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1. Describe in details the synthesis of two named neurotransmitters

SYNTHESIS OF AMINES.

* Norepinephrine
* Serotonin

**Synthesis of Norepinephrine**.

Norepinephrine is [synthesized](https://en.wikipedia.org/wiki/Biosynthesis) from the [amino acid](https://en.wikipedia.org/wiki/Amino_acid) [tyrosine](https://en.wikipedia.org/wiki/Tyrosine) by a series of enzymatic steps in the [adrenal medulla](https://en.wikipedia.org/wiki/Adrenal_medulla) and [postganglionic neurons](https://en.wikipedia.org/wiki/Postganglionic_neuron) of the [sympathetic nervous system](https://en.wikipedia.org/wiki/Sympathetic_nervous_system). While the conversion of tyrosine to dopamine occurs predominantly in the cytoplasm, the conversion of dopamine to norepinephrine by [dopamine β-monooxygenase](https://en.wikipedia.org/wiki/Dopamine_%CE%B2-monooxygenase) occurs predominantly inside [neurotransmitter vesicles](https://en.wikipedia.org/wiki/Synaptic_vesicle). The [metabolic pathway](https://en.wikipedia.org/wiki/Metabolic_pathway) is:

Phenylalanine → Tyrosine → L-DOPA → Dopamine → Norepinephrine

Thus the direct precursor of norepinephrine is [dopamine](https://en.wikipedia.org/wiki/Dopamine), which is synthesized indirectly from the essential amino acid [phenylalanine](https://en.wikipedia.org/wiki/Phenylalanine) or the non-essential amino acid [tyrosine](https://en.wikipedia.org/wiki/Tyrosine). These amino acids are found in nearly every protein and, as such, are provided by ingestion of protein-containing food, with tyrosine being the most common.

Phenylalanine is converted into tyrosine by the enzyme [phenylalanine hydroxylase](https://en.wikipedia.org/wiki/Phenylalanine_hydroxylase), with molecular [oxygen](https://en.wikipedia.org/wiki/Oxygen) (O2) and [tetrahydrobiopterin](https://en.wikipedia.org/wiki/Tetrahydrobiopterin) as [cofactors](https://en.wikipedia.org/wiki/Cofactor_(biochemistry)). Tyrosine is converted into [L-DOPA](https://en.wikipedia.org/wiki/L-DOPA) by the enzyme [tyrosine hydroxylase](https://en.wikipedia.org/wiki/Tyrosine_hydroxylase), with [tetrahydrobiopterin](https://en.wikipedia.org/wiki/Tetrahydrobiopterin), O2, and probably [ferrous iron](https://en.wikipedia.org/wiki/Ferrous) (Fe2+) as cofactors. L-DOPA is converted into dopamine by the enzyme [aromatic L-amino acid decarboxylase](https://en.wikipedia.org/wiki/Aromatic_L-amino_acid_decarboxylase) (also known as DOPA decarboxylase), with [pyridoxal phosphate](https://en.wikipedia.org/wiki/Pyridoxal_phosphate) as a cofactor. Dopamine is then converted into norepinephrine by the enzyme [dopamine β-monooxygenase](https://en.wikipedia.org/wiki/Dopamine_beta-monooxygenase) (formerly known as dopamine β-hydroxylase), with O2 and [ascorbic acid](https://en.wikipedia.org/wiki/Ascorbic_acid) as cofactors. Norepinephrine itself can further be converted into [epinephrine](https://en.wikipedia.org/wiki/Epinephrine) by the enzyme [phenylethanolamine N-methyltransferase](https://en.wikipedia.org/wiki/Phenylethanolamine_N-methyltransferase) with [S-adenosyl-L-methionine](https://en.wikipedia.org/wiki/S-Adenosyl_methionine) as cofactor.

**Synthesis of Serotonin.**

Serotonin (5-hydroxytryptamine) is principally found stored in three main cell types - i) serotonergic neurons in the CNS and in the intestinal myenteric plexus, ii) enterochromaffin cells in the mucosa of the gastrointestinal tract, and iii) in blood platelets. Serotonergic neurons and enterochromaffin cells can synthesize serotonin from its precursor amino acid L-tryptophan, whereas platelets rely upon uptake of serotonin for their stores. Likewise, serotonergic neurons also have the capacity for amine uptake via serotonin transporters. Serotonin is also synthesized in the pineal gland as a precursor for the subsequent enzymatic formation of the pineal hormone melatonin (N-acetyl-5-methoxytryptamine).

