DISORDER OF PURINE AND PYRIMIDINE NUCLEOTIDE METABOLISM AND ITS THERAPY

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Abstract

Background. *Metabolism disorder means indicates a change in a normal metabolism either in qualitative or in quantitative manner. This disorder can be identified through the changes of metabolism productions, possibility of the increase or the decrease of the relevant enzymes activities, or even the absence of an enzyme.*

Objective. *To study the disorder of purine and pyrimidine nucleotide metabolism, the arising disease and its therapy*

Method. *The review is used the 4 books and 2 articles related to the disorder of purine and pyrimidin nucleotide metabolism, the arising disease and its therapy.*

Outcome Measured. *Nucleotide degradation and enzyme activity.*

Results. *This article presents metabolism/catabolism/anabolism and the management of purine and pyrimidine nucleotide metabolism are followed by the metabolism disorder and its therapy. Following this, the nucleotide degradation and the disorder of purine and pyrimidine metabolism in the form of the increasing activity of enzymes or the absence of certain enzymes along with the mechanism of its therapy are presented.*

Conclusion. *The nucleotide degradation and the disorder of purine and pyrimidine metabolism in the form of the increasing activity of enzymes or the absence of certain enzymes along with the mechanism of its therapy are presented*

Keywords : *metabolism disorder, purine nucleotide, pyrimidine, and nucleotide degradation*

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INTRODUCTION

Metabolism disorder refers to the change in a normal metabolism and occurs in a qualitative or in a quantitative manner. The PRPP synthetase enzyme experiences an increasing activity due to a quantitative change. Hypoxanthine-guanine phosphoribosyl transferase (HGPRT) enzyme that plays a role in non-Inosinate-guanilate salvage pathway biosynthesis shows a qualitative change.

This study is aimed to discuss the purine and pyrimidine metabolism disorder. Nucleotide consists of base N binding sugar (ribose) in C1 and phosphate in C5'. Purine Base N includes adenine and guanine. Meanwhile, pyrimidine is included in cytosine, uracil, and thymine.

Purine and pyrimidine nucleotide has a number of important roles and functions. It is including (a) as a universal energy such as *adenosin trifosfat* (ATP); (b) as monomer from nucleic acid both as ribonucleic acid (RNA) and as deoxyribonucleic acid (DNA); (c) active intermediate (zantara) in many biosynthesis processes such as diacylglycerol -diphosphatase (CDP-diacylglycerol) intermediate in phosphor glycerol biosynthesis; (d) component of coenzyme such as oxidized Nicotinamide adenine dinucleotide (NAD^+), flavin adenine dinucleotide (FAD) and (e) metabolic regulator such as cyclic adenosine mono phosphate (cAMP).

Purine nucleotide biosynthesis (Cory, 2006; Elliot and Elliot, 1997; Berg, Tymoczko and Stryer, 2002; Smith and Clark, 2011).

de novo pathway, It is initiated from Phosphoribosyl pyrophosphate (PRPP) to be Inosinate acid (IMP) and then to be Adenosine monophosphate (also known as 5'-adenylic acid), and guanosine monophosphate (GMP):

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PRPP a→ (+Glutamine – Glutamate/Amino phosphoribosyltransferase) 5-phosphoribosyl-1-amine b→ (+Glycine +ATP-ADP-Pi) Glycinamide Ribonucleotide c→ (+N^{10}-Formil THF-THF) Ribonucleotide formiglicynamide d→ (+Gln+ATP-Glu-ADP-Pi) Ribonucleo tida formilglisinamidin e→ (-H_2O) Ribonu cleotide 5-aminoimidasol f→ (+CO_2) Ribonucleotide 5-aminoimidazole 4-carboxylate g→ (+Asp+ATP-ADP-Pi) Ribonucleotide 5- aminoimidazole l-4-N-succino carboxamide h→ i→ (-Fumarate) Ribonucleotide 5-aminoimidazole -4- carboxamides j→ (N^{10}-Formil THF –THF) Inosinate/IMP.

IMP k→ (+Asp+GTP –GDP-Pi) Adenylosuccinate l→ (-Fumarate) Adenylate /AMP.

IMP m→ (+NAD+ -NADH) xantilate n→ (+Gln +ATP –Glu-AMP-PPi) Guanilate/ GMP.

The involved enzymes: (a). glutamine PRPP amidotransferase, (b). GAR synthetase, (c). GAR transformylase, (d). FGAM synthetase, (e). AIR synthetase, (f). AIR carbocslase, (g). SAICAR synthetase, (h). adenylosuccinate liase, (i). AICAR transformylase, (j). IMP cyclohydrolase, (k). adenylosuccinate synthetase, (l). Adenylosuccinate, (m). IMP dehydrogenate, and (n). GMP synthetase.

