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MATRIC NUMBER: 17/MHS07/005

DEPARTMENT:ANATOMY

COURSE : CELLULAR BIOCHEMISTRY; NEUROCHEMISTRY

COURSE CODE : BCH 308

1. SYNTHESIS OF PURINES

. Adenosine Triphosphate

. Adenosine

SYNTHESIS OF ADENOSINE TRIPHOSPHATE.

ATP synthesis involves the transfer of electrons from the intermembrane space, through the inner membrane, back to the matrix. The transfer of electrons from the matrix to the intermembrane space leads to a substantial pH difference between the two sides of the membrane

The combination of the two components provides sufficient energy for ATP to be made by the multienzyme

Complex V of the mitochondrion, more generally known as ATP synthase.

ATP synthase is an enzyme that creates the energy storage molecule adenosine triphosphate (ATP). It is formed from adenosine diphosphate (ADP) and inorganic phosphate (P_i). The overall reaction catalyzed by ATP synthase is:

$$ADP + P_i + 3H^+_{out} \rightleftharpoons ATP + H_2O + 3H^+_{in}$$

The formation of ATP from ADP and P_i is energetically unfavorable and would normally proceed in the reverse direction. In order to drive this reaction forward, ATP synthase couples ATP synthesis during cellular respiration to an electrochemical gradient created by the difference in proton (H^+) concentration across the mitochondrial plasma membrane in eukaryotes or the plasma membrane in bacteria.
During photosynthesis in plants, ATP is synthesized by ATP synthase using a proton gradient created in the thylakoid lumen through the thylakoid membrane and into the chloroplast stroma.

ATP synthase is an F-ATPase. It consists of two main subunits, F_O and F_1, which has a rotational motor mechanism allowing for ATP production. Because of its rotating subunit, ATP synthase is a molecular machine.

Within cells, energy is provided by oxidation of "metabolic fuels" such as carbohydrates, lipids, and proteins. It is then used to sustain energy-dependent processes, such as the synthesis of macromolecules, muscle contraction, active ion transport, or thermogenesis. The oxidation process results in free energy production that can be stored in phosphoanhydrine "high-energy bonds" within molecules such as nucleoside diphosphate and nucleoside triphosphate (i.e., adenosine 5′ diphosphate and adenosine 5′ trisphosphate, ADP, and ATP, respectively), phosphoenolpyruvate, carbamoyl phosphate, 2,3-bisphosphoglycerate, and other phosphagens like phosphoarginine, or phosphocreatine. Among them, ATP is the effective central link—the exchange coin—between energy-producing and the energy-demanding processes that effectively involve formation, hydrolysis, or transfer of the terminal phosphate group.

In general, the main energy source for cellular metabolism is glucose, which is catabolized in the three subsequent processes—glycolysis, tricarboxylic acid cycle (TCA or Krebs cycle), and finally oxidative phosphorylation—to produce ATP. In the first process, when glucose is converted into pyruvate, the amount of ATP produced is low. Subsequently, pyruvate is converted to acetyl coenzyme A (acetyl-CoA) which enters the TCA cycle, enabling the production of NADH. Finally, NADH is used by the respiratory chain complexes to generate a proton gradient across the inner mitochondrial membrane, necessary for the production of large amounts of ATP by mitochondrial ATP synthase. In addition, it should be mentioned that acetyl-CoA can be generated also by lipid and protein catabolism.

ATP is produced by mainly by;

. Glycolysis

. Oxidative phosphorylation

Basic principles of ATP-producing pathways

Glycolysis

Glycolysis is a process by which glucose is partially converted through a series of enzyme-catalyzed reactions into two molecules of pyruvate. Some mammalian cell types (erythrocytes, sperm) and tissues (brain, renal medulla) are able to survive only (or mostly) on the energy derived from glycolysis. The steps comprising the processes leading to the breakdown of the six-carbon glucose into two three-carbon pyruvate molecules can be divided into two phases: the preparatory phase and the so-called “payoff”.

Thus, the second phase of glycolysis provides four molecules of ATP and two of NADH per molecule of glucose, paying the investment of the preparatory phase. The final balance of this process is then: two molecules of ATP, two of NADH (that could directly feed into the respiratory chain), and two of pyruvate. The latter enters the TCA cycle and undergoes complete oxidation in aerobic conditions.

During anaerobic conditions (such as what occurs in muscles during a burst of extreme activity, when oxygen

is not obtained fast enough from the blood), the low oxygen amounts do not allow the complete and efficient oxidation of pyruvate. During these conditions, NADH (produced in large amounts from the citric acid cycle; see next section) cannot be reoxidized to NAD, thus limiting the activity of GAPDH and glucose consumption. Pyruvate is then reduced to lactate with the consumption of one NADH in a process called lactic fermentation catalyzed by lactate dehydrogenase. In this way, the two molecules of NADH produced in glycolysis are consumed in lactic fermentation to restore the NAD reservoir, and the final balance of one glucose degradation is two molecules of ATP. This condition occurs also in aerobic conditions in erythrocytes (that have no mitochondria) or in many cancer cells as was originally observed by doctor Otto Warburg in 1930, and which led to the widely accepted Warburg effect theory

. Citric acid cycle

The starting material for the citric acid cycle is directly provided by the pyruvate coming from glycolysis through the activity of the pyruvate dehydrogenase complex. This

enzymatic complex, composed of multiple copies of the three enzymes pyruvate dehydrogenase (E1), dihydrolipoyl transacetylase (E2), and dihydrolipoyl dehydrogenase (E3), oxidizes pyruvate to acetyl-CoA and CO2 in an irreversible reaction in which the carboxyl group is removed from pyruvate as a molecule of CO2. This reaction is strictly related to the cycle, even if is not comprised in it. The acetyl group introduces two carbons in each turn of the cycle; these carbons will then leave the cycle as CO2.

The first reaction of the citric acid cycle is the condensation of one acetyl-CoA and a molecule of citrate to generate oxaloacetate and is catalyzed by citrate synthase. Citrate is then transformed into isocitrate by aconitase through the formation of cis-aconitate.

During all these processes, only one molecule of ATP (or GTP) is produced, but three molecules of NADH and one of FADH2 (plus one molecule of NADH from pyruvate dehydrogenase), which provide electrons for respiratory chain, are also generated and subsequently result in the production of large amounts of ATP (discussed later).

. Respiratory chain and oxidative phosphorylation.

Respiratory chain comprises a series of components (complexes) conducting electron transfer across the membrane and involved in oxidative phosphorylation (OXPHOS), a process which occurs in aerobic conditions. In eukaryotic cells, electron transport occurs in mitochondria and chloroplasts, whereas in bacteria it is carried out across the plasma membrane. As mentioned, the electron transfer is considered a part OXPHOS, the process through which ADP is phosphorylated into ATP by dint of energy derived from the oxidation of nutrients.

Four protein complexes and ATP synthase, all bound to the IMM, as well as two shuttles are the known players of one of the trickiest mechanisms

The sequential changes are linked to the binding of substrates, phosphorylation, and release of ATP. The three available dimers are never in the same conformational state, and, what is more, the conformational changes in one dimer drive rearrangements in the other (for a more

detailed explanation, refer to [14]). It has been calculated that, for the synthesis of one ATP molecule, four protons are required (three for the ATP synthase rearrangements and one for ATP, ADP, and Pi transport [15]). Once synthesized, ATP can locate inside mitochondrial matrix or be transported into the IMS by the nucleotide exchanger adenine nucleotide translocase (ANT) which passively exchanges ATP with ADP. Once in the IMS, ATP can freely pass the OMM through the voltage-dependent anion channel (VDAC).

ATP production is strongly regulated upon environmental stresses

Phosphorylation of ATP is strongly modulated by environmental stresses, such as hypoxia or heat shock. It has also been demonstrated, both in vitro and in vivo, that intracellular ATP levels are implicated in the regulation of fundamental cellular processes, such as growth, development, and death/survival decisions.

ATP storage.

ATP usually reaches high concentrations within cells, in the millimolar range. Nonetheless, because of the high rate of ATP-dependent processes, together with its low stability in water, ATP content could quickly be depleted if it were not immediately replenished by glycolysis and oxidative phosphorylation. Hence, ATP cannot be stored easily within cells, and the storage of carbon sources for ATP production (such as triglycerides or glycogen) is the best choice for energy maintenance.

