Opioids 1

Dr Ian Napier | Postdoctoral Research Fellow

W326, Blackburn Bldg.

Pain and drug addiction laboratory

Ian.napier@sydney.edu.au

Discipline of Pharmacology

SYDNEY MEDICAL SCHOOL

THE UNIVERSITY OF SYDNEY

Opioids

1

Pain neurons – nociceptors
Signal transduction – from peripheral to central
Descending control of pain
Opioid effects on systems

THE UNIVERSITY OF SYDNEY

Learning outcomes

- Be able to describe different types of opioid receptor
- Name the different endogenous opioids
- Describe cellular actions of opioids
- Describe the process of descending inhibition and disinhibition

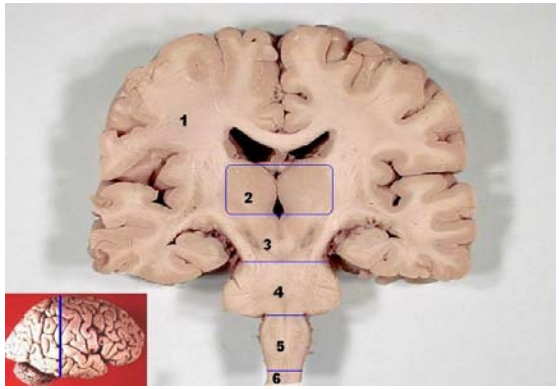
Pain or Nociception?

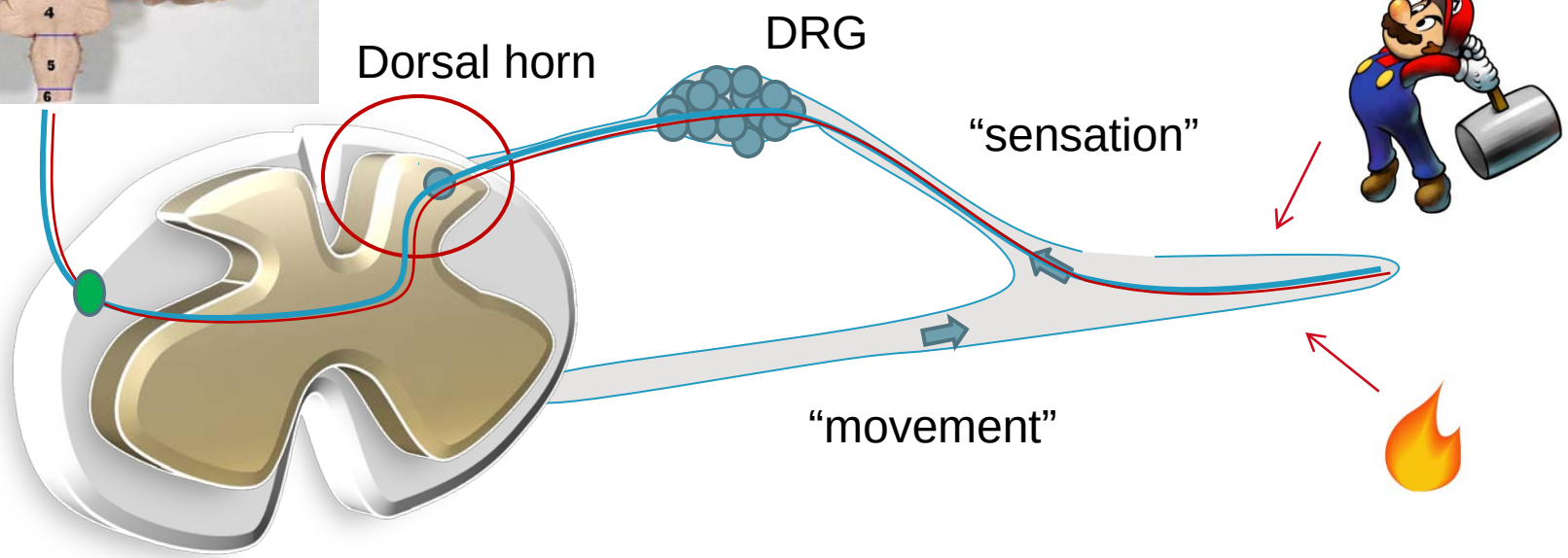
Rene Descartes *Treatise of Man*, 1664

- Nociception
  - detection of noxious information by specialised neurons – nociceptors
- Pain
  - Complex subjective response to noxious information, influenced by experience and situation

