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EXCITOTOXICITY AN IMPORTANT TARGET FOR NEUROPROTECTION

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ABSTRACT

Glutamate is free amino acids that function as an Excitatory Neurotransmitter in the Central Nervous System (CNS). Excess Stimulation of Glutamate receptors i.e. NMDA(N-Methyl-D-Aspartate) receptor by Excitatory Neurotransmitter leading to number of deleterious consequences, such as impairment in Calcium efflux, Free radicals production, Mitochondrial dysfunction and Secondary Excitotoxicity. Excitotoxicity causes motor disorder such as Parkinson's disease & non motor disorder such as Neuropathic pain. Neuroprotection is the only way to prevent Excitotoxicity. Therefore in this review, we summarize various Neuroprotecting agents preventing motor disorder like Parkinson's disease & non motor disorder like Neuropathic pain caused due to Excitotoxocity.

KEYWORDS: ***Glutamate, Excitotoxicity, Neuroprotection, Parkinson disease, Neuropathic pain.***

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INTRODUCTION

Nervous system is the centre of all psychological actions including thought, learning, and memory. The nervous system is in-charge of controlling and looking after homeostasis. It comprises of two fundamental parts, the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS consists of brain and the spinal cord while PNS comprises chiefly of nerves, which are long fiber strands that interface the CNS to every other part of the body. At the cellular level, the nervous system is characterized by the specialtype of cell called the neuron, also known as "nerve cell". Neuron is the functional unit of the nervous system. In a normal human being, around 10,000 crores neurons are present.[1] (Fig 1&2)

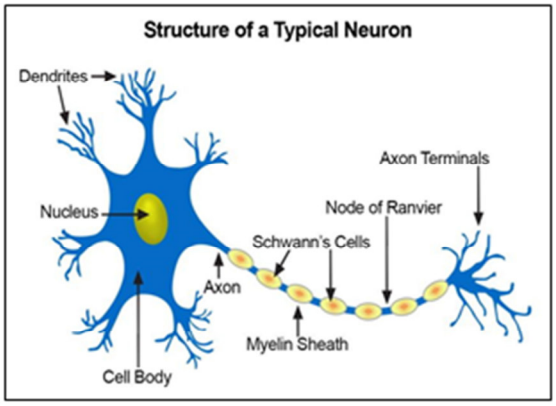


Figure 1
***Structure of Neuron*[17]**

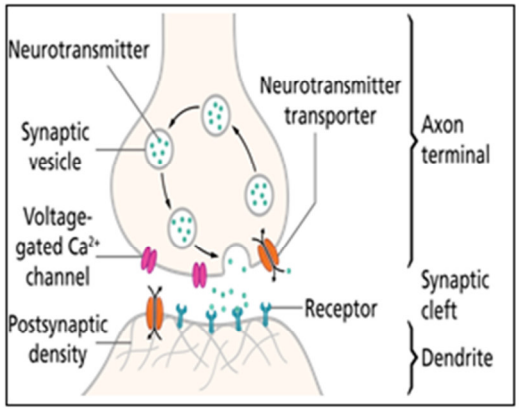


Figure 2
***Structure of Synapse*[18]**

The neurotransmitter is released from the presynaptic neuron (top), this neurotransmitter acts on and stimulates receptor which are present on postsynaptic neuron (bottom).[1]

NEUROTOXICITY

Neurotoxicity is toxicity to the nervous system. The term 'neuro' means neuron, 'toxicity'means damage. It happens when exposed to regular or artificial dangerous substances, which are called neurotoxins, which affect the normal action of the nervous system so as to cause harm to the nervous tissue.The nerve cells convey impulses to the brain and to the different parts of nervous system& these nerve cells are destroyed by neurotoxins. The neurotoxic term is used to depict a substance, condition or state that harms the nervous system or brain, usually by destroying neurons. Some of the most commonlyoccurring brain toxins are β amyloid (Aβ), Glutamate and Oxygen radicals & when they are present in high dosage they may lead to Neurotoxicity and Programmed cell death i.e. Apoptosis. The major cause of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Amyloid Lateral Sclerosis (ALS), etc. is found to be Neurotoxicity.[2] (Fig 3)

CAUSES/ETIOLOGY

Certain causes of Neurotoxicity are enlisted below:[3]

- Excitotoxicity
- Oxidative stress
- Protein aggregation & misfolding
- Neuroinflammation
- Mitochondrial dysfunction

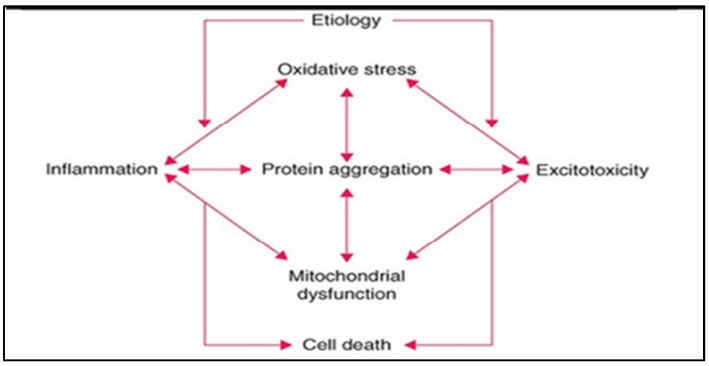


Figure 3
***Etiology of neurotoxicity*[19]**

MECHANISM OF NEUROTOXICITY

The gathering of misfolded proteins is probably going to be a key event in Neurotoxicity. Pathogenic changes may specifically initiate abnormal protein adaptations (as accepted to be the situation with synuclein) or the ability of the cellular machinery to detect and degrade misfolded proteins (Parkin, UCH-L1-Ubiquitin carboxy-terminal hydrolase L1); the part of DJ-1 stays to be unidentified. Oxidative stress, connected to abnormal dopamine metabolism and mitochondrial dysfunction, may promote misfolded protein conformations.[3] (Fig 4)

