Analgetiki

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Uvod

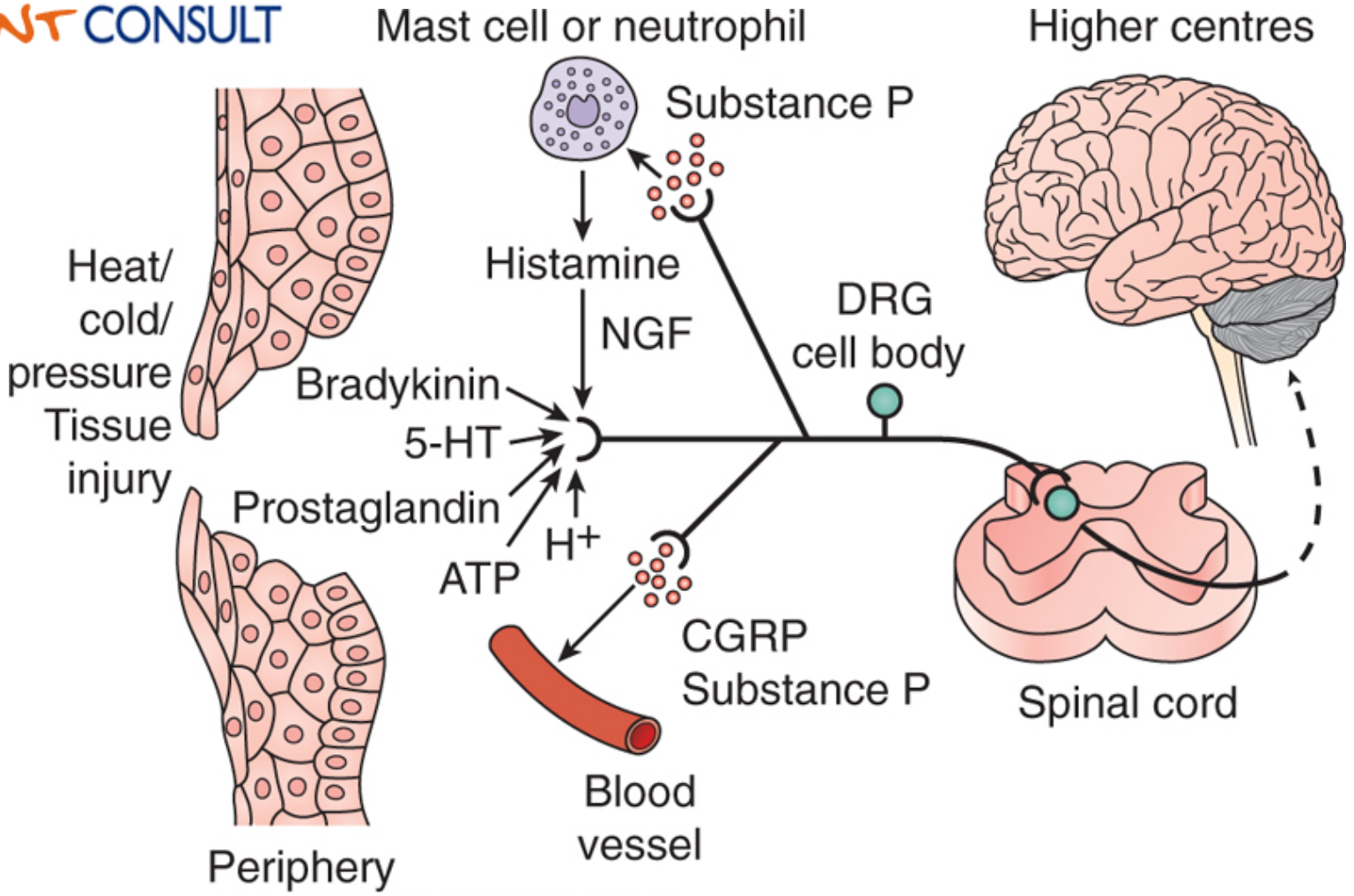
- Bolečina je simptom
- Ozdravljenje osnovne bolezni odpravi tudi bolečino
- Zdravljenje bolečine:
  - skupaj z vzročnim zdravljenjem
  - vzroka bolezni ne poznamo
  - nastanek bolečinskega dražljaja – motnja per se
  - osnovne bolezni ne moremo pozdraviti

Nastanek bolečinskega dražljaja

- Okvara tkiva
  - Vnetje
  - Malignom
  - Bolečina lahko ostaja tudi po prenehanju neposrednega vzroka (fantomska bolečina)
- Nevropatska bolečina – ni direktno povezana z okvaro tkiva

Aferentne poti in mediatorji prenosa

- Polimodalni nociceptorji
- Vlakna C in delno vlakna Aδ (ostra bolečina)
- Nevroni v spinalnih ganglijih
- Zadnji rog medule spinalis (substantia gelatinosa)
- Mediatorji:
  - Hitri: glutamat, ATP,
  - Nevropeptidi: snov P, CGRP (calcitonin gene related polipeptide) – sproščanje tudi v perifernih končičih.

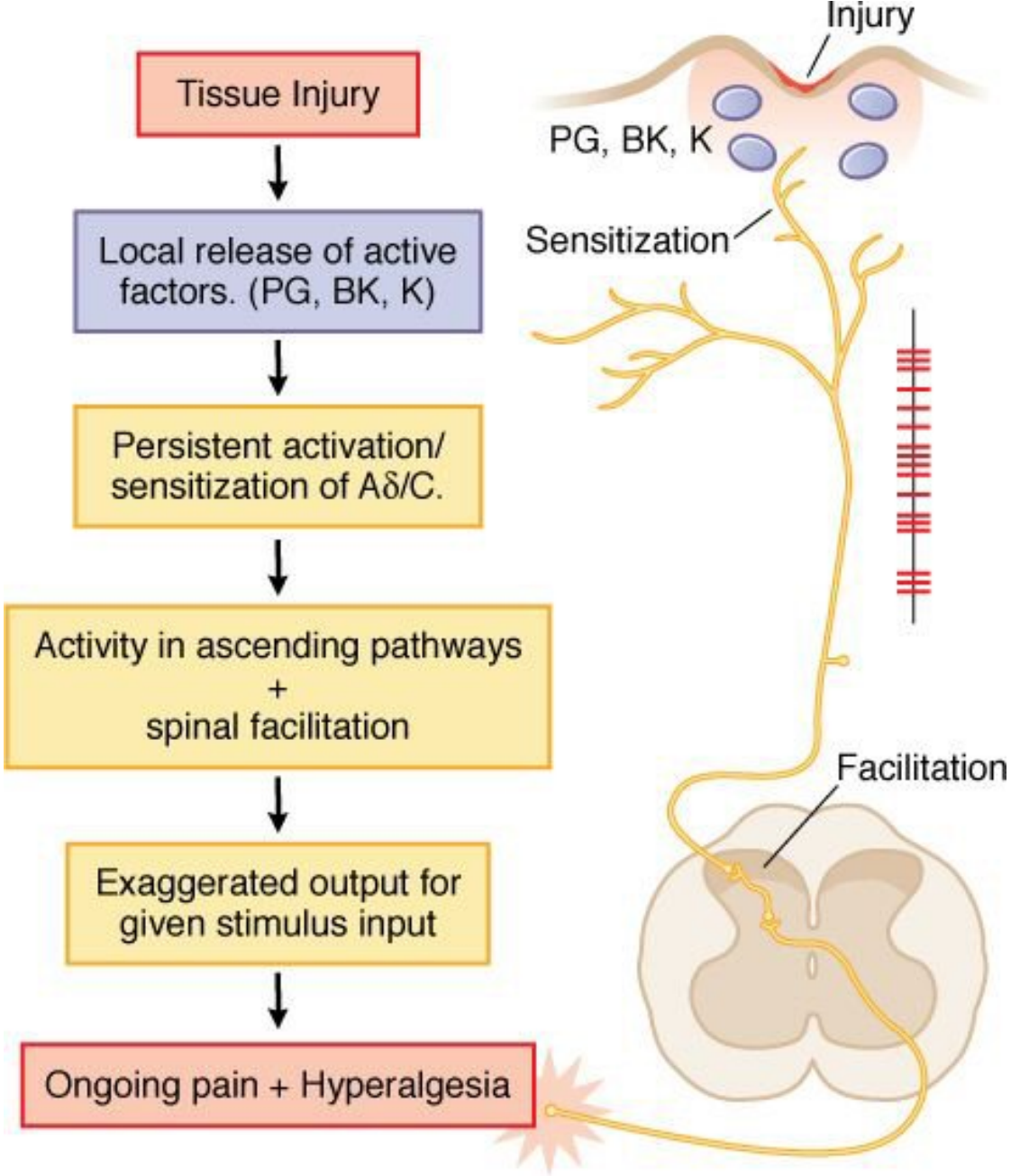


Activation of nociceptive neurons. Various stimuli (physical and chemical) can initiate or enhance the rate of action potential firing in nociceptive primary afferent neurons (i.e. induce pain). These afferent fibres project to the dorsal horn of the spinal cord where they synapse on neurons projecting to higher centres. 5-HT, 5-hydroxytryptamine; ATP, adenosine triphosphate; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; NGF, nerve growth factor. (Adapted from Julius D, Basbaum A I 2001 Nature 413: 203-210.)

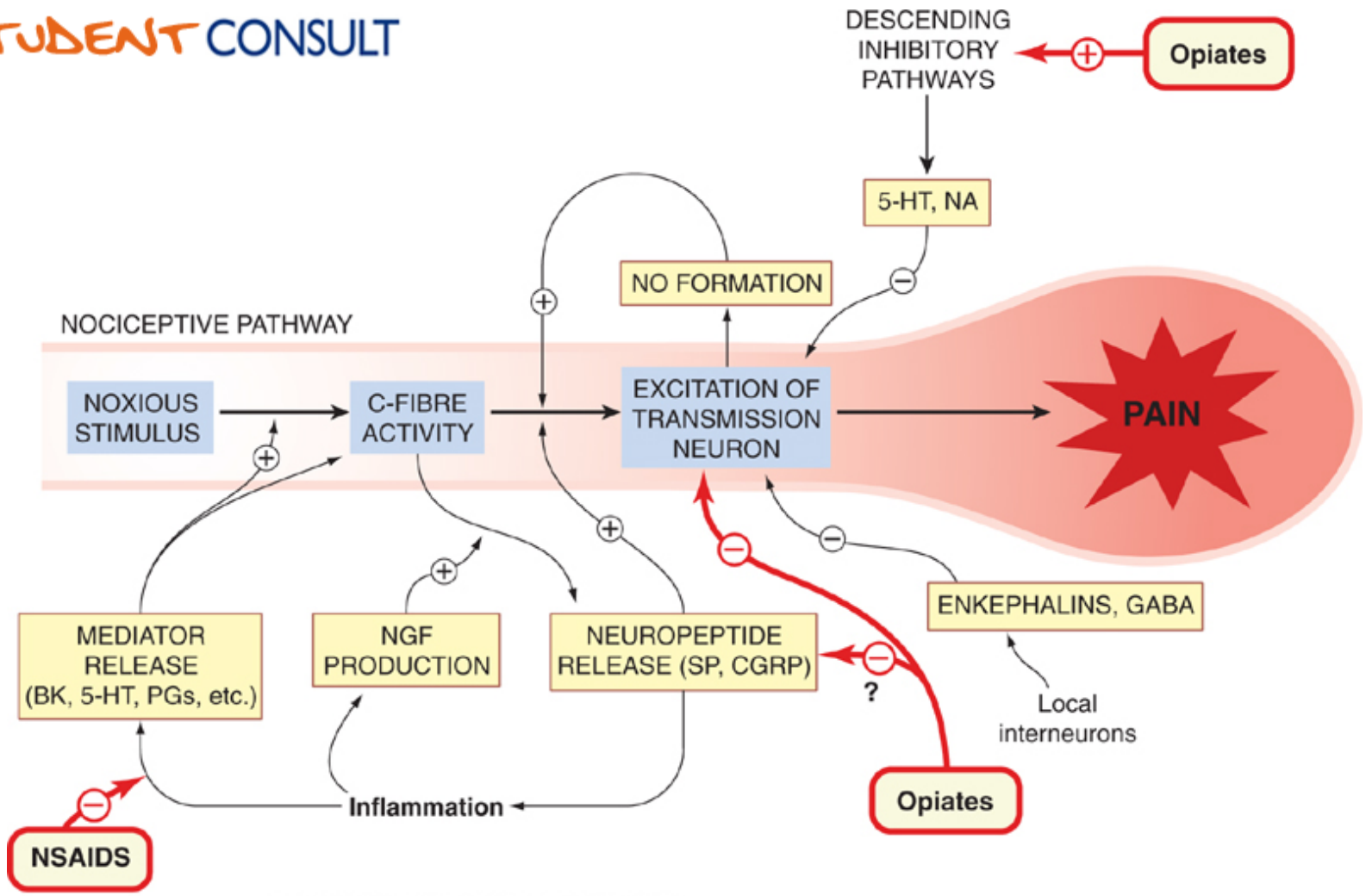
Modulacija v nociceptivni poti

- Hiperalgezija – ob podpražnem bolečinskem dražljaju
- Alodinija (allodynia) – ob neškodljivem dražljaju.

