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PATHOPHYSIOLOGY AND MEDICAL MANAGEMENT OF PAIN

Objectives

- Epidemiology
- Type of pain
- Pathophysiology of pain
- Neuroanatomy of pain
- Molecular mechanism of analgesics
- Medical management of pain

Epidemiology

- NIH 1982
  - Third largest health problem in the world
- Sweden 1999
  - Cross-sectional study found that 49-55% of population was suffering from acute or chronic pain
- Accounts for 80% of visits to physicians
- Taking into account lost wages and social support, cost of chronic pain is between $15,000 and $24,000 per patient per year

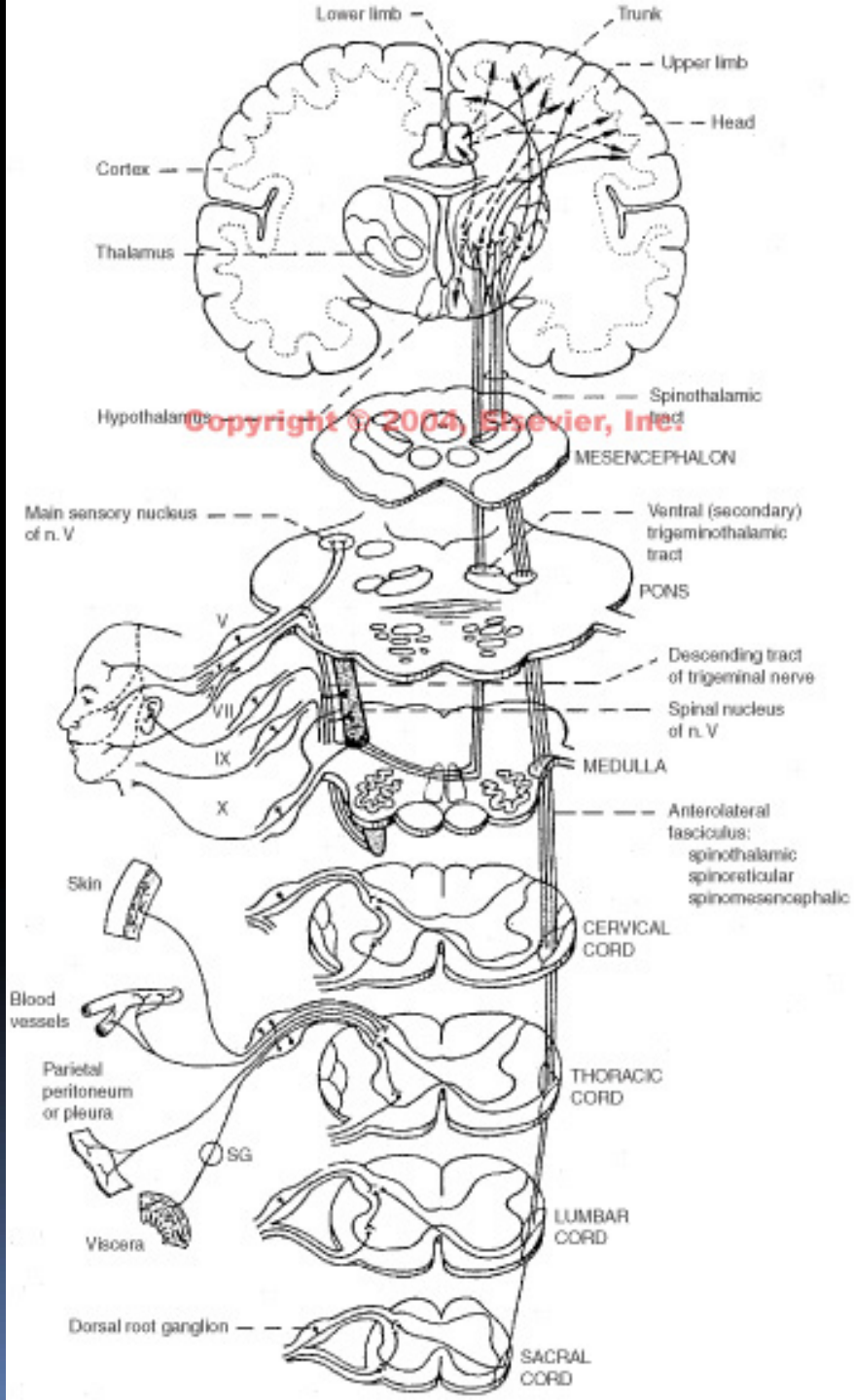
Pain and suffering

- Defined as "unpleasant sensory and emotional experience associated with actual or potential tissue damage."
- Multifactorial aspects of pain and suffering cannot be disregarded
- Acute vs chronic
  - Acute pain becomes classified as chronic pain after 3 months following initial insult

Classification

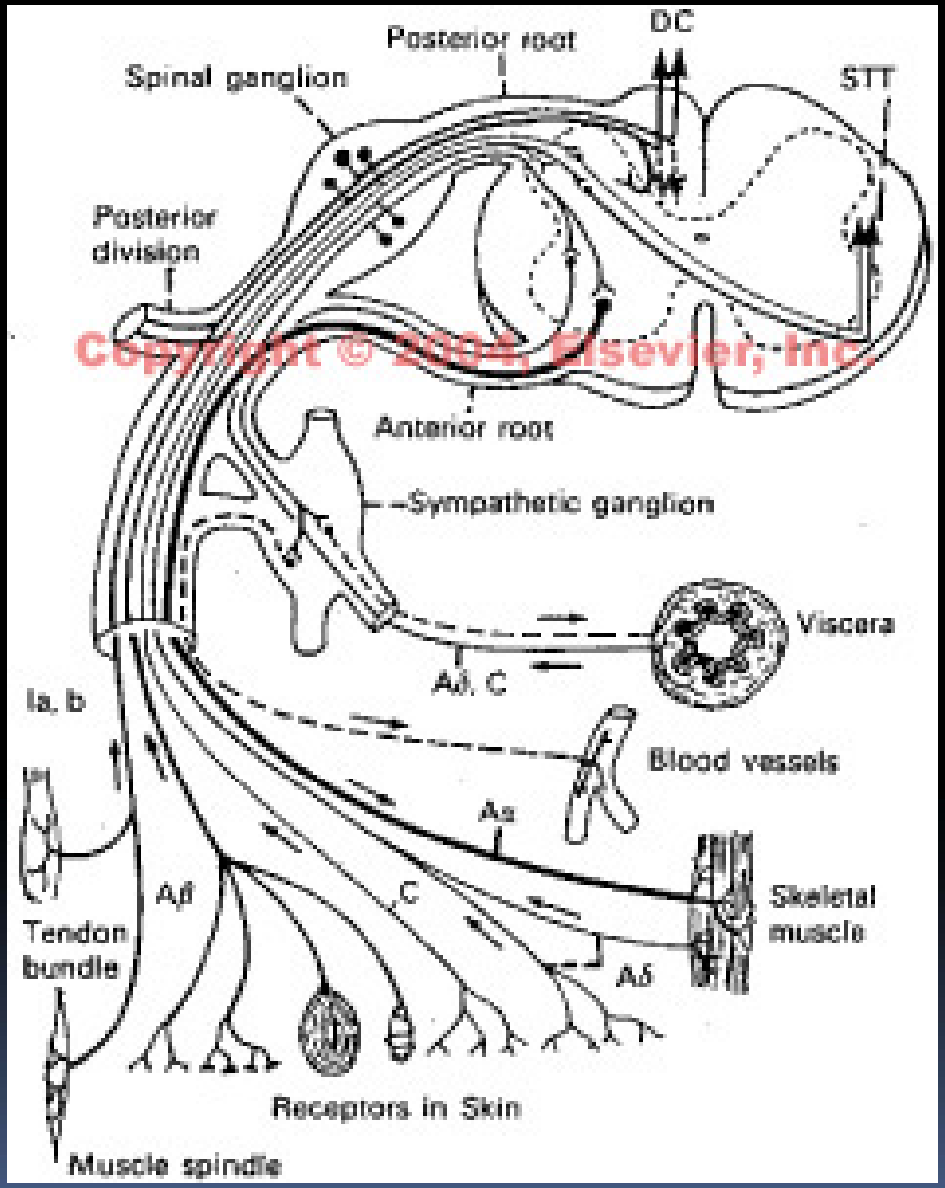
- Nociceptive pain
  - Somatic
  - visceral pain
- Neuropathic pain
  - Sympathetically mediated pain arising from a peripheral nerve lesion with autonomic changes (CRPS I, II)
  - Nonsympathetically mediated pain arising from a peripheral nerve without autonomic change
  - Central pain arising from abnormality in CNS

