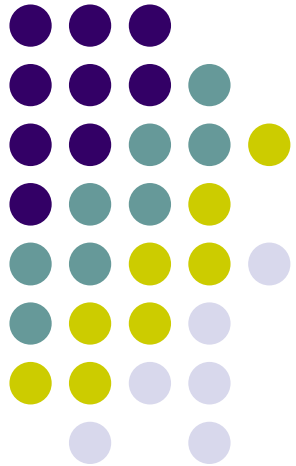
Drugs acting on the CNS



Reasons why understanding the action of drugs on CNS -challenging problem

1. Not only are they of major therapeutic importance

but

Also the drugs that humans most commonly administer to themselves for non-medical reasons (e.g. alcohol, tea and coffee, cannabis, nicotine, opioids, amphetamine and so on).

2. CNS far more complex than any other system in the body, making the understanding of drug effects much more difficult

relationship between the behavior of individual cells and that of the organ as a whole is far less direct in the brain than in other organs.

Classification suggested in 1967 by the World Health Organization

- **Anaesthetic agents**
  Definition: drugs used to produce surgical anaesthesia
  Examples: halothane, propofol
- **Anxiolytics and sedatives**
  Synonyms: hypnotics, sedatives, minor tranquillisers
  Definition: drugs that cause sleep and reduce anxiety
  Examples: barbiturates, benzodiazepine

- **Antipsychotic drugs**
  Synonyms: neuroleptic drugs, antischizophrenic drugs, major tranquillisers
  Definition: drugs that are effective in relieving the symptoms of schizophrenia
  Examples: clozapine, chlorpromazine,
- **Antidepressant drugs**
  Definition: drugs that alleviate the symptoms of depressive illness
  Ex: monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors

- **Analgesic drugs**
  Definition: drugs used clinically for controlling pain
  Examples: opiates, carbamazepine
- **Psychomotor stimulants**
  Synonym: psychostimulants
  Definition: drugs that cause wakefulness and euphoria
  Examples: amphetamine, cocaine and caffeine

- **Psychotomimetic drugs**
  Synonyms: hallucinogens
  Definition: drugs that cause disturbance of perception (particularly visual hallucinations) and of behaviour

  Examples: lysergic acid diethylamide(LSD)
  phencyclidine

Antiepileptic drugs

Synonyms: Anticonvulsants

Definition: describe drugs that are used to treat epilepsy (which does not necessarily cause convulsions) as well as non-epileptic convulsive disorders.

Examples: phenytoin, sodium valproate

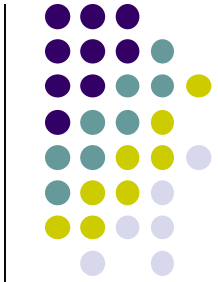
- **Cognition enhancers**

Synonyms: nootropic drugs

Definition: drugs that improve memory and cognitive performance

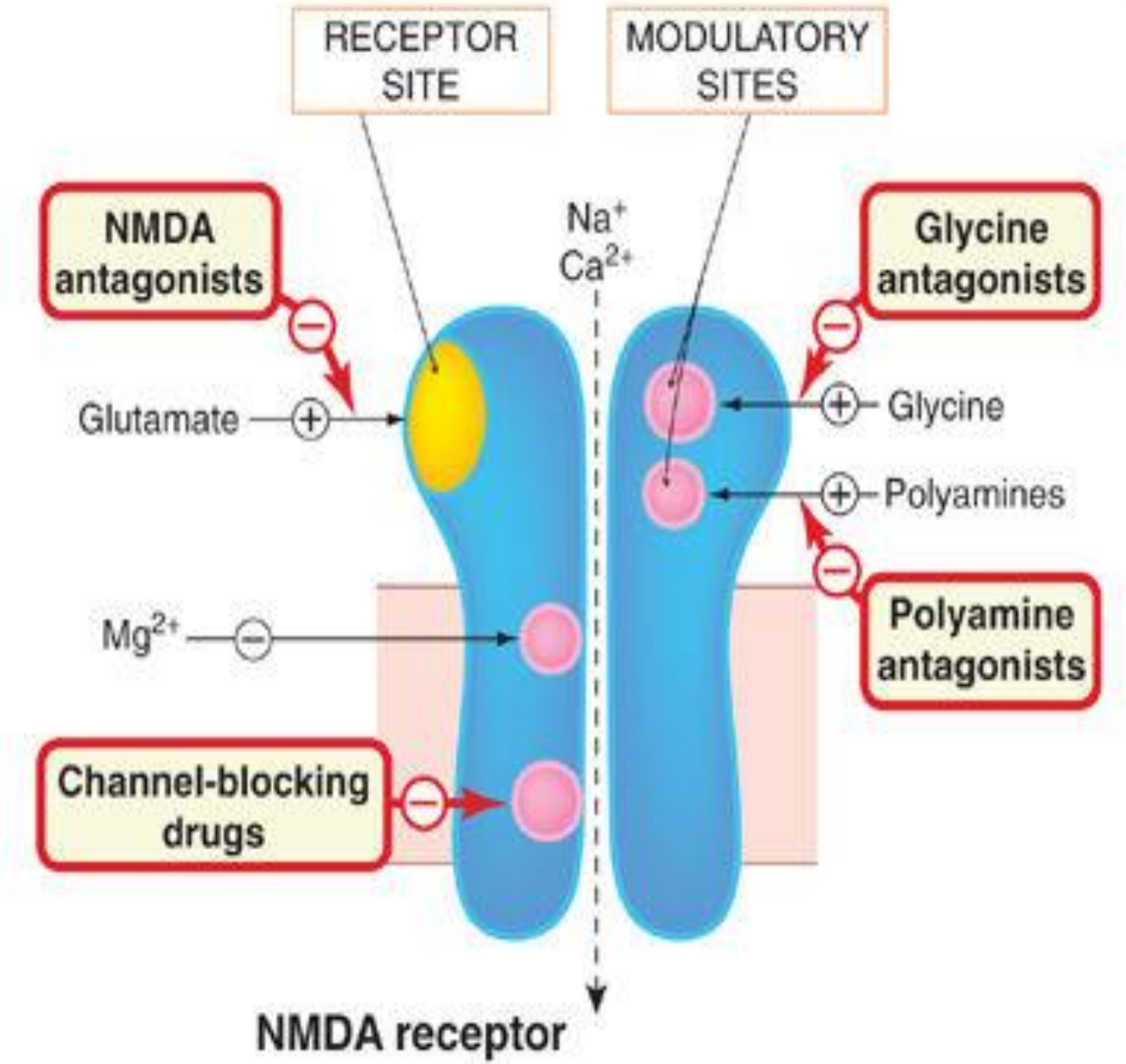
Examples: acetylcholinesterase inhibitors (e.g. **donepezil**, **galantamine**, **rivastigmine**, NMDA receptor antagonists (e.g. **memantine**,), **piracetam**

Alzheimer disease



- Pharmacologic intervention only palliative
- modest short-term benefit.
- None of the currently available therapeutic agents shown to alter the underlying process
- 3 distinguishing features:

1) accumulationof senile plaques (β-amyloid accumulations);
2) formation of numerous neurofibrillary tangles
3) loss of cortical neurons, particularly cholinergic neurons

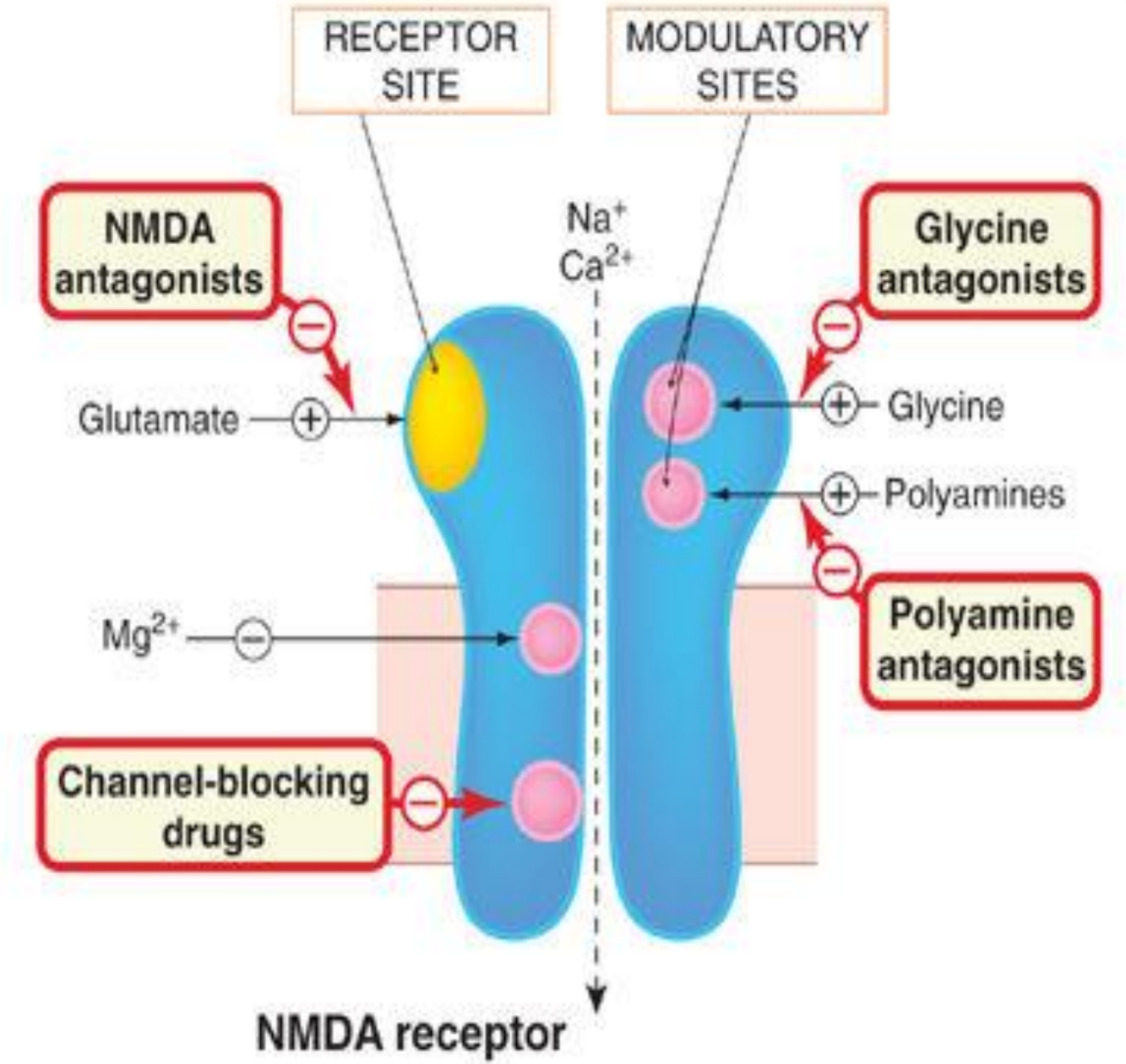

RECEPTOR SITE
MODULATORY SITES
NMDA antagonists
Glycine antagonists
Na+
Ca2+
Glutamate
Glycine
Polyamines
Mg2+
Polyamine antagonists
Channel-blocking drugs
NMDA receptor

Memantine

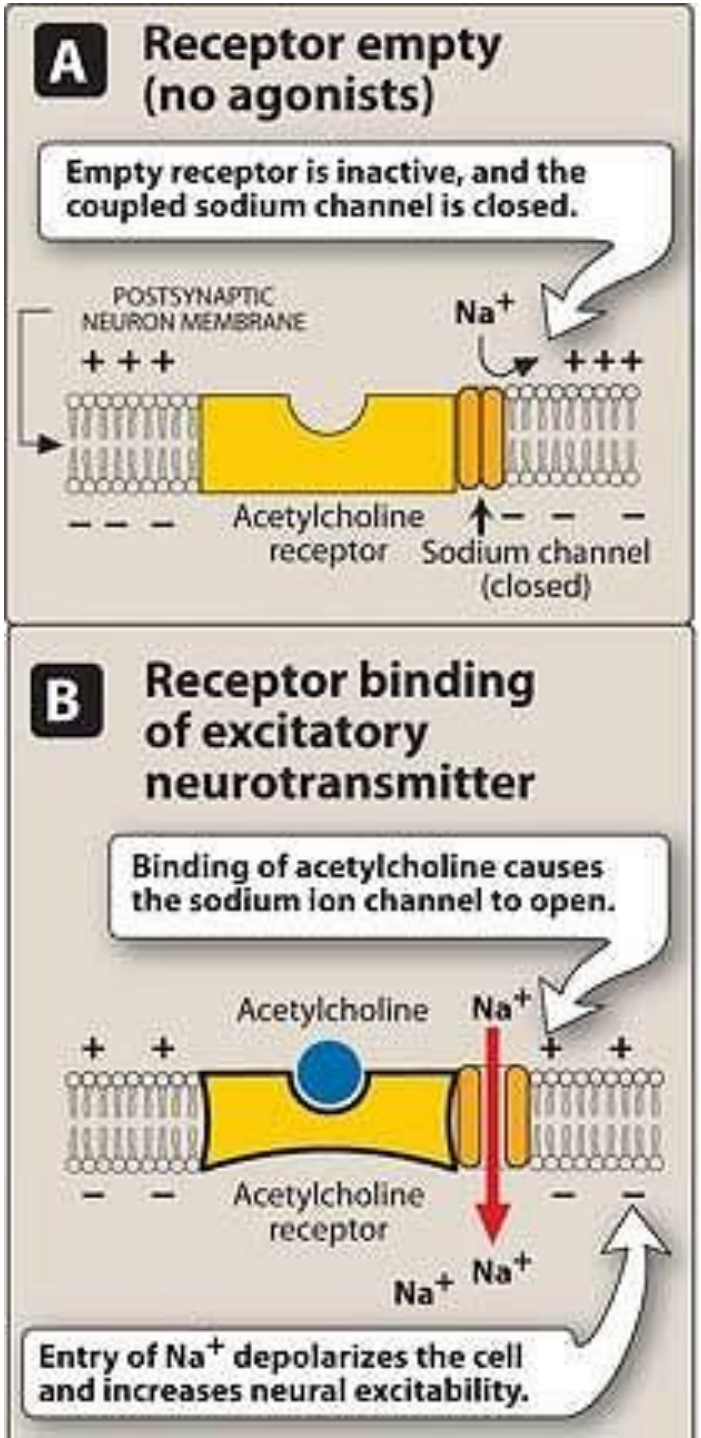
- Stimulation of glutamate receptors in the CNS critical for the formation of certain memories.
- overstimulation of receptors,NMDA type - excitotoxic effects suggested mechanism for neurodegenerative or apoptotic (programmed cell death
- opening of an associated ion channel that allows Na+ and, particularly, Ca2+ to enter the neuron
- Excess intracellular Ca2+ activates processes that ultimately damage neurons

M/A

- Memantine blocks the channels **partially.**
- Curbs the excess NMDA stimulation preserve.
- Still permitting sufficient calcium flow to preserve vital processess.
- A/E: Confusion, agitation and restlessness

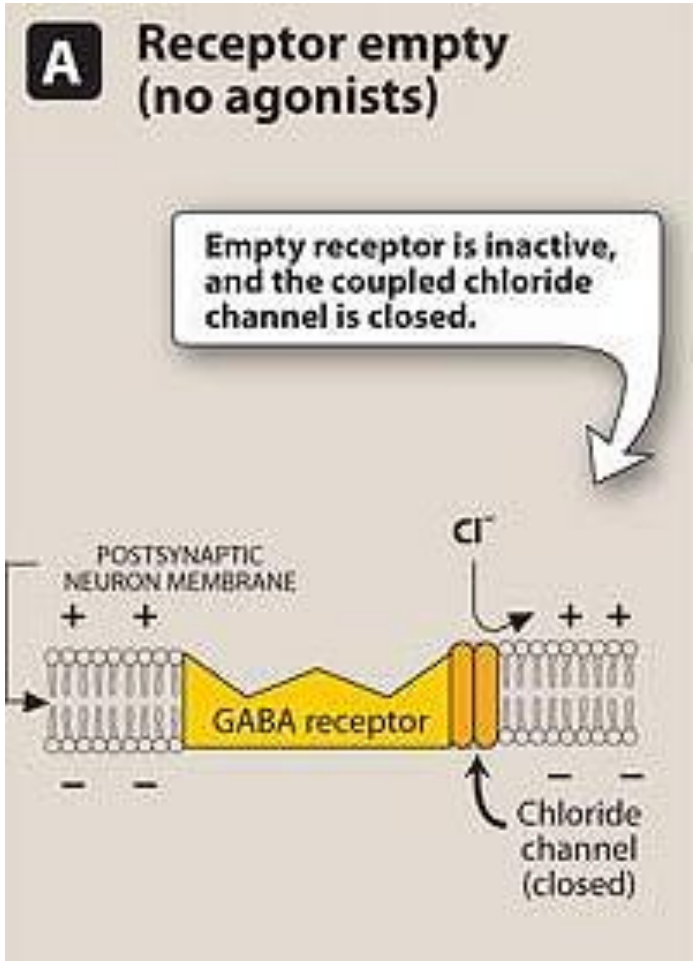

RECEPTOR SITE
MODULATORY SITES
NMDA antagonists
Glycine antagonists
Na+
Ca2+
Glutamate
Glycine
Polyamines
Mg2+
Polyamine antagonists
Channel-blocking drugs
NMDA receptor

