2007-09

M1 - Renal, Fall 2007

Lyons, R.; Burney, R.

<http://hdl.handle.net/2027.42/64946>
http://hdl.handle.net/2027.42/64946
Formation of PRPP: Phosphoribose pyrophosphate

PRPP Use in Purine Biosynthesis:
The First Purine: Inosine Monophosphate
(folates are involved in this synthesis)

Conversion to Adenosine:

Conversion to Guanosine:
Nucleoside Monophosphate Kinases

AMP + ATP $\rightleftharpoons$ 2ADP \hspace{1cm} (adenylate kinase)

GMP + ATP $\rightleftharpoons$ GDP + ADP \hspace{1cm} (guanylate kinase)

- similar enzymes specific for each nucleotide
- no specificity for ribonucleotide vs. deoxyribonucleotide
Ribonucleotide Reductase

Hydroxyurea inhibits this enzyme: chemotherapeutic use

\[ \text{HONH}^-\text{C}^-\text{NH}_2 \]
Regulation of Ribonucleotide Reductase
Nucleoside Diphosphate Kinase

\[ N_1\text{DP} + N_2\text{TP} \iff N_1\text{TP} + N_2\text{DP} \]

\[ dN_1\text{DP} + N_2\text{TP} \iff dN_1\text{TP} + N_2\text{DP} \]

• No specificity for base
• No specificity for ribo vs deoxy
Feed-forward regulation by PRPP

PRPP

IMP

GMP

ATP

GTP

AMP

GTP

ATP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Feed-forward regulation by PRPP
Degradation of the Purine Nucleosides:

Adenosine → H₂O + NH₄⁺ → Inosine → H₂O + pᵢ → Hypoxanthine → Xanthine oxidase → Uric acid

Guanosine → pᵢ + ribose - 1-P → Guanine → H₂O + NH₄⁺ → Xanthine oxidase → Uric acid

Prepared with Diagramme 3.0
“Salvage” Pathways for Purine Nucleotides

APRT - Adenine phosphoribosyl transferase - performs a similar function with adenine.
Adenosine Deaminase Deficiency:

Deoxyadenosine → dAMP → dADP → dATP

Adenosine deaminase (ADA) → Deoxyinosine → Hypoxanthine → Uric acid

2-deoxyribose
Hyperuricemia can be caused by:

- Accelerated degradation of purines:
  - Accelerated synthesis of purines
  - Increased dietary intake of purines
- Impaired renal clearance of uric acid

Allopurinol inhibits xanthine oxidase and reduces blood uric acid levels:

Gout: deposition of urate crystals in joints, “tophi” in cooler periphery
The hands of a patient with a long history of gout, including high serum urate levels
Lesch-Nyhan Syndrome: Defective HGPRT

• hyperuricemia
• spasticity
• mental retardation
• self-mutilation behavior

A defect in APRT does NOT have similar consequences
Myoadenylate Deaminase ‘Fills’ the TCA Cycle in Muscle

\[
\begin{align*}
\text{Adenosine monophosphate} & \rightarrow \text{Inosine monophosphate} \\
\text{H}_2\text{O} & \rightarrow \text{NH}_3 \\
\text{Fumarate} & \rightarrow \text{GDP} + \text{Pi}
\end{align*}
\]
Carbamoyl phosphate synthetase II - a *cytoplasmic* enzyme...

\[
2\text{ATP} + \text{HCO}_3^- + \text{glutamine} + \text{H}_2\text{O} \rightarrow \text{NH}_2\text{C}\text{O}P^2^- + \text{glutamate} + 2\text{ADP} + \text{P}_i
\]

...used for pyrimidine synthesis

\[
\text{carbamoyl phosphate} + \text{aspartate} \rightarrow \text{orotate}
\]
Orotate is linked to PRPP to form Uridine monophosphate:
Newly-synthesized uridine monophosphate will be phosphorylated to UDP and UTP, as described for the purine nucleotides.

UTP can be converted to CTP by CTP Synthetase:
Some UDP is converted to dUDP via ribonucleotide reductase.

The Thymidylate Synthase Reaction:
Methotrexate Inhibits Dihydrofolate Reductase:

Dihydrofolate builds up, levels of THF become limiting, thymidylate synthase is unable to proceed. Follow it with a dose of Leucovorin, a.k.a. formyl-THF.
FdUMP Inhibits The Thymidylate Synthase Reaction:

5-fluorodeoxyuridine monophosphate (FdUMP) inhibits the thymidylate synthase reaction. The inhibitor competes with deoxythymidine monophosphate, which is the product of the reaction catalyzed by thymidylate synthase. The reaction involves the transfer of a methyl group from N5,N10-methylene tetrahydrofolate to deoxyuridine monophosphate (dUMP) to form deoxythymidine monophosphate (dTMP).
Complicated Pathways for Pyrimidine Production:

This figure is primarily a study aid; you do not need to memorize it or reproduce it. The information here merely summarizes material from previous sections.
Pathologies of pyrimidine nucleotide biosynthesis:

Orotic acidurea due to OTC deficiency - please review your Urea Cycle notes.

Hereditary orotic acidurea - deficiency of the enzyme that convert orotate to OMP to UMP. Not common.
Pyrimidine degradation:

Cytidine deaminase converts cytidine to uridine

A phosphorylase removes the sugar

Degradation of the base proceeds (products are unimportant here)
Pyrimidines can be salvaged as well:

Enzyme: Pyrimidine nucleoside phosphorylases
Thymine + deoxyribose-1-phosphate  --> thymidine
(NOT thymidine monophosphate!)

Enzyme: Thymidine kinase - adds the monophosphate back
Thymidine + ATP --> thymidine monophosphate

Herpes Simplex Virus carries its own tk gene
Certain drugs act via the pyrimidine salvage pathway:

\[
\text{Acyclovir} \xrightarrow{\text{HSV thymidine kinase}} \text{AcycloGMP}
\]

\[
\text{5-fluorouracil} + \text{deoxyribose-1-phosphate} \xrightarrow{\text{pyrimidine phosphorylase}} \text{fluorodeoxyuridine} \xrightarrow{\text{uridine kinase}} \text{fluorodeoxyuridine monophosphate (FdUMP)}
\]
5-FU efficacy depends on rate of degradation vs activation

\[
\begin{align*}
\text{5-FU} & \rightarrow \quad \rightarrow \quad \text{FdUMP} \\
& \quad + \text{methylene-THF} + \text{Thymidylate Synthase} \\
& \quad \rightarrow \text{inactivation of TS}
\end{align*}
\]

Degradation
(via dihydropyrimidine dehydrogenase, DPD)

DPD inhibitors can potentiate 5FU activity
Capecitabine mode of action:

Cytosine arabinoside (araC) activation and inactivation: