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GABAPENTIN - A REVIEW

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1. INTRODUCTION NEUROPATHIC PAIN

Pain may be classified as nociceptive pain and neuropathic pain based on the pathological condition. Nociceptive pain is "an appropriate physiological response to a painful stimulus and various modulatory mechanisms are involved, which can usually be controlled with standard analgesics".

Neuropathic pain arises from damage or threat of damage to the somatosensory system that leads to maladaptive nociception. Nociception is activated upon damaging stimulus [i.e., touching a hot stove] or upon tissue injury which activates protective responses [i.e., hand withdrawal from stove, healing response to injured site]. Once a damaging stimulus is sensed, nociceptive neurons send signals from the site of injury [i.e., peripheral nerves], through the dorsal root ganglion [DRG], to the spinal cord [i.e., dorsal horn], which ultimately transports signals to the brain [i.e., ascending control]. These ascending inputs are processed centrally, and descending outputs are carried down through the spinal cord and back to the dorsal horn to modulate pain signals [i.e., descending control] through excitatory and inhibitory neurons. Typically, ascending nociceptive signals cease once the stimulus [i.e., heat, tissue injury] is gone; however, some individuals develop chronic pain [i.e., maladaptive nociception]. In the case of neuropathic pain, maladaptive signalling develops from damage to central or peripheral neurons.[1-5]

1.1 Classification of Neuropathic Pain

The type of damage or related pathophysiology causing a painful neuropathic disorder can be classified as the following:

a. Mechanical nerve injury, e.g. carpal tunnel syndrome, vertebral disk herniation;
b. Metabolic disease, e.g. diabetic poly-neuropathy;
c. Neurotropic viral disease, e.g. herpes zoster, human immunodeficient virus [HIV] disease;
d. Neurotoxicity, e.g. by chemotherapy to treat cancer or tuberculosis;
e. Inflammatory and/or immunologic mechanisms, e.g. multiple sclerosis;
f. Nervous system focal ischemia. e.g. thalamic syndrome [anaesthesia dolorosa];
g. Multiple neurotransmitter system dysfunction e.g. complex regional pain syndrome [CGRP][6].

1.2 Pathophysiology of neuropathic pain

Peripheral Sensitization[7-9]

Peripheral nerve injury is correlated with a local inflammatory reaction of the nerve trunk and the liberated inflammatory mediators sensitize the axotomized nerve fibers. Peripheral or perineural inflammation is measured by plasma extravasation or increased capillary permeability causing inflammatory cell to infiltrate leading to the release of various pronociceptive and pro-inflammatory mediators. This is accompanied by enhanced release of substance P [SP] and calcitonin gene-related peptide [CGRP] because of nerve injury resulting neuropathic hyperalgesia. Bradykinin one among the mediator associated with inflammatory hyperalgesia.

Recent investigations suggest that expression of B1 receptor is absent in neuronal cell during peripheral nerve injury. Prostaglandins namely PGE2 and PGI2 also causes tissue injury sensitizing peripheral nerves.

Central Sensitization

Central sensitization represents a state of heightened sensitivity of dorsal horn neurons to threshold activation and their responsiveness to a synaptic input is augmented. Central sensitization is observed in two forms. Foremost pathway is activity dependent and the activation of nerves is observed in seconds of stimulation of afferent nerves. The pain lasts for a duration of ten minutes. Subsequent pathway is transcription dependent that takes hours to induce and lasts for prolonged duration. Central sensitization is characterized by advent of wind pipe by increasing response to C- fibre stimulation resulting hyperalgesia.[10,11]

