

**The Mechanistic Approach to the Treatment
of Chronic Neuropathic Pain Mirrors the
Treatment of Convulsions and Mood Disorders**

**Elliot S. Krames, MD
San Francisco, California**

Common Mechanisms/Common Treatment Strategies

- Mechanism of persistent pain after peripheral afferent fiber (PAF) injury
- Mechanism of central persistent pain
- Chemical basis of neuropathic pain
 - Na⁺ channels
 - Glutamate
 - GABA
 - monoamines
- Seizures/pathophysiology/pharmacologic management
- Chronic neuropathic pain/pharmacologic management

Principal Mechanisms Causing Induction of Chronic Pain Due to Peripheral Afferent Fiber (PAF) Injury

- activation of damaged PAFs by inflammatory mediators
- increase in the spontaneous excitability and responsiveness of damaged PAF; in particular Na^+ channels
- abnormal patterns of inter-neuronal communication in the dorsal root ganglion (DRG)
- altered phenotype of damaged small C fibres and large A_β fibres
- altered cholecystokinin (CCK) content

Peripheral Afferent Fiber (PAF) Injury

PAF injury leads to a relative increase in the ratio of kinetically rapid, tetrodotoxin (TTX)-sensitive versus kinetically slow, TTX - resistant channels.



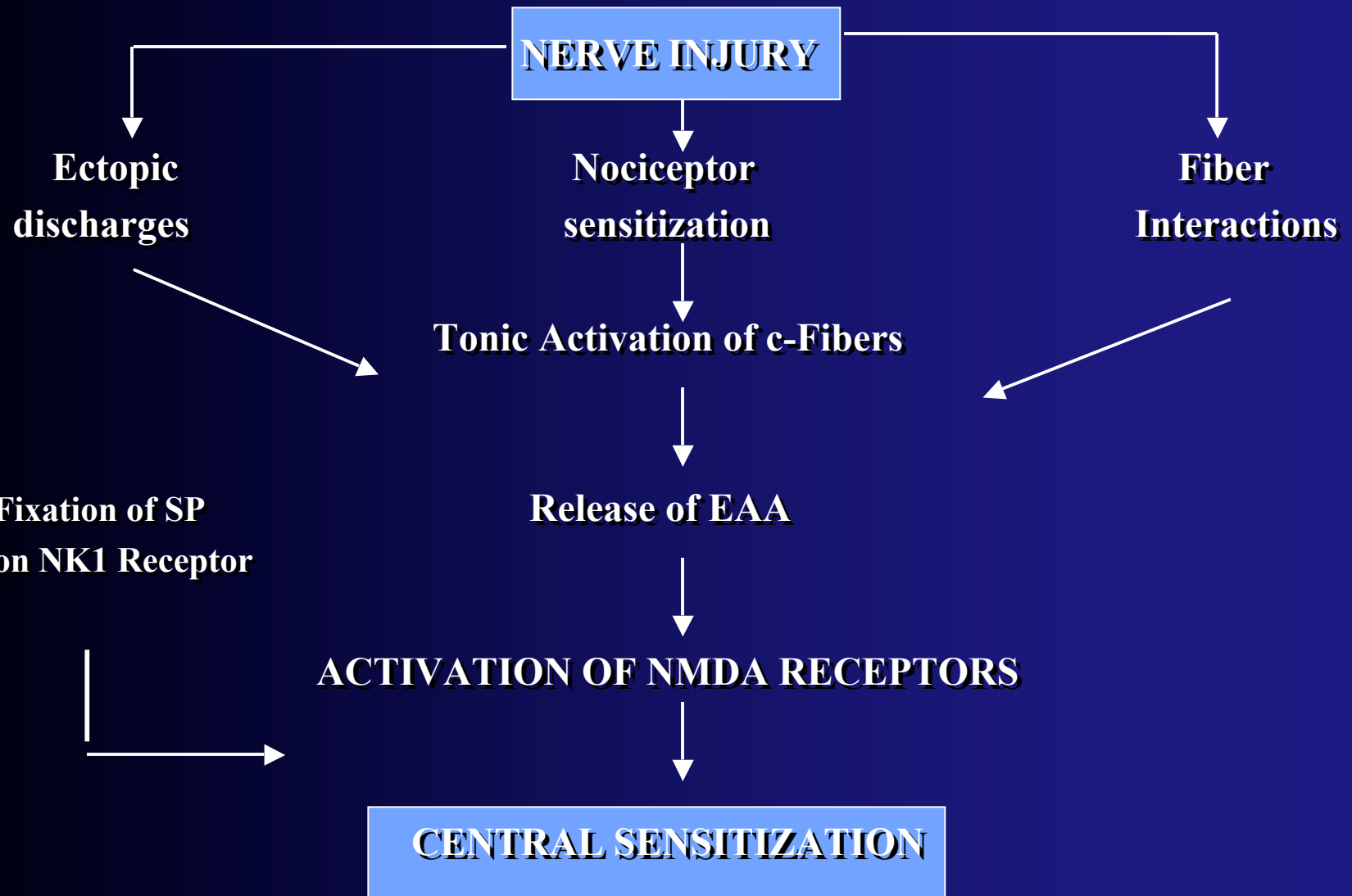
Hyperexcitability and electrical instability
esp. in areas of demyelination



Repetitive firing in response to mild
stimuli

Peripheral Afferent Fiber (PAF) Injury

In addition to changes in the expression levels of Na⁺ channels, their activity (passage of current and inactivation kinetics) may also be rapidly modified by processes of phosphorylation elicited by inflammatory agents.



