Metabolismus purinových a pyrimidinových nukleotidů

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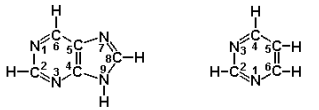
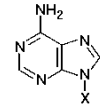
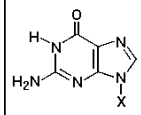
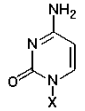
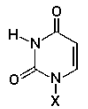
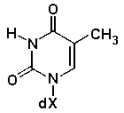
Purinové a pyrimidinové báze, nukleosidy a nukleotidy

Číslování atomů jádra purinu a pyrimidinu

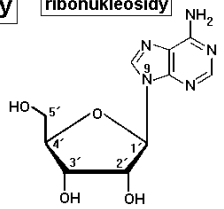


purin pyrimidin

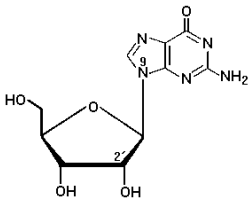
Purinové a pyrimidinové báze a jejich deriváty

vzorec báze X = H dX = H	název báze	nukleosid X = D-ribóza nebo 2´-deoxy-D-ribóza dX = 2´-deoxy-D-ribóza	nukleotid X = D-ribóza-5´-fosfát nebo 2´-deoxy-D-ribóza-5´-fosfát dX = 2´-deoxy-D-ribóza-5´-fosfát
	adenin A	adenosin 2´-deoxyadenosin A	adenosinmonofosfát AMP 2´-deoxyadenosinmonofosfát dAMP
	guanin G	guanosin 2´-deoxyguanosin G	guanosinmonofosfát GMP 2´-deoxyguanosinmonofosfát dGMP
	cytosin C	cytidin 2´-deoxycytidin C	cytidinmonofosfát CMP 2´-deoxycytidinmonofosfát dCMP
	uracil U	uridin (2´-deoxyuridin) U	uridinmonofosfát UMP (2´-deoxyuridinmonofosfát) (dUMP)
	thymin T	thymidin T	thymidinmonofosfát TMP

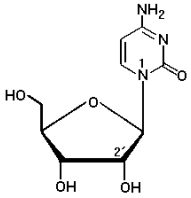
ribonukleosidy



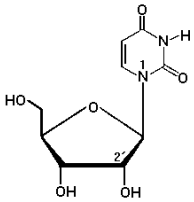
adenosin



guanosin

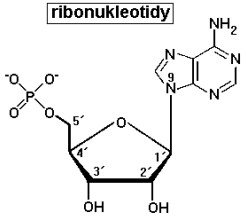


cytosin

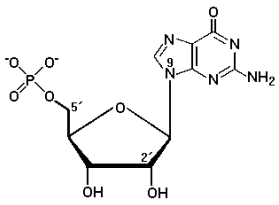


uridin

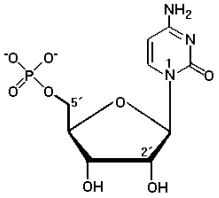
ribonukleotidy



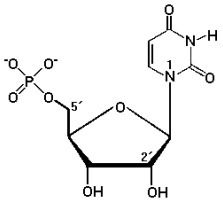
adenosin-5´-monofosfát
(kyselina adenylová)



guanosin-5´-monofosfát
(kyselina guanylová)

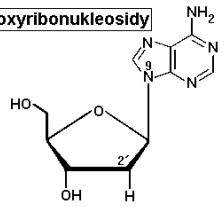


cytosin-5´-monofosfát
(kyselina cytidylová)

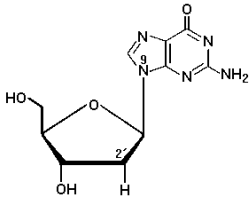


uridin-5´-monofosfát
(kyselina uridylová)

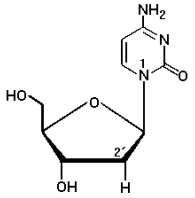
deoxyribonukleosidy



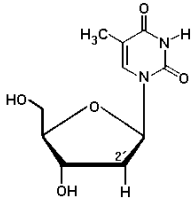
2´-deoxyadenosin



2´-deoxyguanosin

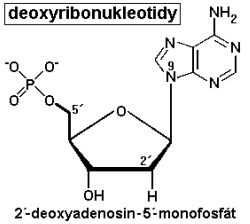


2´-deoxycytosin

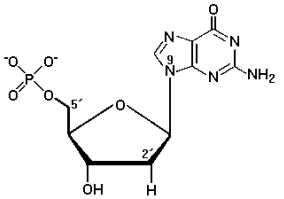


thymidin

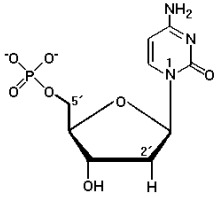
deoxyribonukleotidy



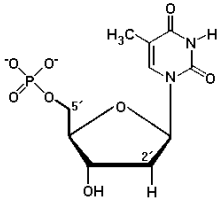
2´-deoxyadenosin-5´-monofosfát
(kyselina deoxyadenylová)



2´-deoxyguanosin-5´-monofosfát
(kyselina deoxyguanylová)

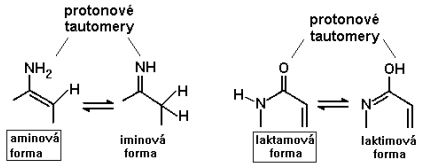


2´-deoxycytosin-5´-monofosfát
(kyselina deoxycytidylová)

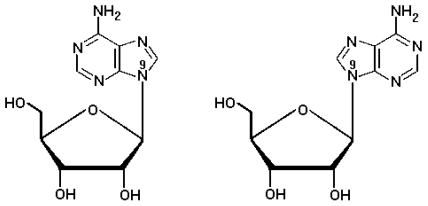


thymidin-5´-monofosfát
(kyselina thymidylová)

Tautomerie funkčních skupin purinů a pyrimidinů



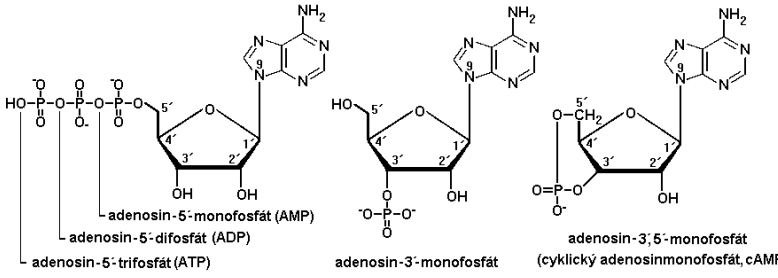
Nukleotidy se mohou vyskytovat jako stabilní *syn* a *anti* konformery β-N-glykosidové vazby