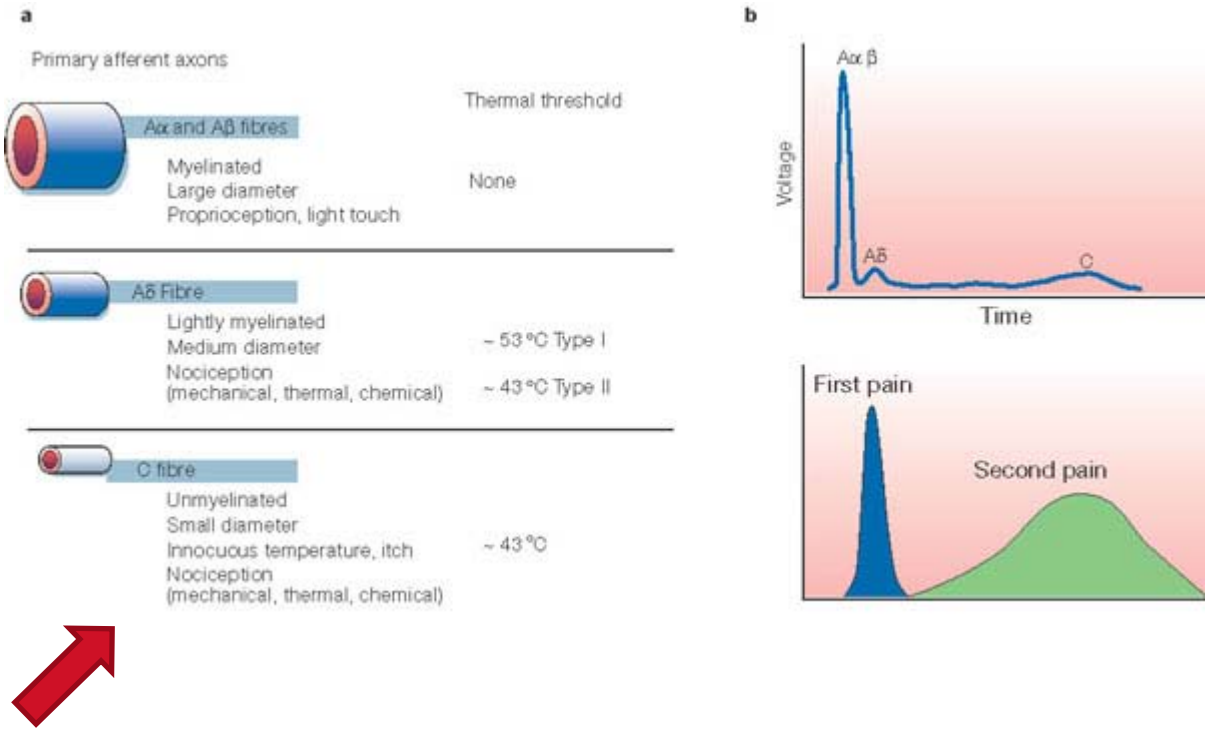
How do sensory neurons transmit information?

Transmitters, receptors, channels and cascades!