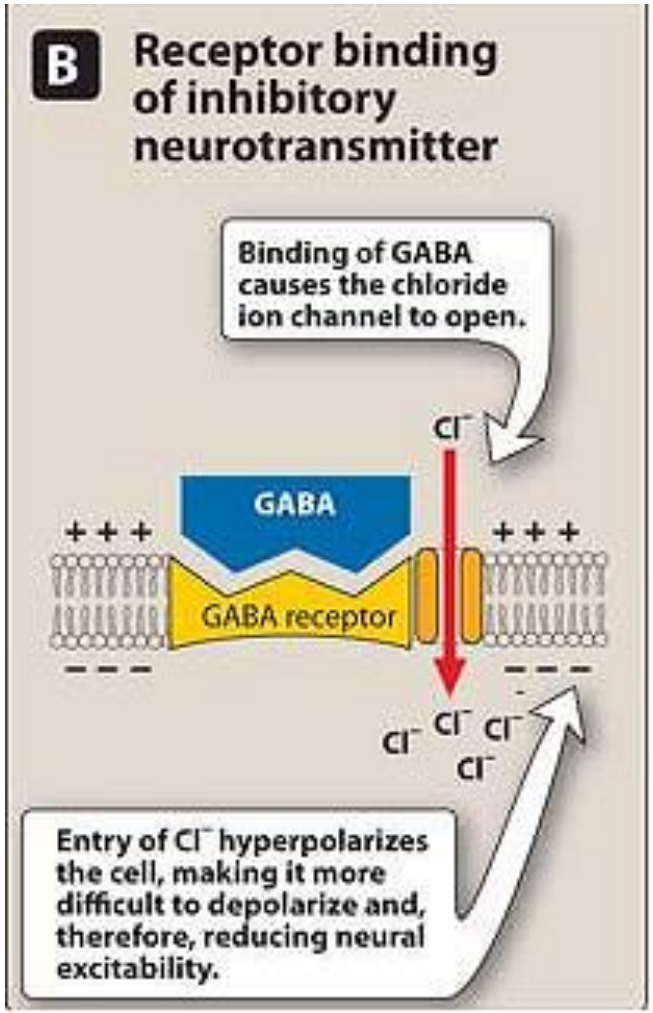
NEUROTRANSMITTER		POSTSYNAPTIC EFFECTS
	Acetylcholine	Excitatory: Involved in arousal, short-term memory, learning and movement.
BIOGENIC AMINES	Norepinephrine	Excitatory: Involved in arousal, wakefulness, mood, and cardiovascular regulation.
	Dopamine	Excitatory: Involved in emotion, reward systems and motor control.
	Serotonin	Excitatory/Inhibitory: Feeding behavior, control of body temperature, modulation of sensory pathways including nociception (stimulation of pain nerve sensors), regulation of mood and emotion, and sleep/wakefulness.
AMINO ACIDS	GABA	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization. Mediates the majority of inhibitory postsynaptic potentials.
	Glycine	Inhibitory: Increases Cl^- flux into the postsynaptic neuron, resulting in hyperpolarization.
	Glutamate	Excitatory: Mediates excitatory Na^+ influx into the postsynaptic neuron.
NEURO-PEPTIDES	Substance P	Excitatory: Mediates nociception (pain) within the spinal cord.
	Met-enkephalin	Generally inhibitory: Mediates analgesia as well as other central nervous system effects.



Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron.

Binding of the inhibitory neurotransmitter, (GABA), causes hyperpolarization of the neuron



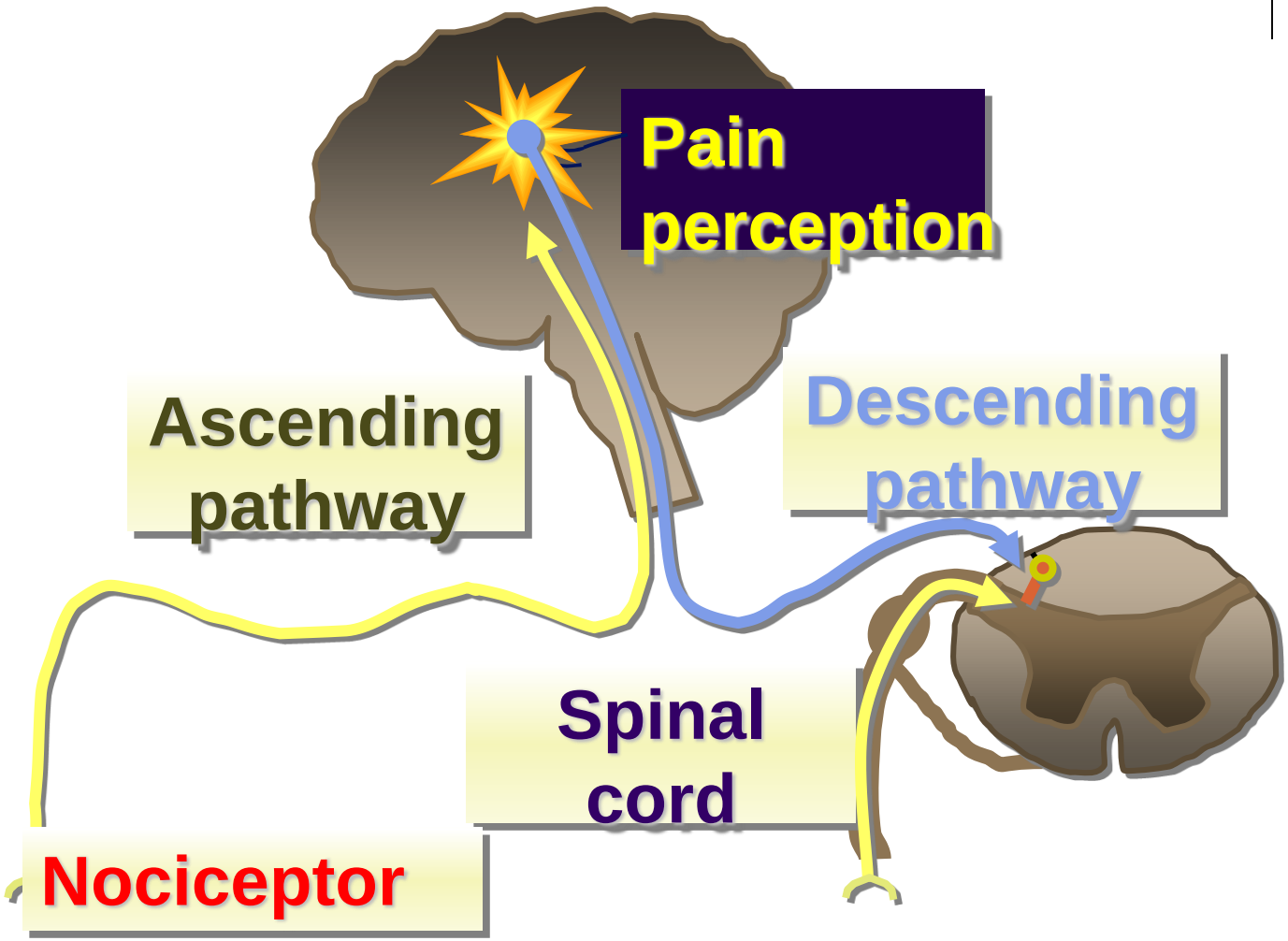


Pain is a disabling accompaniment of many medical conditions

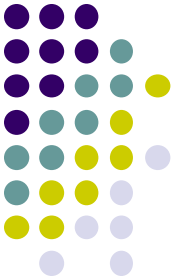
&

Pain control is one of the most important therapeutic priorities.

Pain Transmission

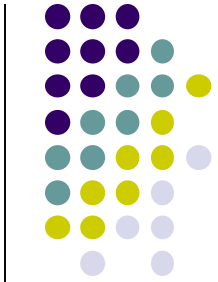


Opportunities for Pain Treatment



- At the receptor
- Along the nerve
- At receptors in spinal column and brain

TYPES OF DRUGS



NARCOTIC ANALGESIC

Opioid analgesics/morphine like

Relieve pain together with drowsiness, sleep /stupor

NON-NARCOTIC ANALGESIC

(nonopioid/NSAID(aspirin like)

A drug that relieves pain without sedation or drowsiness

TYPES OF PAIN

VISCERAL PAIN

Pain arising from a visceral structure and is severe

- ✓ **Pain of MI**
- ✓ **Post operative pain**
- ✓ **Severe burns**
- ✓ **Pain due to fracture of long bones**
- ✓ **Cancer pain**
- ✓ **Pulmonary embolism**

DOC Opioid

Somatic/ Integumental pain

- This type arises from Integumental structures or from connective tissues or due to injuries causing inflammation or inflammatory diseases

- ✓ Headache
- ✓ Myalgia
- ✓ Toothache
- ✓ Pain of arthiritis

DOC
NSAIDs

DEFINATION: Pain

An unpleasant sensory and emotional experience associated with actual or potential tissue damage,or described in terms of such damage

International association for the study of pain

Also be classified as

- ✓ **Nocioceptive:** due to stimulation of nocioceptors
- ✓ **Neuropathic:** due to damage to neural structures leading to neuronal supersensitivity
- ✓ Ischemic pain: Is due to ischemia of a tissue

Acute and chronic pain

Acute pain

Which does not outlast the initiating painful stimulus

(< 3 months duration)

Has major nocioceptive input

(physical trauma, MI, perforated peptic ulcer)

Managed primarily by analgesics

Chronic pain

outlasts the initiating stimulus, regarded as a syndrome.

- Long standing duration
- Emotional and behavioral reaction
- Analgesics and adjuvant drugs required as well as non drug measures
- **Neuropathic pain**, responds poorly to opioids.

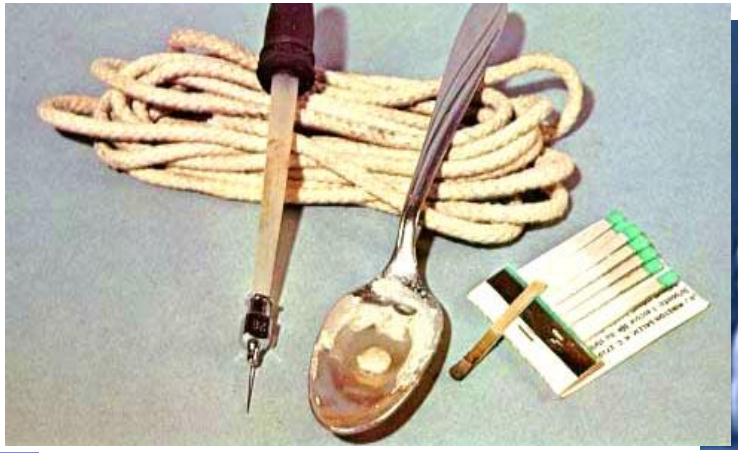
But pain is perfect misery, the worst of evils, and, excessive, overturns all patience.

(John Milton, 1608-1674, Paradise Lost)

OPIOIDS

Narcotic analgesics

"Among the remedies which have pleased Almighty God to give to man to relieve his sufferings, none is so universal and so efficacious as opium."



OPIATES

Sources

Opium poppy *(Papaver somniferum*)

Active ingredients:

Morphine – 10%

isolated in 1803 by Serturner

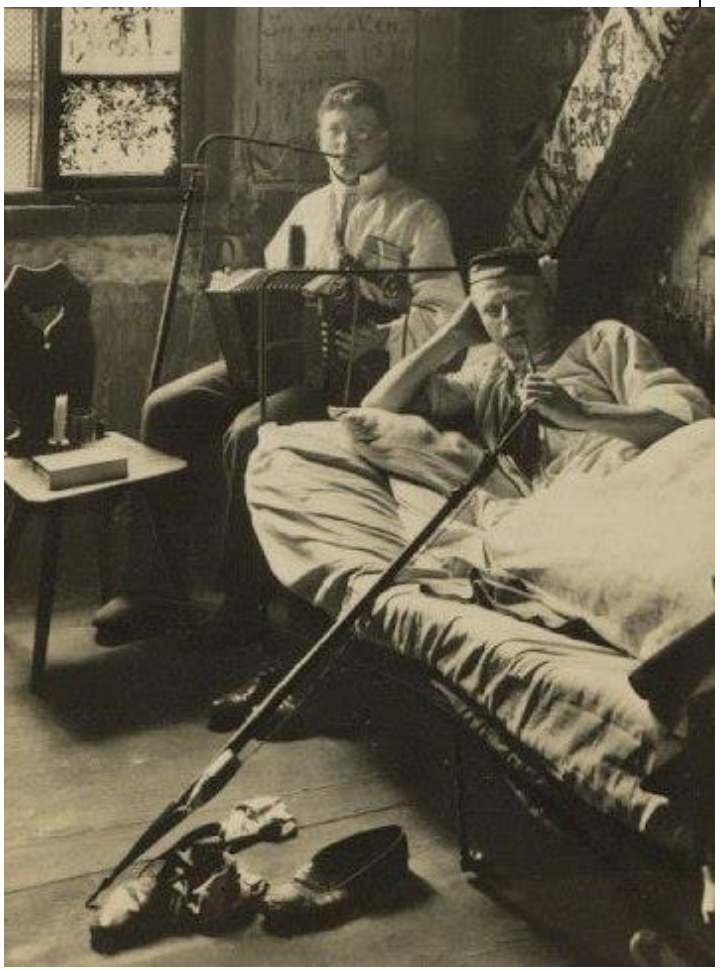
Semi synthetic opioid

Diacetyl morphine (Heroin diamorphine)

10 times more lipid soluble than morphine

Opiates and Opioids

Opium poppy



smoking opium

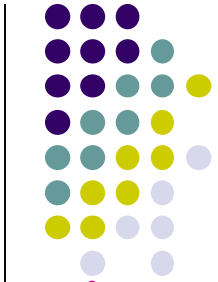
In the civil war in the U.S., the administration of "soldier's joy" often led to "soldier's disease," the opiate addiction brought about by medication of chronic pain states arising from war wounds

OBJECTIVES

1. List the receptors activated by opioid analgesics & endogenous opioid peptides.

2. Identify opioid receptor antagonists and mixed agonist-antagonists.

OBJECTIVES



3. Describe the main P/D and P/K properties of agonist opioid analgesics

4. enlist clinical uses.

5. List the main adverse effects of acute and chronic use of opioid analgesics.

6. Clinical uses of the opioid receptor antagonists.

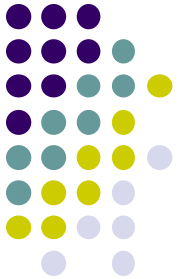
Terminology

- **"opium" is a Greek word meaning "juice," or the exudate from the poppy**

- **"opiate" is a drug extracted from the exudate of the poppy.**

- **"opioid" is a natural or synthetic drug that binds to opioid receptors producing agonist effects.**

History



- Invention of the hypodermic needle in 1856 produced drug abusers who self administered opioids by injection
- Controlling the widespread use of opioids has been **Unsuccessful**

Euphoria

Tolerance

Physiological dependence

Remains the standard against which all drugs that have strong analgesic action are compared.

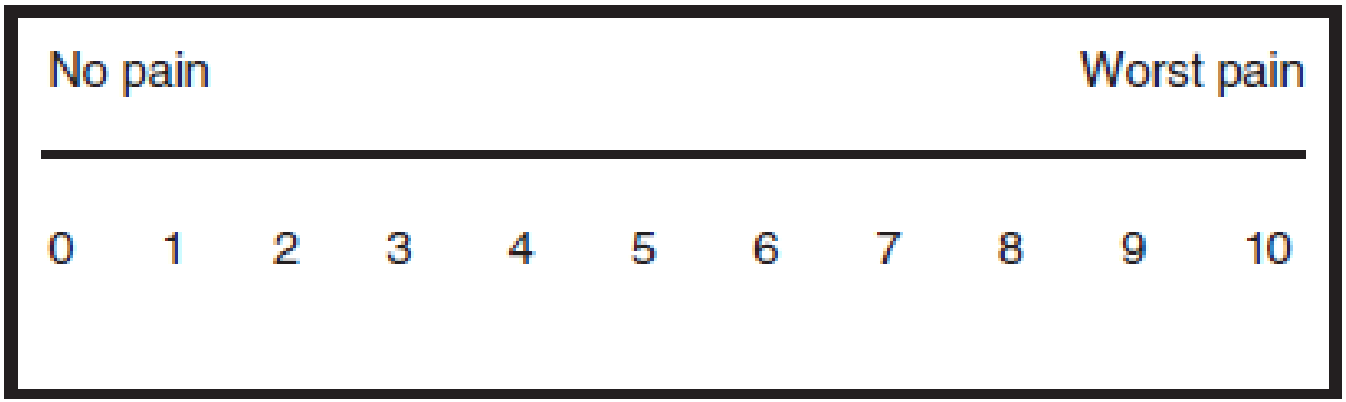
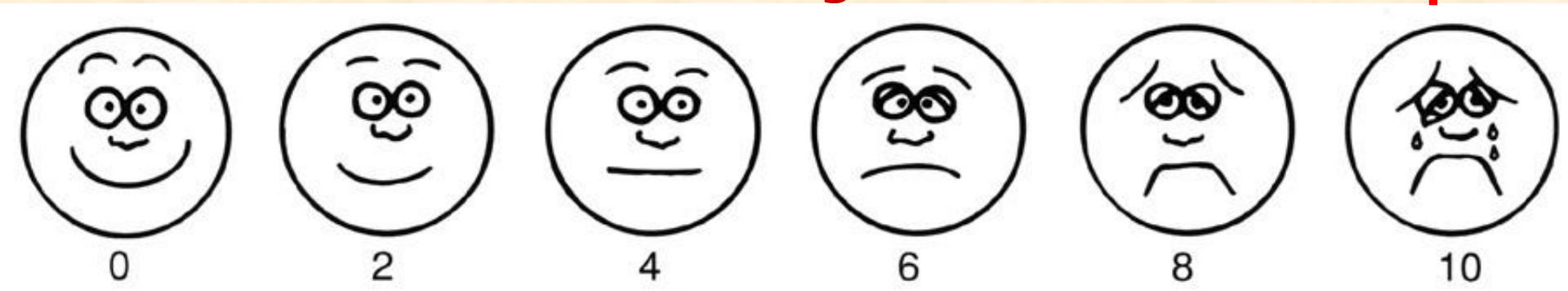


Figure 3-3. Visual Analog Scale (VAS) for the assessment of pain.

