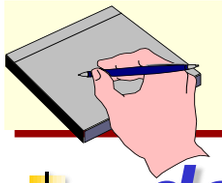
ODESSA NATIONAL MEDICAL UNIVERSITY
DEPARTMENT OF PHARMACOLOGY AND PHARMACOGNOSY

NON-NARCOTIC AND NARCOTIC ANALGESICS

COMPARATIVE CHARACTERISTICS OF ANALGESICS

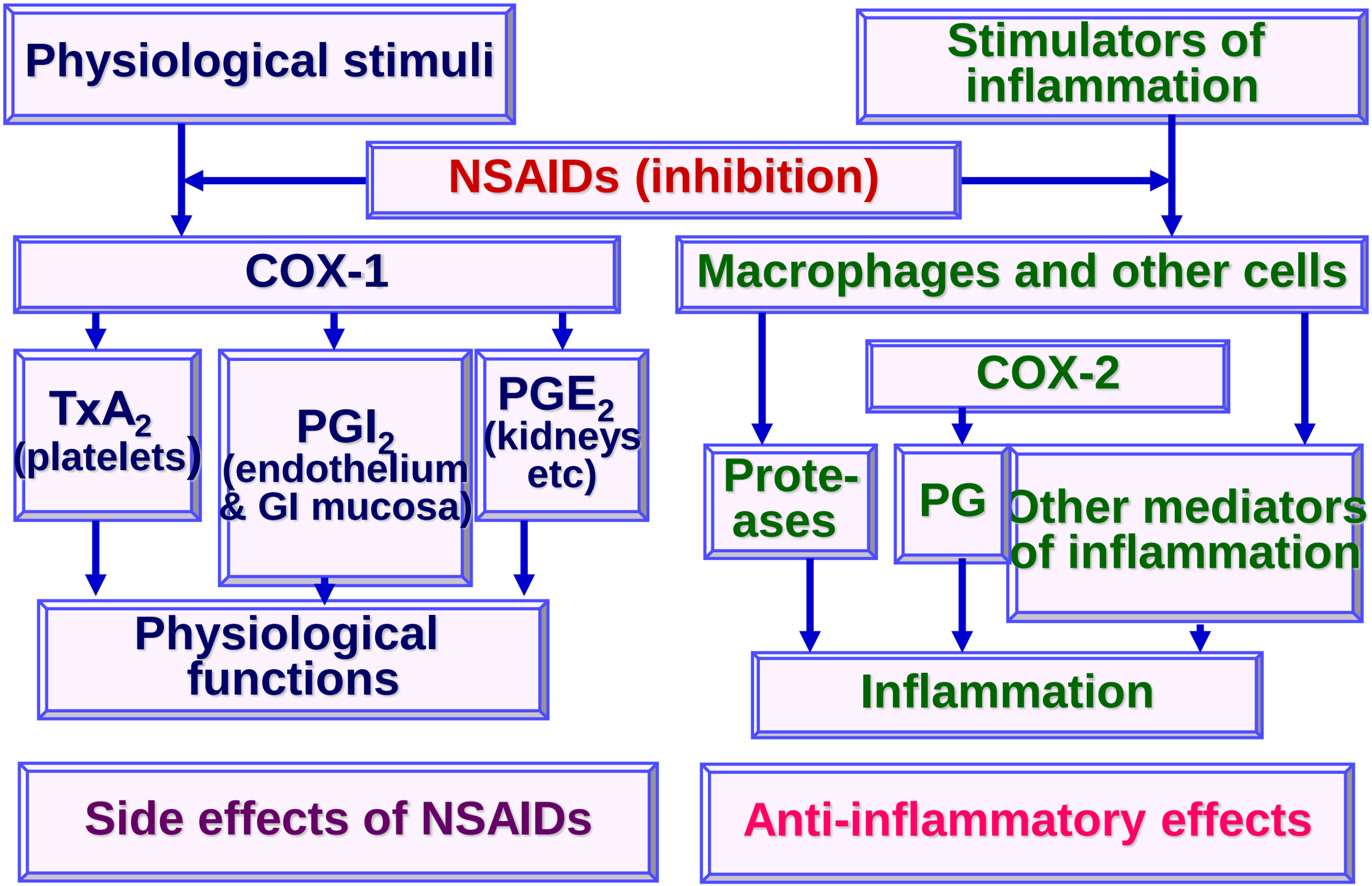
effect	analgesic	
	Narcotic	Non-narcotic
Analgesic	pain of any origin	pain caused by inflammation
Anti-inflammatory	-	+
Anti-fever	-	+
Hypnotic	+	-
Euphoria	+	-
Dependence	+	-
Tolerance	+	-
Breathing depression	+	-