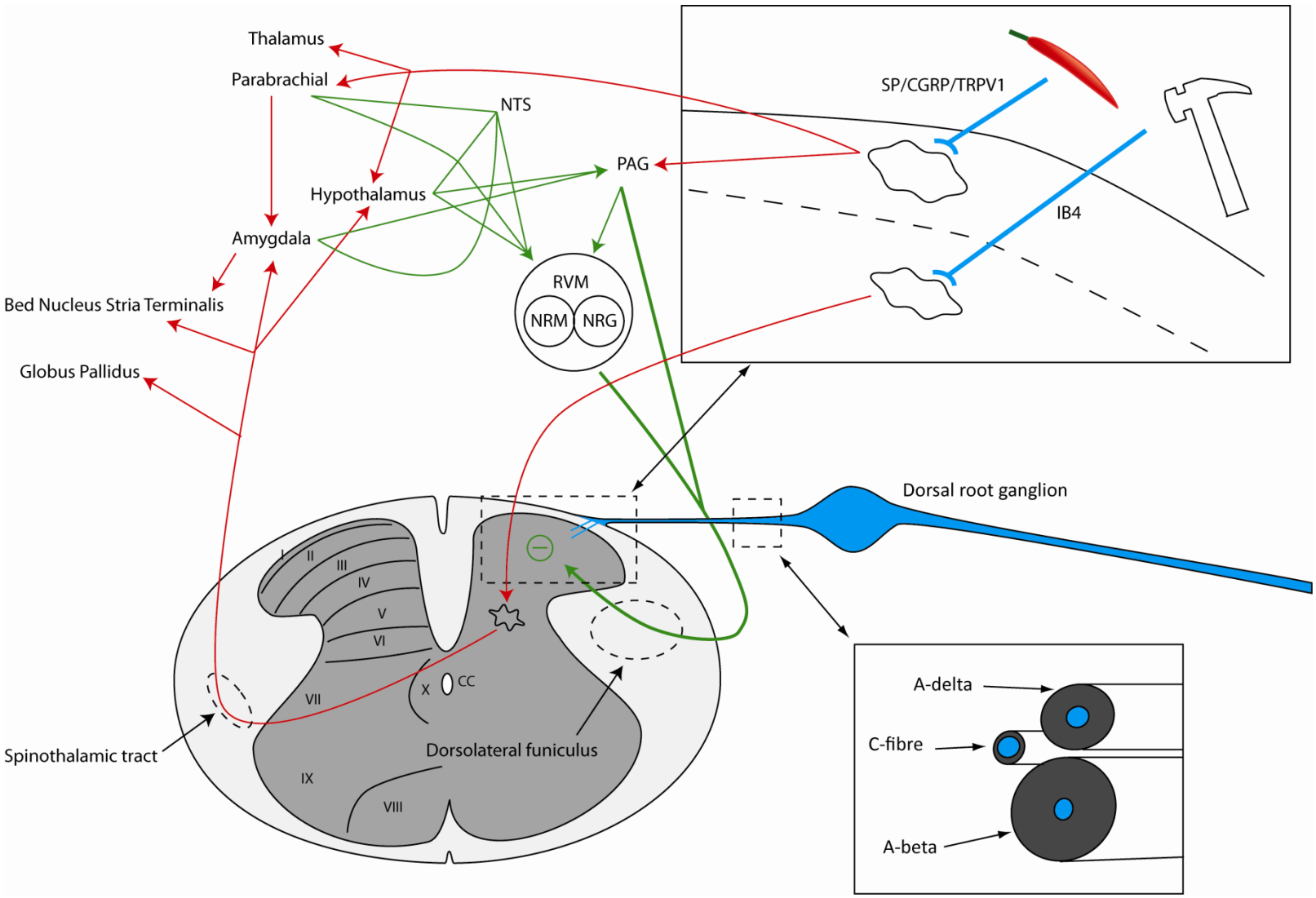


Sensory fibre types



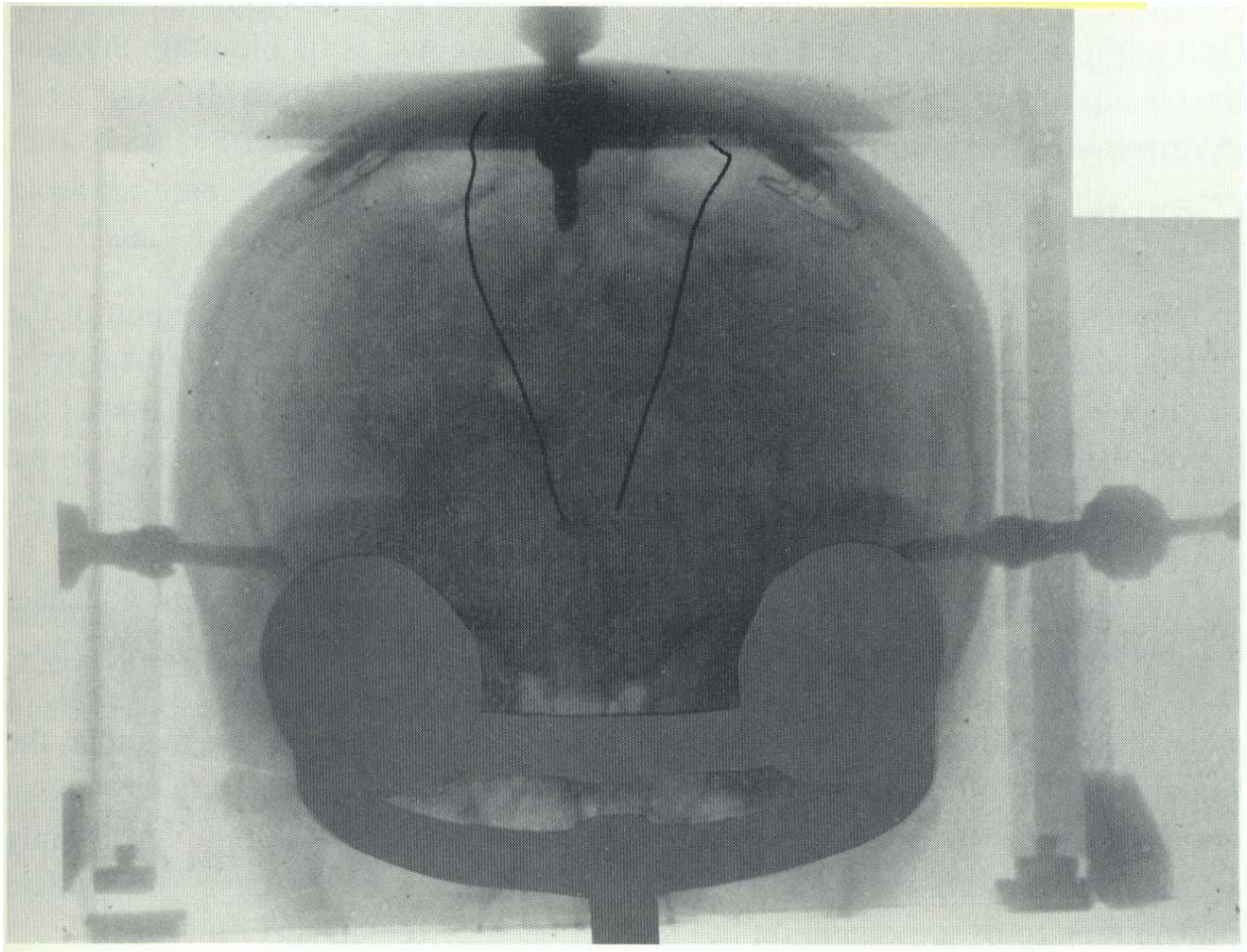
opioids

Descending control of pain

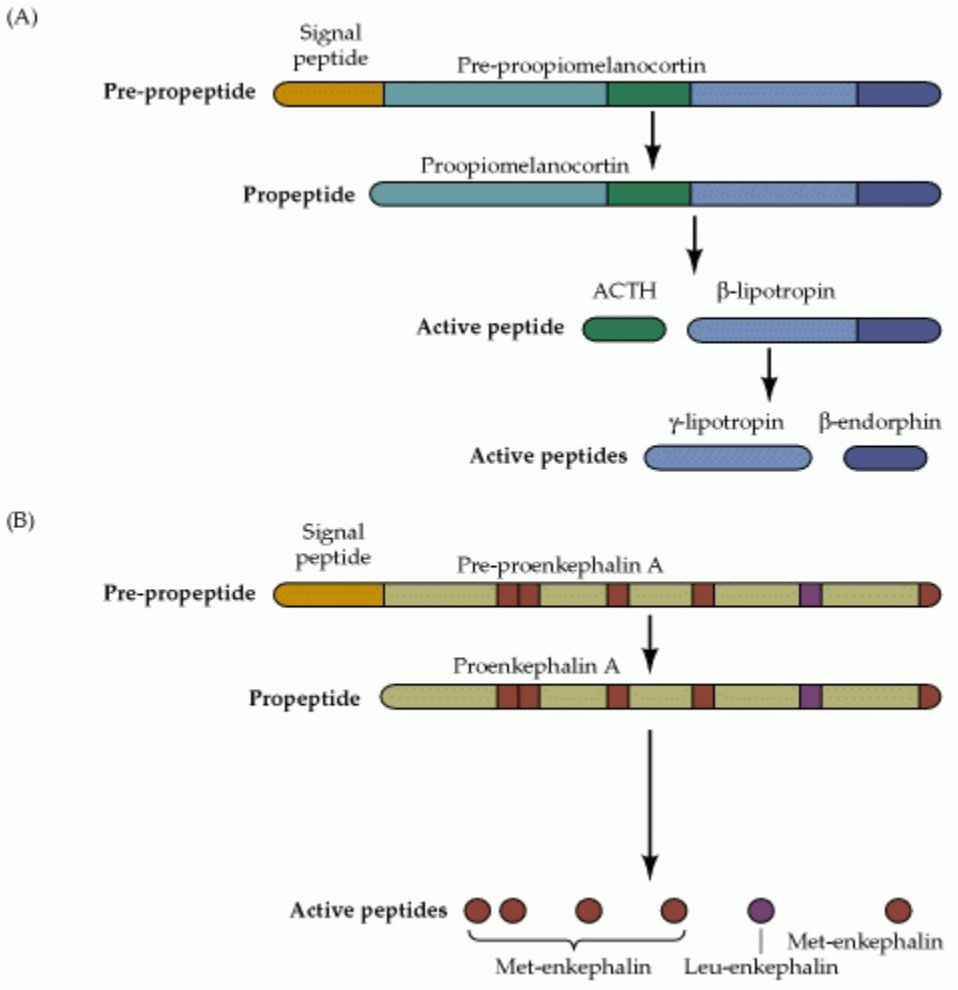


Endogenous opioids mediate analgesia

1970 - Electrical stimulation produced analgesia (periaqueductal grey) reversed by opioid antagonists implicating endogenous opioids



Endogenous opioids



- Opioid peptides discovered in 70s
- 3 classes;
- Pre-proopiomelanocortin – gives rise to B-endorphin and ACTH
- Preproenkephalin – gives rise to met- and leu-enkephalin – found in neurons of lamina I/II as well as PAG
- Dynorphins arise from pre-prodynorphin

Neuroscience, 2nd Ed. Purves D, Augustine GJ, Fitzpatrick D, et al., editors.

Opioid history

- Opium is derived from the juice of the opium poppy, *Papaver Somniferum*.
- Opium extract has been used for thousands of years for social and medicinal uses.
- Morphine was first isolated in 1806 from opium.
- In current pharmacological science the term, opioid refers to any compound that has morphine-like effects, whether endogenous or synthetic, that can be reversed by an antagonist such as naloxone.
- **Laudanum, about 1880-1900**
- was commonly used as a painkiller and a sedative in 19th- and early 20th-century America. In large doses it could also be used as a poison, and figured in several notorious murder cases.

http://www.nlm.nih.gov – 'visible proofs'