Mechanisms of Central Neuropathic Pain:

- Temporal summation of repetitive nociceptive stimulation is a physiologic phenomenon produced by repetitive stimulation of A δ and/or C nociceptors but not by repetitive stimulation of low threshold A β fibers....induces hyperexcitability in 2nd order WDR neurons.
- After induction of hyperexcitability these cells now respond to low-threshold mechanoreceptive A β fibers in a way that is normally induced by A δ and/or C fibers.

Putative Mechanisms of Central Neuropathic Pain

spinal cord injury



Central neuroplastic change



Neuroanatomical change

- Excitotoxicity
- Nerve cell injury/death

Neurochemical change

Increased excitation

- ion channels (Na^+ , Ca^{++})
- EAA(non-NMDA, NMDA)
- Peptides (substance P)
- Opioids

Decreased inhibition

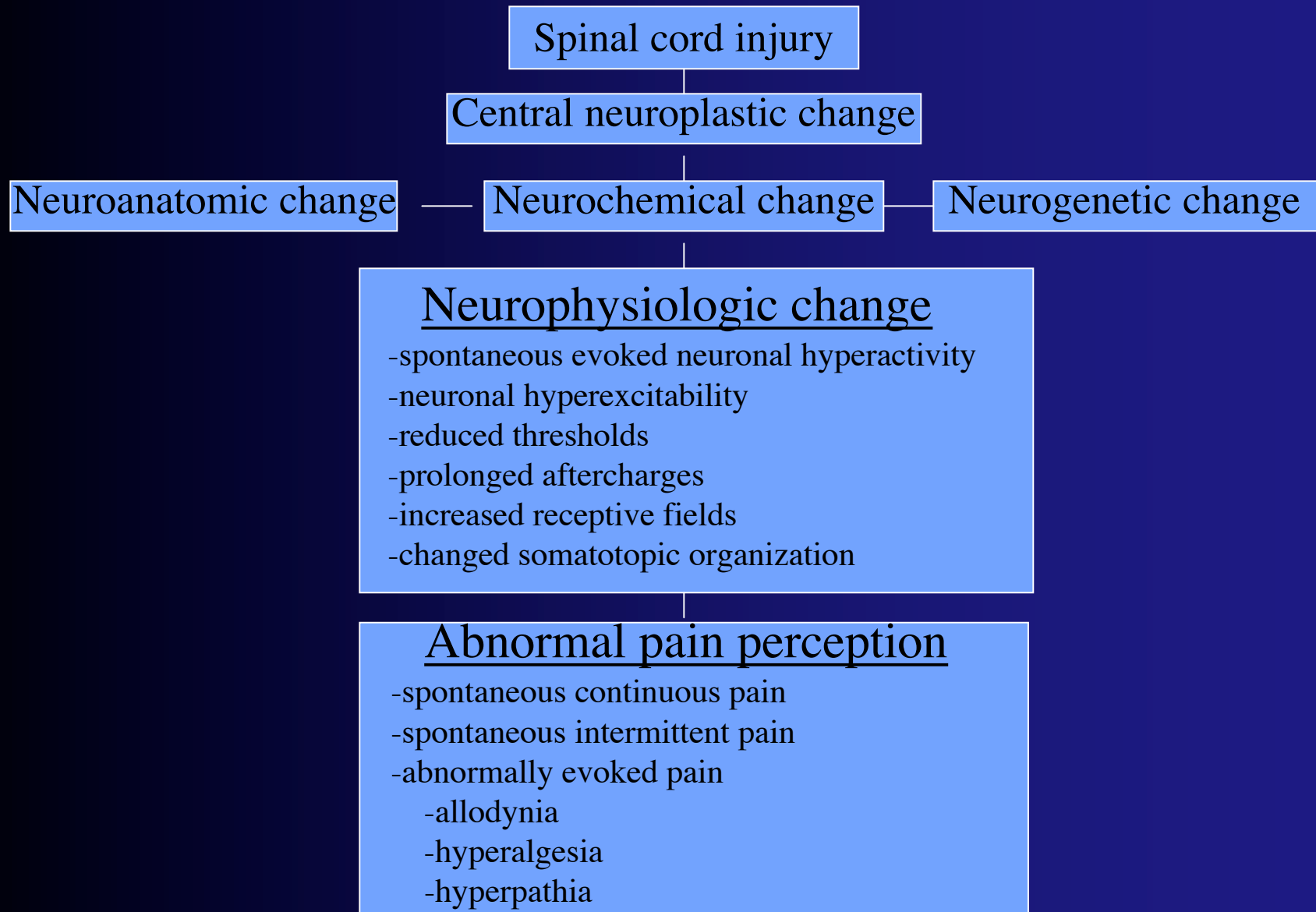
- GABA
- monoamines
- opioids (CCK)

