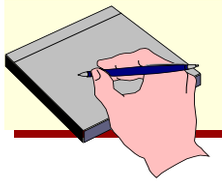
NON-NARCOTIC ANALGESICS, NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs), ANTIPYRETICS

GENERAL CHARACTERISTICS OF NON-NARCOTIC ANALGESICS & NSAIDs.

– synthetic compounds that cause mild analgesic, anti-inflammatory и antipyretic actions, without euphoria and drug-resistance

Around 20 % of population take NSAIDs on regular basis

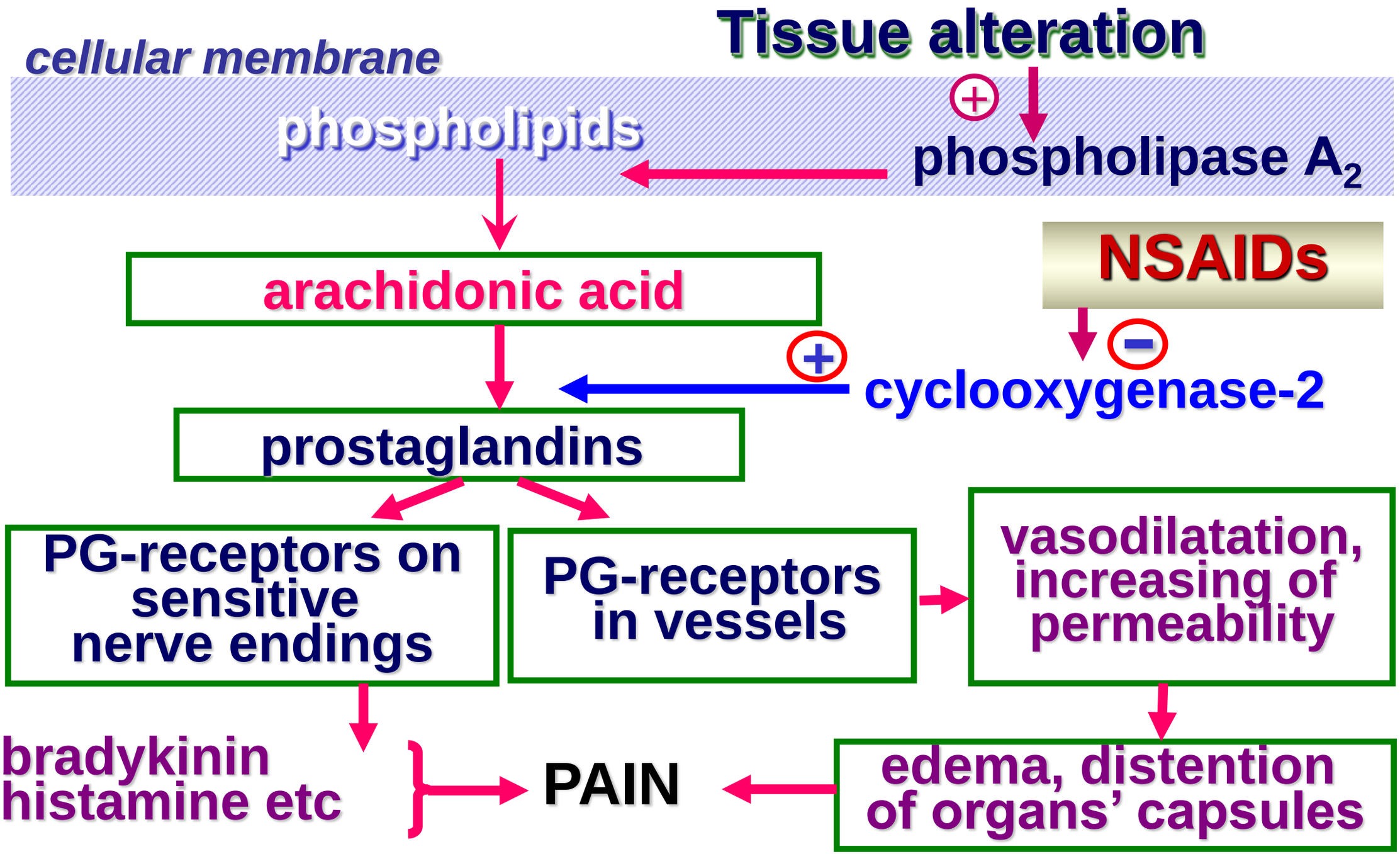
- **World sales for osteoarthritis:**
  in 2001 y. – 1,6 billions USD
  in 2008 y. – 4 billions USD



