Analgesics and Adjuvants for Pain Therapy

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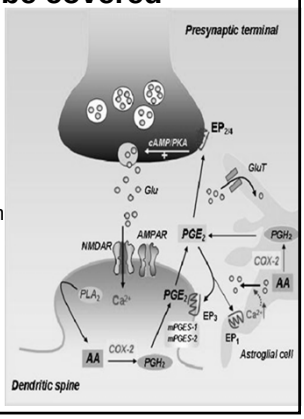
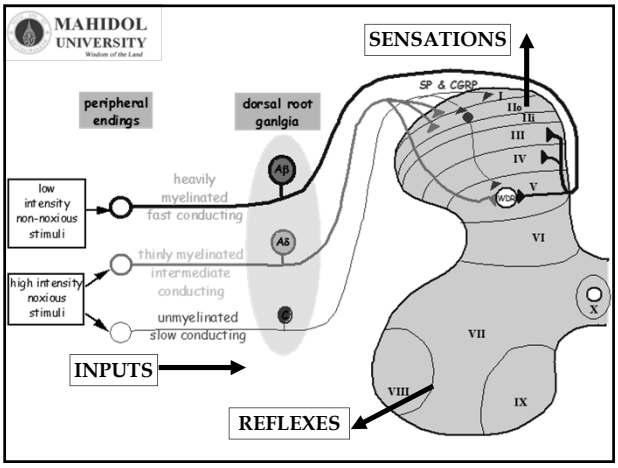
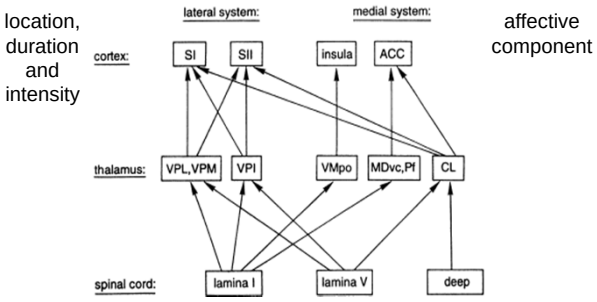
Topics to be covered

- Neurochemistry of pain
- Early pain treatment can reduce sensitization
  - May help avoid acute pain progressing to chronic pain
- Clinical pharmacology of analgesics and adjuvants