Mechanistic flow diagram of nerve injury–evoked nociception

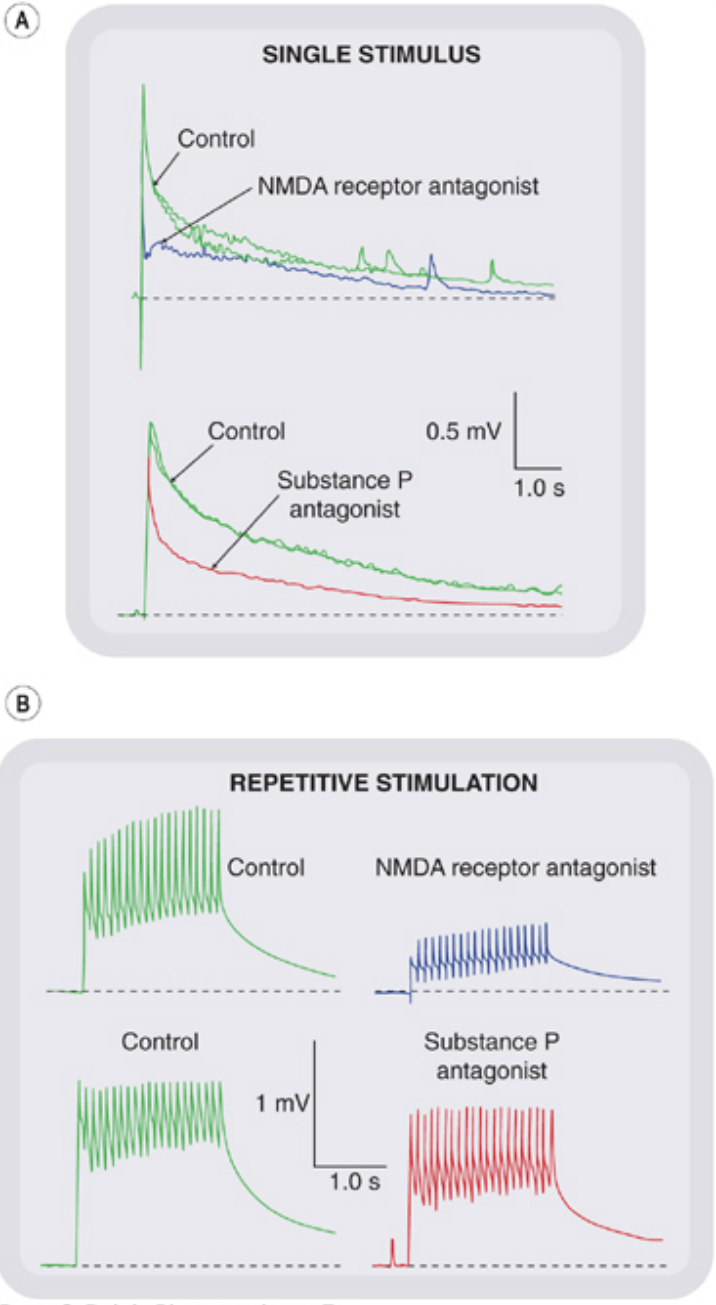


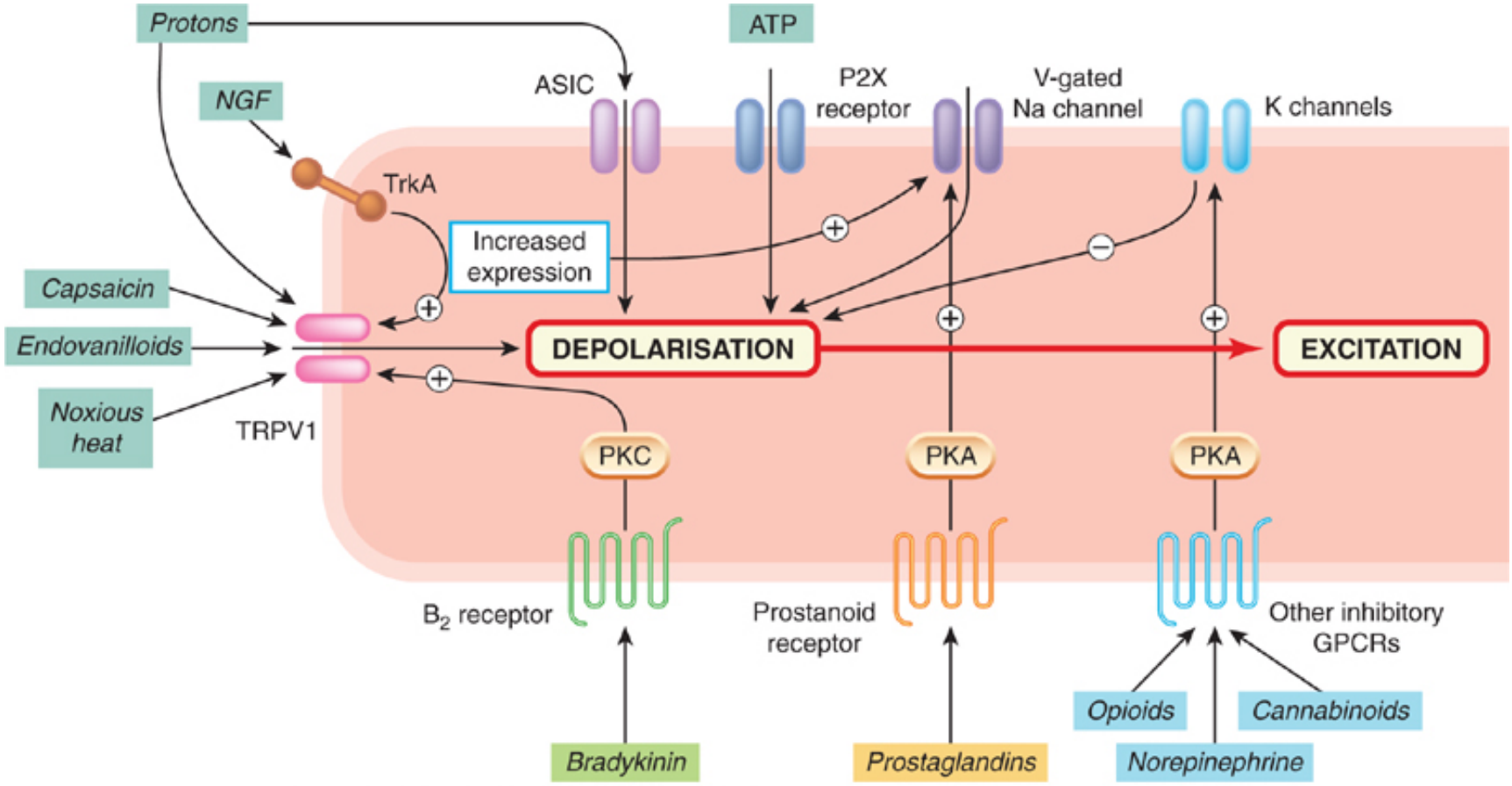
Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com



Summary of modulatory mechanisms in the nociceptive pathway. 5-HT, 5-hydroxytryptamine; BK, bradykinin; CGRP, calcitonin gene-related peptide; NA, noradrenaline; NGF, nerve growth factor; NO, nitric oxide; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandin; SP, substance P.

Effect of glutamate and substance P antagonists on nociceptive transmission in the rat spinal cord. The rat paw was inflamed by ultraviolet irradiation 2 days before the experiment, a procedure that induces hyperalgesia and spinal cord facilitation. The synaptic response was recorded from the ventral root, in response to stimulation of C fibres in the dorsal root with A single stimuli or B repetitive stimuli. The effects of the NMDA receptor antagonist d-AP-5 (see Ch. 37) and the substance P antagonist RP 67580 (selective for neurokinin type 2, (NK2) receptors) are shown. The slow component of the synaptic response is reduced by both antagonists (A), as is the 'wind-up' in response to repetitive stimulation (B). These effects are much less pronounced in the normal animal. Thus both glutamate, acting on NMDA receptors, and substance P, acting on NK2 receptors, are involved in nociceptive transmission, and their contribution increases as a result of inflammatory hyperalgesia. (Records kindly provided by L Urban and S W Thompson.)





Rang et al: Rang & Dale's Pharmacology, 7e

Channels, receptors and transduction mechanisms of nociceptive afferent terminals. Only the main channels and receptors are shown. Ligand-gated channels include acid-sensitive ion channels (ASICs), ATP-sensitive channels (P2X receptors) and the capsaicin-sensitive channel (TRPV1; TRP: Transient Receptor Potential channels), which is also sensitive to protons and to temperature. Various facilitatory and inhibitory G-protein-coupled receptors (GPCRs) are shown, which regulate channel function through various second messenger systems. Growth factors such as nerve growth factor (NGF) act via kinase-linked receptors (TrkA) to control ion channel function and gene expression. B2 receptor, bradykinin type 2 receptor; PKA, protein kinase A; PKC, protein kinase C.

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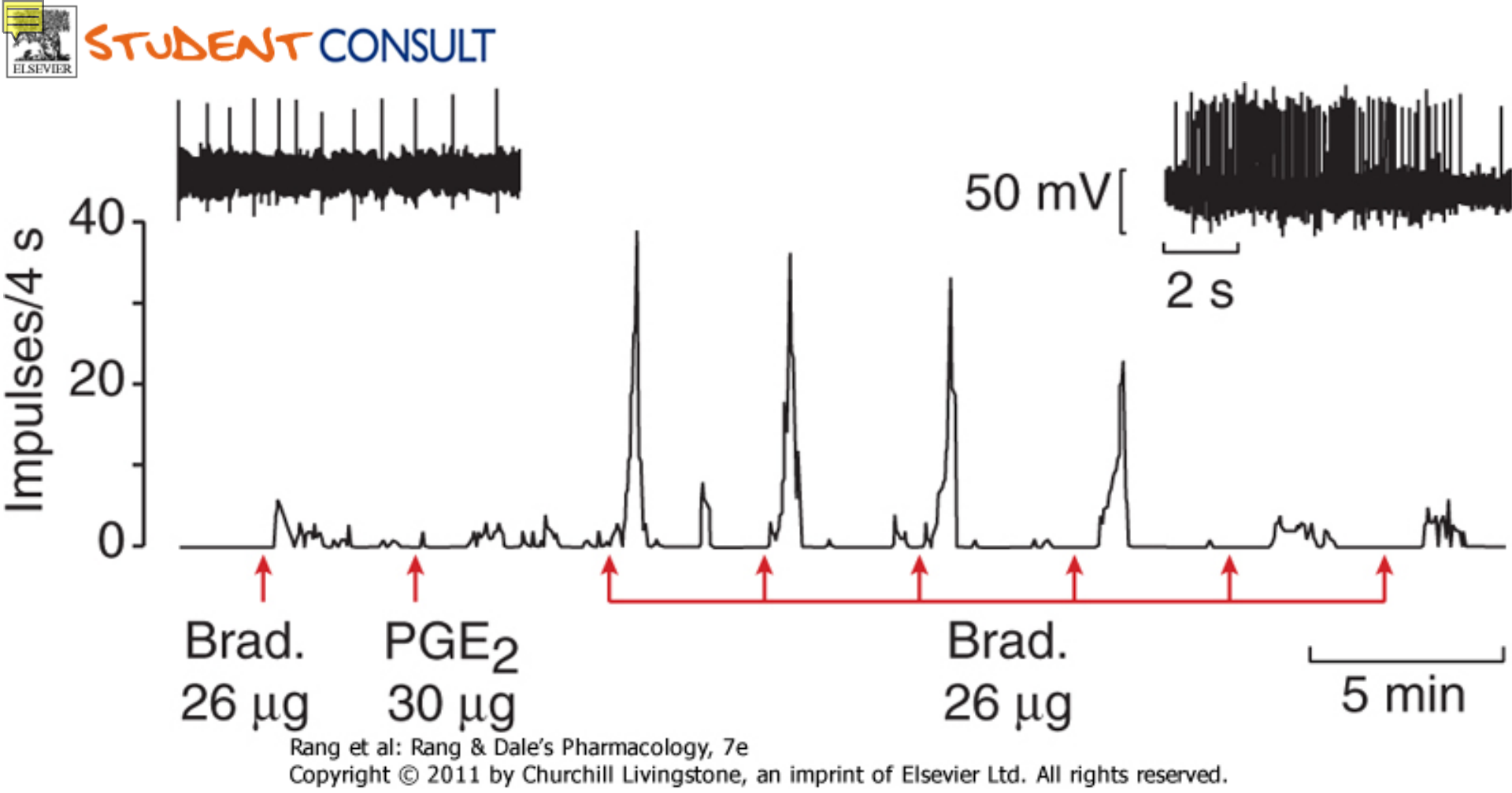
Thermosensitive TRP channels expressed on sensory neurons