CLASSIFICATION OF NSAIDs

- *derivatives of* salicylic acid – acetylsalicylic acid (ASA), methyl salicylate
- *derivatives of* pyrazolone – analgin (metamizol) butadion (phenylbutazone)
- *derivatives of* anilyn - paracetamol (acetaminophen)
- *derivatives of* propionic and antranilic acids – brufen, diclofenac-sodium (voltaren), ketoprofen, mefenamic acid etc
- *derivatives of* acetic acid – indomethacin, etodolac
- *derivatives of* oxicams – piroxicam, meloxicam etc.
- *derivatives of* different groups – ketorolac (ketanov), nimesulide, celecoxib etc.
- combined *agents* – ambene, baralgin, tempalgin, coldrex, pentalgin, solpadein etc

MECHANISM OF ANALGESIC ACTION OF NSAIDs



COMPARISON OF ANALGESIC ACTIVITY OF NSAIDs

ketorolac > piroxicam > diclofenac sodium > naproxen > indomethacin > butadion > mefenamic acid > analgin > brufen > paracetamol > acetylsalicylic acid

COMPARATIVE CHARACTERISTICS OF ANALGESICS

effect	analgesic	
	Narcotic	Non-narcotic
Analgesic	pain of any origin	pain caused by inflammation
Anti-inflammatory	-	+
Anti-fever	-	+
Hypnotic	+	-
Euphoria	+	-
Dependence	+	-
Tolerance	+	-
Breathing depression	+	-

MECHANISMS OF ANTI-INFLAMMATORY EFFECTS OF NSAIDs

- **Inhibition of prostaglandins synthesis** (inhibition of cyclooxygenase)
- **Inhibition of adhesion** (inhibition of cells migration in site of inflammation)
- **Lysosome ⇒ ↓ hydrolytic enzymes release** (proteases, lipases, phosphatases)
- **Anti-alterative action** (↑ collagen stability and its maturation)
- **Antagonism with mediators of inflammation** (↓ histamine, serotonin, bradykinin synthesis)
- **Decreasing of energy supply of inflammation** (inhibition of ATP synthesis, disintegration of phosphorylation, ATP-ase inhibition)
- **Immunotropic action** (↓ specific reaction on antigen, T-lymphocytes proliferation, interleukin synthesis)

ANTIPYRETIC ACTION OF NSAIDs

development of fever → increasing of PGE_2 synthesis in hypothalamus → deposition of cAMP → alteration of Na^+ and Ca^{2+} ratio → ↑ function of heat center → ↑ thermoproduction → raising of body temperature

NSAIDs → decreasing of PGE_2 synthesis → restoring of thermoregulatory center function → increasing of heat release vasodilatation of skin vessels and increasing of sweating

PHARMACOLOGICAL EFFECTS OF MODERN NSAIDS

NSADs	Anti-inflammatory	Analgesic	Antipyretic	Hondro-protective
Meloxicam	■	■	■	■
Nimesulide	■	■	■	■
Celecoxib	■	■	■	■
Ibuprofen	■	■	■	■
Diclofenac	■	■	■	■
ASA /aspirin/	■	■	■	■

STRATEGY OF ANTIPYRETICS USES

- must not be used for «course» administration
- for children with body temperature more than 38,0-38,5 ^{0}C
- should be considered drug's safety, available childhood forms etc

RULES OF NSAIDs PRESCRIPTION

- ✓ **Personal agent's choice:** analgesic effect (first hours) followed by anti-inflammatory (after 10-14 days of regular usage)
- ✓ **Dosing** (up- and down- methods)
- ✓ **Time of ingestion:**
  - after meal; for achievement of rapid analgesic or antipyretic effect should be given 30 min before meal or 2 hrs after meal with 1/2-1 glass of water; after ingestion it is recommended not to lie for esophagitis prevention
  - according to time of maximal disturbances: at morning stiffness it is wise to take a quickly absorbed drug in the morning (naproxen, diclofenac-sodium, aspirin-upsa, ketoprofen) or prescribing of long-acting agents at bedtime

THERAPEUTIC USES OF NSAIDs

- after-operation pain of intermediate intensity
- headache, toothache
- spasms of bile-, urinary ducts (in combination with spasmolytics)
- connective tissue diseases (rheumatoid arthritis, osteoarthritis, back pain, myocarditis, glomerulonephritis etc.), gout (indomethacin, naproxen etc)
- traumas, inflammations (injures, joint dislocation, miositis, neuralgia etc)
- fever during infectional diseases
- Prevention and treatment of thrombosis – ASA (325 mg once in 3 days)