Tasmania's most profitable business, SkyNews Jan 8th 2011

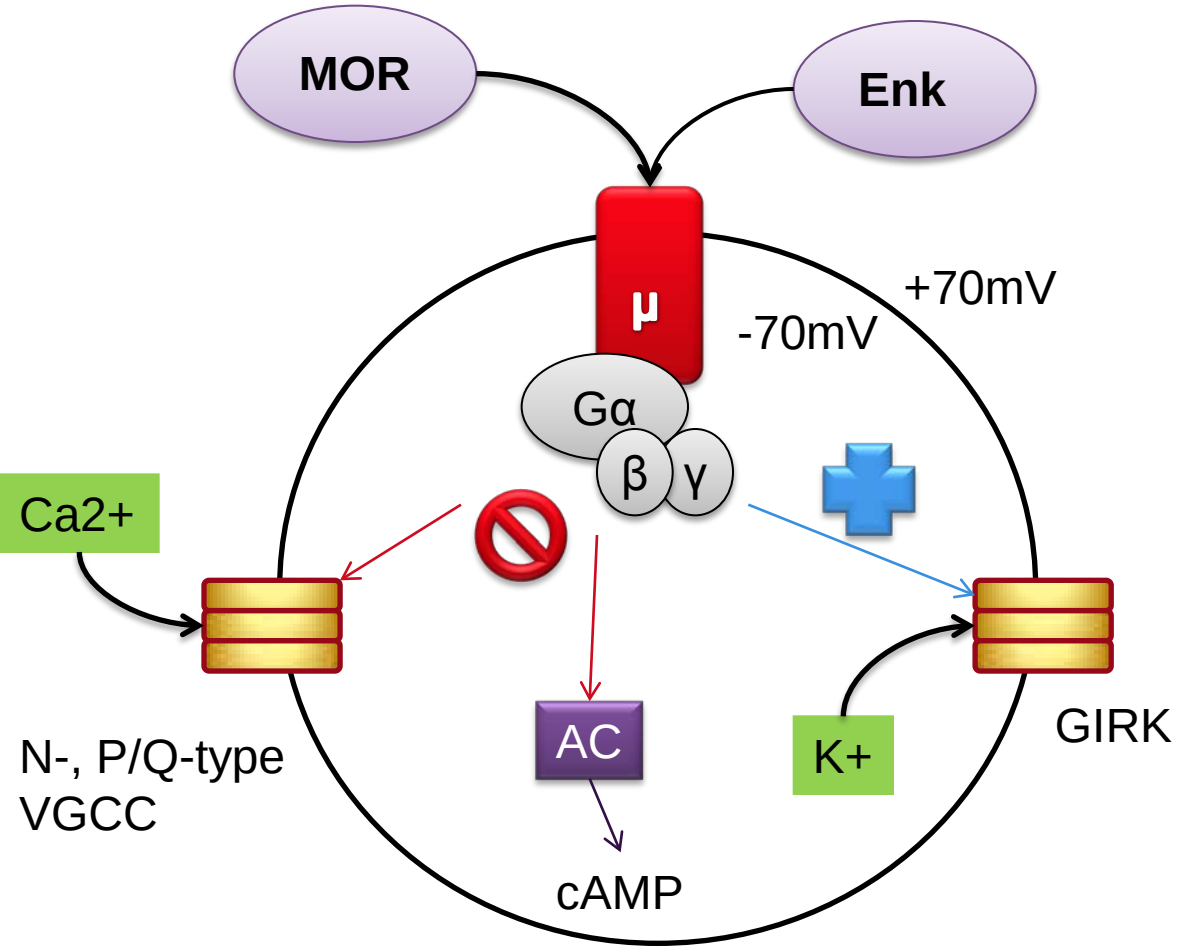
http://www.youtube.com/watch?v=Lro4SvB9XrM&feature=youtu.be

Types of opioid receptor

3 types of opioid receptor

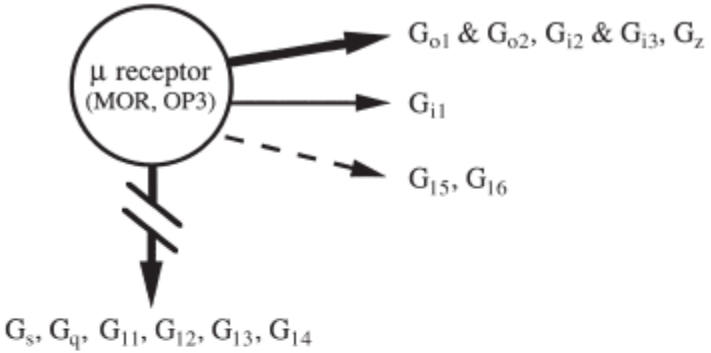
- μ - for morphine (aka MOR, MOP)
  - Strong analgesia, but;
  - Constipation, nausea, respiratory depression, tolerance, dependence
    → Loperamide / codeine
- δ – for vas deferens (aka DOR, DOP)
  - Spinal analgesia, but;
  - Convulsions?, cardiovascular complications
- κ – for ketocyclazocine (aka KOR, KOP)
  - Moderate analgesia, but;
  - Diuresis, dysphoria