NEUROANATOMY OF NOCICEPION



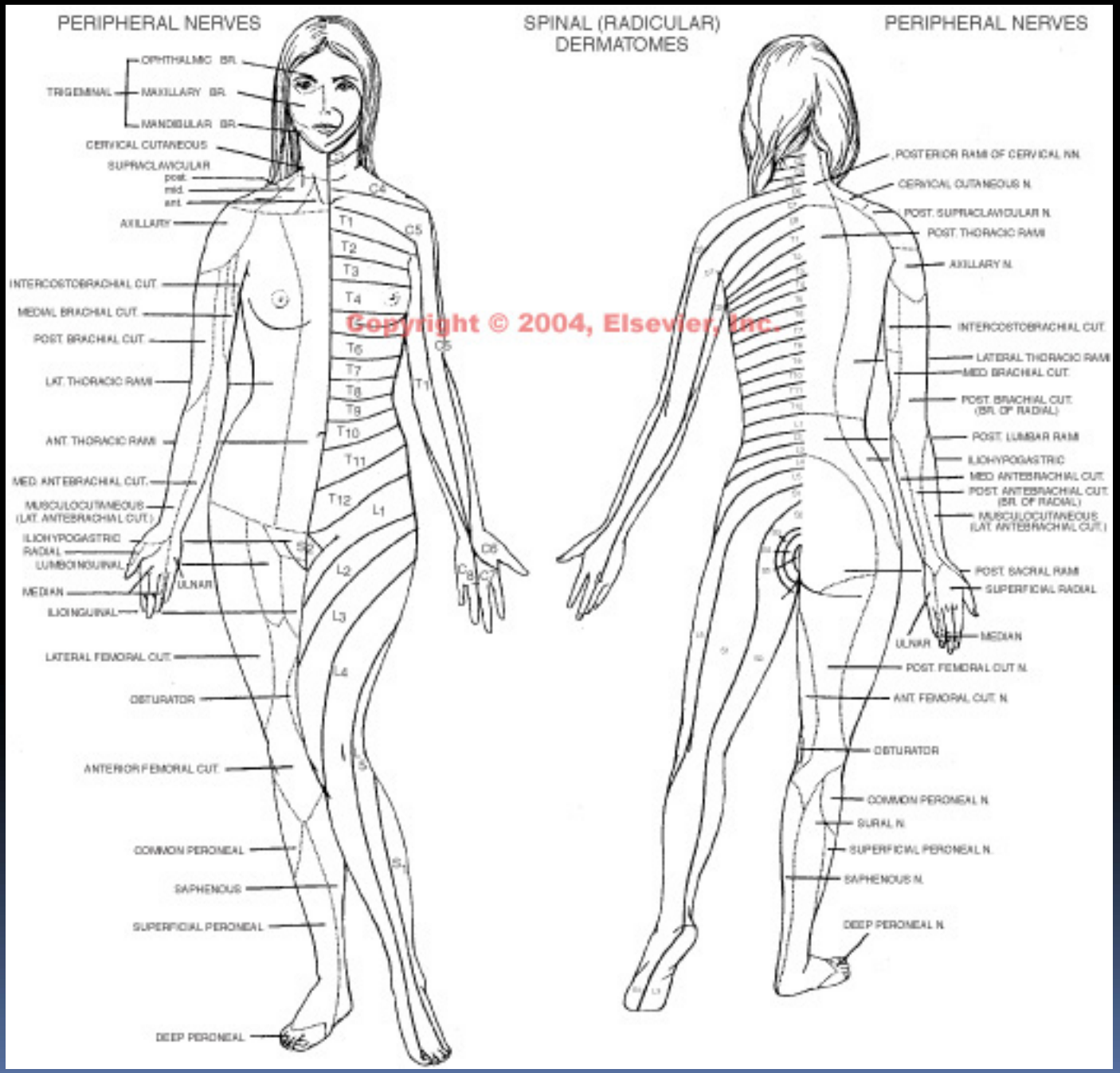
Primary afferent neurons

- Type
  - Aδ – thin, myelinated
  - C fibres – unmyelinated
  - Aβ – large, myelinated, infrequent
- Activators include: thermal, mechanical, chemical
- Unimodal vs. polymodal



