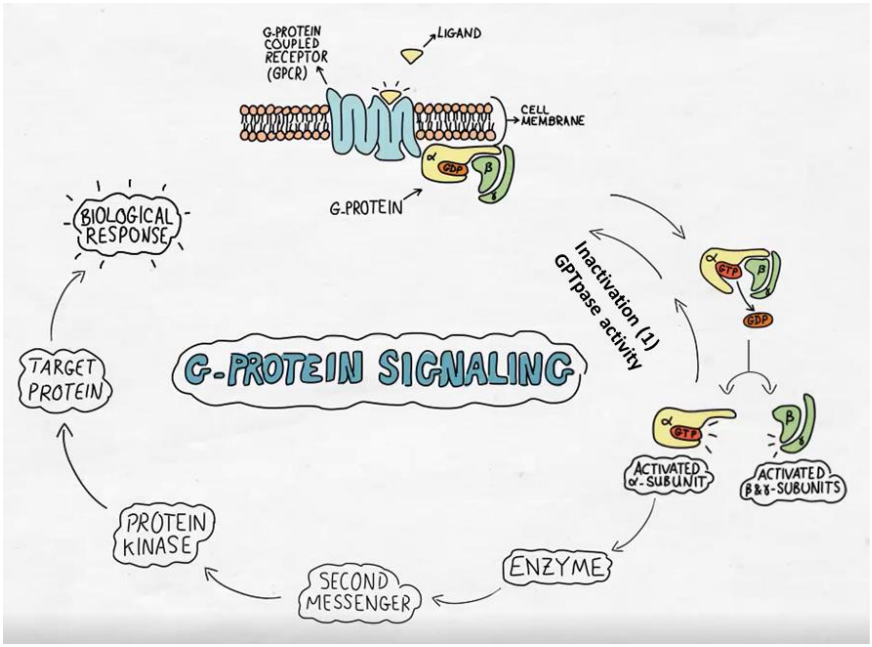
Point 7: According to the type of alpha submit the signal takes a different path.

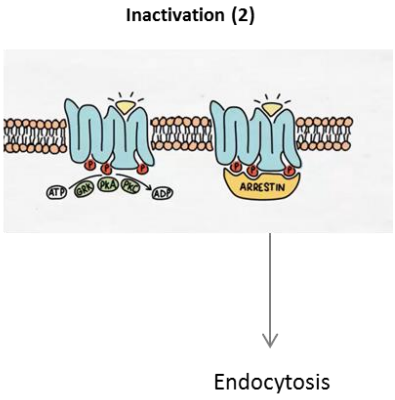
Point 8: In general, the G-protein singling pathway could be switched off in different ways, when the ligand no longer presents the receptor reverse to its resting state and the G-protein exerts its GTPase activity to hydrolyze GTP into GDP and the alpha subunit re-associate with beta and gama submit to stop the signaling process.

Point 9: Another mechanism by which the GPCR firing stops is the inactivation of the receptor itself. When GPCR activates the G-protein it activates the GPCR kinase or GRK at the same time. The GRK together with PKA and PKC phosphorylate the GPCR.

Point 10: The phosphorylated GPCR binds with high affinity to a protein called arrestin, which prevents interaction of the receptor with the G-protein thus stopping the effect of ligand or signaling transduction. The binding of arrestin promotes endocytosis of GPCR.

<u>Schematic diagram illustrating overview of G-protein signaling pathway.</u>





8. **Give a detailed description of events involved in the adenylate cyclase signal transduction pathway with respect to epinephrine binding to the beta-adrenoreceptor of a muscle cell. Limit description of signaling events to nine points and inaction or control mechanisms of pathway to three points. Also present the information in a schematic diagram.**

Or

Describe the events when epinephrine binds to a beta-adrenergic receptor leading to biological response, including its activation, biological response and controlling mechanisms. Limit description of signaling events to nine points and inaction or control mechanisms of pathway to three points. Also present the information in a schematic diagram.

Adenylate cyclase signal transduction pathway:

1. Binding of a ligand causes conformational change in the G-protein coupled receptor.

2. The G-protein coupled receptor binds to the G-protein called Gs-protein.

3. In response to the binding of the G-protein coupled receptor the alpha subunit of Gs-protein undergoes conformational change leading to the release of a GDP molecule and binding of a GTP molecule instead.

4. The alpha subunit bound to GTP dissociates from the beta and gama subunits of Gs-protein and binds to the adenylate cyclase enzyme.

5. Adenylate cyclase converts ATP into a second messenger cAMP.

6. Two molecules of cAMP bind to each of the two regulatory subunits of cAMP-dependent protein kinase A or PKA, causing the release of two catalytic subunits.

7. The catalytic subunits enter the nucleus and phosphorylate its target protein, which is in many cases a transcription factor.

8. The phosphorylated transcription factor, which is active, now binds to a certain promoter or regulator sequence controlling the transcription of the target gene. The cellular response will be exerted by controlling the expression of target genes.

9. In the case of epinephrine binding to the beta-adrenoreceptor of a muscle cell, the Gs-protein activated PKA leads to the activation of glycogen phosphorylase, thereby making glucose-6-phosphate available for glycolysis in a “fight-or-flight” response.

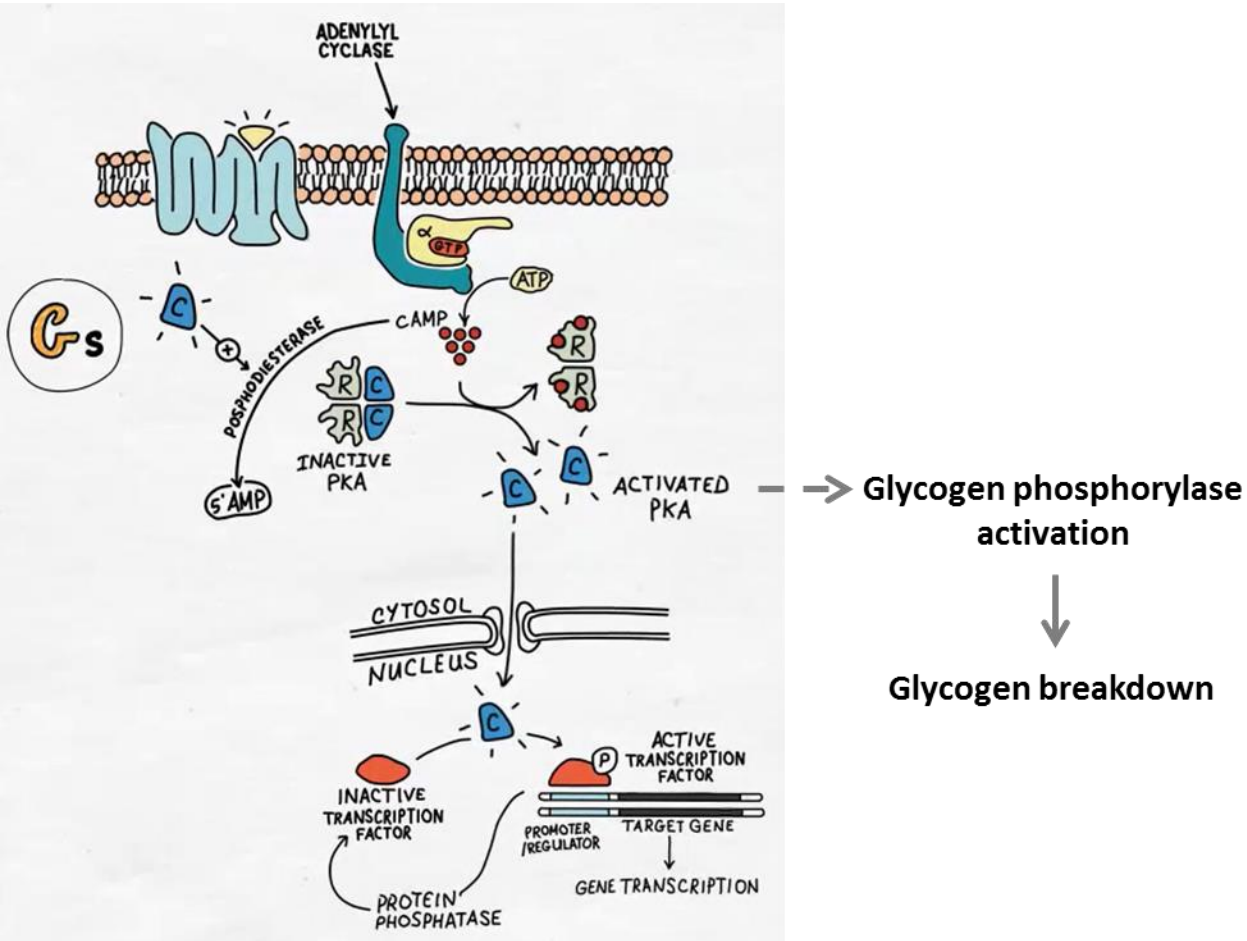
Inactivation/control mechanism:

1. As part of the counteracting mechanisms protein phosphates dephosphorylate the activated proteins, making them inactive and enhancing control of the signaling pathway.

2. Negative feedback or self-controlling mechanisms involves hydrolyses of cAMP to 5'AMP by phosphodiesterase enzyme which are activated by the phosphorylation by protein kinase A. Thus making protein kinase A effect brief and localized.

3. Another way of inhibiting the adenylate cyclase is the release of a signal from the gland bind to the alpha subunit "I" of Gi-protein. Upon ligand binding the activated alpha "I" subunit inhibits the adenylate cyclase enzyme decreasing the cAMP; in response PKA will not be activated, which is an opposite action to the Gs-protein.

