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PATHOPHYSIOLOGY OF EPILEPTOGENESIS: A COMPREHENSIVE REVIEW

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Abstract
There are several neurological disorders that can cause recurrent seizures. Epilepsy is one of them, and is characterized by a persistent predisposition to seizures caused by abnormal neuronal activity in the brain. The relative imbalance between excitatory and inhibitory neurotransmitters may result in epileptic seizures. Pathogenesis of epilepsy can be influenced by changes in the expression of receptors and ion channels regulated by neurotransmitters. A neurotransmitter metabolism error affects the synthesis, breakdown, transport or the cofactors of neurotransmitters. The impairment of neuronal receptors, intracellular signaling, vesicle release, or other synaptic abnormalities can also cause neurotransmitter dysfunction. The main clinical hallmark of some diseases is epilepsy. The purpose of this comprehensive review is to describe the epileptogenic mechanisms as well as the implications arising from mutations in neurotransmitter-mediated receptors and ion channels in epilepsy.

Keywords: Epileptogenesis, Epilepsy, Neurotransmitters, Pathophysiology, Signaling

INTRODUCTION

Epilepsy is a neurological disorder caused by the repeated occurrence of seizures resulting from recurrent, spontaneous, and abnormal electrical discharge from a group of neurons in the brain (Vezzani et al., 2008). The term “epilepsy” is derived from the Greek word “epilambanein”, which means “to seize upon” or “to attack” (Patel et al., 2019). In Ayurveda, epilepsy is defined as Apasmara: APA, meaning negation or loss of; smara, meaning recollection or consciousness (Brennan et al., 2018). The estimated population with epilepsy is between 4-10 per 1000 people. However, in low and middle-income countries this proportion is much higher, between 7 and 14 per 1000 people. Each year, approximately 2.4 million people are globally diagnosed with epilepsy (Lang et al., 2022; Beghi et al., 2023). With a conservative estimate of 1% prevalence of epilepsy, there are more than 12 million persons with epilepsy in India, which contributes to nearly one-sixth of the global burden (Chaunsali et al., 2020). Epilepsy belongs to a group of chronic disorders characterized by the periodic or transistor bursting of excessive electric discharge produced by sudden and recurrent

events of seizures. Seizures are proximal events of abnormal discharge of NTs (Victor et al., 2020). Both seizures and epilepsy are interchangeable. Epilepsy has been diagnosed after two unproved seizures occurring in twenty-four hours. Seizures had classified according to incidence, characteristics, and clinical signs (Moore et al., 2021). seizures had divided into two broad classes of 'partial' and 'generalized' seizures. A recent classification of seizures proposed by the International League Against Epilepsy (ILAE) in 2017 based on clinical manifestations is characterized into three groups: seizures, epilepsies, and epileptic syndrome but the old system is still running due to some limitations and facing some high criticism. Different type of seizures demonstrates different symptoms, and it also varies from person to person (Sharma et al., 2019).

Based on the meta-analysis of GBD, the prevalence rate was slightly higher (50 million) in 1990 than in 2016. Focal Seizures (Partial Seizures) are very prevalent as compared to generalized seizures (Lang et al., 2022). The age-standardized prevalence rate increased by 13.6% from 1990 to 2017. The incidence rate of epilepsy was 61.4 per 1,00,000 per year. Globally the mortality rate of epilepsy was 125000. India has an extensive burden of epilepsy because about 10-12 million people live with epilepsy, and 3 million population suffer from drug-resistant epilepsy. A large number of cases of epilepsy in India are due to developmental delay. The mortality rate is 5 to 10 times greater than the general population (Begley et al., 2022).

Epilepsy affects the different parts of the brain by hyperexcitation and hyper synchronization of brain cells that why epilepsy is called a brain disorder (Gasparini et al., 2019; Fukuyama et al., 2020). Epileptic seizures are appearing in the cortical and subcortical parts of the brain (Engelborghs et al., 2000). In a normal brain, excitatory synaptic activity is tightly regulating the inhibitory activity of the neurons. Some specific mechanisms are responsible for the production of seizures. Epilepsy arises due to the sudden imbalance and shifting of excitatory and inhibitory signaling of the neurons in the brain, as show in fig 1 (Falco-Walter et al., 2020). Due to this modulation in excitatory and inhibitory NTs causes an increase in the Na^+ or Ca^{2+} influx and a decrease in the Cl^- influx that produces depolarization of the neurons, increases the action potential of the neurons, or stimulates excessive neuronal firing in the brain (Falco-Walter et al., 2020; Fukuyama et al., 2020). Hyperexcitation of Cortical neurons is observed under certain conditions (trauma, TBI, viral infection, high fever, genetic mutation) (Russo et al., 1981). Understand some other pathways and factors which take part in the dysregulation of NTs and ion channels, as show in fig 2.