Channel type	TRPA1	TRPM8	TRPV4	TRPV3	TRPV1	TRPV2
Activation temperature (°C)	< 17	8-28	> 27	> 33	> 42	> 52
Chemical activators	Icilin	Menthol	4αPDD	Camphor	Capsaicin	Δ^9-THC
	Wintergreen oil	Icilin		Menthol	Protons	
	Mustard oil	Eucalyptol		Eugenol	Anandamide	
		Geraniol			Camphor	
					Resiniferatoxin	
					Eugenol	

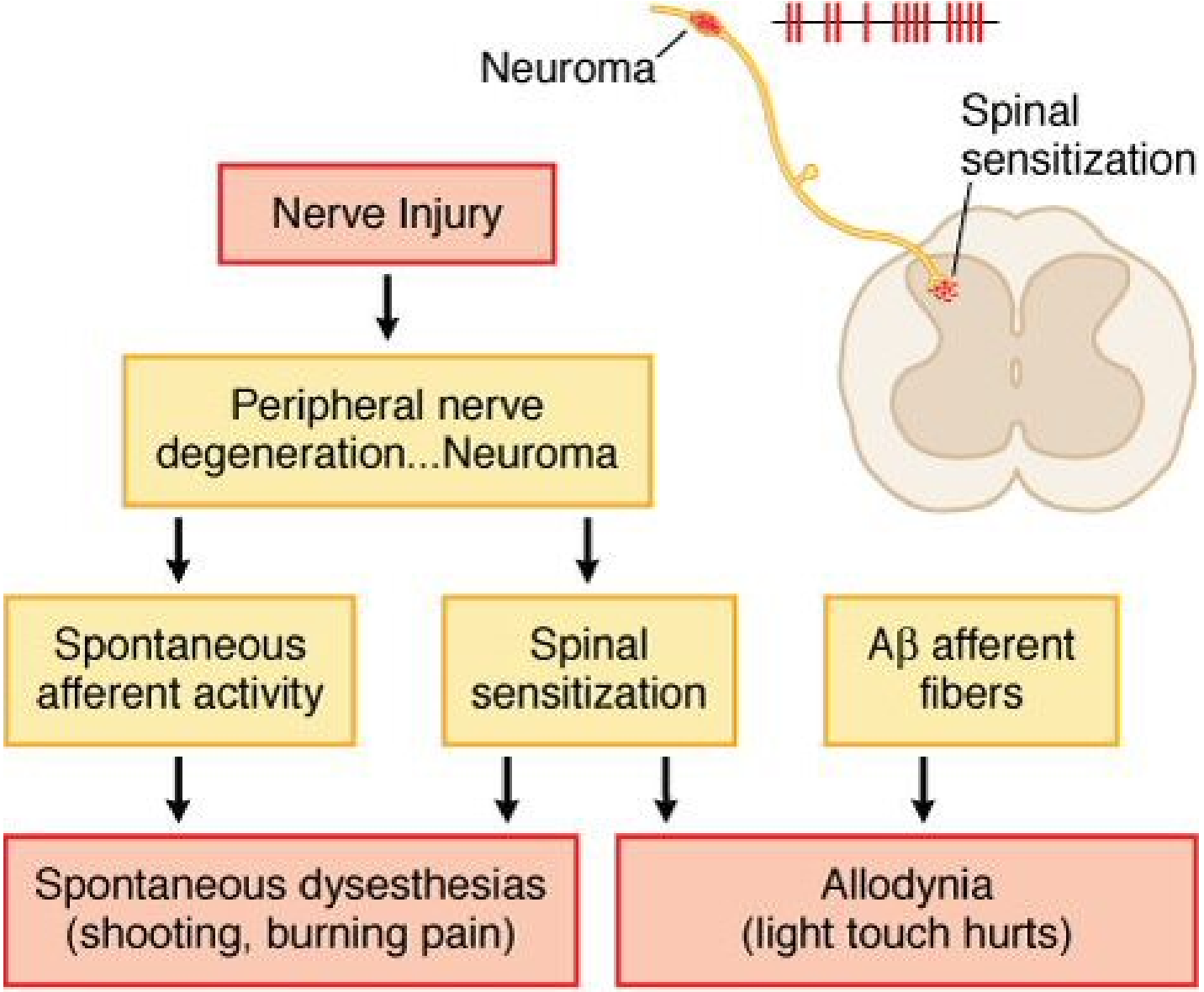
4αPDD 4-α-Phorbol-Didecanoate
Wintergreen oil - methylsalicilate
Resiniferatoxin - analogue of capsaicine (Euphorbia resinifera)



Response of a nociceptive afferent neuron to bradykinin (Brad.) and prostaglandin. Recordings were made from a nociceptive afferent fibre supplying a muscle, and drugs were injected into the arterial supply. Upper records: single-fibre recordings showing discharge caused by bradykinin alone (left), and by bradykinin following injection of prostaglandin (right). Lower trace: ratemeter recording of single-fibre discharge, showing long-lasting enhancement of response to bradykinin after an injection of prostaglandin E2 (PGE2). Prostaglandin itself did not evoke a discharge. (From Mense S 1981 Brain Res 225: 95.)

Transmitorji in modulatorji nociceptivne poti

- Endogeni opioidi
- Različni nevropeptidi (snov P, CGRP)
- Glutamat (receptorji AMPA)
- GABA
- ATP
- 5-HT (inhibitorni nevroni)
- Adenozin



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Opioidi

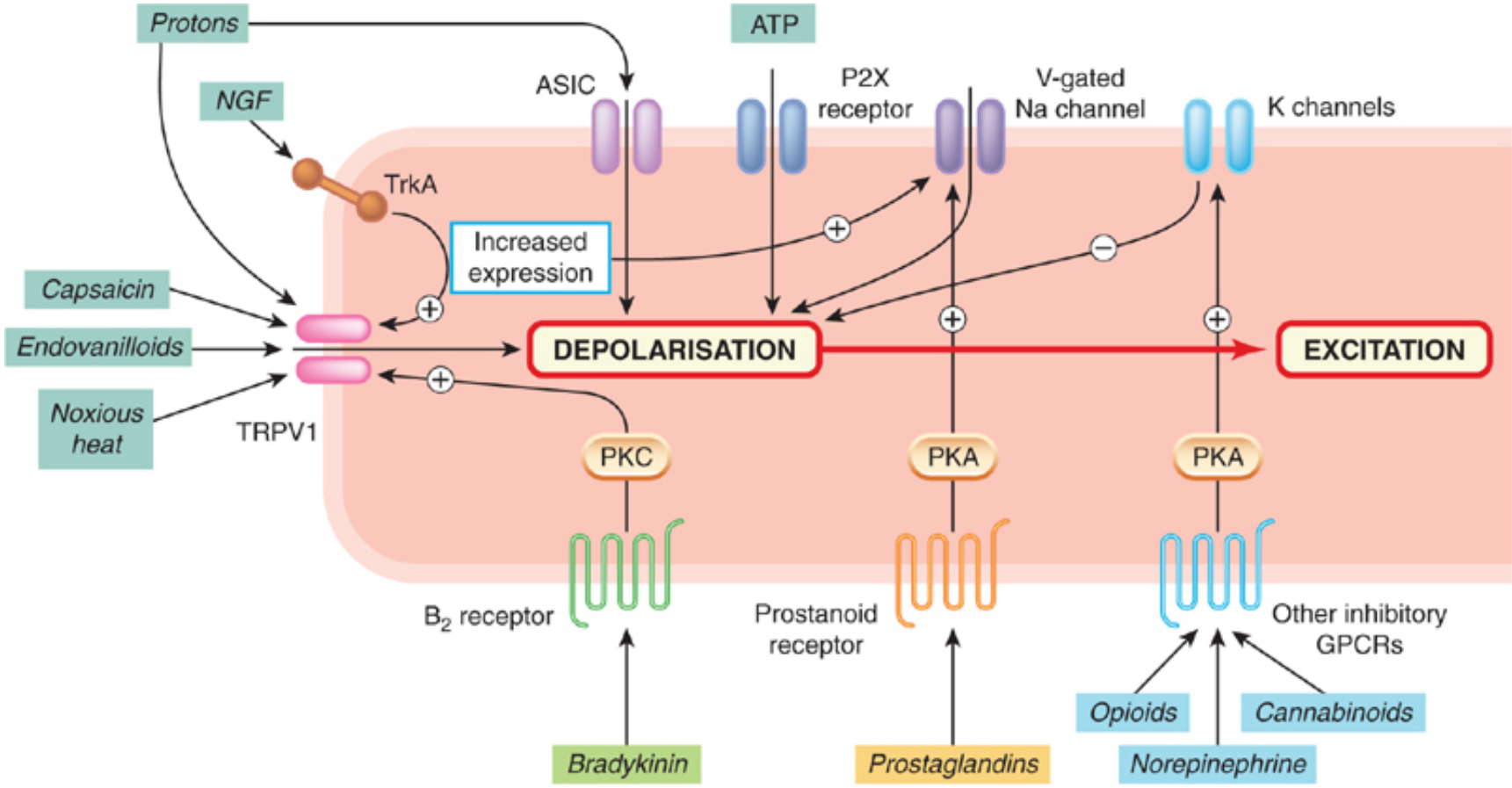
- Opij – ekstrakt iz makovega soka (*Papaver somniferum*) vsebuje morfin in sorodne alkaloide
  - Tinctura opii - Laudanum
- Terminologija:
  - Opioid – snov (endogena ali eksogena), ki povzroča morfinu podobne učinke
  - Opiat – snovi kot morfin in kodein, dobljene iz opija
  - Narkotični analgetik – staro ime za opioide

Učinki opioidov

- Analgezija (prijemališča na različnih nivojih)
- Evforija (pomembna komponenta analgetičnega učinka)
- Depresija dihanja
- Zmanjšanje refleksa kašlja
- Navzea in bruhanje
- Mioza
- Zmanjšana motiliteta GIT
- Toleranca in odvisnost (fizična)

Analgezija

- Posledica delovanja na več nivojih
- Akutna in kronična bolečina – manj učinkoviti pri nevropatski bolečini
- Zmanjšana čustvena komponenta bolečine (limbični sistem)
- Včasih hiperalgezija (aktivacija R NMDA in PKC ?)