syn-konformer adenosinu

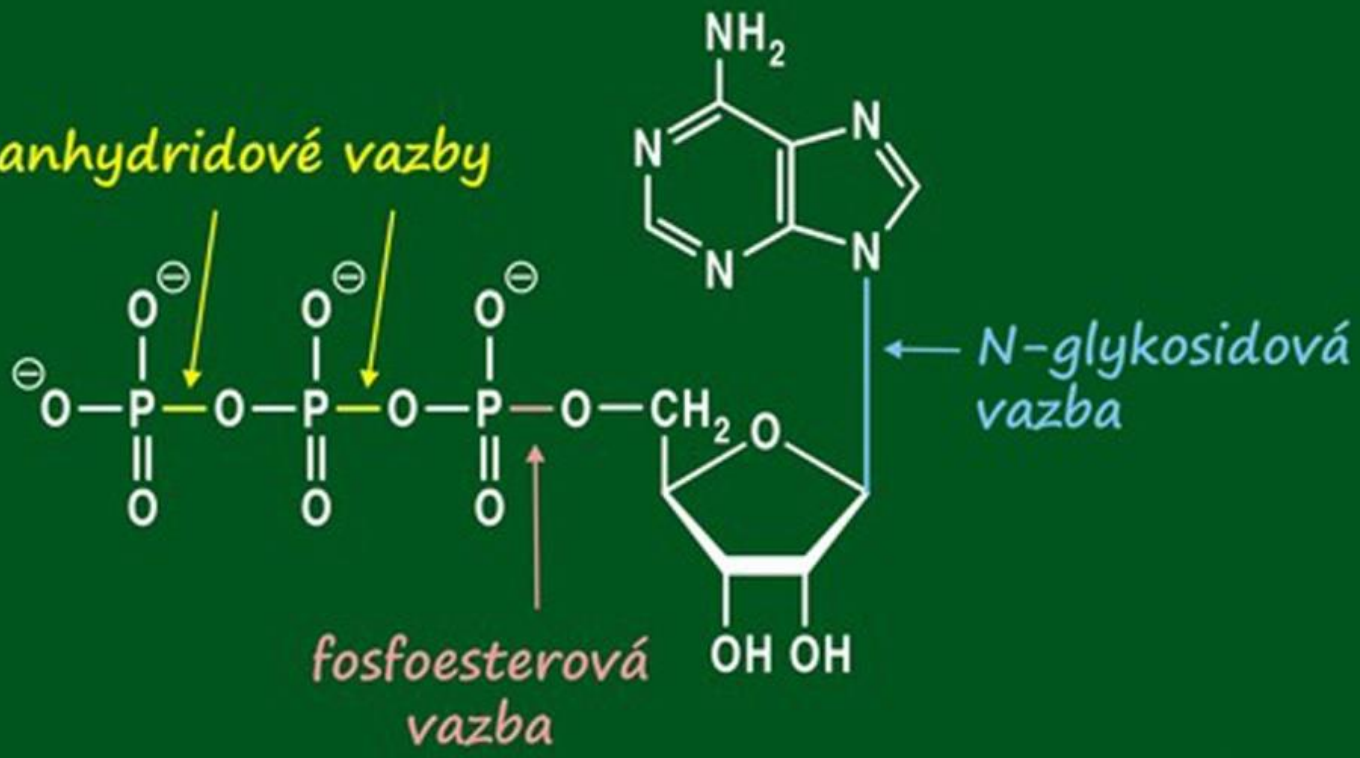
anti-konformer adenosinu

Nukleotidy jsou fosforylované nukleosidy

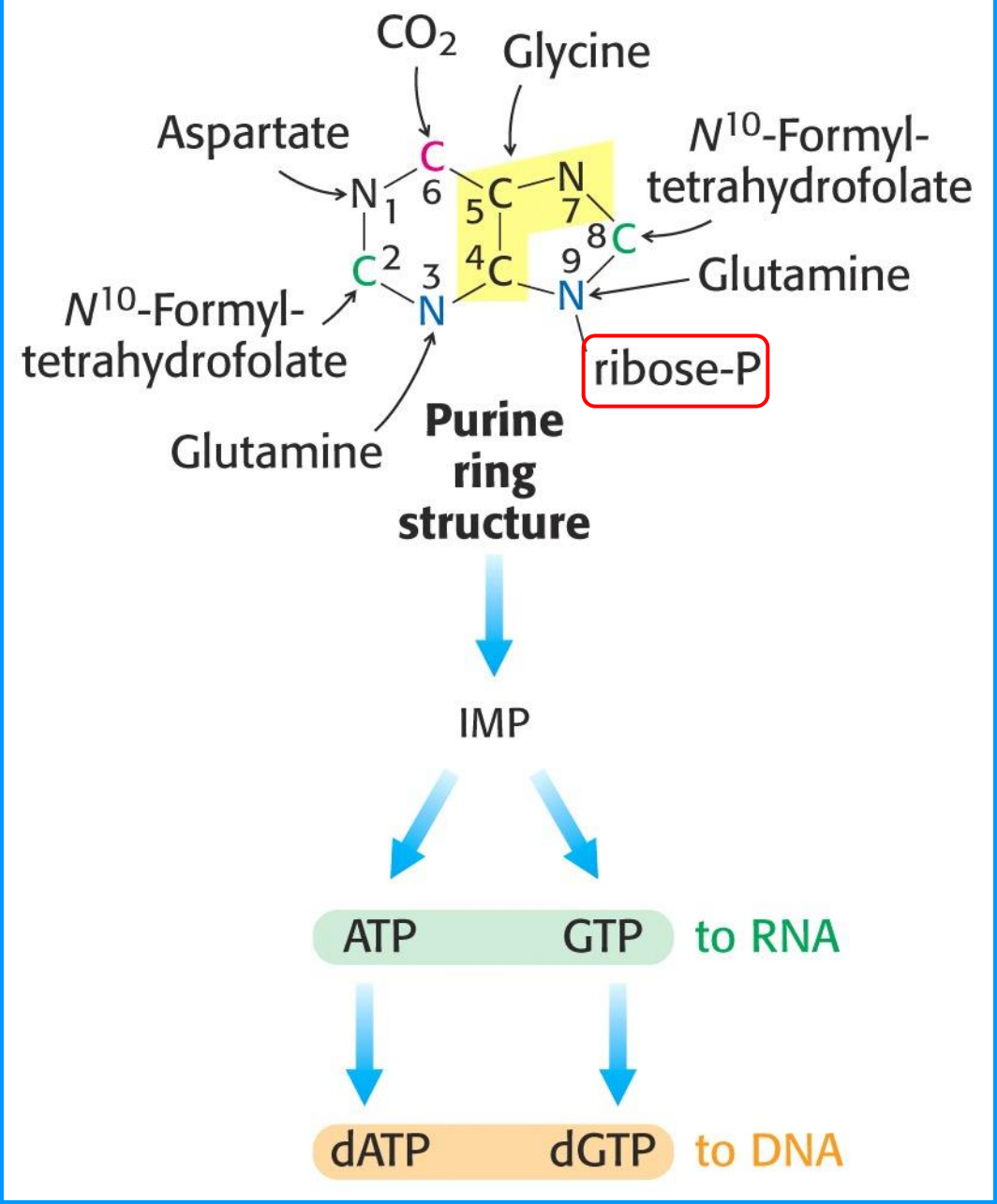


Intramolekulární vazby mezi složkami nukleotidů, např. ATP

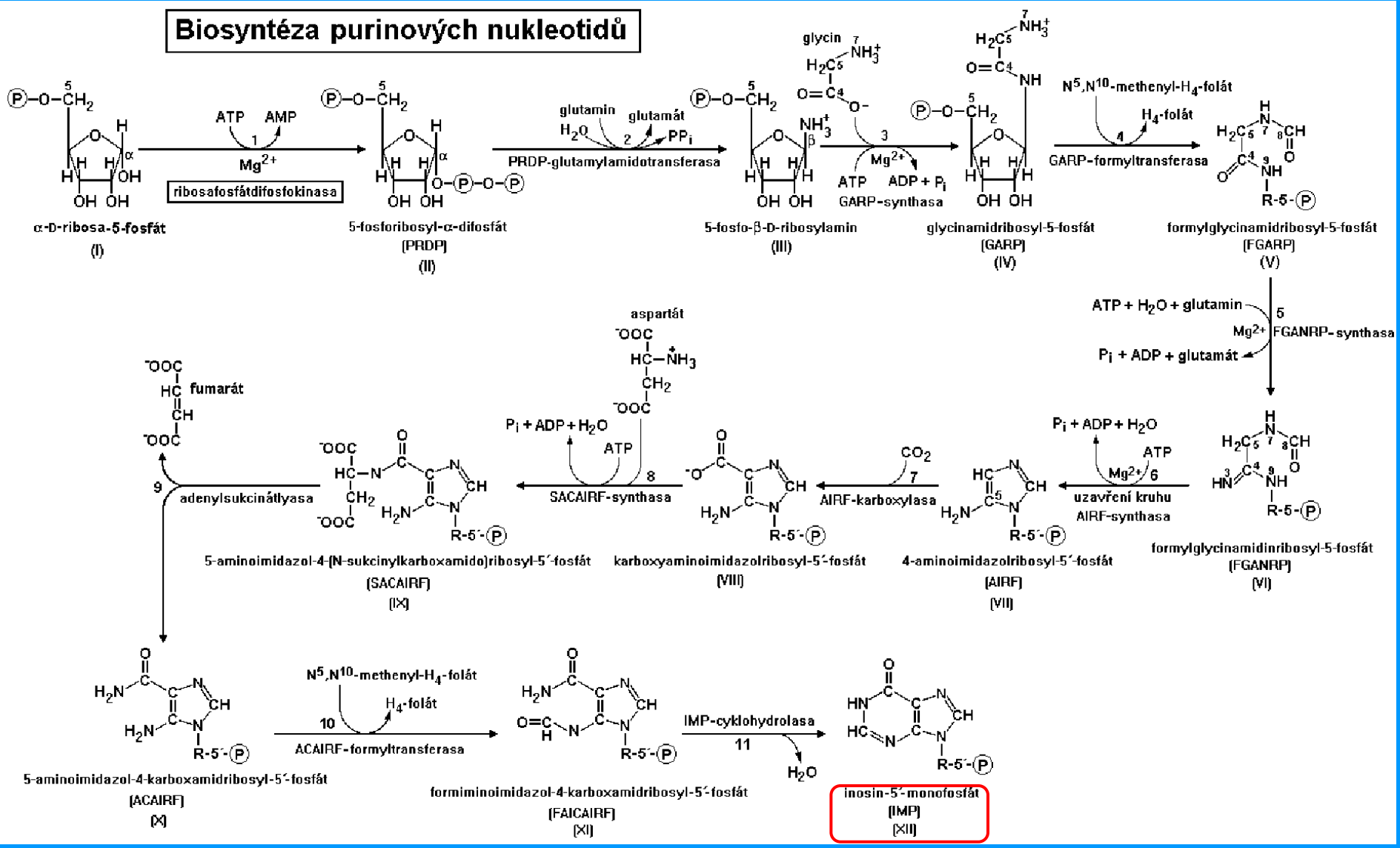
Štěpení anhydridové vazby za standardních podmínek poskytuje energii při pH 7 mezi 30 až 35 kJ/mol ATP. Štěpení esterové vazby mezi ribózou a fosfátem poskytuje jen přibližně 9 kJ/mol ATP.