1. NEUROTRASMITTERS IN EPILEPTOGENESIS

Several NTs are present in the brain that plays a very crucial role in physical, genetic, behavioral, and psychological development. Deregulation of NTs causes several diseases from them one is epilepsy (Dhaher et al., 2021). Loss of NTs causes hypersynchronisation of neurons and these neurons can produce GS and PS. Abnormal discharge of NTs produce sign and symptoms with alternation in motor function, sensation, autonomic functions, behavioral functions, and consciousness (Mastrangelo et al., 2021; Sarikaya et al., 2015). Some NTs are involved in the production of excitation. On the other hand, some NTs act as inhibitory NTs, as show in fig 3 (Arafa et al., 2013).

1) GABA

GABAareceptor act as an antagonist in epilepsy (Palma et al., 2017). Seizures are generated when the inhibitory GABAnergic action decreases. Convulsive and epileptic agents block GABA mediatory inhibition. Repetitive activation of cortical neurons can reduce the inhibitory postsynaptic potential of neurons that decreases the release of GABAergic action (Jacob et al., 2016; Wasterlain et al., 1993). During hypoxia and ischemia, GABA receptors coupled with their agonist produce alteration in ionic gradient, prolong the opening of the Cl^- channel, or increase the conductance of Cl^- ion in the neurons due to accumulation of C^{l-} in the brain cell. Increased concentration of Cl^- affects the redistribution of Cl^- and K^+ transport (Mathern et al., 1999). A low level of GABA and GAD (Glutamic acid decarboxylase) is observed in epilepsy. Epilepsy and epilepsy-associated disease decrease the 3H receptor and BDZ receptors binding site which causes an increase in the frequency of seizures. A low concentration of GABA in CSF is increasing the episodes of seizures

(Sgadòet a., 2011). Several endogenous and exogenous substances are involved in the inhibition of GABAergic transmission via make interaction with GABA receptors or inhibition of GABA synthesis (Sarnat et al., 2021).

2) Glutamate

Glutamate receptors act as an agonist and can elicit seizures in the normal brain (Sandhu et al., 2021). Glutamate consists of two types of receptors 1) Ionotropic receptor (iGluR) and 2) Metabotropic receptors [G- protein-coupled receptor (mGluR) (Chiprés-Tinajero et al., 2021). Overexpression of iGluR and mGluR increases the Ca^{2+} influx into the neuronal membrane and increases the excitation of a neuronal membrane (Kovalenko et al., 2022; Sandhu et al., 2021). Metabotropic receptors (GPCR) are also involved in the production of neuronal excitation via the regulation of secondary messenger cAMP and modulate the activity of synapsis (Sarlo et al., 2021). NMDAR is a subtype ionotropic receptor of glutamate. It plays a crucial role in the development and generation of neuronal excitability in CNS. NMDARs can induce seizures and selective exocytotic cell death of hippocampal neuronal cells. NMDA may release Ca^{2+} from ER (endoplasmic reticulum) via activates of the mGluR that increase the level of Na^{+} and Ca^{2+}. It is able to prolong the opening of the Ca^{2+} channel that cause increase in the release of glutamate (Kovalenko et al., 2021; Sarlo et al., 2021).

a) Inotropic receptor

Neuronal activity increases the release of glutamate in the synapses. NMDA receptors become activated when glutamate is coupled with the NMDA receptors. Activated NMDA receptors increase the Ca^{2+} influx in the synapsis that causes the activation of CaMKII and calcineurin (Akyuz et al., 2021; Needs et al., 2019). Activated CaMKII stimulates the endocytosis of a subtype of AMPA receptor (GluR1) that produced long-term potential excitation of synapsis. Activated calcineurin bind with β 2/3 or γ2 subunit of GABAA receptors that promote the endocytosis of GABAA receptors and decrease the GABA-mediated inhibition in the synapsis that involve the reduction of expression and function of Chloride potassium symporter 5 (KCC2) (Rossi et al., 2022; Sears et al., 2021). Overexpression of KCC2 modulates the equilibrium of Cl^{-} potential. Overexpression of NMDA receptors in the synapsis increases the influx of Ca^{2+} that causes the deregulation of CaMKII activity and causes epileptogenesis, as show in fig 4 (Kovalenko et al., 2022; Needs et al., 2019).