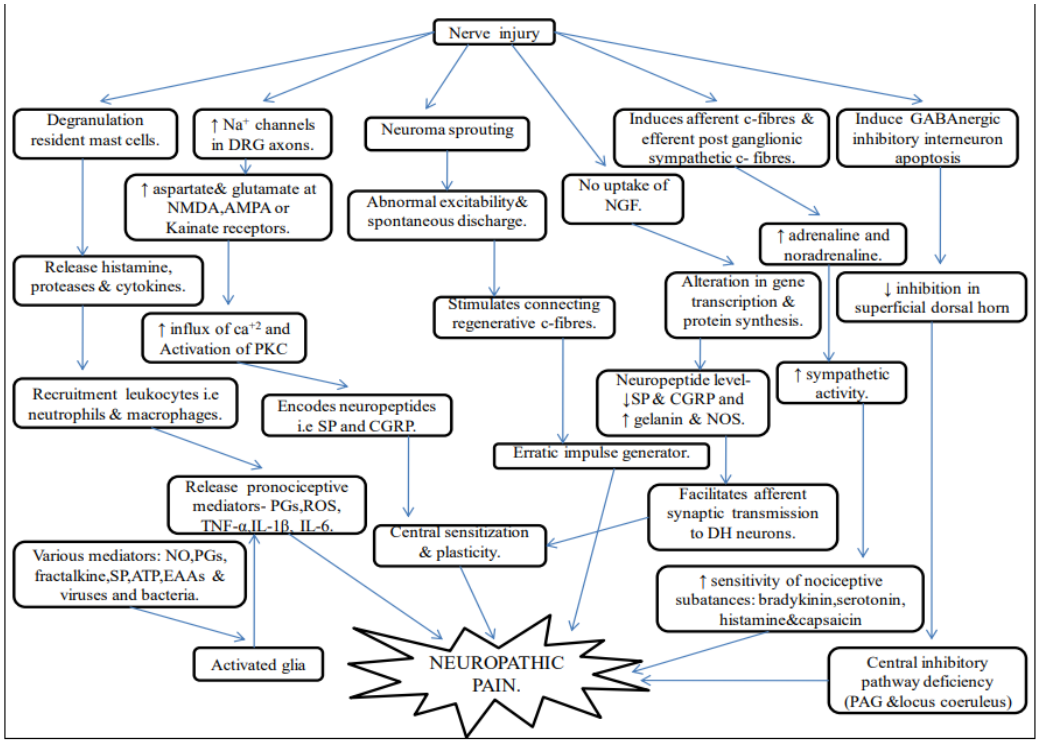

FIG. 1: SUMMARY OF VARIOUS MECHANISM INVOLVED IN THE PATHOPHYSIOLOGY OF NEUROPATHIC PAIN

ATP: Adenosine triphosphate; CGRP- Calcitonin gene-related peptide; DRG:Dorsal root ganglia; EAA: excitatory amino acids; IL: Interleukin; NGF:Nerve growth factor; NMDA:N-methyl-D-aspartate; NO: Nitric oxide; PK: Protein kinase; PG: Prostaglandin; ROS: Reactive oxygen species; TNF: Tumor necrosis factor

Mediators of Neuropathic Pain[12,13]

A. Peripheral inflammatory cells
1. Mast cells
2. Neutrophils
3. Macrophages
4. T-Lymphocytes
5. Schwann cells

B. Central inflammatory cells [Non- neuronal cells]
1. Microglia
2. Astrocytes

C. Immune factors in neuropathic pain conditions
1. Cytokines
2. Interleukin-1β
3. Tumor Necrosis Factor-α
4. Nerve Growth Factor
5. Chemokinines
6. Prostanoid
7. Nitric Oxide[NO] and Reactive Oxygen Species [ROS].

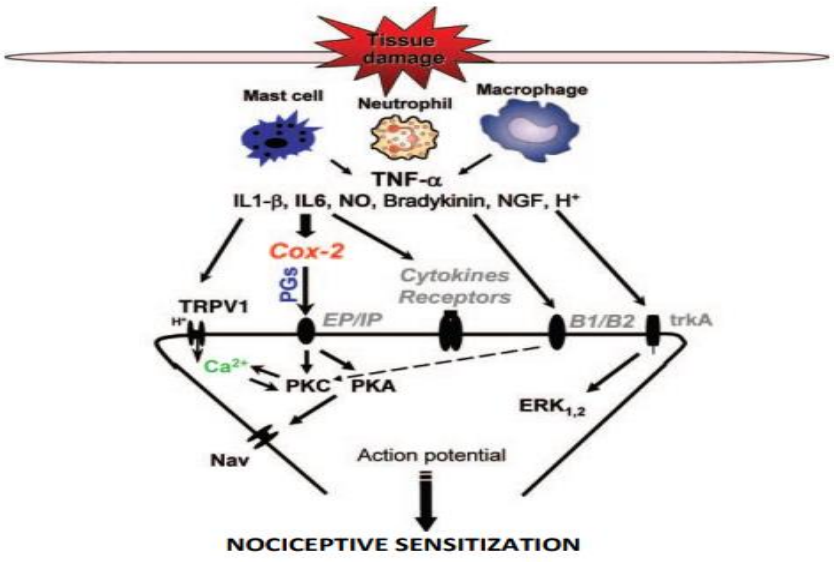

FIG. 2: VARIOUS MEDIATORS OF NEUROPATHIC PAIN

2. GABAPENTIN

2.1 Introduction

Gabapentin [Neurontin] approved in 1993 by the US Food and Drug Administration [FDA] for the treatment of seizure treatment of postherpetic neuralgia. The drug is being prescribed as off label drugs indicated for postherpetic neuralgia.[14]

