



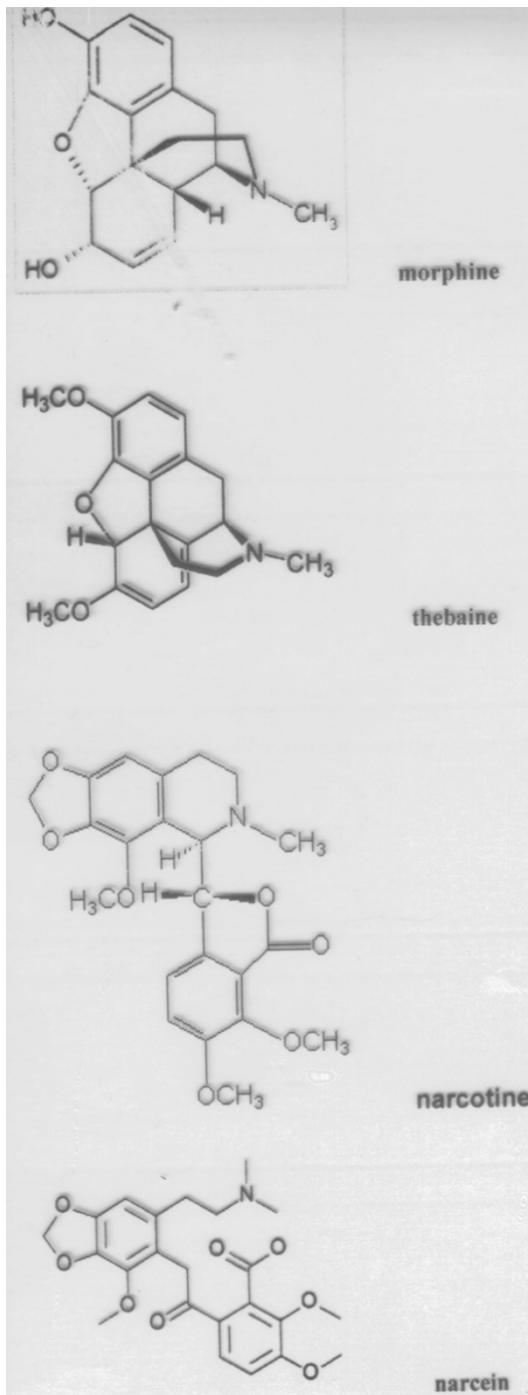
UNIVERSITY of
DEBRECEN

OPIOID ANALGESICS

DRUGS react on OPIOID receptors

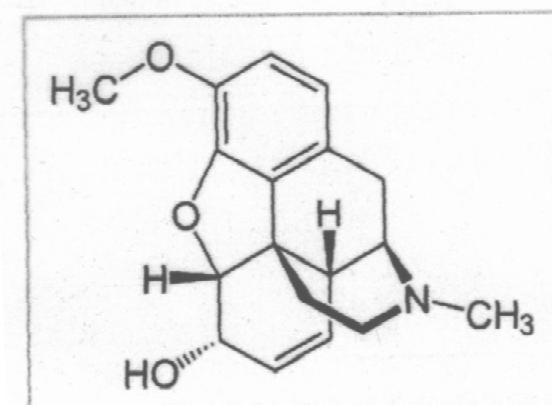
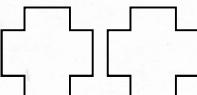
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associate professor

University of Debrecen, Faculty of Medicine,
Dept. of Pharmacology and Pharmacotherapy

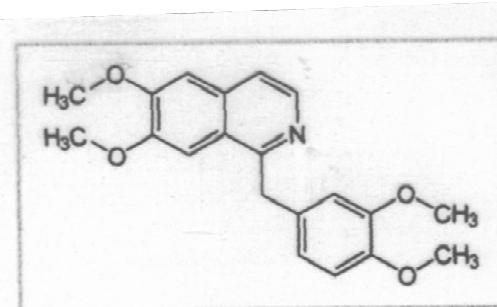


alkaloids in *Papaver somniferum*

Fenantrene derivatives



Kodein



Papaverin

and laudanin

Benzil-
izokinoline
derivatives

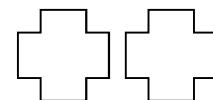
NO opioids !