SYNTHESIS OF ADENOSINE

Adenosine is an organic compound that occurs widely in nature in the form of diverse derivatives. The molecule consists of an adenine, minus one H atom, attached to a ribose, minus one OH group, via a β-N_9-glycosidic bond. Adenosine is one of four nucleoside building blocks to RNA, which is essential for all life. Its derivatives include the energy carriers adenosine mono-, di-, and triphosphate. Cyclic adenosine monophosphate (cAMP) is pervasive in signal transduction. Adenosyl (Ad) is the radical formed by removal of the 5'-hydroxy (OH) group. Ad is found in vitamin B12 and the radical SAM enzymes.[1] Adenosine is also used as a drug.[2]

Adenosine is synthesised from Inosine Monophosphate (IMP) as the nucleotide form (adenosine monophosphate). IMP does not accumulate in the cell but is rapidly converted to AMP and GMP. AMP, which differs from IMP only in the replacement of its 6-keto group by an amino is synthesized in a two-reaction pathway.

Free adenine (and guanine) can be reconverted to corresponding ribonucleotides through salvage pathways requiring the enzyme Adenine phosphoribosyltransferase (APRT) (mediates AMP formation).

2. SYNTHESIS OF AMINES

(CATHECOLAMINES).

. Norepinephrine

. Epinephrine (Adrenaline)

. Acetylcholine

. Dopamine

SYNTHESIS OF NOREPINEPHRINE

Norepinephrine (NE) is the primary neurotransmitter for postganglionic sympathetic adrenergic nerves. It is synthesized inside the nerve axon, stored within vesicles, then released by the nerve when an action potential travels down the nerve. Below are the details for release and synthesis of NE:

The amino acid tyrosine is transported into the sympathetic nerve axon.
Tyrosine (Tyr) is converted to DOPA by tyrosine hydroxylase (rate-limiting step for NE synthesis).
DOPA is converted to dopamine (DA) by DOPA decarboxylase.
Dopamine is transported into vesicles then converted to norepinephrine (NE) by dopamine β-hydroxylase (DBH); transport into the vesicle can by blocked by the drug reserpine.
An action potential traveling down the axon depolarizes the membrane and causes calcium to enter the axon.

Increased intracellular calcium causes the vesicles to migrate to the axonal membrane and fuse with the membrane, which permits the NE to diffuse out of the vesicle into the extracellular (junctional) space. DBH, and depending on the nerve other secondary neurotransmitters (e.g., ATP), is released along with the NE.

The NE binds to the postjunctional receptorand stimulates the effector organ response.

SYNTHESIS OF EPINEPHRINE (ADRENALINE)

Epinephrine is synthesized from norepinephrine within the adrenal medulla, which are small glands associated with the kidneys. Preganglionic fibers of the sympathetic nervous system synapse within the adrenals. Activation of these preganglionic fibers releases acetylcholine, which binds to postjunctional nicotinic receptors in the tissue. This leads to stimulation of NE synthesis within adenomedullary cells, but unlike sympathetic neurons, there is an additional enzyme (phenylethanolamine-N-

Epinephrine, is a hormone and medication. Adrenaline is normally produced by both the adrenal glands and a small number of neurons in the medulla oblongata, where it acts as a neurotransmitter involved in regulating visceral functions (e.g., respiration). It plays an important role in the fight-or-flight response by increasing blood flow to muscles, output of the heart, pupil dilation response and blood sugar level. It does this by binding to alpha and beta receptors. It is found in many animals and some single-celled organisms.