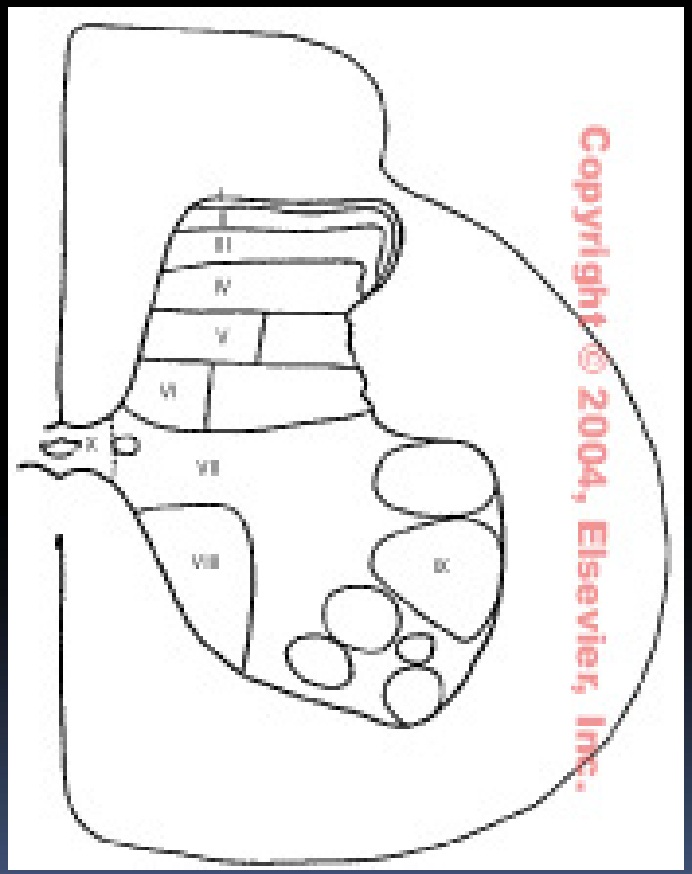
Peripheral nociception

general organization

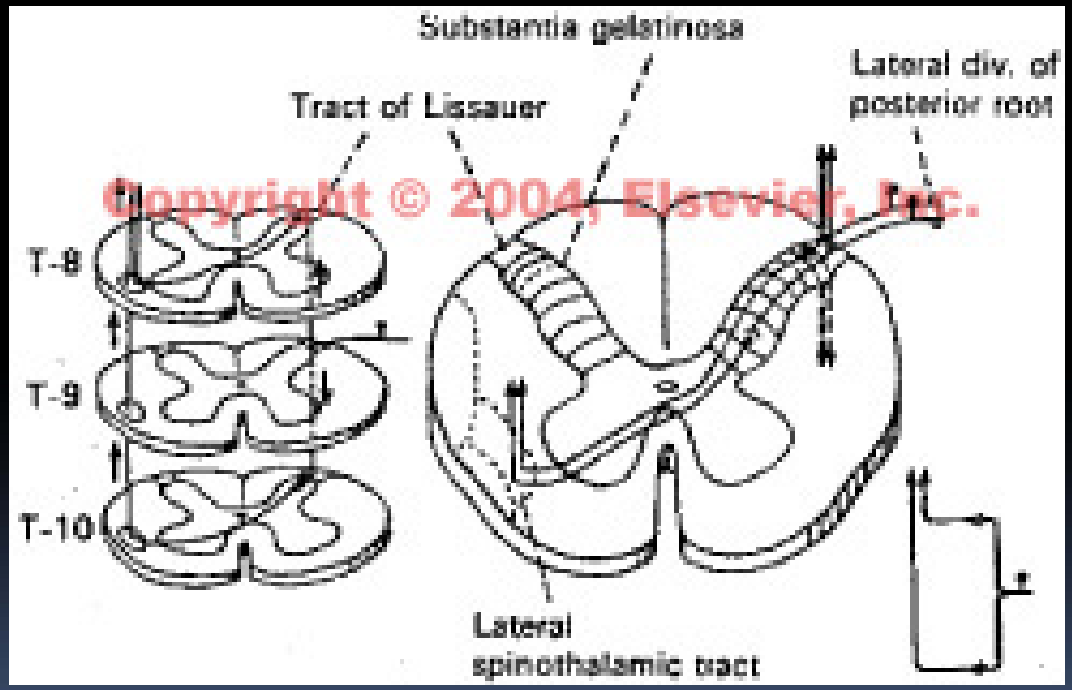


Cytoarchitecture of the grey matter of the spinal cord

- Rexed laminae



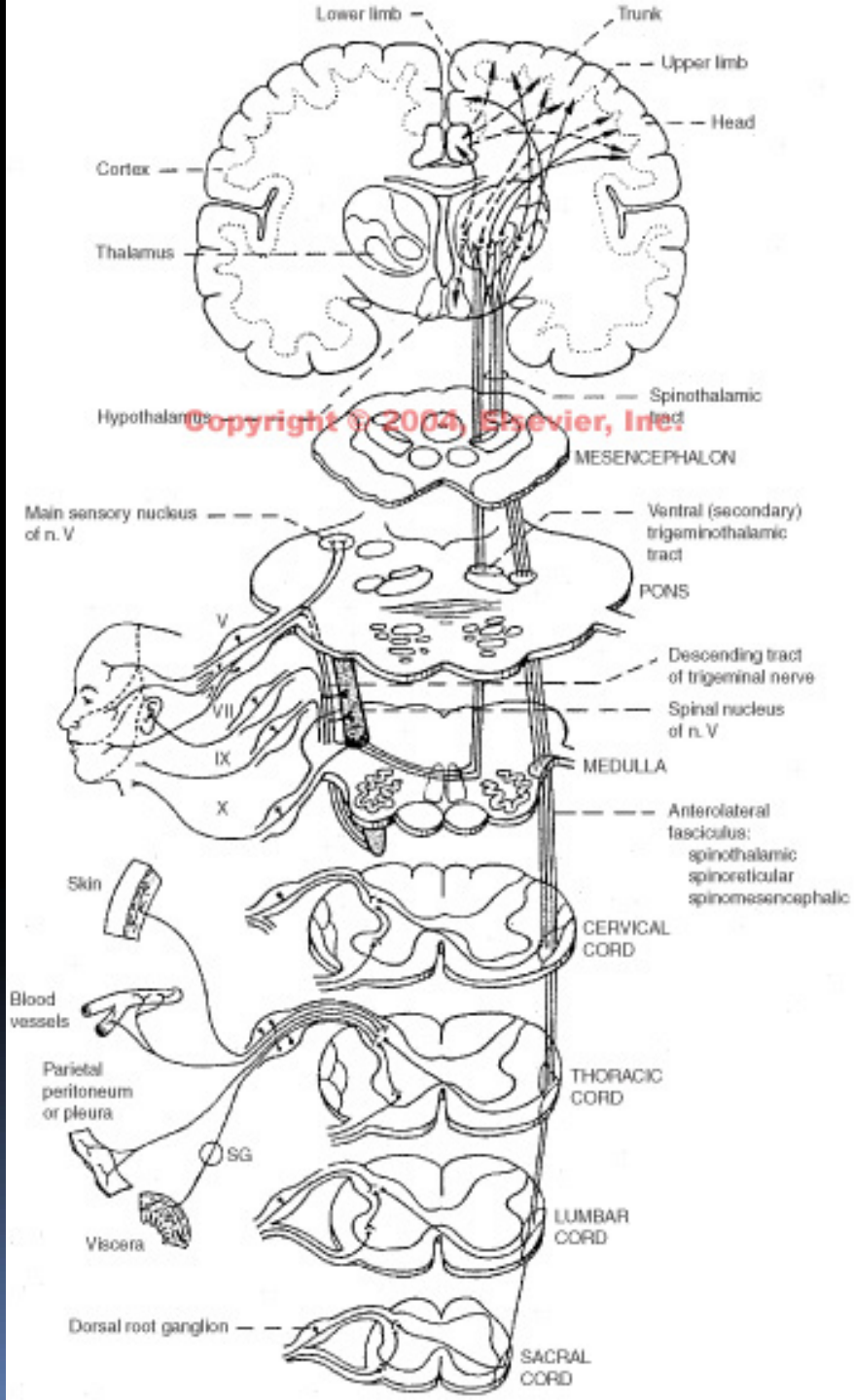
Lissaur’s tract



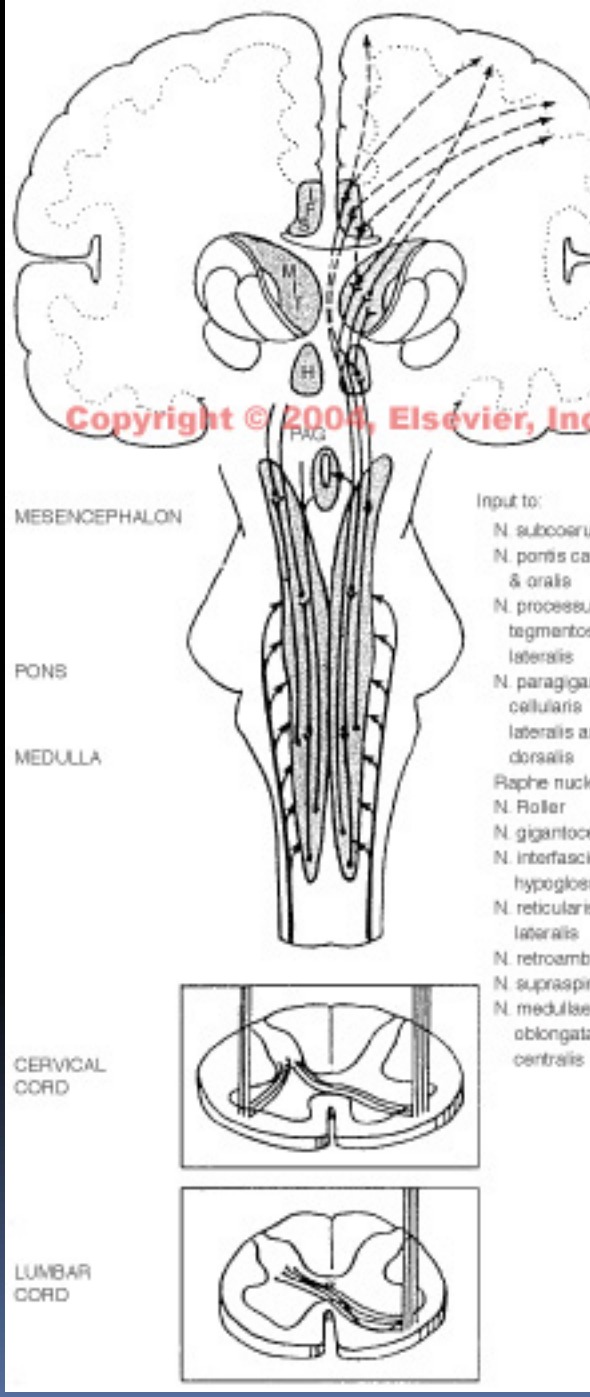
Ascending nociceptive pathways

- Spinothalamic tract
- Spinoreticular tract
- Spinomesencephalic tract
- Dorsal column
- Propriospinal, multisynaptic ascending system