SALICYLATES DOSING

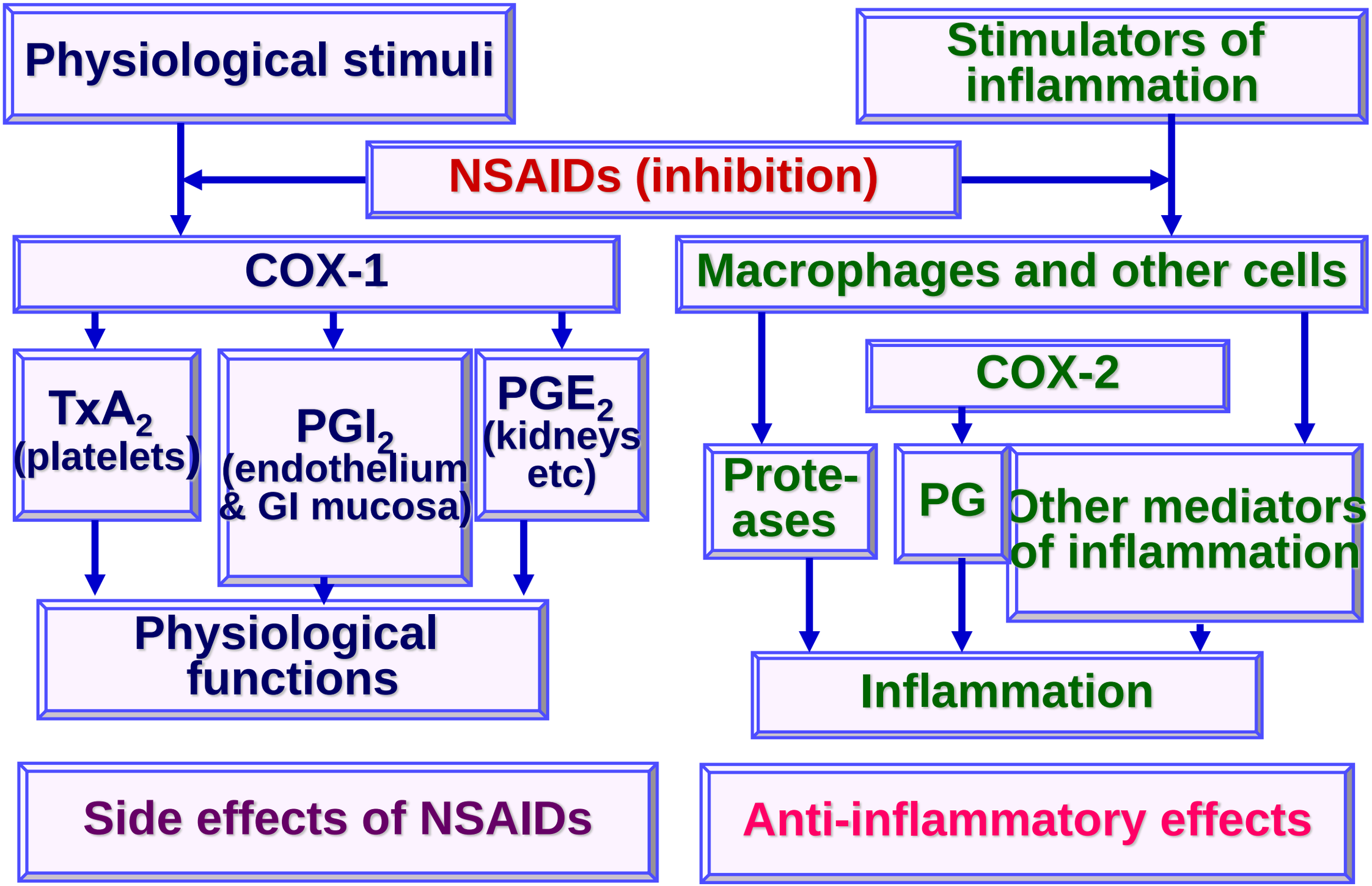
mg/dl blood

	effects	complications
160	intoxication	renal and respiratory failure
	lethal	
	heavy	collapse, coma
	moderate	fever, acidosis, dehydration
80	*mild*	central hyperventilation
		ringing in ears
50	anti-inflammatory (upto 4 g/day)	
20	uricosuric	
10	analgesic	ulcerogenic, hypersensitivity, hemostasis disturbance
	antipyretic	
0	anti-aggregative	

CLASSIFICATION OF NSAIDs ACCORDING TO SELECTIVITY OF CYCLOOXYGENASE INH. (COX-1 & COX-2)

- **inhibitors of COX-1 & COX-2 –** ***majority of modern NSAIDs***
- **selective inhibitors of COX-1 –** ***acetylsalicylic acid*** **(in small doses)**
- **selective inhibitors of COX-2 –** ***nimesulide, meloxicam***
- **highly-active COX-2 inhibitors –** ***celecoxib***

ACTION OF NSAIDs ON COX-1 & COX-2



PHARMACOKINETICS OF NSAIDs

Absorption: **majority – weak acids ⇒ absorption in stomach; if ↑ pH upto 3,5 ↓ ulcerogenic effect but effectiveness as well;**

Administration: **oral, rectal, I.M., I.V., transdermal; possible first-pass effect!**

Plasma protein binding: **50-99 %, ASA replace T_3, T_4, uric acid, phenytoin, oral anticoagulants**