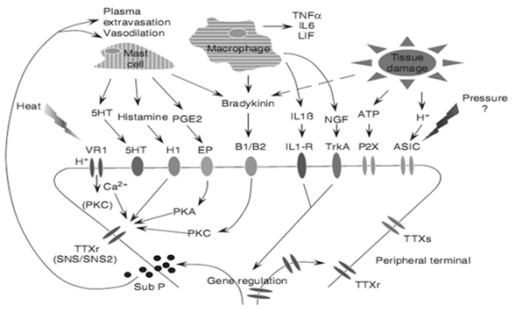


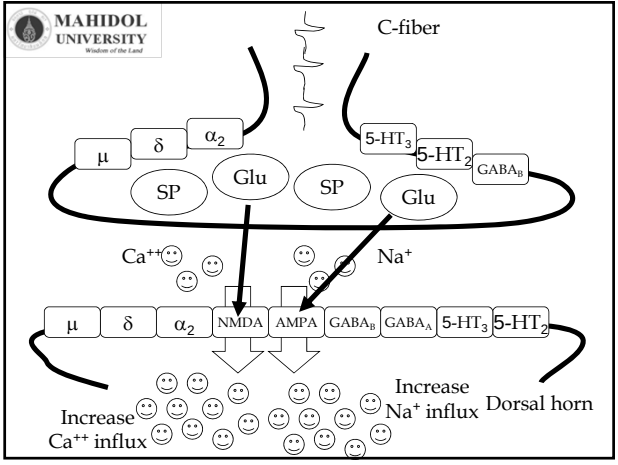


Cortical areas that received information from spinal cord

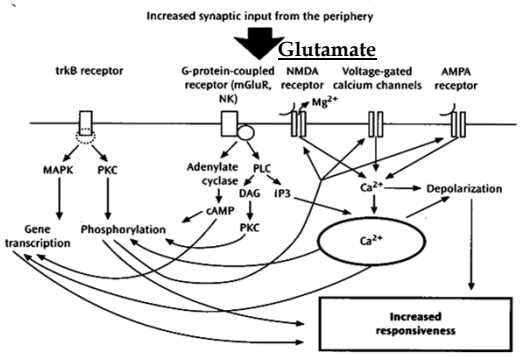


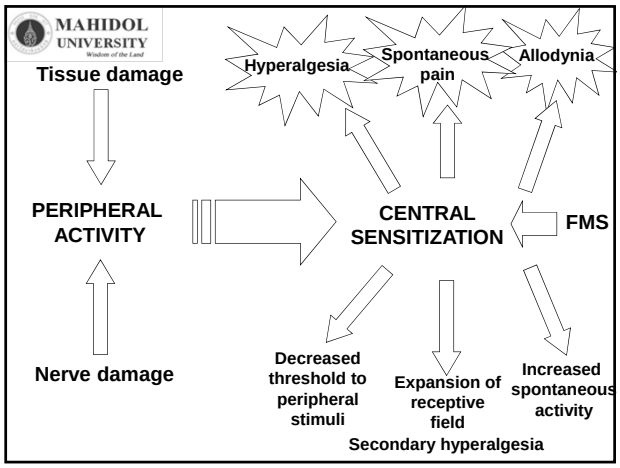
Multiple mediators at the site of injury

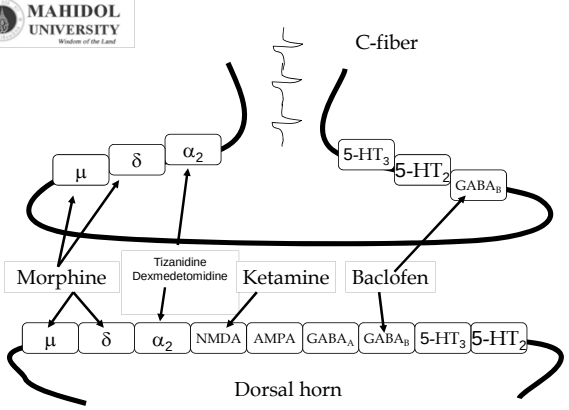




Intracellular events leading to central sensitization



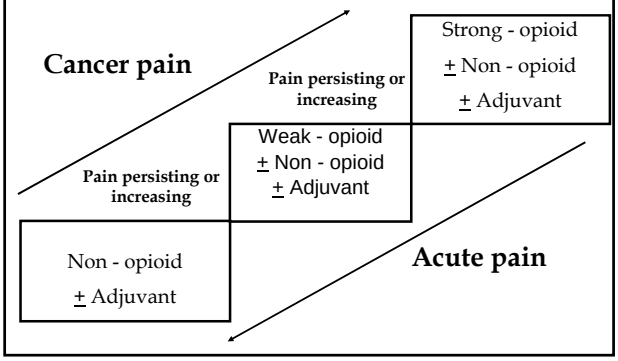




Analgesic classification

1. ***Opioids***
   - no ceiling effect except partial agonists and mixed agonist -antagonist
2. ***Non-opioids***
   - NSAIDs/Coxibs ceiling effect
3. ***Adjuvant analgesic or coanalgesics*** (diverse group of medications that enhance the effects of typical analgesic medications or provide analgesia for certain types of pain)
   - tricyclic antidepressants
   - antiepileptics
   - steroids
   - bisphosphonates, calcitonin