Neurogenetic change

- IEG (immediate early genes)
- Protein Synthesis



Putative Mechanisms of Chronic Pain



**The Chemical Basis of Neuropathic
Pain Happens to Mimick the Chemical
Basis of Mood Disorders and Epilepsy**

Neurochemistry of Neuropathic Pain

- Na⁺ channel mediated nerve membrane hyperexcitability
- Hyperfunction of glutaminergic excitatory mechanisms
- Hypofunction of GABAergic inhibitory mechanisms
- Hypofunction of monoaminergic inhibitory systems

Neurochemistry of Neuropathic Pain

- Na^+ channel mediated nerve membrane hyperexcitability
- Hyperfunction of glutaminergic excitatory mechanisms
- Hypofunction of GABAergic inhibitory mechanisms
- Hypofunction of monoaminergic inhibitory systems

Na⁺ channel mediated nerve membrane hyperexcitability

- Abnormal impulse generation in injured nerves may depend on accumulation of Na⁺ channels in the cell membrane
- Local anesthetics (lidocaine and mexiletine) block voltage-sensitive Na⁺ channels, reducing the number of Na⁺ channels to produce an action potential. (membrane stabilization)
- Local anesthetics effective in both peripheral and central neuropathic pain states

Na⁺ Channels

Na⁺ Channels present in the dorsal root ganglia (DRG) of peripheral afferent fibres (PAF) can be classified into 2 types :

1. *Tetrodotoxin (TTX) - sensitive*

Low threshold channels which rapidly activate and inactivate;

2. *Tetrodotoxin (TTX) - resistant*

High threshold channels with slower kinetics of activation and inactivation.

Na⁺ Channels

Na⁺ Channels present in the dorsal root ganglia (DRG) of peripheral afferent fibres (PAF) can be classified into 2 types :

1. *Tetrodotoxin (TTX) - sensitive*

Low threshold channels which rapidly activate and inactivate;

2. *Tetrodotoxin (TTX) - resistant*

High threshold channels with slower kinetics of activation and inactivation.

Na⁺ Channels modulators

Phenytoin
Carbamazepine
Sodium valproate
Lamotrigine
Topiramate
Mexiletine
Lidocaine
Etc.



blockade of peripheral TTX sensitive
Na⁺ channels in damaged PAFs



Blockage of allodynic reactions

Neurochemistry of Neuropathic Pain

- Na⁺ channel mediated nerve membrane hyperexcitability
- **Hyperfunction of glutaminergic excitatory mechanisms**
- Hypofunction of GABAergic inhibitory mechanisms
- Hypofunction of monoaminergic inhibitory systems

Glutamate Receptors and Nociception

- The excitatory amino acid glutamate plays a significant role in nociceptive processing.
- Glutamate and glutamate receptors are located in the brain, spinal cord and periphery.
- Glutamate acts at several types of receptors including **ionotropic** and **metabotropic** receptors.
- N-methyl-d-aspartate (NMDA) receptor has an important role in some forms of neural plasticity.
- Glutamate interacts with the opioid system and IT or systemic co-administration of glutamate receptor antagonists with opioids enhances analgesia and decreases incidence of tolerance.

Glutamate Receptors and Nociception

- Activation of glutamate receptors in some areas of the brain(thalamus, trigeminal nucleus) is pronociceptive while at other areas of the brain (PAG, VLM), it is antinociceptive.
- Application of glutamate to the spinal cord induces nociceptive behaviours
- Inhibition of glutamate release or glutamate receptors, in the spinal cord or periphery, attenuates both acute and chronic pain in animal models.

Glutamate Receptors

Ionotropic

- N-methyl-D-aspartate (NMDA)
- Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)
- KAINATE

Metabotropic (mGluRs 1-8)

- These receptors are classified into 3 groups based on sequence homology, signal transduction mechanisms and receptor pharmacology
- Coupled to G proteins

Neurochemistry of Neuropathic Pain

- Na⁺ channel mediated nerve membrane hyperexcitability
- Hyperfunction of glutaminergic excitatory mechanisms
- Hypofunction of GABAergic inhibitory mechanisms
- Hypofunction of monoaminergic inhibitory systems

The Role of γ -amino-butyric acid (GABA) in Neuropathic Pain

- The principal inhibitory neurotransmitter in the CNS is γ -amino-butyric acid.
- 60-75% of all synapses in the CNS are GABAergic.
- Loss of GABAergic inhibition may be an important pathogenic mechanism in different types of neuropathic pain and other neurologic disorders.
- Electrophysiologic data exists that neuronal hyperactivity may be down regulated by GABAergic inhibition

γ -amino-butyric acid

- GABA binds to at least 3 different receptors:
 - γ **GABA_a** receptors mediate fast inhibitory synaptic transmissions, therefore, regulating neuronal excitability and rapid changes in mood....In addition to binding sites for GABA, GABA_a receptors bind benzodiazepenes, ethanol, barbiturates, and neurosteroids.
 - γ **GABA_b** receptors mediate slow inhibitory transmissions important in memory, mood and pain
 - γ **GABA_c** receptor role not understood
- A decrease in GABAergic transmission is involved in the pathogenesis of several neurologic disorders including some forms of epilepsy, chronic pain, anxiety and other mood disorders.