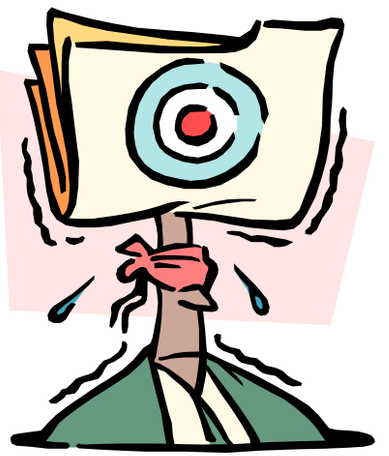
Distribution: **well-penetrate, including BBB (especially at acidosis) !**

Biotransformation: **significant amount of ASA conjugate with glucuronic acid, glycin, undergo oxidation to non-active metabolites; certain are excreted unchanged (ketorolac)**

Excretion: **mainly, via kidneys, urine alkalinization ↑ excretion. T ½ ASA in daily dose 0,6 g – 4-5 hrs, in dose 4 g – upto 15 hrs!**

ULCEROGENIC ACTION OF NSAIDs

- dyspepsia – 30-40 %
- gastric and duodenal erosion or ulcer – 10-20 %
- bleeding and perforation – 2-5 %



Ulcerogenic risk:

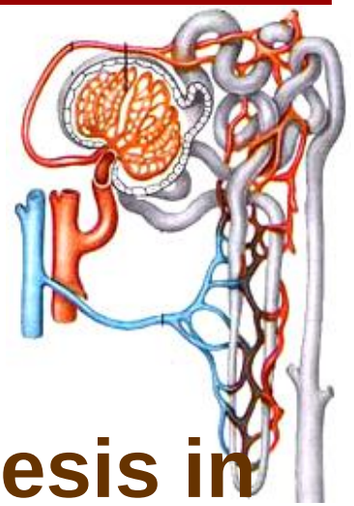
ketoprofen > piroxicam > indomethacin > naproxen > aspirin > diclofenac > analgin > ibuprofen

ULCEROGENIC EFFECTS OF NSAIDs

improvement of drugs' tolerance:

- ✓ **Simultaneous administration of drugs that protect GI mucosa: NSAID + misoprostol, proton pump inhibitors, H_2-antagonists (?), cytoprotectors (sucralfate)**
- ✓ **Changes in treatment strategy: dosage decreasing; shift for parenteral (?), rectal (?) or local application; usage of intestinal-dissolved drugs; usage of pro-drugs (sulindac)**
- ✓ **Usage of selective COX-2 inhibitors (meloxicam, nimesulide, celecoxib)**

NSAIDs NEPHROTOXICITY



(5-10 %):

- **Renal failure:**
  - blockage of PG-E_2 and prostacyclin synthesis in kidneys ⇒ vasoconstriction and ↓ renal bloodflow ⇒ ↓ GFR and diuresis
  - ⇒ disturbance of water-salt balance: water, sodium retention, hypercreatinemia, edema, ↑ ABP (indomethacin, butadion, COX-2 inhibitors)
- **Direct action on renal parenchyma:**
  - acute papillary necrosis (ibuprofen)
  - acute interstitial nephritis – «analgesics nephropathy» (butadion, indomethacin, analgin, ibuprofen, paracetamol)

NSAIDs HEPATOXICITY

Agents	Type of injury	Mechanism of injury	Relative frequency	Morta-lity
Aspirin	hepato-cellular	toxic	dose-dependent	Yes
Butadion	-»-, cholestasis	-»-, hyper-sensitivity	3	Yes
Indome-thacin	hepato-cellular	unknown	2	Yes
Ibuprofen	-»-	-»-	1	Yes
Ketoprofen	enzymes turnover	-»-	1	No
Piroxicam	hepato-cellular	hyper-sensitivity	1	Yes
Diclofenac	-»-	unknown	3	Yes

Paracetamol – direct toxin (at daily dose > 6 g)

Selective COX-2 inhibitors are also hepatotoxic

Dyscrasia caused by NSAIDs

- anemias (hypochromic anemia, hemolytic anemia etc) – pyrazolons, indomethacin, ASA
- thrombocytopenia (cytotoxic reaction of allergic origin)
- leucopenia upto agranulocytosis – pyrazolons
- coagulopathy with bleeding: ↓ platelets aggregation (антиагрегантное) and prothrombin synthesis in liver (mild anticoagulant) – ASA, indomethacin
- methemoglobinemia – paracetamol
- acute intravascular hemolysis with following renal failure (deficiency of glucose-6-phosphate dehydrogenase) – ASA

OTHER ADVERSE EFFECTS OF NSAIDs

- **CNS:** headache, dizziness, fatigue, insomnia, mental confusion (ASA, ketorolac, indomethacin etc – 1- 10 %
- allergic reactions (12-15 %):
  - angioedema, allergic interstitial nephritis, Steven-Johnson, anaphylaxia (especially pyrazolon derivatives)
  - «aspirin asthma», rhinitis, conjuctivitis – ASA
  - allopecia – brufen
  - frequency of appearance: diclofenac > piroxicam > brufen > indomethacin > κetoprofen

OTHER ADVERSE EFFECTS OF NSAIDs

- **cardiovascular toxicity:** ↑ BP, heart beat – celecoxib, myocardiodystrophy – butadion
- **cartilage tissue degeneration**
- **teratogenic** (ASA – palatine dissection in fetus (8-14 per 100 observations); **fetotoxicity** (indomethacin – preterm closing of ductus arteriosum); **prolongation of pregnancy and delivery** (indomethacin etc)
- **mutagenic effect** (↑ chromosomal abberation in lymphocytes – ASA, butadion)
- **Rey's syndrome in children** (heave hepatic encephalopathy with mortality ↑ 50%)

COMPARATIVE TOXICITY OF NSAIDs

agent	*adverse effects*			
	GIT	Liver	Kidneys	Blood
Butadion	++	+++	+++	+++
Indomethacin	+++	+++	+++	+++
Sulindac	+	+	-	-
Diclofenac	+	+	-	+
Ibubrofen	+	-	+	+
ASA	+++	+++	-	+
Ketoprofen	+	-	+	+
Piroxicam	+	-	+	+
Meloxicam	-	-	-	-
Paracetamol	-	+++	+++	+
Ketorolac	++	++	++	-

RISK FACTORS FOR ADVERSE EFFECTS

significant:

- aged patients (over 65 years)
- history of GI-disturbances
- co-existing disease (hypertension, CHF,renal or liver failure)
- long-time (over 3 months) prescribing of NSAIDs
- simultaneous uses of anticoagulants, glucocorticoids, immunosuppressants, ACEI, diuretics

putative:

- Helicobacter pylori infection (?)
- female sex
- smoking, alcohol misuse

EVALUATION OF RISK/ BENEFIT AT NSAIDs ADMINISTRATION

- ⇒ to be defined in every cause personally with the choice of a drug with optimal effectiveness and duration of action (in pain syndrome – long-acting, for long-term treatment – short acting)
- ⇒ to take into account risk of GIT complications
- ⇒ it is necessary to reveal other risk factors and putative drugs interaction
- ⇒ being choosing an analgesic drug let us consider alternative agents
- ⇒ obligatory to inform a patient about adverse effects while prescribing NSAIDs

NARCOTIC ANALGESICS

ИСТОРИЯ

in V century B.C. first notice about poppy

in III century B.C. PARACELS described opium action

in 1803 year V. SERTURNER obtained in crystalloid form кристаллическом виде the main opium alkaloid - morphine

in 1915 year Was synthesized nalorphine, in 1942 year was established its antagonism with morphine

NARCOTIC ANALGESICS

Agents that are able at resorptive action пто suppress pain impulses transmission, aat repetitive uses able to produce physical dependence (drug-abuse)

Sources:

opium *(from Greece. opos - juice)* – dry poppy juice (Papaver somniferum)

Opium alkaloids:

- **fenantrane derivatives:** ***morphine, codeine, tebaine***
- **isoquinolone derivative:** ***papaverine, narcotin***

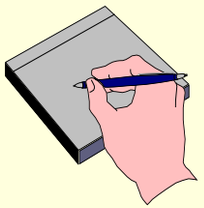
ALAKALOIDS

Alkaline-like plant-origin compounds that contain nitrous

- **solid, colorless, bitter, optically active**
- **alkalines are bases that are badly dissolved in water, well – in organic solvents**
- **salts of alkaloids – visa versa**