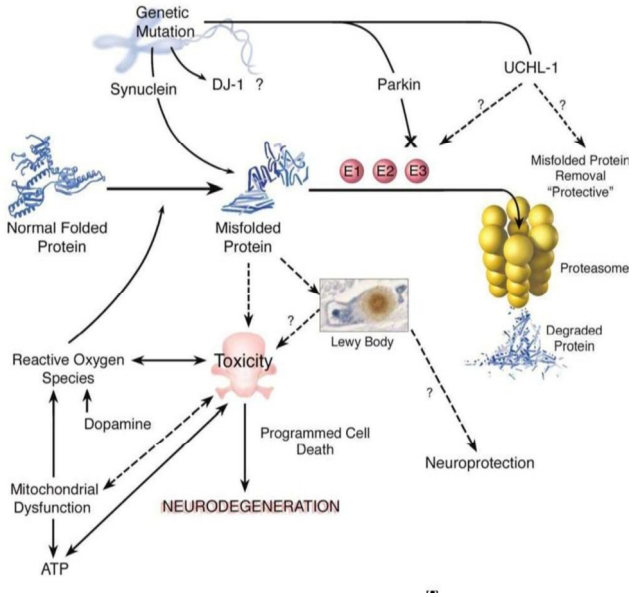


Figure 4
***Mechanism of neurotoxicity*[20]**

EXCITOTOXICITY

EXCITATORY NEUROTRANSMITTER (EAA)

Glutamate belongs to the free amino acids that function as neurotransmitters in the Central Nervous System (CNS). These amino acids include the excitatory neurotransmitters (glutamate and aspartate) and the inhibitory neurotransmitters (GABA, glycine and taurine).[4,5]

METABOLISM AND RELEASE OF GLUTAMATE

Glutamate is fairly, widely and uniformly distributed in the CNS and its concentration is much higher that observed in other tissues. It has an important metabolic role. The metabolic and transmitter pools are linked by transaminase a enzyme that catalyzes the interconversion of glutamate and alpha-oxoglutarate. Glutamate in the CNS comes mainly from either glucose, via the tricarboxylic acid (Krebs) cycle, or glutamine, which is synthesized by glial cells and taken up by the neurons; very little comes from the periphery. The interconnection between the pathways for the synthesis of EAAs and inhibitory amino acids(GABA and glycine) is shown in figure 5.[4,5]

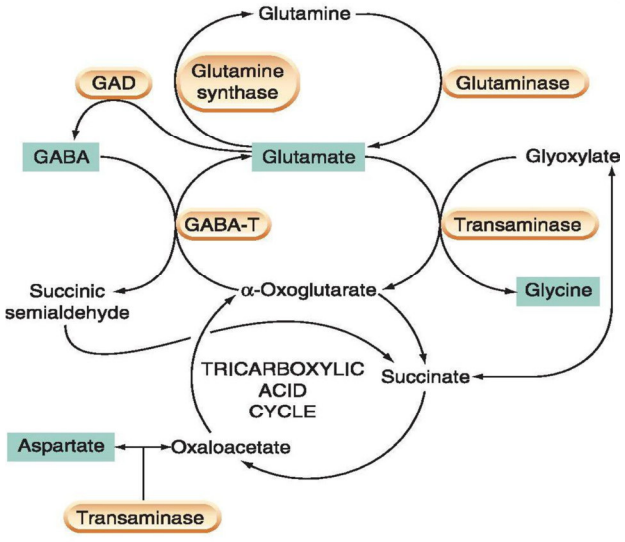


Figure 5
***Metabolism of amino acids.*[4]**

In the same manner as different transmitters, glutamate is put away in synaptic vessels and discharged by calcium-mediated exocytosis.[4]

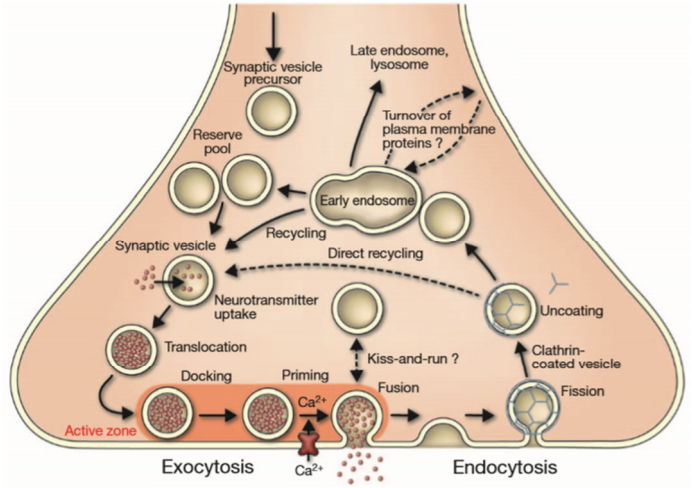


Figure 6
***Release of glutamate by calcium mediated exocytosis*[24]**

Discharged Glutamate is captured to some extent by neurons and also by astrocytes, which is converted into glutamine by glutamine synthase. Astrocytes discharge glutamine by means of a Glutamine transporter, and neuron take it up and synthesizes glutamate.[4]