Assessment of the Pain Patient

One of the most common complaints

No Pain **Distressing Pain** **Unbearable pain**



NO HURT **HURTS LITTLE BIT** **HURTS LITTLE MORE** **HURTS EVEN MORE** **HURTS WHOLE LOT** **HURTS WORST**

Three Opioid Receptors

- Mu
- Kappa
- **Delta**

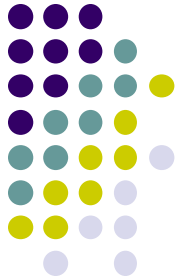
They are found in various brain regions and the spinal medulla

μ, δ, κ, mediate opioid effects: superfamily of G-protein coupled receptors

found where elsewhere ??

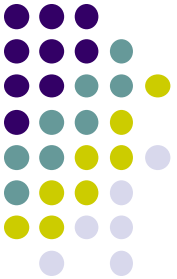
intramural nerve plexuses that regulate the motility of the alimentary and urogenital tracts.

Natural opioids occur in 2 places:



1) In the juice of the opium poppy (morphine and codeine)
2) As endogenous endorphins

Classification according to…..



SOURCE

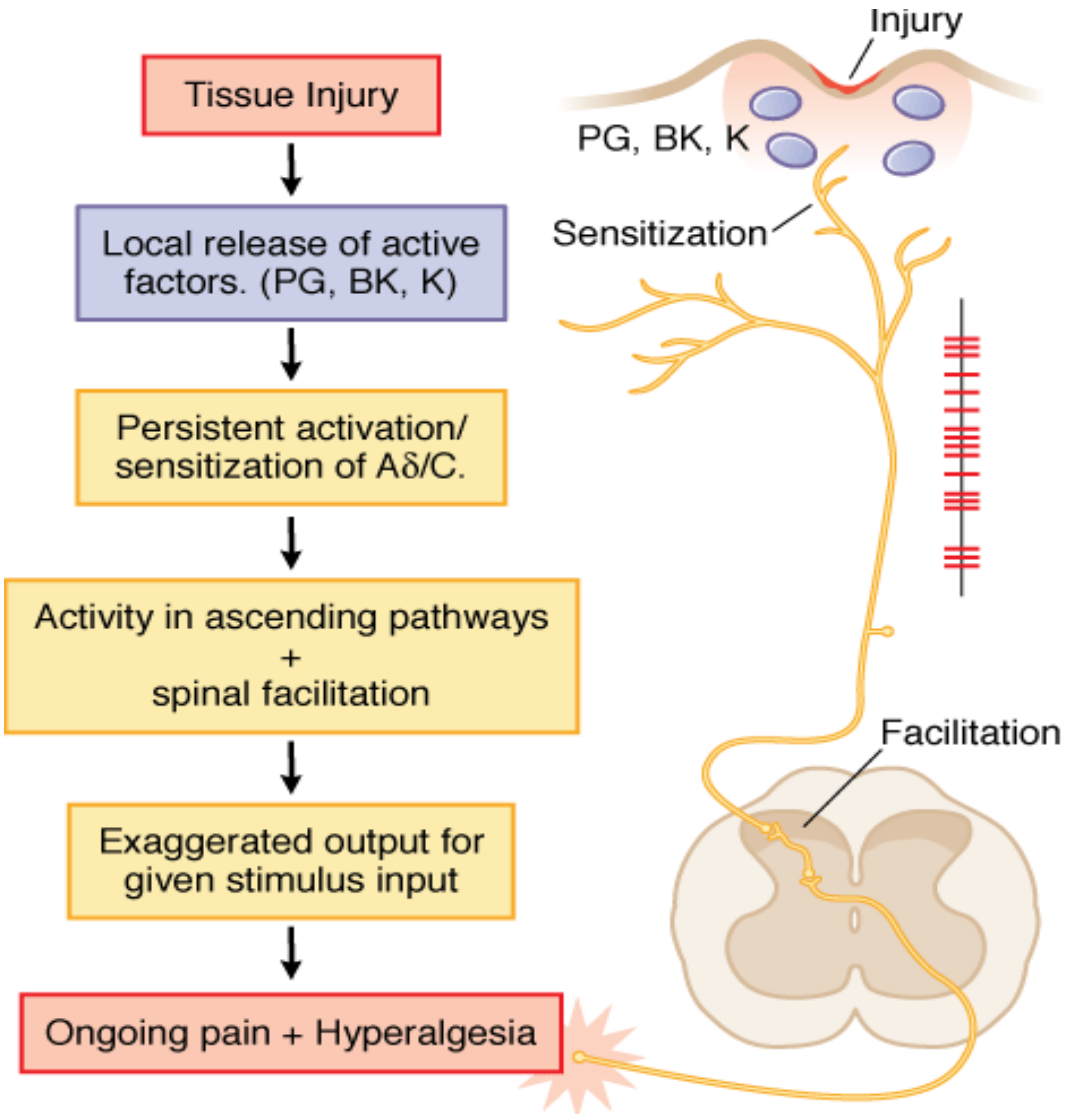
- Natural opium alkaloids:
  morphine,codeine
- Semi synthetic opiates:
  Diacetylmorphine(heroin)
  pholcodeine
- Synthetic opioids:

Pethidine,fentanyl,methadone,dextro propoxyphene,tramadol

Receptor Subtype	Functions	Endogenous Opioids Peptide Affinity
μ(mu)	Supraspinal and spinal analgesia **sedation; inhibition of respiration**; ↓ GIT transit; modulation of hormone and neurotransmitter release	**Endorphins** > enkephalins > dynorphins
δ(delta)	Supraspinal and spinal analgesia; modulation of hormone and neurotransmitter release	**Enkephalins** > endorphins & dynorphins
κ (kappa)	Supraspinal and spinal analgesia; **psychotomimetic effects**; ↓ GIT transit	**Dynorphins**> > endorphins & enkephalins

Spinal sites of action of opioids

Mechanistic flow diagram of tissue injury–evoked nociception



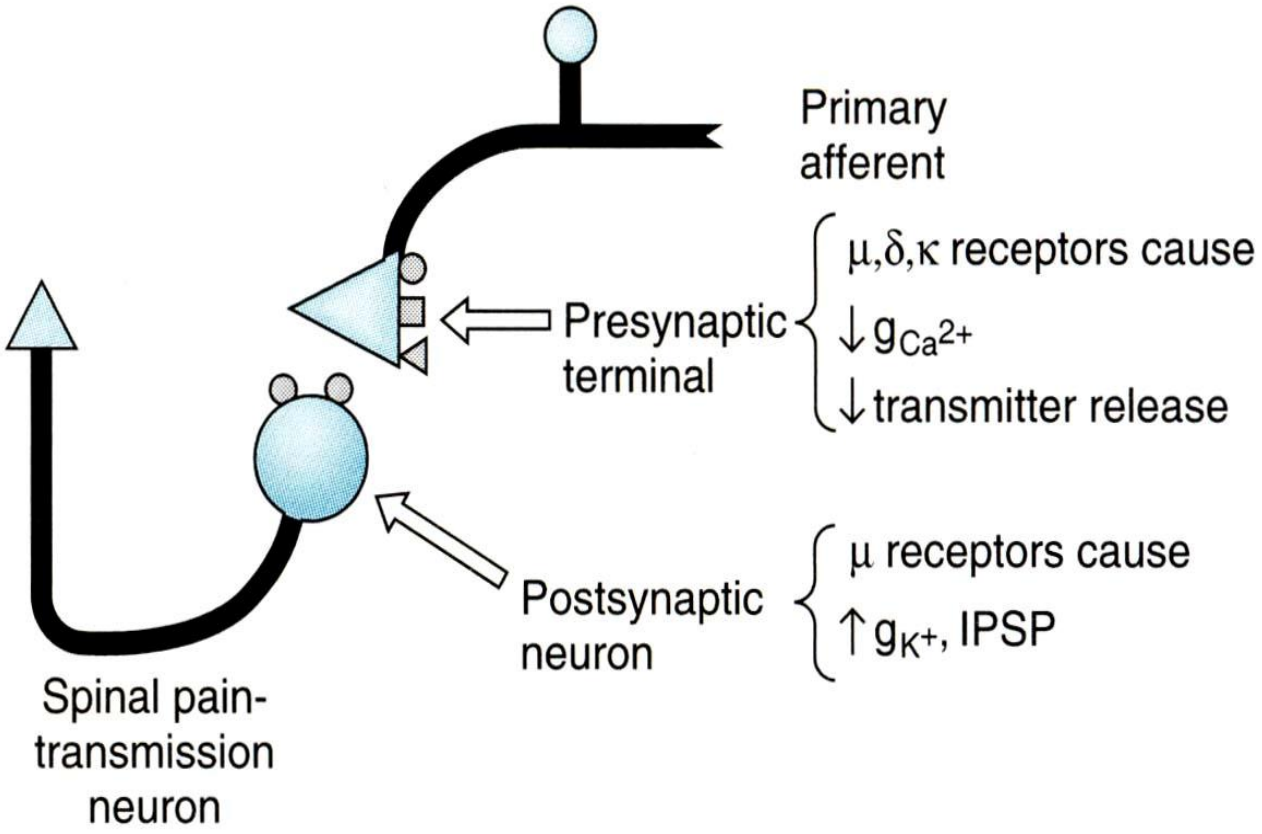
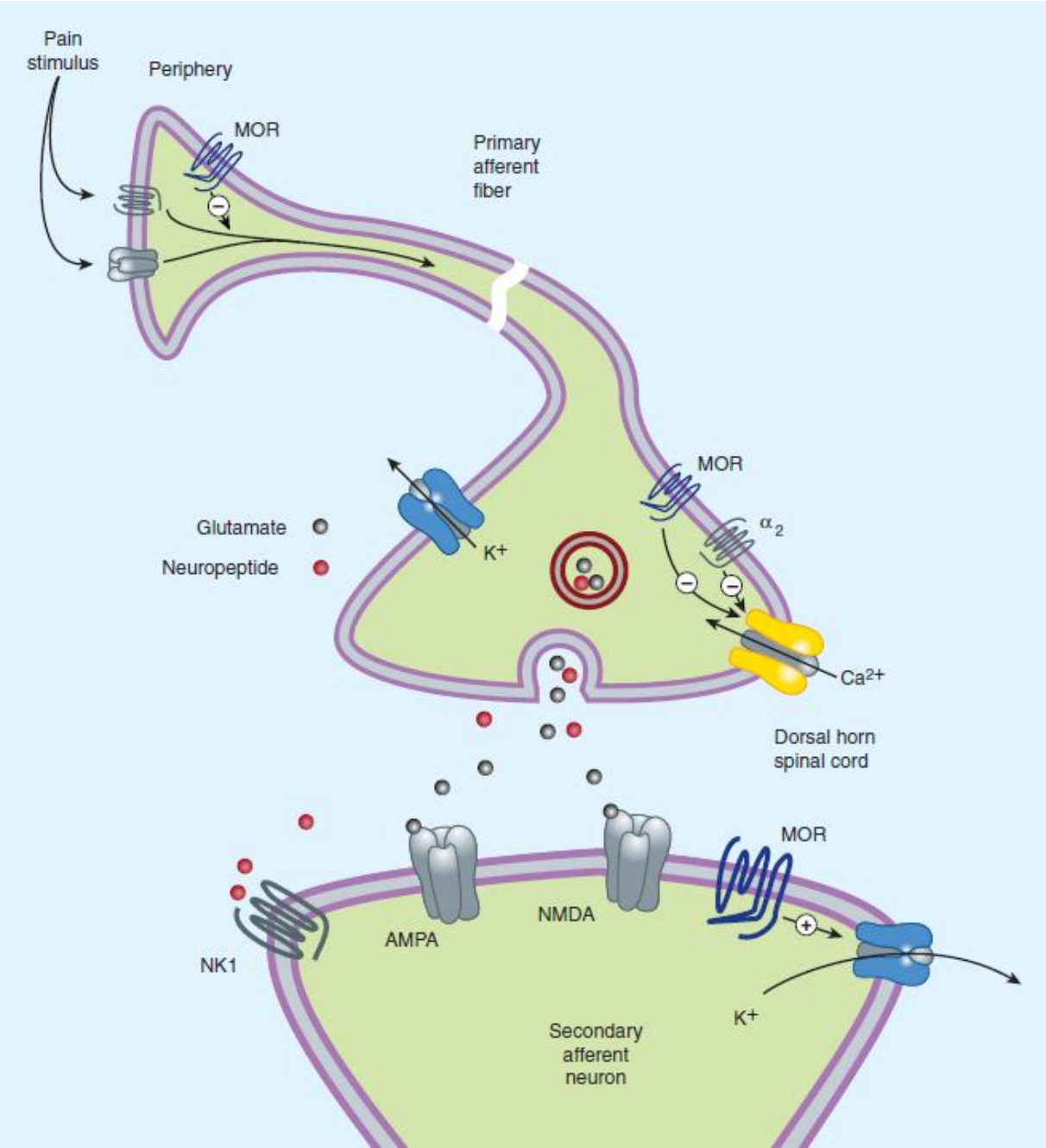
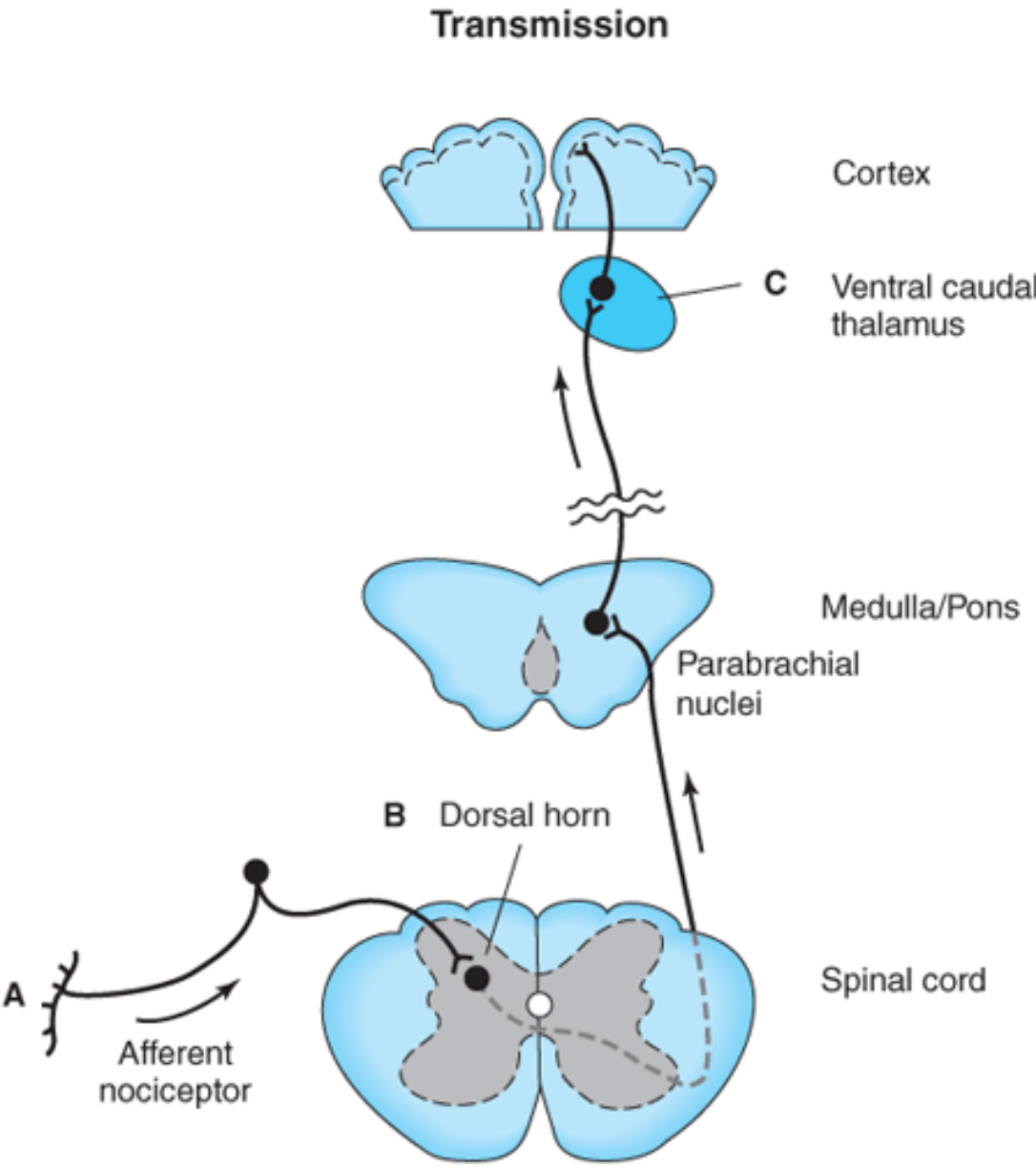


Figure 31–3. Spinal sites of opioid action. Mu, kappa, and delta agonists reduce transmitter release from presynaptic terminals of nociceptive primary afferents. Mu agonists also hyperpolarize second-order pain transmission neurons by increasing K^+ conductance, evoking an inhibitory postsynaptic potential.