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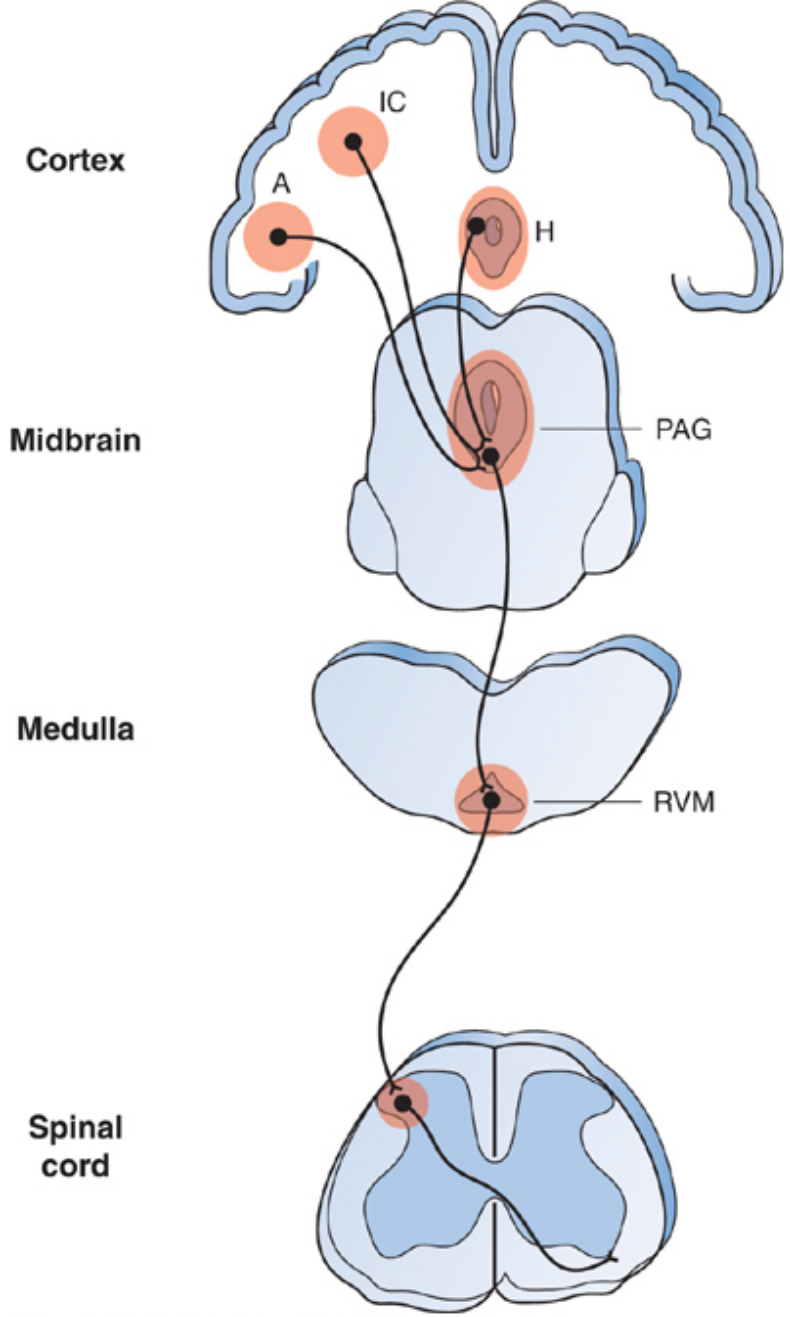
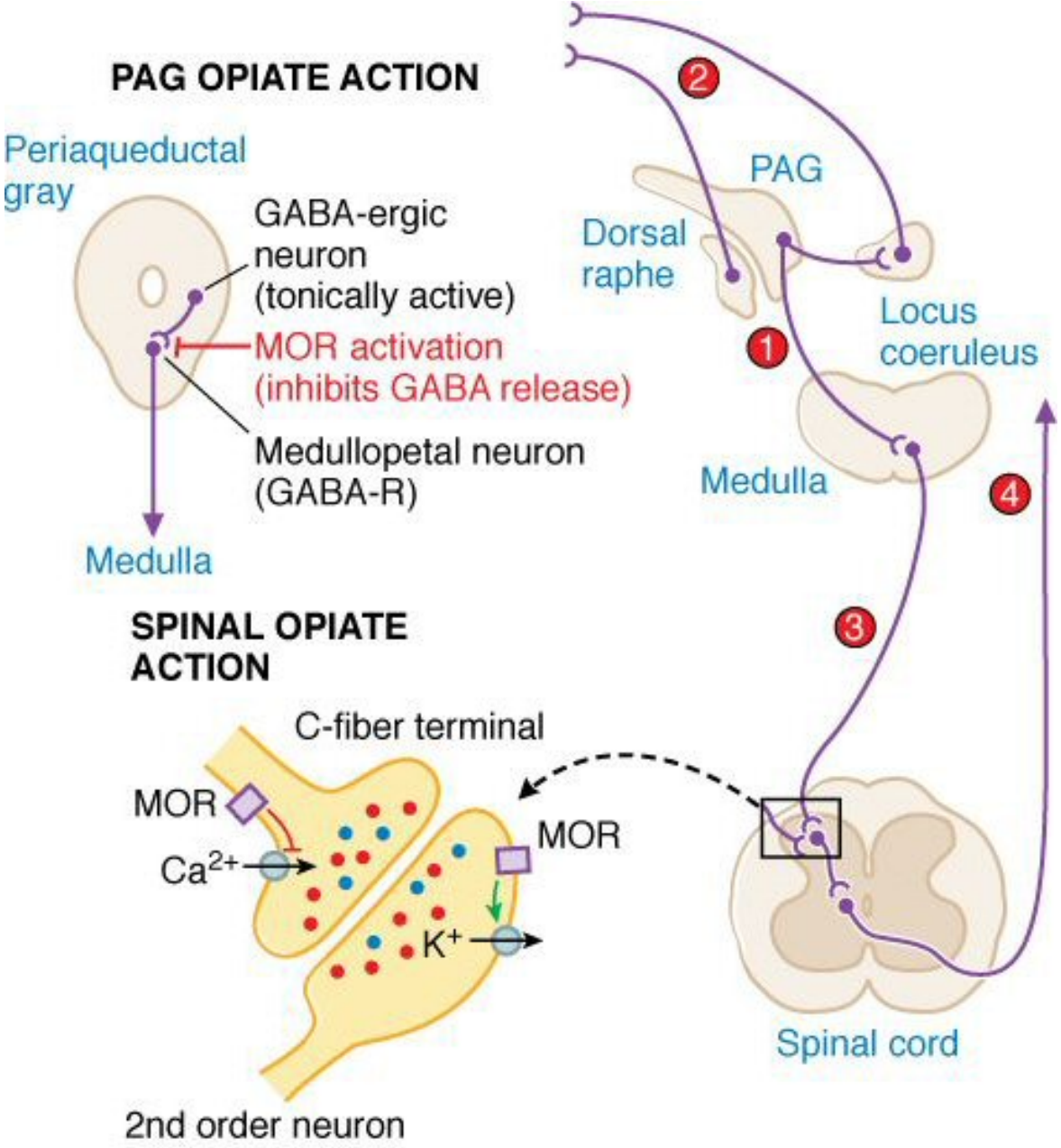
Channels, receptors and transduction mechanisms of nociceptive afferent terminals. Only the main channels and receptors are shown. Ligand-gated channels include acid-sensitive ion channels (ASICs), ATP-sensitive channels (P2X receptors) and the capsaicin-sensitive channel (TRPV1; TRP: Transient Receptor Potential channels), which is also sensitive to protons and to temperature. Various facilitatory and inhibitory G-protein-coupled receptors (GPCRs) are shown, which regulate channel function through various second messenger systems. Growth factors such as nerve growth factor (NGF) act via kinase-linked receptors (TrkA) to control ion channel function and gene expression. B2 receptor, bradykinin type 2 receptor; PKA, protein kinase A; PKC, protein kinase C.

The descending pain control system and sites of action of opioids to relieve pain. Opioids induce analgesia when microinjected into the insular cortex (IC), amygdala (A), hypothalamus (H), periaqueductal grey (PAG) region and rostroventral medulla (RVM) as well as into the dorsal horn of the spinal cord. The PAG receives input from higher centres and is the main output centre of the limbic system. It projects to the rostral ventromedial medulla (RVM). From the RVM, descending inhibitory fibres, some of which contain 5-hydroxytryptamine, project to the dorsal horn of the spinal cord. Shaded areas indicate regions expressing μ-opioid receptors. The pathways shown in this diagram represent a considerable oversimplification. (Adapted from Fields 2001 Prog Brain Res 122: 245-253.)





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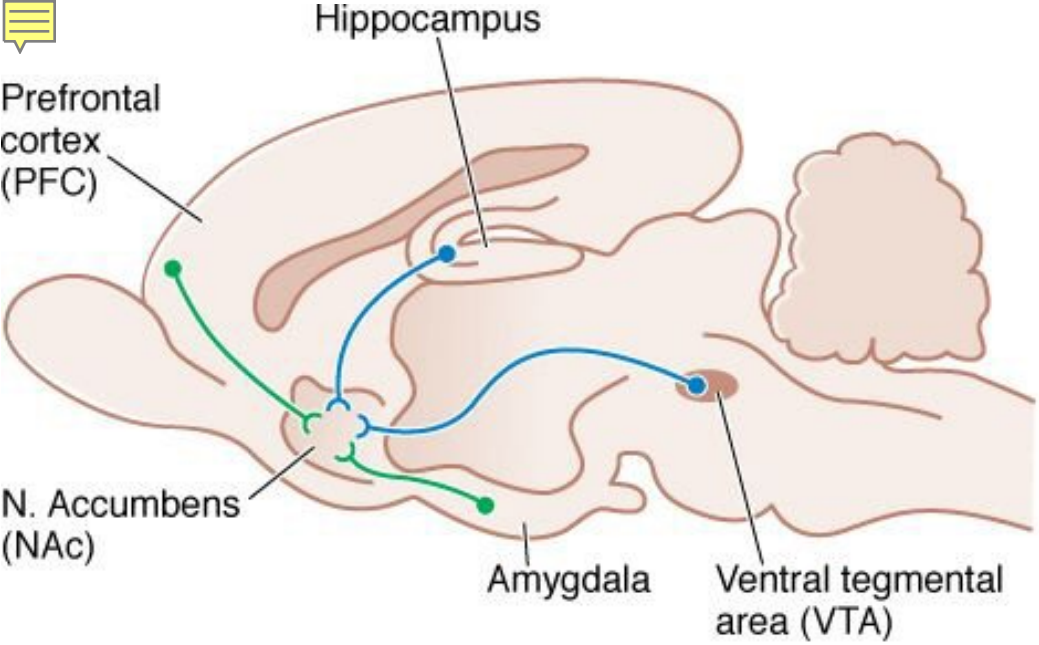
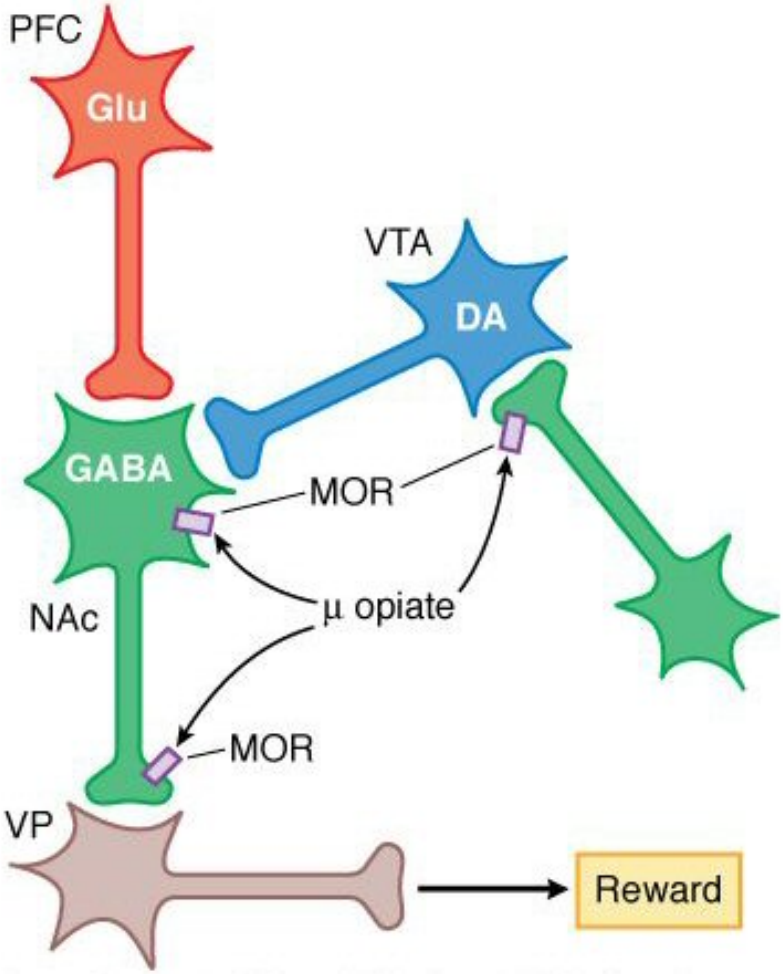
Evforija

- Občutek zadovoljstva in dobro počutje
- Pomembna komponenta pri analgeziji
- Odvisna od okoliščin
- Pri bolnikih s kronično bolečino manj izražena
  - Pri nekaterih od teh bolnikov – nemir (disforia)
- Mehanizem





Schematic pathways underlying rewarding properties of opiates.
Left panel: This saggital section of rat brain displays simplified DA and GABA inputs from the ventral tegmental area (VTA) and prefrontal cortex (PFC), respectively, into the nucleus accumbens (NAc).
Right panel: Neurons are labeled with their primary neurotransmitters. At a cellular level, MOR agonists reduce excitability and transmitter release at the sites indicated by inhbiting Ca2+ influx and enhancing K+ current . Thus, opiate-induced inhibition in the VTA on GABA-ergic interneurons or in the NAc reduce GABA-mediated inhibition and increase outflow from the ventral pallidum (VP), which appears to correlate with a positive reinforcing state (enhanced reward).

Depresija dihanja

- Že pri terapevtskih dozah
- Zmanjšanje občutljivosti respiratornega centra za CO_2
- Zmanjšana frekvenca generatorja dihalne frekvence (pre-Bötzingerjev kompleks)
- Ni depresije drugih centrov v meduli oblongati

Depresija refleksa kašlja

- Ni tesne korelacije z analgetičnim delovanjem
- Mehanizem ni jasen
- Nekateri derivati – bolj izražen tusisedativen učinek (kodein, folkodin – že pri subanalgetičnih dozah)
- Dekstrometorfan (d-izomer levorfanola) – antitusik – nima afinitete za opioidne R – delovanje na R za NMDA (antag.)