WHO Analgesic ladders

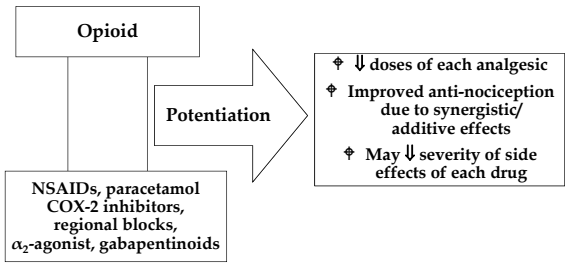


Analgesic selection

- severe, acute pain ---> strong opioids ± coxibs
- moderate, acute pain ---> weak opioids
- mild, acute pain ---> non-opioids
- mild chronic noncancer pain e.g. back pain ---> NSAIDs
- severe chronic noncancer pain e.g. back pain ---> strong opioids ± NSAIDs/ coxibs
- neuropathic pain ---> amitriptyline, carbamazepine ---> gabapentin, pregabalin

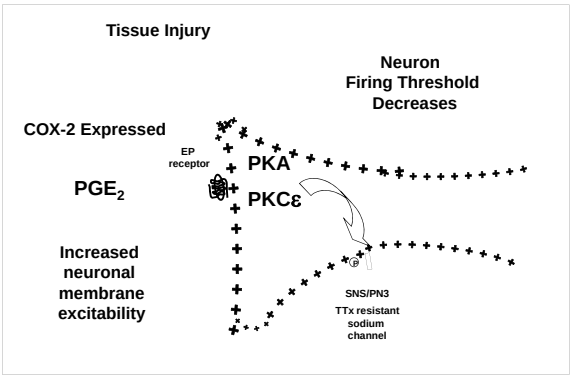
Multimodal Analgesia

AN EXAMPLE

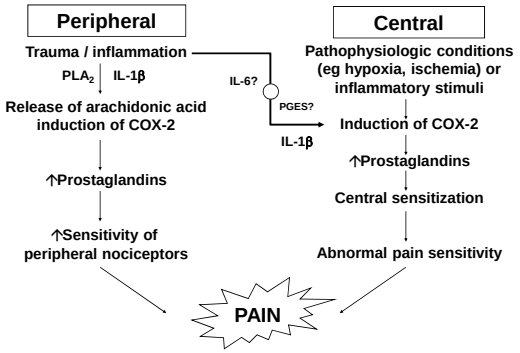


Adapted from Kehlet H, Dahl JB. *Anesth Analg.*, 1993;77:1048–1056.

COX-2 and peripheral sensitization



Role of Prostaglandins in Pain A Working Hypothesis



COX-2 Inhibition and sensitization

- Signal for COX-2 induction likely to persist with peripheral inflammation
- *To minimize sensitization, COX-2 should be inhibited centrally and in the periphery*
  - *as early as possible*
  - *continued until peripheral inflammation resolved*
- Ideal COX-2 inhibitor should be able to act in periphery as well as centrally
  - should readily cross the blood-brain barrier

Chemical classes of NSAIDs and COXIBs

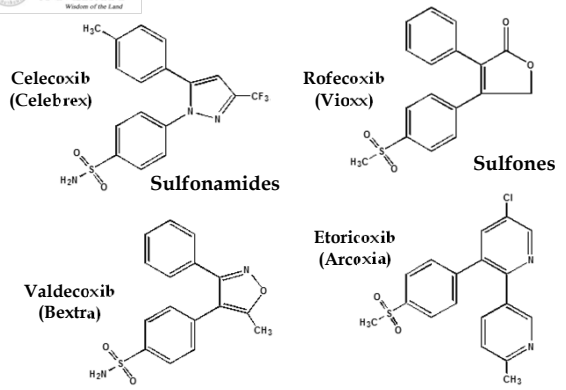
Structural class	Members	
	COX1-selective and non-selective	COX2-selective
Alkanones	Nabumetone	
Anthranilic acids	Meclofenamic acid, mefenamic acid	Meclofenamate esters and amides
Arylpropionic acids	Ibuprofen, flurbiprofen, ketoprofen, naproxen	
Diarylheterocycles	SC560	Celecoxib, etoricoxib, parecoxib, rofecoxib, valdecoxib
Di-*tert*-butyl phenols		Darbufelone
Enolic acids	Piroxicam, tenoxicam, phenylbutazone	Meloxicam
Heteroaryl acetic acids	Diclofenac, ketorolac, tolmetin	Lumiracoxib
Indole and indene acetic acids	Indomethacin, sulindac	Etodolac, indomethacin amides (and esters)
Para-aminophenol derivatives	Acetaminophen	
Salicylic acid derivatives	Aspirin, diflunisal, sulphasalazine	*O*-(acetoxyphenylhept-2-ynyl sulphide (APHS)
Sulphanilides		Nimesulide, flosulide