<u>Schematic diagram representing the adenylate cyclase signal transduction pathway.</u>



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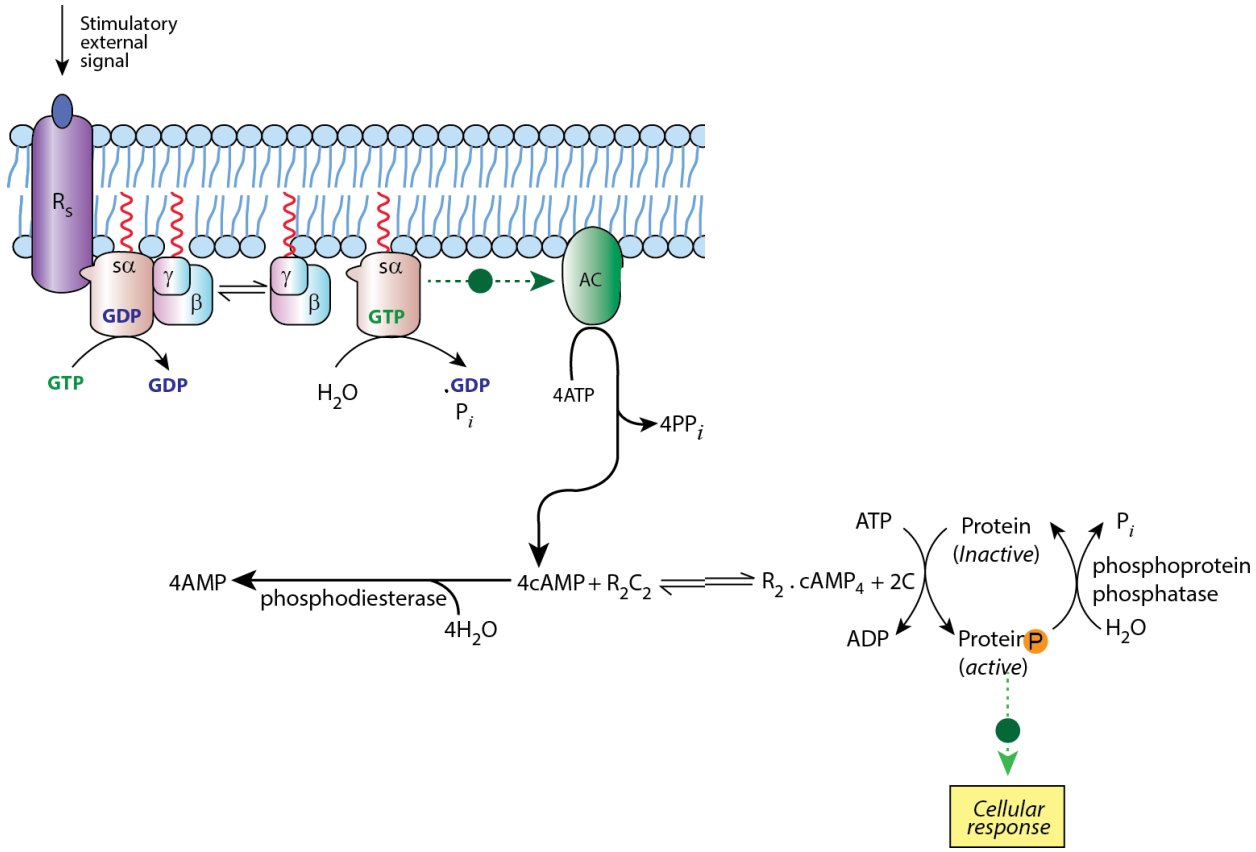

Stimulatory
external
signal
R_s
sα
γ
β
GDP
GTP
GDP
H_2O
.GDP
P_i
sα
GTP
AC
4ATP
$4PP_i$
4AMP
phosphodiesterase
$4H_2O$
4cAMP + R_2C_2
R_2 . $cAMP_4$ + 2C
ATP
ADP
Protein
(*Inactive*)
Protein P
(*active*)
P_i
phosphoprotein
phosphatase
H_2O
Cellular response

9. Highlight the clinical significance of adenylate cyclase signal transduction pathway with respect to cholera and pertussis toxin.

Cholera toxin: A clinical correlate to the adenylate cyclase signal transduction pathway is that the cholera toxin produced by *Vibrio cholera* bacteria alters the alpha "s" subunit of Gs-protein so that it can no longer hydrolyze its bound GTP, causing it to remain in an active state that actives adenylate cyclase indefinitely. The resulting persistence elevation of cAMP concentration causes a large efflux of chloride and water into the gut, leading to severe diarrhea.

Pertussis toxin: The pertussis toxin produced by *Bordetella pertussis* inhibits the alpha "i" subunit of Gi-protein so that adenylate cyclase remains active indefinitely, producing excess cAMP.

10. Describe the phosphoinositide signalizing pathway in 11 points, including its inactivation or controlling mechanisms. Also present the information in a schematic diagram.

Or

Describe the three second messenger's pathway in 11 points, including its inactivation or controlling mechanisms. Also present the information in a schematic diagram.

Phosphoinositide pathway:

1. Binding of a ligand causes conformational change in the G-protein coupled receptor.

2. The G-protein coupled receptor binds to the G-protein called Gq-protein.

3. In response to the binding of G-protein coupled receptor, the alpha subunit of Gq-protein undergoes conformational change leading to the release of a GDP molecule and binding of a GTP molecule instead.

4. The alpha subunit bound to GTP dissociates from the beta and gama subunits of Gq-protein and binds to phospholipase C.

5. The phospholipase C cleaves the membrane lipid phosphatidylinositol-4,5-bisphosphate into inositol-1,4-5-triphosphate and 1,2-diacylglycerol.

6. The inositol-1,4-5-triphosphate binds to an inositol-1,4-5-triphosphate gated channel in the endoplasmic reticulum, causing release of sequestered calcium ions.

7. Calcium ions and 1,2-diacylglycerol together activate the calcium-dependent protein kinase C.

8. Protein kinase C catalyzes phosphorylation of cellular proteins that mediate cellular response.

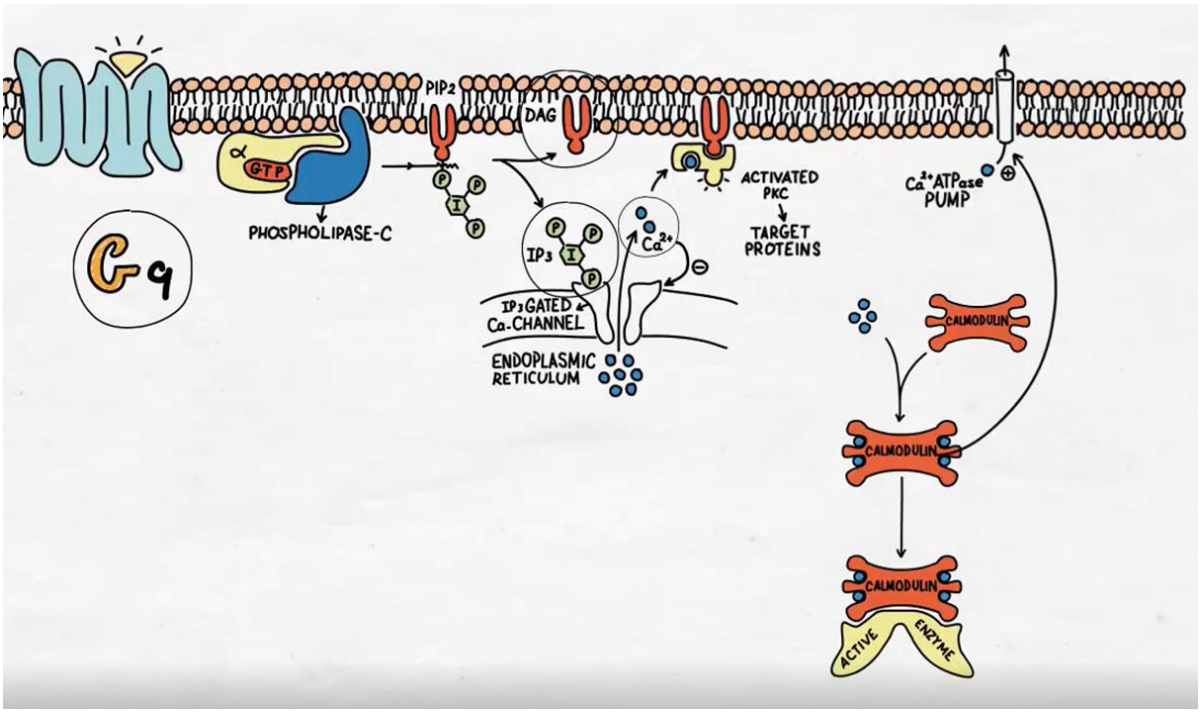
9. Calcium ions also binds to calmodulin. The calmodulin-calcium complex exerts cellular response by activating enzymes.

Inactivation/control mechanism:

10. The negative feedback inhibition of the phosphoinositide pathway is mediated by the calcium. As part of negative feedback of this pathway, increase of the intracellular calcium concentration above certain levels inhibits the inositol-1,4-5-triphosphate-gated calcium channels in the membrane of the endoplasmic reticulum.

11. The formation of the calmodulin-calcium complex itself stimulates the calcium-ATPase pump present in the cell membrane to get rid of the increased concentration of calcium.