Navzea in bruhanje

- Povezana z analgetičnim delovanjem (pri 40% bolnikov)
- Posledica delovanja v area postrema (sprožilna cona)
- Pogosto preneha po začetku terapije.
- Derivati, ki slabo prehajajo v OŽ, manj izražen emetični učinek (morfin-6-glukuronid)

Mioza

- Posledica delovanja v jedru n. oculomotorius
- Ne kaže tolerance
- Derivati, ki blokirajo muskarinske R (petidin), ne kažejo tega učinka

Učinki na GIT

- Povečan tonus gladke muskulature
- Zmanjšana motiliteta (vpliv na absorpcijo drugih zdravil)
- Posledica delovanja na intramuralne živčne pleteže, delno tudi centralno (↓ tonus vagusa)
- Zdravljenje diareje
- Povečan tlak v biliarnem sistemu

Receptorji za opioide

- Ideja o specifičnih receptorjih v 1950 letih
- Odkritje antagonistov (nalorfin, nalokson)
- Receptorji: μ, κ in σ (ni več opioidni R – NMDA)
- Po odkritju endogenih ligandov – R δ
- Kasneje receptor ORL_1 (kloniranje klasičnih R) – nalokson nanj ne deluje, ligand orfanin

Delovanje receptorjev

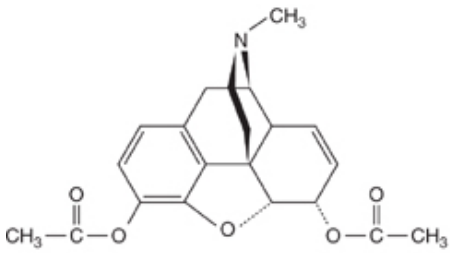
- Metabotropni R
- Inhibicija adenilatne ciklaze
- ↓ odpiranje napetostno-odvisnih Ca^{2+} kanalov
- Stimulacija K^+ tokov skozi različne kanale, med njimi z G proteinom-aktivirani K^+ kanali (inwardly rectifying K^+ channels – GIRK)
- Aktivacija PKC in PLC

Table 41-2. Functional effects associated with the main types of opioid receptor

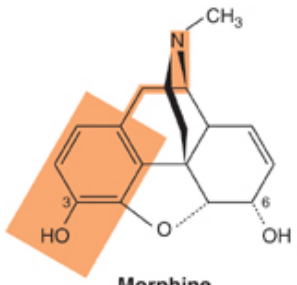
Receptor (classical terminology) Receptor (recommended new terminology)	μ MOPr	δ DOPr	κ KOPr	ORL_1 NOPr
Analgesia				
Supraspinal	+++	-?	-	Antiopioid[a]
Spinal	++	++	+	++
Peripheral	++	-	++	-
Respiratory depression	+++	++	-	-
Pupil constriction	++	-	+	-
Reduced gastrointestinal motility	++	++	+	-
Euphoria	+++	-	-	-
Dysphoria and hallucinations	-	-	+++	-
Sedation	++	-	++	-
Catatonia	-	-	-	++
Physical dependence	+++	-	-	-

[a] ORL_1 agonists were originally thought to produce nociception or hyperalgesia but it was later shown that they reverse the supraspinal analgesic effects of endogenous and exogenous μ opioid receptor agonists.

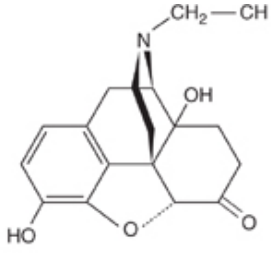
Structures of some opioid analgesics. The red shaded area indicates the part of the morphine molecule that is structurally similar to tyrosine, the N-terminal amino acid in the endorphins. Carbon atoms 3 and 6 in the morphine structure are indicated. Diamorphine (heroin) is 3,6-diacetylmorphine and morphine is metabolised by addition of a glucuronide moiety at either position 3 or position 6.



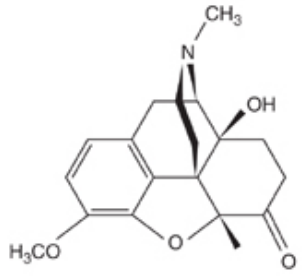
Heroin



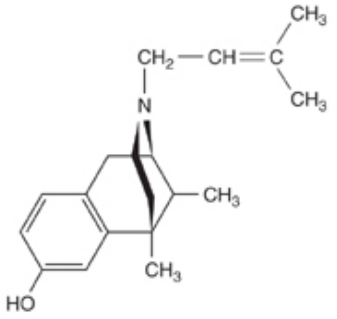
Morphine



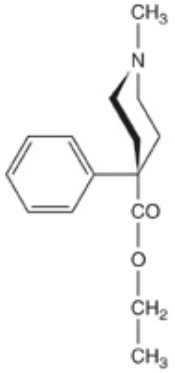
Naloxone



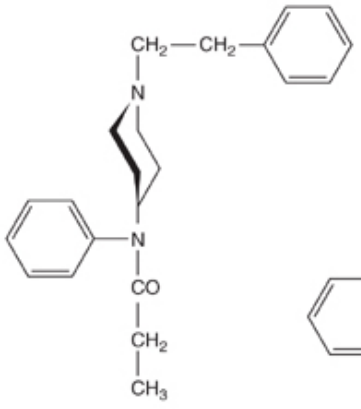
Oxycodone



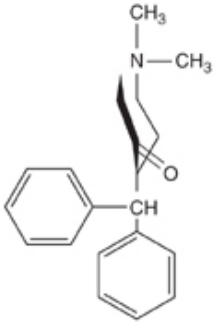
Pentazocine



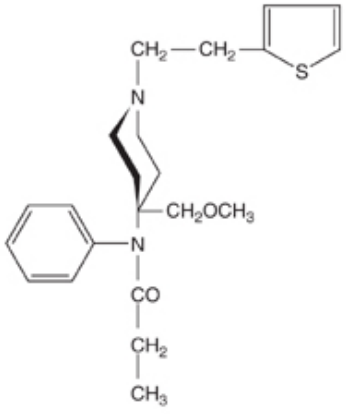
Pethidine



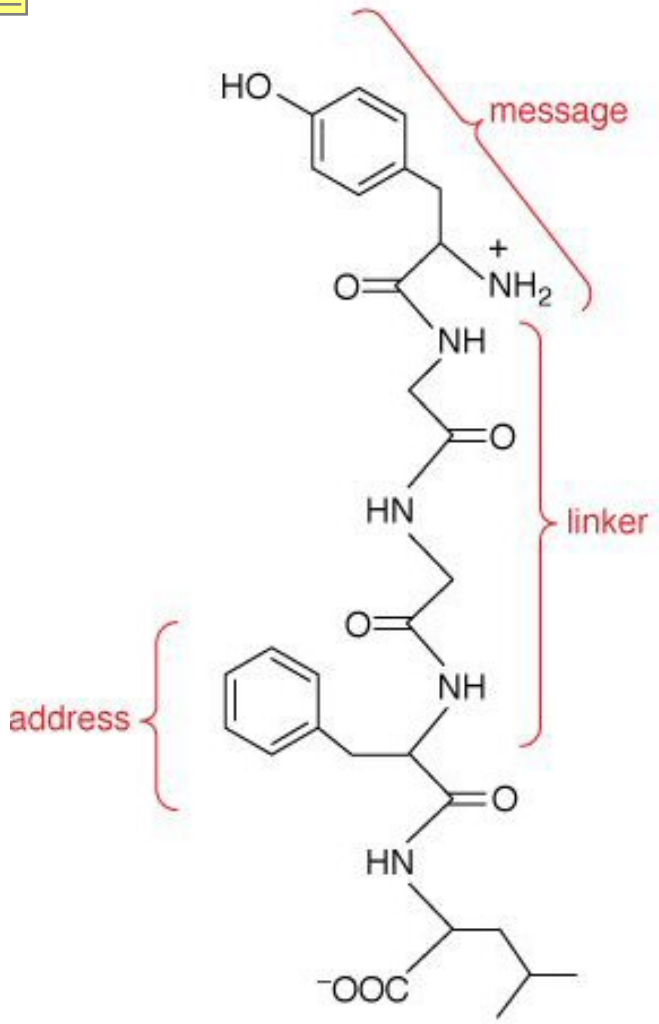
Fentanyl



Methadone

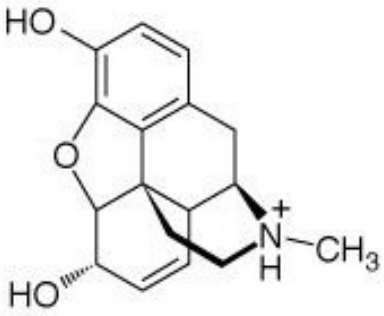


Sufentanyl

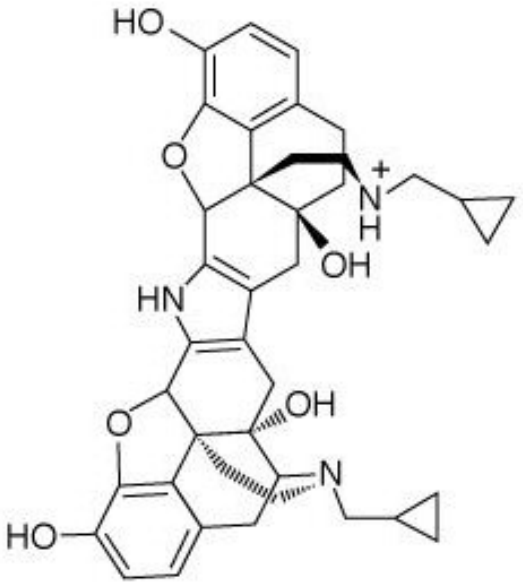


Leu-enkephalin
(δ>μ)

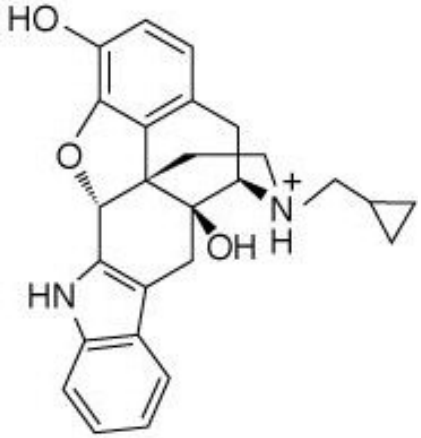
Naltrexone
(μ/δ/κ)



Morphine
(μ)



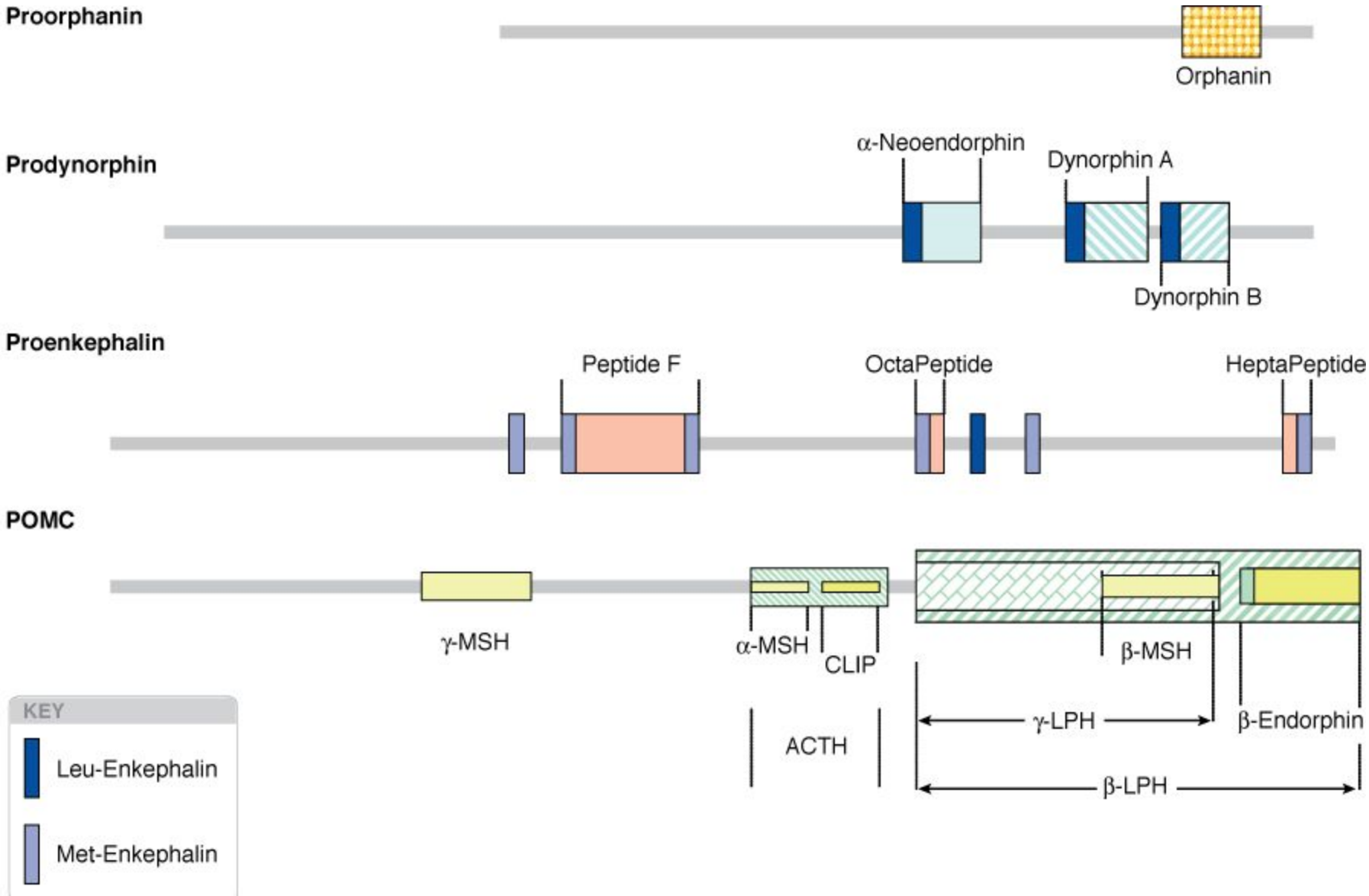
Nor-binaltorphine
(κ)



Naltrindole
(δ)

Endogeni ligandi za opioidne receptorje

- Odkritje 1975 (Hughes in Kosterlitz)
- Enkefalini, endorfini
- Nastanek iz prekurzorskih proteinov:
  - Preopiomelanokortin (POMC)
  - Preprodinorfin
  - Preproenkefalin
- Iz teh prekurzorjev še drugi polipeptidni mediatorji



Peptide precursors. (Reproduced with permission from Akil et al, 1998. Copyright© Elsevier.)

