METABOLISM

= summary of all chemical (and physical) processes included in:

1. Production of energy from internal and external sources
2. **Synthesis** and **degradation** of structural and functional tissue components
3. Excretion of waste products and toxins from body

METABOLIC DISORDERS

1. **Inherited** metabolic disorders (enzymopathies)
2. **Combined** metabolic disorders (DM, gout, degenerative disorder of joints and bones)
3. Metabolic disorders from **external reasons**

METABOLISM

- Proteins
- Saccharides
- Lipids

DIET

Ballanced diet should contain:

– **sugars – saccharides (50 –55 %)**

– **fats (30 %)**

– **proteins (15 –20 %)**

– vitamines, innorganic compounds

– **water** – daily requirements correspond to **2,4 l:**

The daily energy requirement is:

– an adult man ~12600 kJ

– an adult woman ~9200 kJ

– real consumption depends on:

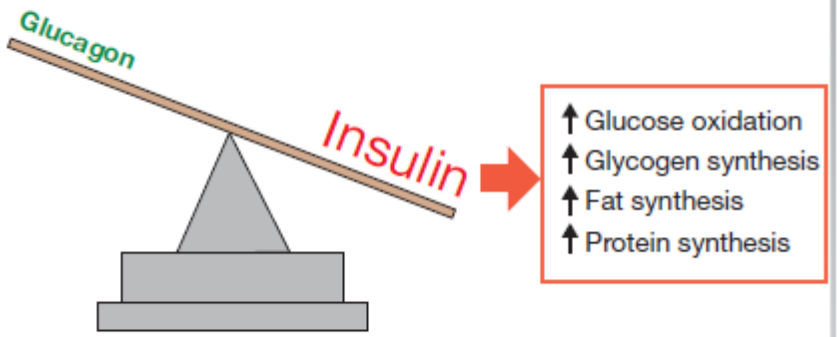
- body weight
- the extent of physical activity
- other physiological and pathophysiological factors

Insulin versus glucagon

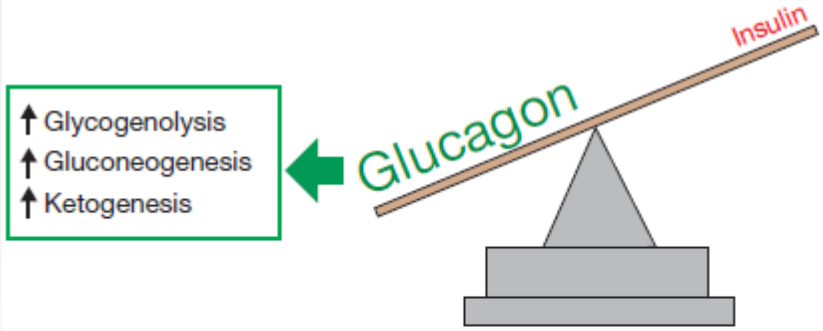
INSULIN AND GLUCAGON

Metabolism is controlled by the insulin : glucagon ratio.

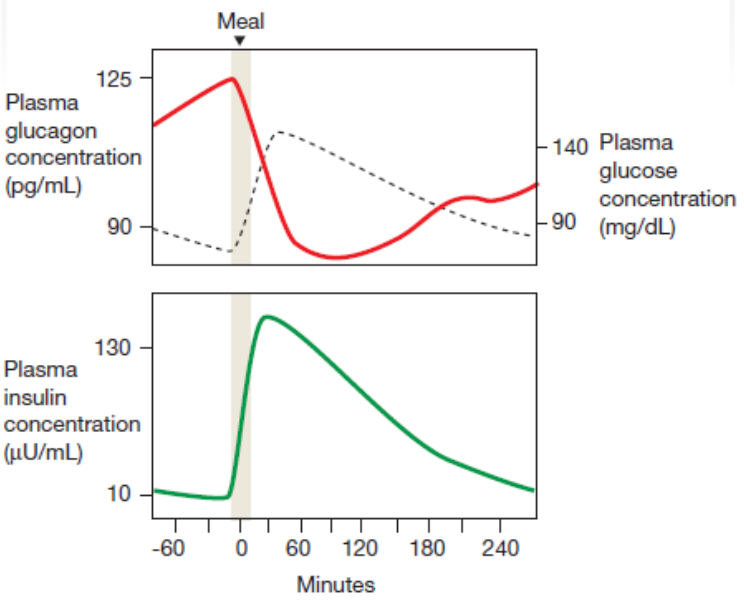
(a) Fed state: insulin dominates



(b) Fasted state: glucagon dominates



(c) Glucose, glucagon, and insulin levels before and after a meal



Condition	Hepatic Glucose Storage (S) or Production (P)[a]	I/G
Glucose availability		
Large carbohydrate meal	4+ (S)	70
Intravenous glucose	2+ (S)	25
Small meal	1+ (S)	7
Glucose need		
Overnight fast	1+ (P)	2.3
Low-carbohydrate diet	2+ (P)	1.8
Starvation	4+ (P)	0.4

[a]1+ to 4+ indicate relative magnitude.

Courtesy of RH Unger.

TABLE 18-4 Summary of Glucose-Counterregulatory Controls*

	Glucagon	Epinephrine	Cortisol	Growth Hormone
Glycogenolysis	√	√		
Gluconeogenesis	√	√	√	√
Lipolysis		√	√	√
Inhibition of: glucose uptake by muscle cells and adipose-tissue cells			√	√

*A √ indicates that the hormone stimulates the process; no √ indicates that the hormone has no major physiological effect on the process. Epinephrine stimulates glycogenolysis in both liver and skeletal muscle, whereas glucagon does so only in liver.

Prolonged starvation

- Decrease energy requirements
- BMR (- 20 to 25 kcal / kg / day)
- A majority of effects is given by hypoinsulinemia, effect on the liver is determined by glucagon
- The gradual increase in the ratio of gluconeogenesis
- Initially increase the rate of proteolysis
- Increasing the rate of lipolysis - activation of hormone-sensitive lipase = mobilization of glycerol and FAs

- Glycerol = an additional substrate for gluconeogenesis; excess of FAs = substrate for muscles (insulin resistance, interference with "activation" of GLUT4) and peripheral tissues = enough glucose to nervous tissue
- Further starvation:
  - Reduction of proteolysis (= reduced production of urea = reduced excretion of water), increasing use of fat for ketogenesis
  - Use of ketones nervous tissue (b-hydroxybutyrate and acetoacetate)
  - Reduction of hepatic gluconeogenesis X increased gluconeogenesis in the kidney (40% of production)
  - Further mobilization of lipids = lipolysis = increase in hepatic ketogenesis (100 g d)
  - Further lipolysis = loss of adipose tissue, hormonal changes (leptin, FSH, LH - anovulation)

Other changes as a result of starvation:

- Loss of K^+ in the initial stage, a stable concentration of 3 mmol/L
- Mg^{2+} - unchanged or only slight hypomagnesemia
- Ca^{2+} - unchanged
- Phosphates – unchanged
- Uric acid – increase (protein catabolism)
- Next changes:
  - ❑ Decreased heart rate (35 t/min, from 4. week slight increase)
  - ❑ Drop of blood pressure
  - ❑ ECG changes - flattening of the T wave, decrease of amplitude of QRS
  - ❑ In cases of extreme starvation - prolongation of the QT interval, T wave inversion, ST segment depression
  - ❑ Why?
    - o The decrease of protein synthesis - myofibrils, myofilaments
    - o Changes in the composition of the ECT/ICT
    - o Losses of trace elements (Cu - ischemia)
    - o Sympathetic (catecholamines) - Arrhythmia

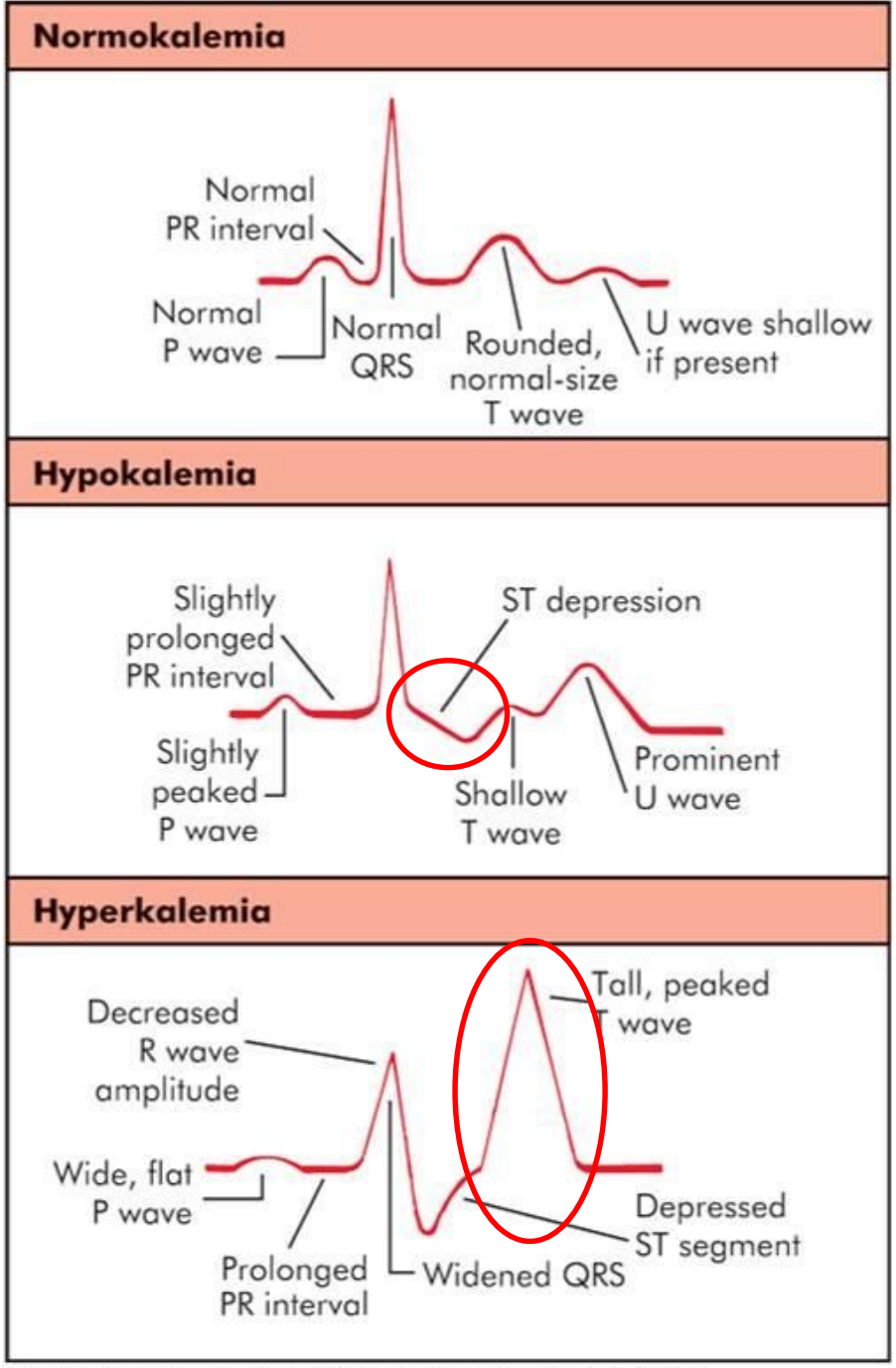


Fig. 4-7. Electrocardiogram Changes with Potassium Imbalance

METABOLIC DISORDERS EXAMINATION

LABORATORY METHODS (biochemistry)

- Lack or absence of metabolite (blood, urine, tissue, cells)
- Overproduction of metabolite
- Pathological storing of metabolite in tissues (histochemistry)
- Pathological metabolite

FINDINGS OF CAUSE OF METABOLIC DISORDER

- Disorder in resorption or excretion (functional load tests)
- Measurement of activity of certain enzymes or enzyme systems

GENEALOGIC EXAMINATION

SCREENING TESTS (fenylketonuria, hyperlipoproteinemia, aminoaciduria, thyroid gland hormones…)

METABOLISM OF SACCHARIDES

1.Source of **energy**
2.Part of glycoproteins, glycopeptides, glycolipids– structural or functional (collagen in basal membranes, mucopolysaccharides, myelin, hormones, receptors…)

Dietary carbohydrates– hexoses (glucose, fructose, galactose)
Key substrate – **glucose**.
Postprandial plasmatic levels of glucose: **3,5 – 6,5mmol/l**
Glycaemia. Hypoglycaemia, hyperglycaemia.
Hypoglycaemia: decreased oxygen supply of CNS
Glycolysis, gluconeogenesis. Humoral control of glycaemia.
Glycolysis: main products – lactate and pyruvate – mean plasmatic concentrations 0,7 and 0,07mmol/l (ratio **10:1** remains even at various turnover); during hypoxia – **30:1** (metabolic acidosis)

•Glucose **turnover**: 2mg/kg/min (11mmol/kg/min)~9g/hr~225g/day

•55% of glucose utilisation – terminal oxidation (CNS)
•20% - glycolysis, lactate back to liver, gluconeogenesis (Cori cycle)
•20% - absorption by liver and splanchnic tissues
•70% consumption of glucose at rest is insulin-independent

•Circulating glucose pool (**pool**) – only a little bigger than expenditure by liver per 1 hour
•Brain oxidation is kept by pool only for approx. 3 hrs
•NECESSITY OF CONTINUOUS GLUCOSE PRODUCTION FROM LIVER during **starving**
•80% - glycogenolysis, 20% - gluconeogenesis (more than 50% from lactate trapped by liver for gluconeogenesis, rest – AA, esp. alanine; lactate from glycolysis in muscles, ery, leu, etc.; AA – from proteolysis of muscles)

•Morning glucose intake – 70% is needed by peripheral tissues (muscles), 30% - splanchnic organs (liver)