Schematic diagram representing the phosphoinositide pathway signal transduction pathway. Abbreviations in the pathway: DAG, 1,2-diacylglycerol; IP3, inositol-1,4,5-triphosphate; PIP2, phosphatidylinositol-4,5-bisphosphate



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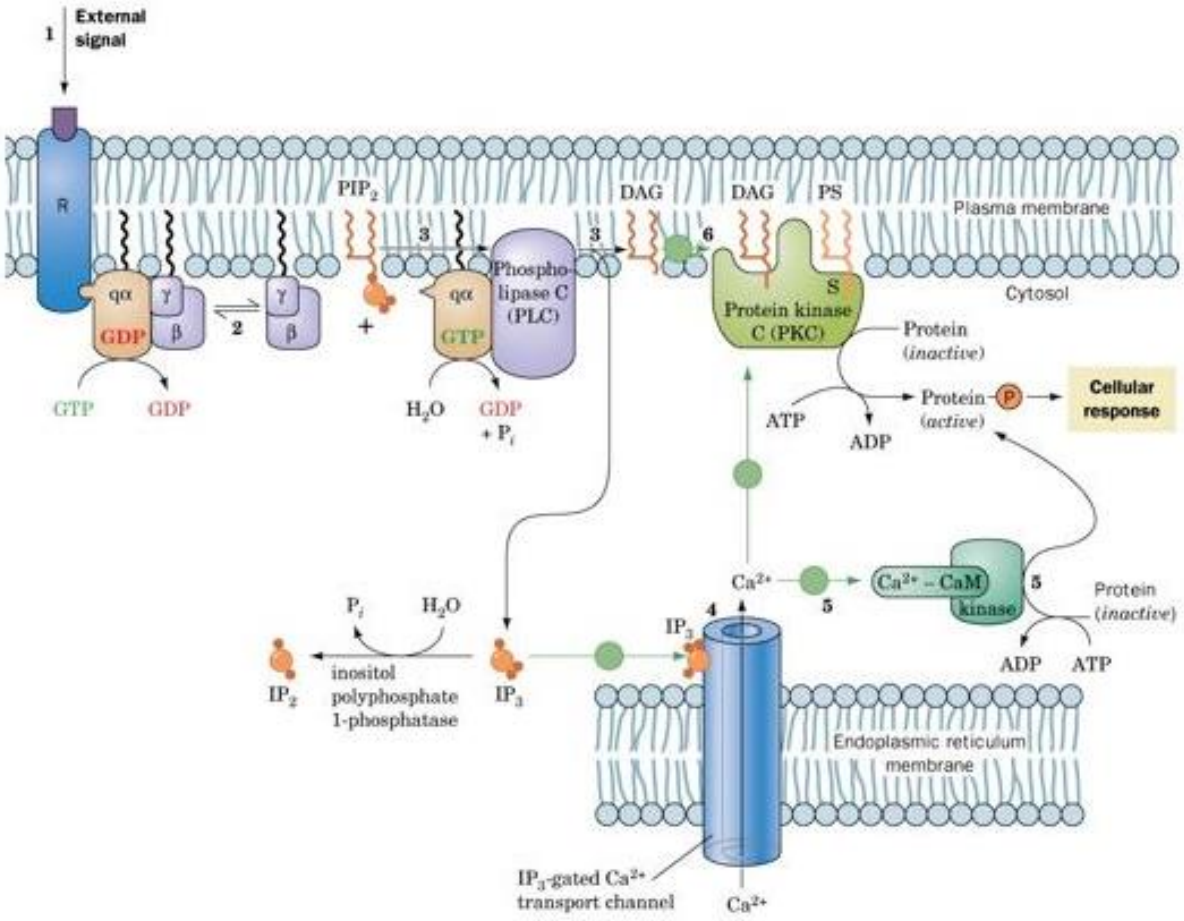

1
External signal
R
PIP2
DAG
DAG
PS
Plasma membrane
Cytosol
qα
GDP
γ
β
2
3
Phospho-lipase C (PLC)
GTP
H2O
GDP + Pi
Protein kinase C (PKC)
S
Protein (inactive)
ATP
ADP
Protein (active)
P
Cellular response
GTP
GDP
Ca2+
Ca2+ – CaM kinase
5
Protein (inactive)
ADP
ATP
Pi
H2O
IP3
4
IP2
inositol polyphosphate 1-phosphatase
Endoplasmic reticulum membrane
IP3-gated Ca2+ transport channel
Ca2+

11. What is nitric oxide?

Answer:

Nitric oxide is a toxic, short-lived gas molecule and has been found to be a signaling molecule in many vertebrate signal transduction processes.

12. List four important biological functions of nitric oxide.

Answer:

Four important biological functions of nitric oxide:

1. Nitric oxide stimulates mitochondrial biogenesis.
2. Nitric oxide is essential for the function of the central nervous system.
3. Nitric oxide is well known as vasodilator of endothelial cells and neurons. One of the most highlighted nitric oxide effects is relieving chest pain and effecting penile erection. The 'wonder drug' Viagra acts by producing nitric oxide and thus improving penile erection in men.
4. Nitric oxide in leukocytes acts as an anti-bacterial agent. In leukocytes nitric oxide combines with superoxide and produces highly reactive hydroxyl radicals, which kill invading bacteria.

13. Name the receptor involved in nitric oxide mediated relaxation of smooth muscle cells.

Answer: G protein-linked receptor.

14. Describe the events involved in nitric oxide mediated relaxation of vascular smooth muscle cells.

Answer:

1) Binding of acetylcholine to G protein receptors causes Inositon-1,4,5-triphosphate production.

2) Inositon-1,4,5-triphosphate releases calcium ions from the endoplasmic reticulum.

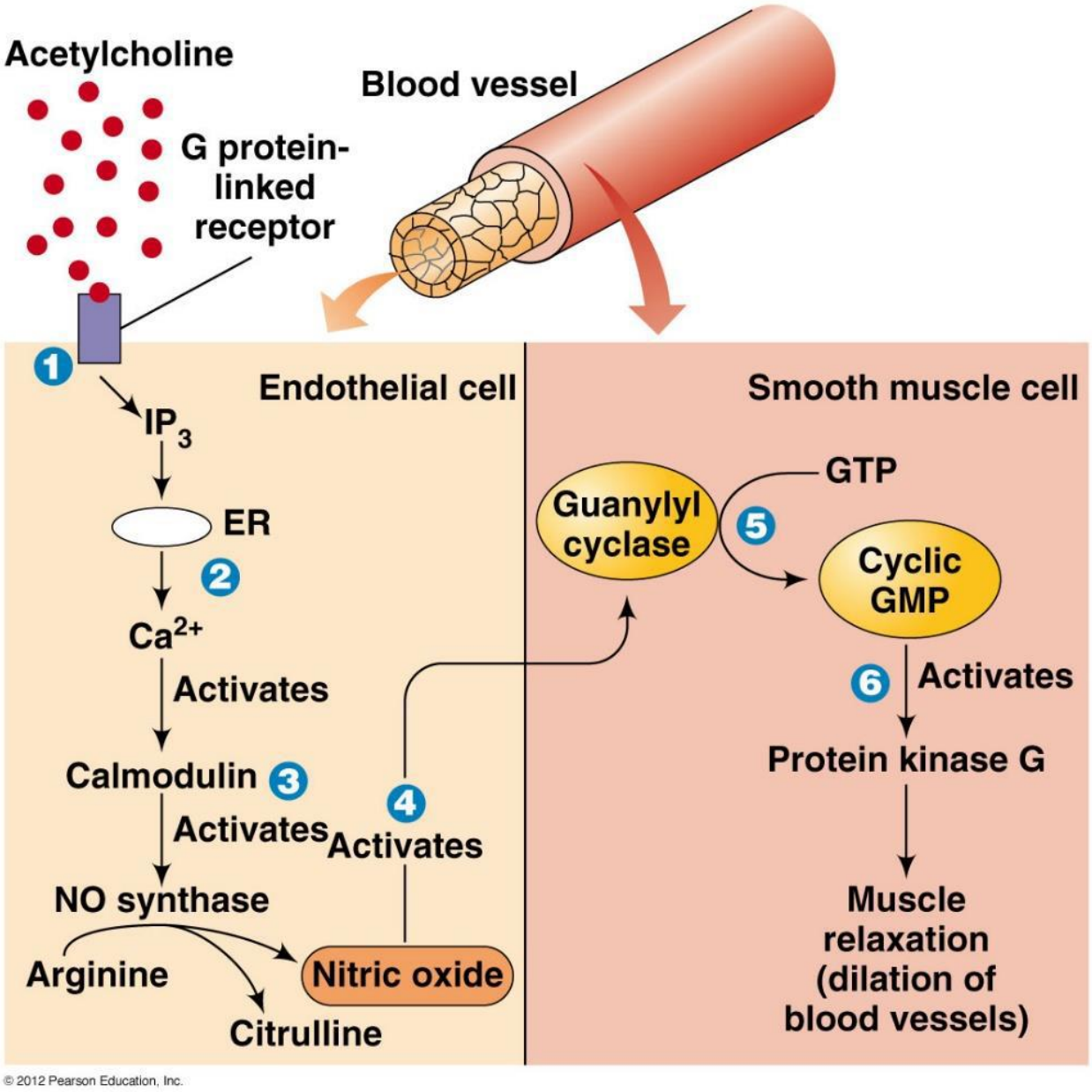
3) Calcium ions and calmodulin form a complex that stimulates nitric oxide synthase to produce nitric oxide.

4) Nitric oxide diffuses from endothelial cells into adjacent smooth muscle cells.

5) In smooth muscle cells, nitric oxide activates guanylyl cyclase to make cyclic GMP.

6) Cyclic GMP activates protein kinase G, which phosphorylates several muscle proteins to induce muscle relaxation.

15. What does the below diagram represent? Describe the signal transduction depicted in the diagram in six points highlighted in the diagram.



Answer:

The diagram represents the signal transduction mechanism of nitric oxide mediated relaxation of vascular smooth muscle cells

Signal transduction process:

1) Binding of acetylcholine to G protein receptors causes Inositon-1,4,5-triphosphate production.

2) Inositon-1,4,5-triphosphate releases calcium ions from the endoplasmic reticulum.

3) Calcium ions and calmodulin form a complex that stimulates nitric oxide synthase to produce nitric oxide.

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Sources

•Berg, JM, Tymoczko JL and Stryer, L. Biochemistry, sixth edition, W.H. Freeman and Company, New York, 2002.