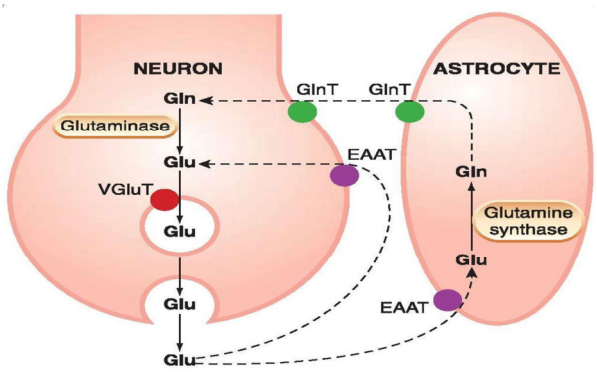


Figure 7
***Transport of glutamate(GLU) and glutamine(GIN) by neurons and astrocytes.*[4]**

GLUTAMATE RECEPTORS

"In both neurons and glial cells", Glutamate acts via two classes of receptors:[5]

1. Ligand gated ion channels (Ionotropic receptors)
   Three groups (AMPA, NMDA &Kinate receptors).
2. G-protein coupled (Metabotropic receptors).
   They are further broken down into three groups and eight subgroups: (mGlu1-mGlu 8).

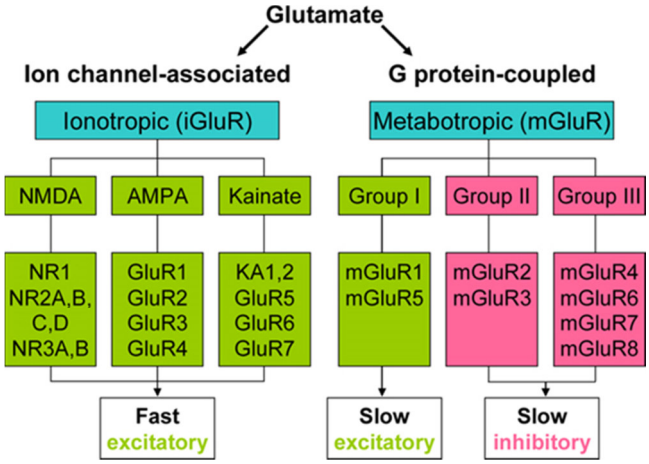


Figure 8
***Types of glutamate receptors*[25]**

GLUTAMATE EXCITOTOXICITY

Excitotoxicity is a vital and all around acknowledged hypothesis proposed by Olney in 1969 to clarify the pathophysiology of brain ischemia. Glutamate excitotoxicity has been recommended to assume a critical role in almost every neurodegenerative diseases. Glutamate excitotoxicity is one of the most important mechanisms known to trigger cell death in CNS disorders. Over-excitation of glutamate receptors, specifically NMDA receptors, allows for an increase in calcium ion (Ca^{2+}) influx due to the lack of specificity in the ion channel opened upon glutamate binding. As Ca^{2+} accumulates in the neuron, the buffering levels of mitochondrial Ca^{2+} sequestration (isolation) are exceeded, which has major consequences for the neuron. Because Ca^{2+} is a secondary messenger and regulates a large number of downstream processes, accumulation of Ca^{2+} causes improper regulation of these processes, eventually leading to cell death. Ca^{2+} is also thought to trigger neuroinflammation, a key component in all CNS disorders. Regardless of its ubiquitous (found all around) part as a neurotransmitter glutamate is very dangerous to neurons, a phenomenon named excitotoxicity. A low concentration of glutamate applied to neurons in culture kills the cells, and the finding in the 1970s that glutamate given orally produces a neurodegeneration in vivo caused considerable alarm, because of the widespread use of glutamate as a 'taste-enhancing' food additive. "The Chinese restaurant syndrome" an acute attack of neck stiffness and chest pain is well known, but so far the possibility of more serious neurotoxicity from dietary glutamate is only hypothetical. If kainic acid is injected locally then it is used to produce neurotoxic lesions experimentally. It acts by overstimulation of local glutamate releasing neuron, and the release of glutamate, acting on NMDA (N-methyl-D-aspartate) and also metabotropic receptors leads to neuronal cell death. The essential factor in excitotoxicity is overloading of calcium ions.[4]The ultimate effect of excitotoxic phenomena is activating apoptotic pathways through the disruption of mitochondrial and bioenergetic homeostasis, as well as the increase of intracellular Ca^{2+} levels and oxidative burden.[5]Hence, Nicotine is also having neuroprotective activity carried out by Kainic acid induced Excitotoxicity. Long term exposure to Nicotine is capable to prevent Excitotoxicity and neuronal degeneration induced by Kainic acid and its analogue in rodents. The protective role of Nicotine is been identified by using behavioural parameter such as Actophotometer i.e., locomoter activity is been measured which is been increased by nicotine exposure, whereas the locomotor activity is diminished in neurodegenerated neuron[6]. Also Excess levels of TNF, and glutamate in the brain across a range of neurodegenerative diseases are crucially linked, high TNF causing extracellular glutamate to accumulate to increased levels that are enough to inhibit synaptic activity and kill neurons[7] Also Dopamine itself is able to produce a calcium signal within cells that may be receptor-mediated, causing release from intracellular calcium stores (in neurons) or receptor-independent in astrocytes, or possibly due to opening of voltage-dependent calcium channels inducing exogenous calcium influx.[8] Neuronal degeneration in adult brain arising during chronic alcohol exposure is, or is likely to be, via "Excitotoxicity"[9] (Fig 6,7,8)