Other pathway: Salvage Pathway

1. Adenine + PRPP a→ Adenylate + PPi
2. Hypoxanthine + PRPP b→ Inosinate + PPi
3. Guanine + PRPP b→ guanylate + PPi
   a. Adenine Phosphoribosyl transferase
   b. Hypoxanthine-guanine phosphoribosyltransferase (HGPRTase)

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Arrangement of Purine Nucleotide Biosynthesis (Cory, 2006; Berg, Tymoczko and Stryer, 2002)

- Ribose 5-phosphate → PRPP → Phosphoribosylamine → 1 IMP → Adenylosuccinate → AMP
- 2. IMP → Xanthylate → GMP
- R 5-F → PRPP is inhibited by IMP, AMP, and GMP
- PRPP → Phosphoribosylamine is inhibited by IMP, AMP, and GMP
- IMP → Adenylosuccinate is inhibited by AMP
- 1 MP → Xanthylate is inhibited by GMP

Pyrimidine Nucleotide Synthesis (Cory, 2006; Elliot and Elliot, 1997; Berg, Tymoczko and Stryer, 2002; Kegg[b], 2013)

Here, it is started from Carbamoyl phosphate to be orotat and afterward to be Uridylic acid (UMP).

Carbamoyl phosphate + aspartate a→ (-Pi) N- Carbamoyl aspartate b→ ($+H^+$ $-H_2O$) Dihydroorotate c→ ($+NAD^+$ $-NADH_2$) Orotat d→ (+PRPP –PPi) orotidylate e→ ($+H^+$ $-CO_2$) uridylate /UMP.

- The involved enzymes:

  a. aspartate transcarbamoylase, b. Dihydroorotase, c. Dihydroorotate dehydro genase, d. Orotate phosphoribosyltransferase, e. orotate Decarboxylase

Interconversion:

UMP + ATP → UDP + ADP (UMP kinase)

AMP + ATP → 2 ADP (Adenylate kinase)

XDP + YTP → XTP + YDP

UDP + UTP → UTP + ADP

CTP Synthesis with amination of UTP:

UTP → (+Glutamine +ATP + H_2O –Glutamate –ADP –Pi $-2H^+$) CTP

Arrangement of Purine Nucleotide Biosynthesis is done by inhibiting the feedback: CTP inhibits aspartate transcarbamoylase (ATCase); UMP inhibits aspartate transcarbamoylase.

Degradation of purine and pyrimidine nucleotide (Cory, 2006; Berg, Tymczko and Stryer, 2002, Kegg[a], 2013, Kegg[b], 2013).

Nucleic acid a→ Nucleotide Guanine b→ Guanosine c→ Guanine d→ Xanthine e→ Uric Acid.

- The involved enzymes:

  a. nuclease, b. nucleotidase, c. purine nucleoside phosphorylase, d. guanase (-NH4+), e. Xanthine oxidase.

Nucleic acid a→ Adenine nucleotide b→ Adenosine c→ Inosine d→ Hypoxanthine e→ Xanthine f→ Uric acid.

Adenine nucleotide g→ IMP h→ Inosine

- The involved enzyme:

  a. nuclease, b. nucleotidase, c. Adenosine deaminase, d. purine nucleoside phosphorylase, e. Xanthine oxidase, f. Xanthine oxidase, g. AMP deaminase, h. nucleotidase.

Metabolism Disorder (Cory, 2006)

Disorder indicates the existence of a change either in quantitative or in qualitative manner. In this part, a number of qualitative disorders and quantitative disorders will be discussed.

1. **The increasing activity of synthetase PRPP** can cause the increase of the concentration of intracellular PRPP.
2. **The activities of HGPRTase are influenced in the *pathway for de novo synthesis of purine nucleotides.*** A. The decrease of salvage pathway for hypoxanthine and guanine, B. The decrease of salvage pathway for hypoxanthine, IMP, and GMP

3. **Deficiency of glucose 6-phosphate** can cause the increase of PRPP concentration (related to the PRPP amidotransferase).

   With the three disorders above, Gout disease can be emerged. It is remarked through the high concentrate of uric acid (either in blood or in urine). The increasing rate of purine nucleotide synthesis (*de novo* synthesis) causes the increase of synthesis followed by its degradation into uric acid. The medical treatment through some medicines includes colchicines, antihyperuricemic agents, and allopurinol. Allopurinol and the result of its metabolism, alloxanthine is an effective xanthine oxidase inhibitor causing the decrease of uric acid level. Meanwhile, the medical treatment with Allopurinol can cause the decrease of the level of uric acid and the decrease of purine nucleotide synthesis.