•Voet, D, Voet, JG and Pratt CW. Principles of biochemistry, third edition, John Wiley & Sons, Inc, 2008

•Video 1: Signal Transduction Animation: https://www.youtube.com/watch?v=FtVb7r8aHco

•Video 2: Signal Transduction Pathways 1: https://www.youtube.com/watch?v=-U2dBURQbjk

•Video 3: G-protein receptor activation video: https://www.youtube.com/watch?v=2_nGMd0COH4

•Video 4: Signaltransduktion: https://www.youtube.com/watch?v=V-z415c6eOU

•Video 5:How Hormones Use G-protein Signaling Pathways: A Video Review of the Basics: https://www.youtube.com/watch?v=wC2_7Ror3qY&t=159s

•Video 6: G Protein Signaling - Handwritten Cell & Molecular Biology: https://www.youtube.com/watch?v=9Bq6qHJaSJs

•Video 7: G Protein linked 2nd Messengers, G protein coupled receptors, GPCRs: https://www.youtube.com/watch?v=3qR9B2JCT_s

•Video 8: Nitric oxide - benefits and side effects: https://www.youtube.com/watch?v=On-jTcLLP9o

SBCH321: UNIT 4 INFORMATION

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UNIT 4: Regulation and integration of metabolism

1. Answer the following question on regulation of glycolysis:

1.1. Glycolysis is regulated at how many enzymatic reactions? Describe the type of regulation.

1.2. Which enzymatic step is the committed step in glycolysis?

1.3. Draw the enzymatic reactions along with the substrate, product, enzyme and co-factors of the enzymatic steps that regulate glycolysis.

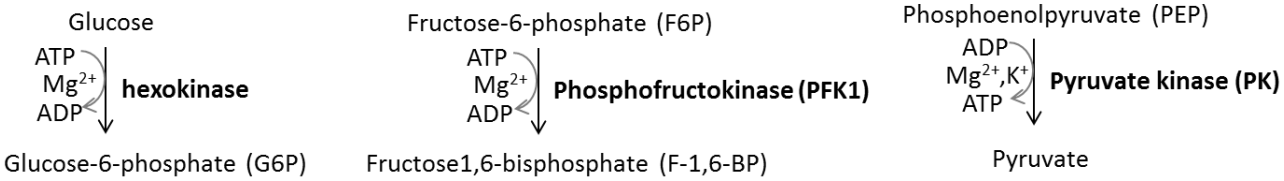
1.4. List the activator(s) and the inhibitor(s) of regulated glycolytic enzymes.

Answers:

1.1. Glycolysis is regulated at three enzymatic steps and all these steps are irreversible. Three glycolytic enzymes are regulated by allosteric regulation.

1.2. Phosphofructokinase (PFK1) is the committed enzymatic step in glycolysis.

1.3.



1.4. Activators and inhibitors of three glycolytic enzymes. In the table the upward arrow indicates high levels of a specific chemical compound.

Enzyme	Hexokinase (HK)	Phosphofructokinase (PFK1)	Pyruvate kinase (PK)
Allosteric Activator(s)	None	↑ ADP ↑ AMP ↑ F-2,6-BP	↑ F-1,6-BP
Allosteric Inhibitor(s)	G6P	↑ ATP ↑ PEP	↑ ATP ↑ Acetyl-CoA ↑ Alanine

2. Answer the following questions on regulation of citric acid cycle/Krebs cycle:

2.1. How many mechanisms are involved in the control of the citric acid cycle? List the mechanisms.

2.2. Through what type of regulation mechanism is the citric acid cycle flux controlled??

2.3. At how many enzymatic reactions is the citric acid cycle regulated? Describe the type of regulation.

2.4. Which enzymatic step is the committed step in the citric acid cycle?

2.5. Draw the enzymatic reactions along with the substrate, product, enzyme and co-factors of the enzymatic steps that regulate the citric acid cycle.

2.6. List the activator(s) and the inhibitor(s) of the regulated citric acid cycle enzymes.

Answer:

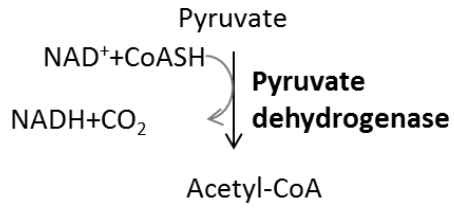
2.1. The citric acid cycle is regulated primarily by three mechanisms: (i) Substrate availability (ii) product inhibition and (iii) competitive feedback inhibition.

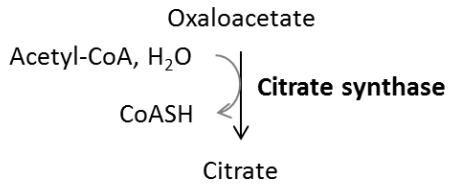
2.2 Allosteric regulation.

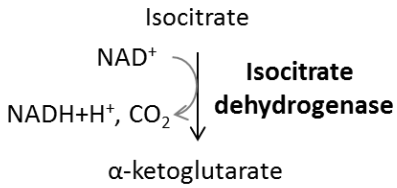
2.3. Four; allosteric regulation.

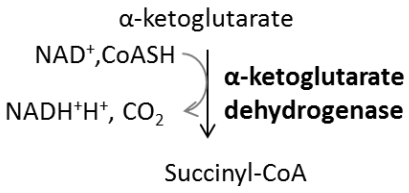
2.4. Citrate synthase.

2.5.









2.6

Enzyme	Citrate synthase	Isocitrate dehydrogenase	α-ketoglutarate dehydrogenase	Pyruvate dehydrogenase
Allosteric Activator(s)	-	↑ ADP ↑Ca^{2+} ↑ NAD^{+}	↑Ca^{2+}	↑Ca^{2+}
Allosteric Inhibitor(s)	↑ ATP ↑ NADH ↑ Succinyl-CoA ↑ Citrate	↑ ATP ↑ NADH	↑ ATP ↑ NAHD ↑ Succinyl-CoA	↑ATP ↑Acetyl-CoA ↑NADH

3. Answer the questions below on the regulation of fatty acid synthesis or degradation.

3.1. Which enzymes play a key role in the regulation of fatty acid biosynthesis and degradation?

3.2. Draw the enzymatic reactions of regulatory enzymes in fatty acid biosynthesis and degradation.

3.3. List the mechanisms involved in regulation of key enzymes that regulate fatty acid biosynthesis and degradation.

3.4. List the allosteric activators and inhibitors of acetyl-CoA carboxylase and carnitine acyl transferase I.

3.5. Explain the effect of phosphorylation on acetyl-CoA carboxylase.

3.6. List the hormones involved in the regulation of acetyl-CoA carboxylase.

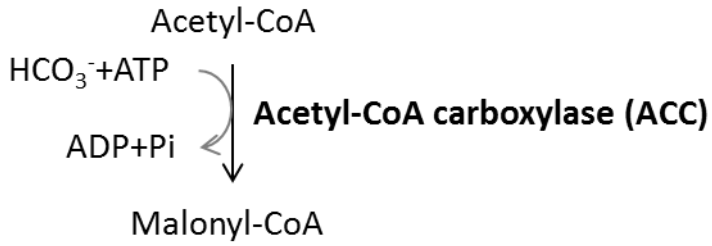
3.7. Draw a schematic diagram showing the regulation of fatty acid synthesis and degradation.

3.8. Explain in ten points the regulation of fatty acid biosynthesis and degradation.

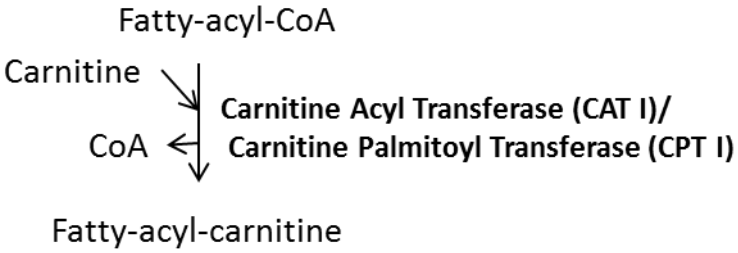
Answers:

3.1. Fatty acid biosynthesis: Acetyl-CoA carboxylase and fatty acid degradation: Carnitine acyl transferase (CAT I)/Carnitine palmitoyl transferase (CPT I)

3.2. Fatty acid biosynthesis:



Fatty acid degradation:



3.3. Fatty acid biosynthesis: Allosteric, covalent and adjustment of enzyme levels

Fatty acid degradation: Allosteric

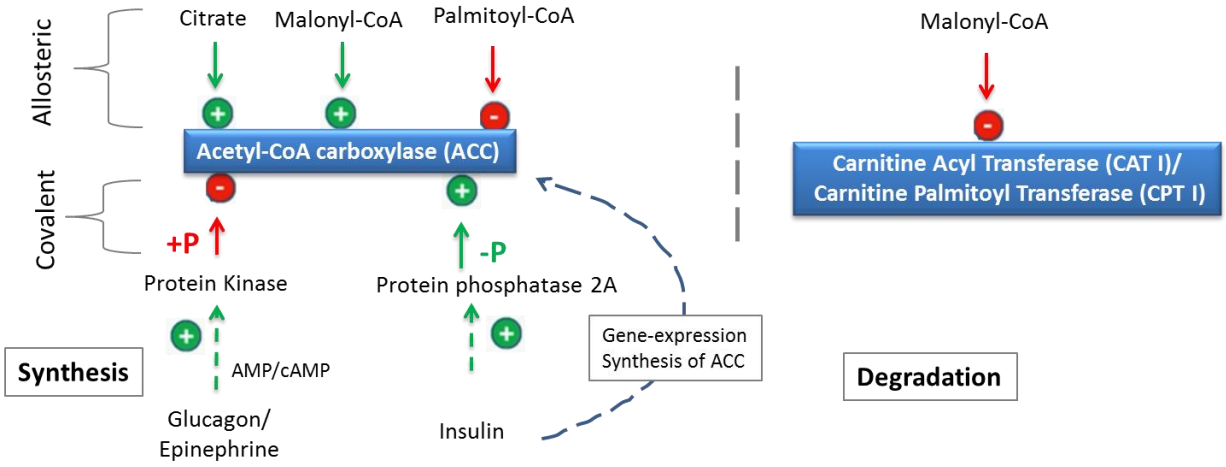
3.4.