Pain stimulus
Periphery
MOR
Primary afferent fiber
MOR
Glutamate
Neuropeptide
K+
α2
Ca2+
Dorsal horn spinal cord
MOR
NMDA
AMPA
NK1
K+
Secondary afferent neuron

Putative sites of action of opioid analgesics

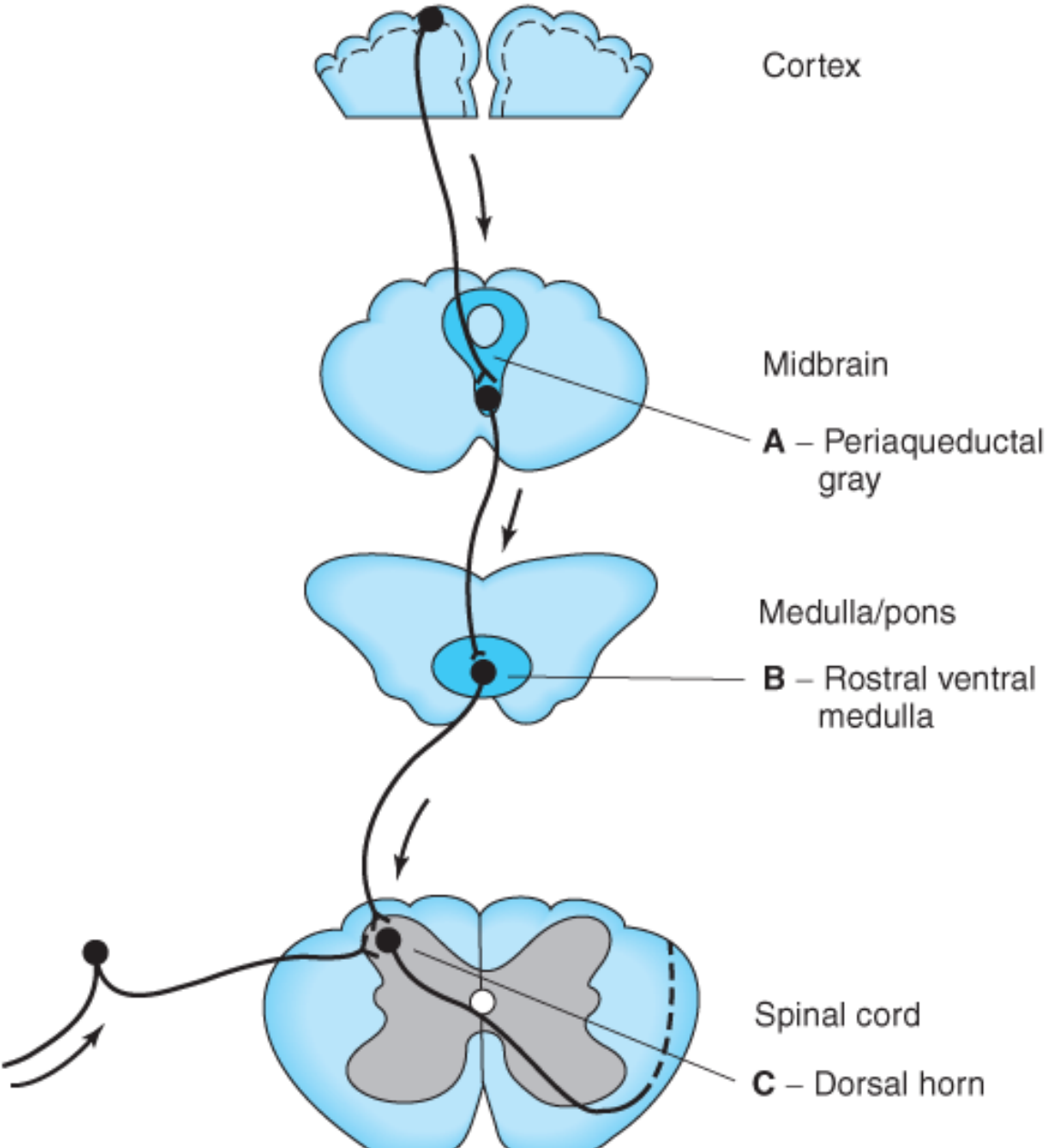


1 st order neuron – from peripheral afferents to dorsal horn(SG) of spinal cord

Second order neuron from SG to STT

Third order neurons from STT to ventral and medial thalmus Medial thalmus also sends projections to somatosensory cortex

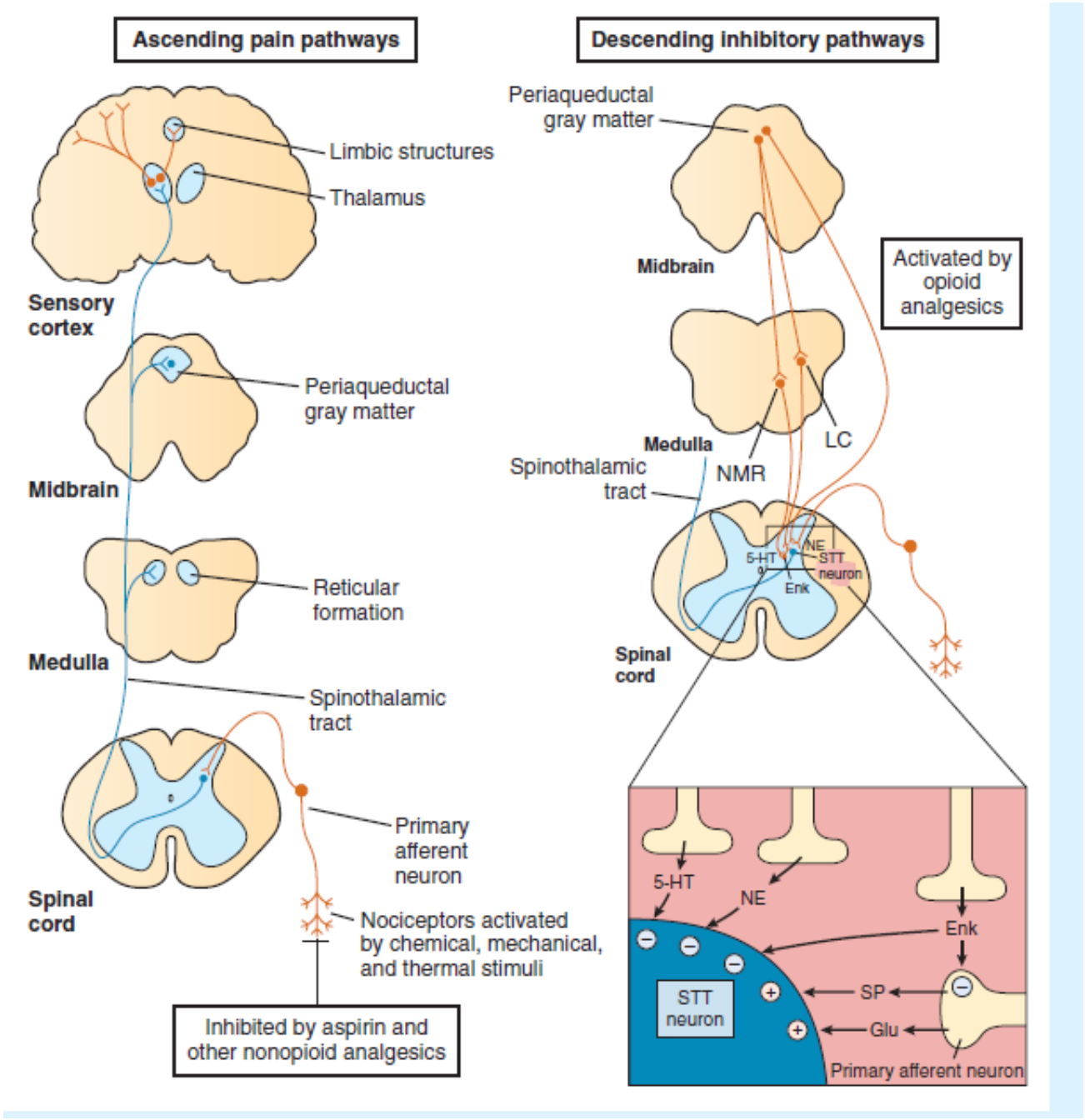
Descending inhibitory pathway

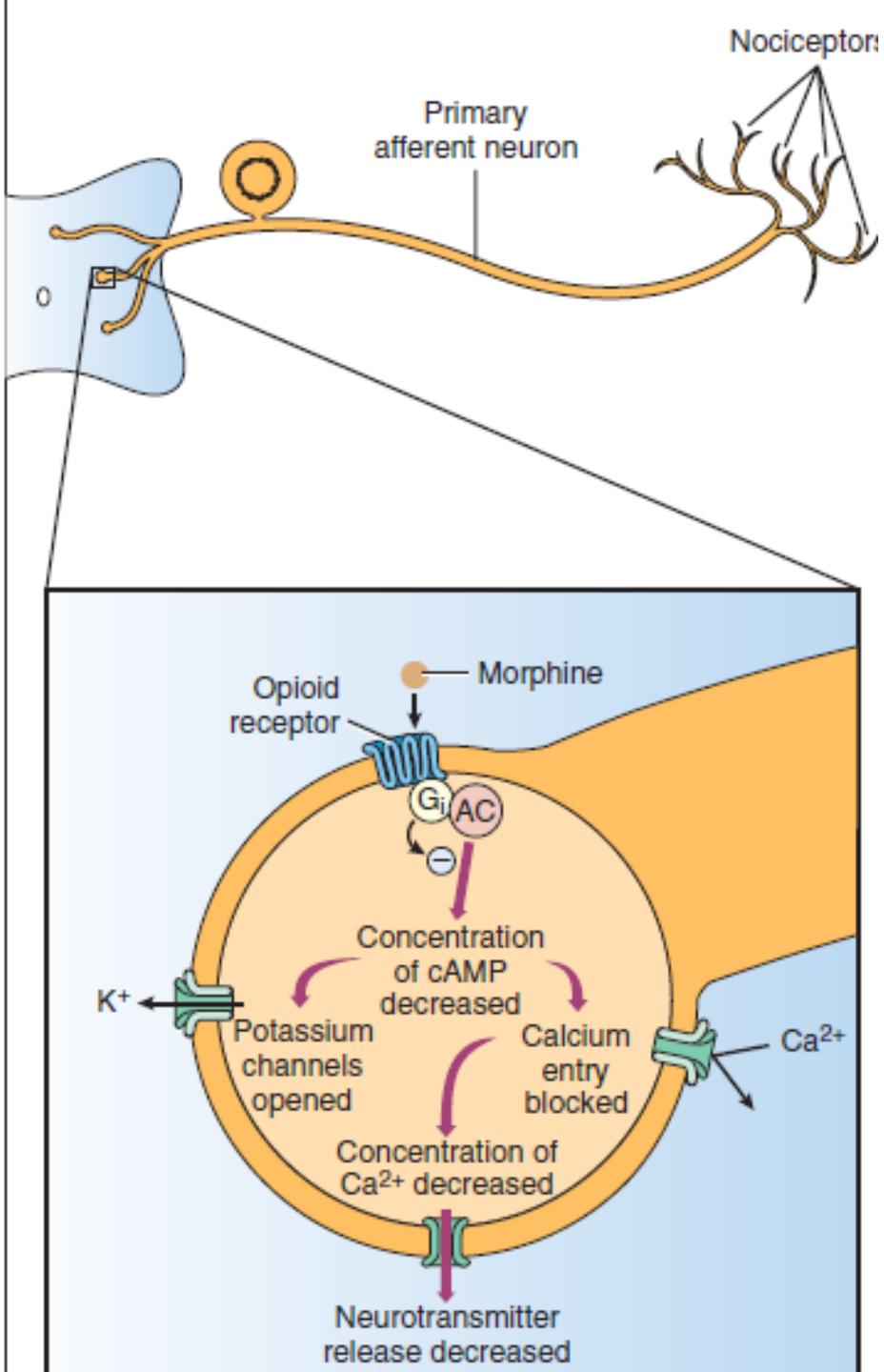


- From somatosensory cortex to midbrain
- Midbrain and brain stem produce significant inhibitory effect on transmission of dorsal horn
- The descending inhibition is mediated by 5 HT,NA and adenosine

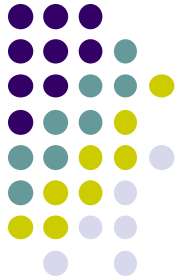
OPIOIDS PRODUCE ANALGESIA BY

1. Facilitation of inhibitory descending pathways by acting at the PAG
2. Inhibition at the thalamic site
3. Inhibition of dorsal horn transmission
4. Inhibition of excitation of peripheral nerve endings


Ascending pain pathways
Limbic structures
Thalamus
Sensory cortex
Periaqueductal gray matter
Midbrain
Reticular formation
Medulla
Spinothalamic tract
Primary afferent neuron
Spinal cord
Nociceptors activated by chemical, mechanical, and thermal stimuli
Inhibited by aspirin and other nonopioid analgesics
Descending inhibitory pathways
Periaqueductal gray matter
Midbrain
Activated by opioid analgesics
Medulla
Spinothalamic tract
NMR
LC
NE
5-HT
STT neuron
Enk
Spinal cord
5-HT
NE
Enk
STT neuron
SP
Glu
Primary afferent neuron


Nociceptors
Primary afferent neuron
Opioid receptor
Morphine
G_i
AC
Concentration of cAMP decreased
K^+
Potassium channels opened
Calcium entry blocked
Ca^{2+}
Concentration of Ca^{2+} decreased
Neurotransmitter release decreased

When administered systemically……



Act simultaneously at multiple sites

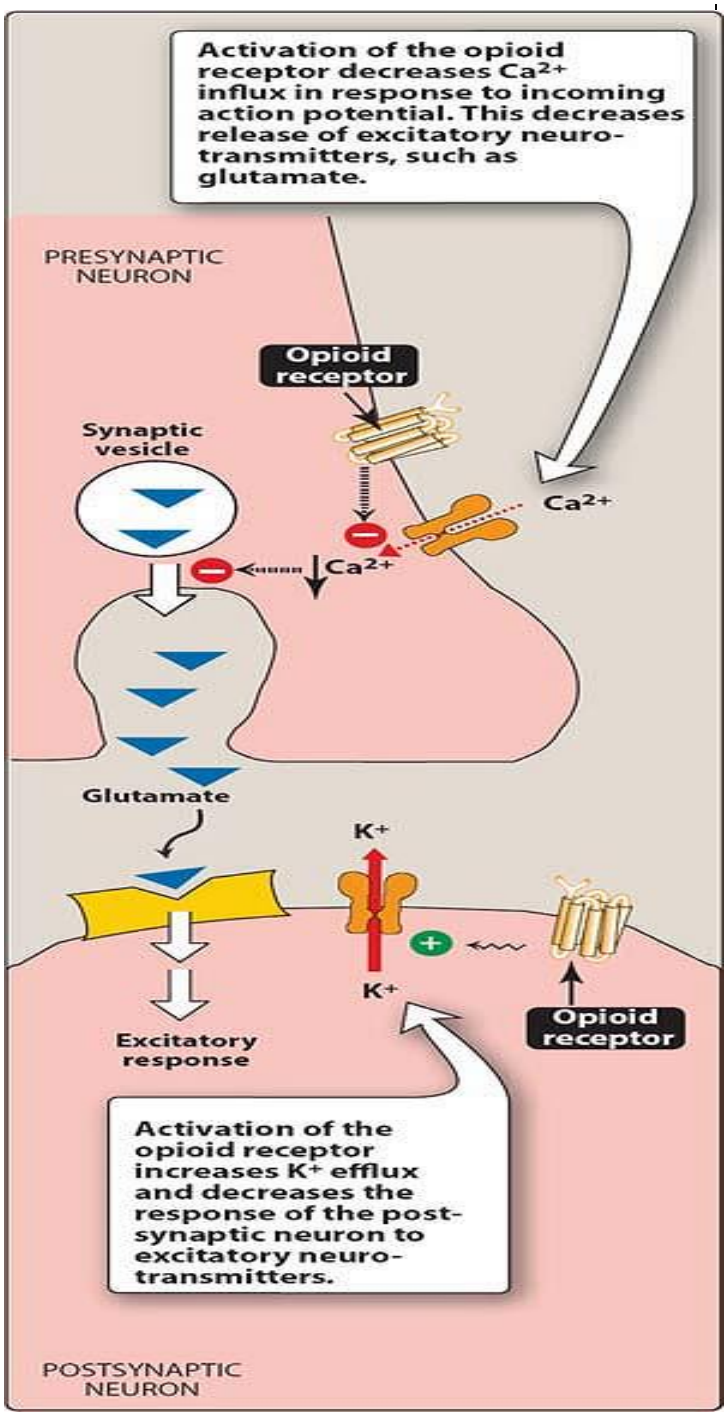
NOT ONLY THE ASCENDING PATHWAYS OF PAIN TRANSMISSION

but also

Leads to activation of **descending inhibitory neurons** that send processess to the spinal cord and inhibit pain transmission neurons

Part of the pain relieving action of exogenous opioids involves the release of endogenous opioid peptides

Mechanism of action of μ-opioid receptor agonists in the spinal cord.



Opioid Analgesics & Antagonists

- Morphine, the prototypical opioid agonist, known to relieve severe pain with remarkable efficacy.

- **Opioid analgesics** include not only the **natural** and **semisynthetic** alkaloid derivatives from opium

but also

includes synthetic surrogates, other opioid-like drugs whose actions are **blocked** by the nonselective antagonist **naloxone**

Pharmacological Effects of opioids

1. **Analgesia**: relief of pain **without** the loss of consciousness
   - Patients are still aware of the presence of pain, but the sensation is not unpleasant.