Nature Reviews Drug Discovery 2007;5:75-85

NSAIDs half-life and their maximum dose

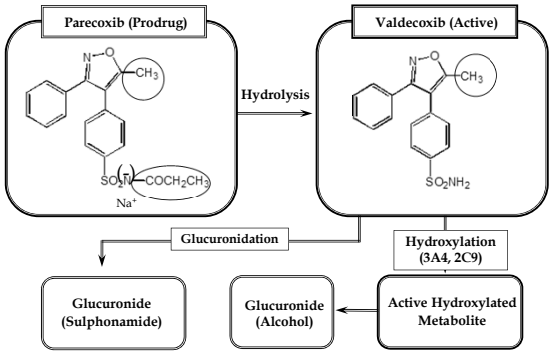
Drugs	Half- life	Starting analgesic dose (mg)	Maximum dose (mg/d)
Diflunisal	7-15	500 q 8-12 h	1500
Ibuprofen	2	400 q 4-6 h	3200
Naproxen	14	250 q 12 h	1000
Ketoprofen	1	25 q 4-6 h	75
Indomethacin	4	25 q 8-12 h	200
Sulindac	8	150 q 12 h	400
Diclofenac	2	50 q 8 h	150
Nabumetone	22	500 q 12-24 h	2000
Mefenamic acid	3-6	200 q 6 h	400
Piroxicam	45	20 q 24 h	20
Meloxicam	20	7.5 q 12-24 h	15

Chemical structures of COX-2 inhibitors



Walter MF, Mason RP. Atherosclerosis 2004;177:235-243

Parecoxib an injectable prodrug of valdecoxib



Major NSAIDs adverse effects

- ***GI bleeding***
- ***Renal*** **(pre-existing heart or kidney disease, use of loop diuretics, or loss of more than 10% of blood volume)**
- ***Congestive heart failure*** **(prior history of heart disease, renal failure, DM or hypertension)**
- ***Dermatologic*** **(Urticaria, rash, Stevens- Johnson syndrome, exfoliative dermatitis)**

  switch to other chemical classes
- ***Respiratory*** **(Bronchospasm, status asthmaticus) Stop NSAIDs (do not switch to other chemical classes, switch to meloxicam, nimusulide, COXIBs)**

Preferential COX-2 inhibitors

- Nabumetone
- Nimesulide
- Meloxicam
- Etodolac
- Acetaminophen (*FASEB J 2008; 22 :383-90)*

COXIBs adverse effects

- Edema from plasma volume expansion (esp high dose)
- Acute kidney injury (Caution should be used when initiating treatment with parecoxib in patients with dehydration. In this case, it is advisable to rehydrate patients first and then start therapy with parecoxib; ***keep adequate hydration***)
- CVS
- GI: delay ulcer healing

Strategic for use of NSAIDs/COXIBs

- Prescribe NSAIDs/COXIBs to patients at low risk of thromboembolic events
- Minimize duration of treatment with NSAIDs/COXIBs to decrease of risk
- Prescribe the lowest effective dose
- Monitor BP, edema, renal function, GI bleeding