opium

TINCTURA OPII

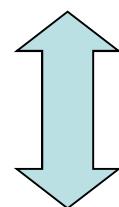
PULVIS OPII



Dose: 150-300 mg

PULVIS DOVERI = Pulvis opii et ipecacuanhae

Atonic type obstipation: morphine+papaverine combinative effect



morfine spastic obstipatio

Dose : 10-30 mg



**Ascending,
afferent pain
transmission pathway**

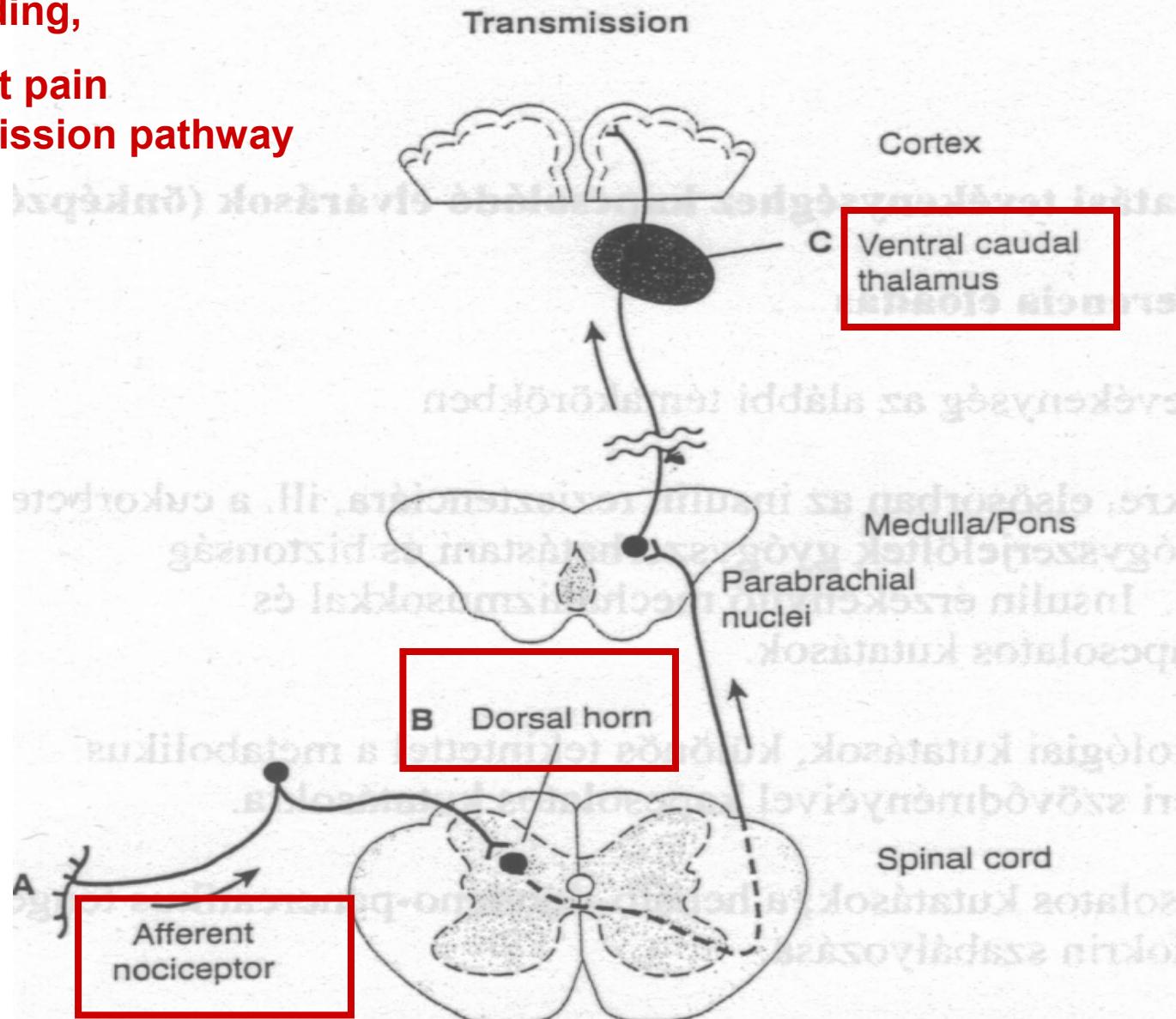
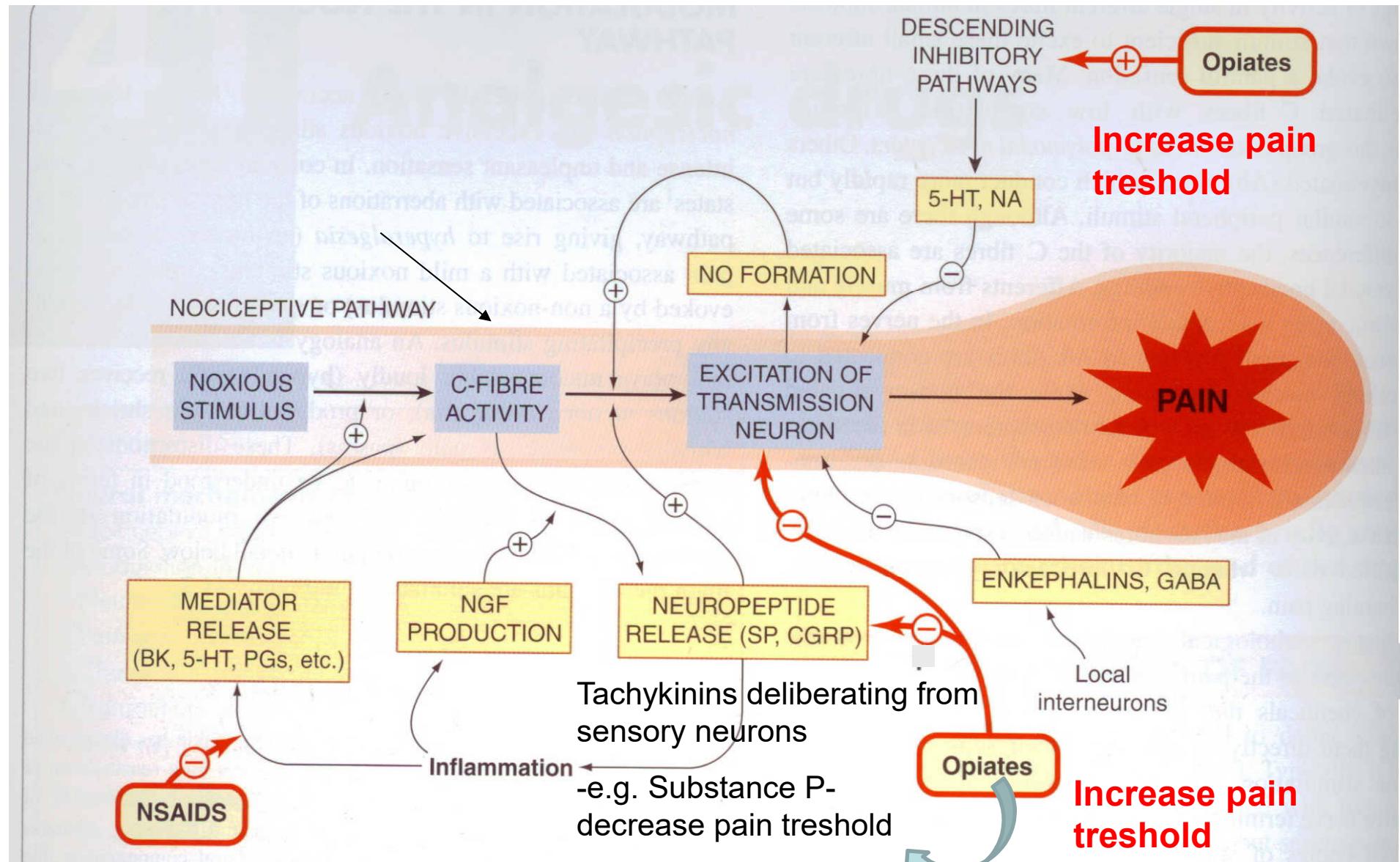


FIGURE 31–2 Putative sites of action of opioid analgesics. Sites of

Katzung et al Basic and Clinical Pharmacology textbook



Complex analgesic effects of opioids are seen in the following slides

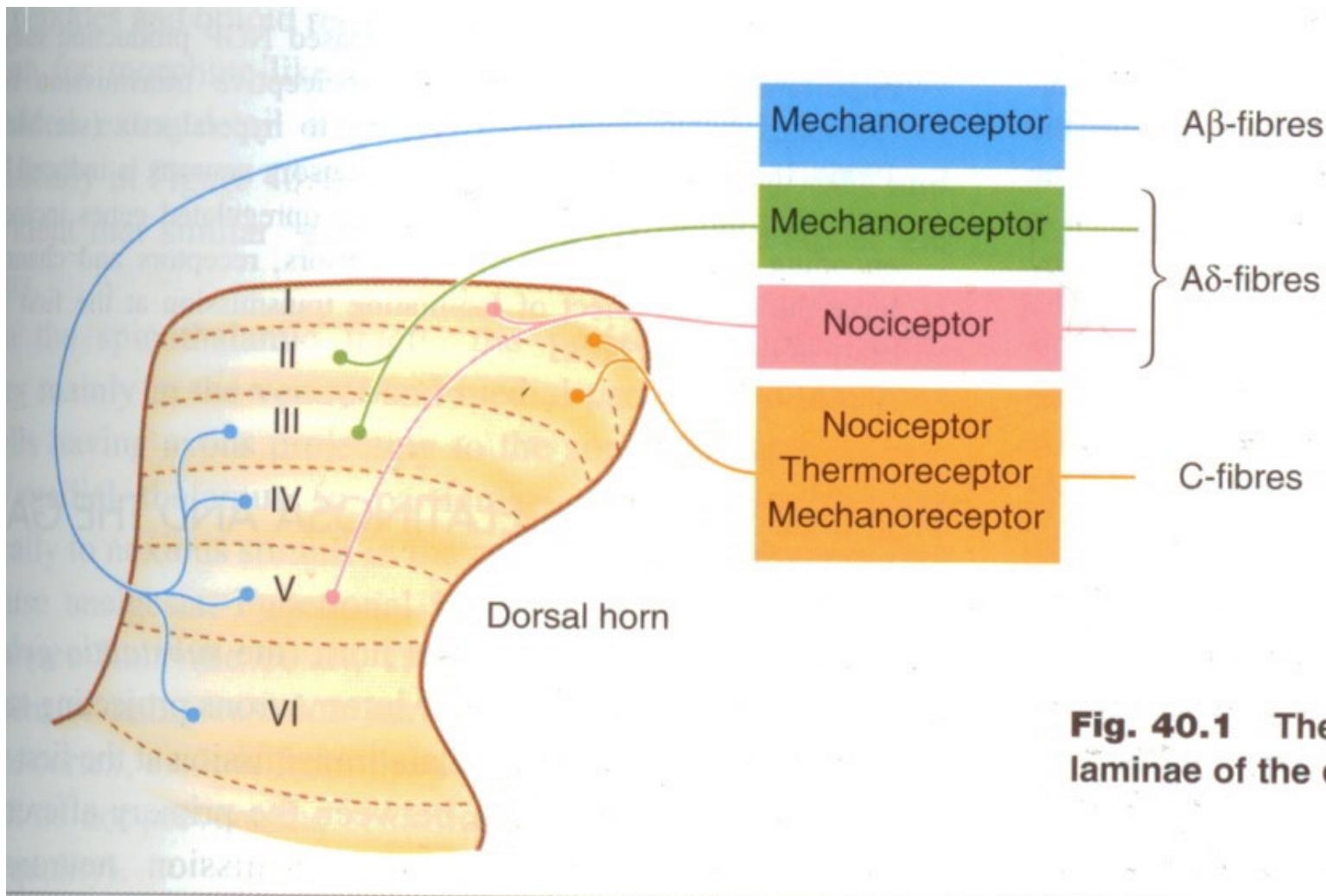
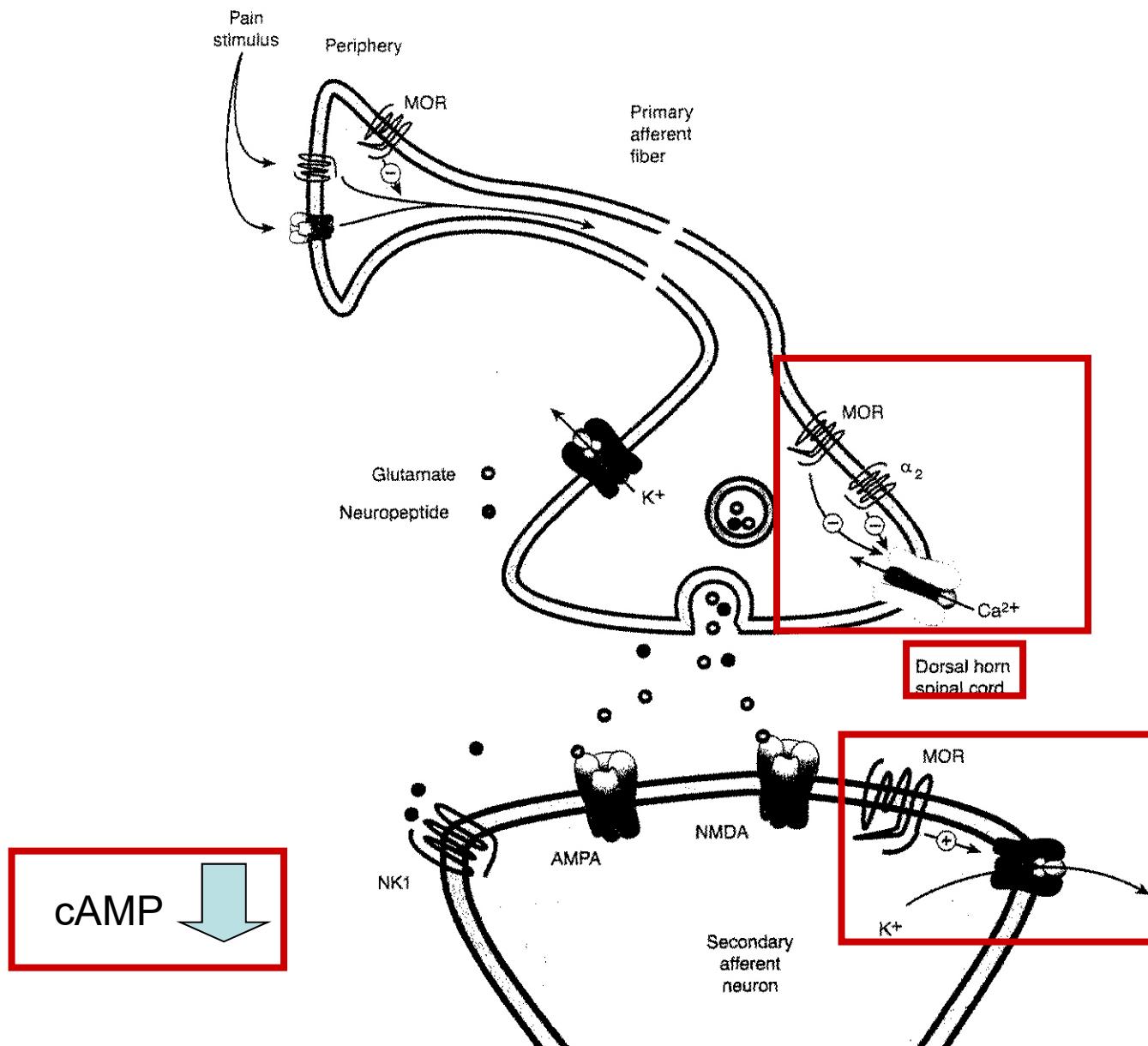


Fig. 40.1 The terminals of the primary afferent fibres in the laminae of the dorsal horn.



Descending inhibitory pathway

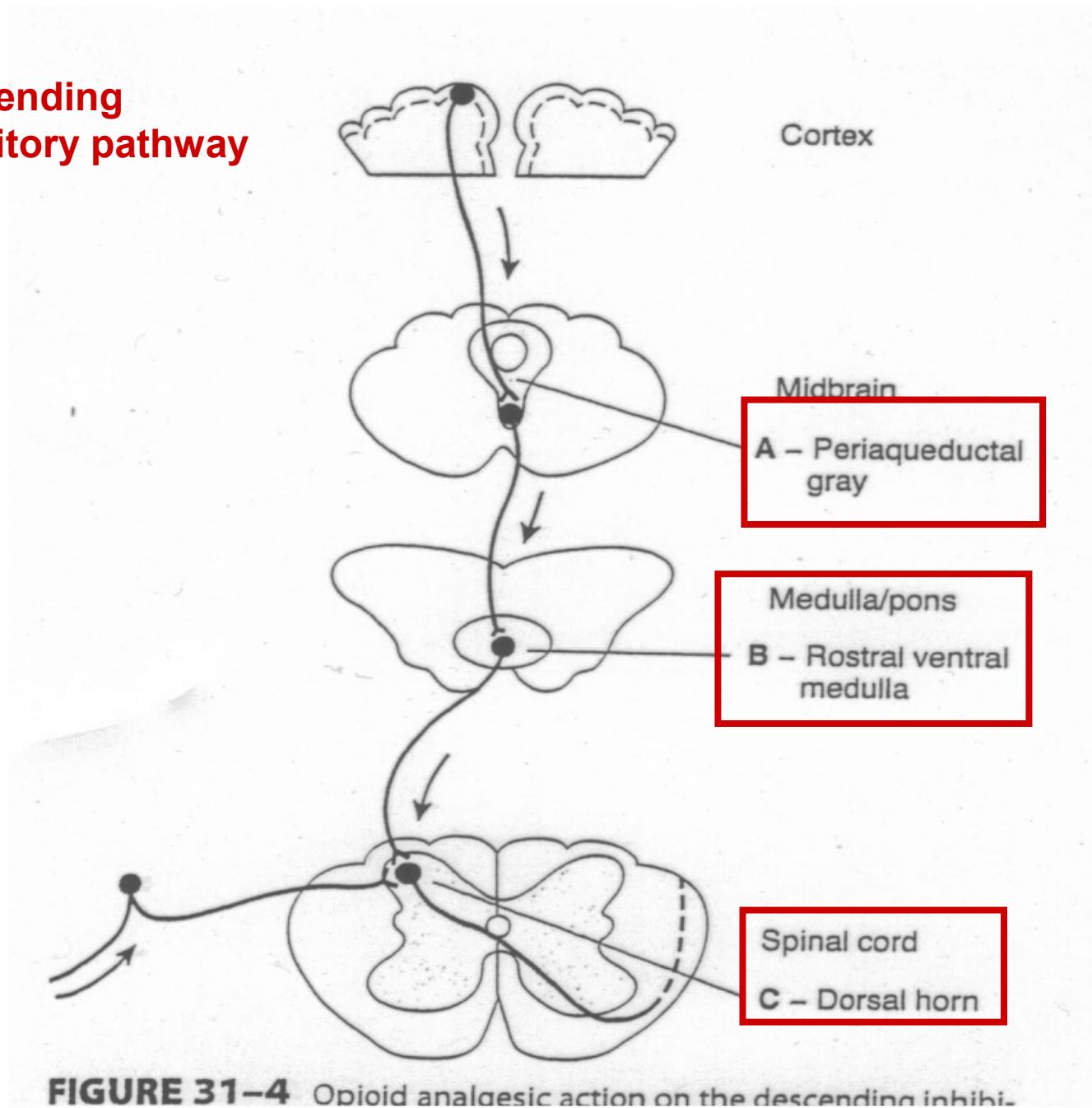
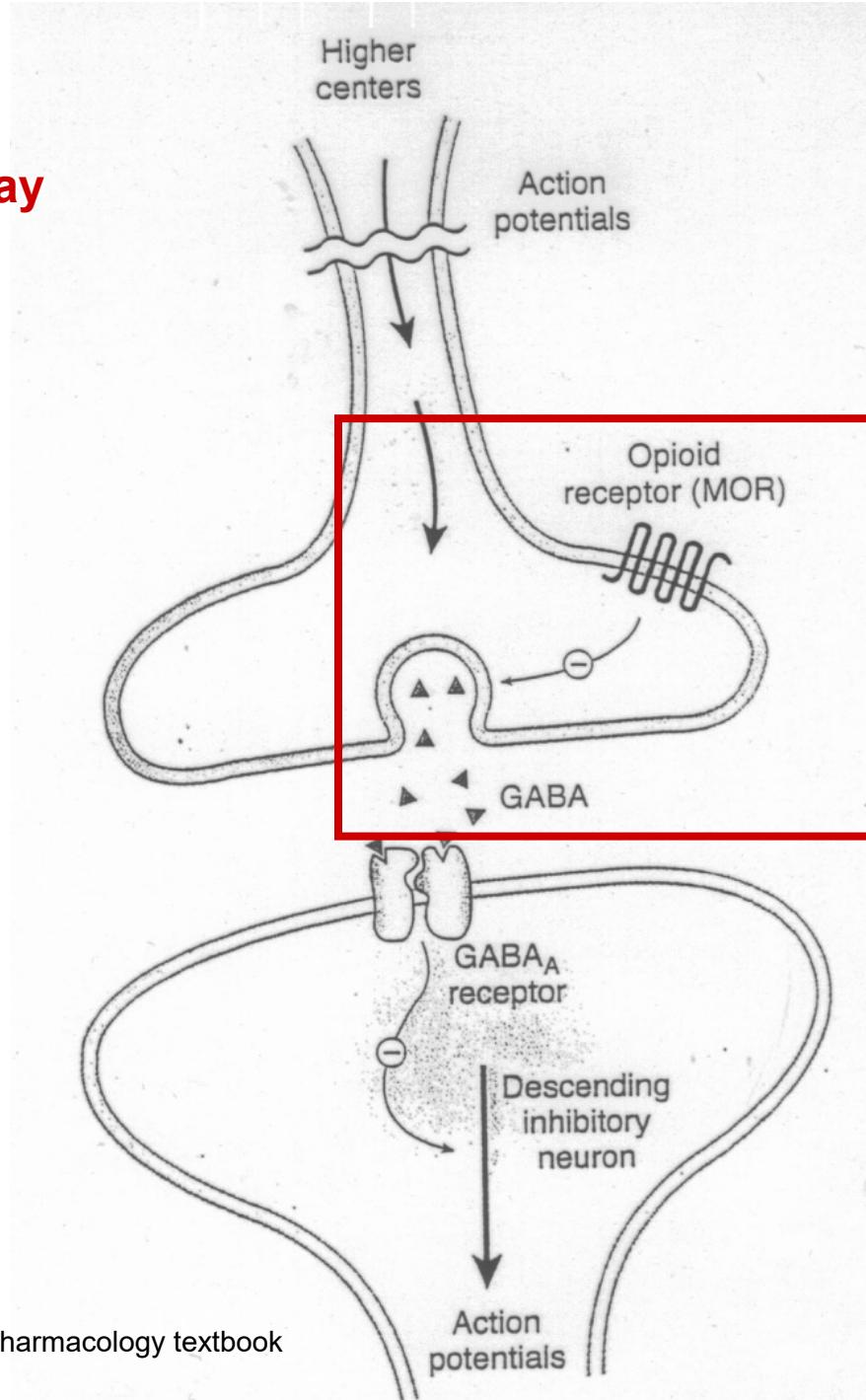
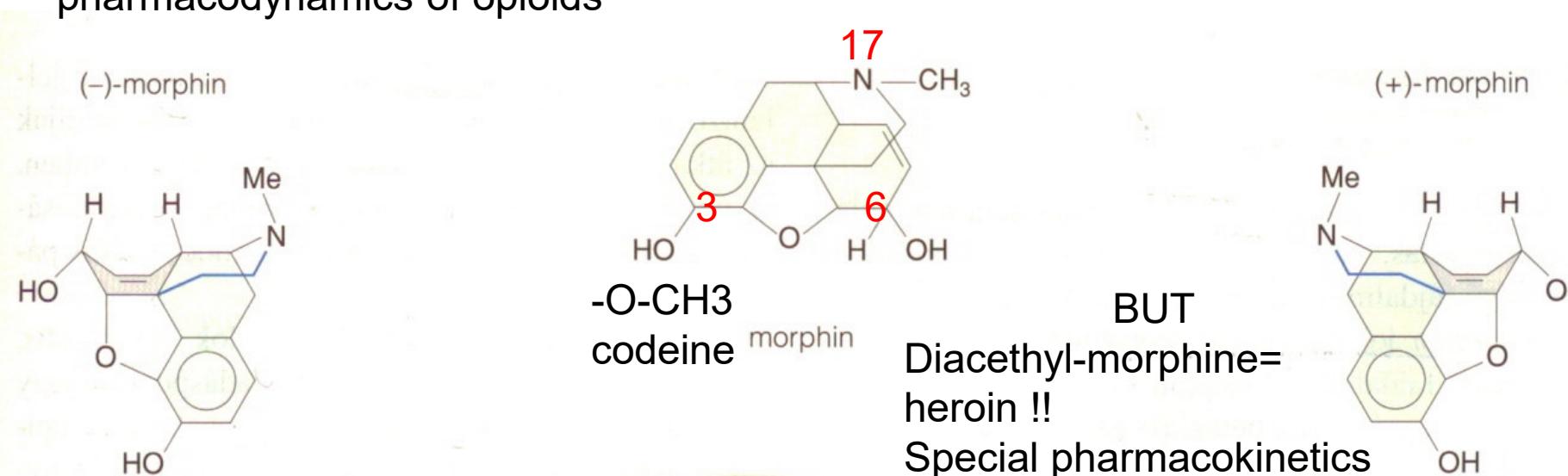


FIGURE 31–4 Opioid analgesic action on the descending inhibitory pathway

Descending inhibitory pathway



Effects of structural changes on pharmacodynamics of opioids



BUT
Diacetyl-morphine=heroin !!
Special pharmacokinetics

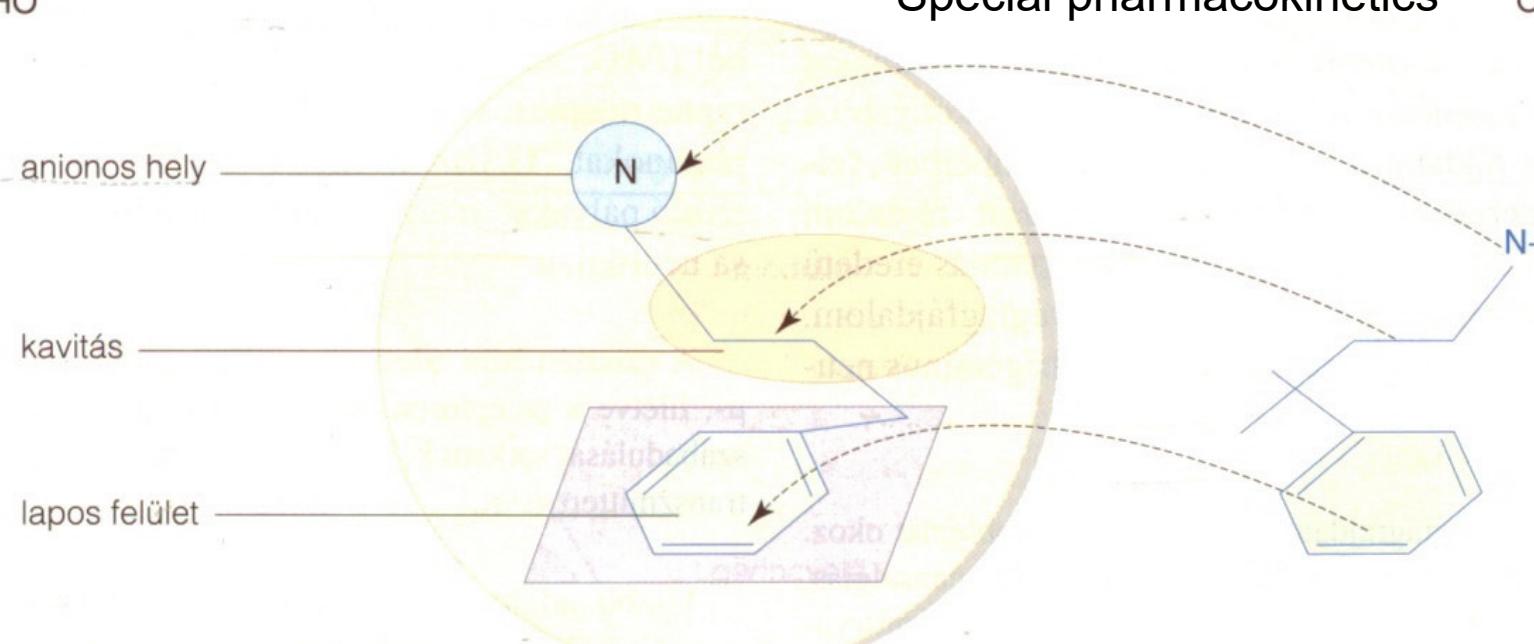


Table 23-1

Endogenous**Opioid Peptides***Selected Endogenous Opioid Peptides*[Leu⁵]enkephalin**Tyr-Gly-Gly-Phe-Leu**[Met⁵]enkephalin**Tyr-Gly-Gly-Phe-Met**Dynorphin A**Tyr-Gly-Gly-Phe-Leu** Arg-Arg-Ile-Arg-Pro-Lys-
Leu-Lys-Trp-Asp-Asn-Gln