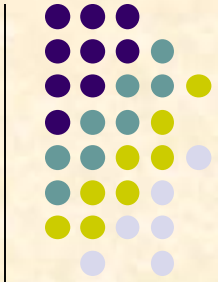
Sedation :Different from hypnotic drugs.*

Drowsiness & clouding of mentation

Why morphine is unique……

When pain does not evoke its usual responses (anxiety, fear, panic, and suffering), a patient's ability to tolerate the pain may be markedly increased

CENTRAL ACTIONS



2.Euphoria: Morphine produces a powerful sense of contentment and well-being.

Role of dopaminergic pathways involving the nucleas accumbens

3. Respiration

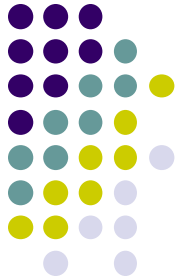
direct effect on the brainstem respiratory centres

- **depress all phases of respiratory activity (rate, minute volume, and tidal exchange)**
- **irregular & aperiodic breathing.**
- **rate falls to 3-4 breaths /min**
- **reduction of the sensitivity of respiratory center neurons to carbon dioxide.**
- **depress ventilation otherwise driven by hypoxia**
- **mechanical effects on airway function by increasing chest wall rigidity and diminishing upper airway patency (Lalley, 2008).**

Factors Exacerbating Opiate-Induced Respiratory Depression

- ***Other medications.*** combination of opiates with other depressant medications, such as general anesthetics, tranquilizers, alcohol, or sedative-hypnotics
- Sleep : natural sleep and depressant effect of morphine is additive ,esp OSA increases the chance of fatal respiratory depression.
- ***Age.*** **Newborns** & **Elderly** patients are at greater risk of depression because of reduced **lung elasticity, chest wall stiffening, and decreased vital capacity.**
- ***Disease:.*** Enhanced depression with asthma ,COPD
- ***Relief of Pain.*** Because pain stimulates respiration, removal of the painful condition reduces the ventilatory drive - apparent respiratory depression

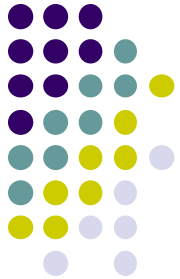
While respiratory depression is not favourable



May be used for therapeutic advantage

- To treat dyspnoea , in COPD ,where air hunger leads to extreme agitation, discomfort and gasping.
- They also find their use in patients who require artificial ventilation.

CENTRAL ACTIONS



4.Sedation and anxiolysis

- Drowsiness and lethargy
- Apathy
- Cognitive impairment
- Sense of tranquility

5.Cough suppression

Opioids suppress the “cough center” in the brain

Stimulatory actions

6.Pupillary constriction

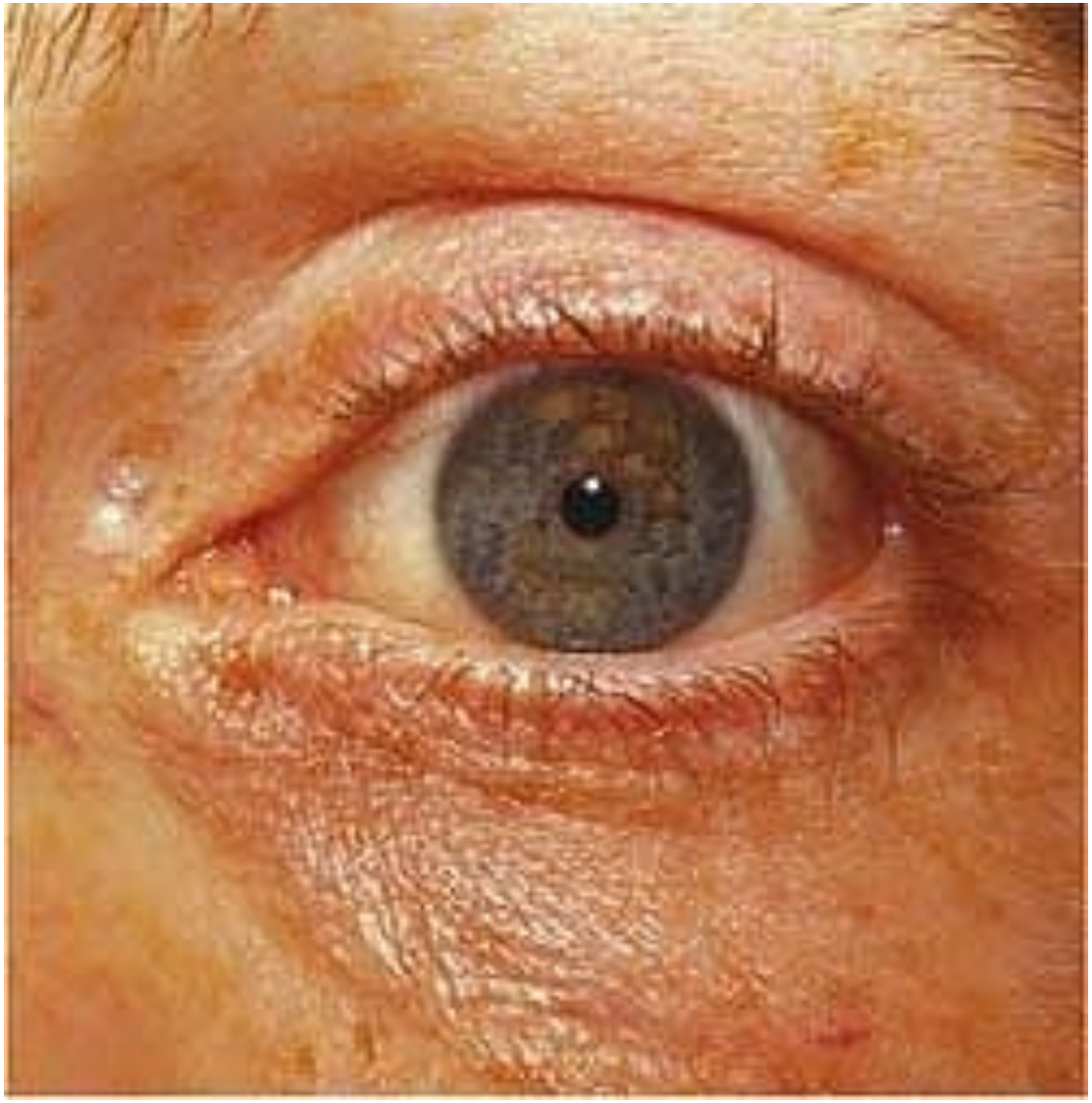
The pinpoint pupil - excites the Edinger-Westphal nucleus of the oculomotor nerve, ↑ parasympathetic stimulation to the eye

little tolerance to the effect, and all morphine abusers demonstrate pinpoint pupils.

7.Nausea and vomiting

Stimulation of receptors in an area of the medulla called the chemoreceptor trigger zone causes nausea and vomiting

Morphine abusers demonstrate pinpoint pupils



Morphine produces an analgesic effect due to

(A) A block of potassium efflux from a neuron

(B) An increase in cyclic AMP accumulation in neuron

(C) A decrease in intracellular calcium in a neuron

(D) Interaction with a Gs protein in the neuron

Pharmacological effects cont'd.

8.Vagal centre-BRADYCARDIA

9.Truncal Rigidity

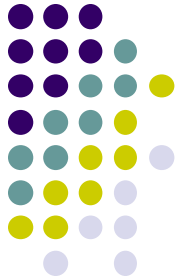
10.CONVULSIONS

Paradoxical effect …

- ✓ Opioid induced hyperalgesia
- ✓ May happen after persistent administration of opioid analgesics
- ✓ Involves activation of bradykinin and NMDA receptors
- ✓ Hence use in chronic pain is controversial

Peripheral action of opioids

Peripheral Effects
Cardiovascular System



no major effect on blood pressure or cardiac rate and rhythm. hypotension and bradycardia .

produce peripheral vasodilation, reduced peripheral resistance, and an inhibition of baroreceptor reflexes.

😐 opioids provoke release of histamine

😐 depression of vasomotor centre

In addition

- Mimics the phenomenon of ischemic preconditioning, where a short ischemic episode paradoxically protects the heart against further ischemia.
- This effect appears to be mediated through receptors signaling through a mitochondrial ATP-sensitive K+ channel in cardiac myocytes

Morphine exerts its well-known therapeutic effect in the treatment of acute myocardial infarction

<u>by decreasing</u>

preload, inotropy& chronotropy

altering determinants of myocardial O2 consumption

2. Not a direct action…..

Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase the cerebrospinal fluid (CSF) pressure

3.Effect on motor tone

- Seen at higher doses.
- Rigidity of chest wall and masseter severe enough to compromise respiration.
- Myoclonus may result.
- Is due to inhibition of inhibitory interneurons in the ventral horn of spinal cord.

4.Histamine release: from mast cells, causing urticaria, sweating, and vasodilation, bronchoconstriction.

5.Hormonal actions: inhibits release of GnRH and CRH, ↓ LH, FSH& ACTH, Testosterone and cortisol ↓.

↑ **Antidiuretic hormone →urinary retention**.

- Morphine inhibits the urinary voiding reflex
- increases the tone of the external sphincter and the volume of the bladder
- Catheterization sometimes required after therapeutic doses of morphine.

4.GIT

Decreases gastric motility,

amplitude of the nonpropulsive type of rhythmic, segmental contractions is ↑, but propulsive contractions are ↓

↕

CONSTIPATION

Spasm of pyloric,ileocaecal and anal sphincters

&

Sphincter of Oddi

Opioid receptors(u type) densely distributed in enteric neurons between myenteric and submucosal plexi and on variety of secretory cells.

IMMUNE SYSTEM

- immunosuppressive, and increased susceptibility to infection and tumor spread observed.

Effects on skin

- Skin flushed.
- Pruritis and itching is a diabling complication .
- Not reversed by naloxone.
- Can follow systemic as well as intraspinal injections (epidural or intrathecal)

Tolerance &Physical Dependence

- ***Tolerance*** :Over time, drug loses effectiveness and ↑ dose reqd to produce same physiological response.

- ***Dependence*** : complex changes in the homeostasis of an organism causing disturbance of the homeostatic set point of the organism if the drug is stopped. Disturbance revealed -opioids stopped abruptly, resulting in ***withdrawal.***

- ***Addiction*** is a behavioral pattern characterized by compulsive use of a drug and overwhelming involvement with its procurement and use.
- **Tolerance and dependence are physiological responses seen in all patients- not predictors of addiction**

Mechanism???????

receptor recycling.

- Normally, activation of receptors by endogenous ligands results in endocytosis followed by resensitization and recycling of the receptor

- *failure* of morphine to induce endocytosis of the opioid R

Receptor uncoupling

OPIOID ROTATION

Table 31–3. Degrees of tolerance that may develop to some of the effects of the opioids.

High	Moderate	Minimal or None
Analgesia Euphoria, dysphoria Mental clouding Sedation Respiratory depression Antidiuresis Nausea and vomiting Cough suppression	Bradycardia	Miosis Constipation Convulsions Antagonist actions

Which of the following action is mediated by kappa receptor activation

a) Cerebrovascular dilatation
b) Euphoria
c) Spinal analgesia
d) Psychologic dependence

Sedation

Urinary retention

Constipation

Potential for addiction

Nausea

Respiratory depression

You are on your way to take pharmacology MCQ examination and you suddenly get an attack of diarrhoea.Which over the counter opioid with antidiarrhoeal action will u ask for?

a) **Codeine**
b) **Loperamide**
c) **Dextromethorphan**
d) **morphine**

Which of the following statements about morphine is correct?

A. used to relieve pain caused by severe head injury.

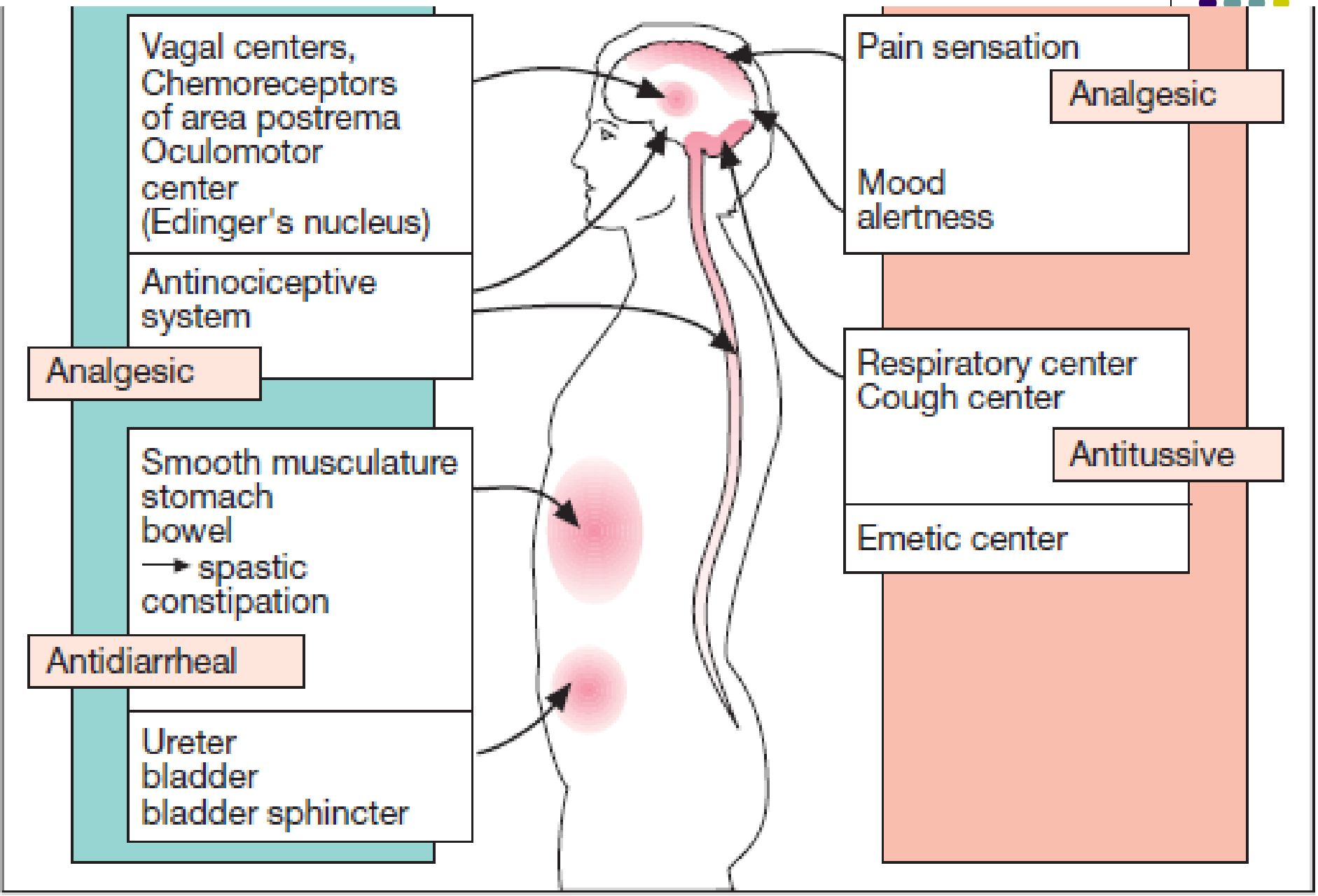
B. rapidly enters all body tissues, including the fetus.

C. Causes diarrhea.

D. Most effective by oral administration.

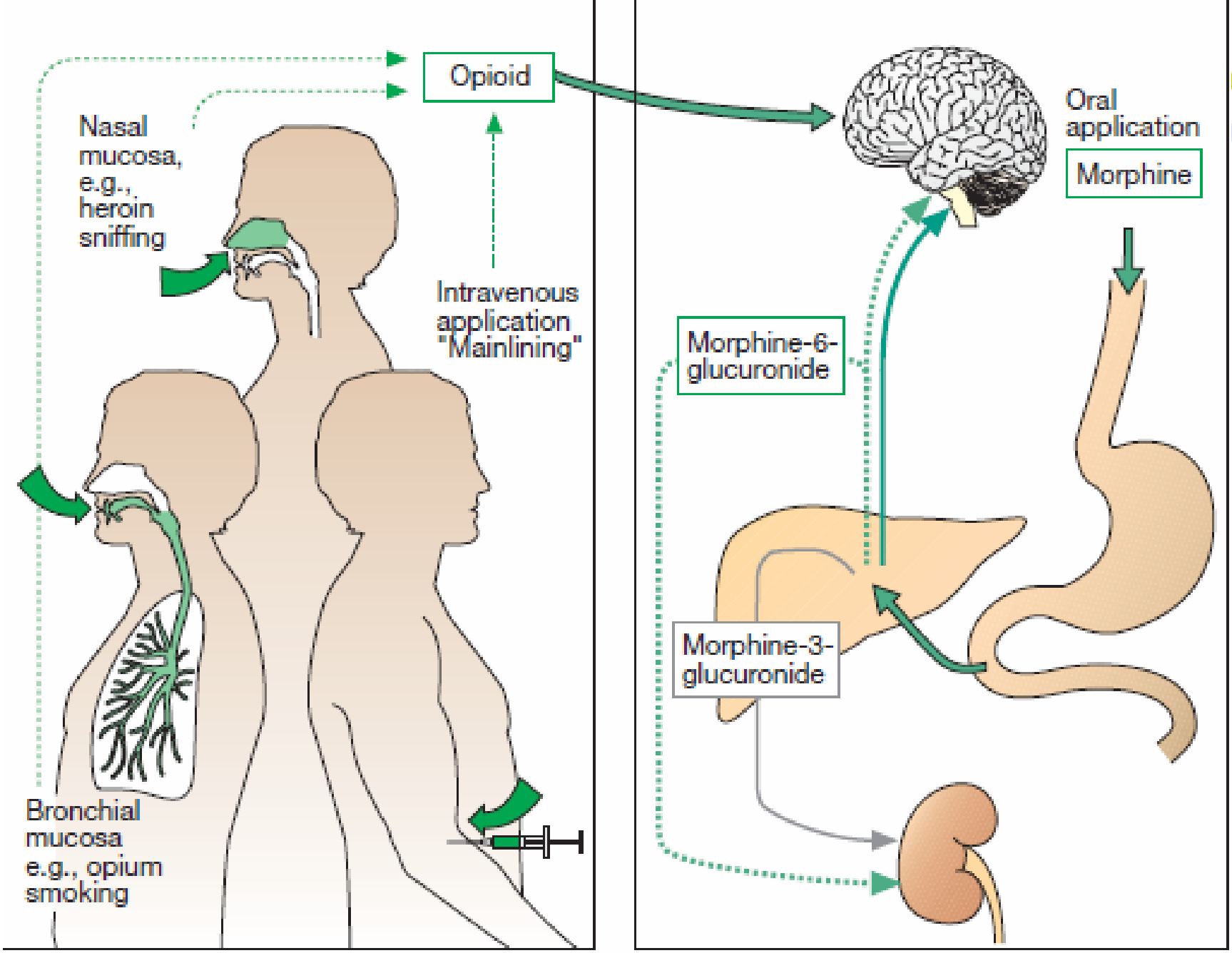
E. Withdrawal symptoms relieved by naloxone

Effects of opioids



Morphine administration

- oral morphine **not given** due to erratic oral availability
- significant variable first pass effect from person to person
- rapidly enters all body tissues, including the fetuses of pregnant women- not be used for analgesia during labor


Opioid
Nasal mucosa, e.g., heroin sniffing
Intravenous application "Mainlining"
Bronchial mucosa e.g., opium smoking
Oral application
Morphine
Morphine-6-glucuronide
Morphine-3-glucuronide
Application and rate of disposition
Metabolism of morphine

- Morphine-6-glucuronide is excreted by the kidney
- **Renal failure**, accumulation of the metabolite
- explaining morphine's potency and long duration in patients with compromised renal function.