CLASSIFICATION OF NSAIDs

- *derivatives of* salicylic acid – acetylsalicylic acid (ASA, aspirin), methylsalicylate
- *derivatives of* pyrazolon – analgin (metamizole), butadion (phenylbutazone)
- *derivatives of* anylin - paracetamol (acetaminophen)
- *derivatives of* phenylpropionic, phenylacetic and antranyl acids – ibuprofen, diclofenac-sodium, ketoprofen, mefenamic acid и др.
- *derivatives of* indolacetic acid – indomethacin, etodolac
- *derivatives of* oxicams – pyroxicam, meloxicam
- *derivatives of* different groups – ketorolac, nimesulid, celecoxib etc.
- Combined *agents* – baralgin, tempalgin, pentalgin, solpadein etc.

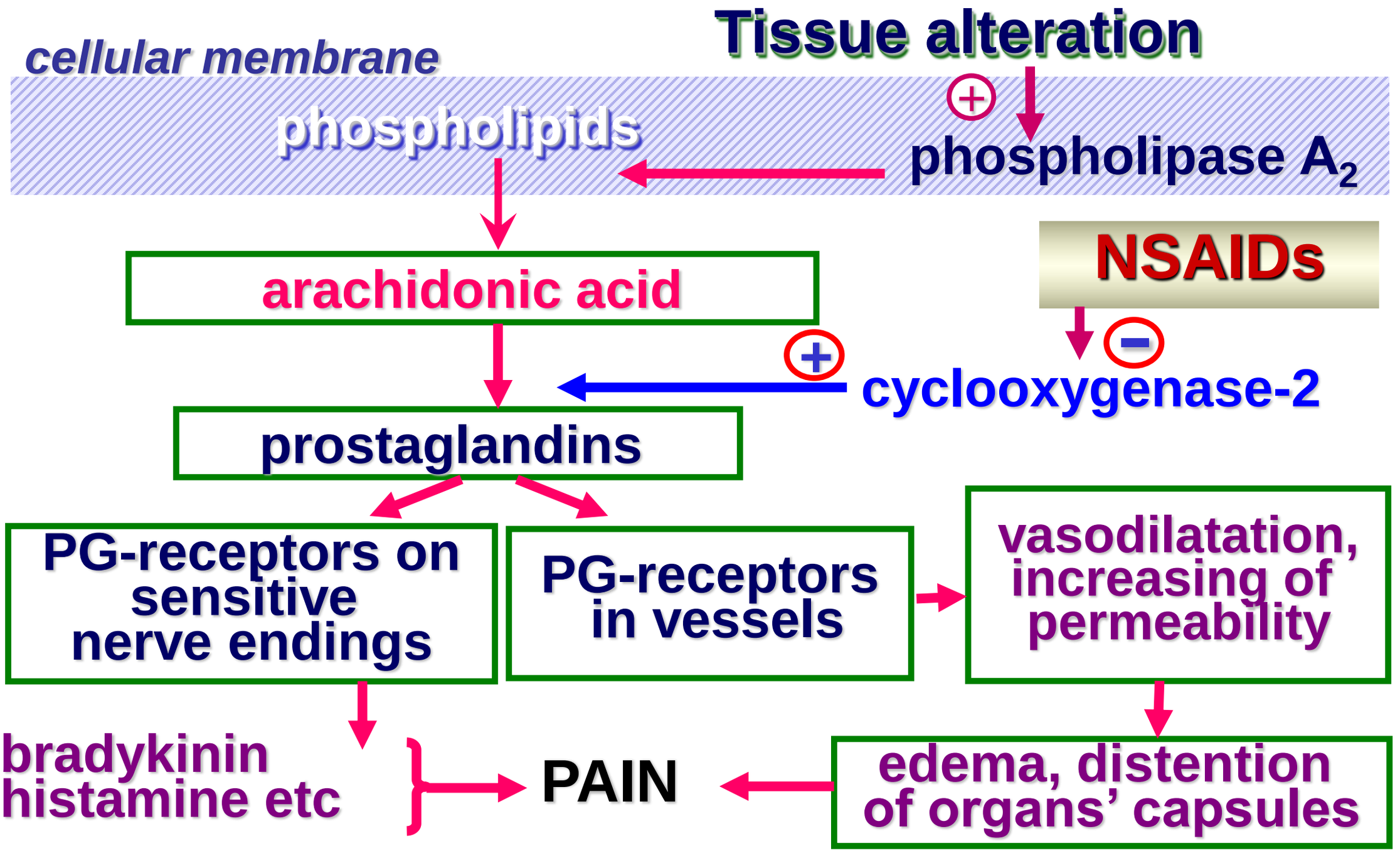
ACTION OF NSAIDs ON COX-1 & COX-2