Inactivation reactions

- **Tanin, iodides →**
- **Potassium permanganate → universal oxidizer**

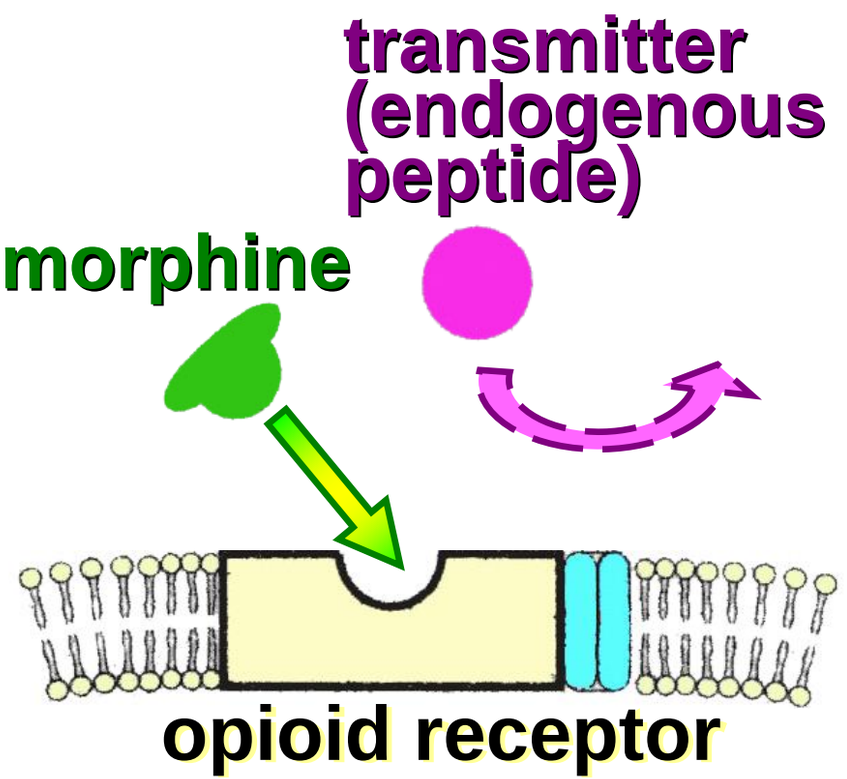


CLASSIFICATION OF NARCOTIC ANALGESICS ACCORDING TO CHEMICAL STRUCTURE

- derivatives of fenantren:
  - opium alkaloids – *morphine, codeine, omnopon*
  - synthetic analogues – *ethylmorphine, buprenorpine, nalbuphine, nalorphine, naloxone, naltrexone*
- derivatives of benzomophans – *pentazocine*
- derivatives of piperidine – *promedol (trimeperidine), fentanyl, loperamide*
- derivatives of heptanone – *methadone*
- different chemical groups – *tramadol etc*

CLASSIFICATION ACCORDING TO AFFINITY TO OPIOID RECEPTORS

- **Agonists:**
  - **Strong (full) –** ***morphine, promedol, fentanyl, methadone***
  - **Moderate –** ***codeine, omnopone***
- **Agonists-antagonists:** ***buprenorphine, nalorphine, pentazocine, tramadol***
- **Antagonists:** ***naloxone, naltrexone***



FUNCTION OF OPIOID RECEPTORS

Opioid receptors (μ, κ, δ, ε, σ) – *lipoprotein sites with high affinity to endogenous peptides (enkephalines, endomorphines) and narcotic analgesics in neuronal membranes that transmit pain impulses*

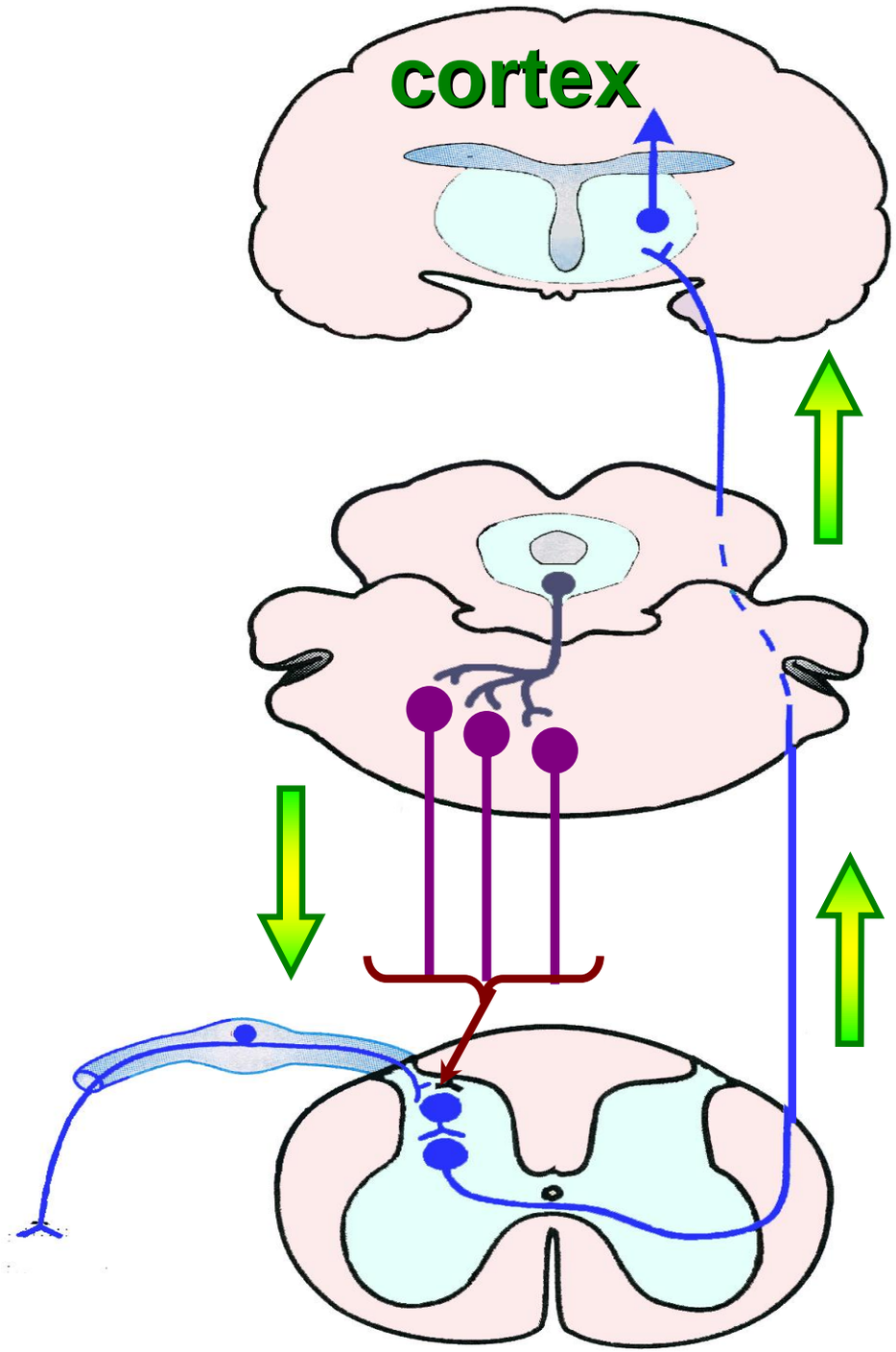
properties	*μ (mu)*	*κ (kapa)*	*δ (delta)*
Activation	analgesia, dependence, euphoria, vegetative reactions	analgesia, sedation, miosis	emotion, seizures, vegetative reactions
Activators: • endogenous peptides • narcotic analgesics	β-endorphines мет-enkephalines morphine, fentanyl, promedol etc	dinorphine neoendorphine pentazocine, buprenorphine etc	leu-enkephaline -