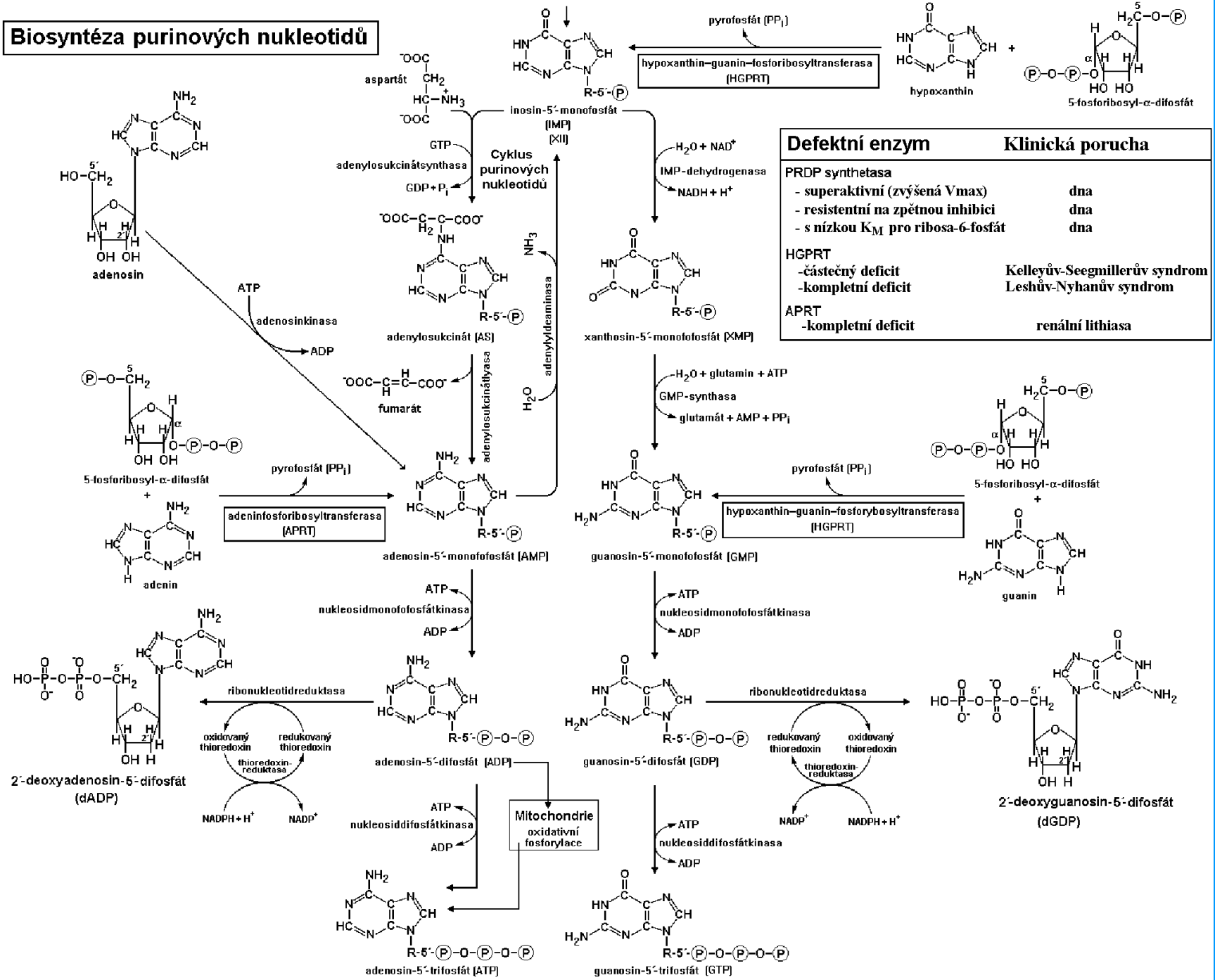
Biosyntéza struktury purinového jádra probíhá jeho postupnou výstavbou od PRPP