Dynorphin B

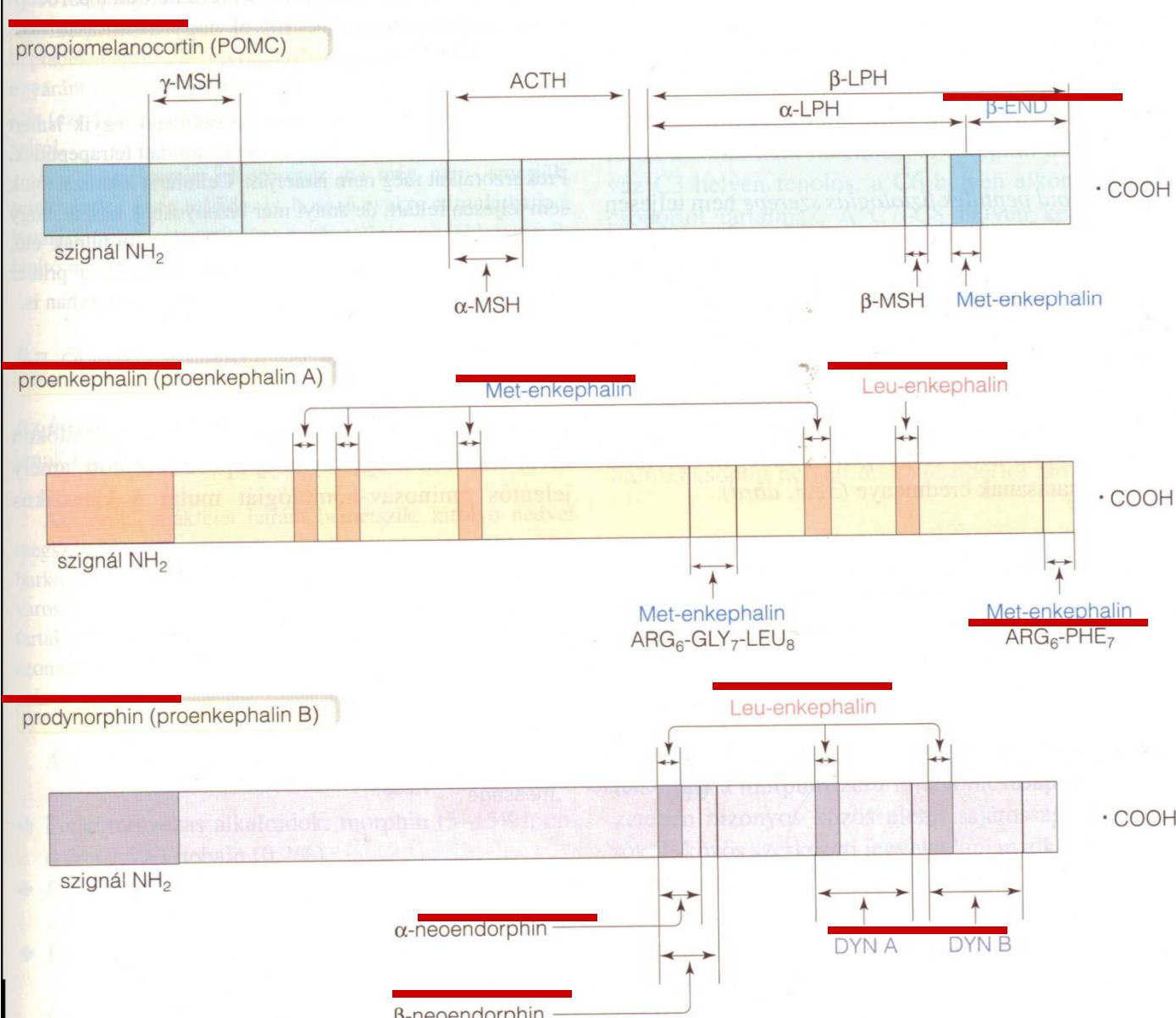
Tyr-Gly-Gly-Phe-Leu Arg-Arg-Gln-Phe-Lys-Val-
Val-Thr α -Neoendorphin**Tyr-Gly-Gly-Phe-Leu** Arg-Lys-Tyr-Pro-Lys β -Neoendorphin**Tyr-Gly-Gly-Phe-Leu** Arg-Lys-Tyr-Pro β_h -Endorphin**Tyr-Gly-Gly-Phe-Met** Thr-Ser-Glu-Lys-Ser-Gln-
Thr-Pro-Leu-Val-Thr-Leu-Phe-Lys-Asn-Ala-
Ile-Ile-Lys-Asn-Ala-Tyr-Lys-Lys-Gly-Glu*Novel Endogenous Opioid-Related Peptides*Orphanin FQ/Nociceptin**Phe-Gly-Gly-Phe** Thr-Gly-Ala-Arg-Lys-Ser-
Ala-Arg-Lys-Leu-Ala-Asn-GlnEndomorphin-1

Tyr-Pro-Trp-Phe

Endomorphin-2

Tyr-Pro-Phe-Phe

Selected Synthetic Opioid Peptides



32.2. ábra. A három opioid peptidcsalád proteinprekurzorainak sematikus ábrázolása

Met-enkephalin szekvenciája: Tyr–Gly–Gly–Phe–Met;
(Rövidítések – ENK: enkephalinok; DYN: dynorphin; END: endorphin)