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*

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

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/	■	■	■	■

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)

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**

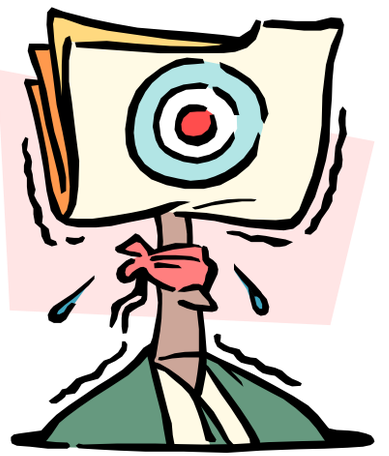
Distribution: **well-penetrate, including BBB (especially at acidosis) !**

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:

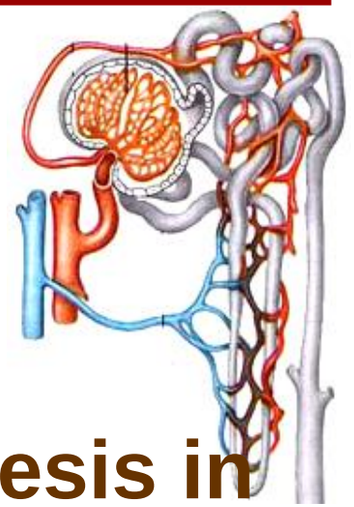
ketoprofen > piroxicam > indomethacin > naproxen > aspirin > diclofenac > analgin > ibuprofen

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 cause 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 > ketoprofen