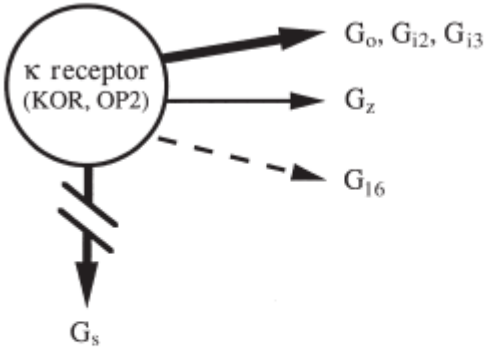
Opioids act to block neurotransmitter release

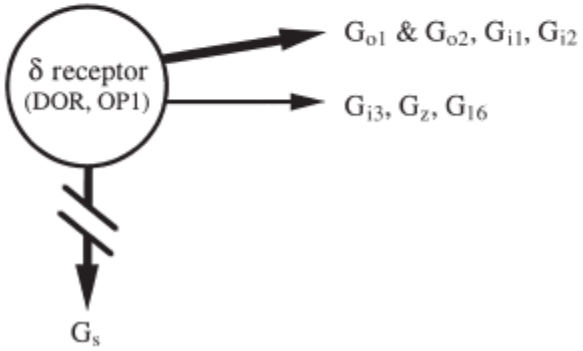


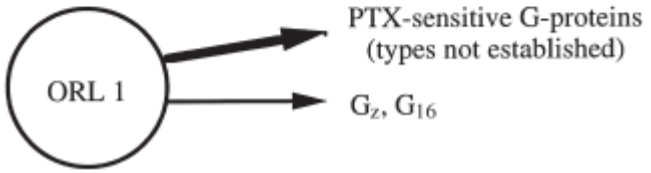
Which Gα-proteins?

Generally the same Gα-proteins for all ORs









ORs May couple to
Go – Go1 & Go2
Gi – Gi1, Gi2, Gi3

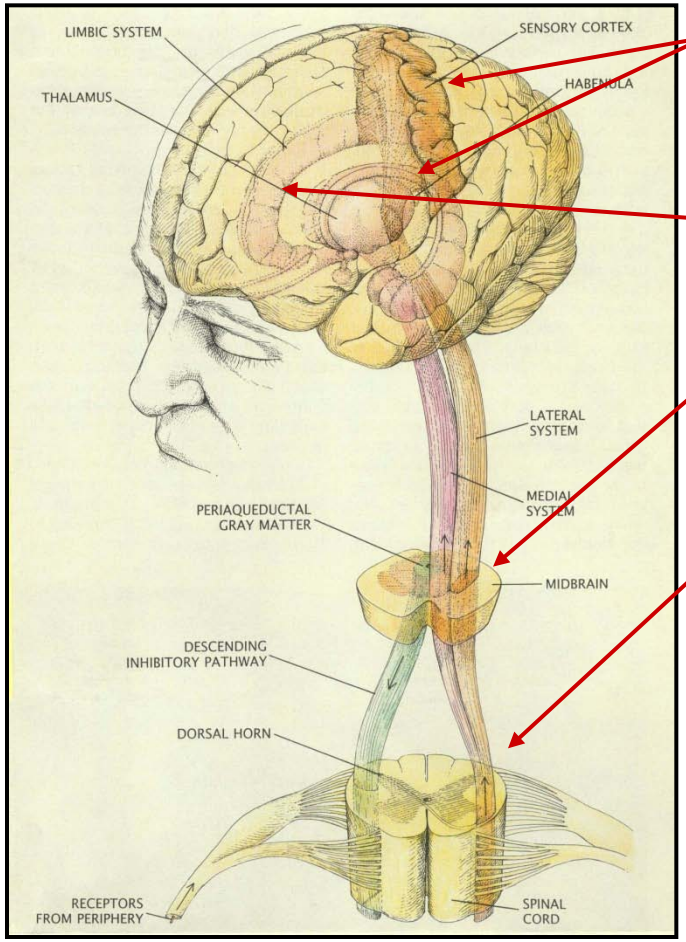
Connor and Christie 1999

Physiological consequences of opioids

- Adenylyl cyclase
  - Inhibition of voltage-dependent ‘pacemaker’ I_h – cation non-selective current activated at hyperpolarised potentials to depolarise membrane
  - The voltage dependence is regulated by cAMP, opioids shift voltage dependence to more negative potentials
- Increase in potassium conductance
  - All three ORs activate GIRK potassium conductance through membrane delimited β/γ subunits
- Decrease in calcium conductance
  - Similar to potassium channels, β/γ subunits