•20-30% of consumed glucose – oxidised during 3-5 hrs to cover needs of GIT, 70-80% stored as glycogen (muscle, liver)

•Muscle glycogen – later transported to liver (lactate from glycolysis in muscles, re-uptake, gluconeogenesis in liver, glycogenolysis)

•During maximal absorption of exogenous glucose – release of glucose from liver is suppressed (insulin and glucagon facilitate this process)

LIVER GLUCOSTAT

- Maintaining the constant blood glucose

- Endocrine control:

- glycogenolysis (glucagon, adrenaline, noradrenaline = activation of glycogen phosphorylase)
- why only liver and not muscles? (glucose-6-phosphatase in liver)
- gluconeogenesis (glucagon, adrenaline, noradrenaline, glucocorticoids, thyroid hormones)

GLYCOSURIA

- **Alimentary glycosuria** (renal threshold for glucose = 10 mmol/l)

- Inhibitors of SGLT2

- **Renal glycosuria** (congenital deficiency of glucose transport in the kidneys, blood glucose is normal)

METABOLISM OF LIPIDS

- Fat – approx. **50%** of daily amount of substrates for oxidation (100gr, 900kcal)
- Main and **most profitable** form of energy store
- Daily intake: approx. **100gr** (40% of daily diet)
- Main component of dietary sources and stores in body: **triglycerides**
- No strict dietary recommendation (part of FA synthetised in liver and adipose tissue)
- BUT: 3-5% of FA are polyunsaturated!!! – **ESSENTIAL FA**
- Precursors of membrane phospholipids, glycolipids, prostaglandins
- Cholesterol – part of membranes, precursor of bile acids, steroid hormones; daily intake – 300-600mg/day, synthesised too
- Lipoproteins: transport of lipids by blood plasma
- Apoproteins (from liver or intestine), catalytic function, receptors

•**Chylomicrons** – from diet, lowest density, **lipoprotein lipase** (endothelium of capillaries), activation by apoprotein C-II, transport of HDL
•Free FA absorbed by adipocytes (resynthesis of triglycerides, store) and other tissues (oxidation)
•Rest of lipoprotein particles (more cholesterol) – chylomicron rests – degradation in liver
•**VLDL** – endogenous synthesis in liver (less in intestine), in postabsorption phase
•Dense, more cholesterol, longer plasmatic half-time
•Speed of production: 15-90g/day
•Beginning of metabolism – see chylomicrons
•Products of lipoprotein lipase effect – **IDL** (intermediate-density lipoprotein)
•50% IDL – back to liver (as chylomicron rests)
•50% IDL – enriched by cholesterol – **LDL**
•Circulating LDL – transport of cholesterol into cells
•Absorption of LDL, IDL, rests of ch. – apoproteins, receptors, endocytosis
Uptake of **LDL-cholesterol** into cells – **down regulation** of LDL receptors (slowed resorption) and slowed synthesis de novo

•**HDL –** long plasmatic half-time, synthesis in liver and intestine
•Facilitation of other particles movement
•Exchange of key apoproteins
•They accept molecules of free cholesterol, estherify them (lecithin-cholesterol-acetyltransferase) and incorporate back to particles
•Main effect: acceleration of clearance of triglycerides from plasma and regulation of ration free:estherified cholesterol

•**Free FA**
•Average concentration: 400μM/l
•Bound to molecules of albumins
•Fast turnover (approx. 8g/hr): 50% - oxidation, 50% - reestherification to triglycerides

•Total **cholesterol**: 185mg/l
•LDL cholesterol: 120mg/l
•HDL cholesterol
•Arteriosclerosis, genetic predisposition (LDL apo or receptor)

METABOLIC DISORDERS - SACCHARIDES

1. **Diabetes mellitus**
2. **McArdle syndrom:** glycogenesis from deficiency of myophosphorylase
   Accumulation of glycogen in muscles
   Muscle stiffness, rigor during exercise, lower tolerance of load
3. **Galactosemia** (inherited deficiency of phosphogalactosauridyltransferase; disorders of growths and development)

METABOLIC DISORDERS - LIPIDS

1. **HYPERLIPIDEMIA, HYPERLIPOPROTEINEMIA**
2. **INFREQUENT DISORDERS OF LIPID METABOLIS**

Ad 1) 5% of population

Primary and secondary forms

Arteriosclerosis

- **Hyperlipoproteinemia induced by lipids**
- **Familiar hypercholesterolemia (xantomatosis)**
- **Mixed hyperlipoproteinemia**
- **Familiar hypercholesterolemia with hyperlipemia**
- **Saccharides-induced triglyceridemia**
- **Secondary hyperlipoproteinemia** (dependent; alimentary)

Ad 2)

- **Lipidoses**
- **Abetalipoproteinemia** (LDL, VLDL)
- **Analfalipoproteinemia** (HDL)
- **Inherited defect acetyltranspherase LCAT** (accumulation of lecithin)