Circulation 2005;112:759-70

Drug-drug Interaction of NSAIDs/COXIBs

- ***Pharmacodynamics drug interactions***
  - Antagonism
    - Ibuprofen and naproxen attenuates antiplatelet activity of low dose aspirin
  - Increasing ADRs
    - Plasma volume expansion: antidiabetics (pioglitazone, high dose sulfonylureas)
    - Increasing bleeding risk: corticosteroids/antiplatelets/anticoagulants
- ***Pharmacokinetics drug interactions***
  - CYP2C9 inhibitors, such as fluoxetine,fluconazole, isoniazid, sulfamethoxazole and amiodarone may increase plasma level of some NSAIDs/COXIBs (*ibuprofen, indomethacin, flurbiprofen, celecoxib, valdecoxib, lornoxicam, tenoxicam, meloxicam and piroxicam)*

Weak Opioids

- Codeine (max dose 240-360 mg/d)
- Dextropropoxyphene
- Tramadol (max dose 400 mg/d)

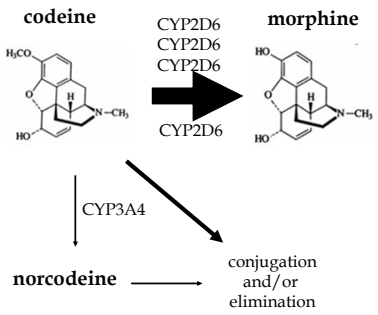
Tramadol Characteristics

- Weak mu and kappa receptor agonist (Approximate 1/10 as potent as morphine)
- O-desmethyl metabolite (M1 metabolite) 6 times more potent than tramadol, half life 7.4 h
- *Inhibit 5-HT and NE reuptake (induce nausea, dizziness and tachycardia)*
- *M1 excreted via kidney unchanged and may increase respiratory depression in renal failure*
- Reduce seizure threshold, increase seizure risk with SSRI, TCAs

Tramadol maximum dose per day

- Adult dose : 400 mg/day
- Over age 75 years : 200-300 mg/day
- Renal Insufficiency (CrCl <30 ml/min)
  - Reduce dosing frequency to every 12 hours
  - Do not exceed 200 mg per day

Metabolism of codeine



Opioid Clearance is Reduced in Renal Diseases

- Morphine : accumulation of M6G
- Pethidine : accumulation of norpethidine (active metabolite, half life 30 h)
- Tramadol : accumulation of M1
- Oxycodone : accumulation of noroxycodone and oxymorphone

Drugs used in neuropathic pain

- **Sodium channel blockers**
  - antiepileptics (phenytoin, carbamazepine, oxcarbazepine)
  - local anaesthetics (lidocaine)
  - mexiletine
- **Antidepressants** **(enhance descending inhibitory pathway)**
- **Drugs that enhance GABA function**
  - gabapentin, valproate, clonazepam
- **Drugs that block specific N-type Ca Channel**
  - gabapentin, ziconotide, pregabalin
- **NMDA antagonists**
- **Opioids**

Symptoms of neuropathic pain

1. **Negative symptoms**
   (diminished sensitivity to pain or stimulation)
   - hypoalgesia
   - hypoesthesia

Symptoms of neuropathic pain (cont.)

2 . **Positive symptoms**

2.1 Spontaneous sensations (stimulus-independent pain)
- continuous (burning, stabbing)
- paroxysmal (shooting, lancinating)
- spontaneous abnormal sensation (dysesthesia and paresthesia)

2.2 Evoked sensations (stimulus-evoked pain)
- hyperalgesia
- allodynia

Peripheral mechanisms of neuropathic pain

- Up-regulation of Na^+ channel and calcium channel
- Ectopic discharge
- Ephaptic cross talk (transfer of nerve impulse from one axon to anothers)

  Ephases = abnormal electrical connections occurred between adjacent demyelinated axons
- Sympathetically maintained pain (ephapses between sensory and sympathetic fibers)
- Neurogenic inflammation following neural injury

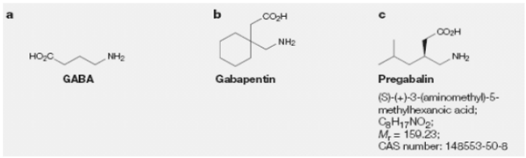
Calcium channels plasticity

- Neuropathy induces plasticity
  - N-type enhanced
  - No changes in P- and T-type
  - No role of L-type
- Inflammation induces plasticity
  - N-type and P-type enhanced