	Allosteric activators	Allosteric inhibitors
Acetyl-CoA carboxylase	Citrate, malonyl-CoA	Palmitoyl-CoA
Carnitine Acyl Transferase I	-	Malonyl-CoA

3.5. Phosphorylation makes Acetyl-CoA carboxylase inactive and dephosphorylation makes the enzymes active.

3.6. Glucagon, epinephrine and insulin

3.7.



4. Answer the questions below on amino acids degradation/synthesis.

4.1. What is the difference between ketogenic and glucogenic amino acids? List ketogenic and glucogenic amino acids and amino acids that belong to both categories.

4.2. Describe the strategy for amino acids degradation.

4.3. Into how many central metabolic molecules can the standard 20 amino acids can be degraded? List the molecules.

4.4. Provide an overview on amino acid catabolism and draw a schematic diagram showing channeling of the carbon skeleton into different molecules.

4.5. Describe the process of deamination of amino acids. List one enzyme and its mechanism of regulation involved in this process. List its activators and inhibitors.

Answers:

4.1. A ketogenic amino acid is an amino acid that can be degraded directly into acetyl-CoA, which is the precursor of ketone bodies. Ketogenic amino acids cannot be converted to glucose, as both carbon atoms in the ketone body are ultimately degraded to carbon dioxide in the citric acid cycle. A glucogenic amino acid is an amino acid that can be converted into glucose through gluconeogenesis.

Ketogenic amino acids: Leucine and lysine

(tip: remembered as all the "L" amino acids)

ketogenic and glucogenic amino acids: Phenylalanine, isoleucine, tryptophan and tyrosine

(tip: remembered by the useful mnemonic "FITT")

Glucogenic amino acids: Threonine, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, methionine, proline, serine and valine

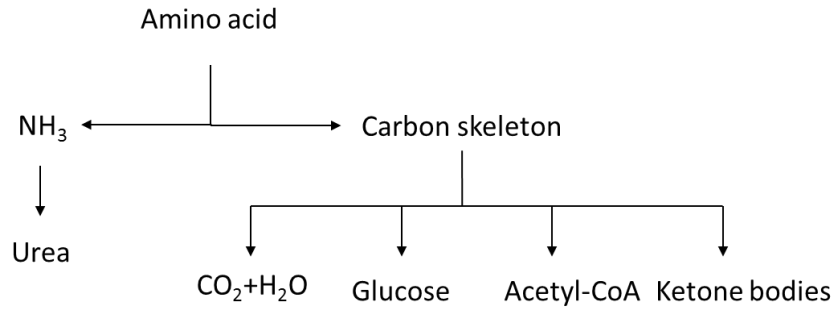
4.2. The strategy of amino acid degradation is to transform the carbon skeletons into major metabolic intermediates that can be converted into glucose or an oxidized citric acid cycle.

4.3. Seven; the molecules are: Pyruvate, acetyl-CoA, acetoacetyl-CoA, α-ketoglutarate, succinyl-CoA, fumarate, and oxaloacetate.

4.4.

Amino acid degradation often involves removal of the amino group and its incorporation into urea for disposal. The remaining carbon skeleton (α-keto acid) can be broken down to carbon dioxide and water or converted to glucose, acetyl-CoA, or ketone bodies.

A schematic diagram representing the amino acid catabolism is shown below:



4.5. Most amino acids are deaminated by transamination, the transfer of their amino group to an α-keto acid of the original amino acid and a new amino acid. The predominant amino group acceptor is α-ketoglutarate, producing glutamate and the new α-keto acid. The enzymes that catalyze transamination are called aminotransferases or transaminases. Glutamate dehydrogenase is such an enzyme that performs oxidative deamination of glutamate yielding ammonia and α-ketoglutarate. The ammonia will be eliminated into urea. The regenerated α-ketoglutarate will be used for synthesis of different molecules or different transamination reactions.

Glutamate dehydrogenase (GDH) is the key enzyme in the regulation of oxidative deamination of amino acids. This enzyme is controlled by an allosteric mechanism. GDH is allosterically inhibited by GTP and NADH (signaling abundant metabolic energy) and activated by ADP and NAD+ (signaling the need to generate ATP).

5. Answer the questions below on regulation of the pentose phosphate pathway.

5.1. What is the main factor that regulates the pentose phosphate pathway?

5.2. State how many different phases are present in the pentose phosphate pathway and list the phases.

5.3. What metabolic need dictates the different phases of the pentose phosphate pathway?

5.4. What is the committed step of the oxidative phase of the pentose phosphate pathway?

5.5. Describe the regulatory mechanism involved in the regulation of the committed step of the oxidative phase of the pentose phosphate pathway?

5.6. Which enzyme is involved in the regulation of the oxidative phase of the pentose phosphate pathway? Deduce the enzymatic reaction involving substrates and product. List the activators and inhibitors of the enzyme.

Answers:

6.1. Metabolic need

6.2. Two; oxidative phase and non-oxidative phase

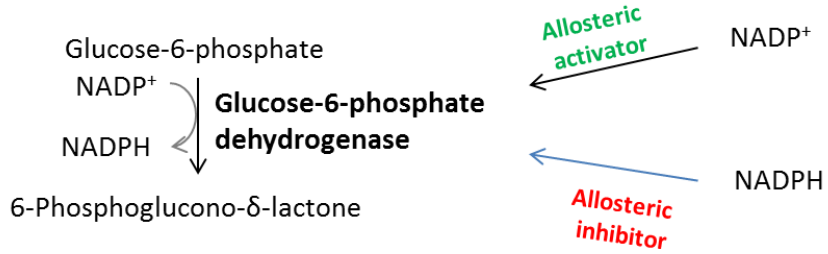
6.3. Oxidative: equal amount of NADPH and ribulose-5-phosphate

Non-oxidative phase: Needs large amounts of ribulose-5-phosphate and does not need NADPH

6.4. Conversion of glucose-6-phosphate to 6-phosphoglucono-δ-lactone is the committed enzymatic step in the oxidative phase of the pentose phosphate pathway.

6.5. Allosteric

6.6. Glucose-6-phosphate dehydrogenase



Activator: $NADP^+$

Inhibitor: NADPH

6. Answer the following question on the regulation of gluconeogenesis.

6.1. State at how many enzymatic reactions gluconeogenesis is regulated and describe the type of regulation.

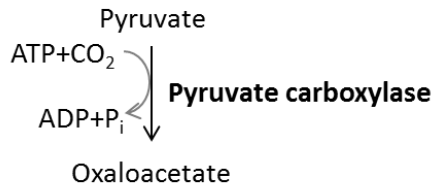
6.2. Draw the enzymatic reactions along with the substrate, product, enzyme and co-factors of the enzymatic steps that regulate gluconeogenesis.

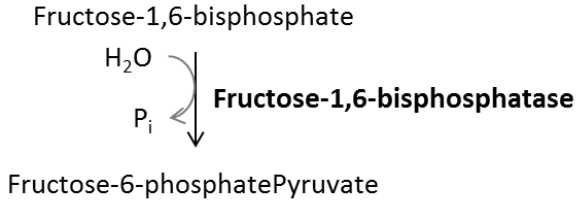
6.3. List the activator(s) and the inhibitor(s) of regulated gluconeogenesis enzymes.

Answer:

6.1. Gluconeogenesis is regulated at two enzymatic steps. Two gluconeogenesis enzymes are regulated by allosteric regulation.

6.2.





6.3.

Enzyme	Pyruvate carboxylase	Fructose-1,6-bisphosphatase
Allosteric Activator(s)	↑ Acetyl-CoA	↑ ATP
Allosteric Inhibitor(s)	-	↑ AMP ↑ Fructose-2,6-bisphosphate

7. Answer the questions below on the regulation of glycogen metabolism.

7.1. How many types of mechanisms of regulations exist for glycogen metabolism? List the names of the mechanisms.

7.2. Which hormones influence glycogen metabolism?

7.3. State how many primary enzymes are involved in the regulation of glycogen metabolism and list their names.

7.4. Present the regulation of glycogen metabolism in a schematic diagram with a simplistic view that involves hormonal control via different enzymatic reactions. Clearly indicate the mechanism of regulation.