BROWN ADIPOSE TISSUE

LIPIDS: structural, neutral and brown

Specific localisation

Sympathetic innervations of vessels and also adipocytes

Several drops of fat in adipocyte

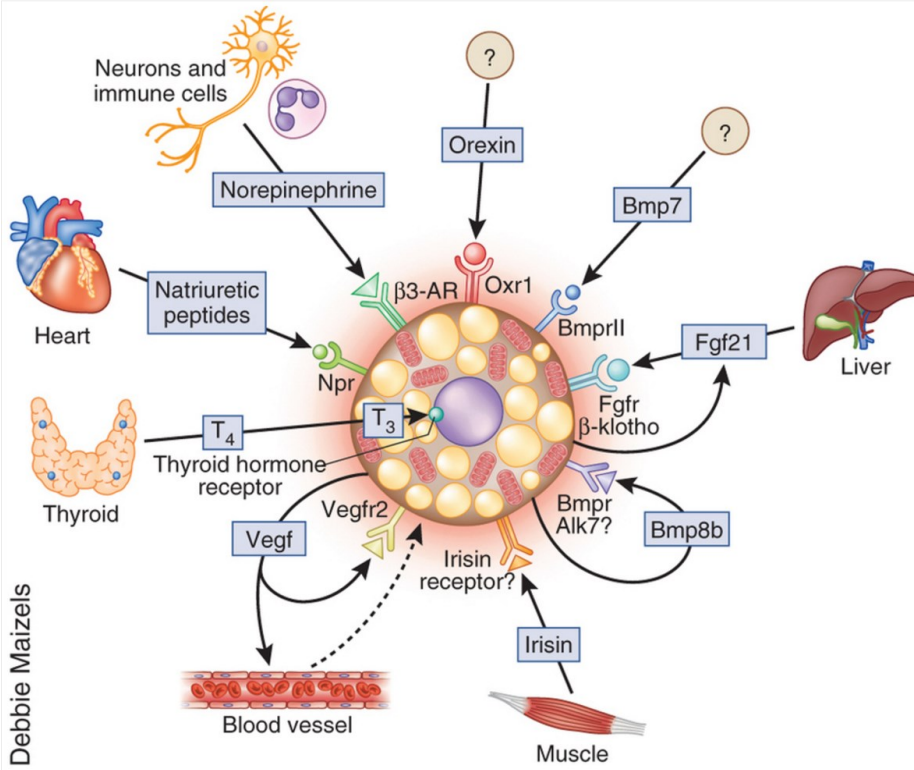
More mitochondria

Production of heat

Adaptation to cold

After meal – increased production of heat

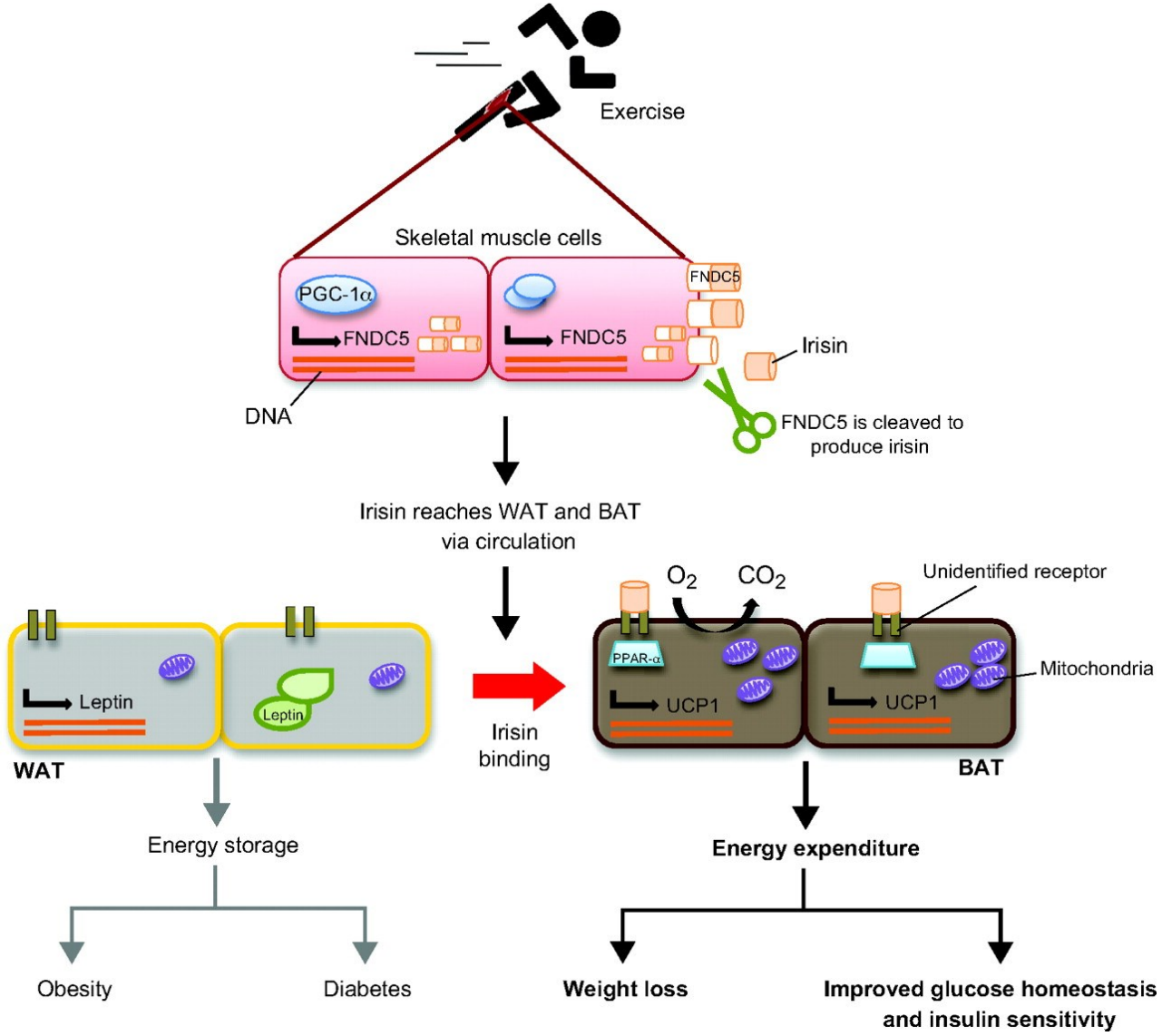
- Irisin = ??? (transformation of white fat to brown...), production increased during physical exertion?
- FGF21 = increased intake of Glu by peripheral tissues, increased oxidation of FAs
- Natriuretic peptides, ANP - increased lipolysis; protection against low temperatures?
- Bmp8b = produced by brown adipocytes and some hypothalamic nuclei - regulation of sympathetic activity
- T4/T3 - increasing the expression of thermogenic genes



In rodents, a number of tissues and cell types have been found to secrete factors that regulate brown and beige adipose activity through systemic, autocrine and paracrine mechanisms. Neurons and alternatively activated macrophages secrete norepinephrine; cardiac tissue secretes natriuretic peptides; liver and BAT secrete Fgf21; muscle secretes irisin; and thyroid secretes the hormone T_4 (which is then converted to T_3). BAT also produces Bmp8b and Vegf, which increase thermogenic function in an autocrine manner. Additionally, orexin and Bmp7 promote brown fat development, but their cellular source is unknown. Oxr1, oxidation resistance 1; Alk7 (also called Acvr1c), activin A receptor type 1C.

http://www.nature.com/nm/journal/v19/n10/fig_tab/nm.3361_F4.html

Peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α



Castillo-Quan JI: From white to brown fat through the PGC-1 alpha-dependent myokine irisin: implications for diabetes and obesity. *Disease Models & Mechanisms 2012, 5(3):293-295.*

Exercise-induced adipose tissue browning through PGC-1α and irisin. Exercise increases the expression levels of PGC-1α in the muscle. This, in turn, upregulates the expression of FNDC5, a type I membrane protein, which is C-terminally cleaved and secreted as irisin into the circulation. Binding of irisin to an unknown receptor on the surface of adipocytes in WAT changes their genetic profile. In particular, irisin induces the expression of PPAR-α, which is thought to be an intermediate downstream effector that increases the expression of UCP1 (highly expressed in BAT and a marker of browning). The browning of WAT is associated with augmented mitochondrial density and oxygen consumption. Browning is accompanied by an increase in the energy expenditure profile, leading to favourable effects on metabolism.