Neurochemistry of Neuropathic Pain

- Na⁺ channel mediated nerve membrane hyperexcitability
- Hyperfunction of glutaminergic excitatory mechanisms
- Hypofunction of GABAergic inhibitory mechanisms
- Hypofunction of monoaminergic inhibitory systems

In the 1970's and 1980's, it was demonstrated that....

- Stimulation within periaqueductal gray (PAG) of the midbrain or pontomedullary raphe magnus (RM) produces opioid receptor analgesia.
- Lesioning of the PAG or RM attenuates analgesia produced by systemic morphine.
- Serotonergic and nonserotonergic neurons, but not PAG neurons project to the superficial dorsal horn of the spinal cord, a region critical for nociceptive processing.

Although pain modulation was originally thought of as a pain inhibitory system, evidence now supports the idea that endogenous pain facilitation also occurs!

Tonic levels of serotonin (5HT) may either attenuate or enhance glutamatergic synapses in the dorsal horn of spinal cord:

- Low dose 5HT facilitates AMPA-receptor-mediated excitatory postsynaptic currents (EPSC's) evoked by dorsal root entry zone stimulation.
- High dose 5HT inhibit these EPSC's.
- Dorsal root stimulation in the presence of 5HT often evokes an otherwise silent NMDA-receptor-mediated EPSC.
- Therefore, 5HT can modulated synaptic transmission bidirectionally in a concentration-dependent manner.

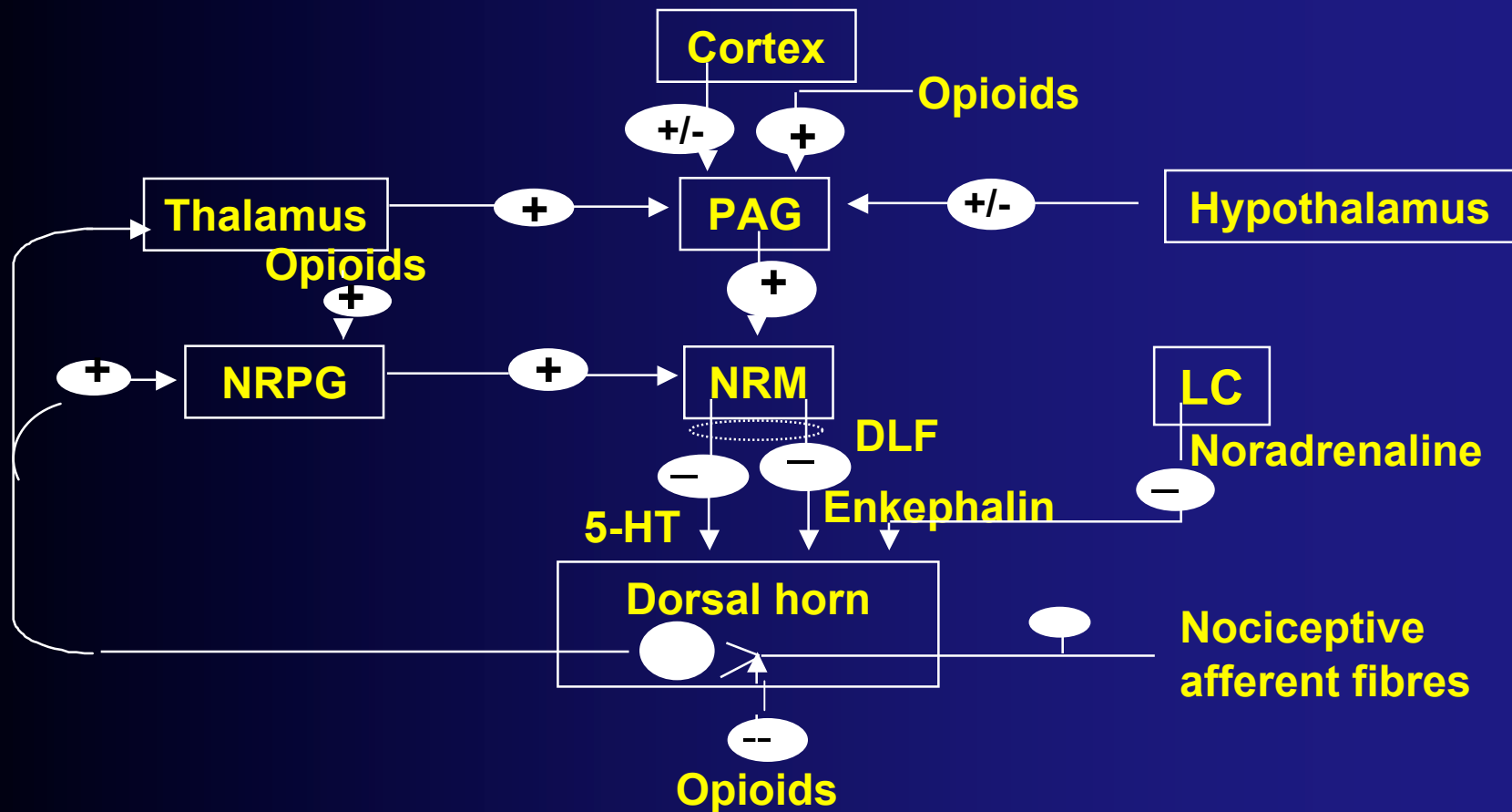
Descending inhibitory pathways and monoamine receptors