250-260 AMINO ACIDS

Table 40.1 Functional effects associated with the main types of opioid receptor

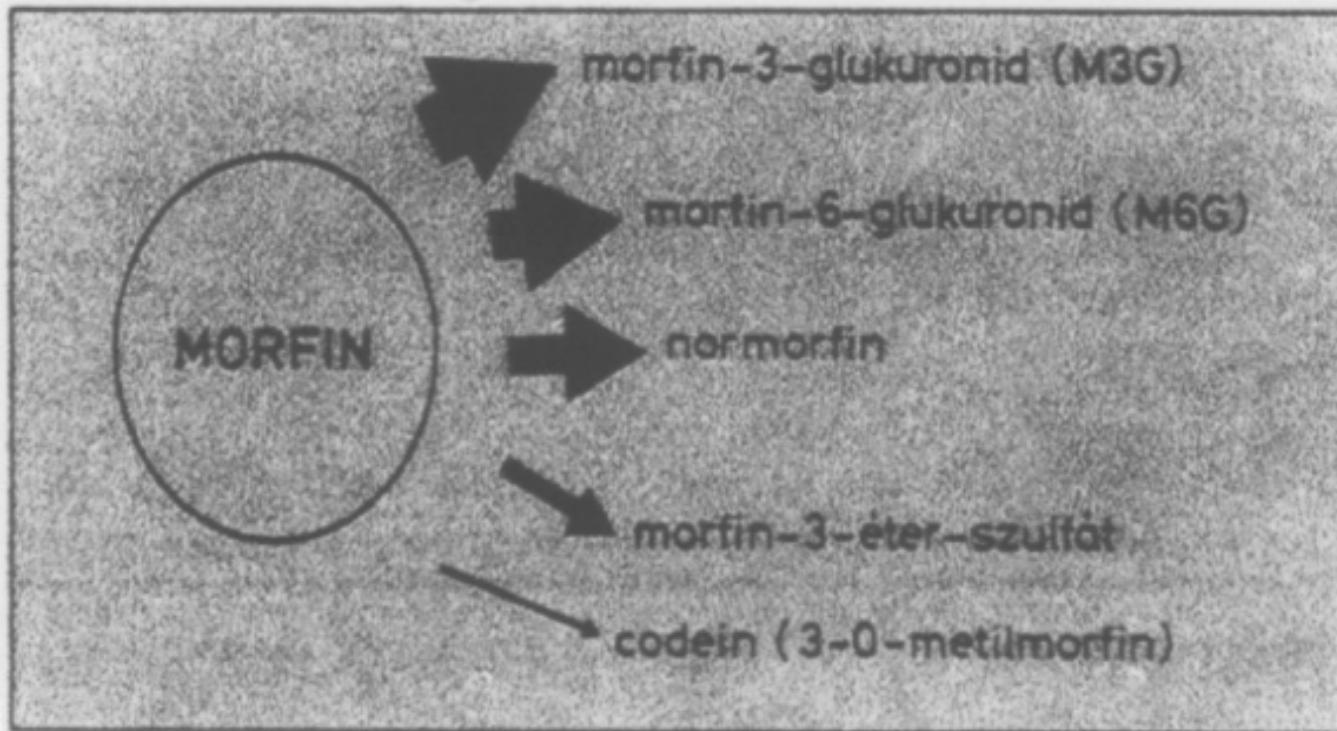


	μ	δ	κ
Analgesia			
Supraspinal	+++	-	-
Spinal	++	++	+
Peripheral	++	-	++
Respiratory depression	+++	++	-
Pupil constriction	++	-	+
Reduced GI motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Physical dependence	+++	-	+

Table 40.2 Selectivity of opioid drugs and peptides for receptor subtypes

	μ	δ	κ
Endogenous peptides			
β -Endorphin	+++	+++	+++
Leu-enkephalin	+	+++	-
Met-enkephalin	++	+++	-
Dynorphin	++	+	+++
Opiate drugs			
<i>Pure agonists</i>			
Morphine, codeine, oxymorphone, dextropropoxyphene	+++	+	+
Methadone	+++	-	-
Meperidine	++	+	+
Etorphine, brezazocine	+++	+++	+++
Fentanyl, sufentanil	+++	+	-

BIOTRANSFORMATION OF MORPHINE



ANALGESIA FOR PATIENTS WITH CANCER

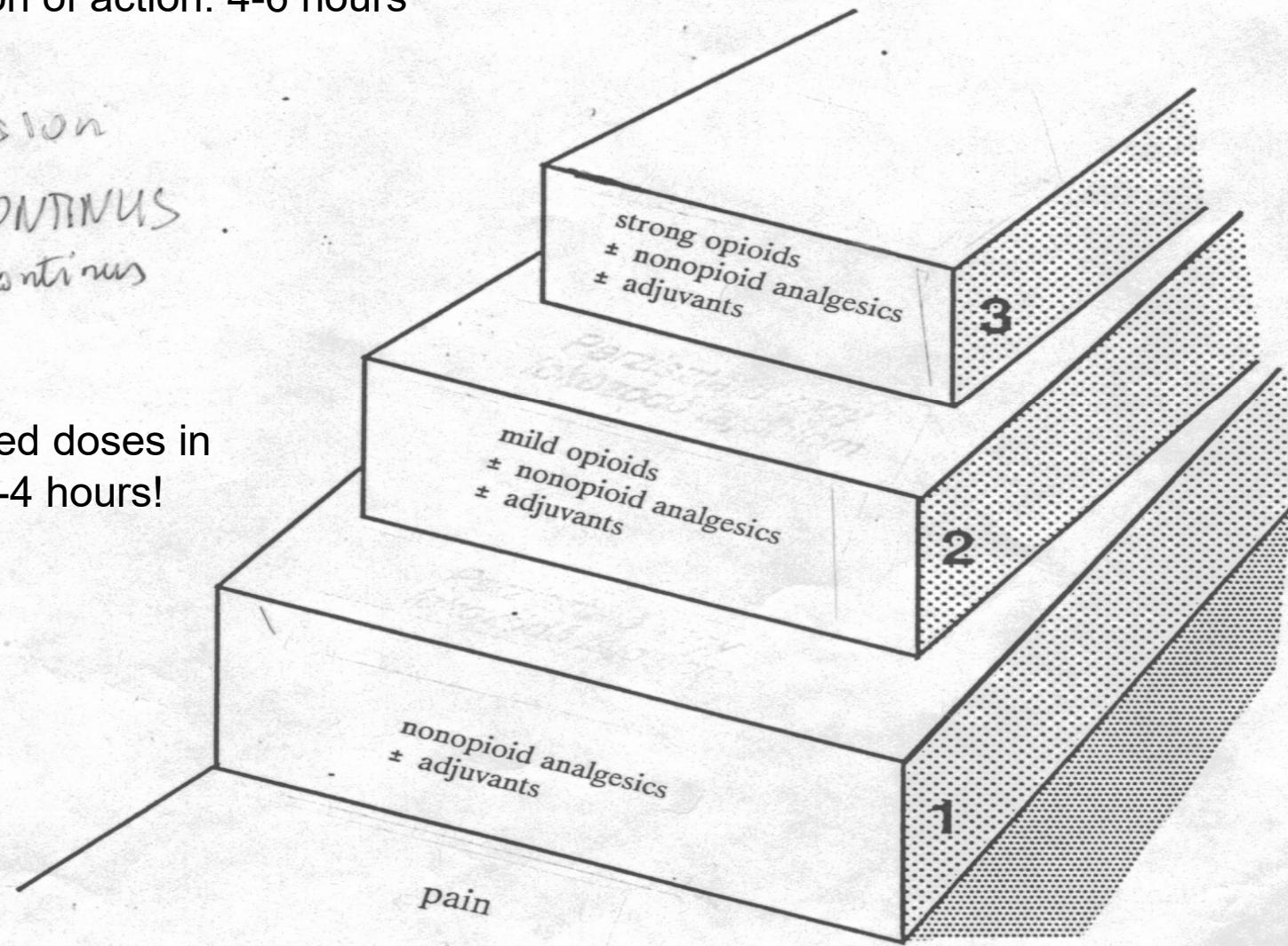
Duration of action: 4-6 hours

M-Esion

MST-CONTINUUS

DNC - Continus

Repeated doses in
every 3-4 hours!



Pharmacological therapeutical and side effects of morphine

In CNS

Analgesia

Euphoria

Sedation

Respiratory depression

Cough suppression

Nausea, vomiting

Miosis, pinpoint pupil

Muscle rigidity

Peripherally

Obstipation

Biliary pressure increases

Urinary retention

Uterus relaxation

Cardiovascular depression

Histamin deliberation

*Endocrine effects: ADH, ST increase, LH decreases

*Immunosuppression

**Centrally effects are also included*

CLINICAL APPLICATIONS of OPIOIDS

Pain

Anxiety, fear of death in connection with shock sy

to prevent aggravation of shock, e.g. AMI

Dyspnoe with acute left ventriculaR INSUFFICIENCY

Perioperative medication

Diarrhoe

Terminal stages

Opioid abuse

CONTRAINDICATIONS OF OPIOIDS

ASTHMA BRONCHIALE, COPD

HEPATIC AND RENAL FAILURE

PREGNANCY

COLITIS ULCEROSA

PANCREATITIS

In HEAD INJURIES - CO₂ retention with vasodilatation

Hyothyreodism with myxedema

Adrenal insufficiency (Addison

TOLERANCE IN VARIOUS EFFECTS OF MORPHINE

High	moderate	lack of tolerance

Analgesia sedation depression of breath euphoria antidiuretic effect emetic effect cough suppression	bradycardia hypotension	miosis constipation epileptiform convulsions antagonist effect

Table 40.2 Selectivity of opioid drugs and peptides for receptor subtypes

	μ	δ	κ
Endogenous peptides			
β -Endorphin	+++	+++	+++
Leu-enkephalin	+	+++	-
Met-enkephalin	++	+++	-
Dynorphin	++	+	+++
Opiate drugs			
<i>Pure agonists</i>			
Morphine, codeine, oxymorphone, dextropropoxyphene	+++	+	+
Methadone	+++	-	-
Meperidine	++	+	+
Etorphine, brezazocine	+++	+++	+++
Fentanyl, sufentanil	+++	+	-
<i>Partial mixed agonists</i>			
Pentazocine, ketocyclazocine	+	+	++
Nalbuphine	+	+	(++)
Nalorphine	++	-	(++)
Buprenorphine	(+++)	-	++
<i>Antagonists</i>			
Naloxone	+++	+	++
Naltrexone	+++	+	+++