Biosyntéza purinových nukleotidů

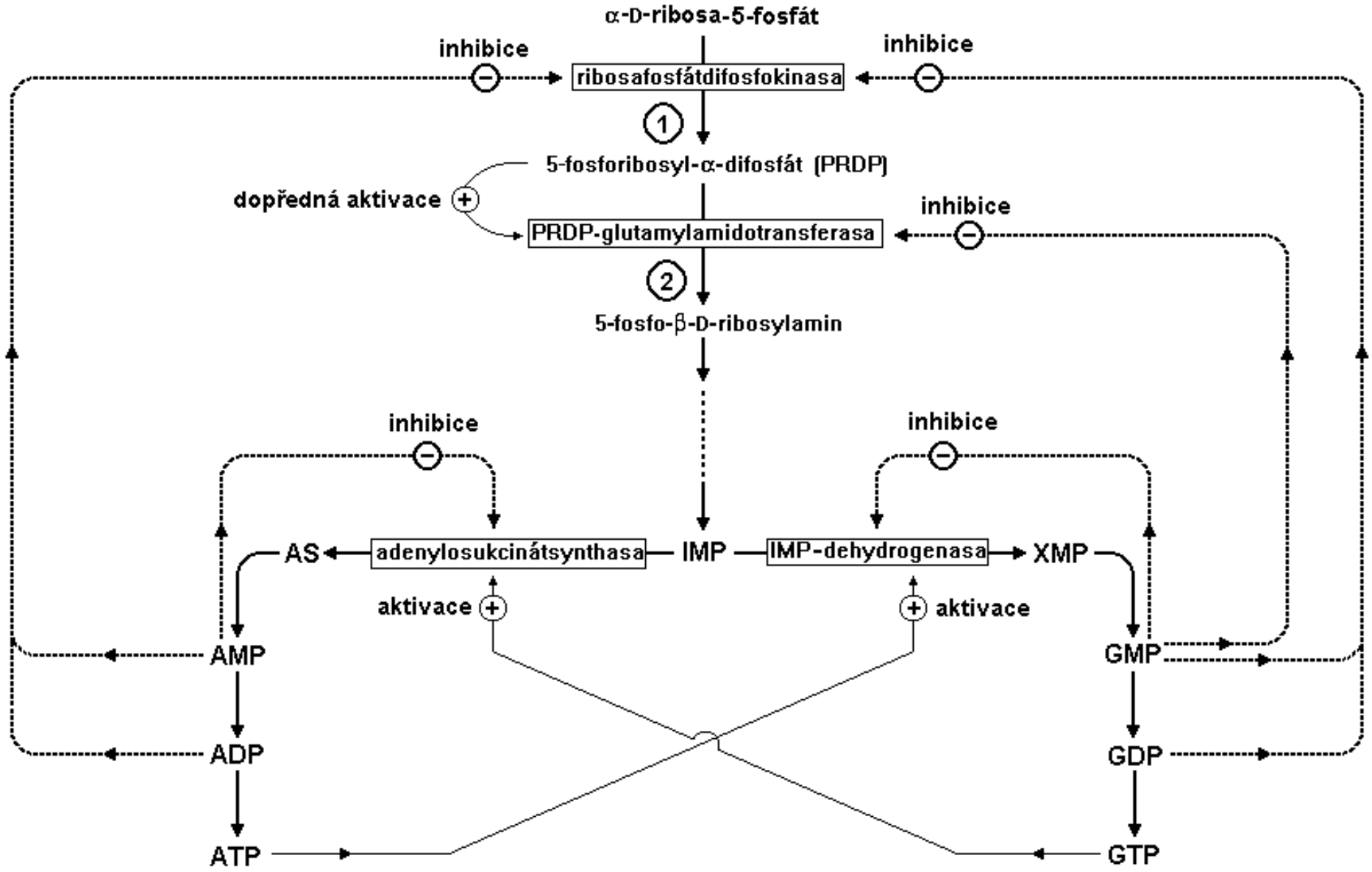


Biosyntéza purinových nukleotidů

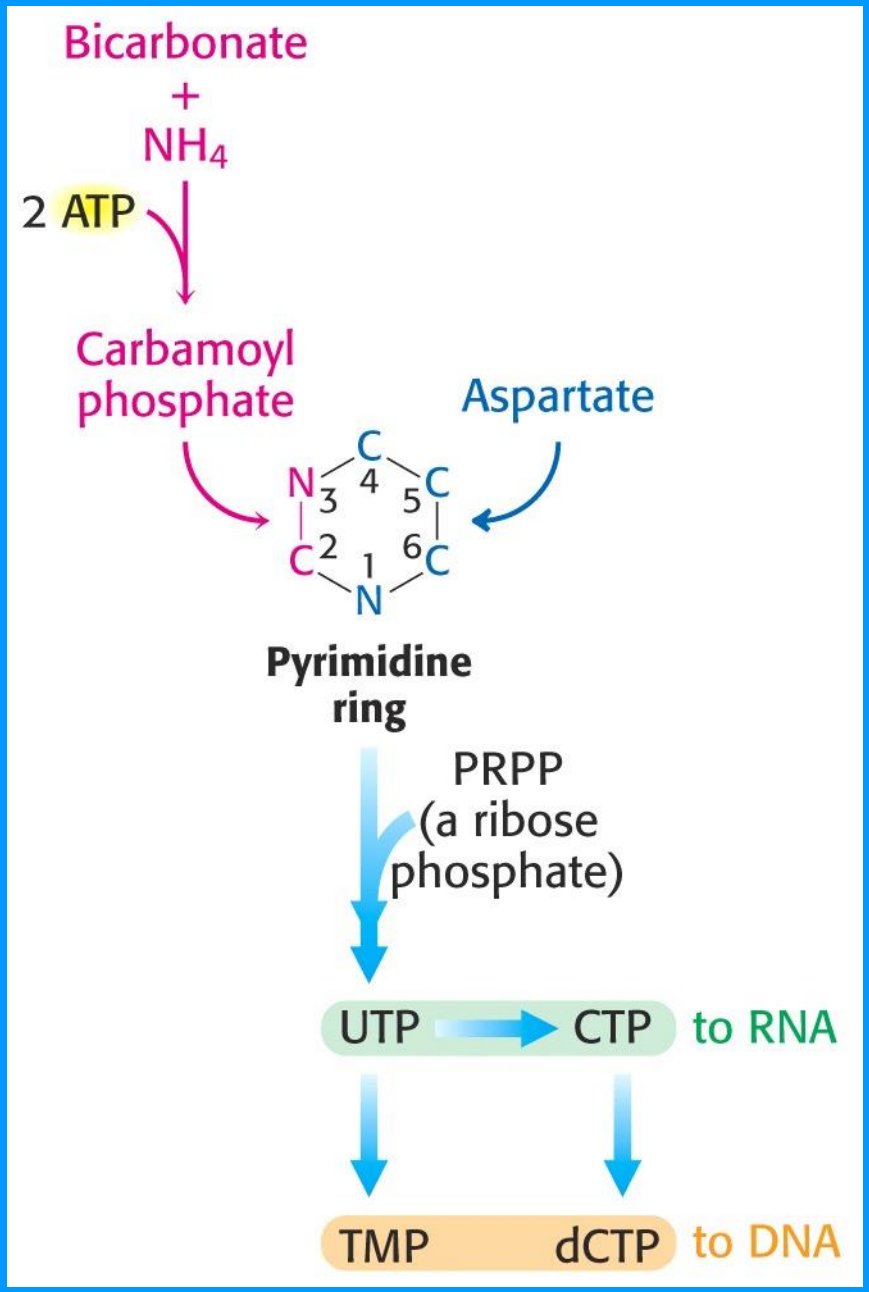


Defektní enzym	Klinická porucha
PRDP synthetasa	
- superaktivní (zvýšená Vmax)	dna
- resistentní na zpětnou inhibici	dna
- s nízkou K_M pro ribosa-6-fosfát	dna
HGPRT	
-částečný deficit	Kelleyův-Seegmillerův syndrom
-kompletní deficit	Leshův-Nyhanův syndrom
APRT	
-kompletní deficit	renální lithiasa

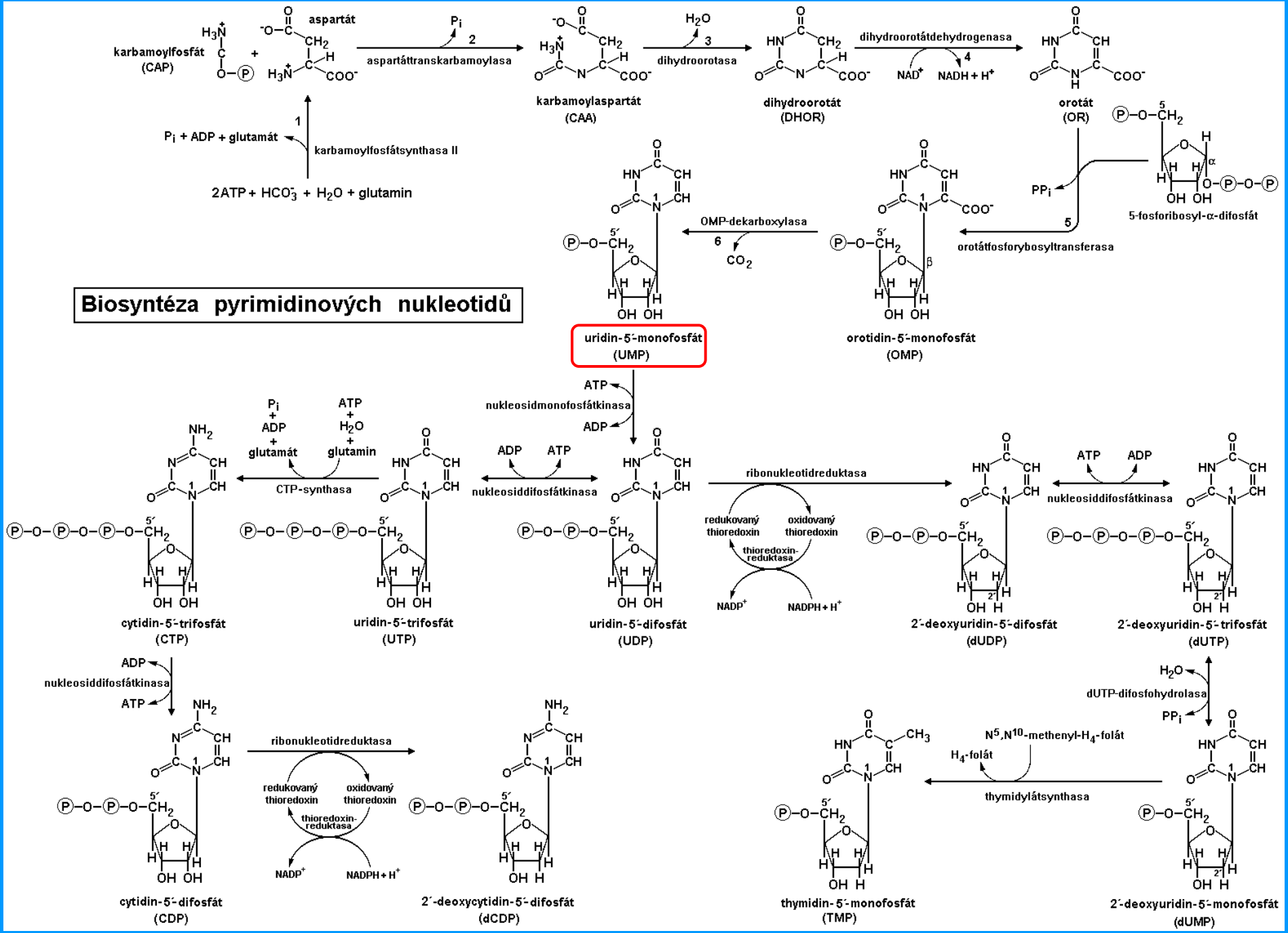
Schema regulace biosyntézy purinových ribonukleotidů