b) Metabotropic receptor

Activation of specific group I mGluR promote the epileptogenesis in CA3 pyramidal cell. Group 1 GluR agonist activates the mGluR1/5 (a subtype of group I mGluR) (Cingolani et al., 2019) in the CA3 pyramidal cell of the hippocampus. Activated mGluR1/5 promotes the dissociation of heterotrimeric G protein in Gα and Gβγ, or activation of Src and ERK1/2 MAPK (Cingolani et al., 2019; Wong et al., 2002) Dissociated Gα activates the PLCβ (Phospholipase C-β) that involve in the hydrolysis of PIP_2 into IP_3 and DAG. IP_3 increases the release of Ca^{2+} from ER and DAG increases the activity of PKC (Protein Kinase C). Dissociated Gβγ promotes the reduction of K^{+} conductance and increases the voltage dependent intrinsic neuronal activity, as show in fig 2 (Kłodzińska et al., 1999; Qian et al., 2016).

2. ASTROGILOSIS IN EPILEPTOGENESIS

TBI is the most common cause of epilepsy because the injured area has recovered by reactive astrogliosis. About 14-20% of patients with TBI have a chance to develop epilepsy (Golub et al., 2020). It is a star-shaped glial cell that consists of 30% part of the CNS and provides metabolic and physical support to the neurons. It is found nearly to the synapsis and works as an NTs, transporter, receptor, and ion channel (Song et al., 2022). As we know, astrogliosis regulates the development, plasticity, and hyperexcitability of the neurons, and it also controls the release of NTs. It converted into reactive astrogliosis after the morphological and genetic changes. Some studies demonstrate that alternation in morphology and genetic pattern can cause epilepsy (Song et al., 2020; Yang et al., 2021). Astrocyte proliferation increases after injury because a shield of the scar has formed around

the injured area. The glial scar seals the injured area and protects the healthy area of the brain from damage by preventing the influx of harmful substances (Fukuyama et al., 2022). TBI produces cerebral ischemia after the scar formation that increases the production and accumulation of lactic acid in the brain causing modulation and elevation of excitatory ions and NTs (Verhoog et al., 2020; Sano et al., 2021).

Modulation of NTs increases the glutamate level in the brain and increases the production of ROS species (Sandhu et al., 2021). Overstimulation of glutamate levels causes an increased extracellular NMDA-mediated Ca^{2+} level. Elevated Ca^{2+} concentration in the brain causes hyperexcitability and develops a seizure, as show in fig 2. The proliferation of astrocytes also plays a crucial role in the generation of inflammation. Astrocytes elevate the liberation of inflammatory mediators such as TNF-α and IL-1β that activate the NMDA receptors that enhance NMDA and induce Ca^{2+} influx. Excessive Ca^{2+} influx involves the production of ROS that cause hyperexcitability of neurons that produce episodes of epilepsy (Fukuyama et al., 2022; Verhoog et al., 2020).

3. CYTOKINES IN EPILEPTOGENESIS

Cytokines are prototypic inflammatory mediators. It consists of TNF-α, IL-1β, IL-6, NFKβ, chemokines, an acute-phase protein, and a complementary system. It produces neurotoxicity via autocrine and paracrine transporter mechanisms. Epileptic patients have a high level of cytokines in serum and CSF (Soltani et al., 2022; Vishwakarma et al., 2022).