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%)**

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NARCOTIC ANALGESICS

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***

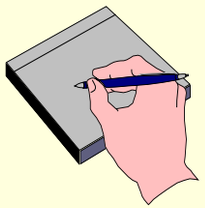
ALAKALOIDS

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*

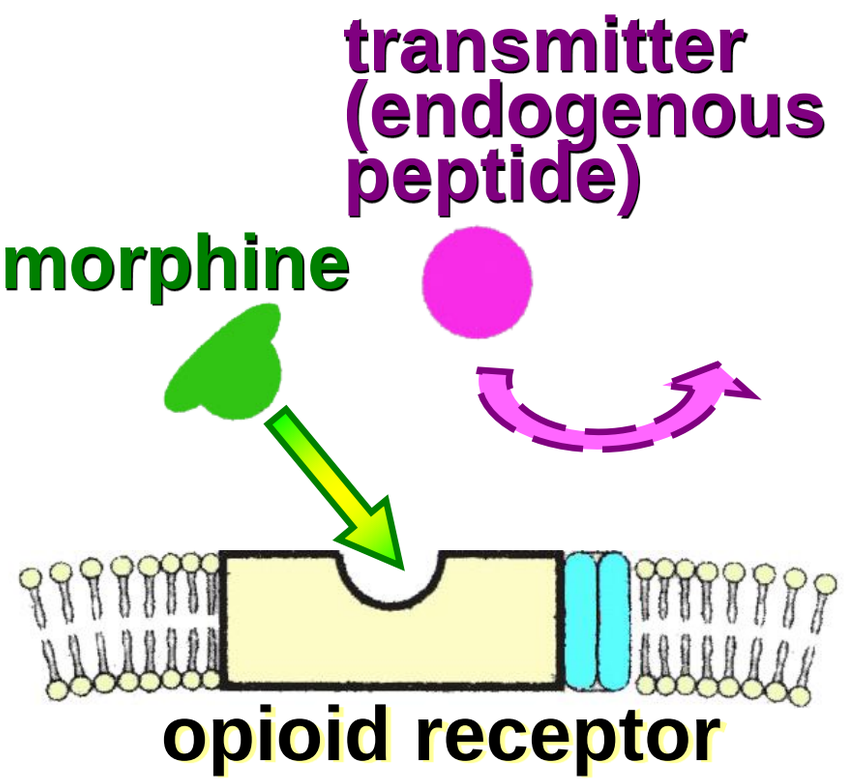
FUNCTION OF OPIOID RECEPTORS

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 -

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***

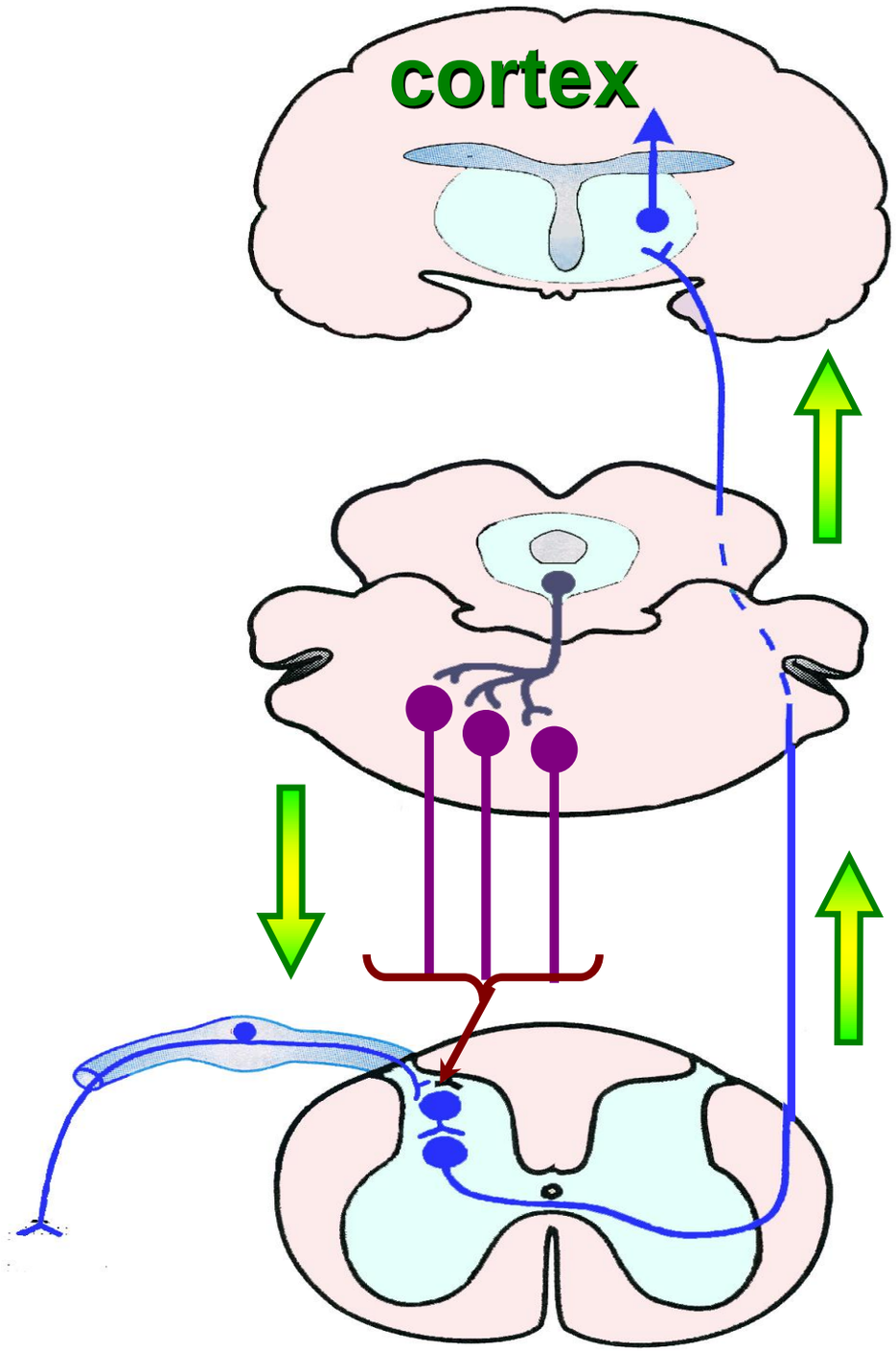


SITES OF MORPHINE'S ACTION

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 висцеральных болях

STAGES OF MORPHINE ACTION

I

II

III

sleep

euphoria

withdrawal

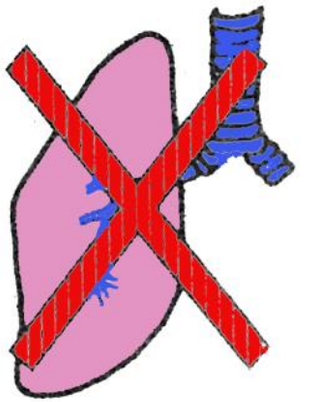
analgesia