Monoamines exert inhibitory or excitatory actions via distinct receptor subtypes differentially coupled to intracellular transduction systems.

<i>Receptors</i>	<i>Transduction systems</i>	<i>Effect</i>
5-HT_{1A}	Open K⁺ channel	- hyperpolarize DH - antinociception
5-HT_{2A}	Activate PLC	- depolarize DH - nociception
5-HT₃	Open Ca⁺⁺ channel	- depolarize DH - nociception
a₁	Positively couple with adenylyate cyclase	- nociception
a_{2A}	Negatively couple with adenylyate cyclase	- inhibit nociception

Injection of the GABA_a receptor antagonist, bicuculline, into the PAG reduces the responses of dorsal horn neurons to noxious heat for 30-60 minutes, producing antinociception, and excites RM off cells.

This analgesia produced by injecting bicuculline into the PAG is mediated by a presynaptic inhibition of afferents carrying noxious thermal information to the dorsal horn. This presynaptic inhibition is mediated by μ -opioid and α -adrenergic receptors.



The descending control system, showing postulated sites of action of opioids on pain transmission. Opioids excite neurons in the *periaqueductal grey matter* (PAG) and in the *nucleus reticularis paragigantocellularis* (NRPG), which in turn project to the rostroventral medulla, which includes the *nucleus raphe magnus* (NRM). From the NRM, 5-HT- and enkephalin-containing neurons run to the *substantia gelatinosa* of the dorsal horn, and exert an inhibitory influence on transmission. Opioids also act directly on the dorsal horn. The *locus ceruleus* (LC) sends noradrenergic neurons to the dorsal horn, which also inhibit transmission. The pathways shown in this diagram represent a considerable over-simplification, but depict the general organisation of the supraspinal control mechanisms. Light pink boxes represent areas rich in opioid peptides. (DLF = dorsolateral funiculus) (For more detailed information, see Fields & Basbaum 1989)

Tricyclic Antidepressants

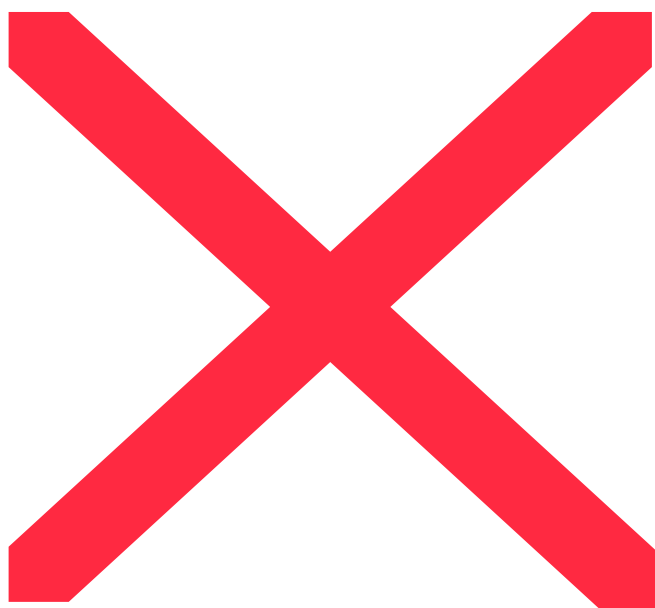
Tricyclic antidepressants

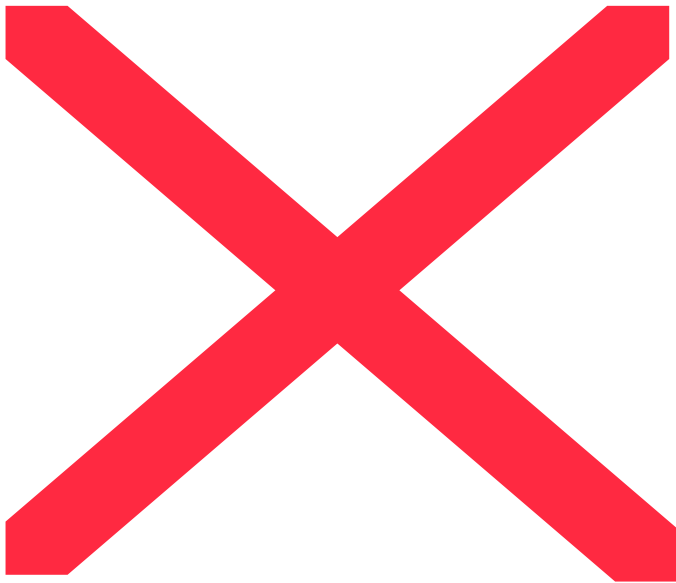
- Inhibit 5-HT and NE reuptake
- α_1 antagonist
- muscarinic antagonist
- histamine antagonist
- *Amitriptyline* is also a potent 5-HT_{2A} antagonist.