Interleukine-1 consist three ligands such as: IL-1α, IL-1β and IL-1Ra. The level of IL-1 is low in the CNS. In certain pathological conditions, the level of IL-1 has elevated. IL-1β is responsible for ROS generation and takes part in excitability (Yazdanpanah et al., 2022). Cytokines IL-1β are located on hippocampal pyramidal neurons along with NMDA receptors. IL-1β activates the sphingomyelinase and Src kinase in the hippocampus and, they provoke phosphorylation of the NR2B subunit of the NMDA receptor that produces NMDA-mediated Ca^{2+} influx that causes hyperexcitability (Vishwakarma et al., 2022; Numis et al., 2019). IL-1β inhibits the glutamate reuptake that increases the glial release via TNF-α production. TNF-α is (a tumor necrosis factor) present in the hippocampus, and it works as a dichromate. It activates the p55 and p75 receptors (Chen et al., 2023). TNF-α modulates the chemical balance of the AMPA receptor on synapsis that increases the excitability through the interaction of the p55 receptor that activates the apoptosis signal-regulating kinase-1 is a key event in the death of neurons and also prevents GLuR2 subunit at the neuronal membrane that produces Ca^{2+} influx into the neurons that causes hyperexcitability (Soltani et al., 2022). TNF-α increases extracellular glutamate levels, and it also increases the glutamate release via activation of NO synthetase in astrocytes that produces hyperexcitability. It also activates the IL-1R1 which may trigger the NF-kB. NF-kB directly takes part in the production of Pro IL-6 (that stimulates the IL-6) and NO (Atabakin et al., 2023; Aulická et al., 2022; Meng et al., 2020).

IL-6 receptor complex consists of a unit of IL-6R and two molecules of gp130 (glycoprotein130) transmembrane protein found in all classes of cytokines receptors. When IL-6 is expressed in the brain acts as an agonist of glutamate and drops the concentration of GABA that leads to a decrease in the GABA-mediated inhibition and causing depolarization of neurons (Castañeda et al., 2020; Korotkov et al., 2020).HMGB1 (high-mobility group box-1) is release signals in dangerous conditions like injury or stress. HMGB1 activates several kinases (MAPK, PKA, PKC) that alter voltage-dependent K^+, Na^+, and Ca^{2+} channels rapidly and produce neuronal excitability in dangerous conditions (Castañeda et al., 2020).

a) NEUROPEPTIDES IN EPILEPTOGENESIS

It consists of two types of receptors P1 and P2. Out of them, P2 takes part in epileptogenesis. P2 receptors are further subdivided into P2X and P2Y. The subclass of P2X is P2X7 that express in neurons and glial cells of the brain. P2X7 is an ATP-gated non-selective cation permeable ionotropic receptor (Tekgul et al., 2020). When ATP converts into ADP activates the P2X7 receptor. This is a key event in the stimulation of microglia, modulates neuronal excitability in the hippocampus, and produces a neuroinflammatory response (Tekgul et al., 2020; Cui et al., 2019). These events elevate

the damage in the brain and generate excitability of neurons or alter the ion channels. On the other side, P2Y receptor subclasses bind to the different G-protein coupled receptors and exert their action. P2Y1,2,4,6,11 receptors bind with Gq/G11 receptors that activate the phospholipase C and IP3 activity and increase the Ca influx into the cell. P2Y12,13,14 receptors coupled with Gi/o inhibit adenylcyclase and modulate the ion channel. Adenylcyclase activates the cyclic AMP that produces neuronal excitability (Santos et al., 2023; Wang et al., 2021; Yeo et al., 2022).

b) REACTIVE OXYGEN SPECIES (ROS) IN EPILEPTOGENESIS

Naturally, oxygen is present in divalent forms (unreactive form) and univalent forms (reactive form). The univalent oxygen species has generated from the atoms or groups of atoms that have a tendency to accept electrons and consist of unpaired electrons. This univalent species is known as reactive oxygen species (ROS) (Godinho et al., 2021). The single oxygen species, superoxide, hydroxyl ion, free radicals, or hydrogen peroxide, all are ROS. The brain is the hub of the generation of ROS (Terrone et al., 2020; Devi et al., 2008). ROS generated from the non-enzymatic process (UV irradiation) as well as the enzymatic process (ROS generated in the cell due to modulation in enzyme activity). The frequency of ROS production has to depend on the presence or availability of oxygen and the number of ROS-producing enzymes in the tissue. ROS generated by NOX (NADPH oxidase), NADPH, mitochondria, xanthine oxidase, and lipoxygenaseas show in fig 4 (Terrone et al., 2019; Walker et al., 2023; Xu et al., 2022).