SITES OF MORPHINE'S ACTION

III level

II level

I level



intermediate brain (thalamus)

middle brain (central grey matter)

medulla oblongata (raphes nuclei)

posterior horns of spinal cord

alteration

ANALGESIC ACTION OF NARCOTIC ANALGESICS

- insignificant increasing of pain threshold
- inhibition of pain transmission in spinal cord
- presence of пanti-anxety and euphoric effects, supression of pain expectation etc
- mainly effective during chronic visceral pain

STAGES OF MORPHINE ACTION

I

II

III

sleep

euphoria

withdrawal

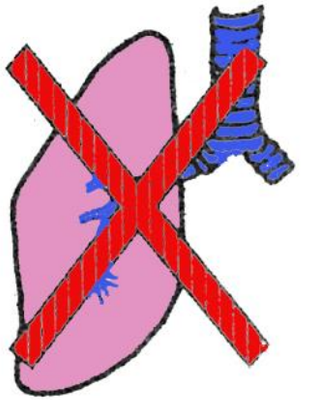
analgesia

during first use

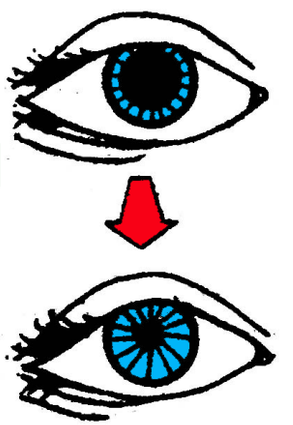
during prolong misuse

MORPHINE PHARMACODYNAMIC

CNS:



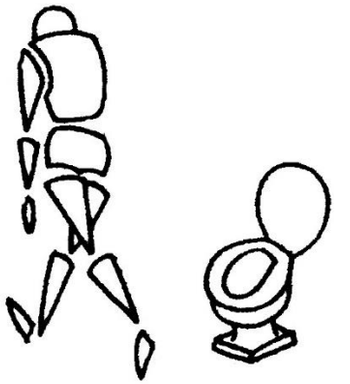
- ***Brain cortex:*** **euphoria ("rash"), sedation, shallow sleep**
- ***Medulla oblongata:***
  - **respiratory center – ↓ (decreasing of frequency and amplitude of breathing excursion, decreasing of CO_2 sensitivity)**
  - **cough center – ↓**
  - **heat center – ↓ (hypothermia)**
  - **n. vagus center – ↑ (bradycardia, bronchospasm etc)**
  - **vomiting center – ↑ or ↓**



- ***Middle brain:*** **↑ center of III cranial nerve pair (miosis)**
- ***Spinal cord:*** **↑ spinal tendon reflexes**

MORPHINE PHARMACODYNAMIC

- **CVS:** insignificant dropping of BP, bradycardia, increasing of intracranial pressure
- **breathing:** bronchospasm
- **GIT:** ↑ tonus, spasm of gastric, intestinal, Oddi's sphincters, but ↓ peristaltic ⇒ prolong evacuation of meal from stomach (8-12 hrs), constipation and spasmogenic effects (colics)
- **urinary bladder:** ↓ urination (sphincters' spasm, ↑ secretion of ADH), but ↑ tonus ⇒ colic; **uterus:** ↓ tonus



PHARMACOKINETICS OF NARCOTIC ANALGESICS

Administration: **the majority are well-absorbed from oral, nasal, GI mucosa**

Bioavailability: **undergo first-pass effect ⇒ S.C., I.M., I.V., transdermal (fentanyl), oral (codeine);**

Plasma-protein binding: **20-96 %**

Distribution: **cinitially well penetrate into CNS, lungs, liver, kidneys, spleen; later – into skeletal muscles (reservoir), fat tissues**

Biotransformation: **significant part metabolized in polar non-active compounds, esters (heroin), hydrolyzed to morphine; part conjugated with glucuronic acid (morphine etc).**

Excretion: **via kidneys, partially with bile**

T ½ of morphine – 4-6 hrs!