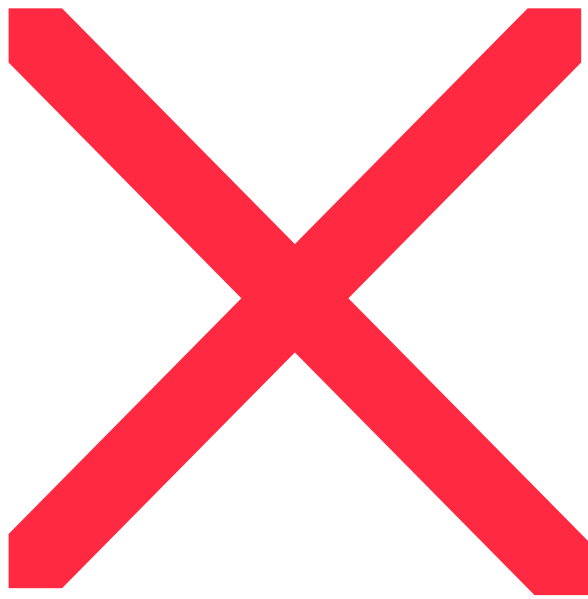
Antidepressants in Neuropathic Pain

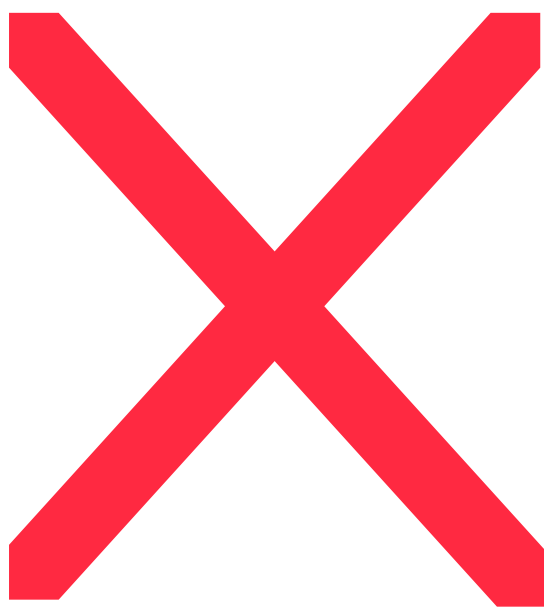
McQuay HJ, Moore RA. An evidence based resource for pain relief. Oxford University Press. March 1998.

Condition	# of Trials	Antidepressant improve/total	Placebo improve/total	Relative benefit (95% confidence limits)
Diabetic neuropathy	13	180/260	73/205	1.9 (1.6-2.4)
Post-herpetic neuralgia	3	43/77	8/68	4.8 (2.4-9.4)
Atypical facial pain	2	62/88	30/85	2.0 (1.5-2.8)
Central pain	1	10/15	1/15	10 (1.5-69)









Side Effects of Effects of Tricyclics

Side effect of blockade	Cholinergic/ muscarinic	Alpha ₂ adrenergic	Histaminergic H ₁ and H ₂	Dopaminergic
Blurry vision	Π			
xerostomia	Π			
Sinus tachycardia	Π			
Constipation	Π			
Urinary retention	Π			
Memory dysfunction	Π			
sedation			Π	
dizziness		Π	Π	
Weight gain			Π	
hypotension		Π	Π	
Extrapyramidal Sx				Π
Akathesia				Π
dystonia				Π
Tremor/rigidity				Π
akinesia				Π
Tardive dyskinesia				Π

The rationale underlying the use of antiepileptic drugs for neuropathic pain rests on the fact that epilepsy and neuropathic pain share similar chemical mechanisms.