Gabapentin 1-[amino methyl] cyclohexane acetic acid is a novel anti-epileptic agent, originally developed as a gamma amino butyric acid [GABA], a mimetic compound to treat spasticity and has been shown to have potent anti convulsive effect. Physicians prescribe the drug to the patients with unapproved indications. The indication of Gabapentin has been increased to 64% in the last five years. The main reason behind drastic increase in the usage is replacing the use of opioids due to epidemic abuse. The cost, pain regulation, familiarities with minimal side effects also made it as safe alternate to opioids. Due to this reason the indication for gabapentin has been slowly replaced for neuropathic pain preferring widely for the treatment of fibromyalgia, chronic pain and migraine headaches. It is widely indicated as first line drug for diabetic neuropathy, post herpetic neuralgia and central neuropathic pain.[15]

The abuse rate of gabapentin is markedly increasing from 15% to 22%. A subsequent study of a US commercial insurance claims database found a direct relationship between all-cause and drug-related inpatient hospital and emergency department utilization and increasing degrees of gabapentin overuse. Patients with prolonged overuse of concomitant gabapentin and opioids were significantly more likely to experience an all-cause or drug-related inpatient hospital stay and more specifically, an inpatient hospital stay or emergency department visit for altered mental status or respiratory depression.[16,17]

2.2 Mechanism of action

Gabapentin has no direct GABAergic action and does not block GABA uptake or metabolism. Gabapentin blocks the tonic phase of nociception induced by formalin and carrageenan and exerts a potent inhibitory effect in neuropathic pain models of mechanical hyperalgesia and mechanical or thermal allodynia.

Gabapentin binds preferentially to neurons in the outer layer of the rat cortex at sites that are distinct from other anticonvulsants. It is likely that gabapentin acts at intra cellular sites as the maximal anticonvulsants effect is achieved 2 hours after an intra venous injection of gabapentin in rats. These occurs after the plasma and interstitial fluid concentrations have peaked and reflects the additional time required for intra neuronal transport.[18]

Several theories have been proposed to explain the cellular mechanism of its anticonvulsants effect. The most favoured theory involves an interaction with a yet undescribed receptor linked with the L-system amino acids transporter protein. Suman chauhan *et al.* demonstrated that L amino acid potentially inhibited binding of an active enantiomer of gabapentin. This was further supported by Taylor *et al.*, who showed that the potent anticonvulsant, 3-iso butyl GABA potentially and sterio selectively bind to the same receptor. These findings renewed interesting in the isolation of the receptor protein that is responsible for this anticonvulsants effect.[19]

Other proposed bio chemical events in the CNS that may explain the anti-epileptic effect include the increased extracellular GABA concentrations in some regions of the brain caused by an increased activity of glutamic acid decarboxylase that produces GABA and a decreased breakdown by GABA decarboxylase, using magnetic resonance imaging[MRI] spectroscopy. Increase in GABA levels in the brain after administration of GABAPENTENE, there is no evidence that GABAPENTENE increases intra neuronal GABA concentrations, binds GABA-A or GABA-B receptors or exerts any GABA mimetic action.

Other effects of Gabapentin have been described but are not considered to play a significant pharmacodynamic role. Small decrease in the release of mono amine neurotransmitters [dopamine/nor adrenaline and serotonin] and the attenuation of sodium dependent action potentials after prolonged exposure to gabapentin.[20]

The mode of action of gabapentin in the treatment of neuropathic pain has not been fully elucidated. Early studies indicated that Gabapentin had only a central anti allodynic effect. Gabapentin has been shown to inhibit ectopic discharge activity from injured peripheral nerves. The mechanisms of the anti-allodynic effects of gabapentin include: CNS effects [potentially at spinal cord or CNS level] due to either enhanced inhibitory input of GABA mediated pathways [and thus reducing excitatory input levels]: antagonism of NMDA receptors and antagonism of calcium channels in the CNS and inhibition of peripheral nerves. The antagonism of the NMDA receptor and calcium channel blockade have the most supporting evidence. Field *et al.* , discounted an antihyperalgesic action via opioid receptor binding after demonstrating that morphine tolerance does not reduce its antihyperalgesic effect.[21]

Intrathecal administration of gabapentin blocks thermal and mechanical hyperalgesia without affecting sympathetic outflow or acute nociception and this suggest spinal site of action.