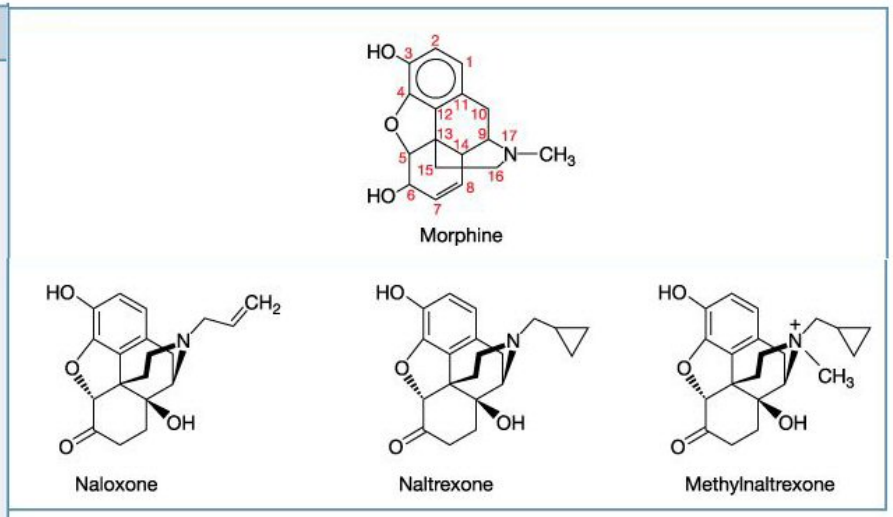
Actions, Selectivities of Some Opioids at μ, δ, and κ Receptors

	RECEPTOR TYPES		
OPIOID LIGANDS	μ	δ	κ
Endogenous Peptides			
Met-enkephalin (**Tyr-Gly-Gly-Phe-Met**)	++	+++	
Leu-enkephalin (**Tyr-Gly-Gly-Phe-Leu**)	++	+++	
β-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)	+++	+++	
Dynorphin A (**Tyr-Gly-Gly-Phe-Leu**-Arg-Arg-IIe-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)	+	+	+++
Endomorphin-1 (Tyr–Pro–Trp–Phe–NH_2)	+++		
Nociceptin (orphanin FQ) (Phe-Gly-Gly-Phe-Thr-Gly-Ala-Arg-Lys-Ser-Ala-Arg-Lys-Leu-Ala-Asn-Gln)	–	–	–

The number of symbols is an indication of potency; the ratio for a given drug denotes selectivity.These values are obtained primarily from in vivo/in vitro animal pharmacological work and in ligand binding and activity studies and should be extrapolated to humans with caution.

Source: Reproduced with permission from Raynor et al, 1994.

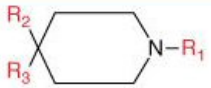
Nonproprietary name	Chemical radicals and position[a]			Other changes†
	3	6	17	
Morphine	—OH	—OH	—CH_3	—
Heroin	—$OCOCH_3$	—$OCOCH_3$	—CH_3	—
Hydromorphone	—OH	=O	—CH_3	(1)
Oxymorphone	—OH	=O	—CH_3	(1), (2)
Levorphanol	—OH	—H	—CH_3	(1), (3)
Levallorphan	—OH	—H	—$CH_2CH{=}CH_2$	(1), (3)
Codeine	—OCH_3	—OH	—CH_3	—
Hydrocodone	—OCH_3	=O	—CH_3	(1)
Oxycodone	—OCH_3	=O	—CH_3	(1), (2)
Nalmefene	—OH	$=CH_2$	—CH_2—cyclopropyl	(1), (2)
Nalorphine	—OH	—OH	—$CH_2CH{=}CH_2$	—
Naloxone	—OH	=O	—$CH_2CH{=}CH_2$	(1), (2)
Naltrexone	—OH	=O	—CH_2—cyclopropyl	(1), (2)
Buprenorphine	—OH	—OCH_3	—CH_2—cyclopropyl	(1), (4)
Butorphanol	—OH	—H	—CH_2—cyclobutyl	(1), (2), (3)
Nalbuphine	—OH	—OH	—CH_2—cyclobutyl	(1), (2)
Methylnaltrexone	—OH	=O	—(N)—CH_2—cyclopropyl, N—CH_3	(1), (2)

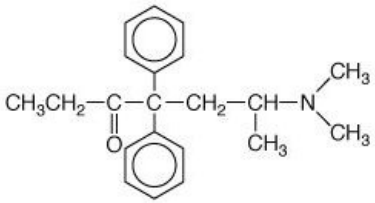


[a]The numbers 3, 6, and 17 refer to positions in the morphine molecule, as shown above. †Other changes in the morphine molecule are: (1) Single instead of double bond between C7 and C8: (2) OH added to C14: (3) No oxygen between C4 and C5: (4) *Endo*etheno bridge between C6 and C14: 1-hydroxy-1,2,2-trimethylpropyl substitution on C7.

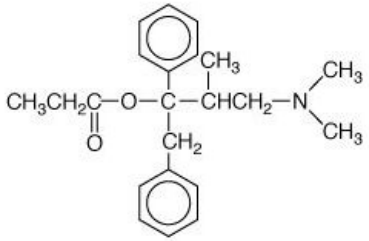
Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Structures of morphine-related opiate agonists and antagonists.



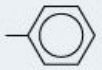
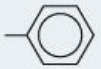
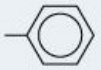
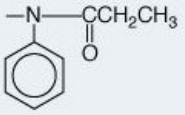
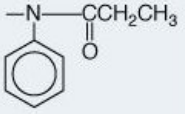
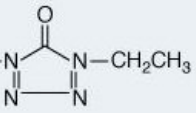
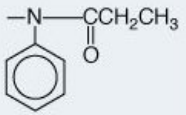
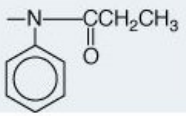


Methadone



Propoxyphene

Chemical structures of piperidine and phenylpiperidine analgesics.

Compound	R_1	R_2	R_3
Meperidine	$-CH_3$		$-COCH_2CH_3$ (O)
Diphenoxylate	$-CH_2CH_2-C(CN)$		$-COCH_2CH_3$ (O)
Loperamide	$-CH_2CH_2-C-C(=O)-N(CH_3)_2$		$-OH$
Fentanyl	$-CH_2CH_2-$ 	$-H$	 $-N-C(=O)CH_2CH_3$
Sufentanil	$-CH_2CH_2-$ 	$-CH_2OCH_3$	 $-N-C(=O)CH_2CH_3$
Alfentanil	$-CH_2CH_2-N$  $N-CH_2CH_3$	$-CH_2OCH_3$	 $-N-C(=O)CH_2CH_3$
Remifentanil	$-CH_2CH_2C(=O)-O-CH_3$	$-C(=O)-O-CH_3$	 $-N-C(=O)CH_2CH_3$

Actions, Selectivities of Some Opioids at μ, δ, and κ Receptors

	RECEPTOR TYPES		
OPIOID LIGANDS	μ	δ	κ
Agonists			
Etorphine	+++	+++	+++
Fentanyl	+++		
Hydromorphone	+++		+
Levorphanol	+++		
Methadone	+++		
Morphine[a]	+++		+
Sufentanil	+++	+	+
DAMGO[a] ([D-Ala^2,MePhe^4,Gly(ol)^5]enkephalin)	+++		
DPDPE[b] ([D-Pen^2,D-Pen^5]enkephalin)		++	
[D-Ala^2,Glu^4]deltorphin		++	
DSLET ([D-Ser^2,Leu^5]enkephalin-Thr^6)	+	++	
SNC80		++	
Bremazocine	+++	++	+++
Buprenorphine	P		– –
Butorphanol	P		+++
Ethylketocyclazocine	P	+	+++
Nalbuphine	– –		++
Spiradoline[c]	+		+++
U50,488[c]			+++
U69,593[c]			+++

[a]Prototypical μ-preferring. [b]Prototypical δ- preferring. [c]Prototypical κ- preferring. [d]Universal ligand. [e]Irreversible ligand. + agonist; –, antagonist; P, partial agonist. The number of symbols is an indication of potency; the ratio for a given drug denotes selectivity. These values are obtained primarily from in vivo/in vitro animal pharmacological work and in ligand binding and activity studies and should be extrapolated to humans with caution.

Source: Reproduced with permission from Raynor et al, 1994.

Actions, Selectivities of Some Opioids at μ, δ, κ Receptors

	RECEPTOR TYPES		
OPIOID LIGANDS	μ	δ	κ
Antagonists			
Naloxone[d]	– – –	–	– –
Naltrexone[d]	– – –	–	– – –
CTOP[a]	– – –		
Diprenorphine	– – –	– –	– – –
β-Funaltrexamine[a,e]	– – –	–	++
Naloxonazine	– – –	–	–
nor-Binaltorphimine	–	–	– – –
Naltrindole[b]	–	– – –	–
Naloxone benzoylhydrazone	– – –	–	–

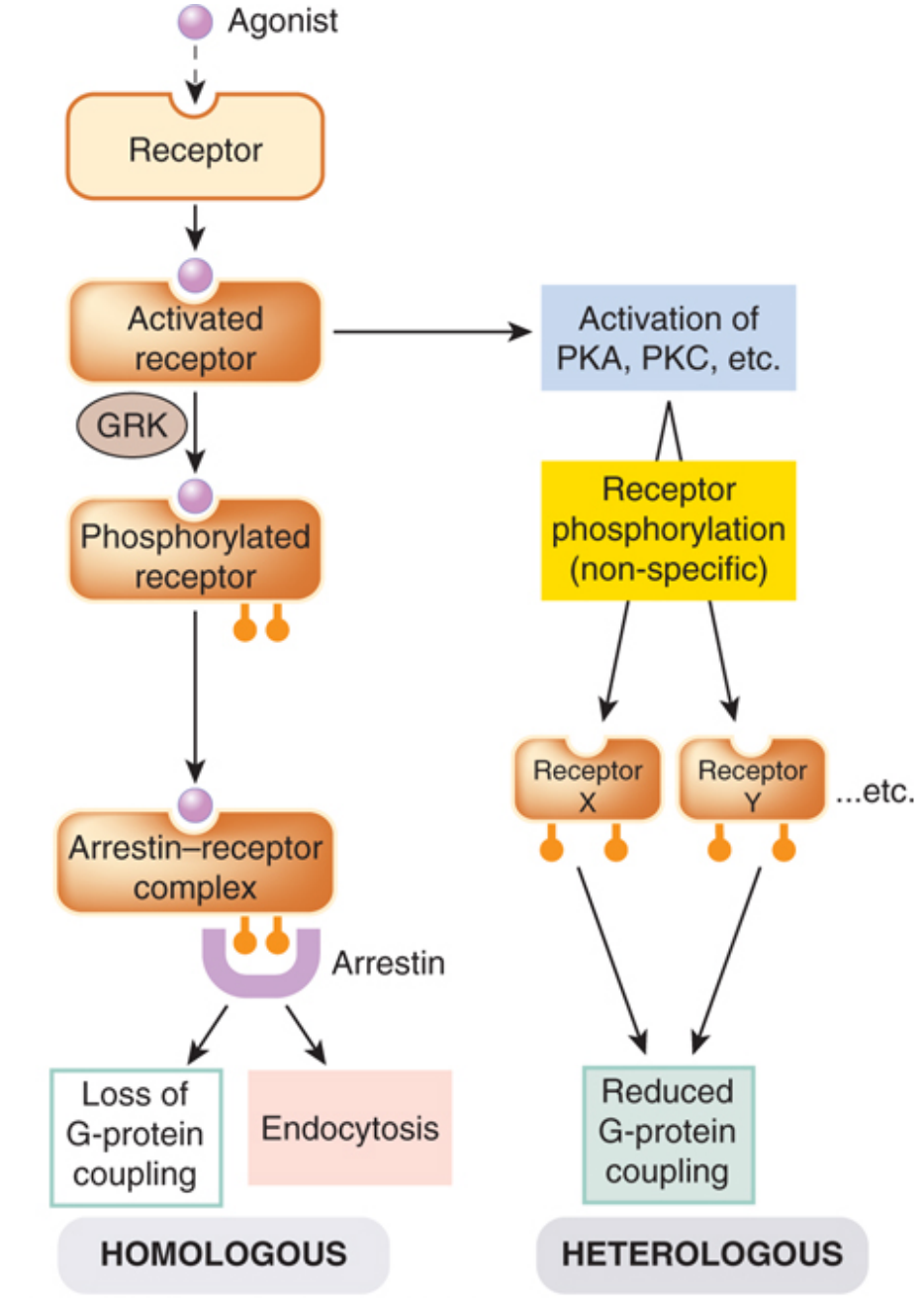
[a]Protoypical μ-preferring. [b]Prototypical δ- preferring. [c]Prototypical κ- preferring. [d]Universal ligand. [e]Irreversible ligand. + agonist; –, antagonist; P, partial agonist. The number of symbols is an indication of potency; the ratio for a given drug denotes selectivity.These values are obtained primarily from in vivo/in vitro animal pharmacological work and in ligand binding and activity studies and should be extrapolated to humans with caution.