Pathophysiology of Seizures

Increased EAA Activity

- Increased Excitatory Amino Acid Transmission
- Increased sensitivity to EAA
- Progressive increase in glutamate release during kindling
- Increased glutamate and aspartate at start of seizure
- Upregulation of NMDA receptors in kindled rats

Decrease GABA Activity

- Decreased binding of GABA and benzodiazepines
- Decreased Cl⁻ currents in response to GABA
- Decreased glutamate decarboxylase activity (synthesizes GABA)
- Interfere with GABA causes seizures

Anticonvulsants

Classification of Anticonvulsants

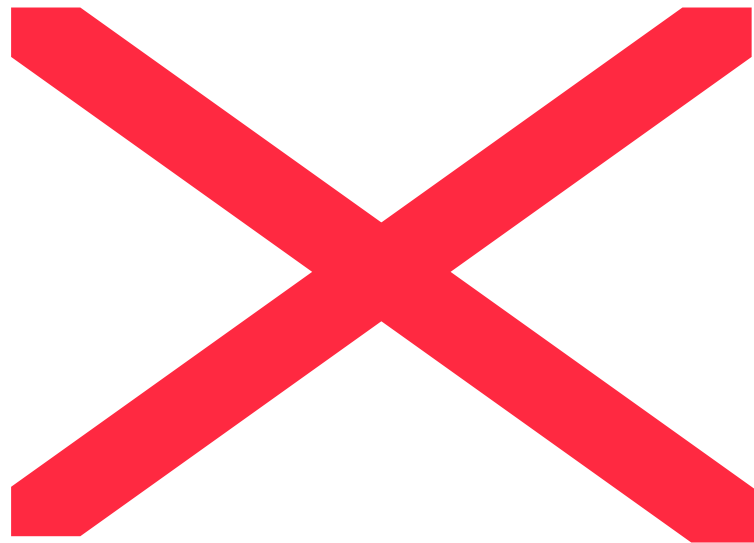
Classical

- Phenytoin
- Phenobarbital
- Primidone
- Carbamazepine
- Ethosuximide
- Valproic Acid
- Trimethadione

Newer

- Lamotrigine
- Felbamate
- Topiramate
- Gabapentin
- Tiagabine
- Vigabatrin
- Oxycarbazepine
- Levetiracetam
- Fosphenytoin
- Others

AED's in Development



Mechanisms of Action of Antiepileptic Drugs

- Sodium channel effects
- Potassium channels and GABA release
- GABAergic effects
- Glutamate regulation-neuroprotection..
antagonism of metabotropic receptors
- Calcium channels and transmitter release

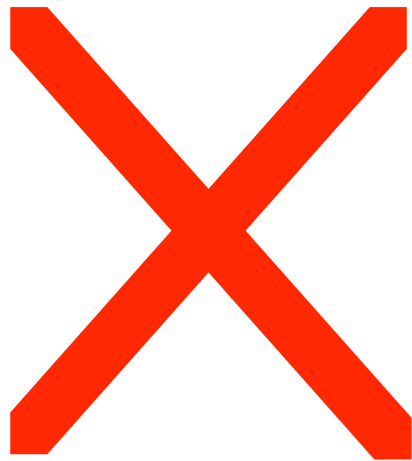
Mechanism of Anticonvulsants

Action on Ion Channels	Enhance GABA Transmission	Inhibit EAA Transmission
<p>Na⁺: Phenytoin, Carbamazepine, Lamotrigine Topiramate Valproic acid</p> <p>Ca⁺⁺: Ethosuximide Valproic acid</p>	<p>Benzodiazepines (diazepam, clonazepam) Barbiturates (phenobarbital) Valproic acid Gabapentin Vigabatrin Topiramate Felbamate</p>	<p>Felbamate Topiramate</p>
<p>Na⁺: For general tonic-clonic and partial seizures</p> <p>Ca⁺⁺: For Absence seizures</p>	<p>Most effective in myoclonic but also in tonic-clonic and partial Clonazepam: for Absence</p>	

Mechanisms for Enhancing GABAergic Activity

- Stimulation of GABA_a receptors
- Increasing release of GABA from glial cells
- Inhibition of GABA transaminase
- Increase of GABA synthesis and release
- Inhibition of reuptake of GABA by neurons and glial cells

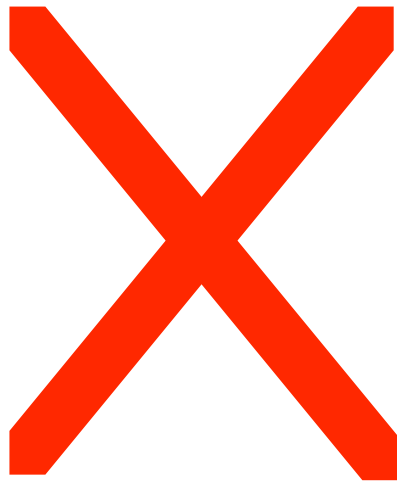
Enhancing GABA Activity/Mech.. #1



Agonism of GABA_a Receptors:

This effect of Benzodiazepenes is due primarily to allosteric agonism of the GABA-A receptor.