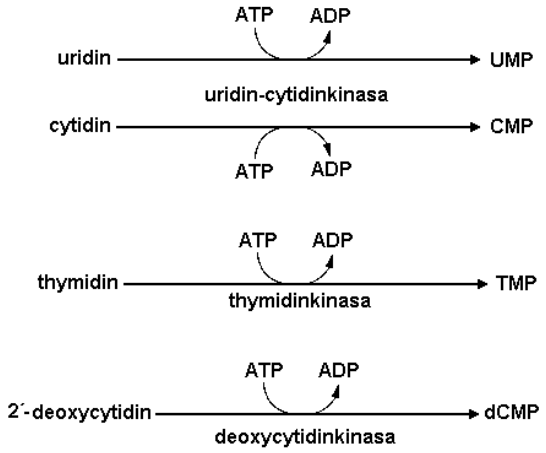
Biosyntéza struktury pyrimidinového kruhu probíhá nezávisle na PRPP



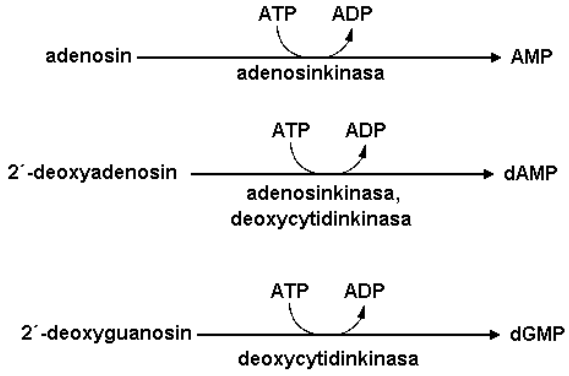
Biosyntéza pyrimidinových nukleotidů



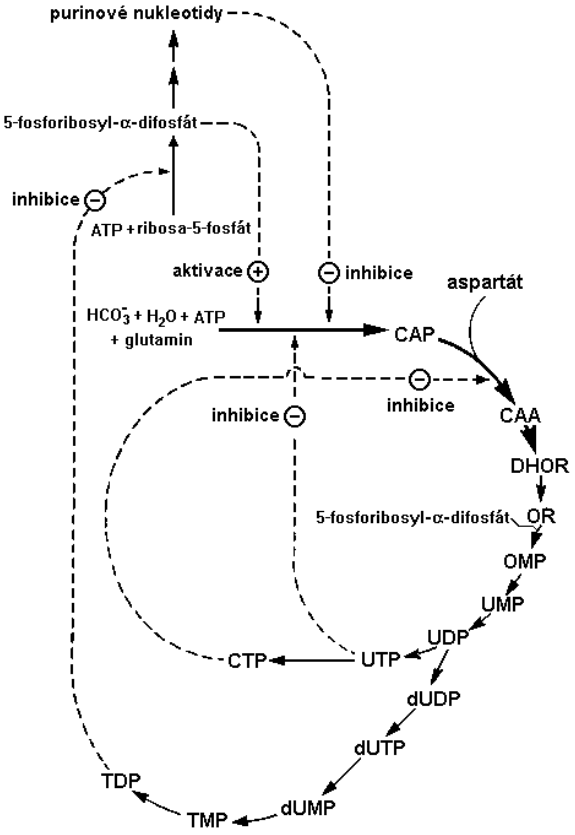
Reutilizace pyrimidinových nukleotidů



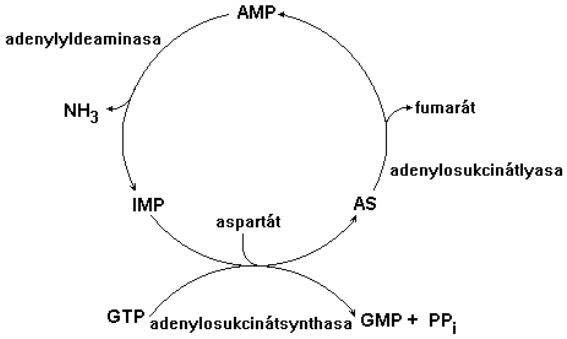
Reutilizace purinových nukleotidů



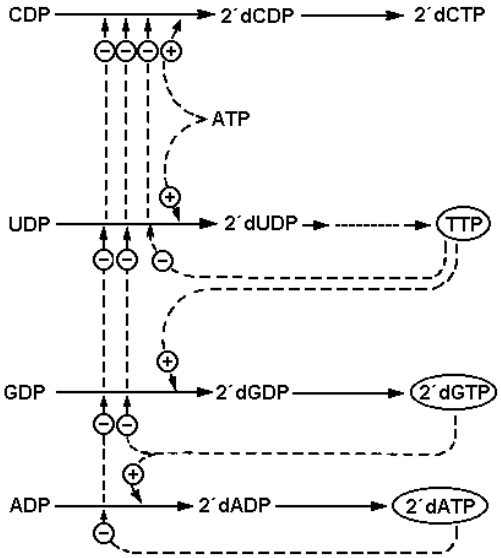
Regulace biosyntézy pyrimidinových nukleotidů