Source: Reproduced with permission from Raynor et al, 1994.

Toleranca

- Definicija: (s t učinek ↓)
- Lahko že po 1 dozi morfina (živalski poskusi)
- Kaže se pri večini učinkov morfina (analgezija, emeza, evforija, resp. depresija)
- Veliko manj izražena pri miozi in konstipaciji
- Mehanizem:
  - Desenzitizacija receptorja μ (manjši pomen)
  - Dolgoročne prilagoditvene spremembe na celični, sinaptični in na ravni nevronskega mrežja
- Kaže se pri vseh derivatih, ki delujejo na isti receptor

Desensitisation of G-protein-coupled receptors (GPCRs). Homologous (agonist-specific) desensitisation involves phosphorylation of the activated receptor by a specific kinase (GPCR kinase, GRK). The phosphorylated receptor (P-R) then binds to arrestin, causing it to lose its ability to associate with a G-protein, and to undergo endocytosis, which removes the receptor from the membrane. Heterologous (cross-) desensitisation occurs as a result of phosphorylation of one type of receptor as a result of activation of kinases by another. PKA and PKC, protein kinase A and C, respectively.



Fizična odvisnost

- Abstinenčni pojavi po prenehanju dajanja (nemir, drget, rinoreja, piloerekcija)
- Pri počasnem zmanjševanju odmerka manj izraženi
- Razlaga:
  - Posledica prilagoditvenih sprememb na prisotnost opioida
  - hiperekscitabilnost spinalnih refleksov
  - ↑ tonus Sy (↑ aktivnost nevronov v LC) – klonidin zmanjša
  - ↑ aktivnost R NMDA (antagonisti)

Characteristics of the main opioid analgesic drugs I

Drug	Use(s)	Route(s) of administration	Pharmacokinetic aspects	Main adverse effects	Notes
Morphine	Widely used for acute and chronic pain	Oral, including sustained-release form Injection[a] Intrathecal	Half-life 3-4 h Converted to active metabolite (morphine-6-glucuronide)	Sedation Respiratory depression Constipation Nausea and vomiting Itching (histamine release) Tolerance and dependence Euphoria	Tolerance and withdrawal effects not common when used for analgesia
Diamorphine (heroin)	Acute and chronic pain	Oral Injection	Acts more rapidly than morphine because of rapid brain penetration	As morphine	Not available in all countries Metabolised to morphine and other active metabolites
Hydromorphone	Acute and chronic pain	Oral Injection	Half-life 2-4 h No active metabolites	As morphine but allegedly less sedative	Levorphanol is similar, with longer duration of action
Oxycodone	Acute and chronic pain	Oral, including sustained-release form Injection	Half-life 3- 4.5 h	As morphine	Claims for less abuse potential are unfounded
Methadone	Chronic pain Maintenance of addicts	Oral Injection	Long half- life (> 24 h) Slow onset	As morphine but little euphoric effectAccumulation may occur	Slow recovery results in attenuated withdrawal syndrome because of long half-life

[a] Injections may by given intravenously, intramuscularly or subcutaneously for most drugs.

Characteristics of the main opioid analgesic drugs II

Drug	Use(s)	Route(s) of admin	Pharmacokinetic aspects	Main adverse effects	Notes
Pethidine	Acute pain	Oral Intramuscular injection	Half-life 2-4 h Active metabolite (norpethidine) may account for stimulant effects	As morphine Anticholinergic effects Risk of excitement and convulsions	Known as meperidine in USA Interacts with monoamine oxidase inhibitors
Buprenorphine	Acute and chronic pain Maintenance of addicts	Sublingual Injection Intrathecal	Half-life about 12 h Slow onset Inactive orally because of first-pass metabolism	As morphine but less pronounced Respiratory depression not reversed by naloxone (therefore not suitable for obstetric use) May precipitate opioid withdrawal (partial agonist)	Useful in chronic pain with patient-controlled injection systems
Pentazocine	Mainly acute pain	Oral Injection	Half-life 2-4 h	Psychotomimetic effects (dysphoria) Irritation at injection site May precipitate opioid withdrawal (μ antagonist effect)	Nalbuphine is similar
Fentanyl	Acute pain Anaesthesia	Intravenous Epidermal Transdermal patch	Half-life 1-2 h	As morphine	High potency allows transdermal administration Sufentanil is similar
Remifentanil	Anaesthesia	Intravenous infusion	Half-life 5 min	Respiratory depression	Very rapid onset and recovery

Characteristics of the main opioid analgesic drugs III

Drug	Use(s)	Route(s) of admin	Pharmacokinetic aspects	Main adverse effects	Notes
Codeine	Mild pain	Oral	Acts as prodrug Metabolised to morphine and other active metabolites	Mainly constipation No dependence liability	Effective only in mild pain Also used to suppress cough Dihydrocodeine is similar
Dextropropoxyphene	Mild pain	Mainly oral	Half-life 4 h Active metabolite (norpropoxyphene) with half-life 24 h	Respiratory depression Mav cause convulsions (possibly by action of norpropoxyphene)	Similar to codeine No longer recommended
Tramadol	Acute (mainly postoperat. and chronic pain)	Oral Intravenous	Well absorbed Half-life 4- 6 h	Dizziness May cause convulsions No respiratory depression	Mechanism of action uncertain Weak agonist at opioid receptors Also inhibits noradrenaline uptake

[a] Injections may by given intravenously, intramuscularly or subcutaneously for most drugs.

Table 18–5 World Health Organization Analgesic Ladder[a]

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 concurrentsymptoms that exacerbate pain, and/or provideindependent analgesic activity for specifictypes 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.

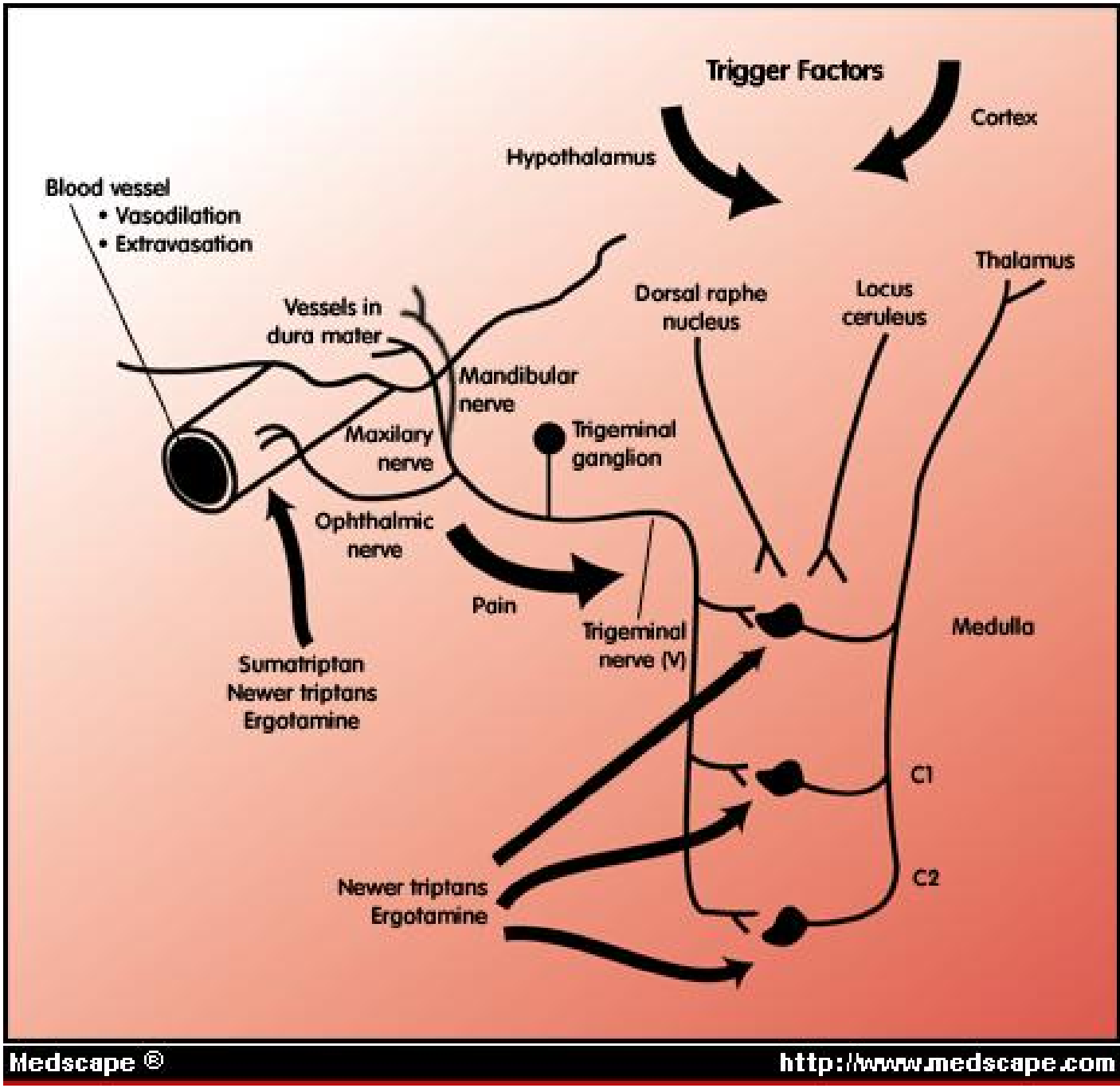
Step 3 Moderate to Severe Pain or Pain Uncontrolled after Step 2
Sustained release/long-acting opioid ATC or continuous infusion + short-acting opioid as required ± non-opioid ± adjuvant agent

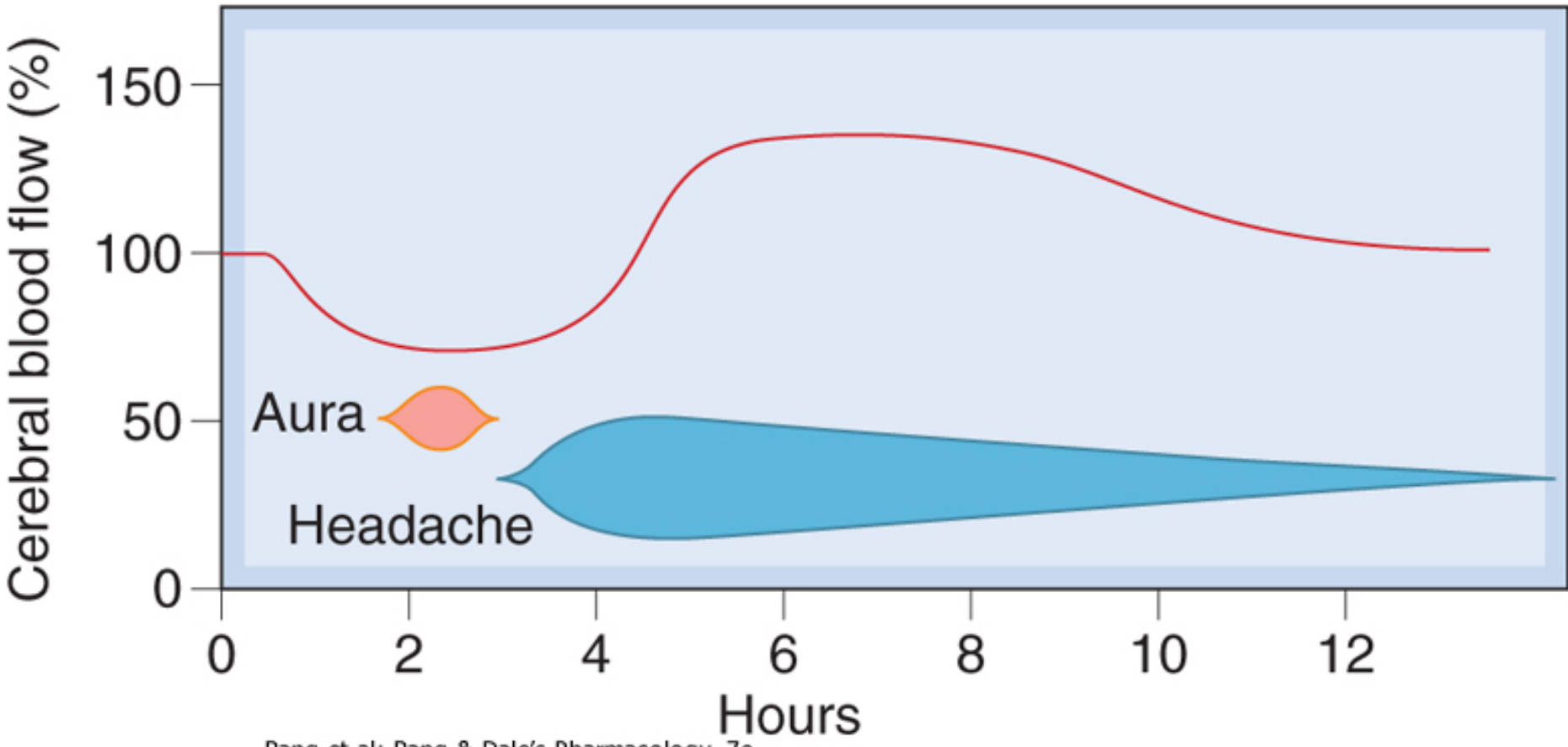
- Sustained release oxycodone, morphine, oxymorphone or transdermal fentanyl is indicated.