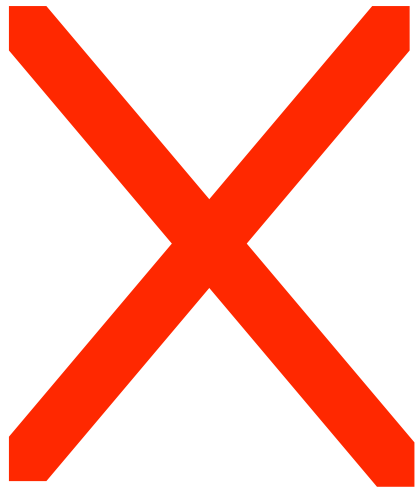
Enhancing GABA Activity/Mech.. #2



Increased release of GABA From Glial Cells:

Gabapentin appears to have multiple modes of action, including increasing GABA release from glial cells, increasing GABA synthesis by enhancing the activity of glutamic acid carboxylase (GAD), weakly binding to Ca^{++} Channels, and at high concentrations, inhibiting action of GABA transaminase.

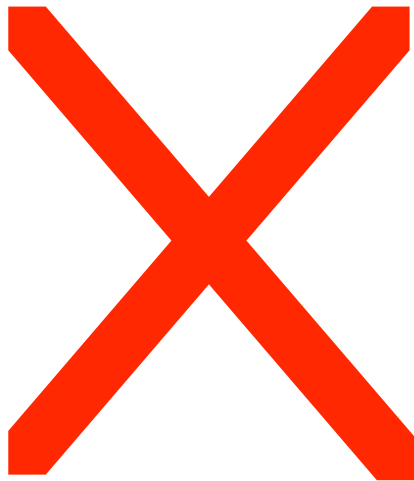
Enhancing GABA Activity/Mech... #3



Inhibition of enzymatic Breakdown of GABA:

Vigabatrin (not approved for US use) works primarily and valproate works in part by inhibiting GABA transaminases, the enzyme that metabolizes GABA after its reuptake by the GAT-1 transporter

Enhancing GABA Activity/Mech.. #4



Selective inhibition of GABA uptake:

SGRIs inhibit the action of GABA without increasing the total amount of GABA in the CNS and without affecting physiologic control of GABA release. The only SGRI currently available is tiagabine

Mechanism of drugs with strong GABAergic activity

Drug	GABAergic mechanism	GABAergic Potency	Comments
Benzodiazepines	Agonism at GABA-A receptors	Strong	Increases rate of GABA-A chloride channel opening
Phenobarbitol	Agonism at GABA-A receptors	Strong	Prolongs duration of opening of GABA-A chloride channel
Gabapentin	Increases GABA release from glial cells	Strong	Increases total cerebral GABA
Vigabatrin	Inhibits GABA transaminase	Strong	Increases total GABA
Valproate	Multiple mechs...:GABA transaminase inhibition and increase in synthesis and release	Strong	Increase in total GABA
Tiagabine	Selective inhibition of GABA reuptake	Strong	GABA release remains under physiologic control; no increase in total GABA

Efficacy of Anticonvulsants

McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. *BMJ*. 1995; 311(7012):1047-52.

Condition	# of Trials	Anticonvulsant improved/total	Placebo Improved/total	Relative Benefit (95% confidence limits)
Diabetic Neuropathy	3	56/68	26/68	1.9 (1.4-2.7)
Trigeminal neuralgia	3	178/315	41/224	3.1 (2.3-4.1)
Migraine prophylaxis	2	63/74	17/77	3.7 (2.4-5.9)
Other pain syndromes	1	5/14	1/15	5.4 (0.7-40)

Adverse Events: Complaint Rates

AED Minus Placebo Rates

No. (AED/Placebo)	GBP (543/378)	TGB (494/275)	VGB (406/311)	LTG (711/419)	TPM (113/174)
CNS	29	22	33	87	78
Psychological	16	22	44	7	73
General	0	22	12	28	29
Summary Complaint score	45	22	89	122	180

Gabapentin

- analog of GABA but does not interact with GABA receptor or interfere with GABA metabolism
- ↑ GABA level
- bind with “ gabapentin binding site ”

Gabapentin pharmacokinetics

- Rapidly absorbed orally, no effect of foods
- no protein binding
- is not metabolized
- no enzyme induction / inhibition effect
- excreted unchanged via urine



dose titration in patient with renal insufficiency

- $t_{1/2} \sim 5-7$ h
- bid or tid dosing

Gabapentin dosage and side effects

- 600 - 3,600 mg/day
- Side Effects:
 - γ somnolence
 - γ dizziness
 - γ ataxia
 - γ fatigue
 - γ nystagmus and vertigo
 - γ weight gain

Efficacy of gabapentin in mechanical allodynia

	Static	Dynamic
Gabapentin	+++	+++
Pregabalin	+++	+++
Morphine	+++	-
Amitriptyline	+++	-

static=pressure (von Frey)

dynamic=stroking (cotton wool)

In Conclusion

- Neurochemical mechanisms of convulsions, mood disorders, and chronic pain, including disordered production or delivery of Na⁺ or Ca⁺⁺ channels, monoamines, GABA and EAA's are similar, therefore, pharmacologic treatment strategies are also similar
- The treatment of chronic pain, similar to the treatment of convulsions rests on membrane stabilization and/or the pharmacologic manipulation of GABA, EAA's, and monoamines.
- Know side effects and efficacy profiles for the drugs intended

Thank You!