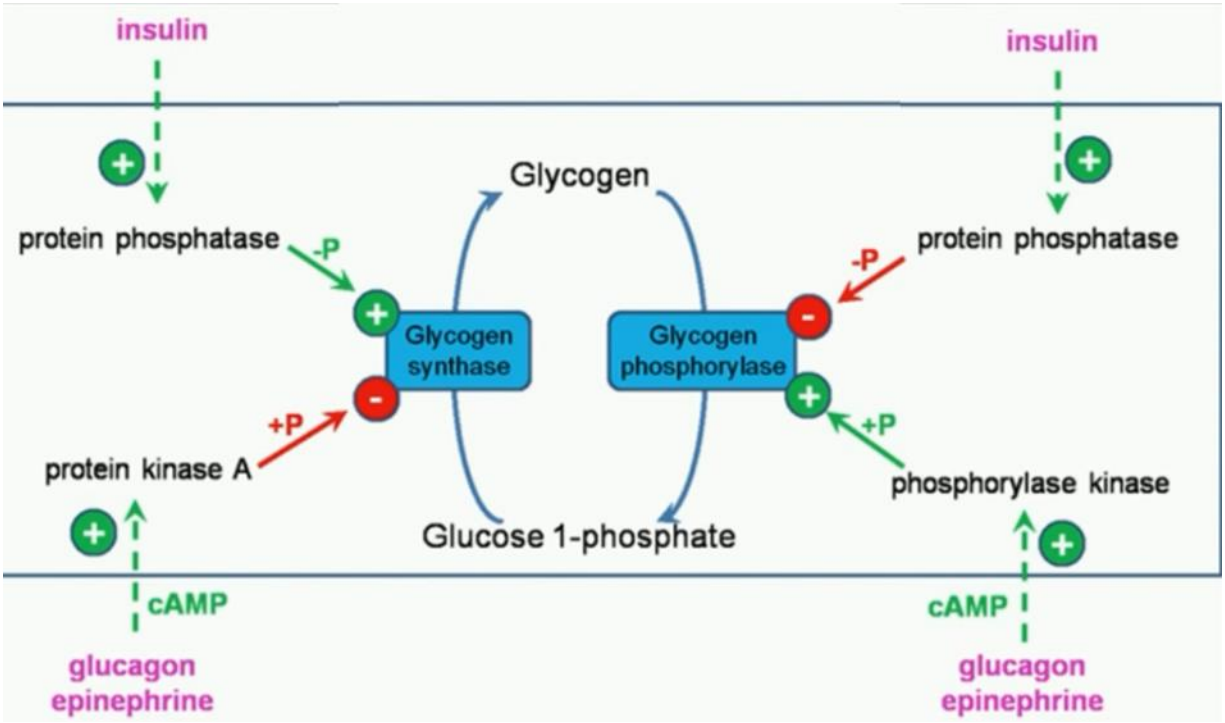
Answers:

7.1. Two. Glycogen metabolism is regulated by hormonal regulation and covalent regulation.

7.2. Insulin, glucagon and epinephrine.

7.3. Five. (i) Protein phosphatase (ii) Protein kinase A (iii) Phosphorylase kinase (iv) Glycogen phosphorylase (v) Glycogen synthase.

7.4.



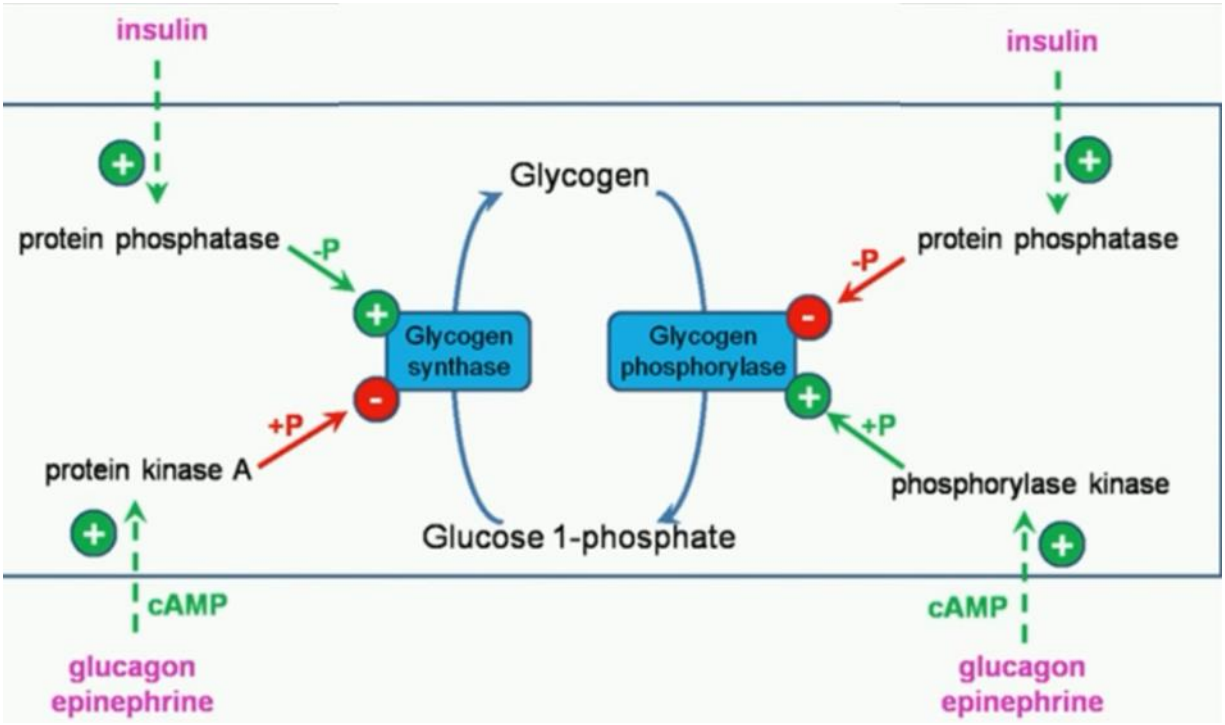
7.5. Answer the following questions using the diagram below.

7.5.1. What does the diagram represent?

7.5.2. Explain the metabolic pathway regulation by glucagon/epinephrine.

7.5.3. Explain the metabolic pathway regulation by insulin.

7.5.4. Explain the activity of glycogen synthase and glycogen phosphorylase in terms of phosphorylation and de-phosphorylation.



Answers:

7.5.1. Glycogen metabolism regulation

7.5.2. Glucagon or epinephrine is a hormone that increases the production of glucose-1-phosphate by breaking down glycogen in order to increase or normalize blood glucose levels. Both hormones exert their effect via second messenger cAMP, which activates phosphorylase kinase and protein kinase A by phosphorylation. The activated phosphorylase kinase further activates glycogen phosphorylase by phosphorylation. The activated glycogen phosphorylase phosphorylates glycogen to glucose-1-phosphate. Glucose-1-phosphate will be subsequently utilized for generation of glucose and other derivatives. The activated protein kinase A also phosphorylates glycogen synthase. However, contrary to glycogen phosphorylase, the phosphorylated glycogen synthase is inactive and stops conversion of glucose-1-phosphate to glycogen. The activation of glycogen phosphorylase and inactivation of glycogen synthase by glucagon/epinephrine increases the blood glucose levels.

7.5.3. Insulin is a hormone that reduces blood glucose levels and promotes glycogen synthesis. Insulin exerts its effect by dephosphorylating glycogen phosphorylase and glycogen synthase. Dephosphorylation has different effects on both enzymes. Dephosphorylation of glycogen

phosphorylase inactivates the enzyme and stops conversion of glycogen to glucose-1-phosphate. On the other hand, dephosphorylation activates glycogen synthase and promotes synthesis of glycogen.

7.5.4.

	Phosphorylation	dephosphorylation
Glycogen synthase	Inactivates enzyme	Activates enzyme
Glycogen phosphorylase	Activates enzyme	Inactivates enzyme

8. Answer the questions below on the regulation of the urea cycle

8.1. State how many different mechanisms exist for regulating the urea cycle and list the mechanisms.

8.2. State how many enzymes are involved in long-term regulation of the urea cycle and list the enzymes.

8.3. Describe briefly how the urea cycle is regulated by gene-expression and enzyme synthesis. Explain the status of enzymes in relation to a high-protein diet, low-protein diet and starvation.

8.4. Which enzyme is involved in the committed enzymatic reaction of the urea cycle? Draw the enzymatic reaction.

8.5. How is carbamoyl phosphate synthetase I regulated? List any one regulator of this enzyme.

8.6. How does arginine affect the activity of carbamoyl phosphate synthetase I?

8.7. Present a schematic diagram representing the allosteric regulation of the urea cycle. Also depict the role of arginine.

Answers:

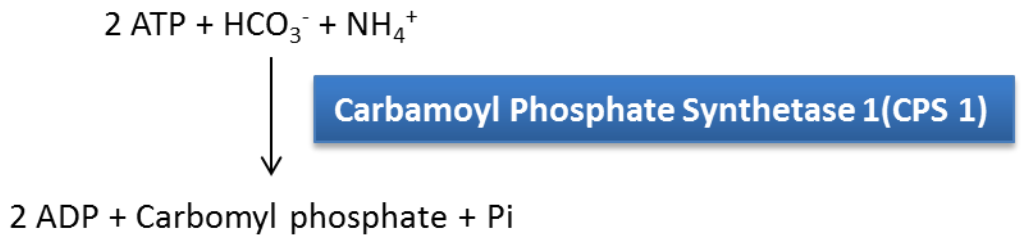
8.1. There are two mechanisms by which the urea cycle is regulated: (i) Adjustment of enzyme levels (long-term regulation and (ii) allosteric regulation (short-term regulation)

8.2. Five enzymes. (i) Carbamoyl phosphate synthetase I (ii) Argininosuccinate synthetase I (iii) Arginosuccinase (iv) Arginase (v) Ornithine transcarbamoylase.

8.3. Synthesis of all five enzymes involved in the urea cycle is upregulated based on nitrogen flux (substrate availability). High nitrogen flux induces synthesis of all five enzymes of the urea cycle and thus increases urea production. A high-protein diet induces synthesis of all five enzymes of the urea cycle, as more of amino acids are available, resulting in a high nitrogen flux. A low-protein diet inhibits synthesis

of all five enzymes of the urea cycle, as a low amount of amino acids is available and the nitrogen flux is thus low. Starvation induces synthesis of all five enzymes of the urea cycle, as degradation of proteins leads to a high nitrogen flux.