Pathway of catecholamine biosynthesis. Synthesis of epinephrine and norepinephrine is regulated by catecholamine synthesizing enzymes. Synthesis of catecholamines starts with conversion of phenylalanine to L-tyrosine, which is converted to L-dopa by tyrosine hydroxylase (TH). L-dopa is processed to dopamine by L-aromatic amino acid decarboxylase (AAAD), from where norepinephrine is formed by dopamine-β-hydroxylase (DBH). Finally, epinephrine is synthesized by addition of a methyl group to norepinephrine by

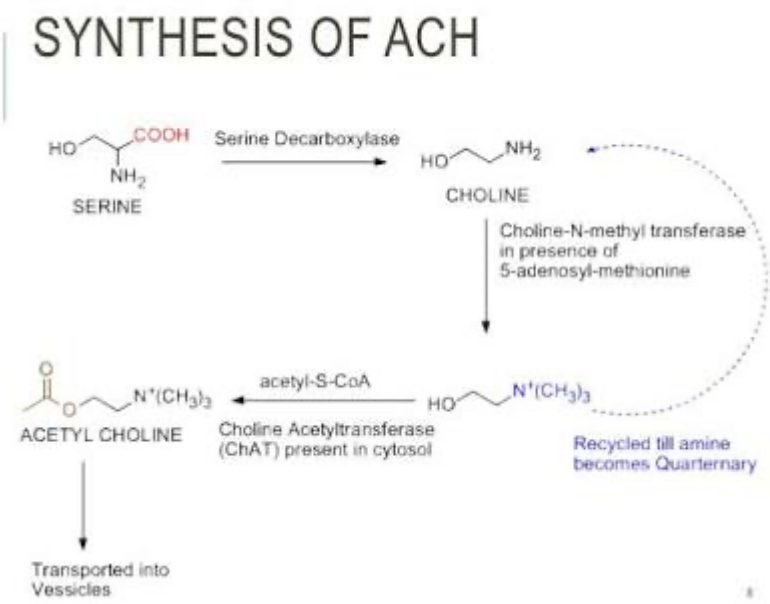
phenylethanolamine-N-methyltransferase (PNMT). Norepinephrine and epinephrine both act as neurotransmitters for sympathetic innervation.

SYNTHESIS OF ACETYLCHOLINE

Acetylcholine (ACh) is an organic chemical that functions in the brain and body of many types of animals (and humans) as a neurotransmitter—a chemical message released by nerve cells to send signals to other cells, such as neurons, muscle cells and gland cells.[1] Its name is derived from its chemical structure: it is an ester of acetic acid and choline. Parts in the body that use or are affected by acetylcholine are referred to as cholinergic. Substances that interfere with acetylcholine activity are called anticholinergics.

Acetylcholine is synthesized in certain neurons by the enzyme choline acetyltransferase from the compounds choline and acetyl-CoA. Cholinergic neurons are capable of producing ACh. An example of a central cholinergic area is the nucleus basalis of Meynert in the basal forebrain. The enzyme acetylcholinesterase converts

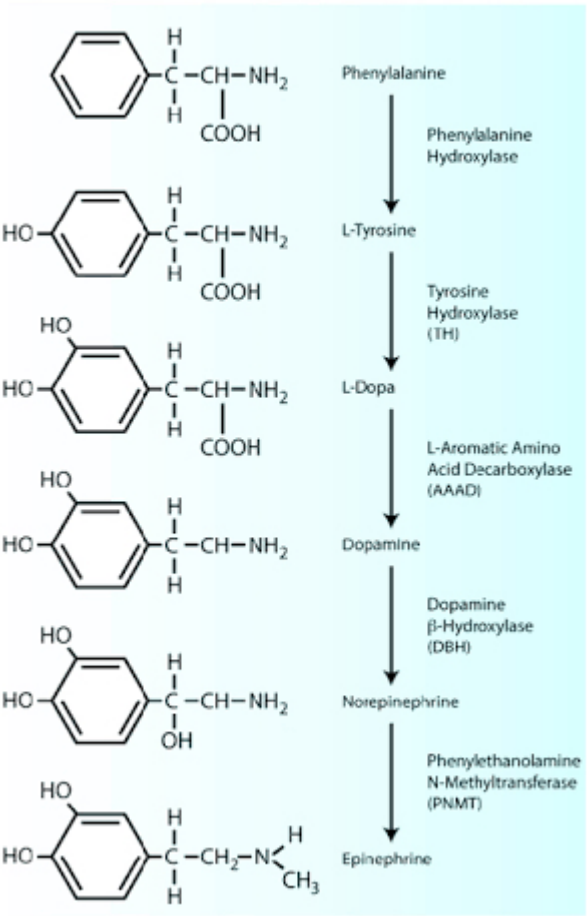
acetylcholine into the
inactive metabolites choline and acetate. This enzyme is abundant in the synaptic cleft, and its role in rapidly clearing free acetylcholine from the synapse is essential for proper muscle function. Certain neurotoxins work by inhibiting acetylcholinesterase, thus leading to excess acetylcholine at the neuromuscular junction, causing paralysis of the muscles needed for breathing and stopping the beating of the heart.