MECHANISM OF EXCITOTOXICITY

Various mechanisms involving excitotoxicity are enlisted as follows:[10] (Fig 9,10,11)

1. Elevation of intracellular calcium,
2. Accumulation of oxidizing free radicals,
3. Impairment of mitochondrial function,
4. Activation of apoptotic and autophagic programs.

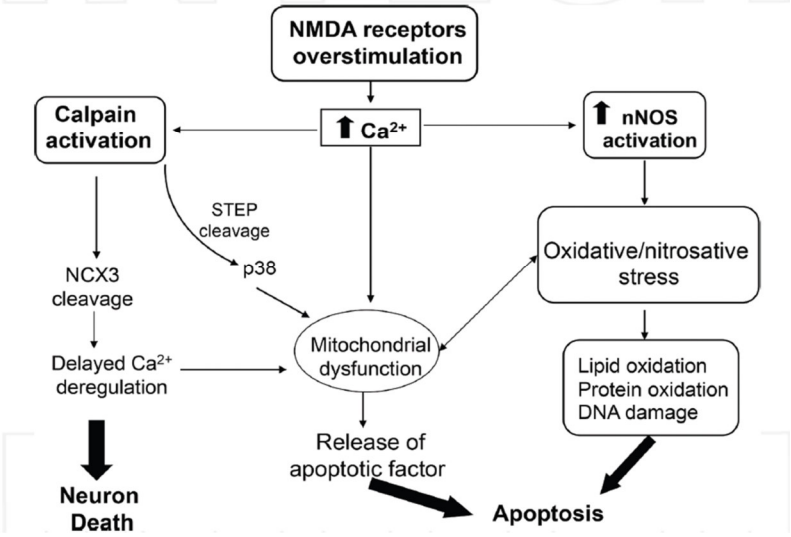


Figure 9
***Mechanism of excitotoxicity*[11]**

MOLECULAR MECHANISM OF EXCITOTOXICITY

The mechanism by which Excitotoxicity occurs and leads to cell death are as follows:[4,11]

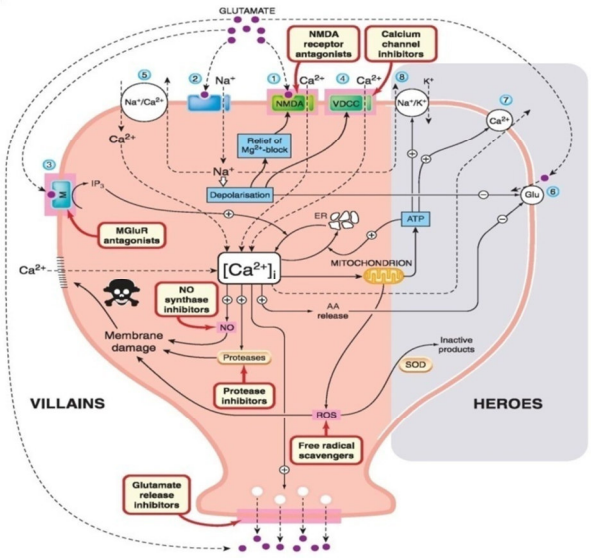
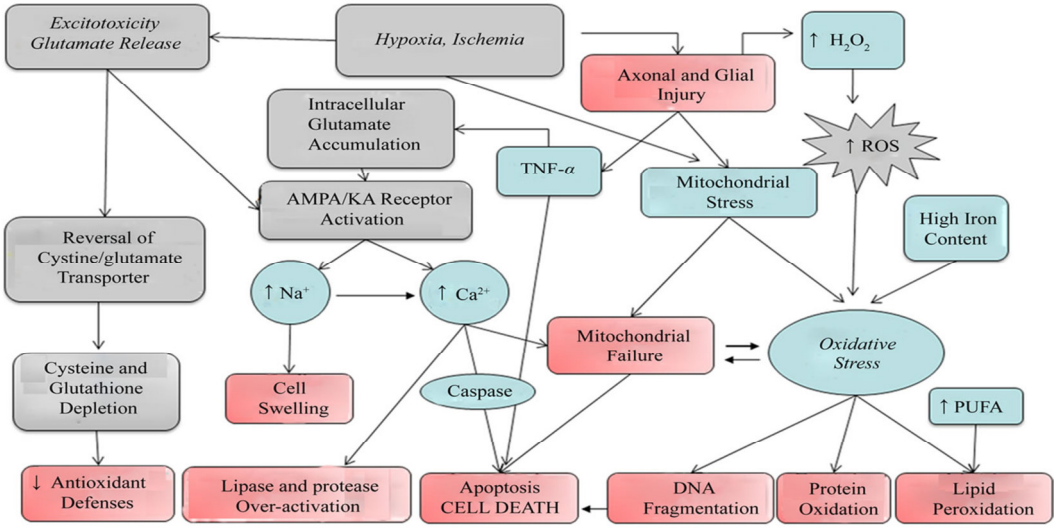