The brain generates ROS in a resting state, and the production of ROS has increased along with the activity of the brain. Generally, ROS generated when the imbalance between free radicals and antioxidants has occurred (Godinho et al., 2021; Walker et al., 2023).The mechanism of ROS production has started when the Ca^{2+} and Na^{+} enter via NMDA receptors into the cell. Several disease conditions may enhance the level of Ca^{2+} and Na^{+} in the cell which causes it to convert NADPH to $NADP^{+}$ by activation of NOX. $NADP^{+}$ takes part in the production of ROS (PATEL et al., 2022).
Both ROS and $NADP^{+}$ covert NO (nitric acid) into the reactive form $OONO^{-}$ (peroxynitrite) and $OONO^{-}$ causing the damage of DNA, inactivation of the enzyme, and lipid peroxidation (Frantseva et al., 2000). Excessive efflux of Ca^{2+} in the cell with ROS causes the depolarization of the mitochondrial membrane via activation of DNA repair enzymes [Poly ADP ribose (PAR), PAR polymerase (PARP)] that decrease the level of NADPH which results from the decrease in the production of ATP (Devi et al., 2008, Puttacharyet al, 2015). The deficiency of ATP produces energy failure and imbalances the cellular ionic gradients. ROS production and accumulation of Ca^{2+} ion into the mitochondria result from the formation of mitochondrial permeability transition pore (mPTP) that disturb the function of mitochondria and permit the movement of cytochrome C into the cytosol that causes cell death (apoptosis) (Frantseva et al., 2000; Roma-Mateo et al., 2015). In mitochondria complex, I and complex III are the primary sites for the production of ROS. They produce ROS by electron leak mechanism from ETC (electron transport chain). ROS decreases the production of ATP by inhibiting complex I, which causes a decrease in the membrane potential of mitochondria and a decrease in the production of ATP (Puttacharyet al, 2015). Complex III is mainly involved in the production of superoxide ion and directly contribute to the production of ROS (Geronzi et al., 2018; Méndez-Armenta et al., 2014).

CONCLUSION

Epileptogenic changes in the brain are caused by inflammation and increased neurogenic activity post-seizure. The contribution of microglia to this process needs to be better understood in order to control it. This balance is largely mediated by glutamate and gamma-aminobutyric acid (GABA); abnormal changes in these molecules may result in irreversible neuronal damage. Neurotransmitter systems and ion channels play a crucial role in neuronal excitability. This will contribute to the development of still more specific and efficient therapeutic interactions in the area of clinical neurology by understanding epilepsy pathophysiology and epileptogenesis.

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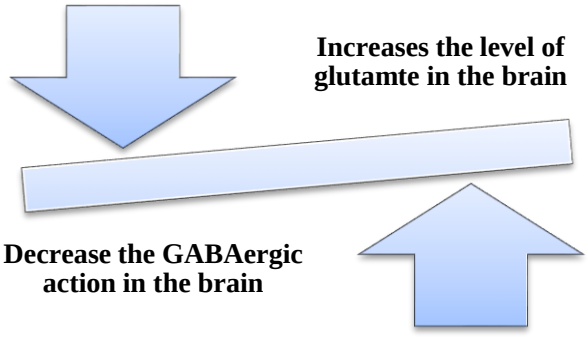