METABOLISM OF PROTEINS

- Proteins = AA bound by peptide bonds (above 100 AA)
- Peptides (2-10 AA), polypeptides (10-100 AA)
- Primary, secondary, tertiary a quarterly structure of protein

Proteins, lipoproteins, glycoproteins

Total proteins in body: **10** kg

Metabolically active: **6** kg (e.g.60%)

Proteolysis of muscles: **50** g of proteins / day

Minimal daily intake: **50** g

Protein **minimum**: **0,5 g / kg** of body mass

Protein **optimum**: **0,7 g / kg** of body mass

Increased supply (growth, convalescence, pregnancy, lactation): **1,5 – 2,0**

AMINOACIDES

- Essential (not synthesised)
- Non-essential (from glucose metabolism – citrate cycle)
- **Aminoacid pool**
- Need of essential AA: **0,5 – 1,5 g / day**
- Disorders of proteosynthesis
- Optimal source of E-AA:NE-AA milk, eggs
- During growth: **40%** E-AA, in adults: **20%**

- **Precursors**: purines, pyrimidines, polyamines, phospholipids, creatin, carnitin, donors of methyl group, catecholamines, thyroid gland hormones, neurotransmitters

Amino acids - the surplus in food

Degradation, used as an energy source

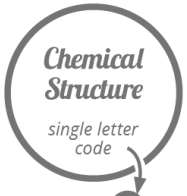
AMK as other substrates:

- Glucogenic AMK – synthesis of carbohydrates
- Ketogenic AMK – lipids and ketones

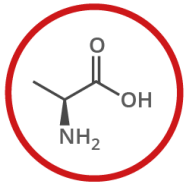
A GUIDE TO THE TWENTY COMMON AMINO ACIDS

AMINO ACIDS ARE THE BUILDING BLOCKS OF PROTEINS IN LIVING ORGANISMS. THERE ARE OVER 500 AMINO ACIDS FOUND IN NATURE - HOWEVER, THE HUMAN GENETIC CODE ONLY DIRECTLY ENCODES 20. 'ESSENTIAL' AMINO ACIDS MUST BE OBTAINED FROM THE DIET, WHILST NON-ESSENTIAL AMINO ACIDS CAN BE SYNTHESISED IN THE BODY.

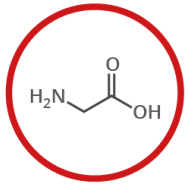
Chart Key: ALIPHATIC | AROMATIC | ACIDIC | BASIC | HYDROXYLIC | SULFUR-CONTAINING | AMIDIC | NON-ESSENTIAL | ESSENTIAL



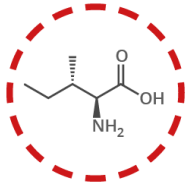
NAME (A)
three letter code
DNA codons



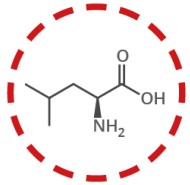
ALANINE (A)
Ala
GCT, GCC, GCA, GCG



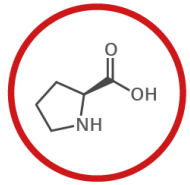
GLYCINE (G)
Gly
GGT, GGC, GGA, GGG



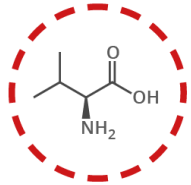
ISOLEUCINE (I)
Ile
ATT, ATC, ATA



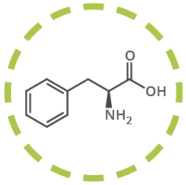
LEUCINE (L)
Leu
CTT, CTC, CTA, CTG, TTA, TTG



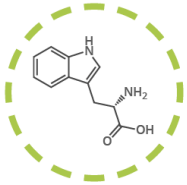
PROLINE (P)
Pro
CCT, CCC, CCA, CCG



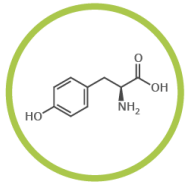
VALINE (V)
Val
GTT, GTC, GTA, GTG



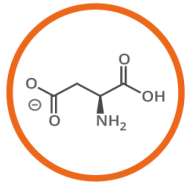
PHENYLALANINE (F)
Phe
TTT, TTC



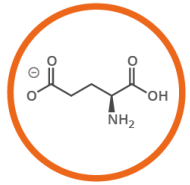
TRYPTOPHAN (W)
Trp
TGG



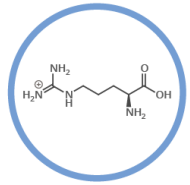
TYROSINE (Y)
Tyr
TAT, TAC



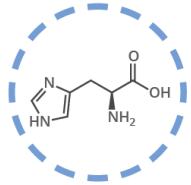
ASPARTIC ACID (D)
Asp
GAT, GAC



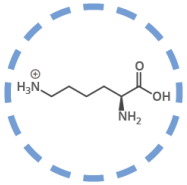
GLUTAMIC ACID (E)
Glu
GAA, GAG



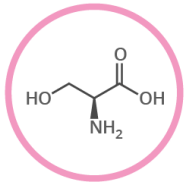
ARGININE (R)
Arg
CGT, CGC, CGA, CGG, AGA, AGG



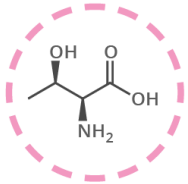
HISTIDINE (H)
His
CAT, CAC



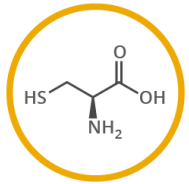
LYSINE (K)
Lys
AAA, AAG



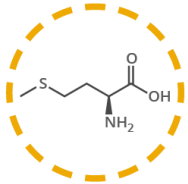
SERINE (S)
Ser
TCT, TCC, TCA, TCG, AGT, AGC



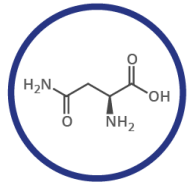
THREONINE (T)
Thr
ACT, ACC, ACA, ACG



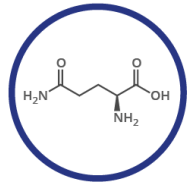
CYSTEINE (C)
Cys
TGT, TGC



METHIONINE (M)
Met
ATG



ASPARAGINE (N)
Asn
AAT, AAC



GLUTAMINE (Q)
Gln
CAA, CAG

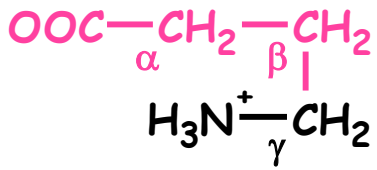
Note: This chart only shows those amino acids for which the human genetic code directly codes for. Selenocysteine is often referred to as the 21st amino acid, but is encoded in a special manner. In some cases, distinguishing between asparagine/aspartic acid and glutamine/glutamic acid is difficult. In these cases, the codes asx (B) and glx (Z) are respectively used.