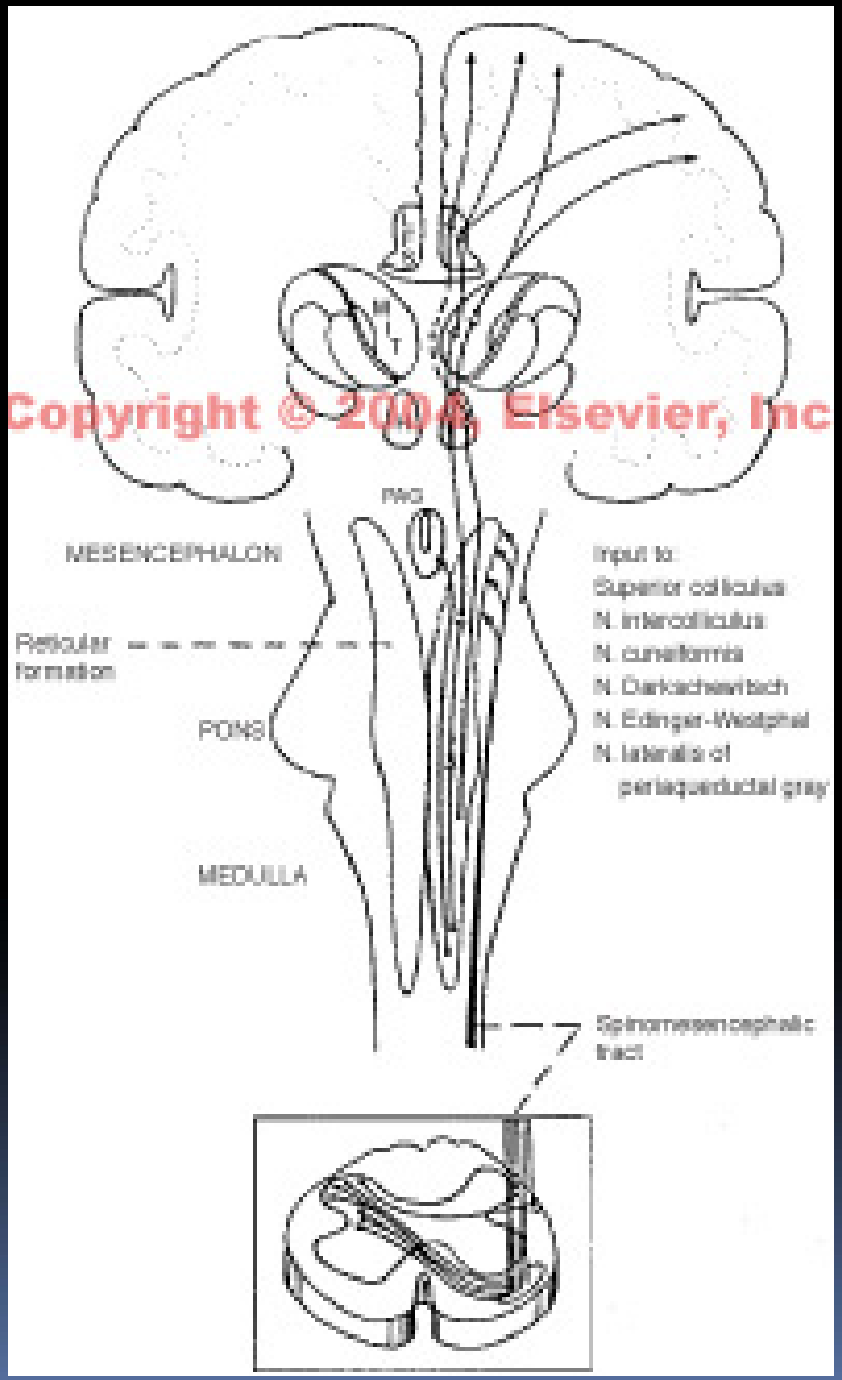
Spinothalamic tract



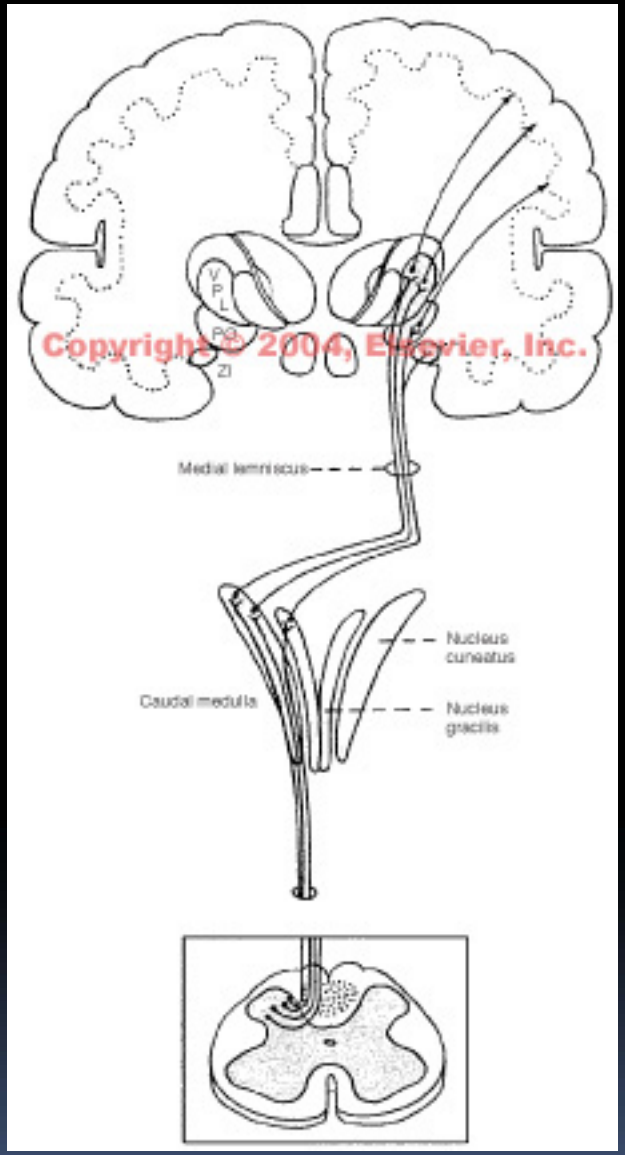
Spinoreticular tract

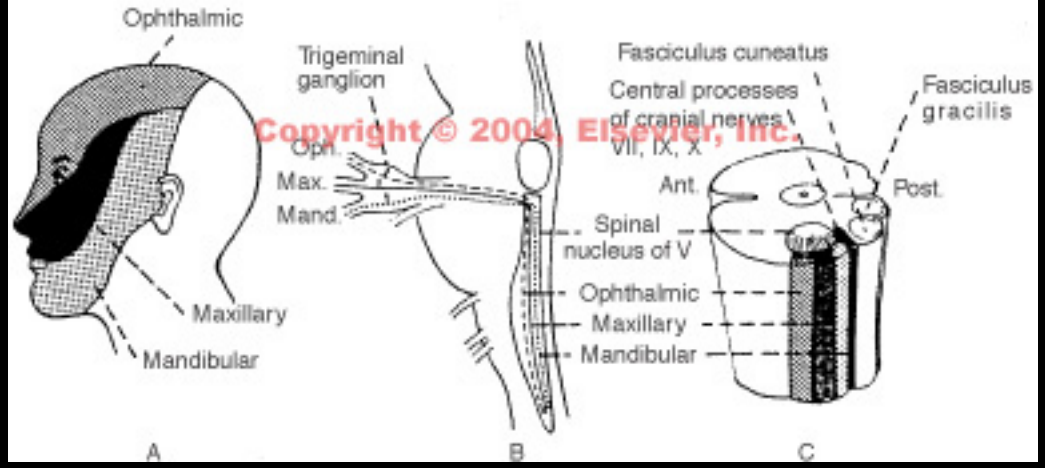


Spinomesencephalic tract

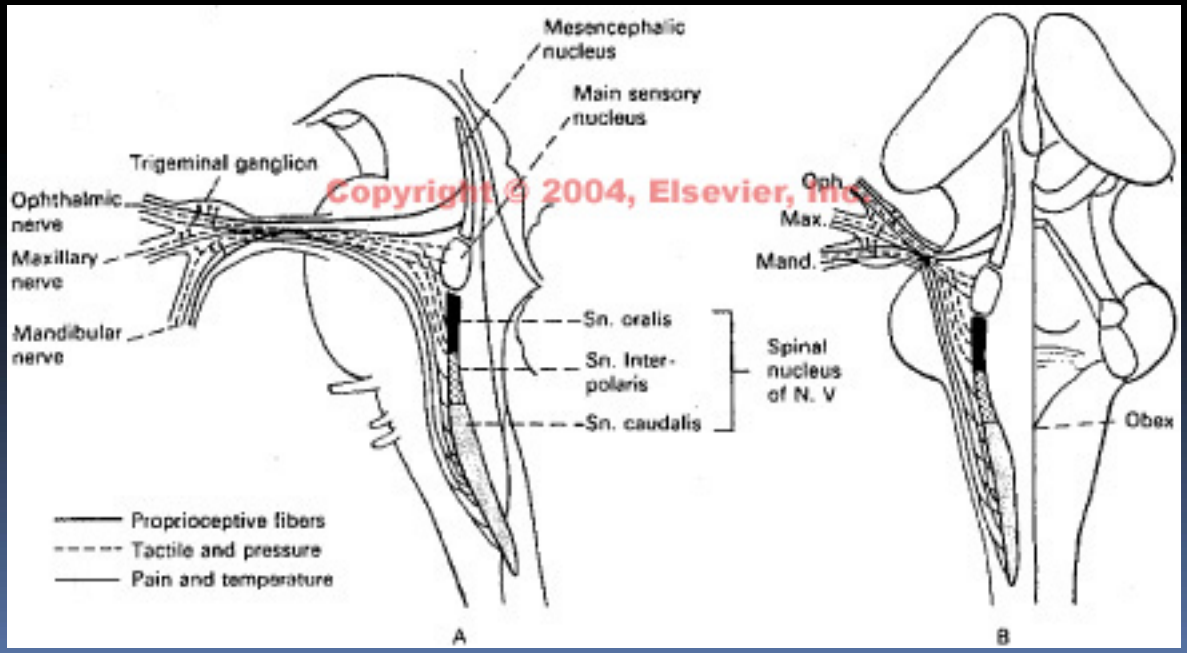


Dorsal column postsynaptic system

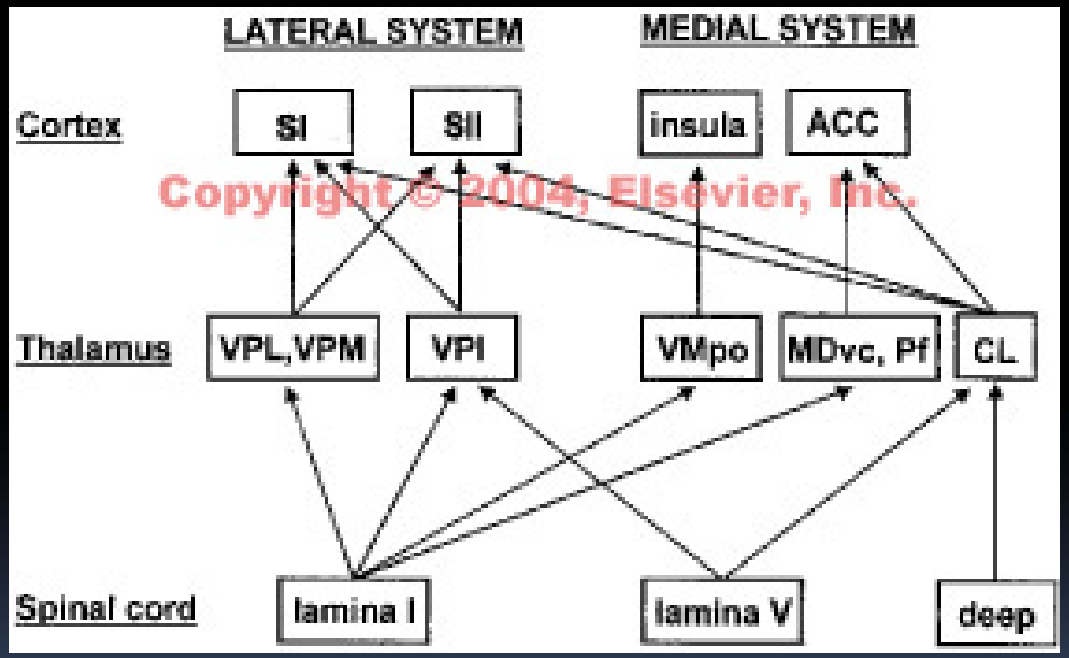




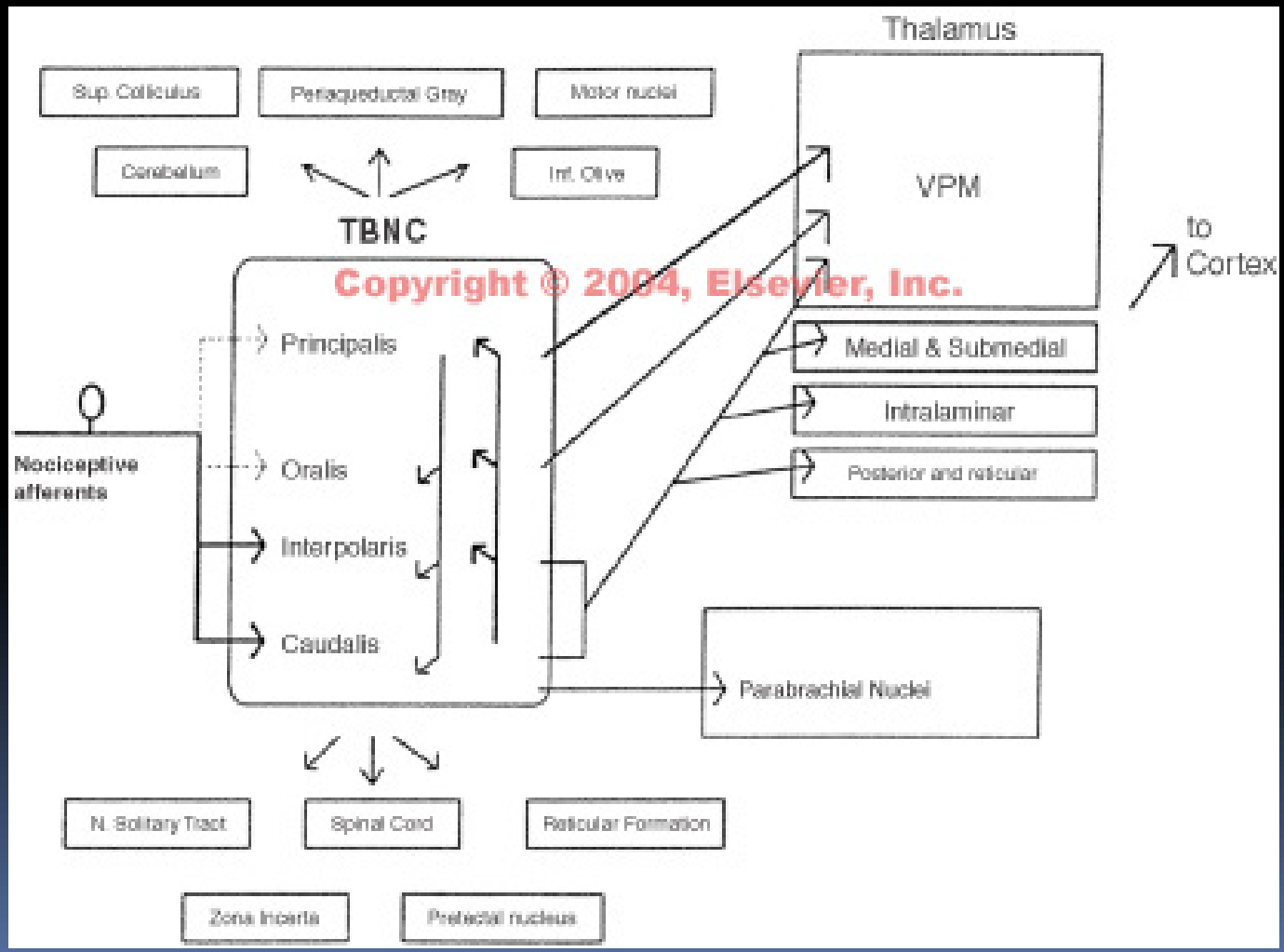
The trigemminal nerve and nucleus



Cortical projections

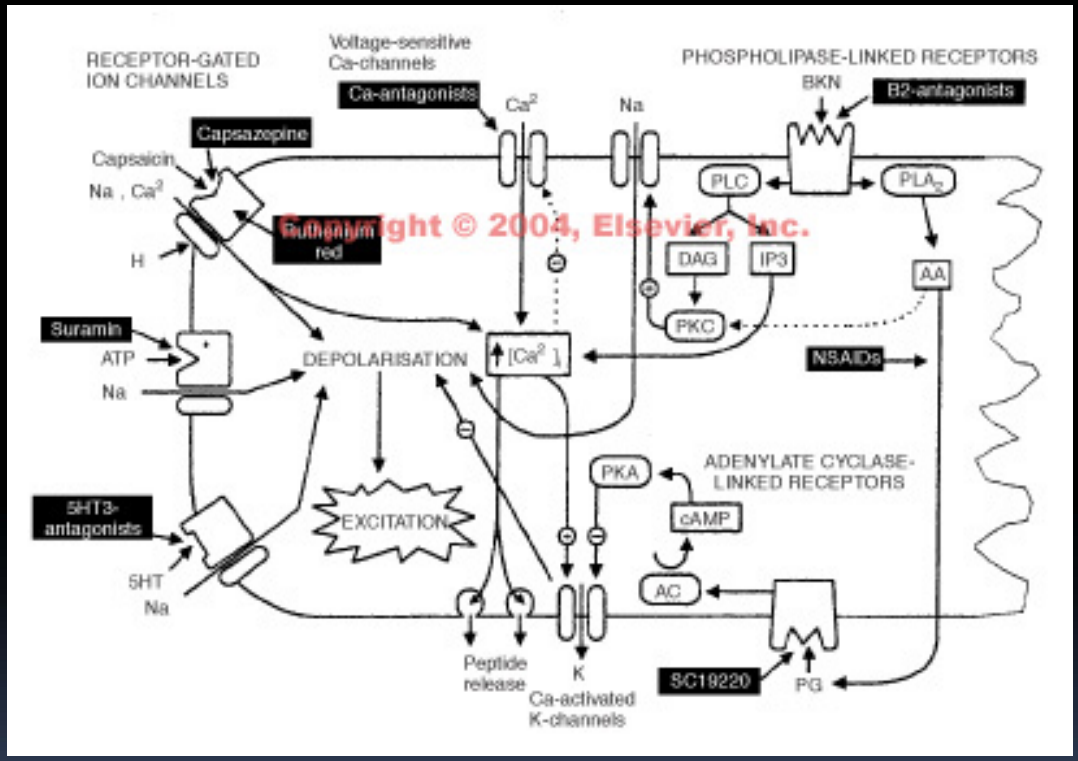


Connections of trigeminal brainstem

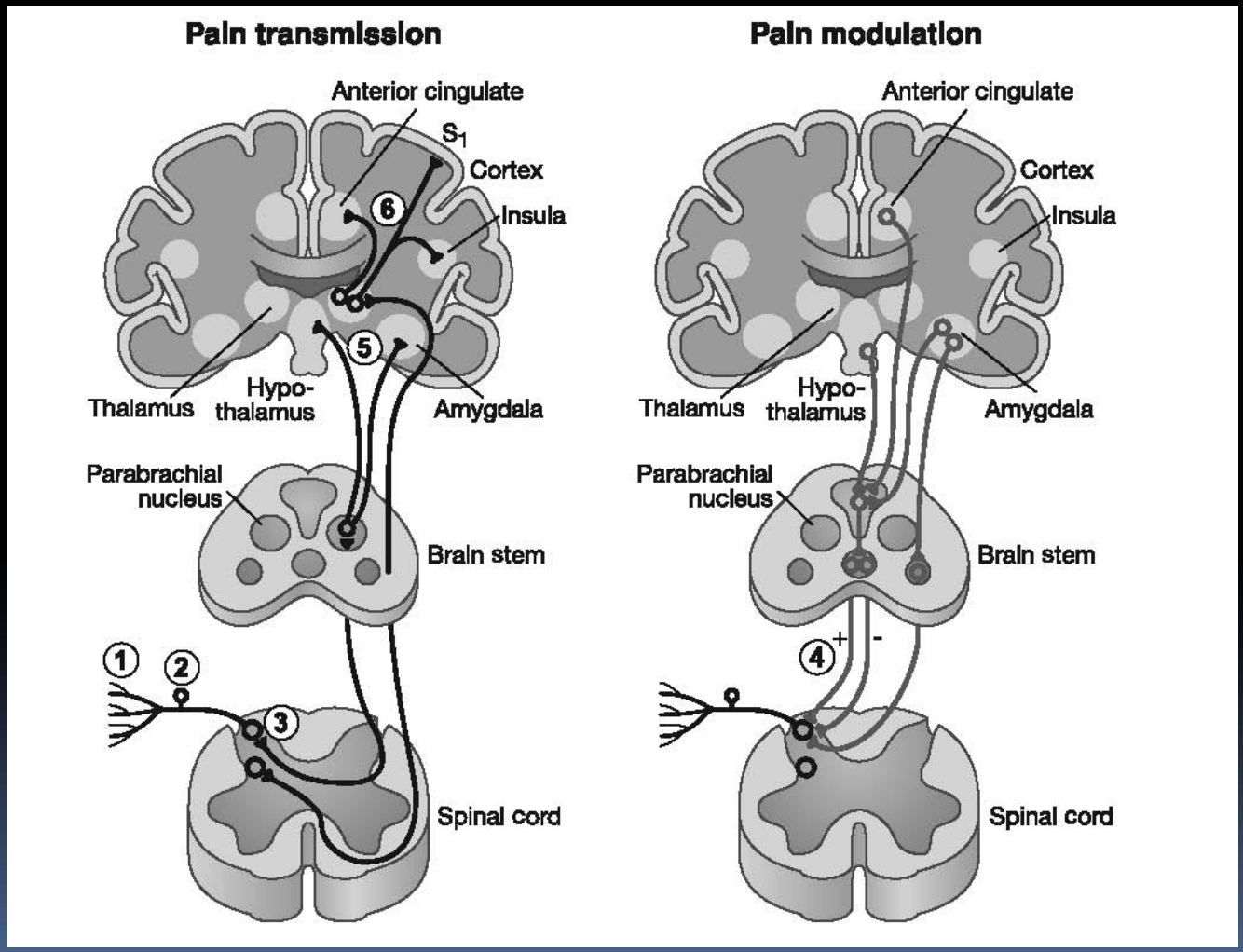


Nociceptive transduction mechanisms

- Thermal
- Chemical
- Mechanical

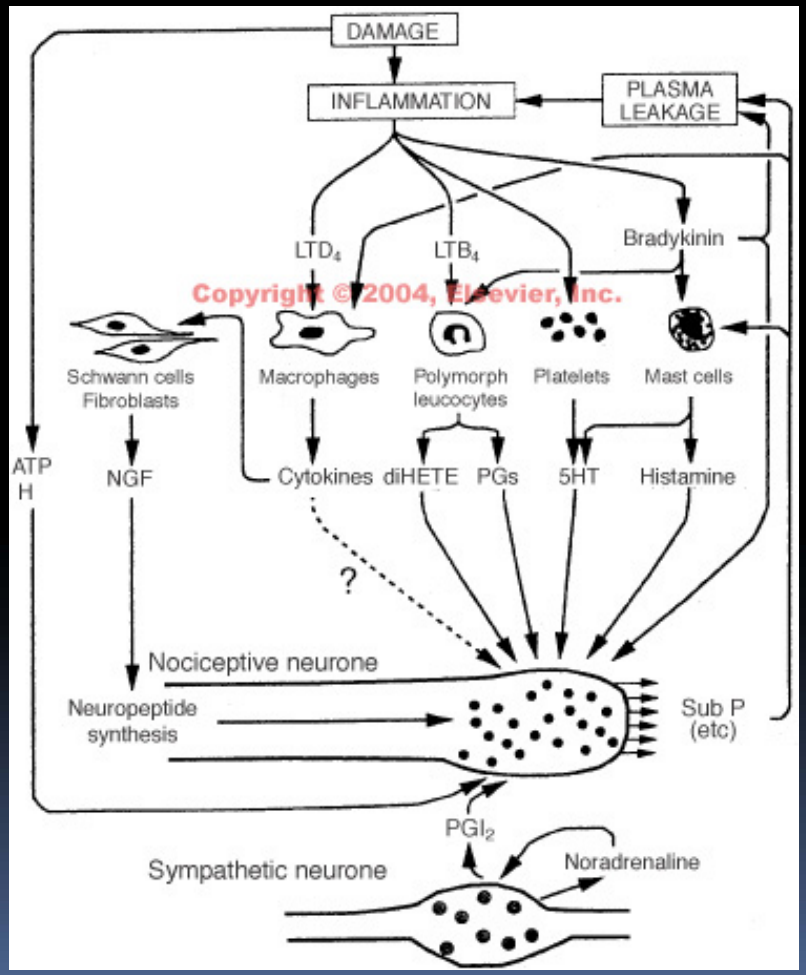


Inhibitory pathways



MECHANISMS OF NEUROPATHIC PAIN AND HYPERALGESIA

Primary hyperalgesia



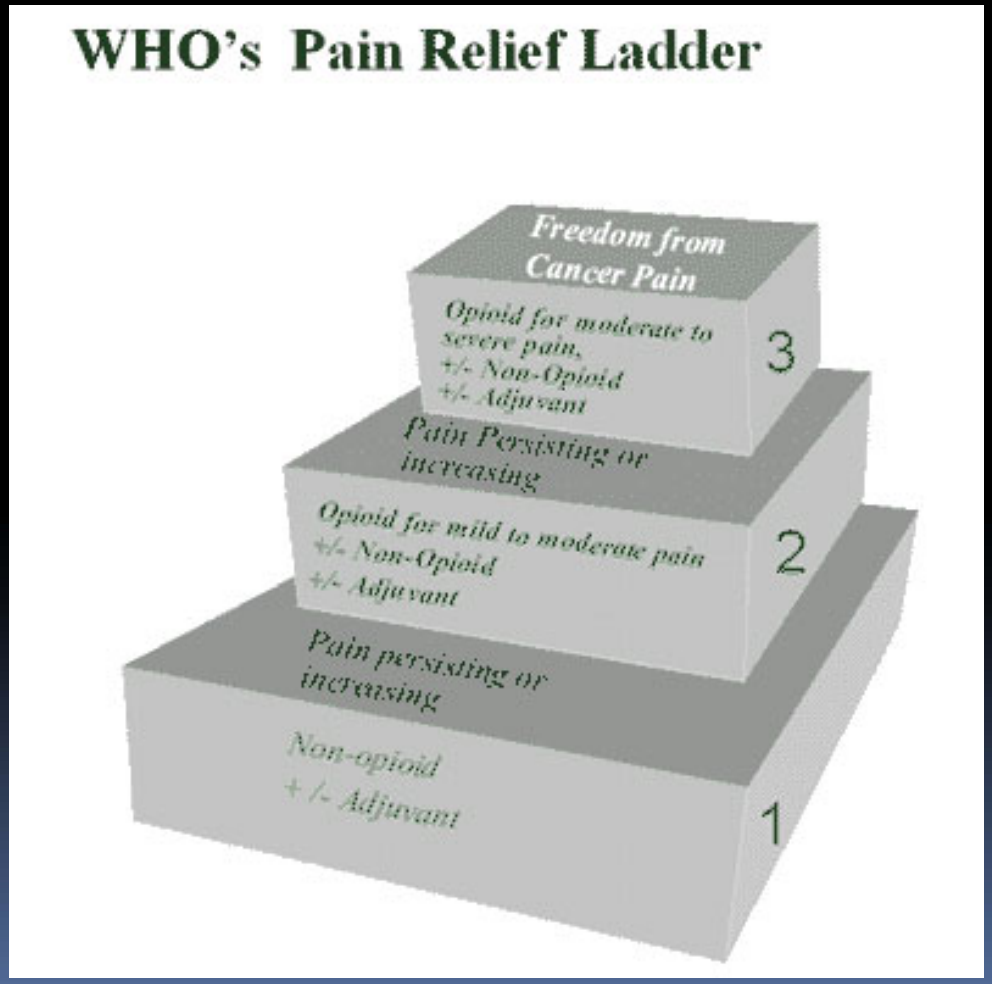
Secondary Hyperalgesia

- occurs with synthesis and release of excitatory and neuromodulatory molecules from primary afferent neurons that sensitize higher order nociceptive neurons