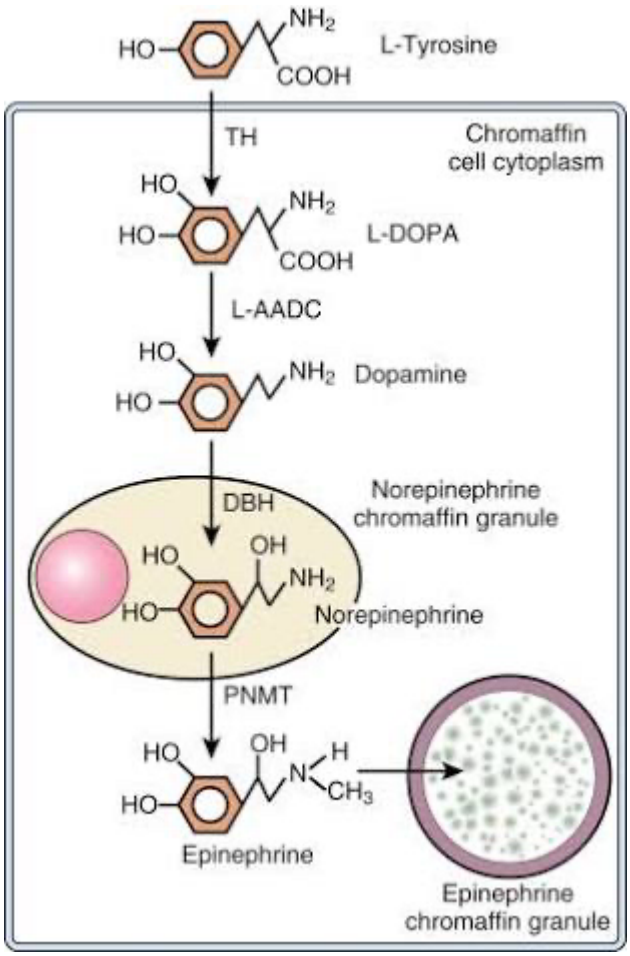


SYNTHESIS OF DOPAMINE

Dopamine is synthesized from the amino acid tyrosine, which is taken up into the brain via an active transport mechanism. Tyrosine is produced in the liver from phenylalanine through the action of phenylalanine hydroxylase. Tyrosine is then transported to dopamine containing neurons where a series of reactions convert it to dopamine [15,16]. Within catecholaminergic neurons, tyrosine hydroxylase catalyzes the addition of a hydroxyl group to the meta position of tyrosine, yielding L-dopa. This rate-limiting step in catecholamine synthesis is subject to inhibition by high levels of catecholamines (end- product inhibition). Because tyrosine hydroxylase is normally saturated with substrate, manipulation of tyrosine levels does not readily impact the rate of catecholamine synthesis. Once formed, L-dopa is rapidly converted to dopamine by dopa decarboxylase, which is located in the cytoplasm. It is now recognized that this enzyme acts not only on L-dopa but also on all naturally occurring aromatic L-amino acids, including tryptophan, and thus it is more properly termed aromatic amino acid decarboxylase.

Pathway of catecholamine biosynthesis




HO
NH2
COOH
L-Tyrosine
TH
Chromaffin
cell cytoplasm
HO
HO
NH2
COOH
L-DOPA
L-AADC
HO
HO
NH2
Dopamine
DBH
Norepinephrine
chromaffin granule
HO
HO
OH
NH2
Norepinephrine
PNMT
HO
HO
OH
N
H
CH3
Epinephrine
Epinephrine
chromaffin granule