Ionization states of amino acids as a function of pH:

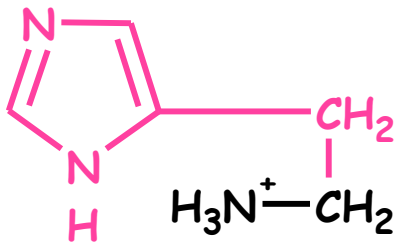
Determination of p*K*1, p*K*2 and p*I* of alanine
p*I* =(p*K*1 + p*K*2) / 2 (isoelectric point, p*I* = 6)

Isoelectric point = p*I*

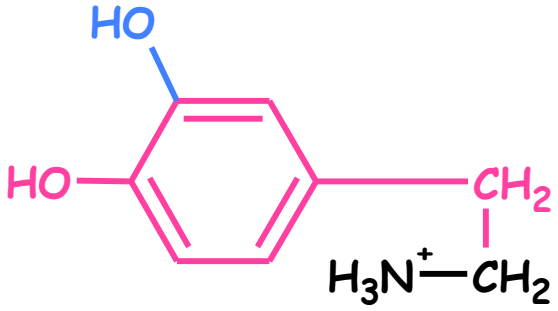
Derivatives of AMK with physiological functions



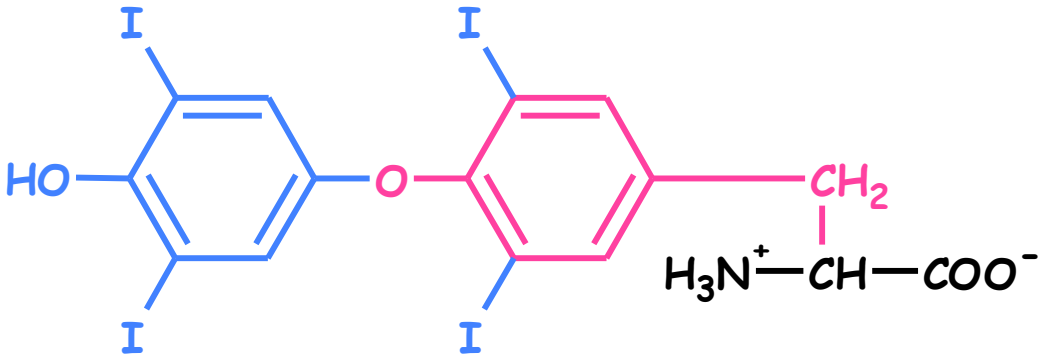
γ-Aminomáselná kyselina (GABA)



Histamin



Dopamin



Thyroxin

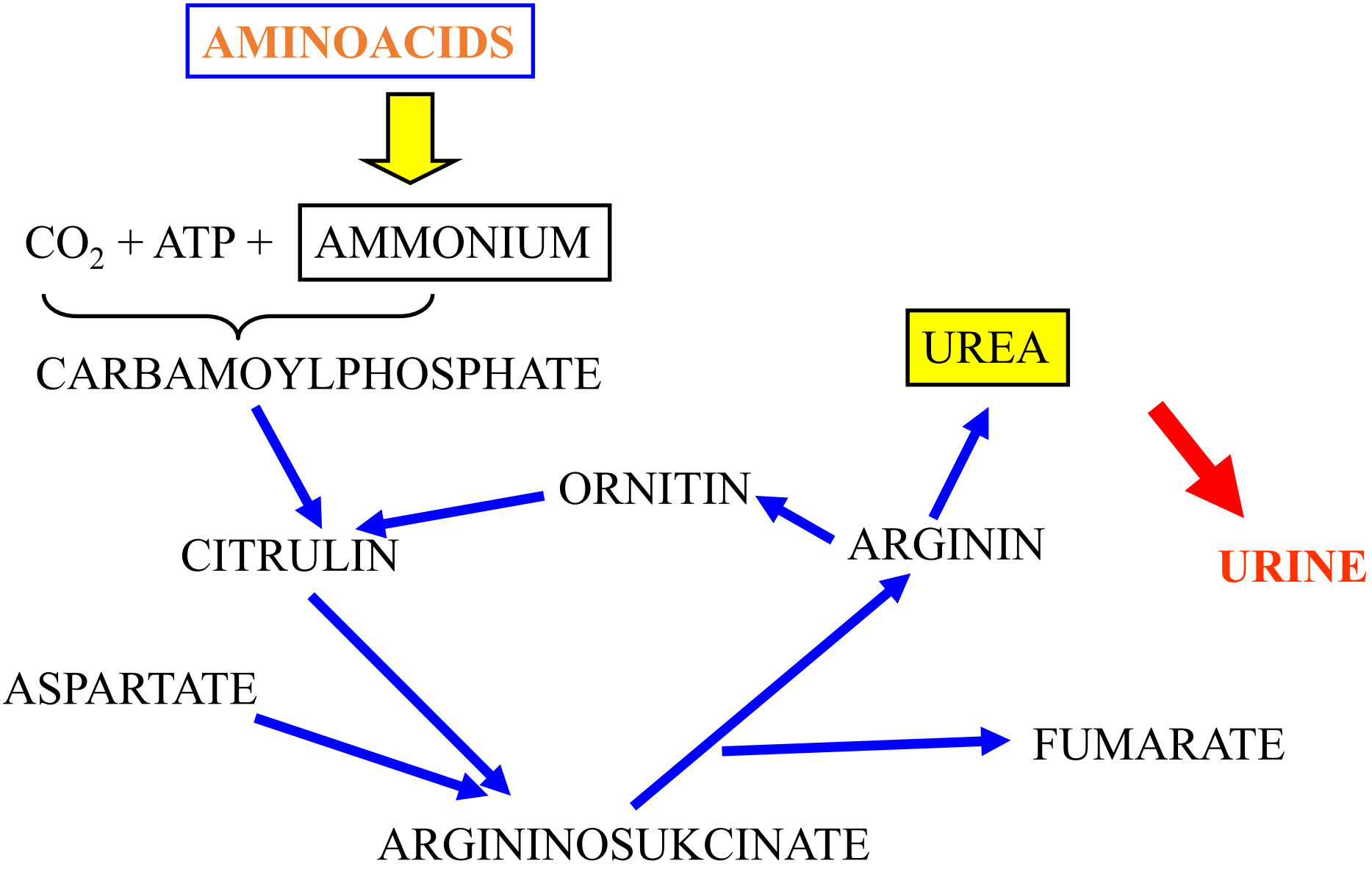
DEGRADATION OF PROTEINS

Binding to **ubiquitin** (74 AA).

Oxidation to CO_2 and H_2O after removing the amino-group (deamination).

Gluconeogenesis (except of leucin), **ketogenesis** (5AA, acetoacetate or CoA precursors), **ureagenesis** (all AA, ammonium bound to glutamin or alanine, liver, Krebs-Henseleit cycle).

Regulated speed of degradation (muscle hypertrophy, atrophy of denerved or non-stimulated muscle).


AMINOACIDS
CO_2 + ATP +
AMMONIUM
CARBAMOYLPHOSPHATE
UREA
ORNITIN
CITRULIN
ARGININ
URINE
ASPARTATE
FUMARATE
ARGININOSUKCINATE

Degradation of proteins

- **lysozomes**
  - Extracellular proteins
  - Membrane proteins
  - Proteins with long half-time
  - Process does not require **ATP**

- **cytosol**
  - Metabolic proteins
  - Proteins with short half-time
  - Process requires ATP and *ubiquitin*

METABOLISM OF PURINES AND PYRIMIDINES

Purines and pyrimidines – physiological meaning of **nucleosides** (reactants with ribose); from diet or synthesis de novo from AA in liver; RNA is in balance with AA pool, DNA is stabile.

Recirculation or catabolism, eventually excretion in urine.
Pyrimidines – CO_2 and NH_3, purines – uric acid.