Figure 10
***Molecular mechanism of excitotoxicity*[4]**



***Schematic diagram explaining* figure 10**[4]

NEUROPROTECTION

Neuroprotection refers to protection of neuronal structure as well as function. A basic mechanism includes elevated levels in oxidative stress, mitochondrial dysfunction, excitotoxicity, inflammatory changes, iron accumulation, and protein accumulation. Of these mechanisms, neuroprotective medicines frequently target Oxidative stress and Excitotoxicity, both of which are exceedingly connected with CNS disorders. Not only oxidative stress and excitotoxicity trigger neuron cell but also they have synergistic impacts that reason significantly more damage than all alone. In this manner, excitotoxicity and oxidative stress is a vital part of neuroprotection. Common neuroprotective medications are glutamate antagonists and antioxidants, which intend to decrease excitotoxicity and oxidative stress individually.[12]

NEUROPROTECTION AGAINST EXCITOTOXICITY GLUTAMATE ANTAGONISTS

Glutamate antagonists are the essential treatment used to prevent excitotoxicity in CNS disorders. The objective of these antagonists is to hinder the official binding of glutamate to NMDA receptors with the end goal that decreases Ca^{2+} ion and subsequently excitotoxicity can be avoided. Various glutamate antagonist have been investigated as alternatives in CNS disorders, yet numerous are found to lack adequacy or have unbearable symptoms. The following are a portion of the medications that have promising outcomes for what's to come:

- Estrogen: 17β-Estradiol controls excitotoxicity by blocking NMDA receptors and also other glutamate receptors.
- Ginsenoside: Results from the examination indicate ginsenoside weakens glutamate excitotoxicity. Vitally, clinical
- preliminaries for the medication in patients with ischemic stroke demonstrate it to be effective and additionally noninvasive.
- Progesterone: Administration of progesterone is notable to help in the anticipation of optional wounds in patients with traumatic brain damage and stroke.

- Simvastatin: Administration in models of Parkinson's disease has been appeared to have neuroprotective effects including mitigating effects because of NMDA receptor modulation.
- Memantine: As a less-affinity NMDA antagonist that is uncompetitive, memantine hinders NMDA initiated excitotoxicity.[12]

NMDA ANTAGONISTS AND NEUROPROTECTORS

Neuroprotectors (NP) contain another new gathering of medications that decrease excitotoxicity, opposing the overstimulation of EAA (Excitatory amino acids) and its intracellular effects.There are many trials studying these sequences. We can analyze the main items based on neuroprotective action: [12]

NMDA ANTAGONIST

The NMDA receptor is a complex structure, with binding sites for divalent cations, polyamines and glycine, including the ligand-binding site. Glutamate is the principle agonist; glycine and polyamide are co-agonists of the NMDA receptor-channel complex. An antagonist officially binds to this receptor and produces neuroprotective effects in various animal models. NMDA antagonists are of two types i.e., Competitive & non-competitive NMDA antagonist. The Competitive antagonist crosses the hematoencephalic barrier weakly & it have elevated potency and specificity & they compete with glutamate. The non-competetive antagonist prevents the Ca^{2+}influx by acting on some specific places of NMDA present on cell membrane. The Drugs include Dizocilpin (MK 801), selfotel, cerestat, dextromethorphan. Cerestat is a noncompetitive antagonist which shown milder impacts on the NMDA receptor. Fig 12.

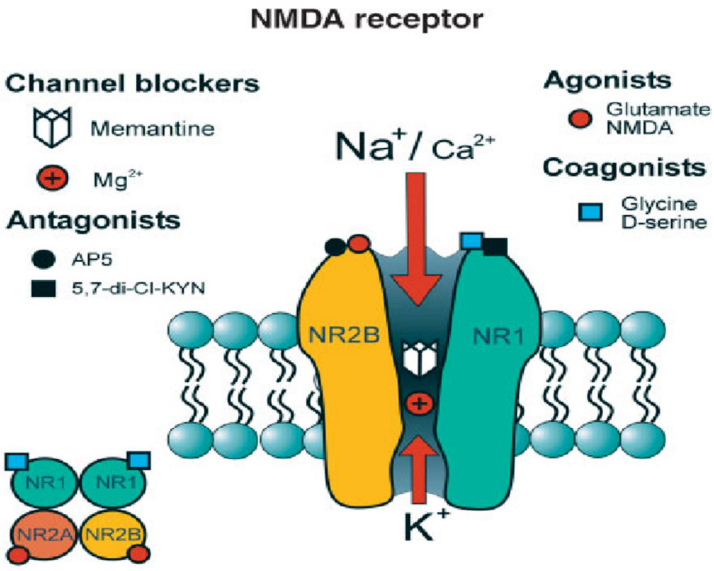


Figure 11
***NMDA receptor antagonist*[26]**

GABA AGONISTS

While glutamate is an essential EAA in the brain, GABA is the most important inhibitory Neurotransmitter. The potential activity of GABA may switch the harmful impacts of glutamate through hyper-polarization of the neuronal membrane. For example: Chlomethiazole

AMPA ANTAGONISTS

This is another possible method of neuroprotection, as AMPA additionally assumes a vital part in the elevation of Ca^{2+} inside the cells. The most examined medication in this group is the NBQX, this medication is extremely nephrotoxic and clinical investigations not found it effective.

