Human tissue information processing

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Abstract:-In this paper the metabolisms of the purines and pyrimidines and their nucleosides and nucleotides have examined. The biomedical important is de novo synthesis which is permitting purine and pyrimidine analogs with potential as anticancer drugs to be incorporated into DNA. The synthesis rates of purine and pyrimidine oxyribonucleotides and deoxyribonucleotides are subject to precise regulation. The obtained results of investigation in this paper have shown human tissue information processing incorporating nucleic acids.

Keywords: Purine bases, pyrimidine bases, physicochemical properties, DNA, RNA, tissue.

1 Introduction

The nucleotides participate in a wide variety of biochemical processes. Perhaps the best known role of purine and pyrimidine nucleotides is to serve as the monomeric precursors of RNA and DNA[1-4]. However, the purine ribonucleotides serve also as the ubiquitous high energy source, ATP, as regulatory signals (cycle AMP [cAMP] and GMP [cGMP]), and as components of the coenzymes and of the methyl group donor S adenosil methionine. The pyrimidine nucleotides in addition to providing monomeric precursors for nucleic acid synthesis, also serve as high energy intermediates, such as UDP - glucose and UDP-galactose in carbohydrate metabolism and CDP-acylglycerol in lipid synthesis.

The heterocyclic bases purine and pyrimidine are the parent molecules of nucleosides and nucleotides. Nucleotides are ubiquitous in living cells, where they perform numerous key functions. Examples include incorporation, as their ribose (RNA) or deoxyribose (DNA) monophosphates, into nucleic acids, energy transduction (ATP) , parts of coenzymes (AMP) acceptors for oxidative phosphorylation (ADP) allosteric regulators of enzyme activity, and second messengers (cAMP), cGMP.

The structure and function of the purines and pyrimidines and their nucleosides and nucleotides were studied in numerous literature.

In this paper the metabolism of the purines and pyrimidines and their nucleosides and nucleotides have examined.

2 Biomedical important

Synthetic analogs of naturally occurring nucleotides find application in cancer chemotherapy as enzyme inhibitors and can replace the naturally occurring nucleotides in nucleic acids. Therapeutic attempts to inhibit the growth of cancer cells or certain viruses have often employed administration of analogs of bases, nucleosides, or nucleotides that inhibit the synthesis of either DNA or RNA.Such compounds include 5-fluorouracil, 5'-iodo-2'-deoxyuridine, 6-thioguanine,6-mercaptopurine, 6- azauridine, and arabinosyl cytosine. as azauridine. Allopurinol, a purine analog, is widely used in the treatment of gout.

Neither nucleotides nor their parent purine and pyrimidine bases in the diet are incorporated into human tissue nucleic acids or into purine or pyrimidine coenzymes such as ATP or NAD. Even when a diet rich in nucleoproteins is ingested, human subjects form the constituents of tissue nucleic acids from amphibolic intermediates. This de novo synthesis permits purine and pyrimidine analogs with potential as anticancer drugs to be incorporated into DNA. The rates of synthesis of purine and pyrimidine oxy- and deoxyribonucleotides are subject to precise regulation. Mechanisms have evolved to ensure production of these compounds in quantities and at times appropriate to meet varying physiologic demand. In addition to de novo synthesis, these include “salvage” pathways for reutilization of purine or pyrimidine bases released by degradation of nucleic acids in vivo. Human diseases that involve abnormalities in purine or pyrimidine metabolism include gout, Lesch-Nyhan syndrome, Reye’s syndrome, adenosine deaminase deficiency, and purine nucleoside phosphorylase deficiency.

3 Structure and properties of purine and pyrimidine base

Purine and pyrimidine bases that occur in the nucleotides are derived by substitution on the ring
structures of the parent substances, purine and pyrimidine.

The three major pyrimidine bases present in the nucleotides of both procaryotes and eukaryotes are cytosine, thymine, and uracil. The purine bases adenine and guanine are the two major purines found in living organisms. Two other purine bases, hypoxanthine and xanthine, occur as intermediates in the metabolism of adenine and guanine. In humans, a completely oxidizes purine base, uric acid, is formed as the end product catabolism.