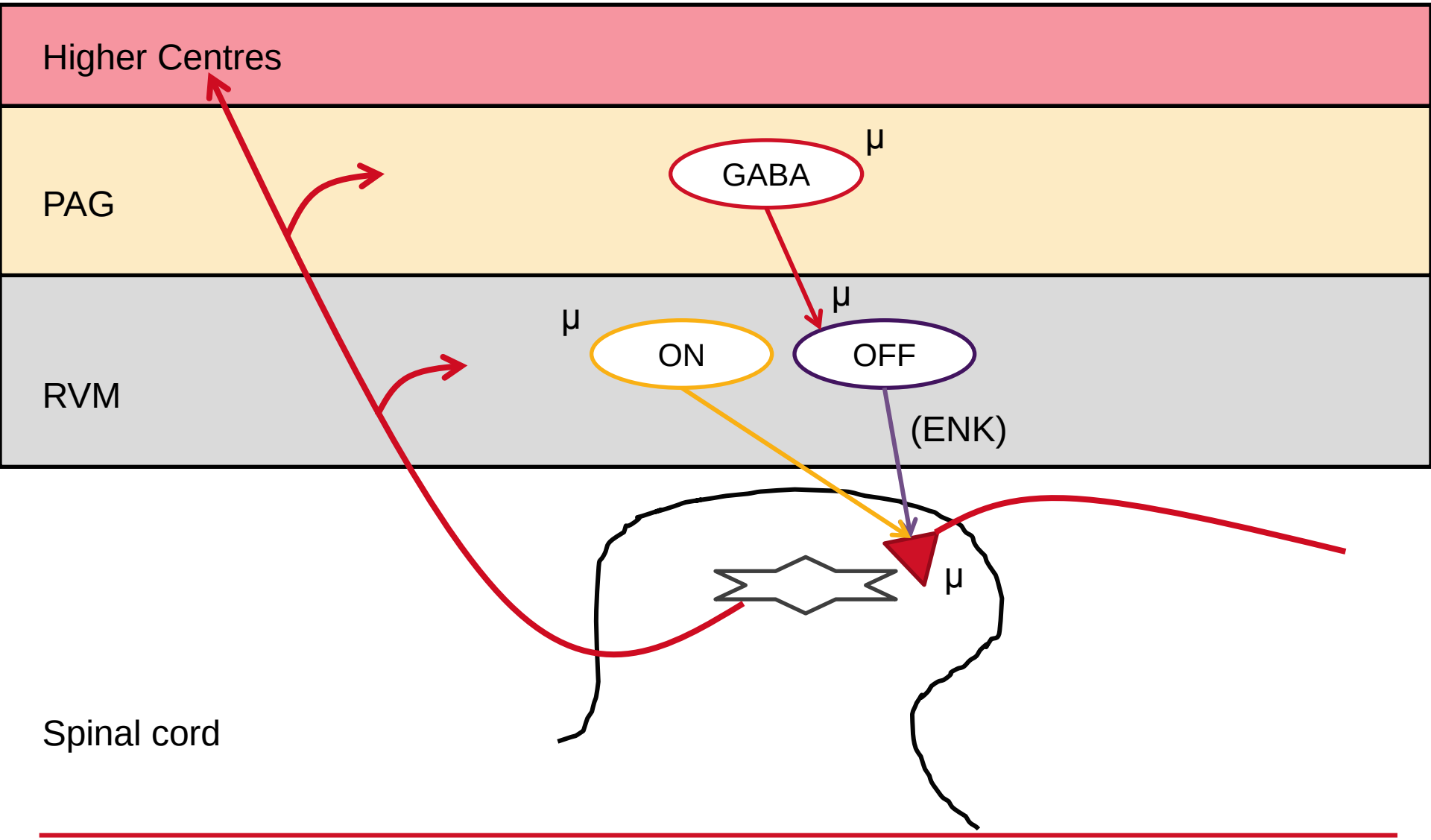
Where do opioids work?

Opioids act at all levels of pain pathways



- Forebrain: lateral sensory system (thalamus, cortex)
- Forebrain: medial system emotional responses (limbic system)
- Midbrain and brainstem: descending systems (PAG, raphe nuclei)
- Spinal cord: sensory modulation (dorsal horn)

Mechanisms of descending inhibition



Functional effects associated with opioid receptors

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

Rang and Dale p512

Endogenous opioid targets

	μ	δ	κ	ORL1/NOP
β-endorphin	+++	+++	+	-
Leu-enkephalin	++ (PA)	+++	+	-
Met-enkephalin	++	+++	+	-
Dynorphin	+	+	+++	-
Nociceptin/ Orphanin FQ	-	-	-	+++

Table 41-3. Endogenous opioid peptides and receptor-selective drugs

Nociceptin/ Orphanin FQ receptor (NOP)

Effect of N/OFQ administration

Anxiolytic, anti-arrhythmic, bradycardia, hypotension, vasodilation, induces withdrawal symptoms, feeding, hearing?, immunity, learning and memory, renal function, differential effects on reward (cocaine, ethanol, morphine), sexuality, thermoregulation, pain (controversial ?? !! ?? !! ??)