TO DECREASE INTRACELLULAR CA^{2+} ACTIVATION

It is another plausibility to prevent excitotoxicity. A few medications such as: GM-1, that blocks the translocation of CPK (Creatine phosphokinase); Dantrilene sodium; a few medications that decrease intracellular Ca^{2+}.

INHIBITORS OF THE PATHWAYS OF NO BALANCE

The NO produced using nNOS assumes a critical part in the production of free radicals and it brings great outcomes. 7-nitroindazole is still under clinical examinations; it hinders the nNOS and has no activity on eNOS. Lubeluzole hinders the production of the NO pathways and furthermore helps keeping the elevation of extracellular glutamate in the brain.

FREE RADICALS SCAVENGERS

Well-known understood free radical scavengers like tocopherol, selenium, b-carotene, have little activity on neuronal tissue. Tirilazad is another new scavenger under clinical study.

SODIUM CHANNEL ANTAGONISTS

Na^+ plays an important role; the blocking of pre-synaptic sodium channels, leads to stabilization of neuronal membrane which thus, prompts the blocking of pre-synaptic glutamate discharge. A few medications,

similar to antiepileptics, have this property: lamotrigine, phenytoin, fos-phenytoin, riluzole, lifarizine.

GLUTAMATE RELEASE INHIBITORS

Another process which can be utilized as a part of neuroprotection. A few investigations are in progress with various medications with uncertain outcomes: Omega-canotoxins; synthetic toxin SNX-111, has an important side effect; it Inhibits adrenaline discharge prompting severe hypotension; nalmepene (opioid receptor rival); dexamethasone has an important side effect in this issue, since it can elevate the glutamate discharge or decreasing glutamate re-uptake.

GROWTH FACTORS

Some Growth factors may have a Neuroprotection activity. Angiogenic variables may be neuroprotective and are determinant for neuronal survival. PDGF (platelet derived growth factor) is highly present in the white matter suggesting that PDGF may apply its function in white matter, participating either in the recovery of damaged axons or in glial scar formation. Thus PDGF is probably going to be Angiogenic and Neuroprotective.

ACIDOSIS

Several in vitro experiments explained with evidence that glutamate receptors could be deactivated by extreme acidosis. In experimental studies, the combination of extracellular extreme acidosis and glutamate-receptor blocker gives more protection to the neurons than the glutamate receptor inhibitor alone.

HYPOTHERMIA

It can decrease the glutamate discharge and can be utilized as a neuroprotective activity. Hyperthermia has a contrary impact.

POTASSIUM CHANNEL ACTIVATORS

Recent evidence recommends that activation of potassium channel on neurons, can effectively affect neuronal ischemia and potential therapeutic implications. A few medications are under Clinical trials.

EXCITOTOXICITY: A POTENTIAL TARGET IN SOME DISEASES NEUROPATHIC PAIN

Pain usually results from activation of nociceptive afferents by actually or potentially tissue damaging stimuli. Neuropathic pain is a complex, chronic pain state that usually is accompanied by tissue injury. With Neuropathic pain, the nerve fibres themselves may be damaged, dysfunctional or injured.[13] Fig13,14

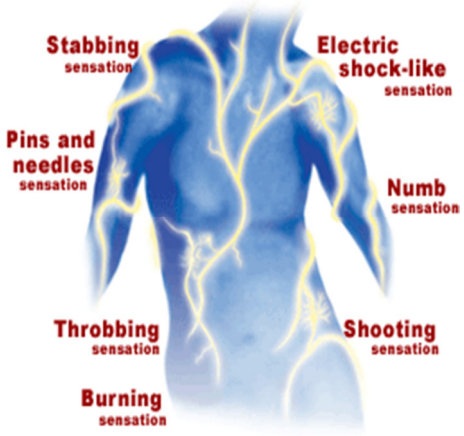


Figure 12
Neuropathic pain[21]

SYMPTOMS[13]

- Continuous burning pain.
- Intermittent shooting, lancinating pain.
- The types of pain arise in allodynia and hyperalgesia.

CAUSES[13]

Certain causes are enlisted below:

- Alcoholism
- Vitamin deficiencies
- Autoimmune diseases
- Diabetes
- Multiple sclerosis
- Back, leg, and hip problems

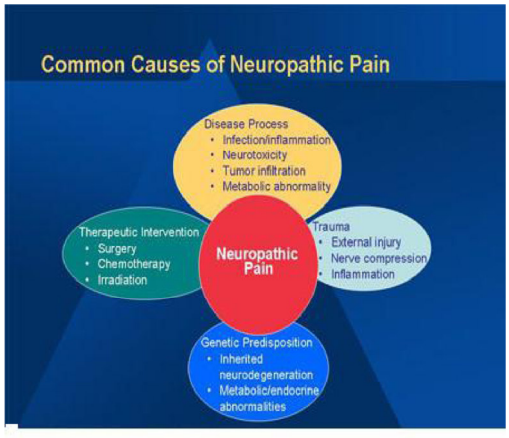


Figure 13
***Common causes of neuropathic pain*[22]**

CLASSIFICATION OF NEUROPATHIC PAIN[13]

It is classified in to two types:

1. Peripheral Neuropathic pain
2. Central Neuropathic pain

MECHANISMS OF NEUROPATHIC PAIN[13]

Peripheral mechanisms: (Fig15) It includes

- Oxidative stress
- Demyelination
- Cytokine mediated inflammation
- Sodium ion channel dysfunction