4. Which of the following opioids is so lipophilic that it is marketed in a skin patch used to treat chronic pain?
   (A) morphine
   (B) naltrexone
   (C) scopolamine
   (D) methadone
   (E) fentanyl

5. In a case of an opioid overdose, naloxone can be given in repeated doses because of which property of naloxone?

(A) may have a shorter half-life than the opioid agonist

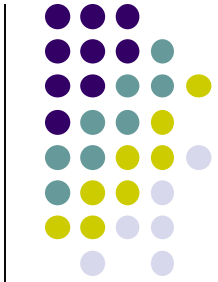
(B) is effective only at high cumulative doses

(C) is needed to stimulate the respiratory center

(D) is safe only in extremely small doses

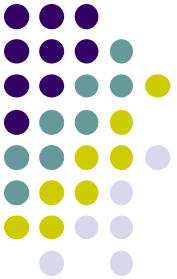
(E) is only a partial opioid agonist

Contraindications and cautions



- Respiratory diseases (BRONCHIAL ASTHMA)
- Undiagnosed acute abdomen
- Head injury
- Neonates and elderly
- Renal and hepatic Diseases

Classification according to…..

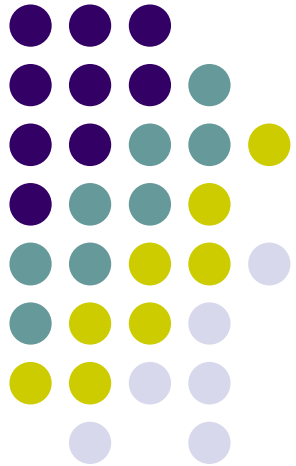


SOURCE

- Natural opium alkaloids:
  morphine,codeine
- Semi synthetic opiates:
  Diacetylmorphine(heroin)
  pholcodeine
- Synthetic opioids:

Pethidine,fentanyl,methadone,dextro propoxyphene,tramadol

Specific opioid agents



Codeine- moderate agonist

- ✓ **analgesia -due to conversion to morphine, antitussive effects due to codeine itself.**
- ✓ **less potent analgesic than morphine, but has a higher oral effectiveness.**
- ✓ **good antitussive activity at subanalgesic doses.**
- ✓ lower potential for abuse than morphine - produces dependence. produces less euphoria
- ✓ **often used in combination with aspirin or acetaminophen.**
- ✓ The greater oral efficacy -reflects lower first-pass metabolism
- ✓ **moderate to low affinity for opioid receptors,**
- ✓ **conversion to morphine by CYP2D6.**

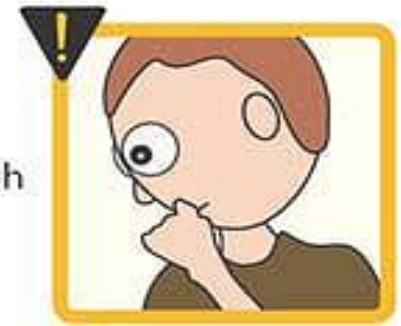
Some actions of codeine

Analgesia

Sedation

Euphoria

Dry Cough



Term	Definition
Opiate	A drug derived from alkaloids of the opium poppy
Opioid	The class of drugs that includes opiates, opiopeptins, and all synthetic and semisynthetic drugs that mimic the actions of the opiates
Opioid peptides	Endogenous peptides that act on opioid receptors
Opioid agonist	A drug that activates some or all opioid receptor subtypes and does not block any
Partial agonist	A drug that can activate an opioid receptor to effect a submaximal response
Opioid antagonist	A drug that blocks some or all opioid receptor subtypes
Mixed agonist-antagonist	A drug that activates some opioid receptor subtypes and blocks other subtypes

Mu and Kappa Receptor Activation

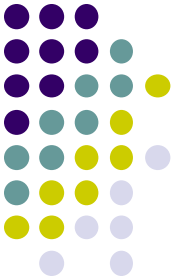
Response		Mu	Kappa
Analgesia		★	★
Respiratory Depression		★	
Euphoria		★	
Dysphoria			★
Decrease GI motility		★	★
Physical Dependence		★	

Mu and Kappa Receptors

DRUGS	MU	KAPPA
Pure Agonists	Agonist	Agonist
Agonist-Antagonist	Antagonist	Agonist
Pure Antagonists	Antagonist	Antagonist

OPIOID ANALGESICS AND ANTAGONISTS

Buprenorphine :Partial u agonist and *k* antagonist



STRONG AGONISTS

- *Alfentanil*
- *Fentanyl*
- *Heroin*
- *Meperidine*
- *Methadone*
- *Morphine*
- *Oxycodone*
- *Remifentanil*
- *Sufentanil*

MODERATE/LOW AGONISTS

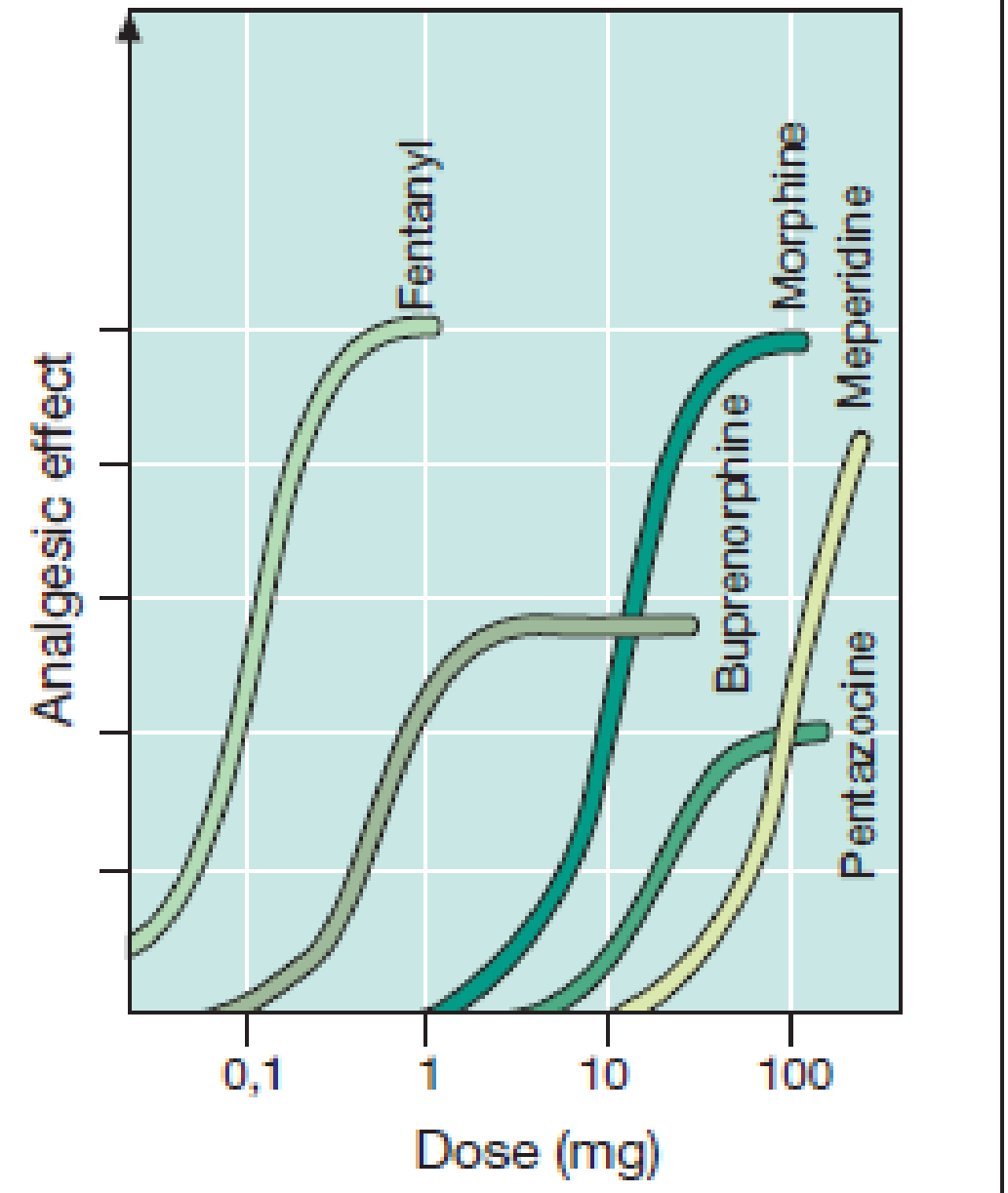
- *Codeine*
- *Propoxyphene*

MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS

Buprenorphine
Butorphanol
Nalbuphine
Pentazocine

ANTAGONISTS

Nalmefene
Naloxone
Naltrexone



. Opioids: dose-response relationship

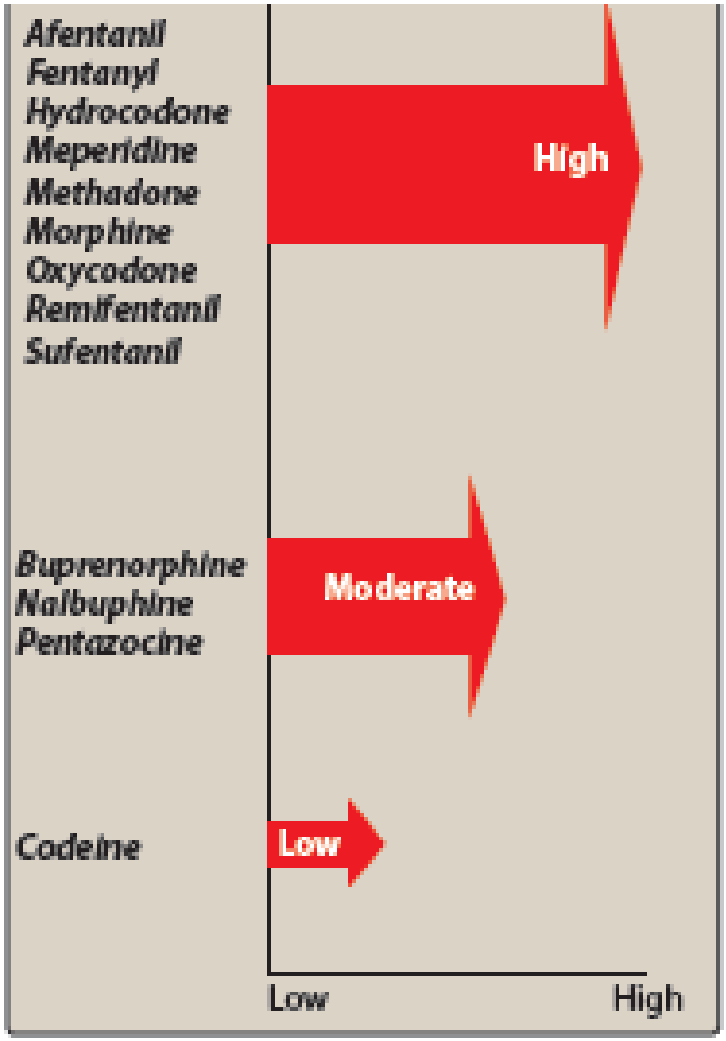


Figure 14.3
A comparison of the maximum efficacy of commonly used narcotic analgesics.

Meperidine (pethidine)

1. Synthetic opioid structurally unrelated morphine.
2. used for acute pain.
3. depresses respiration similar to morphine,
4. no significant cardiovascular action when given orally.
5. ↑ **es cardiac rate**.,
6. dilates cerebral vessels, ↑ CSF pressure
7. contracts smooth muscle to a **lesser extent**

- ✓ analgesia for severe pain.
- ✓ no clinical utility in diarrhea / cough.
- ✓ produces less ↑ in urinary retention
- ✓ less effects on uterine smooth muscle

  opioid commonly employed in obstetrics
- ✓ well absorbed from the GIT
- ✓ useful when an orally administered, potent analgesic needed.
- ✓ duration of action of 2 to 4 hours, which is shorter than that of morphine

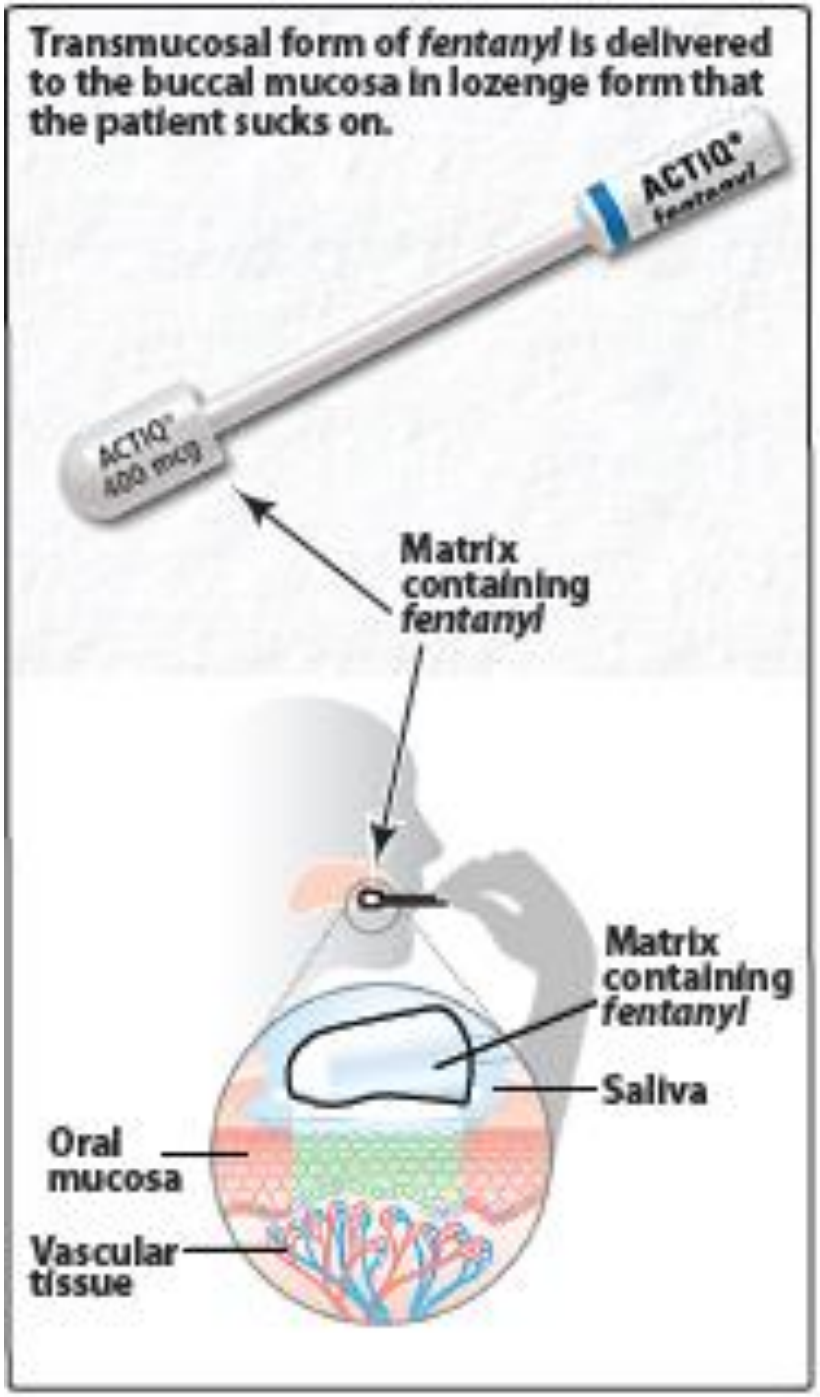
- Meperidine is N-demethylated to normeperidine /Norpethidine
- Anxiety, tremors, muscle twitches, and rarely, convulsions due to the accumulation of THIS toxic metabolite