In natural materials, unusual bases occur in he addition to the 5 major described bases. Some of these unusual substituted bases are present only in the nucleic acids of bacteria and viruses, but many are also found in the DNA and transfer RNAs of both procaryotes and eukaryotes. For example, both bacterial and human DNA contain significant quantities of 5-methylcytosine, bacteriophages contain 5'-hydroxymethyl-cytosine. Unusual bases presenting the messenger RNA molecules of mammalian cells include N2, N6-dimethyladenine, and N7-methylguanine. An uracil modified at theN3 position by the attachment of an (α-amino, α-carboxyl)-propyl group has also been detected in bacteria.

In plants, a series of purine bases containing methyl substituents occurs. Many have pharmacologic properties. Examples are coffee, which contains caffeine (1,3,7-trimethylxanthine), tea, which contains theophylline (1,3-dimethylxanthine).

Because of keto-enol tautomerism, these aromatic molecules can exist in a lactim or lactam form, the latter is by far the predominant tautomer of guanine or thymine under physiologic conditions.

At neutral pH, guanine is the least soluble of the bases, followed in this respect by xanthine. Although uric acid as urate is relatively soluble at a neutral pH, it is highly insoluble in solutions with a lower pH, such as urine. Guanine is not a normal constituent of human urine, but xanthine and uric acid do occur in human urine. These latter 2 purines frequently occur as constituents of urinary tract stones.

4 Nucleosides and nucleotides

The free bases are much less abundant in nature than are their nucleosides and nucleotides. The nucleoside is composed of a purine or a pyrimidine base to which a sugar (usually either D-ribose or 2-deoxyribose) is attached in β–linkage at N9 or N1, respectively. Thus, the adenine ribonucleoside adenosine consists of adenine with D-ribose attached at N9. Guanosine consists of guanine with with D-ribose attached at N9. Uridine is cytosine with ribose attached at its N1 position. Uridine consists of ribose attached at the position of uracil.

The 2'-deoxyribonucleosides consist of 2'-deoxyribose attached to purine or pyrimidine bases. Attachment of the ribose or 2-deoxyribose to the ring structure is through an glycosidic bond, which is relatively acid labile. Although, theoretically, free rotation of the sugar moiety and the purine or pyrimidine

Ring structure occurs about this N-glycosidic bond, steric hindrance in fact hinders free rotation. In the naturally occurring nucleosides, the anti conformation is strongly favored over the syn form. The anti form is necessary for the proper positioning of the complementary purine and pyrimidine bases in the double stranded B-form of deoxyribonucleic acid.

Nucleotides are nucleosides phosphotylated on one or more of the hydroxyl groups of the sugar (ribose or deoxyribose). Thus, adenosine monophosphate(AMP or adenyate) is adenine + ribose +phosphate. 2'-Deoxyadenosine monophosphate (dAMP or deoxyadenylate) consists of 2'-deoxyribose + phosphate. The only sugar commonly found attached to uracil is ribose, and that commonly found attached to thymine is 2'-deoxyribose. Therefore, thymic acid (TMP) is thymine +2-deoxyribose +phosphate, and uridylic acid (UMP) is uracil +phosphate. DNA is a polymer of thymidic acid, 2'-deoxycytidilic acid, 2'-deoxyadenylic acid, and 2'-deoxyguanylic acid. RNA is a polymer containing uridylate, citydilate, adenylate, and guanylate.

There are expectations to the above structures of nucleotides. For example, in tRNA riboestes occasionally attached to uracil at the 5 position, establishing a carbon-to-carbon linkage instead of the usual nitrogen –to-carbon linkage. This unusually compound is called pseudo uridine (ψ). tRNA molecules contain another unusual nucleotide structure, i.e. thymine attached to ribose monophosphate. Pseudouridylic acid (ψMP) is similarly rearranged from uridylic acid after the t RNA molecule has been synthesized.