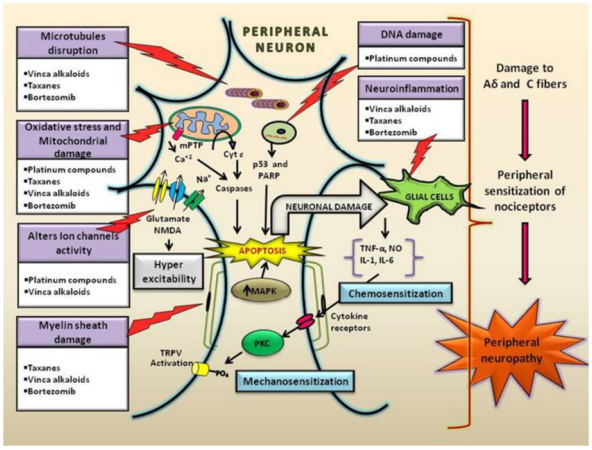


Figure 14
***Peripheral mechanism*[14]**

CENTRAL MECHANISMS (Fig15) It includes:

- Glutamate/NMDA receptor mediated sensitization
- Network dysfunction in the dorsal spinal cord
- P2X4R Inspiral microglia

PERIPHERAL MECHANISM SODIUM ION CHANNEL DYSFUNCTION

Voltage-gated sodium (Na^+) channels play a key part in membrane excitation in neurons. These channels have a basic part in the development and support of a few pain disorders, including inflammatory pain, neuropathic pain, and central pain associated with spinal cord injury. Influx of Na^+ through voltage-gated Na^+ channels causes depolarization of membrane, which is incharge of production and conduction of the action potential in the axon and actuation of presynaptic Ca^{2+}channels for exocytosis. Voltage-gated Na+ channels additionally balance the resting membrane potential and subthreshold motions of the membrane potential, which decide the excitability of the neuron and its axon. Hyperalgesia, is caused by the increase in release of excitatory neurotransmitters, for example, glutamate or substance P and the synaptic viability. While several neurotransmitters assume to take part in the System, receptors and enzymes such as the AMP-activated protein kinase (AMPK) activators likewise assume basic parts in the sensation of pain and the control of the components. Indications of neuropathic pain can be identified with the shivering, creeping, and burning sensations. Some key players required for signalling of pain may consists of the discharge of neurotransmitters and neuropeptides, for example, glutamate and

substance P; receptors, for example, the AMPA, NMDA, and Glu receptors; the catalysts, for example, AMP-activated protein kinase activators ; and the gatekeepers which consists of the sodium and calcium channels. Brain derived neurotrophic factors (BDNF), nerve growth factors (NGF), and glia-cell derived neurtrophic factors (GDNF) additionally impact neuropathic pain. Neurotrophins, which are generally engaged with the improvement of sensory system and neuronal plasticity, can intervene and demonstrate the hidden mechanism of neuropathic pain. In addition, various different neuropeptides, for example, endomorphins, dynorphin A, and galanin can likewise prompt stimulation of nerves. The modification of every player in the signal transductions cascade contribute to primary afferent hyperexcitability; all things considered, prompting the perception of neuropathic pain.[14]

CENTRAL MECHANISM GLUTAMATE/NMDA RECEPTOR MEDIATED SENSITIZATION

Centrally sensitizations refer to the process through which a condition of hyperexcitability is set up in the central nervous system, prompting enhanced processing of nociceptive (pain) messages. Although various mechanisms have been included in central sensitization by focusing: modification in glutamatergic neurotransmission/NMDA receptor-mediated hypersensitivity, loss of tonic inhibitory controls (disinhibition) and glial neuronal interaction.[15] Fig16