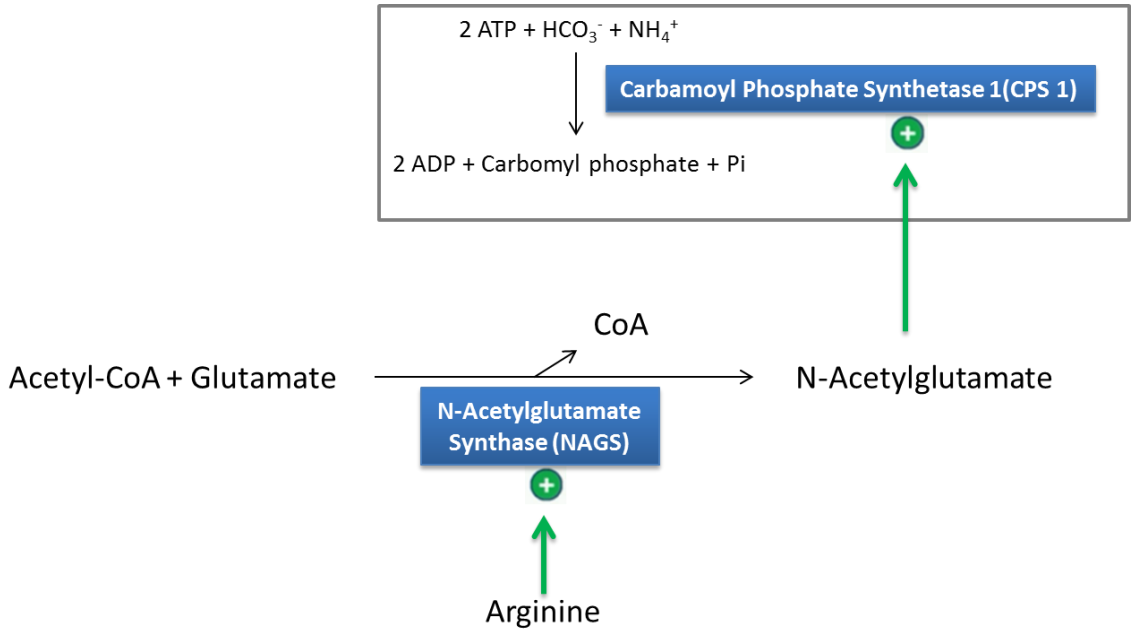
8.4. Carbamoyl phosphate synthetase I reaction is the committed enzymatic reaction in the urea cycle.



8.5. Carbamoyl phosphate synthetase (CPS I) is allosteric-regulated and N-acetylglutamate is the allosteric activator of this enzyme.

8.6. Arginine is an allosteric activator of N-acetylglutamate synthase, which synthesises the N-acetylglutamate, the allosteric activator of carbamoyl phosphate synthetase (CPS I). Thus arginine indirectly activates CPS I by increasing the amount of N-acetylglutamate.

8.7.



9. Answer the questions below on ketone bodies.

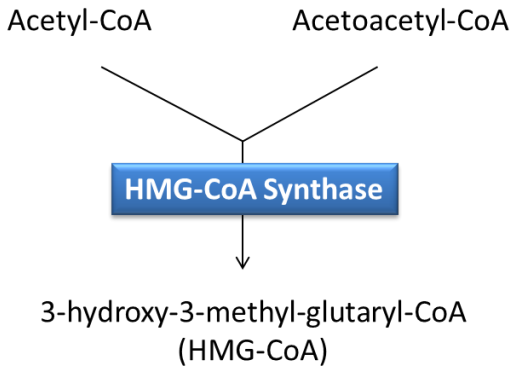
9.1. Which enzyme is involved in the regulation of ketone body synthesis? Deduce the enzymatic reaction involving substrates and product.

9.2. Describe the regulation of ketone body synthesis. Also draw a schematic diagram showing the regulation of ketone body synthesis.

Answers:

9.1. HMG-CoA synthase

Enzymatic reaction:

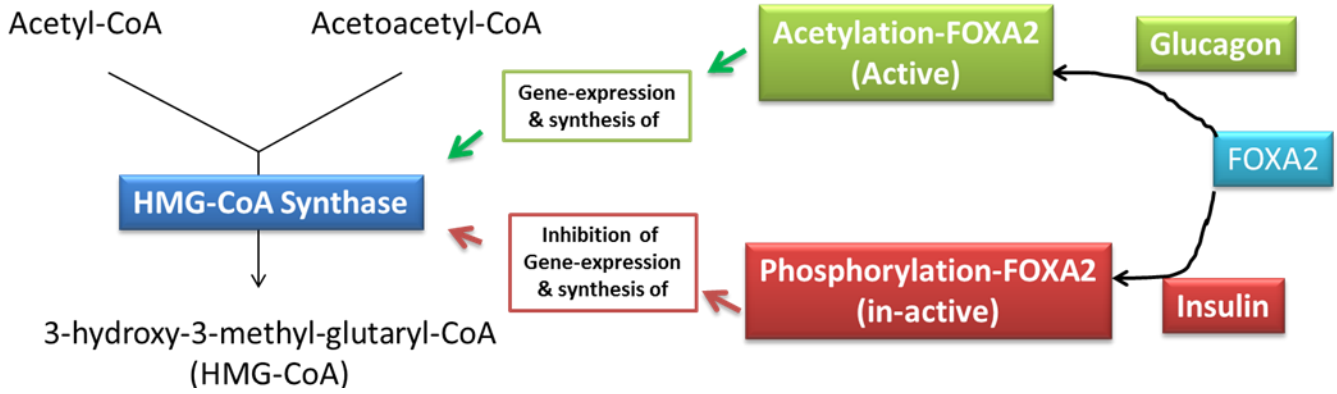


9.2. Ketone body synthesis is highly regulated at a rate-limiting step catalyzed by HMG-CoA synthase. Expression of this enzyme is regulated by two hormones, glucagon and insulin. Both hormones exert their effect on synthesis of HMG-CoA by FOXA2 (Forkhead box A2) transcription factor.

Glucagon increases the synthesis of HMG-CoA synthase and promotes ketone body synthesis. Glucagon exerts its effect by activating the FOXA2 by acetylation. The acetylated FOXA2 causes gene expression and thus synthesis of HMG-CoA synthase enzyme.

On the other hand, insulin inhibits the synthesis of HMG-CoA synthase and thus stops ketone body synthesis. Insulin exerts its effect by inactivating the FOXA2 by phosphorylation. The phosphorylated FOXA2 inhibits the synthesis of HMG-CoA synthase enzyme.

The schematic diagram below represents the regulation of ketone body synthesis.



10. Answer the questions below on the integration of metabolism

10.1. Draw a schematic diagram representing the integration of major metabolic pathways in terms of fuel metabolism in mammals and describe how these pathways are integrated.

10.2. List the three important molecules in metabolism.

10.3. Describe the central role of glucose-6-phosphate in metabolism, highlighting its fate and the conditions dictating its fate.

10.4. Illustrate the metabolic fates of glucose-6-phosphate.

10.5 Illustrate the metabolic fates of pyruvate.

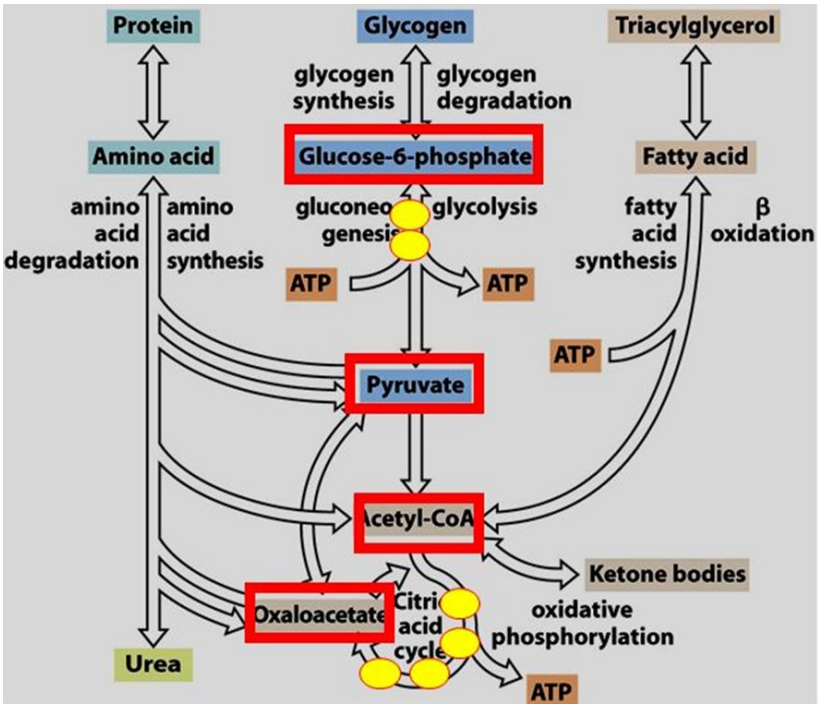
10.6. Illustrate the metabolic fates of acetyl-CoA.

10.7. Describe the metabolic fates of pyruvate and the significance of these fates.

10.8. Describe the metabolic fates of acetyl-CoA and the significance of these fates.

Answers:

10.1. Schematic diagram representing the integration of major metabolic pathways in terms of fuel metabolism in mammals:



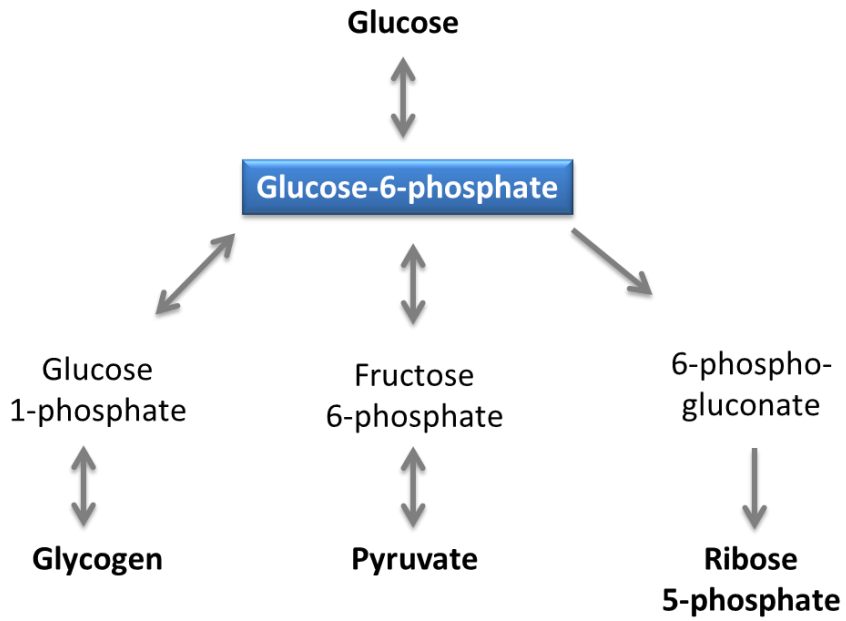
Integration of major metabolic pathways:

Proteins, glycogen, and triacylglycerols are built up from and broken down into smaller units: amino acids, glucose-6-phosphate and fatty acids. Oxidation of those fuels yields metabolic energy in the form of ATP. Pyruvate (a product of glucose and amino acid degradation) and acetyl-CoA (a product of glucose, amino acid, and fatty acid degradation) occupy positions in mammalian fuel metabolism. Compounds that give rise to pyruvate, such as oxaloacetate, can be used for gluconeogenesis; acetyl-CoA can give rise to ketone bodies, but not glucose. The amino group is disposed of through urea synthesis.