Fentanyl

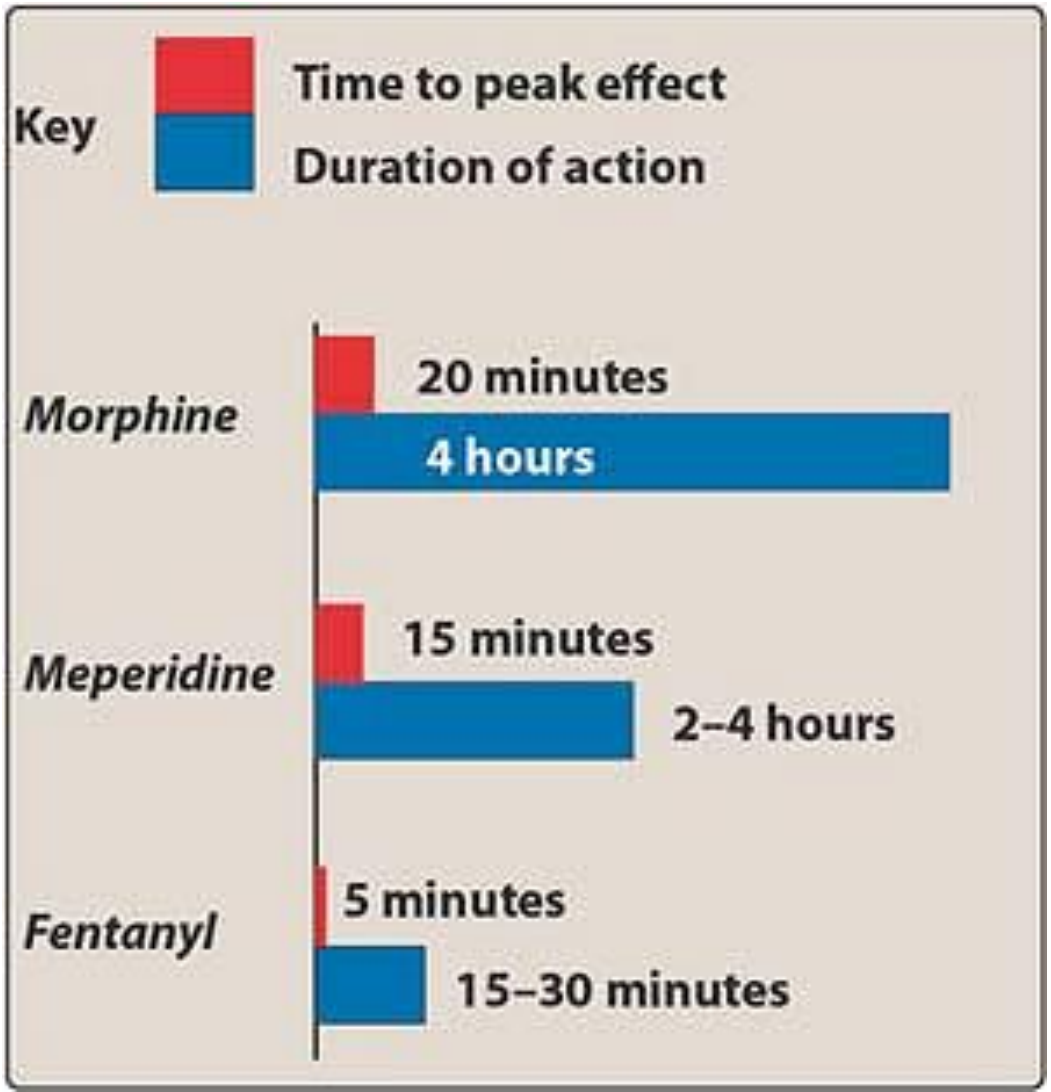
- 100-fold the analgesic potency of morphine
- used in anesthesia.
- highly lipophilic , rapid onset and short duration of action (15 to 30 minutes).
- injected IV, epidurally, or intrathecally.
- oral transmucosal /transdermal patch available.[Note: The transdermal patch creates a reservoir of the drug in the skin.

- Few cardiac effects
- Muscular rigidity, primarily of abdomen/ chest wall,
- life-threatening hypoventilation, the fentanyl patch is contraindicated in the management of acute and postoperative pain

Sufentanil, alfentanil, and remifentanil


Transmucosal form of *fentanyl* is delivered to the buccal mucosa in lozenge form that the patient sucks on.
ACTIQ®
fentanyl
ACTIQ®
Matrix containing *fentanyl*
Matrix containing *fentanyl*
Saliva
Oral mucosa
Vascular tissue

Time to peak effect and duration of action of several opioids administered intravenously.



Methadone

- long-acting μ receptor agonist
- Outstanding properties are its analgesic activity, its efficacy by the oral route, its extended duration of action in suppressing withdrawal symptoms in physically dependent individuals
- 90% bound to plasma proteins,
- T1/2 -15 to 40 hours.

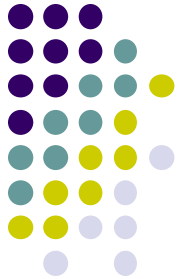
Methadone Maintenance

The Gold Standard

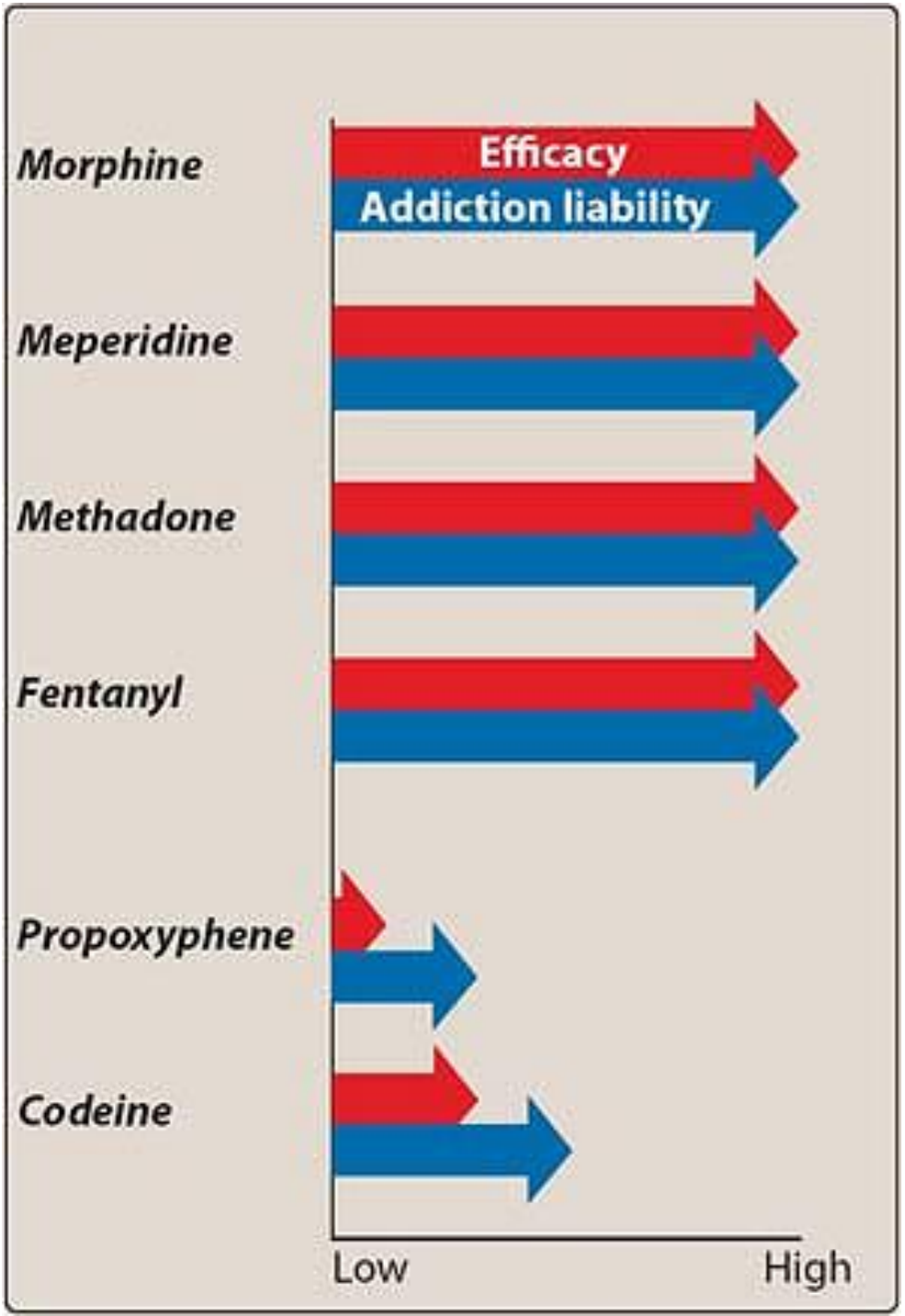
Why Methadone???

- Firmly bound to tissues including brain
- Repeated dosing → accumulation in tissues
- Administration discontinued, low concentrations maintained in plasma by slow release from extra vascular binding sites.
- relatively mild but protracted withdrawal syndrome (days to weeks)

METHADONE

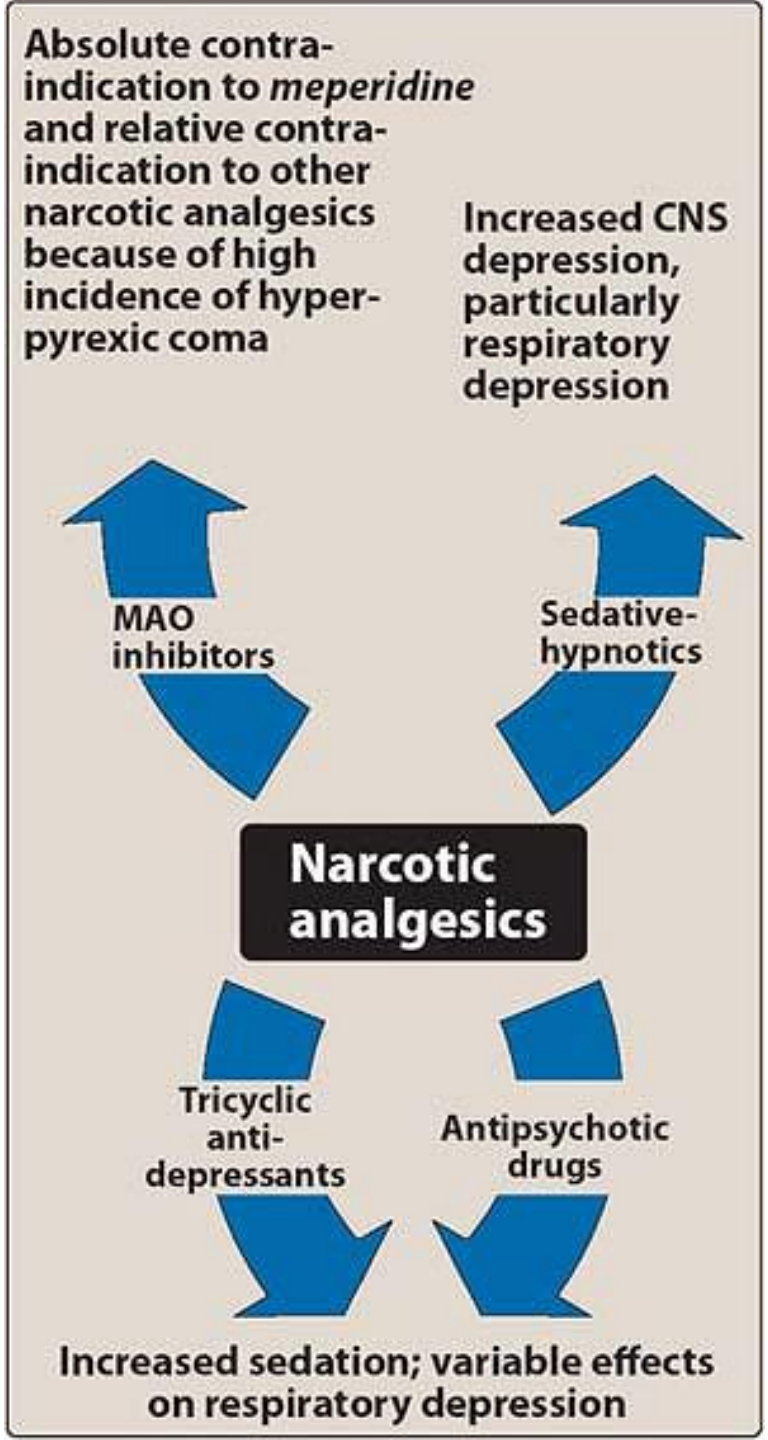


➔ equal in potency to morphine but induces less euphoria



A comparison of the maximum efficacy and addiction/abuse liability of commonly used narcotic analgesics

4. Which of the following opioids is so lipophilic that it is marketed in a skin patch used to treat chronic pain?
   (A) morphine
   (B) naltrexone
   (C) scopolamine
   (D) methadone
   (E) fentanyl



Drugs interacting with opioid analgesics

A heroin addict entering a rehabilitation program requires that he take methadone. Methadone is effective in this situation because it:

A. Is an antagonist at the morphine receptors.

B. Has less potent analgesic activity than heroin.

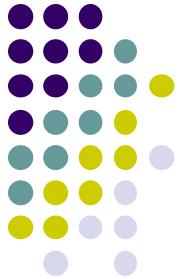
C. Is longer acting than heroin;

D. Does not cause constipation.

E. Is non addictive.

Tolerance and Dependence

Failure to continue administering the drug



- withdrawal or abstinence syndrome
- Reflects an exaggerated rebound from the acute pharmacologic effects of the opioids.

OPIATE WITHDRAWAL

- Not life-threatening but associated with severe psychological and moderate physical distress.
- onset of withdrawal symptoms typically occurs 8 to 16 hours after cessation of the use of heroin or morphine.
- Autonomic disturbances and myalgias tend to appear first.

- Peak effects 36-48 hours, after which most of the signs and symptoms gradually subside
- By 7-8 days, most of the effects have disappeared
- Some may persist for months

Stage I: Up to 8 hours

Anxiety

Drug craving

Stage II: 8–24 hours

Anxiety

Insomnia

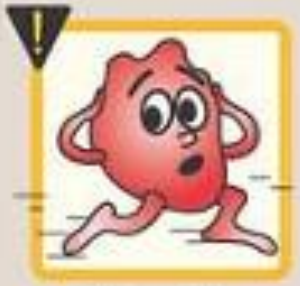
GI Disturbance

Rhinorrhea

Mydriasis

Diaphoresis

Stage III: Up to 3 days

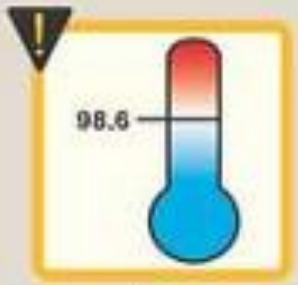


Tachycardia

Nausea, vomiting

Hypertension

Diarrhea



Fever

Chills

Tremors

Seizure

Muscle spasms

MANAGEMENT

- Commonly used replacement medication is **methadone**, dose 20 to 40 mg/day by mouth

After 2 or 3 days of stabilization, the dose can be gradually tapered over 1 to 3 weeks

- **Clonidine**

0.1 to 0.2 mg / 8 hours. ↑to 0.8 to 1.2 mg/day. Subsequently, clonidine is tapered over a 10- to 14-day period.

- Nonspecific treatment for opiate withdrawal benzodiazepines /chloral hydrate for anxiety and sleep

- prochlorperazine for GI symptoms.

- **Propoxyphene and/or NSAIDs** may help in treating myalgia

Mixed Agonist-Antagonists &Partial Agonists

- Drugs that **stimulate one receptor** but **block another**.
- Effects depend on previous exposure to opioids
- Opioids naïve:mixed agonist-antagonists show agonist activity and **are used to relieve pain.**
- Opioid dependent, : may show primarily blocking effects ➔produce **withdrawal symptoms.**

Pentazocine

Agonist at κ, weak antagonist at μ receptors.