URIC ACID

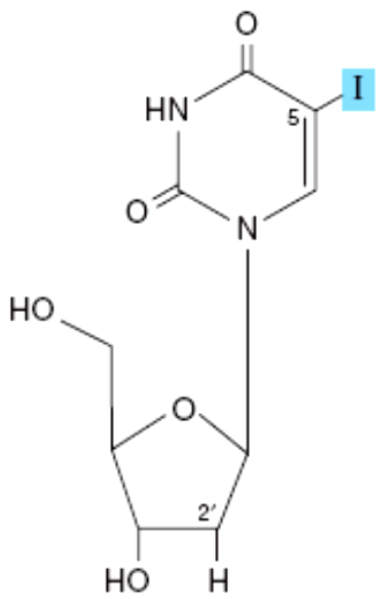
Excreted in urine.
4mg/100ml of blood plasma
Kidney: filtration, resorption (98% filtration), tubular secretion (80%)
Daily: approx. 1g excreted in urine
Disorder in uric acid metabolism – gout.
Hyperuricemia – *primary* (overproduction) or *secondary* (reduced excretion, increased intake of purines in diet, blood disorders).

Synthesis of purines/pyrimidines

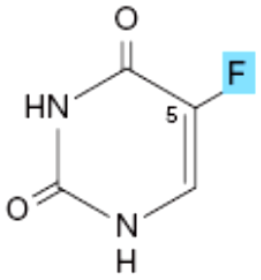
- de novo (new synthesis of purine/pyrimidine ring)
- „saving“ reactions (synthesis from nucleotides and bases)
  - ➢ is more energy saving than de novo synthesis
  - ➢ They decrease the synthesis de novo
  - ➢ substrates: a) bases (adenine, guanine, hypoxanthine)
    PRDP

    b) ribonucleosides
    ATP

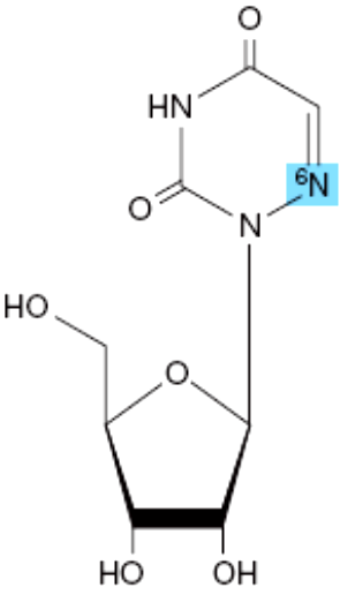
Analogs of bases and nucleotides are used as cytostatics



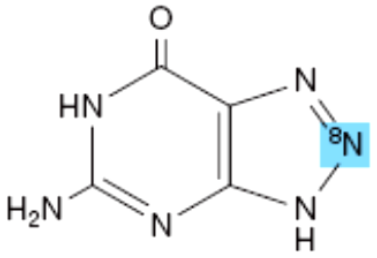
5-Iodo-2′-deoxyuridine



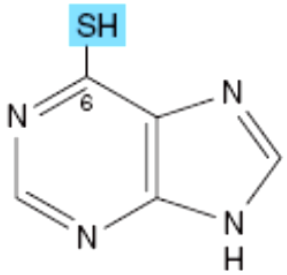
5-Fluorouracil



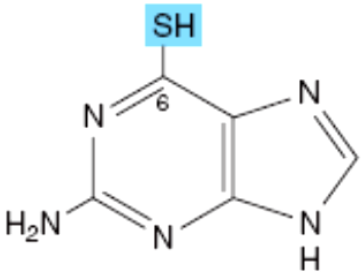
6-Azauridine



8-Azaguanine



6-Mercaptopurine



6-Thioguanine

Figure 33–12. Selected synthetic pyrimidine and purine analogs.

Harper´s Illustrated Biochemistry 26th ed./ R.K.Murray; McGraw-Hill Companies, 2003, ISBN 0-07-138901-6.

GOUT (arthritis urica)

•Primary and secondary gout

•Acute (gouty attack) and chronic (chalkstones, urolithiasis) form

•General metabolic disorder - disease of purine metabolism

•Local **cumulating** of uric acid salts (urate) in tissues, urine (joints, kidneys), primary **hyperuricemia**

•Gouty attacks – repeated attacks of arthritis, typical localisation – metatarsophalangeal joint (**podagra**; omagra, cheiragra…)

•Hurtfulness during attack – phagocytosis of urates grains

•Therapy: NSA, colchicin – inhibition of fagocytosis, allopurinol – inhibition of xantinoxidase, phenylbutazon and probenecid – inhibition of resorption

NITROGEN BALANCE

Necessity to keep AA pool. AA mixtures.

Amount of N in urine – indicator of intensity of irreversible disintegration of proteins and AA.

Nitrogen balance: amount of N in urine = amount of N in dietary proteins

- Negative nitrogen balance: loss exceeds intake (starvation, immobilisation, catabolism, **lack of E-AA!!!**…)
- Positive nitrogen balance: intake exceeds loss (anabolic drugs, growth, convalescence…)

Synthesis and degradation of body proteins: 3–4g/kg of body mass (balanced diet)

From this amount: 5% - synthesis of albumins and proteins with fast-exchange in liver

In deficient diet (energetically, amount of proteins or E-AA) – proteosynthesis deceleration, compensatory –degradation deceleration (BUT of lower extent→ loss of body proteins)

CREATIN AND CREATININ

CREATIN

Synthesis in liver (methionin, glycin, arginin).
Phosphorylation in skeletal muscle – **phosphocreatin**.

CREATININ

From phosphocreatin, in urine.
Speed of excretion is relatively constant.

CREATINURIA

Physiological – in children, in pregnancy, after pregnancy, occasionally in non-pregnant.
During muscle catabolism – in enormous amounts (starving, DM, myopathy, thyreotoxicosis…)