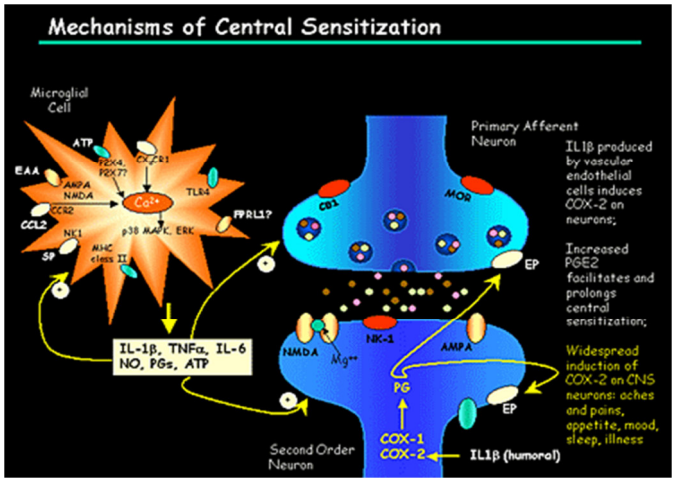


Figure 15
***Central mechanism*[23]**

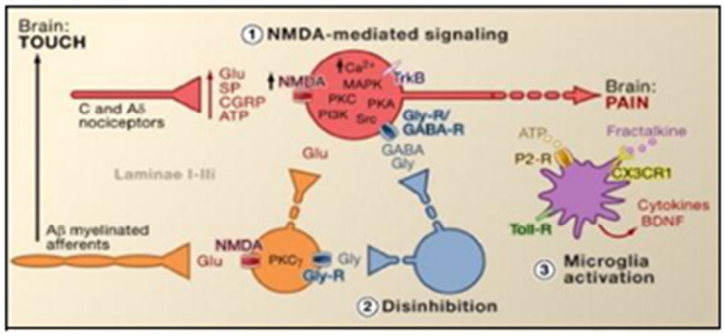


Figure 16
***NMDA mediated sensitization*[27]**

CENTRAL SENSITIZATION GLUTAMATE/NMDA RECEPTOR-MEDIATED SENSITIZATION

After intense excitement or persistent damage, activated C and Adnociceptors discharges various neurotransmitters, including glutamate, substance P, calcitonin-gene related peptide (CGRP), and ATP, onto output neurons in lamina I of the superficial dorsal horn (red). As a result, regular NMDA glutamate receptors situated in the postsynaptic neuron would now be able to signal, elevates intracellular calcium, and initiate a large group of calcium dependent signalling pathways and secondary messengers including mitogen-activated protein kinase (MAPK), protein kinase C (PKC), protein kinase A (PKA), phosphatidylinositol 3-kinase (PI3K), and Src. This events will elevates the excitability of the output neuron and stimulates the transmission of pain messages to the brain.[15]

DISINHIBITION

Under normal conditions, inhibitory neurons (blue) consistently discharge GABA and additionally glycine (Gly) to diminish the excitability of lamina I output neurons and balance pain transmission (inhibitory tone). In any case, in the setting of damage, this blockage can be lost, bringing about hyperalgesia. Moreover, disinhibition can enable non-nociceptive myelinated Aβ primary afferents to connect with the pain transmission circuit to such an extent that ordinarily harmless boosts

are currently seen as difficult This happens, to some extent, through the disinhibition of excitatory PKCγ communicating interneurons in inward lamina II.[15]

MICROGLIAL ACTIVATION

Peripheral nerve damage stimulates discharge of ATP and the chemokine fractalkine that will stimulate microglial cells. Specifically, initiation of purinergic P2-R receptors, CX3CR1, and Toll-like receptors on microglia (purple) brings about the discharge of Brain derived neurotrophic factor (BDNF), which through activation ofTrkB receptors communicated by lamina I yield neurons, leads to hyperalgesia and allodynia. Activated microglia likewise discharge a large group of cytokines, for example, tumour necrotic factor α (TNFα), interleukin-1β and 6 (IL-1β, IL-6), and different elements. Acute pain is caused by the arrival of glutamate from the sensory terminals of nociceptors, producing excitatory postsynaptic currents (EPSCs) in second dorsal horn neurons. This happens basically through stimulation of postsynaptic AMPA and kainite subtypes of ionotropic glutamate receptors. The subsequent increment in calcium produces Hyperalgesia. [15]

NEUROPROTECTION AGAINST NEUROPATHIC PAIN

Neuropathic pain (NP) afflicts millions of people worldwide and has been estimated to occur in as much as 7% of the population. The Neuroprotection against Neuropathic pain is been carried out by NMDA antagonists& Opioids.[16]

NMDA ANTAGONISM

The N-methyl-D-aspartate (NMDA) receptor assumes to play a major part in neuropathic pain and in opioid toleranceDevelopment. Dextromethorphan is a NMDA antagonist at high dosages. Tests in both animals as well as peoplehave built up that NMDA blocker, for example, ketamine and dextromethorphan can inhibit neuropathic pain as well as opioid tolerance. Unfortunately, just a few of NMDA blocker are clinically available and their utilization is restricted because of short half-life (dextromethorphan), weak activity (memantine) or unsuitable reactions (ketamine).[12]

OPIOIDS

Opioids are not the first-line medications for neuropathic pain. A few opioids, especially methadone and ketobemidone, have NMDA blocking effect but not inhibiting their μ-opioid agonist properties. Methadone, it is a racemic mixture; just the L-isomer is an intense μ-opioid agonist. The D-isomer does not have opioid agonist activity but have NMDA blocking effect; D-methadone is pain relieving. Clinical investigations are in advance to test the viability of d-methadone in neuropathic pain disorders.[12]

CONCLUSION

Excitotoxicity may lead to motor diseases like Parkinson Disease,& also non motor disorder like Neuropathic pain Neuroprotection against Neuropathic pain is achieved by NMDA antagonists & opioids. Excess Stimulation of Glutamate receptors i.e. NMDA receptor by Excitatory Neurotransmitter leading to number of deleterious consequences, such as impairment in Calcium efflux, Free radicals production, Dysfunctioning of Mitochondria and Secondary Excitotoxicity. With the study of this review, now, we conclude that Neuroprotection against Excitotoxicity can be achieved by various neuroprotectors like NMDA antagonist, GABA agonists, AMPA antagonists, By reducing intracellular Ca^{2+} mobilization, Inhibitors of the pathways of NO modulation, Free radical scavengers, Sodium channel blocker, Glutamate release inhibitors, Growth factors, Acidosis, Hypothermia Potassium channel activators.

AUTHOR CONTRIBUTION STATEMENT

The author Mrs. Rachana D. Sarawade provided author Vikas Vasant Pawar the title and gaven guidance about the contents of the review article. The author Vikas Vasant Pawar obtained the data, analyzed the data & compiled the data in proper manner & Computed the data as per journals Instructions. The author Mrs. Rachana D. Sarawade supervised the author Vikas Vasant Pawar's computed data with Plagiarism & Technical check.

CONFLICT OF INTEREST

Conflict of interest declared none.

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