- Neuromodulators include calcitonin gene-related peptides, vasoactive intestinal peptides and somatostatin

MEDICAL MANAGEMENT OF PAIN

General principles



Classes of pharmaceuticals

- Adjuvants
- NSAIDS
- Opioids
- Tricyclic antidepressants
- Others
- Anti-convulsants
- Adjunctive therapies

Adjuvants

- Benzodiazipines
- Anti-spasmodics
- Non-TCA anti-depressants

NSAIDS

The NSAIDs

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The nonsteroidal antiinflammatory drugs

NSAID	Trade name	Usual dose
Carboxylic acids		
Aspirin (acetylsalicylic acid)	Multiple	2.4-6 g/24h in 4-5 divided doses
Buffered aspirin	Multiple	Same
Enteric-coated salicylates	Multiple	Same
Salsalate	Disalcid	1.5-3.0 g/24h BID
Diflunisal	Dolobid	0.5-1.5 g/24h BID
Choline magnesium trisalicylate	Trilisate	1.5-3 g/24h BID-TID
Proprionic acids		
Ibuprofen	Motrin, Rufen, OTC	OTC:200-400 mg QID; Rx: 400-800 mg; max 3200 mg/24h
Naproxen; Enteric	Naprosyn, Anaprox, OTC: Alleve	250, 375, 500 mg BID; 225 mg BID
Fenoprofen	Nalfon	300-600 mg QID
Ketoprofen	Orudis; Oruvail	75 mg TID; q day
Flurbiprofen	Ansaid	100 mg BID-TID
Oxaprozin	Daypro	600 mg; 2 tabs per day
Acetic acid derivatives		
Indomethacin	Indocin, Indocin SR	25, 50 mg TID-QID; SR:75 mg BID; rarely >150 mg/24h
Tolmetin	Tolectin	400, 600, 800 mg; 800 to 2400 mg/24h
Sulindac	Clinoril	150, 200 mg BID; some increase to TID
Diclofenac (plus misoprostol)	Voltaren; Cataflam; (Arthrotec)	50, 75 mg BID (50 mg BID)

Opioids

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Properties of opioid receptors

Mu
Mu1
Supraspinal analgesia
Bradycardia
Sedation
Mu2
Respiratory depression
Euphoria
Physical dependence
Delta
Spinal analgesia
Respiratory depression
Kappa
Spinal Analgesia
Respiratory depression