COMPARATIVE CHARACTERISTICS OF NARCOTIC ANALGESICS

indicators	morphine	promedol	fenta-nyl	penta-zocine	trama-dol
dose (mg)	10	20-40	0,1	30	50-100
duration of action (hrs)	4-5	3-4	0,5	2-3	3-5
euphoria	+++	++	+	+	+
respiratory depression	+++	++	++++	+	+
hemodynamic	↓ HR	Unchanged	↓ BP, ↓ HR	↑ BP, ↑ HR	↓ BP, ↑ HR
spasmodic effect	+++	++	+++	+	+
nausea, vomiting %	35-40	2-35	Rarely	2-6	5
withdrawal	+++	+++	++	++	+

THERAPEUTIC USES OF NARCOTIC ANALGESICS

- **Serious traumas and burns** (morphine, promedol, fentanyl etc.)
- **Myocardial infarction** (fentanyl etc.)
- **Pulmonary edema** (morphine, promedol)
- **Renal and liver colics, acute pancreatitis** (pentazocine, promedol, fentanyl, omnopone etc)
- **Uncurable cancer** (morphine, promedol etc)
- **Preanesthetic medication & postoperative period** (pentazocine, morphine, promedol, fentanyl)
- **Neuroleptanalgesia, ataralgesia** (fentanyl)
- **Spinal analgesia** (morphine)
- **Pain relieve during delivery** (pentazocine, promedol)

ADVERSE EFFECTS OF NARCOTIC ANALGESICS

- **restlessness, tremor, hyperactivity (if dysphoria)**
- **respiratory depression**
- **nausea,vomiting, constipation, urine retention**
- **postural hypotension (if hypovolemia),**
  ↑ intracranial pressure,
- **Itching, angioedema (after parenteral administration)**
- **tolerance, including cross-resistance: begins after 1st dose; more quickly develop for analgesic, euphoric, respiratory depression, later - to hypotensive, vomiting, antidiuretic effects; but not to myorelaxant, constipative, convulsive**
- **psychical and physical dependence – drug-abuse**

ABUSE – CHRONIC POISONING

- **psychical dependence:** euphoria, emotional indifference lead to abuse;
- **physical dependence:** accompanied with tolerance; the main goal – to avoid withdrawal syndrome
- **withdrawal syndrome:**
  1. acute phase (7-10 days):
     - ✓ after 8-10 hrs – lacrimation, yawning, rhinorhea, sweating
     - ✓ after 36-48 ч – insomnia, tiredness, rigor, «goose» skin, nausea, vomiting, myalgia, uncontrolled movements, dyspnea, fever, hypertension, diarrhea
  2. protracted phase (26-30 weeks) – hypotension, bradycardia, hypothermia, mydriasis, ↓ respiration
- **during disease progression:** alteration of psychical activivty (irritability, flaccidity, decreasing of self-estimation), loss of appetite, of skin sensitivity, sweating and other vegetative disturbances

CONTRAINDICATION FOR NARCOTIC ANALGESICS

- For children under 1 year (morphine – after 3 years)
- Pregnancy, lactation
- Brain traumas, stroke
- Respiratory depression
- Cahexia
- “Acute abdomen” (before diagnosis will be established)
- Chronic pain syndrome, except cancer

ACUTE POISONING BY NARCOTIC ANALGESICS

- mental confucion, coma
- miosis, followed by mydriasis
- hyphothermia
- hypotension
- breathing is rare (2-4 per min), that can turn to Chein-Stoke
- urine retention
- preserving of spinal tendal reflexes (unlike barbiturates !)
- acidosis

Opium-user, 1872
V.Vereschagin

Tre reason of death – respiratory cencer depresssion !

FIRST AID AT POISONING BY NARCOTIC ANALGESICS

- **Breathing restoration (mechanical ventilation)**
- **Antidote therapy**
  - **Physiological antagonists:**
    - ✓ **competitive – naloxone (0,001-0,004 I.V.)**
    - ✓ **non-competitive – atropine**
  - **Physical – adsorbents**
  - **Chemical – potassium permanganate**
  - **Stomach lavage**
  - **Speeding up of drugs' excretion (hydration & dehydration therapy)**
  - **Hemosorbtion**
- **Symptomatic therapy:**
  - **Myotroic anti-spasmodic**
  - **Alkaline solution**
  - **cardiotonic**
  - **Catheterization of urinary bladder**