Zdravila za zdravljenje glavobolov

- Antipiretični analgetiki (AA, nesteroidna protivnetna zdravila – NSAID)
- Zdravila za zdravljenje migrene
  - zdravila ob akutnih napadih
  - zdravila za profilakso
- Le izjemoma narkotični analgetiki

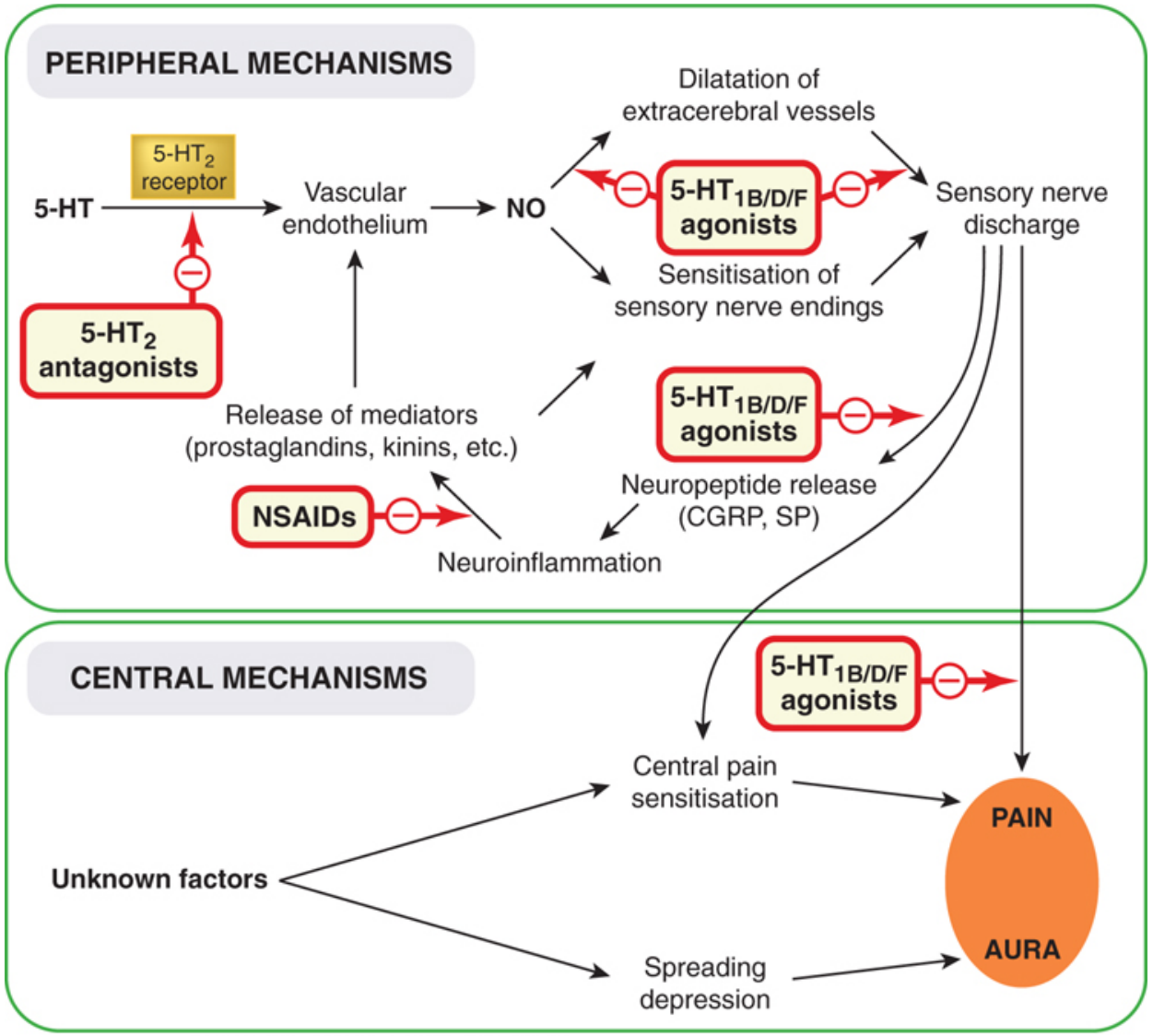
Mehanizmi nastanka migrene - strukture





Cerebral blood flow changes during migraine. (After Olesen et al. 1990 Ann Neurol 28: 791-798.)l

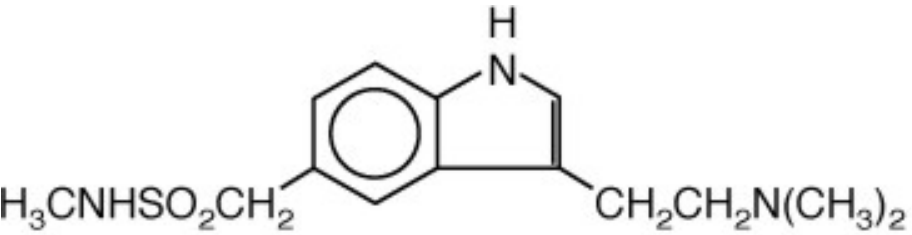
Postulated pathogenesis of migraine. The initiating event is uncertain but may be an abnormal neuronal discharge set off by emotional or biochemical disturbances. This leads to localised 'spreading depression', which causes the aura and may also lead to sensitisation of central pain pathways. In migraine without aura, the primary event is excitation (cause unknown) of nociceptive nerve terminals in the meningeal vessels, leading to the cycle of neurogenic inflammation shown in the upper part of the diagram. 5-HT, 5-hydroxytryptamine; CGRP, calcitonin gene-related peptide; NO, nitric oxide; NSAIDs, non-steroidal anti-inflammatory drugs; SP, substance P.



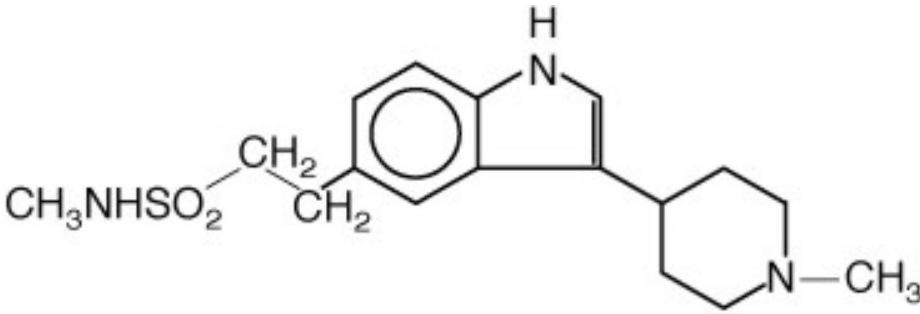
Drugs for acute attacks of migraine (Rang and Dale's Pharmacology)

Drug(s)	Mode of action	Side effects	Pharmacokinetic aspects	Notes
Sumatriptan	5-$HT_{1B/1D/1F}$ receptor agonist Constricts large arteries, inhibits trigeminal nerve transmission	Coronary vasoconstriction, dysrhythmias	Poor oral absorption, hence delayed response, Can be given s.c., Does not cross blood-brain barrier Plasma half-life 1.5 h	Effective in ~70% of migraine attacks Short duration of action is a drawback Contraindicated in coronary disease
Almotriptan Eletriptan Frovatriptan Naratriptan Rizatriptan Zolmitriptan	As sumatriptan; additional actions on CNS	Side effects less than with sumatriptan	Improved bioavailability and duration of action Able to cross blood-brain barrier	Similar to sumatriptan; but improved pharmacokinetics and reduced cardiac side effects
Ergotamine	5-HT_1 receptor partial agonist; also affects α-adrenoceptors Vasoconstrictor Blocks trigeminal nerve transmission	Peripheral vasoconstriction, including coronary vessels Nausea and vomiting Contracts uterus and may damage fetus	Poorly absorbed Can be given by suppository, inhalation, etc. Duration of action 12-24 h	Effective, but use limited by side effects

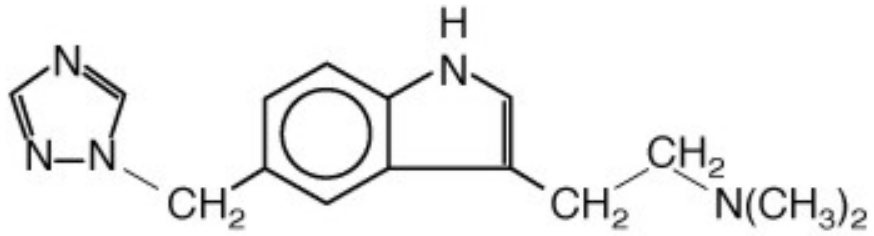
Struktura triptanov



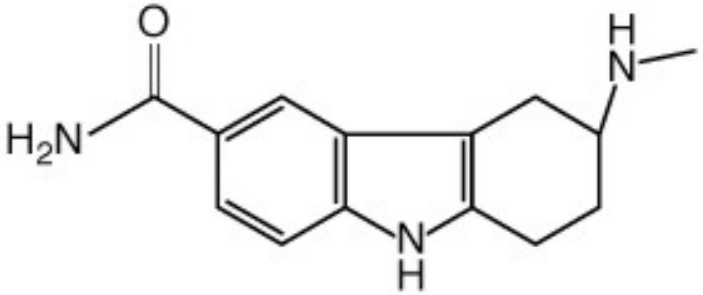
SUMATRIPTAN



NARATRIPTAN



RIZATRIPTAN



FROVATRIPTAN

Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

Structures of representative triptans (selective 5-HT1 receptor agonists).

Interakcije dihidro-ergotamina in sumatriptana z receptorji za različne mediatorje

Receptor		Vrednosti K_i (nM)	
		Dihidroergotamin	Sumatriptan
Serotoninski	$5\text{-}HT_{1D}$	0,55	6,7
	$5\text{-}HT_{1A}$	0,83	120
	$5\text{-}HT_{1B}$	6,2	35
	$5\text{-}HT_{1E}$	8,8	920
	$5\text{-}HT_{2C}$	39	>10 000
	$5\text{-}HT_{2A}$	78	>10 000
Adren-ergični	$alfa_1$	6,6	>10 000
	$alfa_2$	3,4	>10 000
Dopa-minski	D_2	98	>10 000

Drugs for prophylaxis of migraine (Rang and Dale's Pharmacology)

Drug(s)	Mode of action	Side effects	Pharmaco-kinetics	Notes
Methysergide	5-HT_2 receptor antagonist/partial agonist	Nausea, vomiting, diarrhoea Retroperitoneal or mediastinal fibrosis (rare but serious)	Used orally	Effective, but rarely used because of side effects and insidious toxicity
Pizotifen	5-HT_2 receptor antagonist Also histamine antagonist	Weight gain, antimuscarinic side effects	Used orally	
Cyproheptadine	5-HT_2 receptor antagonist Also blocks histamine receptors and Ca^{2+} channels	Sedation, weight gain	Used orally	Rarely used
Propranolol and similar drugs	β-adrenoceptor antagonists Mechanism of antimigraine effect not clear	Fatigue, bronchoconstriction	Used orally	Effective and widely used for migraine

Še druga zdravila za profilakso migrene

- Triciklični antidepresivi (amitriptilin…)
- Blokatorji kalcijevih kanalov (nifedipin)
- Antiepileptiki (topiramat, valproat)
- Klonidin (antihipertenziv)