Fig 1 Imbalance of GABA inhibitory and glutamate excitatory NTs in the neurons

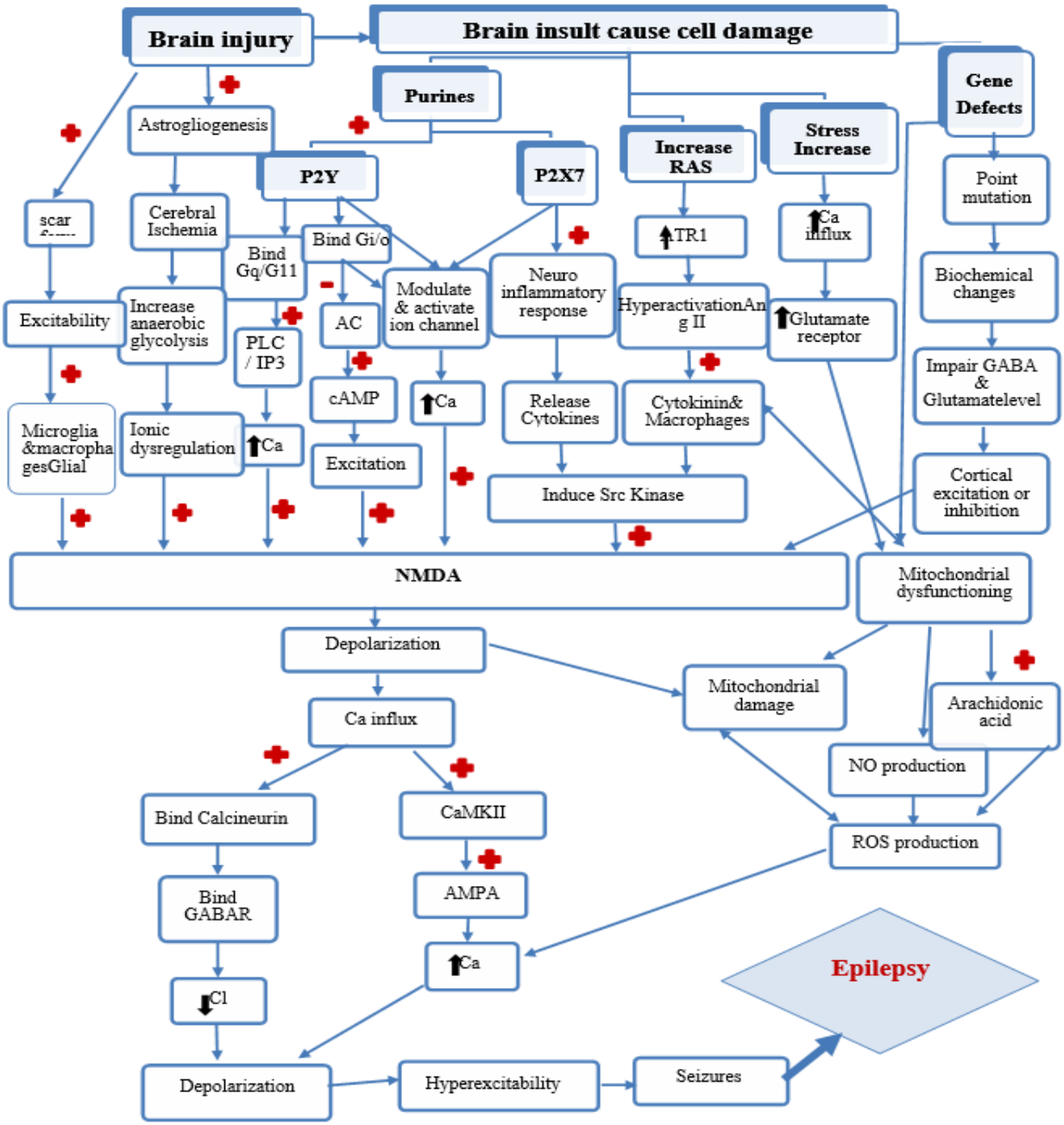

Fig 2Pathophysiology in epileptogenesis

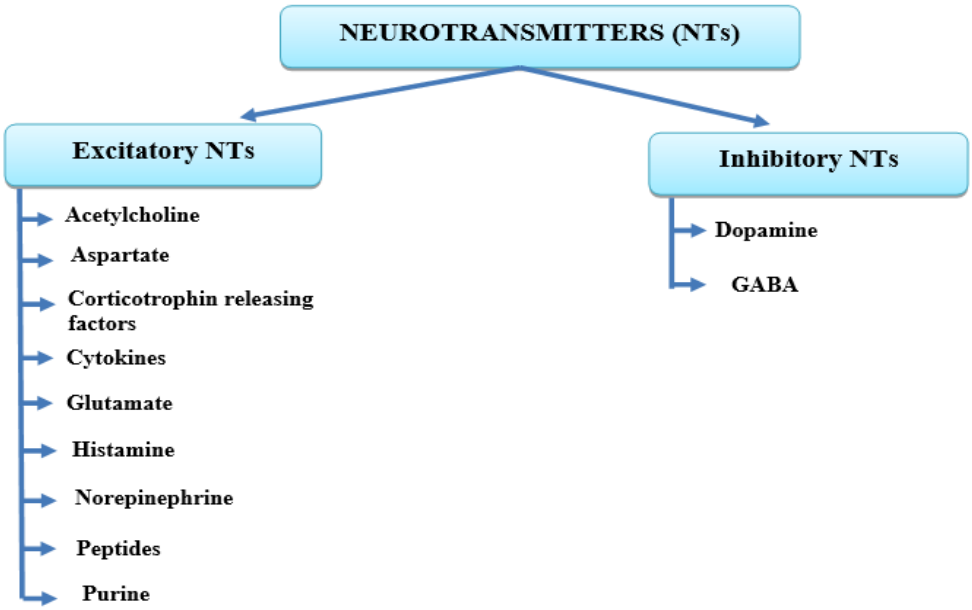