The biochemical pathway for serotonin synthesis initially involves the conversion of L-tryptophan to 5-hydroxytryptophan by the enzyme L-tryptophan hydroxylase (TPH), which has been found both in cytosolic and particulate brain cell fractions. This enzyme provides the rate-limiting step for serotonin synthesis, in the same manner that norepinephrine and dopamine synthesis in adrenergic and dopaminergic neurons is controlled by the ability of the related enzyme, L-tyrosine hydroxylase, to convert L-tyrosine to L-dihydroxyphenylalanine (L-DOPA). Some inhibitors of TPH (e.g. α-propyldopacetamide) are also active against tyrosine hydroxylase, whereas others such as p-chlorophenylalanine are more selective for TPH. Although p-chloroamphetamine and fenfluramine can also inhibit TPH, they have important actions (including neurotoxic effects) upon various other regulatory processes of serotonergic neuronal function. The identification of two enzyme isoforms, called TPH1 and TPH2, which are apparently associated selectively with peripheral tissues and the brain, respectively, suggests the possibility that drug inhibitors with specificity for targeting individual isoforms may be found in the future.

The subsequent metabolic step in the synthesis of serotonin (and also norepinephrine or dopamine) involves the decarboxylation of 5-hydroxytryptophan (and L-DOPA) by the action of the cytosolic enzyme L-aromatic amino acid decarboxylase. Inhibitors of this enzyme include the drugs benserazide and carbidopa, which do not cross the blood brain barrier, and are used clinically to prevent peripheral decarboxylation of the L-DOPA administered as a precursor for central dopamine formation in Parkinsonian patients.

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](file:////wiki/Enzyme) that creates the energy storage molecule [adenosine triphosphate](file:////wiki/Adenosine_triphosphate) (ATP). It is formed from [adenosine diphosphate](file:////wiki/Adenosine_diphosphate) (ADP) and inorganic [phosphate](file:////wiki/Phosphate) (Pi). The overall reaction catalyzed by ATP synthase is:

ADP + Pi + 3H+out ⇌ ATP + H2O + 3H+in

The formation of ATP from ADP and Pi 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](file:////wiki/Cellular_respiration) to an [electrochemical gradient](file:////wiki/Electrochemical_gradient) created by the difference in [proton](file:////wiki/Hydron_(chemistry)) (H+) concentration across the [mitochondrial](file:////wiki/Mitochondrial) plasma membrane in [eukaryotes](file:////wiki/Eukaryotes) or the [plasma membrane](file:////wiki/Plasma_membrane) in bacteria. During [photosynthesis](file:////wiki/Photosynthesis) in plants, ATP is synthesized by ATP synthase using a proton gradient created in the [thylakoid lumen](file:////wiki/Thylakoid_lumen) through the thylakoid membrane and into the [chloroplast stroma](file:////wiki/Chloroplast_stroma). ATP synthase is an [F-ATPase](file:////wiki/F-ATPase). It consists of two main subunits, FO and F1, which has a rotational motor mechanism allowing for ATP production.Because of its rotating subunit, ATP synthase is a [molecular machine](file:////wiki/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 and
* 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.

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 order. 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. 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](file:////wiki/Organic_compound) that occurs widely in nature in the form of diverse derivatives. The molecule consists of an [adenine](file:////wiki/Adenine), minus one H atom, attached to a [ribose](file:////wiki/Ribose), minus one OH group, via a β-N9-[glycosidic bond](file:////wiki/Glycosidic_bond). Adenosine is one of four [nucleoside](file:////wiki/Nucleoside) building blocks to [RNA](file:////wiki/RNA), which is essential for all life. Its derivatives include the energy carriers [adenosine mono-, di-, and triphosphate](file:////wiki/Adenosine_triphosphate). [Cyclic adenosine monophosphate](file:////wiki/Cyclic_adenosine_monophosphate) (cAMP) is pervasive in [signal transduction](file:////wiki/Signal_transduction). Adenosyl (Ad) is the radical formed by removal of the 5'-hydroxy (OH) group. Ad is found in [vitamin B12](file:////wiki/Vitamin_B12) and the [radical SAM](file:////wiki/Radical_SAM) enzymes. Adenosine is also used as a drug.

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).