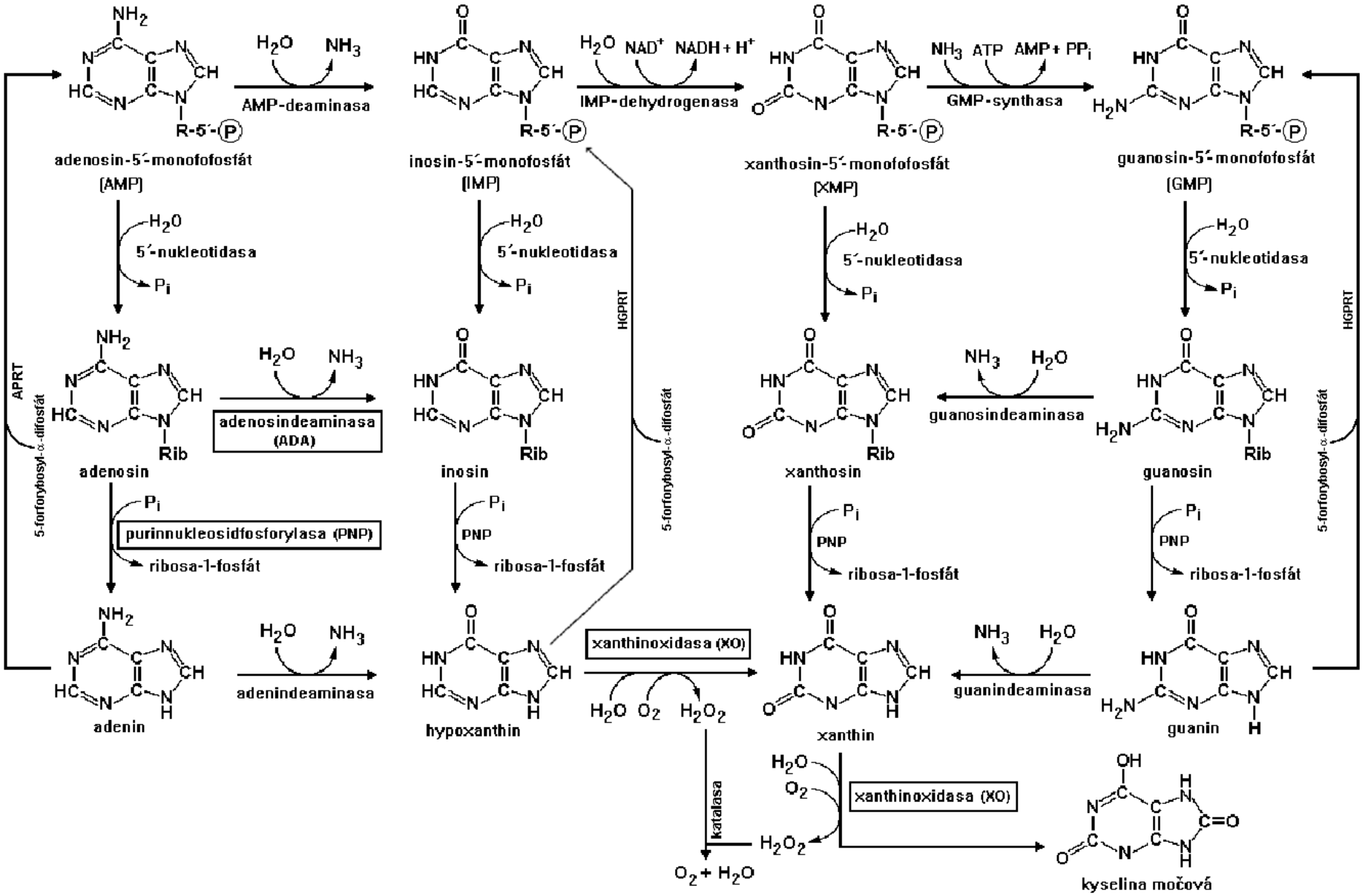
Cyklus purinových nukleotidů



Regulační síť biosyntézy deoxyribonukleotidů

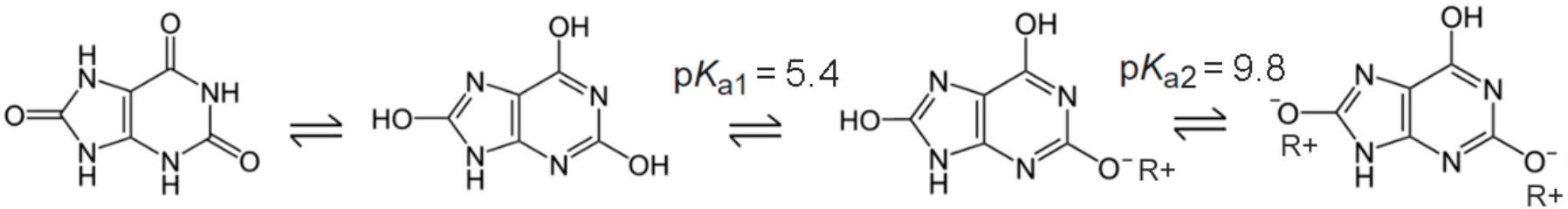


Katabolismus purinových nukleotidů



Tautomerie a disociace kyseliny močové

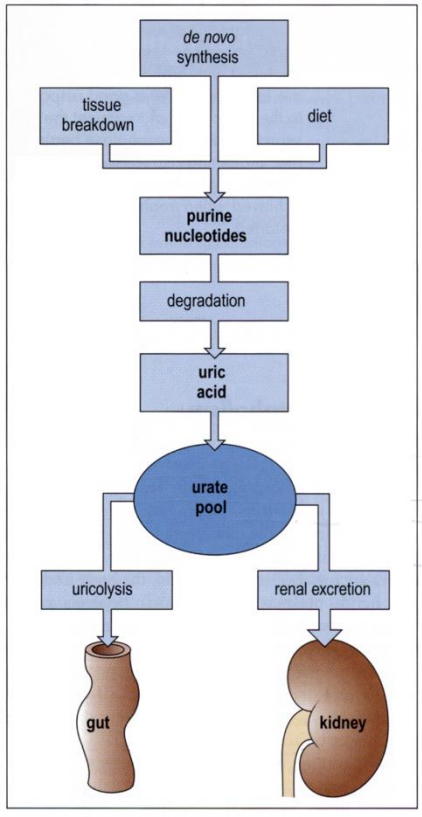
Tautomers of uric acid and urate

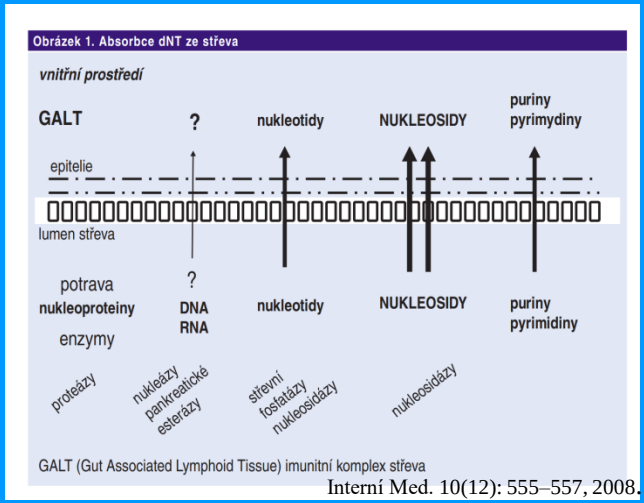


Lactam form Lactim form Urate salts

98 - 99 % ionised at pH 7.4

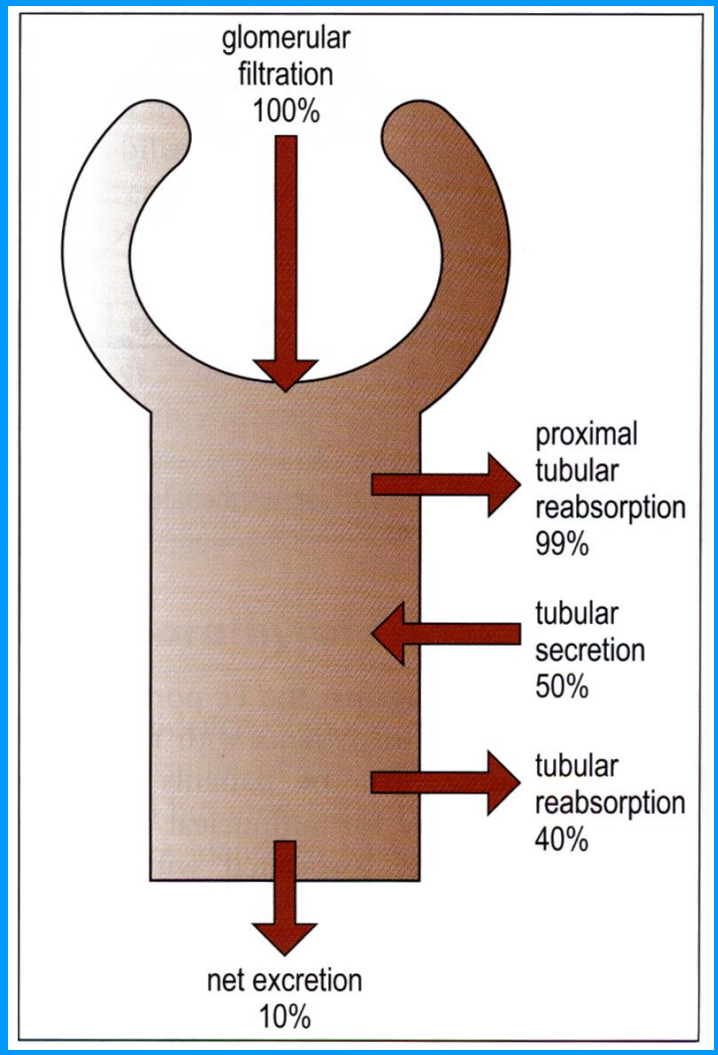
Původ purinových nukleotidů

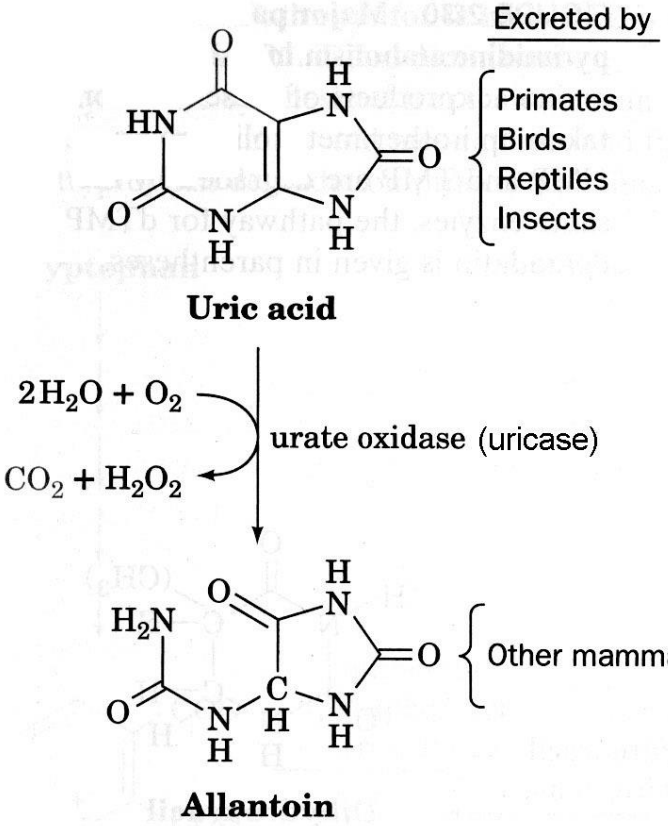




Interní Med. 10(12): 555–557, 2008.

Zpracování kyseliny močové ledvinami





Uric acid determination

Test principle

$$\text{uric acid} + 2\,H_2O + O_2 \xrightarrow{\text{uricase}} \text{allantoin} + CO_2 + H_2O_2$$

$$H_2O_2 + \text{TBHB}^{**} + \text{4-aminophenazone} \xrightarrow{\text{POD}^{*}} \text{quinoneimine dye} + 2\,H_2O + HBr$$

(512 nm)

*POD = peroxidase

** TBHB = 2,4,6,-tribromo-3-hydroxybenzoid acid

Normal values of uricemia
(i.e. the concentration of uric acid and urates in the venous blood serum)

Childrens of age between 0 month - 15 years	**120 - 360 μmol/l**
Men, since 15 years of age	**200 - 420 μmol/l**