Fig 3 Type's of excitatory and inhibitory NTs involved in epileptogenesis

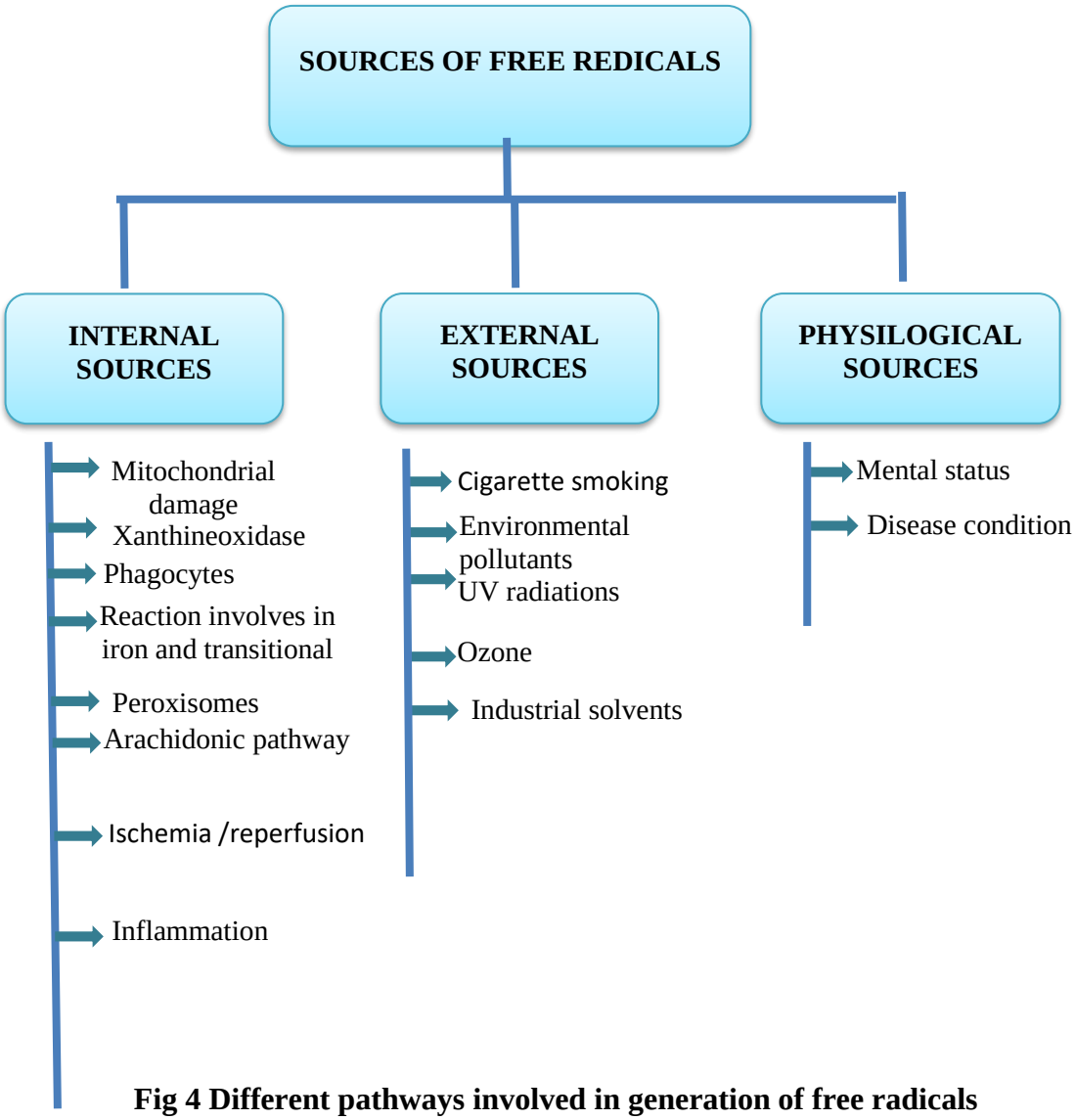

Fig 4 Different pathways involved in generation of free radicals