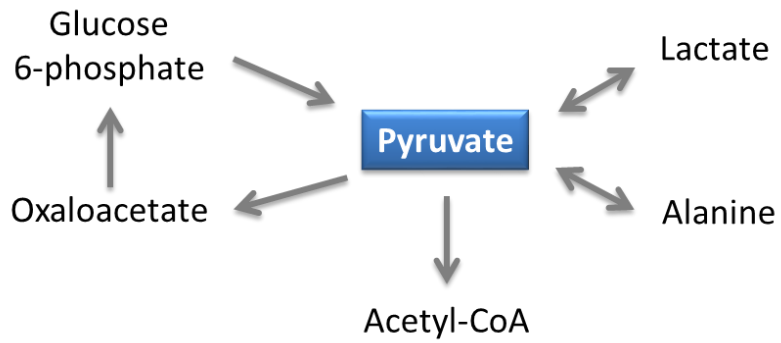
10.2. Glucose-6-phosphate, pyruvate and acetyl-CoA

10.3. Glucose entering a cell is rapidly phosphorylated to glucose 6-phosphate and is subsequently stored as glycogen, degraded to pyruvate, or converted to ribose 5-phosphate. Glycogen is formed when glucose 6-phosphate and ATP are abundant. In contrast, glucose 6-phosphate flows into the glycolytic pathway when ATP or carbon skeletons for biosynthesis are required. Thus, the conversion of glucose 6-phosphate into pyruvate can be anabolic as well as catabolic. The third major fate of glucose 6-phosphate, to flow through the pentose phosphate pathway, provides NADPH for reductive biosynthesis and ribose 5-phosphate for synthesis of nucleotides. Glucose 6-phosphate can be formed by the mobilization of glycogen or it can be synthesized from pyruvate and glucogenic amino acids by the gluconeogenic pathway.

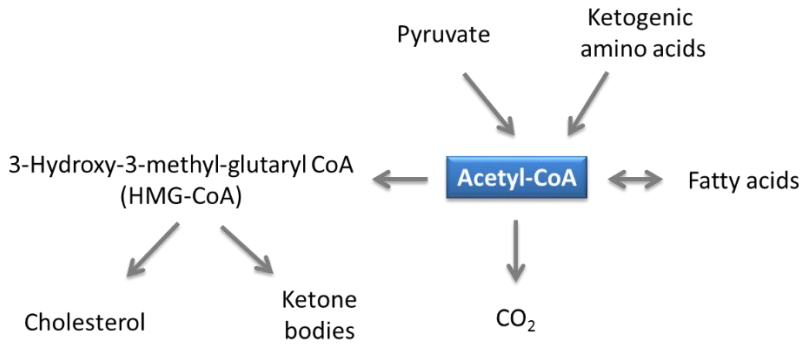
10.4.


Glucose
Glucose-6-phosphate
Glucose
1-phosphate
Fructose
6-phosphate
6-phospho-
gluconate
Glycogen
Pyruvate
Ribose
5-phosphate

10.5.


Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
Acetyl-CoA

10.6.



10.7.

This three-carbon alpha-ketoacid is another major metabolic junction. Pyruvate is derived primarily from glucose-6-phosphate, alanine and lactate. Pyruvate can be reduced to lactate by lactate dehydrogenase to regenerate NAD+. This reaction enables glycolysis to proceed transiently under anaerobic conditions in active tissues such as contracting muscle. The lactate formed in active tissue is subsequently oxidized back to pyruvate in other tissues. The essence of this interconversion is that it buys time and shifts part of the metabolic burden of active muscle to other tissues. Another readily reversible reaction in the cytoplasm is the transamination of pyruvate, an alpha-ketoacid, to alanine, the corresponding amino acid.

A third fate of pyruvate is its carboxylation to oxaloacetate inside mitochondria, the first step in gluconeogenesis. This reaction and the subsequent conversion of oxaloacetate into phosphoenolpyruvate bypass an irreversible step of glycolysis and hence enable glucose to be synthesized from pyruvate. The carboxylation of pyruvate is also important for replenishing intermediates of the citric acid cycle. Acetyl CoA activates pyruvate carboxylase, enhancing the synthesis of oxaloacetate, when the citric acid cycle is slowed by a paucity of this intermediate. A fourth fate of pyruvate is its oxidative decarboxylation to acetyl CoA.

10.8.

The major sources of this activated two-carbon unit are the oxidative decarboxylation of pyruvate and the beta-oxidation of fatty acids. Acetyl CoA is also derived from ketogenic amino acids. The fate of acetyl CoA, in contrast with that of many molecules in metabolism, is quite restricted. The acetyl unit can be completely oxidized to CO2 by the citric acid cycle. Alternatively, 3-hydroxy-3-methylglutaryl CoA can be formed from three molecules of acetyl CoA. This six-carbon unit is a precursor of cholesterol and of ketone bodies, which are transport forms of acetyl units released from the liver for use by some

peripheral tissues. A third major fate of acetyl CoA is its export to the cytoplasm in the form of citrate for the synthesis of fatty acids.

11. Answer the questions below on the effect of hormones on fuel metabolism.

11.1. Describe the effects of the hormones insulin, glucagon and epinephrine on fuel metabolism in muscle, adipose tissue and the liver in tabular format, using arrows.

11.2. Explain briefly the role of these hormones in the fed state and fasted state/stress.

Answers:

11.1.

Tissue	Insulin	Glucagon	Epinephrine
Muscle	↑ Glucose uptake	No effect	↑ Glycogenolysis
	↑ Glycogen synthesis		
Adipose tissue	↑ Glucose uptake	↑ Lipolysis	↑ Lipolysis
	↑ Lipogenesis		
	↓ Lipolysis		
Liver	↑ Glycogen synthesis	↓ Glycogen synthesis	↓ Glycogen synthesis
	↑ Lipogenesis	↑ Glycogenolysis	↑ Glycogenolysis
	↓ Gluconeogenesis		↑ Gluconeogenesis

11.2. Fed state: Immediately after a meal, when glucose and fatty acids are abundant, insulin signals tissues to store fuel as glycogen (liver and muscle) and triaclglycerols (adipose tissue and liver). Insulin also stimulates tissues other than the liver to take up glucose via the GLUT4 transporter.

Fasted state/stress:

In the fasted state/stress, glucagon stimulates the liver to release glucose and adipose tissue to release fatty acids. During stress, epinephrine elicits a similar response. In addition, epinephrine also signals the muscle for glycogenolysis.

Sources

•Berg, JM, Tymoczko JL and Stryer, L, Biochemistry, sixth edition, W.H. Freeman and Company, New York, 2002.

•Voet, D, Voet, JG and Pratt CW. Principles of biochemistry, third edition, John Wiley & Sons, Inc, 2008.

•Glycolysis: Video 1: https://www.youtube.com/watch?v=ODGA3labyi4

•Citric acid cycle/Krebs cycle

- Video 2: https://www.youtube.com/watch?v=gQkfwq0DaiI
- Video 3: https://www.youtube.com/watch?v=w47MiUnhbGM

•fatty acid synthesis/degradation

Video 4: https://www.youtube.com/watch?v=A2mQPCtKA6U

Video 5: https://www.youtube.com/watch?v=_SmWabaHfWY

Video 6: https://www.youtube.com/watch?v=_AUwgQu30LU

•Metabolic fate of amino acids

Video 7: https://www.youtube.com/watch?v=Sy-rfy5Mdc0

Video 8: https://www.youtube.com/watch?v=GT-9sgGMIkQ

•Pentose phosphate pathway Video 9: https://www.youtube.com/watch?v=sYn5AfJWSls

•Gluconeogenesis Video 10: https://www.youtube.com/watch?v=oCgrOn59ri4&t=191s

•Glycogen metabolism Video 11: https://www.youtube.com/watch?v=LJYTFtiTVXA & Video 12: https://www.youtube.com/watch?v=oWp51lQUE_I

•Urea cycle videos 13 & 14: https://www.youtube.com/watch?v=FFjs0vuCkXI & https://www.youtube.com/watch?v=K3rVr_SfXo8

•Ketone bodies:

- von Meyenn, F, Porstmann, T, Gasser, E, Selevsek, N, Schmidt, A, Aebersold, R and Stoffel, M. 2013. Glucagon-induced acetylation of Foxa2 regulates hepatic lipid metabolism. Cell metabolism, 17(3):436-447.
- Howell, JJ and Stoffel, M. 2009. Nuclear export-independent inhibition of Foxa2 by insulin. Journal of Biological Chemistry, 284(37):24816-24824.

Video 15: https://www.youtube.com/watch?v=AK9Q2Cll8y4

- Effect of hormones on fuel metabolism Video 16:
  https://www.youtube.com/watch?v=8UriZwNl4n4