Women, since 15 years of age	**140 - 340 μmol/l**

Normal values of uricuria
(i.e. the daily excretion of uric acid and urates in the urine)

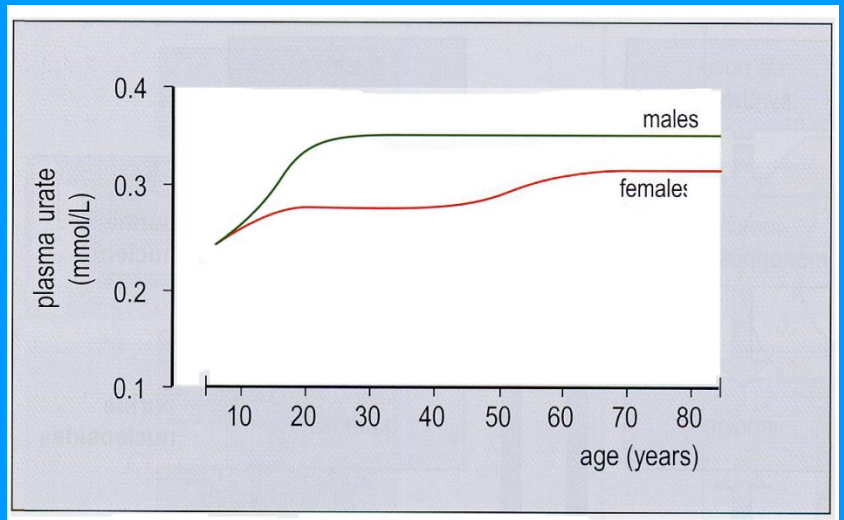
1.5 - 4.5 mmol/24 hours

Classification of patients with hyperuricemia.

I. Normal excretion of urate; renal disorder responsible for elevated serum urate.

II. Excessive excretion of urate because of overproduction.
   - A. Secondary to other disease, eg, cancer, psoriasis.
   - B. Known enzyme defects responsible for overproduction.
     1. PRPP synthetase abnormalities.
     2. Hypoxanthine-guanine phosphoribosyltransferase deficiencies.
     3. Glucose-6-phosphatase deficiencies.
   - C. Unrecognized defects.

Sodium urate crystals in urine



Mean plasma urate concentrations in men and women.

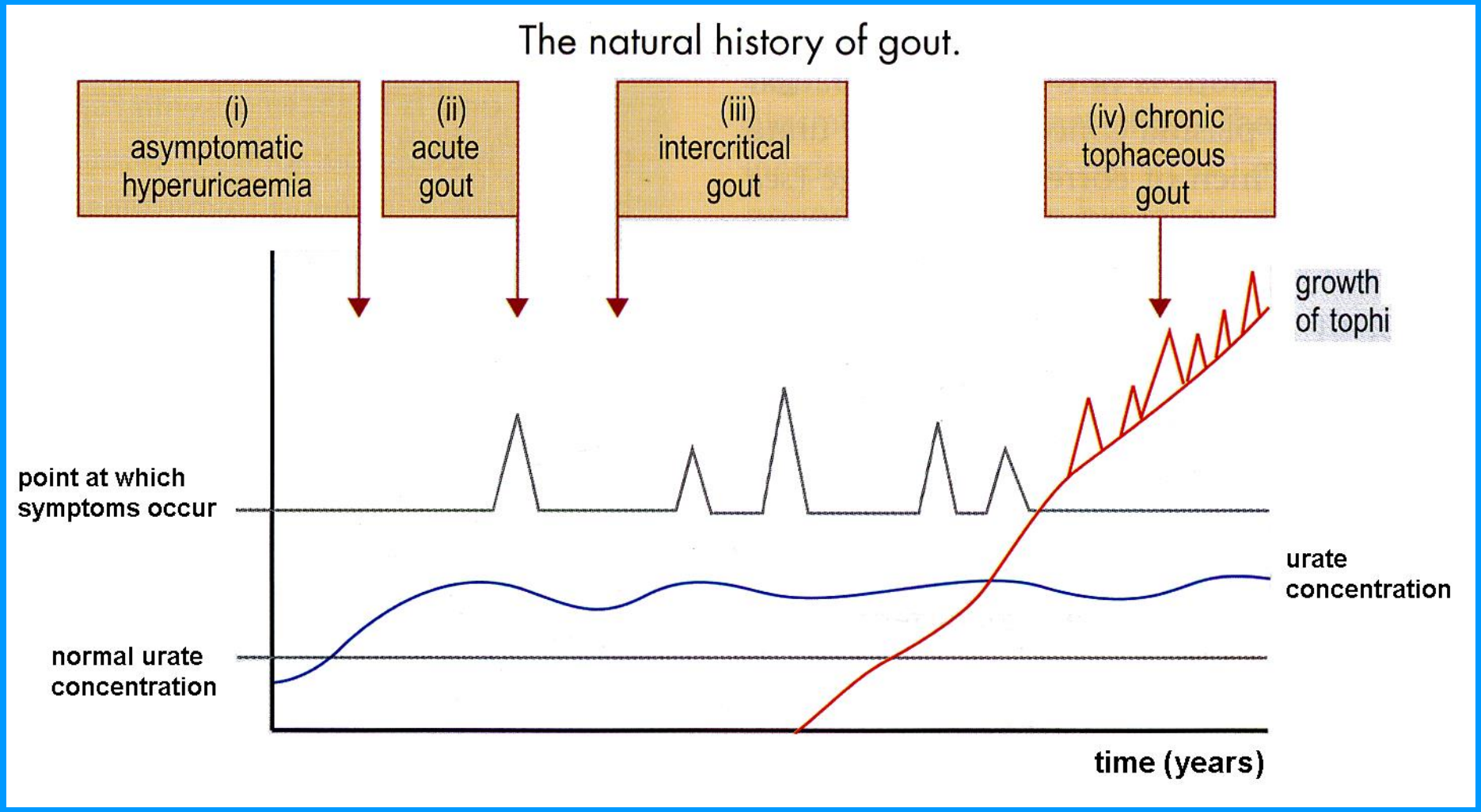
Plasma urate (mmol/L)	Risk of developing gout (%)
<0.41	1
0.42–0.47	1
0.48–0.53	4
>0.54	50

Fig. 15.10 Risk of developing gout in relation to plasma urate concentration. The figures are the incidences per year per 1000 men. A similar trend is apparent in women but few women have plasma urate concentrations >0.48 mmol/L.