N-type calcium channels and pain

- Found almost exclusively on neurons especially at high levels in the presynaptic terminals
- Complexed with proteins that are involved in neurotransmitter secretion, including syntaxin, synaptotagmin and SNAP-25
- *α_{1B} and $\alpha_2\delta1$ subunits are upregulated in DRG neurons following nerve injury or tissue inflammation*

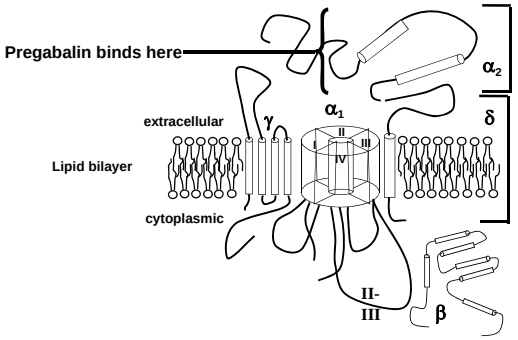
Structures of gabapentinoids



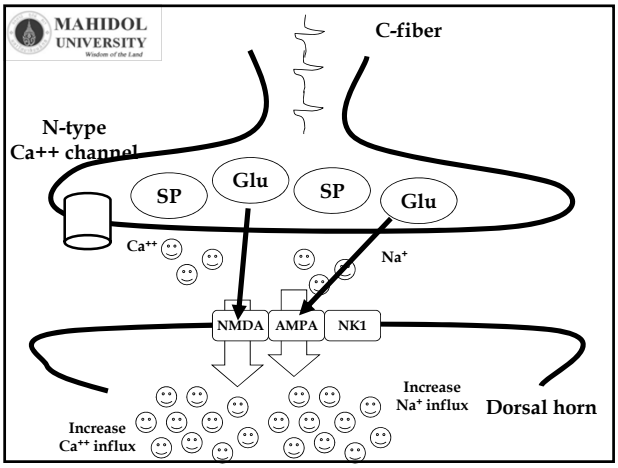
Pregabalin is a lipophilic analogue of GABA substituted at the 3-position to facilitate diffusion across the blood–brain barrier.
Binds to neurons at the $\alpha 2$-δ subunit of voltage-gated calcium channels (brain and spinal cord)

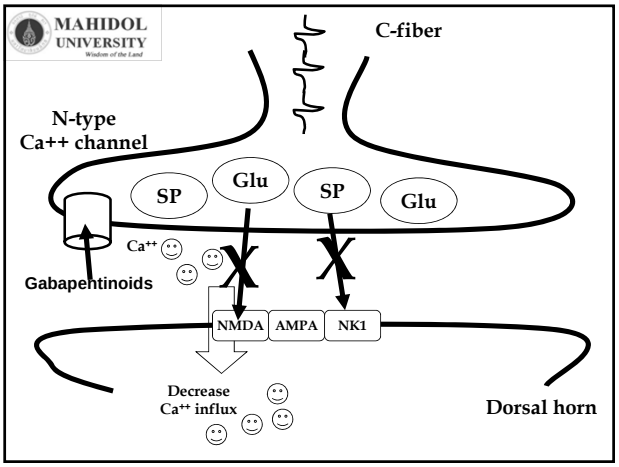
Nature Rev Drug Disc 2005;4:455

Pregabalin binds to the α_2-δ subunit of voltage-gated calcium channels



Arikkath J, Campbell KP. *Curr Opin Neurobiol* 2003; 13: 298-307





α_2-δ modulators: differences between pregabalin and gabapentin

	Pregabalin	Gabapentin
Anticonvulsant activity (rat electroshock)	*1.3 mg/kg (ED_{50})*	*9.1 mg/kg (ED_{50})*
Neuropathic pain activity (rat diabetes)	*3 mg/kg (MED)*	*10 mg/kg (MED)*
Absorption	*Non-saturable across dose range*	*Saturable*
Oral bioavailability	*≥90%*	*≤50%*
Excretion	*renal*	*renal*