The abbrevations A,G,C,T, and U may be used to designate the nucleotides that contain adenine, guanine, cytosine thymine, or uracil, respectively. For example, guanosine containing 2'-deoxyribose would be designated dG (deoxyguanosine) and the corresponding monophosphate with the pphosphate esterified to the carbon 3 of the deoxyribose moiety designated dG-3'-MP. Generally, when the phosphate is esterified to the carbon 5 of the ribose or deoxyribose moiety, the prefixed primed (5') is omitted. For example, guanosine 5'-monophosphate
would be abbreviated GMP, while the 5'-monophosphate of 2'-deoxyguanosine would be designated dGMP. When 2 or 3 phosphates are attached to the sugar moiety in the acid anhydride form, the abbreviations DP (diphosphate) and TP (triphosphate) are added to the abbreviations for the corresponding purine or pyrimidine nucleoside. Because the phosphate are in the acid anhydride form - a low entropy situation-the phosphates are said to be high energy ones, i.e., high potential energy. The hydrolysis of 1 mol ATP to ADP releases about 7 x 4.16 kJ of potential energy.

Free nucleotides also perform important functions in tissues.

The functional moieties of many vitamins are coenzyme nucleotides with structures analogous to purine and pyrimidine nucleotides.

Mammals and most lower vertebrates are prototrophic for purines and pyrimidines, i.e., they synthesize purine and pyrimidine nucleotides de novo.

5 Metabolism

Mammals and most lower vertebrates are prototrophic for purines and pyrimidines, i.e., they synthesize purine and pyrimidine nucleotides de novo.

In human and other mammals, purine nucleotides are synthesized to meet the needs of the organism for the monomeric precursors of nucleic acids and for those other functions.

In some organisms (birds, amphibians, and reptiles), the synthesis of purine nucleotides has an additional function, which is to serve as the chemical vehicle to excrete nitrogen waste products as uric acid. Such organisms are referred to as uricotelic, whereas those organisms which dispose of nitrogenous waste products in the form of urea, as humans do, are referred to as ureotelic. Because the uricotelic organisms must dispose of their nitrogenous wastes in the form of uric acid, they synthesize purine nucleotides at a relatively greater rate than do ureotelic organisms. However the steps involved in de novo purine nucleotide synthesis in mammals (ureotelic) are analogous of those in birds (uricotelic).

Information on the source of the various atoms of the purine base obtained by tracer studies in birds, rats, and humans.

The biosynthetic pathway for the synthesis of purine nucleotides can be summarized in the following steps. The first step in the synthesis of purine nucleotides is the formation of 5-phosphoribosyl-1-pyrophosphate (PRPP). The conversion of ribose 5-phosphate and ATP to AMP +PRPP is not however unique to the synthesis of purine nucleotides. PRPP also serves as precursors of the pyrimidine nucleotides and required for the synthesis of NAD and NADP, 2 coenzymes derived from niacin.

PRPP then react with glutamine in a reaction catalyzed by phosphor ribosylpyrophosphate amidotransferase to form 5-phosphoribosylamime. The reaction is accompanied by the displacement of pyrophosphate and the formation of glutamate. Although other mechanism have been proposed for the synthesis of 5- phosphoribosylamime, the physiological important reaction in mammalian tissues is that catalyzed by the amidotransferase. 5-phosphoribosylamime, then reacts with glycine to produce glycinamide ribosylphosphate. Synthesis of purine and pyrimidine deoxyribonucleotides occurs by direct reduction at the 2'-carbon in the ribose moiety of the corresponding nucleotide, not by synthesis of the entire nucleotide utilizing 2'-deoxy analog of PRPP.

Several antimetabolites that are glutamine analogs are effective inhibitors of purine biosynthesis.

Conversion of AMP and GMP to their respective nucleoside diphosphates and nucleoside triphosphates occurs in 2 successive steps. The successive transfers of phosphate groups from ATP are catalysed by nucleoside monophosphate kinase and nucleoside diphosphate kinase, respectively. The enzyme that phosphorylates adenylate is also called myokinase.