Causes of hyperuricaemia

Increased urate formation	Decreased renal urate excretion
Primary	**Primary**
increased purine synthesis:	idiopathic
idiopathic	
inherited	**Secondary**
metabolic disease	chronic renal disease
	increased renal reabsorption/ decreased secretion:
Secondary	thiazide diuretics
excessive dietary purine intake	salicylates (low doses)
disordered ATP metabolism:	organic acids (e.g. lactic acid, hence alcohol)
alcohol	lead
tissue hypoxia	
increased nucleic acid turnover:	
malignant disease	
psoriasis	
cytotoxic drugs	

Fig. 15.9 Causes of increased formation of uric acid and reduced uric acid excretion by the kidneys. Note that salicylates reduce uric acid excretion at low doses only; at high doses (>4 g/24 h) aspirin is uricosuric as it blocks the tubular reabsorption of uric acid.

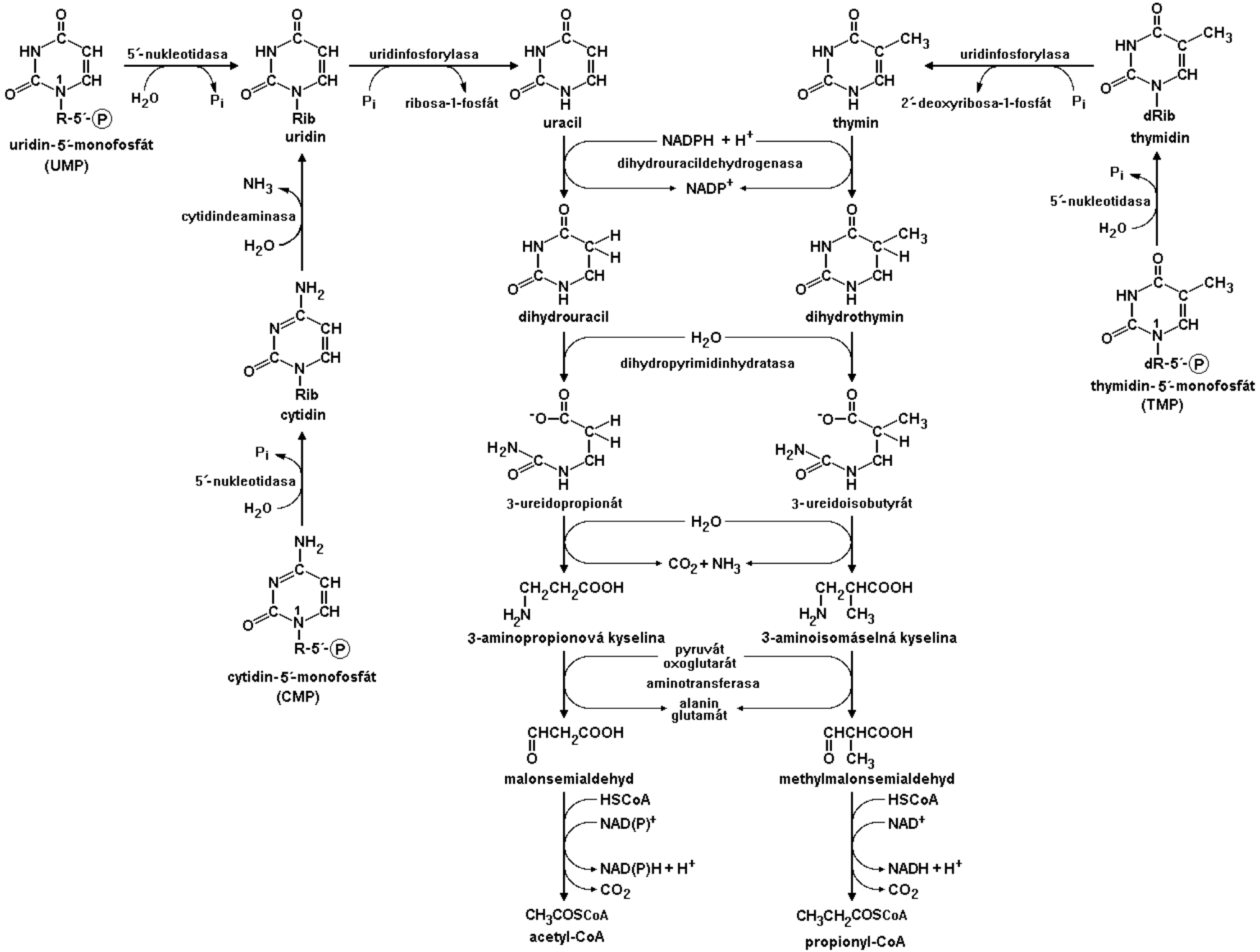

The natural history of gout.
(i) asymptomatic hyperuricaemia
(ii) acute gout
(iii) intercritical gout
(iv) chronic tophaceous gout
growth of tophi
point at which symptoms occur
urate concentration
normal urate concentration
time (years)

Inherited disorders of purine metabolism and their associated enzyme abnormalities.

Clinical Disorder	Defective Enzyme	Nature of the Defect	Characteristics of Clinical Disorder	Inheritance Pattern
Gout	PRPP synthetase	Superactive (increased V_{max})	Purine overproduction and overexcretion	X-linked recessive
Gout	PRPP synthetase	Resistance to feedback inhibition	Purine overproduction and overexcretion	X-linked recessive
Gout	PRPP synthetase	Low K_m for ribose 5-phosphate	Purine overproduction and overexcretion	Probably x-linked recessive
Gout	HGPRTase[1]	Partial deficiency	Purine overproduction and overexcretion	X-linked recessive
Lesch-Nyhan syndrome	HGPRTase[1]	Complete deficiency	Purine overproduction and overexcretion; self-mutilation	X-linked recessive
Immunodeficiency	Adenosine deaminase	Severe deficiency	Combined (T cell and B cell) immunodeficiency, deoxyadenosinuria	Autosomal recessive
Immunodeficiency	Purine nucleoside phosphorylase	Severe deficiency	T cell deficiency, inosinuria, deoxyinosinuria, guanosinuria, deoxyguanosinuria, hypouricemia	Autosomal recessive
Renal lithiasis	Adenine phosphoribosyltransferase	Complete deficiency	2,8-Dihydroxyadenine renal lithiasis	Autosomal recessive
Xanthinuria	Xanthine oxidase	Complete deficiency	Xanthine renal lithiasis, hypouricemia	Autosomal recessive

[1]HGPRTase = hypoxanthine-guanine phosphoribosyltransferase

Katabolismus pyrimidinových nukleotidů



Inherited disorders of pyrimidine metabolism and their associated enzyme abnormalities.

Clinical Disorder	Defective Enzyme	Characteristics of Clinical Disorder	Inheritance Pattern
β-Aminoisobutyric aciduria	Transaminase	No symptoms; frequent in Asians.	Autosomal recessive
Orotic aciduria, type I	Orotate phosphoribosyltransferase and orotidylate decarboxylase	Orotic acid crystalluria, failure to thrive, and megaloblastic anemia. Immunodeficiency. Remission with oral uridine.	Autosomal recessive
Orotic aciduria, type II	Orotidylate decarboxylase	Orotidinuria and orotic aciduria, megaloblastic anemia. Remission with oral uridine.	Autosomal recessive
Ornithine transcarbamoylase deficiency	Ornithine transcarbamoylase	Protein intolerance, hepatic encephalopathy, and mild orotic aciduria.	X-linked recessive