Sedation
Sigma
Dysphoria, delirium
Hallucinations
Tachycardia, hypertension

Opioids

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Opioid analgesics for chronic pain

	Formulation	Usual starting dose	Duration of action
Strong agonists			
Fentanyl	Transdermal patches	**	72 hrs
	Transdermal iontophoretic systems	**	24 hrs
	Buccal tabs	**	≥1 hr
	Transmucosal lozenges	**	≥1 hr
Hydromorphone	Oral: tabs, soln	2-8 mg	4-6 hrs
Meperidine	Oral: tabs, syrup	50 mg	3-4 hrs
Methadone	Oral: tabs, soln	5-10 mg	8 hrs
Morphine	Oral: IR tabs	15-60 mg	4-6 hrs
	Oral: ER tabs, MS Contin	**	8 hrs
	Oral: Oramorph SR	**	8 hrs
	Oral: Kadian, ER caps	**	12 hrs
	Oral: Avinza, ER caps	**	24 hrs
Oxycodone	Oral: Oxy IR, IR tabs	5-10 mg	4-6 hrs
	Oral: Oxycontin, ER tabs	**	12 hrs
Oxymorphone	Oral: Opana, IR tabs	5-20 mg	4-6 hrs
	Oral: Opana ER, ER tabs	**	12 hrs
Weak agonists			
Codeine	Oral tabs	30-60 mg	4 hrs
Hydrocodone	Combination only	5-10 mg	4 hrs

Pharmaceuticals used for neuropathic pain

Drug/drug class	Major effect on neuropathic pain
Tricyclic antidepressants	Inhibition of serotonin and norepinephrine reuptake, blockade of sodium and calcium channels and NMDA receptors
Serotonin norepinephrine reuptake inhibitors	Inhibition of serotonin and norepinephrine reuptake
Lidocaine	Blockade of voltage-dependent sodium channels
Carbamazepine/oxcarbazepine	Blockade of voltage-dependent sodium channels
Lamotrigine	Blockade of voltage-dependent sodium channels and inhibition of glutamate release
Gabapentin/pregabalin	Blockade of the $\alpha_2\delta$ subunit of voltage gated calcium channels
Tramadol	Opioid agonist, inhibition of serotonin and norepinephrine reuptake

NMDA, *N*-methyl-D-aspartate.

What's missing?

- Other analgesics
- Novel anagesics
- Delivery of analgesia
- Surgical pain management