Formation of purine deoxyribonucleotides is performed by synthesis of purine and pyrimidine deoxyribonucleotides which occurs by direct reduction at the 2'-carbon in the ribose moiety of the corresponding nucleotide, not by synthesis of the entire nucleotide utilizing a 2'-deoxy analog of PRPP. Reduction at the 2'-carbon occurs only after the purine and pyrimidine nucleotides have been converted to their respective nucleoside diphosphates. In some bacteria, cobalamin (vitamin B₁₂) is required for this reductive process, although it is not required for the same reaction in mammals. Reduction of ribonucleoside diphosphates to deoxyribonucleoside diphosphates is catalysed by ribonucleotide reductase and requires thioredoxin (a protein cofactor), thioredoxin reductase (a flavoprotein), and NADPH as cofactor. The immediate electron donor to the nucleotide is thioredoxin that has been reduced by NADPH. The reversible oxidation-reduction of thioredoxins catalyzed by thioredoxin reductase. Reduction of ribonucleoside diphosphates by reduced thioredoxins only when they are actively synthesizing DNA and dividing.
6 Tissue specify of purine biosynthesis

Not all human tissues catalyze the de novo synthesis of purine nucleotides. Erytrocites and polymorphonuclear leukocites are incapable of synthesizing 5-phosphoribosylamine and therefore are independent upon exogenous purines for the formation of purine nucleotides (Fig.1). Peripheral lymphocytes do possess some ability to synthesize purines de novo. Mammalian brain appears to have a reduced content of PRPP amidotransferase, indeed, it has been suggested that the human brain is dependent upon exogenous purines for the formation of purine nucleotides. Mammalian liver is a major site of purine nucleotide synthesis and provides purines in the form of bases or nucleosides to be salvaged and utilized by those tissues incapable of synthesizing purines de novo.

The most important regulator of de novo purine biosynthesis is the intracellular concentration of PRPP.

7 Biosynthesis of pyrimidine

Although the pyramidine nucleus is simpler and its synthetic pathway briefer than that of the purine structure, the share several common precursors. PRPP, glutamine, CO₂, and aspartate are required for the synthesis of all pyramidine and purine nucleotides. For the thymidine nucleotides and for all purine nucleotides, tetrahydrofolate derivates are also necessary. There is one striking difference between the synthesis of pyramidine nucleotides and that of purine nucleotides, namely, that the synthesis of the purine nucleotides commences with ribose phosphate as an integral part of the earliest precursor molecule, whereas the pyrimidine base is formed and attachment of the ribose phosphate moiety delayed until the later steps of the pathway.

The first step uniquely committed to the biosynthesis of pyrimidines is the formation of carbamoyl phosphate from glutamine, ATP, and CO₂ in a reaction catalyzed by the carbamoyl phosphate synthase in the cytosol. The carbamoyl phosphate synthase enzyme responsible for the early steps in urea synthesis resides in the mitochondria.

A ring structure can then be formed from carbamoyl aspartate by loss of H₂O catalyzed by the enzyme dihydroorotase.

Fig.1 De novo synthesis purine control

In a subsequent dehydrogenation step catalyzed by dihydroorotate dehydrogenase and utilizing NAD as a cofactor, orotic acid is formed. Then a ribose phosphate moiety is added to orotic acid to form orotidylate (orotidine monophosphate, OMP). This reaction is catalyzed by orotate phosphoribosyltransferase, an enzyme analogous to the hypoxanthine-guanine phosphoribosyl-transferase, and the adenine phosphoribosyl-transferase, involved in the phosphoribosylation of performed purine rings.

The first true pyrimidine ribonucleotide is formed by the decarboxylation of orotidylate to form uridilate (UMP-uridine monophosphate). Dihydroorotate dehydrogenase is mitochondrial, all the other enzymes in the de novo pyrimidine nucleotide pathway are in the cytosol.

By mechanisms analogous to those described for the further phosphorylation of the purine nucleoside.
monophosphates, the pyrimidine nucleoside monophosphates are converted to their diphosphate and triphosphate derivatives. UTP is aminated to CTP by glutamine and ATP. The reduction of the pyrimidine nucleoside diphosphates occurs by a mechanism also analogous to that described for the purine nucleotides.