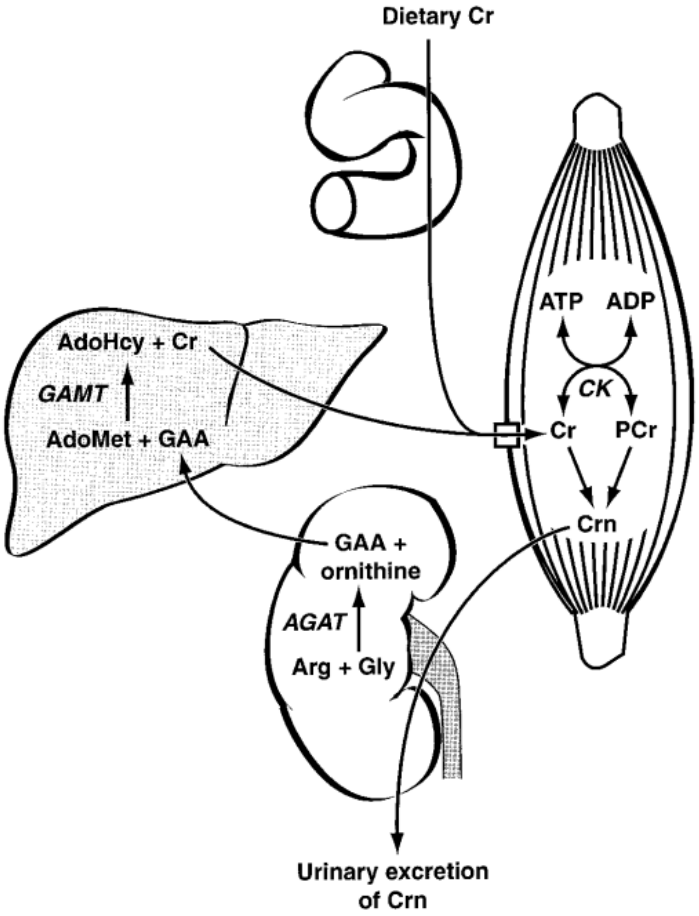
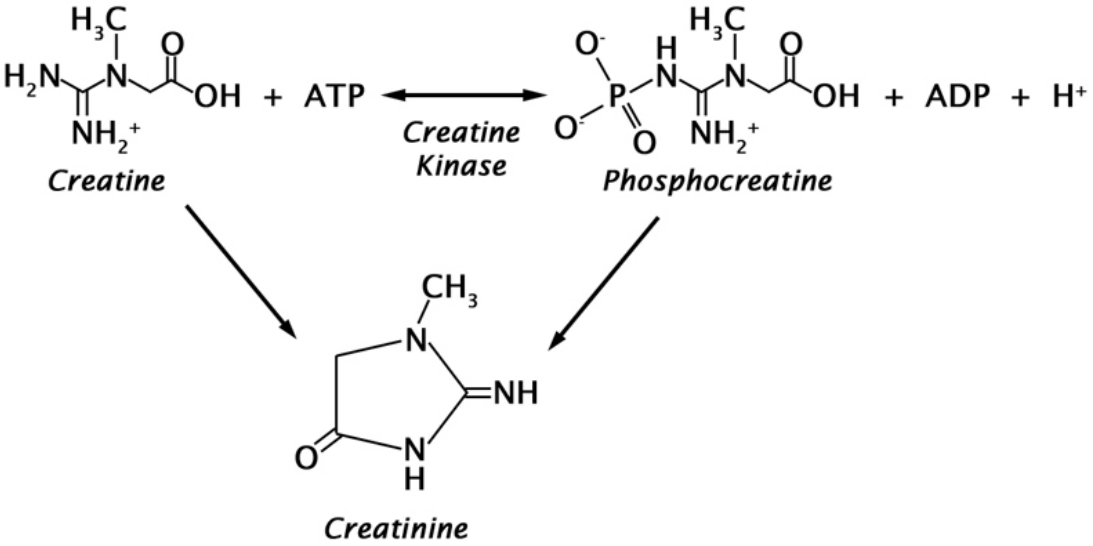


FIG. 4. Major routes of Cr metabolism in the mammalian body. The most part (up to 94%) of Cr is found in muscular tissues. Because muscle has virtually no Cr-synthesizing capacity, Cr has to be taken up from the blood against a large concentration gradient by a saturable, Na^+- and Cl^--dependent Cr transporter that spans the plasma membrane (□). The daily demand for Cr is met either by intestinal absorption of dietary Cr or by de novo Cr biosynthesis. The first step of Cr biosynthesis probably occurs mainly in the kidney, whereas the liver is likely to be the principal organ accomplishing the subsequent methylation of guanidinoacetic acid (GAA) to Cr. It must be stressed that the detailed contribution of different bodily tissues (pancreas, kidney, liver, testis) to total Cr synthesis is still rather unclear and may vary between species (see text). The muscular Cr and PCr are nonenzymatically converted at an almost steady rate (~2% of total Cr per day) to creatinine (Crn), which diffuses out of the cells and is excreted by the kidneys into the urine.



Wyss M, Kaddurah-Daouk R: Creatine and creatinine metabolism. *Physiol Rev 2000, 80(3):1107-1213.*

METABOLIC DISORDERS – PROTEINS

QUANTITATIVE CHANGES

Proteinemia = plasmatic level of proteins.
Controlled:

1. Supply with full-value proteins and their use
2. Synthesis of proteins
3. Protein catabolism and loss from organism

Ad 1) nutrition disorders, special dietary trends
Ad 2) liver disorders, endocrine diseases
Ad 3) liver and muscles release E-AA when proteins are reduced in diet

METABOLIC DISORDERS – PROTEINS

QUALITATIVE CHANGES

1. Dysproteinemia = change in representation of particular proteins (fractions shift) – nephrotic syndrome, cirrhosis, acute inflammatory reactions, chronic inflammatory reactions, tumours

2. Paraproteinemia = presence of pathological imunoglobulines (with no antibodies specificity) – monoclonal immunopathy

3. Defect proteinemia = some components of plasma proteins are missing or lowered (1/10 – 1/1000 normal values) – syndromes of immunodeficiency, symptomatic hypo- and dysgamaglobulinemia (familiar lack of IgA), polyclonal hypergamaglobulinemia

METABOLIC DISORDERS – AMINOACIDES

1. Disorders of AA metabolism during hypovitaminoses and avitaminoses – vit.C (colagen synthesis– proline hydroxylation; metabolic osteopathy, haemorrhage, poor healing), vit.B6 (tryptophan metabolism – lack of nicotinic acid)

2. Disorders of AA metabolism during liver diseases – regulation of plasmatic level of AA (transamination, oxidation, decarboxylation, deamination, ammonia, urea, kidneys); badly soluble AA (cystine, tyrosine) may form crystals in urine; liver encephalopathy, liver coma, glutamine in coeliolymph

AMYLOIDOSIS

= infiltration of organs by amyloid (complex of protein with polysaccharide)

Mechanism of disease is alteration of immune system.

Primary and secondary amyloidosis

Primary – idiopathic; infliction of heart, muscles, GIT; elderly patients; no gender differences

Secondary – complication of chronic inflammatory diseases, tumours; more frequent; infliction of kidney (most often), lien, liver, adrenal glands

	Disease	Precursor protein
Loss-of-function	**Albinism**	**tyrosinase**
	Cancer	**P53 tumor suppressor**
	Cystic Fibrosis	**CFTR**
	Haemophilia disorders	**FV, FVII, FVIII, FIX, FX, FXI, FXIII**
	Marble brain syndrome	**carbonic anhydrase II**
	Phenyl keton uria	**phenylalanine hydroxylase**
Gain-of-toxic-function	**Alzheimer's disease**	**Ab-Protein**
	Primary systemic amyloidosis	**Ig Light Chain**
	Familial amyloidotic polyneuropathy	**transthyretin**
	Type II diabetes	**islet Amyloid Poly Peptide**
	ALS	**superoxide dismutase**
	Parkinson's disease	**α-synuclein**
Infectious misfolding	**Creutzfeldt Jakob disease**	**prion protein**
	Mad cow disease	**prion protein**
	Kuru	**prion protein**