during first use

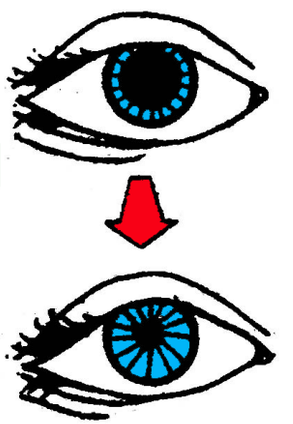
during prolong misuse

MORPHINE PHARMACODYNAMIC

CNS:



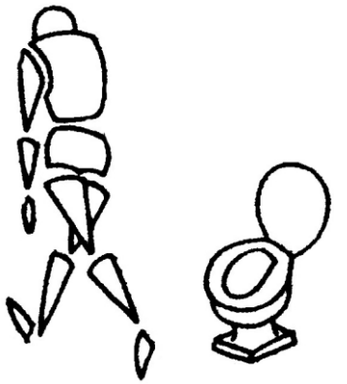
- ***Brain cortex:*** **euphoria ("rash"), sedation, shallow sleep**
- ***Medulla oblongata:***
  - **respiratory center – ↓ (decreasing of frequency and amplitude of breathing excursion, decreasing of CO_2 sensitivity)**
  - **cough center – ↓**
  - **heat center – ↓ (hypothermia)**
  - **n. vagus center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



- ***Middle brain:*** **↑ center of III cranial nerve pai (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

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 – naloxne (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**