Pain:

Supraspinal injection of N/OFQ results in hyperalgesia/ anti-opioid activity and blocks morphine induced analgesia in PAG injections

Spinal injection results in analgesia

However, both generalisations are contentious with data supporting and arguing against both claims

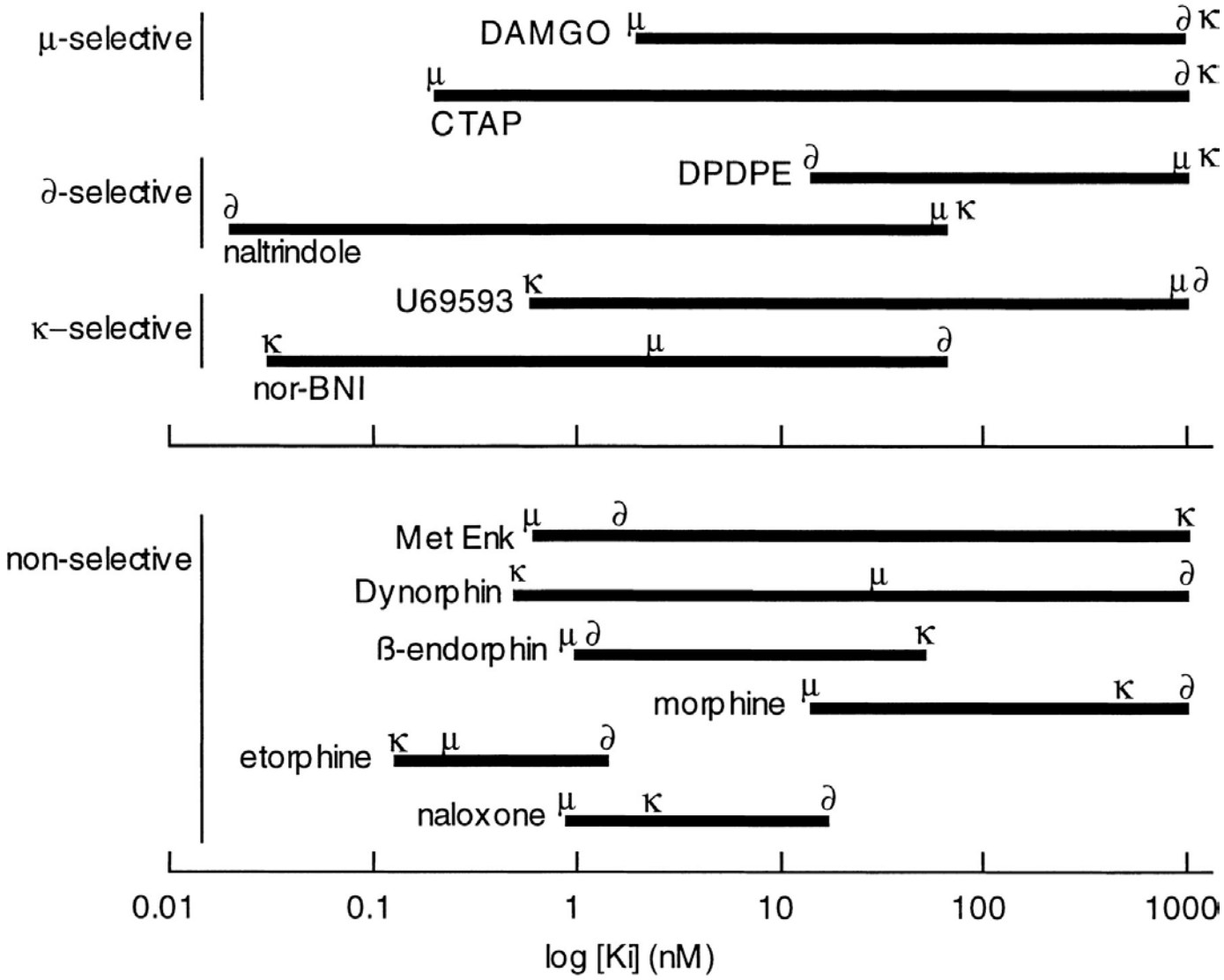
Peripheral high dose injection can be analgesic. Again, contentious issue.

Actions *may* be blocked by naloxone

Opioid agonists and antagonists

- Pure agonists
  - Eg peptides, or non-peptides (eg etorphine, methadone)
  - Have high affinity for MOR and generally lower for DOR, KOR
- Partial agonists
  - Eg morphine
  - Have lower intrinsic efficacy than full agonists
- Mixed agonist-antagonists
  - Eg nalorphine (original MOR antagonist) and pentazocine
  - Combine KOR agonist activity with MOR antagonist
- Antagonists
  - Eg naloxone
  - Block the effects of opioids

Opioid agonists and antagonists



Physiol Rev
January 1, 2001 vol. 81 no. 1 299–343

Summary

- ‘Pain’ signals carried to brain via nociceptors
  - Medium diameter, lightly myelinated, fast/sharp
  - Small diameter, unmyelinated, slow/dull
- Opioid receptors are Gαi/o-protein coupled receptors, activation of which causes hyperpolarisation;
  - Blockade of Ca-channels, activation of K-channels and reduction in AC
- Opioids exert analgesic effects by;
  - Inhibiting ascending excitatory pathways (spinal cord)
  - Enhancing descending inhibitory pathways (Brain/PAG)

Reading

- Rang and Dale 7th Edition chapter 41 pages 503 - 524
- **Cellular and Synaptic Adaptations Mediating Opioid Dependence**. Williams et al 2001. Physiol Rev. 81(1): 299-343