4. **The absence of HGPRTase protein means the absence of HGPRTase activities.**

   This disorder can bring an effect of the emergence of *Lesch-Nyhan* syndromes that include

   - Remarked by hyperuricemia
   - Causing the neurological problems, one of which is mental disorder
   - The role of HGPRTase has an effect on the reaction of nucleotide synthesis from hypoxanthine and guanine.
   - The absence of HGPRTase of Hypoxanthine and guanine has resulted in the absence of any reaction.
   - Salvage causes the increase of PRPP concentrate and the decrease of IMP or GMP
   - Both cause the increase of *de novo* synthesis of purine nucleotide.
   - The activity of IMP dehydrogenate in brain is very low and the absence of HGPRTase can cause the decrease of the number of intracellular GTP that in turn cause the decrease of salvage pathway of guanine. GTP refers to the candidate of Tetrahydrobiopterin cofactor essential in both neurotransmitter synthesis and protein synthesis.
   - The medical treatment with Allopurinol will decrease the number of uric acid formation, and releases the problem that can cause the formation of uric acid sodium.
   - Patient with Lesch-Nyhan is marked with the decrease of HGPRTase activity, the absence of salvage pathway of hypoxanthine and guanine, the dysfunction of PRPP making the *de novo* synthesis of purine nucleotide unstoppable.
   - Until recently, no any solution has been found for solving the neurological problem. Patients are dead for kidney damage due to the deposit of uric sodium.

5. **The increasing activity of *cytosolic 5'-nucleotidase***

   - The substrates for the enzymes are 5'AMP or 5'UMP in which the activity can increase 6 – 10 higher
   - This disorder can marked with the slower improvement, *ataxia, seizures, severe language deficit*, *hyperactivity, short attention span,* and less social interaction
   - The increase of 5'nucleotidase activity can cause the deficiency of nucleotide → The medical treatment is done by giving uridine orally.

6. **The disorder of purine nucleoside degradation**

   - The disorder can cause the immunodeficiency:
     a. Adenosine deaminase deficiency, also called ADA deficiency
     b. Purine nucleoside phosphorylase deficiency (PNP-deficiency)
   - Substrate for ADA : adenosine and deoxyadenosine

- Substrate for PNP: Inosine, Guanosine, Deoxyinosine, Deoxyguanosine.
- Deficiency of ADA is related to the immunodeficiency including the function of cell T and cell B.
- Deficiency of PNP is related to the immunodeficiency including the function of cell T.
- Immunodeficiency in concentration of intracellular dATP and S-adenosylhomocysteine is very increasing/large
- Hypothesis:
  a. Deficiency ADA → high dATP concentration inhibits Ribonucleotide reductase with a consequence of inhibiting the DNA synthesis.
  b. Deoxyadenosine inactivates S-adenosylhomocysteine hydrolase making the decrease of S-adenosylhomocysteine used in the methylation from base N in RNA and DNA.
  c. The increase of adenosine concentration leads to the increase of cAMP.
- Enabling the dysfunction of immune system
- Medical treatment on children with deficiency of ADA is by blood transfusion, bone marrow transplant, ADA-PEG, gene therapy.
- Each of them has weakness

7. **The increase of nucleotide degradation**
   - Nucleotide is from degradation of nucleate acid originating from the death of cell.
   - The medical treatment for cancer patients with radiation therapy or with chemotherapy will cause the concentration of uric acid in blood increase.
   - The medical treatment to decrease the concentration of uric acid with Allopurinol
   - The increase of uric acid is due to the degradation of purine nucleotide resulting in the increase of uric acid level due to the degradation of purine nucleotide that results in xanthine and is catalyzed by xanthine oxydase resulting in uric acid.
   - Allopurinol refers to a compound inhibiting xanthine oxydase.
8. **The increase of purine nucleotide synthesis on child**
   - Increasing four times higher than the normal one
   - The increasing uric acid concentration in urine
   - Autism
   - The condition of mental introversion is reflected to egoism and unawareness
9. **The disorder of *de novo* synthesis of pyrimidine nucleotide**
   - Characteristic: slow growth, increasing concentration of orotat acid in urine
   - Disorder of Orotat phosphoribosyltransferase or Orotidine decarboxylase,
   - Combined with synthetase UMP
   - Therapy with uridine per oral
   - Uridine → UMP → UDP furthermore → UTP inhibits Carbamoyl phosphate synthetase →orotat synthesis.

CONCLUSION

By studying the disorder of metabolism/anabolism/catabolism, it is important to explain the mechanism of the disease in order to overcome or conduct a therapy and its therapy mechanism.

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