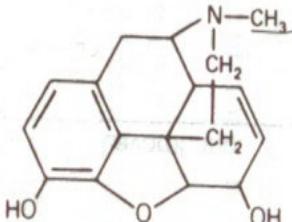
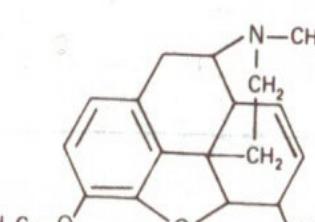
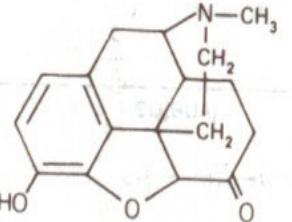
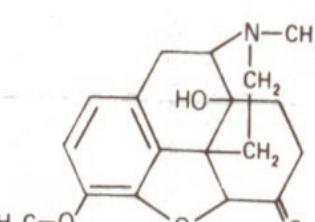
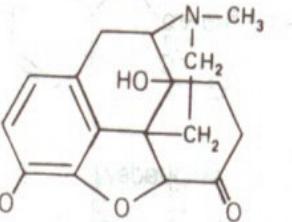
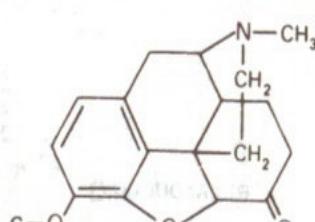
Blue= agonist

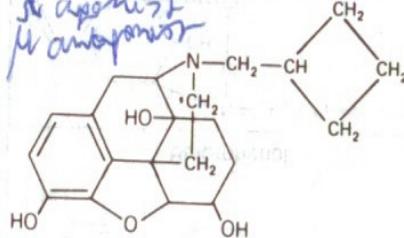
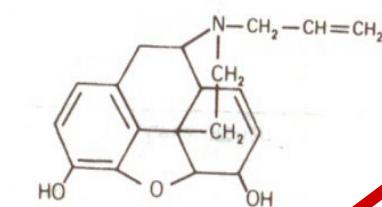
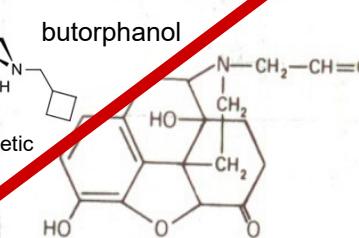
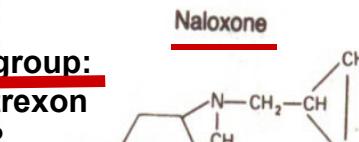
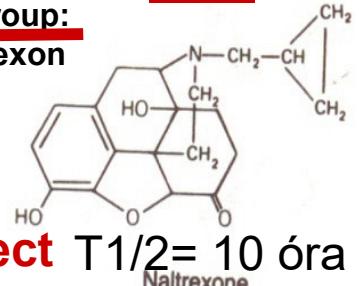
Black= Antagonist effect

1. Mixed agonist-antagonist

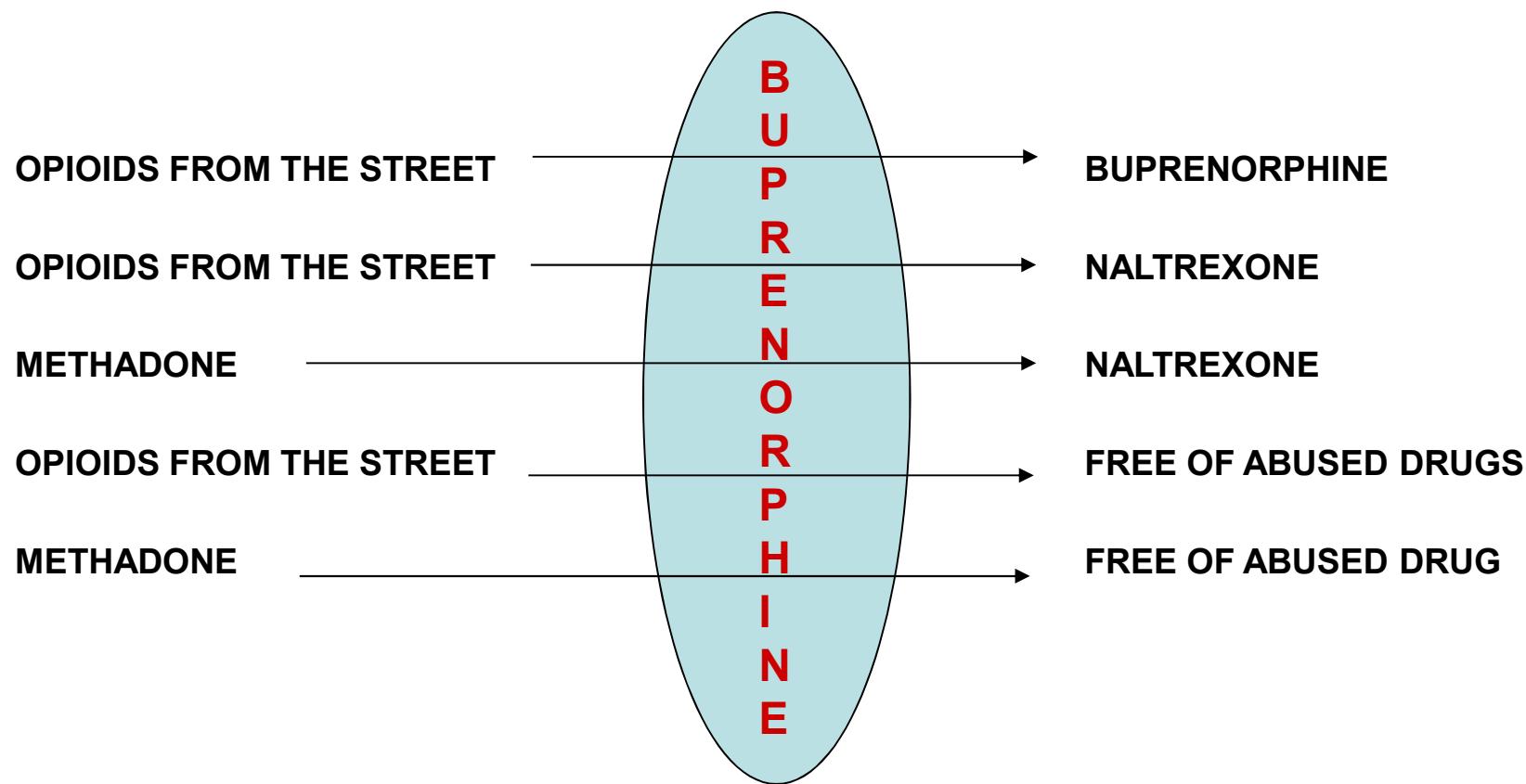
2. Partial agonist

3. Pure antagonist effects

Chemical structures of opioid analgesics	
Strong Agonists	Mild to Moderate Agonists
 Morphine	 Codeine
 Hydromorphone	 Oxycodone
 Oxymorphone	 Hydrocodone

Mixed Agonist-Antagonists	Antagonists
<i>X agonist Δ antagonist</i>  Nalbuphine	 Nalorphine ¹
 Buprenorphine	 butorphanol synthetic
 PAMORA group: Methylnaltrexon RELISTOR	 T1/2= 1-2 h Naloxone
 Naltrexone	Pure antagonist effect T1/2= 10 óra

BUPRENORPHINE BRIDGE THERAPY



UROD = ultrarapide opioid detoxification in durable general anesthesia

Bupropion+ naltrexon (MYSIMBA)

Effects in CNS: mesolimbic dopaminergic reward pathways and hypothalamus

bupropion has **dopamine + NA uptake weak inhibitory effect**

+ naltrexon which is μ (mu) opioid receptor antagonist and potentiates effects of bupropion

Anorexigene + decrease of fat tissue even in visceral fat

Pharmacokinetics: p.o. bioavailability: 5-6 %, with meals is higher

T1/2 : naltrexon 10 hours

bupropioné 21 h - 2x a day administration
excretion even to the breast milk !

bupropion inhibits **CYP 2D6 – drug interactions !!**

CYP2B6 inducers enhance toxicity of bupropion e.g. carbamazepine, phenytoin

Adverse effects:

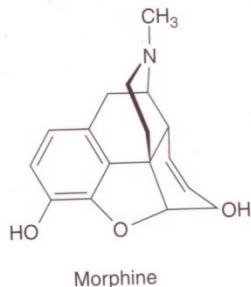
Epileptiform convulsions, psychotic symptoms with suicid actions, anxiety, insomnia, tremor, head-ache, tinnitus, vertigo, fever

hypertension, palpitation, angina pectoris, arthralgia, myalgia,,
nausea, mild hepatotoxicity, colica abdominalis, pruritus, sweating

CONTRAINDICATION: epilepsy, risk for suicid actions, MAO-I therapy, uncontrolled hypertension, addiction of opioids/ethanol/benzodiazepines, malignancies in CNS, hepatic and renal insufficiencies, pregnancy, childhood

Strong agonists

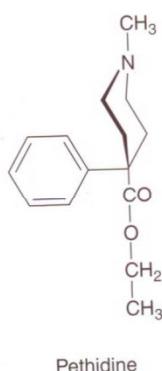
Synthetic opioid derivatives



DOLARGAN – petidine=meperidin

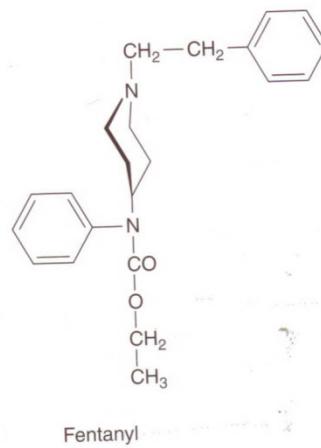
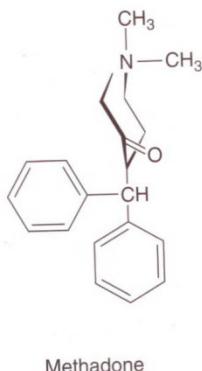
For short-term therapy!
Shorter duration of action
Orthostatic hypotonia
Antimuscarinic effect!

Less side effects
than in the case of morphin



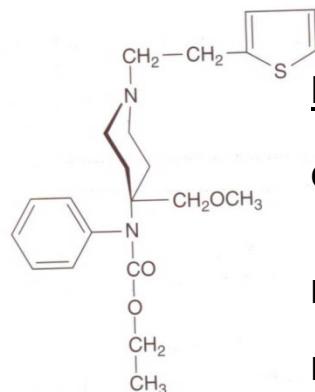
DEPRIDOL - metadone

longer duration of action
better bioavailability
Development of tolerance is
more slowly



DUROGESIC TTS - fentanyl

100x potency
Much serious respiratory depression
+
Muscle rigidity – even in thoracic
respiratory muscles !!



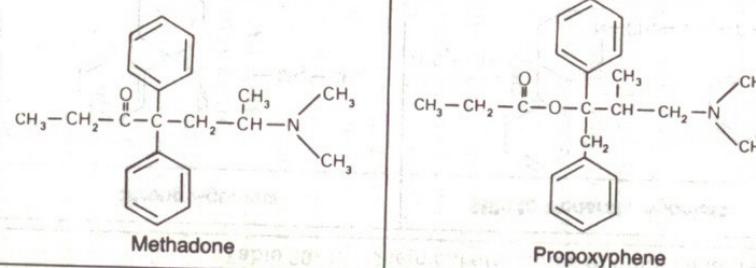
Neurolept analgesia:

Opioid+antipsychotic combination

Morphin + haloperidol

Fentanyl + droperidol

fenylheptylamines



Synthetic opioid derivatives

Basic Structure	Strong Agonists	Mild to Moderate Agonists	Mixed Agonist-Antagonists
Phenylpiperidines	 Meperidine Fentanyl	 Diphenoxylate	
Morphinans	 Levorphanol	 Ioperamide IMODIUM	 Butorphanol
Benzomorphans		 tramadol	 Pentazocine

422

¹ Not a pure antagonist. See text for explanation.

Effects of MEPERIDINE compared with MORPHINE

meperidine = pethidine:

Shorter duration of action (2-4 hours)

Less hypnotic

Does not suppress cough

No obstipation

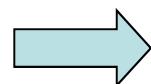
Less risk for urinary retention

for uterus relaxation

Moderate effect on biliary pressure

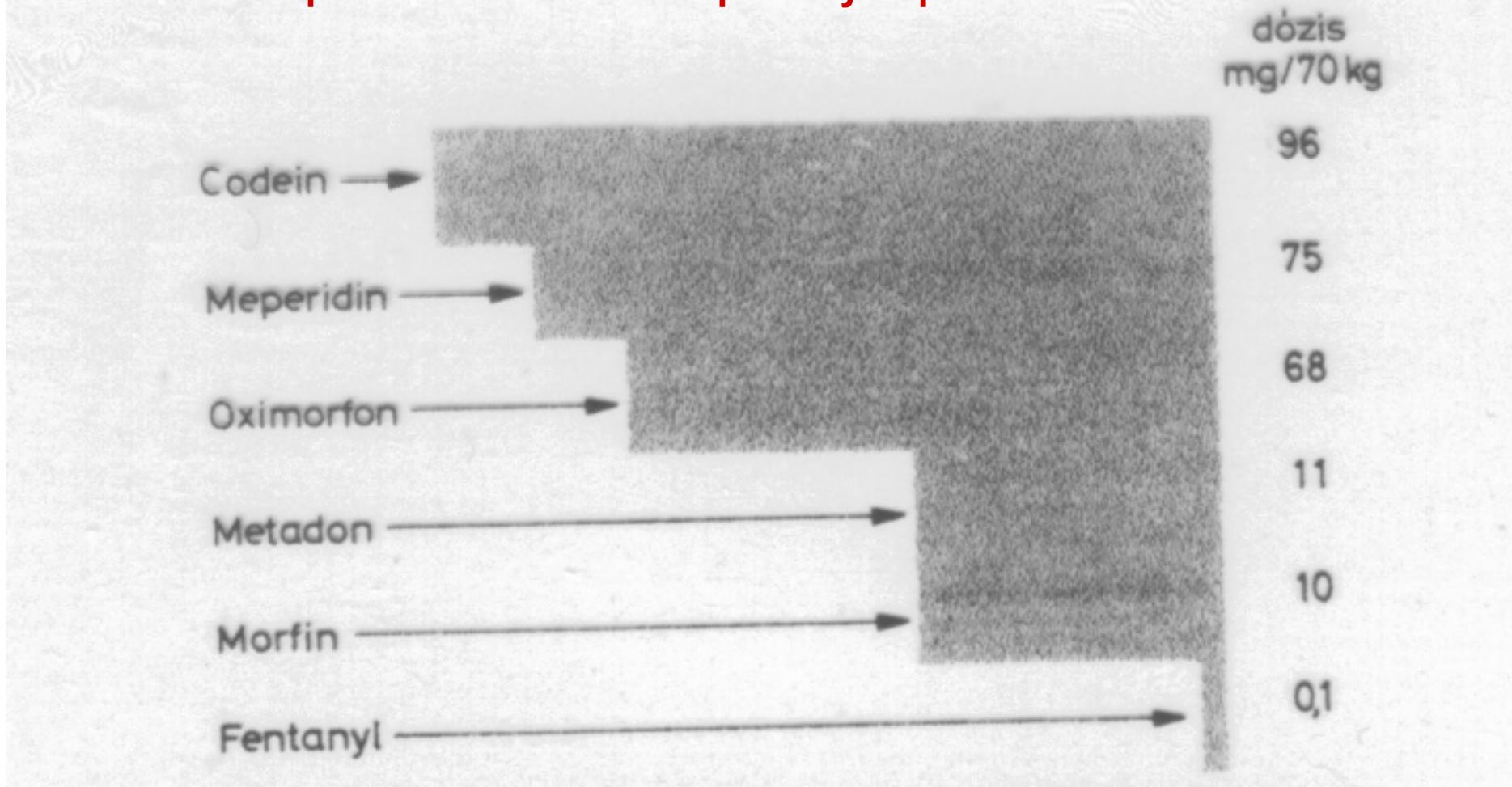
Weaker miotic effect

Normeperidine metabolite is epileptogenic



Only for short-term therapies !!

Equivalent doses for respiratory depression



ADDICTIVE POTENTIALS OF OPIOIDS

Nalorfin

Nalbufin

Pentazocin

Codein

Buprenorfin

Meperidin

Morfin

Fentanyl

Metadon

Oximorfon

Heroin