- Relieves moderate pain.
- administered either orally /parenterally.
- Produces ↓ euphoria compared to morphine.
- ↑ doses, respiratory depression and dysphoria
- High doses ↑ B.P ,CAN increase the work of the heart.
- doesn't antagonize the respiratory depression of morphine
- precipitate a withdrawal syndrome in a morphine abuser.
- Ceiling effects analgesia & respiratory depression above 50 to 100 mg

Buprenorphine

- Semisynthetic, highly lipophilic opioid
- 25 to 50 times more potent than morphine.
- Partial mu receptor agonist
- Tight binding to u, dissociates slowly from receptors.
- half-life for dissociation :166 minutes as opposed to 7 minutes for fentanyl
- well absorbed by most routes
- potential advantage of buprenorphine over methadone is that there is less withdrawal discomfort after cessation
- 0.4-0.8 mg sublingually/im,sc.im

Morphine should be used with caution / not used in all of the following conditions, Except

a) **Bronchial Asthma**
b) **Head injury**
c) **Acute abdominal pain**
d) **Left ventricular failure**

Which of the following opioid analgesic should not be used for pain of acute myocardial infarction ?

a. Morphine
b. Buprenorphine
c. Pethidine
d. Pentazocine

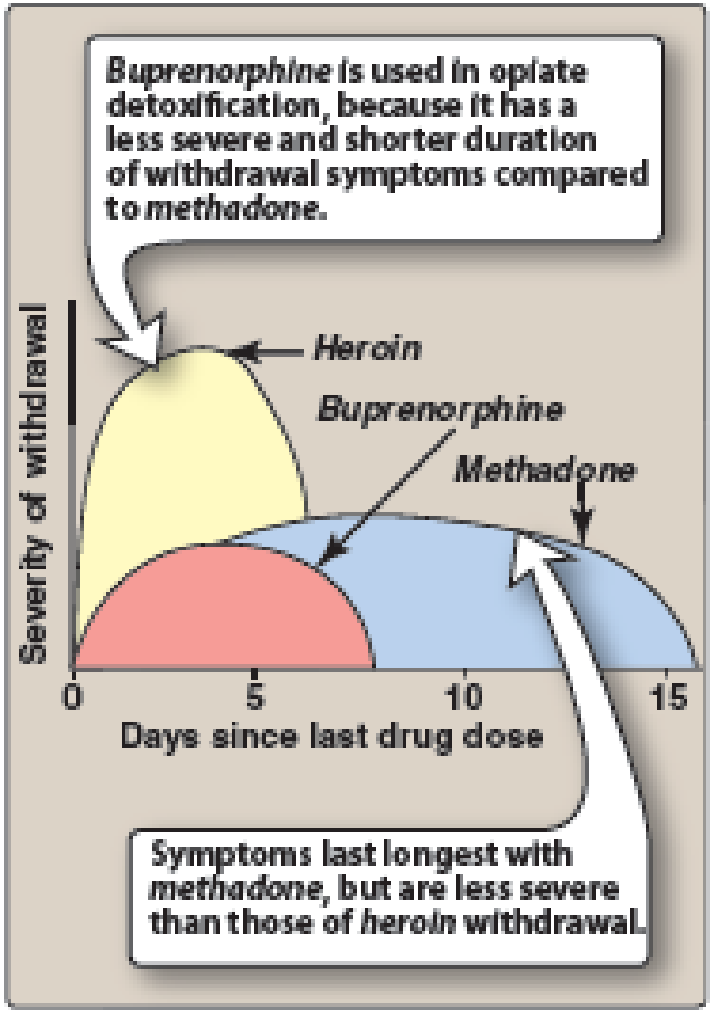


Figure 14.8
Severity of opioid-withdrawal symptoms after abrupt withdrawal of equivalent doses of *heroin*, *buprenorphine*, and *methodone*.

Tramadol.

- weak μ-opioid receptor agonist. 1/6000 that of morphine
- Part of its analgesic effect -**Inhibition of uptake of NE &5HT.**
- Mild-to-moderate pain, effective as morphine or meperidine.
- **severe or chronic pain**, less effective.
- less neonatal respiratory depression.
- 68% bioavailability, *O*-demethylated metabolite 2-4 as potent as parent drug
- supplied as racemic mixture, more effective than either enantiomer alone. The (+)-enantiomer binds to μ receptor and inhibits 5HT uptake.
- The (-)-enantiomer inhibits norepinephrine uptake and stimulates α2 adrenergic receptors

Tramadol.

maximum recommended daily dose is 400 mg.

side effects

nausea

vomiting

dizziness

dry mouth

sedation

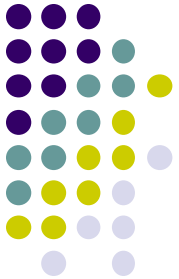
headache

▼**Less Respiratory depression,**

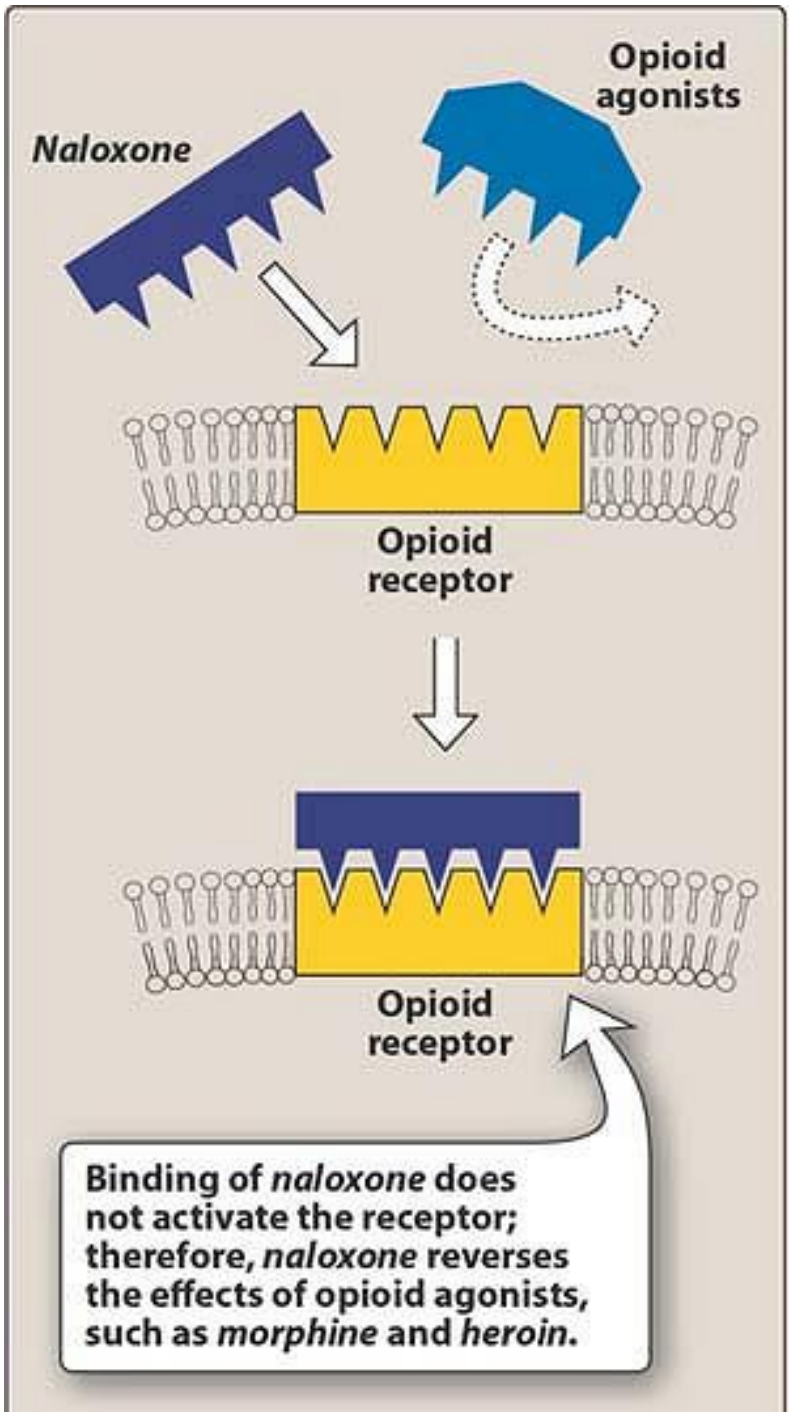
▼**Less degree of constipation**

▼**can cause seizures and possibly exacerbate seizures**

Antagonists



- Naloxone
- *Nalmefene*
- Naltrexone


Opioid agonists
Naloxone
Opioid receptor
Opioid receptor
Binding of naloxone does not activate the receptor; therefore, naloxone reverses the effects of opioid agonists, such as morphine and heroin.

Naloxone

- Produces no pharmacological effect on its own
- **reverses the coma and respiratory depression of opioid overdose**
- patient revived and alert.
- **displaces bound opioid molecules rapidly**
- T1/2 60- 100 min ,dose:0.4-0.8 mg IM/IV
- Patient treated and recovered may **lapse back** into respiratory depression.
- precipitates withdrawal symptoms in opioid abusers

5. In a case of an opioid overdose, naloxone can be given in repeated doses because of which property of naloxone?

(A) may have a shorter half-life than the opioid agonist

(B) is effective only at high cumulative doses

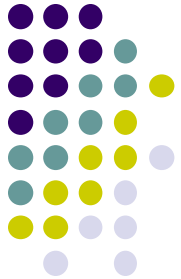
(C) is needed to stimulate the respiratory center

(D) is safe only in extremely small doses

(E) is only a partial opioid agonist

- Low dose naloxone : 0.04 mg useful in treatment of adverse effects commonly associated with intravenous or epidural opioids
- Methynaltrexone bromide approved by FDA for the treatment of constipation in patients with advanced disease
- It does not cross the blood brain barrier

Naltrexone



actions similar to those of naloxone.

- **longer duration of action than naloxone,**
- **efficacy by the oral route**
- **maintenance drug for addicts in R_x programs**
- blocks the pleasurable effects of heroin. This would be expected to discourage continued drug abuse.
- Patients must, of be fully detoxified from narcotics before beginning therapy.
- beneficial in treating chronic alcoholism by an unknown mechanism;
- Naltrexone is **HEPATOTOXIC.**,DOSE 50-100 MG OD

Alternative Routes of Administration

1)Patient Controlled Analgesia (PCA)

Intraspinal Infusion.

- **Rectal Administration** -morphine, hydromorphone, and oxymorphone are available in rectal suppository formulations.

well tolerated in most children

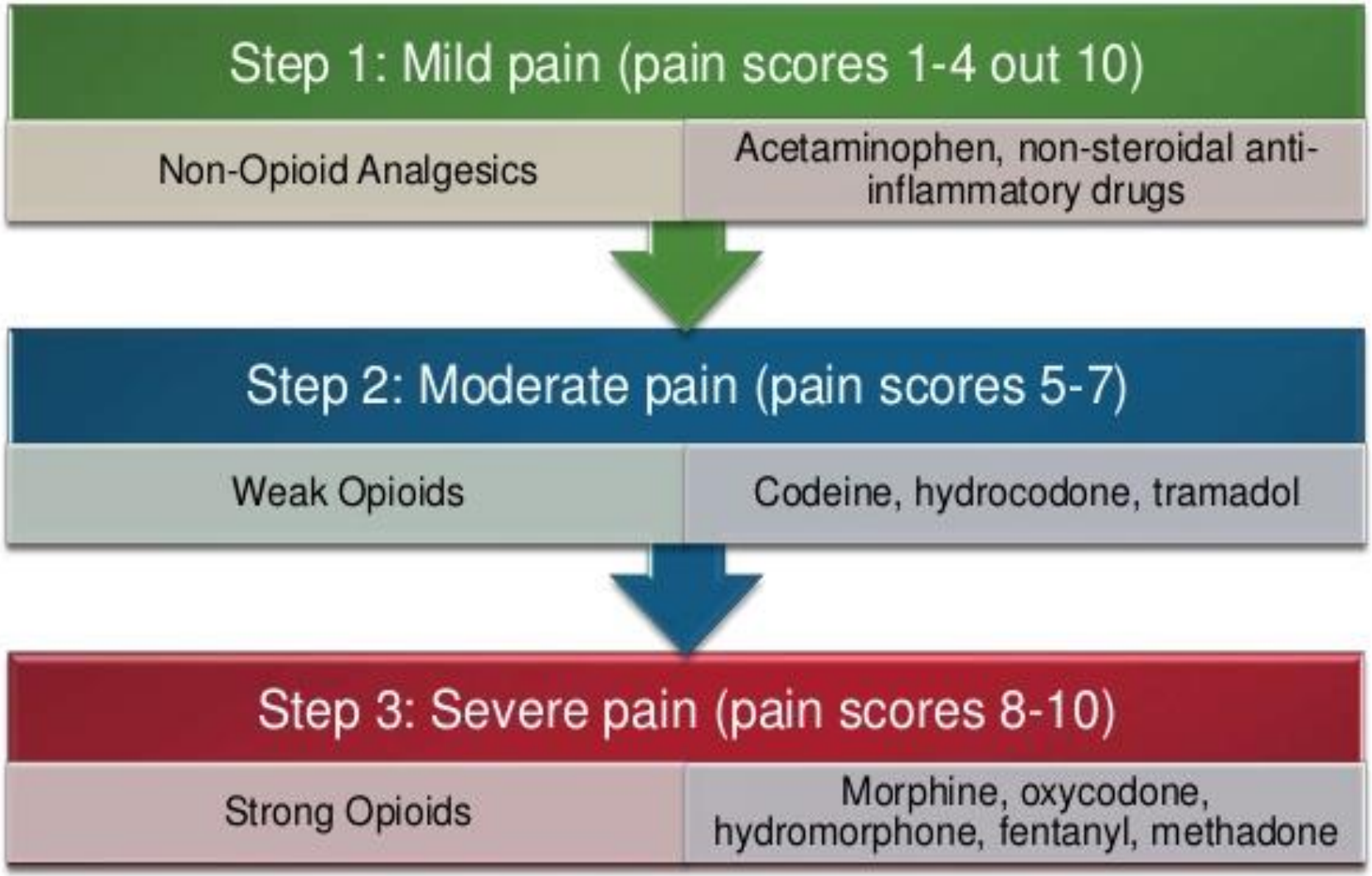
- **Oral Transmucosal Administration**
- **Transdermal or Iontophoretic Administration**

Pain of Terminal Illness and Cancer Pain

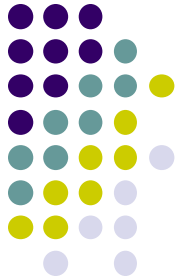
- **not indicated in all cases of terminal illness, but the analgesia, tranquility, and even euphoria afforded by the use of opioids can make the final days far less distressing for the patient and family.**
- ***no patient should ever wish for death because of a physician's reluctance to use adequate amounts of effective opioids*.**
- **may entail the regular use of opioid analgesics in substantial doses.**
- **Such patients, may be physically dependent, are not "addicts" even though they may need large doses on a regular basis.**

Physical dependence is not equivalent to addiction

Pain Management: WHO Analgesic Ladder



World Health Organization Analgesic Ladder



Step 1 Mild to Moderate Pain

Non-opioid ± adjuvant agent

Acetaminophen or an NSAID should be used, unless contraindicated.

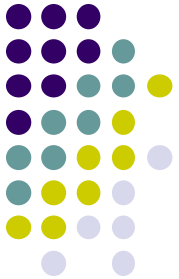
Adjuvant agents are those that enhance analgesic efficacy, treat concurrent symptoms that exacerbate pain, and/or provide independent analgesic activity for specific types of pain.

- **Step 2 Mild to Moderate Pain or Pain Uncontrolled after Step 1**
- Short-acting opioid as required ± non-opioid around the clock (ATC) ± adjuvant agent
- Morphine, oxycodone, or hydromorphone should be added to acetaminophen or an NSAID for maximum flexibility of opioid dose.

- **Step 3 Moderate to Severe Pain or Pain Uncontrolled after Step 2**

- Sustained release/long-acting opioid ATC or continuous infusion + short-acting opioid as required ± non-opioid ± adjuvant agent
- Sustained release oxycodone, morphine, oxymorphone or transdermal fentanyl is indicated.

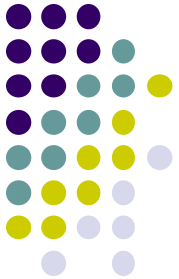
Novel nonopioid treatments for pain



- Myriad marine toxins target GPCR's ,neurotransmitter transporters
- One which is FDA approved for treatment of chronic pain is **Ziconotide**
- **Synthetic copy of neuroactive cone snail toxin**
- **Blocks the N type calcium channels on nocioceptive afferents in dorsal horn of spinal cord**
- **This leads to blockade of neurotransmitters involved in nocioception**

Ziconotide

- Given intrathecally as a continuous infusion by a controlled microinfusion pump
- Dose is titrated from 2.4 ug/day – 19.2 ug/day
- Used to treat severe pain in whom all other treatments have failed or who are allergic /unsuitable for opioid use
- Hallucinations and other CNS sideeffects
- Not an opiate ,effects are not reversed with naloxone



That brings to an end the analgesics

NSAIDs as well as opioids

All Gujarat Pharmacology UG Quiz-2018

Register today @Dept. of Pharmacology, SMT NHLMMC

9426418842, Quiz date -19th Sep, 2018

For NHLITES…

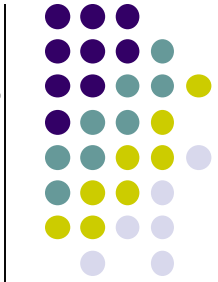
- Its not late : register yourself…
- Screening round for team selection from the college

5 th sept 2018,10 AM

- The two teams wil be made in the chronology of marks obtained
- Whole course for screening round
- Four attendences will be given to attend on the day of the quiz

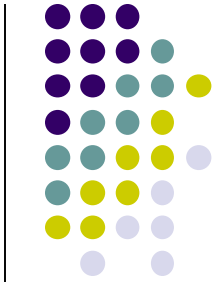
- I am a vasodilating beta-blocker with NO donor potential.
- I have taken birth at CDRI india, I am used as a oral contracetive with a popular brand name
- I am used as a replacement agent in Addisons disease. I am having potent mineralocorticoid activity and I am active orally.
- I am chemically related to thiazides. I inhibit insulin release from beta cells, by acting on potassium channels, and can cause vasodilatation and fall in blood pressure.

- I am a drug shown to prolong life in patients with chronic heart failure. But I do not have positive inotropic action. I can cause gynaecomastia and hirsuitism as An adverse effect
- I am a troubleshooter for young teenage females with pimples. But pregnant females shun me as I harm their babies. I am related to a vitamin.
- I am a prokinetic agent. However, I am not appropriate for routine use because of serious cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.



- I am an alpha 2 receptor agonist, useful for migraine, ADHD in children and also as antihypertensive agent.
- I am a natural plant alkaloid and useful in acromegaly, parkinsons and type 2 Diabetes, I am also used to suppress lactation
- I am a partial agonist at a nicotinic receptor and I am useful to help people who are addicted to smoking to quit the habit.

Features associated with neuropathic pain



- **Allodynia**

pain due to a stimulus which does not normally provoke pain

- **Hyperalgesia**

An increased response to a stimulus which is normally painful

- **Paraesthesia**

Abnormal sensation ,‘pins and needles’

- **Dyaesthesia**

A painful paraesthesia ,eg burning foot pain in diabetic neuropathy