Central mechanisms of neuropathic pain

- Central reorganization of Ab fibers (sprouting of Ab from lamina III to lamina I,II)
- ↑ mRNA for SP and NK1 receptors
- ↓ opioid binding sites
- Central sensitization
- Loss of inhibitory interneurons

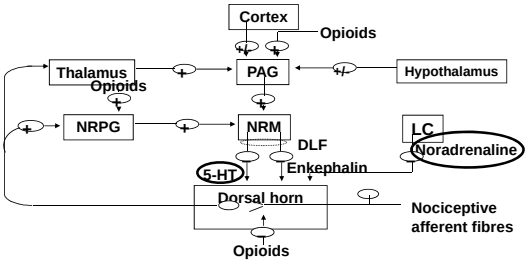
Tricyclic antidepressants

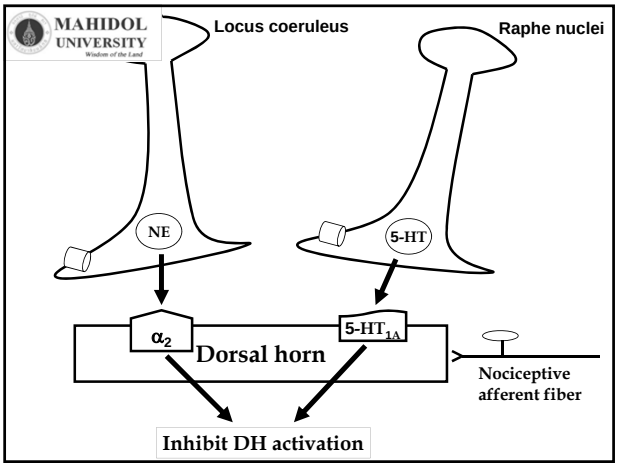
- Inhibit 5-HT and NE reuptake
- α_1 antagonist
- muscarinic antagonist
- histamine antagonist

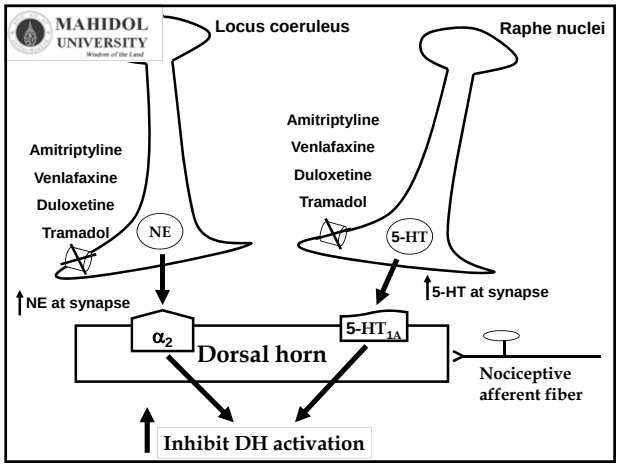
Amitriptyline

is also potent 5-HT_{2A} antagonist, NMDA receptor antagonist and sodium channel blocker

The descending inhibitory pain pathway







Drug Dosage

- Amitriptyline: start with 10-25 mg hs and titrate q 3 d up to 75-150 mg/d; evaluate at 1-2 weeks for therapeutic and side effects
- Gabapentin: start with 100 or 300 mg hs and titrate by 300 mg q 3 or 7 d up to 1800-3600 mg in 3 divided doses; first follow up in 2 weeks
- Pregabalin: start with 50 mg hs and titrate up to 300 mg/d within 1 week based on efficacy and tolerability
- Tramadol: start with 37.5 or 50 mg hs and titrate up to 200-400 mg/d in 3 divided doses
- Duloxetine: start with 30 mg OD and titrate up to 60-90 mg

Undertreated Pain

- Negative emotions – anxiety,depression
- Sleep deprivation
- Existential suffering
- Adverse immunological sequale
  - Impaired immune response
  - Decreased natural killer cells