Although gabapentin does not bind to GABA-A or GABA-B receptors they reduce breakdown of GABA-ergic pathways seems unlikely to be responsible for its anti-allodynic effect because GABA receptor antagonists do not reduce these effect.[22]

The NMDA receptor complex is a ligand gated ion channel that mediates an influx of calcium ion when activated. The NMDA receptor complex has a number of binding sites for various ligands that regulate its activity including the strychnine insensitive glycine binding site, phencyclidine binding site, poly amine binding site redox modulatory site and a proton sensitive site. Partial depolarisation of the neuron after glutamine activation will release a magnesium plug and allow calcium influx into the neuron. These receptors are found in high concentrations in the hippocampus and have ascribed a key role in the process of central sensitisation of painful stimuli, commonly known as the windup phenomenon, leading to hyperalgesia. Evidence linking gabapentin to the NMDA receptor follows research demonstrating the reversal of the antihyperalgesic effect of the gabapentin by D serine, an agonist at the NMDA glycine binding site. However, receptor binding studies have failed to demonstrate a direct binding site for gabapentin for the NMDA receptor.[23]

The $\alpha 2\delta$ subunit of the voltage dependant calcium channel is a binding site for a gabapentin and the S isomer pregabalin. Because only gabapentin and the S isomer of pregabalin produce antihyperalgesic effect. It is postulated that the antihyperalgesic action for gabapentin and is mediated by its binding to this site on the voltage dependant calcium channel. Fink *et al.*, showed that, in the rat neocortex, gabapentin inhibits neuronal calcium influx in a concentration dependent manner by inhibiting P\Q type calcium channels. The decreased calcium influx reduces excitatory amino acids [glutamate] release leading to decreased AMPA receptor activation and noradrenaline release in the brain. These findings support the hypothesis that calcium channels inhibition mediates the analgesic effect of gabapentin in chronic neuropathic pain. A decrease in potassium ion evoked glutamate release from rat neocortical and hippocampal slices by gabapentin has been demonstrated.[24,25]

2.3 Pharmacokinetics

Gabapentin available only as oral preparations is absorbed in the small intestine by a combination of diffusion and facilitated transport. Its transport by binding to an unidentified, receptor linked to a saturable L amino acids transport mechanism. As this carrier dependant transport is saturable, the bioavailability of gabapentin varies inversely with dose. The bioavailability of a 300mg dose is ~ 60%, whereas that of a 600mg dose is ~40% and these decreases to ~35% at steady state with doses of 1600mg three times daily. Peak plasma levels [Cmax] of gabapentin is 2.7 – 2.99mg.1^{-1} and is achieved in 3 – 3.2 hours after ingestion of a single 300mg capsule. As a result of dose dependent saturable absorption of gabapentin, Cmax increases less than threefold when the dose is tripled from 300 to 900mg.[26-28]

In extensive distribution is reflected in a volume of distribution of ~ 0.62 -0.8 1.kg^{1}. amount of drug in cerebrospinal fluid is 80% of plasma concentrations with respect to plasma concentration is 20%.

Gabapentin is not metabolised in humans and is eliminated unchanged in the urine. It undergoes first order kinetics elimination and renal impairment will consequently decrease. Elimination is observed in a linear fashion with a good correlation with creatinine clearance. The elimination half-life of gabapentin is between 4.8 and 8.7 hours. Gabapentin is removed by haemodialysis, patients in renal failure should receive there maintenance dose of gabapentin after each treatment. Unlike other anticonvulsants drugs, it does not induce or inhibit hepatic microsomal enzymes.[29-32]

2.4 Side effects

Teratogenic effects, central hypoventilation or respiratory failure, deficits visual field, myopathy, self-harm or suicidal behaviour, mitochondrial toxicity, somnolence, dizziness and diarrhoea.

Higher doses of gabapentin can be used and its side effects can be still avoided; the variations in the effects of gabapentin depends more on the route of administration.[33-35]

2.5 Adverse drug reaction

Gabapentin is well tolerated with few serious adverse effects. Since 1995, the reported adverse events are somnolence [20%], dizziness [18%], ataxia [13%] and fatigue [11%]. The most serious adverse side effects were convulsions [0.9%] M Clean *et al.*, in a large open label multicentre study involving 2216 patients to examine the safety and tolerability of gabapentin of an adjunctive therapy in seizure control.