The formation of thymidylate (TMP-thymidine monophosphate) is the one reaction in pyrimidine nucleotide biosynthesis that requires a tetrahydrofolate donor of a single carbon compound. In order to continue to use the folate carrier, the cell must reduce dihydrofolate to tetrahydrofolate, a reaction carried out by the enzyme dihydrofolate reductase. Thus, dividing cells that by necessity are generalizing TMP and dihydrofolate are especially sensitive to inhibitors of dihydrofolate reductase. An example of such an inhibitor is methotrexate (amethopterin, a widely used anticancer drug.

Furthermore, carbamyl phosphate synthase is sensitive to feedback inhibition by both purine and pyrimidine nucleotides and activation by PRPP. Thus, there several sites at which there is significant cross-regulation between purine and pyrimidine nucleotide synthesis.

8 Clinical disorders
8.1 Clinical disorders of purine metabolism

The predominant form of uric acid is determined by the pH of its milieu (e.g., blood, urine, cerebrospinal fluid). Thus, under physiologic conditions, at the usual pH of physiologic fluids, only uric acid and its monosodium salt, sodium urate, are found. In a fluid where the pH is less than 5.75, the predominant molecular species will be uric acid. In a fluid at pH 5.75, the concentration of sodium urate will equal that of uric acid. At a pH greater than 5.75, sodium urate will predominate in the solution.

The miscible urate pool in the body is reflected by the sodium urate concentration in the serum. When this level exceeds the solubility of sodium urate in serum (hyperuricemia), crystals of sodium urate may precipitate. The solubility of sodium urate in serum at 37 °C is 7 mg/dl. Crystals of sodium urate can collect and deposit in soft tissues, particularly in or about joints. These urate deposits are referred to as tophi. Accumulation of sodium urate crystals in the tissues including phagocytosis of the crystals by polymorphonuclear leukocytes in joint spaces, can lead to an acute inflammatory reaction called acute gouty arthritis.

8.1.1 Lesch-Nyhan syndrome and Von Gerke’s disease

Some individuals with urate overexcretion greater than 600mg/uric acid per 24 hours can be categorized as having secondary hyperuricemia. They have other disease processes such as cancer or psoriasis that lead enhanced tissue turnover.

Finally, there are persons with identifiable enzyme defects, including abnormalities of PRPP synthetase, the HGPRTase (hypoxanthine-guanine phosphoribosyl transferase) deficiencies, both the complete Lesch-Nyhan syndrome and incomplete deficiencies and glucose-6-phosphatase deficiency von Gierke’s disease. There exists also a group of patients exhibiting idiopathic overproduction hyperuricemia, which will certainly be regarded as a heterogeneous group of disease ons the molecular bases for their metabolic defects are recognized.

7.2 Clinical disorders of pyrimidine metabolism

The end products of pyrimidine metabolism, unlike those of purine metabolism, are highly water soluble compounds such as CO₂, ammonia, β – alanine, and propionate. Thus, in circumstances where pyrimidine overproduction occurs, clinically detectable abnormalities are rarely evident. In in cases of hyperuricemia associated with severe PRPP overproduction, there is concomitant overproduction of pyrimidine nucleotides with increased excretion of compounds such as β – alanine.

In specific liver mitochondrial failure, such as in Reye’s syndrome, there is a secondary orotic acid-urea.

8 Conclusions

This paper illustrated purine and pyrimidine metabolisms. The biosynthesis was control by enzymes. Enzymes were demonstrated successfully control and deficiencies recognition.

The obtained results in the frame of this investigation show metabolisms information processing in the human body.

Results of this investigation can be applied in the other domain in biomedical engineering.

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Notation

AMP- adenine monophosphate
ADP- adenine diphosphate
ATP- adenine triphosphate
CTP- cytosine triphosphate
DP- diphosphate
GDP- guanine diphosphate
GMP- guanine monophosphate
GTP- guanine triphosphate
HGPRTase- hypoxanthine-guanine phosphoribosyl transferase
IMP- inosine monophosphate
MP- monophosphate
NADPH- cofactor
OMP- orotidine monophosphate
PRPP- phosphoribosyl-pyrophosphate
TMP- thymidine monophosphate
TP- triphosphate
UMP- uridine monophosphate
UTP- uridine triphosphate

9 References