The relative safety of gabapentin is supported by case reports of massive overdoses of the drug. *Fisher et al.*, reported a patient ingested with 48.9gms of gabapentin from which a full recovery was achieved after symptoms of lethargy and dizziness. *Verma et al.*, reported a case of sustained massive overdose of gabapentin in a patient and haemodialysis three times a week taking 1800mg of gabapentin per day. The gabapentin was decreased to 600mg post dialysis and the patient suffered no clinically significant toxicity.

Recent case report has suggested that gabapentin may cause reversible acute renal allograft dysfunction and stevens - Johnson syndrome. Following the exacerbation of myasthenia gravis in a patient after a three months course of gabapentin 400mg.day^{-1} that improved with the cessation of gabapentin, *Boneva et al.*, treated rats with experimental auto immune myasthenia gravis with high doses of gabapentin and observed a transient decrease in amplitude of muscle contraction with repetitive nerve stimulation. The authors suggested that gabapentin can

possibly unmask myasthenia gravis and therefore should be used with caution in patients with this disease.[36,37]

2.6 Drug interactions

Studies shown that gabapentin, an antiepileptic drug has a low profile of interaction with other drugs. Specifically, review stated that gabapentin lacks interactions with hepatic enzymes, plasma proteins and other drugs, making suitable for elderly patients suffering from hepatic diseases. Gabapentin has a low profile of pharmacokinetic and pharmacodynamic interactions with other antiepileptic drugs.

Another review about drug combinations for alleviating epilepsy concluded that gabapentin has a more favourable pharmacokinetic profile, but it is not totally exempt from interactions with other drugs. Gabapentin can be useful for particular patient groups such as patients with cancer, transplants, anticoagulant treatments and HIV infection. Gabapentin due to its weak pharmacokinetic parameters used in combination with other antiepileptic drugs also shows few drug interactions.[38]

Studies reported that the combinations of gabapentin with antidiuretic drugs [such as ethacrynic acid and hydrochlorothiazide] do not alter the anticonvulsant activity of gabapentin [either single or chronic doses of antidiuretics].

Studies also proved that gabapentin lacks drug interactions with contraceptive drugs like norethindrone acetate and ethinylestradiol.

A study on the interactions between gabapentin and morphine reported inconsistent results. Specifically, a rodent study reported lack of pharmacokinetic interactions, but other rodent studies showed the presence of pharmacodynamic interactions [behavioural synergism]. However, other human investigations showed pharmacokinetic and pharmacodynamic interactions between morphine and gabapentin.[39]

Different reports suggest that gabapentin has a low profile of interaction with other drugs, hepatic enzymes and plasma proteins. In addition, gabapentin is recommended for special groups such as elderly patients suffering from hepatic diseases, patients with cancer.

On the other hand, different investigations have reported that gabapentin shows interactions with other drugs such as losartan and ethacrynic acid and induce motor impairment. Gabapentin can interact with caffeine and diminish its anticonvulsant effects. Gabapentin can interact synergistically with tramadol or metamizole for alleviating pain. Gabapentin can interact with antiepileptic drugs [phenytoin, mefloquine], antacids [magnesium oxide, cimetidine, nonselective nonsteroidal anti-inflammatory drugs [naproxen], reducer of serum uric acid concentrations [sevelamer] and morphine.[40,41]

2.7 Contraindications

Literature review supports the use of gabapentin in patients with myasthenia gravis or myoclonus problems. Elevated levels of acetylcholine receptor antibodies in serum are identified in case of patients with myasthenia gravis. Pyridostigmine is used to improve the health condition. Literature review also reported that there is a decline in electrophysiological responses of nerve.

Clinical study reported worsening or onset of myoclonus after gabapentin treatment [1.9%] within 2 weeks after starting gabapentin treatment. The doses related to these problems ranged from 600 to 1800 mg. After the discontinuation of gabapentin or clonazepam regimen, the myoclonus ceased without major consequences.[42-44]

2.8 Uses of gabapentin

Preclinical and clinical studies supports the use of gabapentin in neuropathic pain and in a number of specific chronic pain syndromes. Tricyclic antidepressants, opioids and other anticonvulsants have been used in the treatment of chronic pain but are associated with numerous adverse effects. Gabapentin may become an attractive therapeutic option because of its relative lack of interactions and serious adverse effects. Its efficacy can be established in neuropathic pain and other types of chronic pain. For example, for the treatment of non-neuropathic pain, anxiety disorder and bipolar disorder. Gabapentin is approved for the treatment of focal seizures however, it is not effective for generalized epilepsy.[45-48]

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