Elucidating the Dopaminergic Neurotoxicity of Kainic acid

By

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A thesis submitted to the Graduate Faculty of
Auburn University
in partial fulfillment of the
requirements for the Degree of
Master of Science

Auburn, Alabama
December 12, 2020

Keywords: Kainic acid, oxidative stress, N27, M17 cells,
excitotoxicity, neurotoxicity

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Abstract

Dopamine is an essential catecholamine neurotransmitter in the central and peripheral nervous system. This monoaminergic neurotransmitters is required for the maintenance of several physiological functions (control of movement, mental functions (mood and decision making), prolactin secretion, emesis, appetite, cardiovascular system (heart/blood vessel), gastrointestinal tract motility, sexual function, and diuresis). Degeneration of dopaminergic neurons in the central and peripheral nervous system arises due to several highly complicated neurotoxic mechanisms and pathways. Among the various neurotoxic mechanisms, excitotoxicity has a great impact on the survival of the dopaminergic neurons. Most of the present neurotoxins primarily target tyrosine hydroxylase (rate limiting step) to exert its dopaminergic neurotoxicity. Since dopaminergic neurotoxicity is a complex endeavor, it will be appropriate to have a neurotoxin with multiple pharmacodynamic effects. Interestingly, kainic acid is an accepted and established excitatory neurotoxin which exerts its effect by binding to kainate (glutamate) receptor to enhance excessive calcium influx, increase proxidant generation, induce mitochondrial dysfunction and apoptosis or necrosis which triggers neurodegeneration leading to neuronal death. Currently, the neurotoxic potency of kainic acid as compared to the well-known dopaminergic neurotoxins are not clearly elucidated. Hence, this study compared the dopaminergic neurotoxicity of kainic acid with various endogenous and exogenous neurotoxins using valid *in vitro* dopaminergic neuronal models. Our finding clearly indicates that as compared to the existing valid and scientifically accepted dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP^+), kainic acid has significantly less dopaminergic neurotoxicity. Consequently, kainic acid can be used as an adjuvant to enhance the dopaminergic neurotoxicity. Further *in vivo* studies will be done in the future to investigate the potentiating / synergistic role of kainic acid on dopaminergic neurotoxicity.

Acknowledgment

I would say thank you to my mentor Dr. Muralikrishnan Dhanasekaran for his patience and support to teach me and guide me academically to be productive and professional. I would not forget the effort that Dr. Mohammed Majrashi put on me to lead the lab before he left to complete his academic journey in his country. Thank you to all my lab members Mohammed Almaghrabi, Aishah Harshan, and Sindhu Ramesh for guiding me and teaching me about the lab techniques. Moreover, I would say thank you to my committee members, Dr. Randall Clark, Dr. Jack Deruiter, and Dr. Timothy Moore to motivate me and give me the opportunity to show my project in front of them. Finally, I would say thank you to my father who supported me financially to study in the USA and stayed with me during the whole academic life.

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List of Abbreviations

AADC Aromatic L-Amino Acid Decarboxylase

AC Adenyl Cyclase

ADHD Attention Deficit Hyperactivity Disorder

ADP Adenosine diphosphate

AEDs Anti-epileptic Drugs

AMPA α-Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid

BALB/c Albino Laboratory-Bred Strain

BBB Blood Brain Barrier

BH_4 Tetrahydrobiopterin

BSA Bovine Serum Albumin

Ca^{++} Calcium

cAMP Cyclic Adenosine Monophosphate

cGMP Guanosine 3',5'-Cyclic Monophosphate

CNS Central Nervous System

CSF Cerebrospinal Fluid

CTZ Chemoreceptor Trigger Zone

CYP3A Cytochrome P4503A

D_1 Dopamine 1 Receptor

D_2 Dopamine 2 Receptor

D_3 Dopamine 3 Receptor

D_4 Dopamine 4 Receptor

D_5 Dopamine 5 Receptor

DA Dopamine

DAC Diacylglycerol

DARPP-32 Dopamine Regulated Neuronal Phosphoprotein

DATs Dopamine Transporters

DBH Dopamine Beta Hydroxylase

DMEM Dulbecco's Modified Eagle Medium

DMSO Dimethylsulfoxide

DOPAC 3,4-Dihydroxyphenyl acetic acid

EEG Electroencephalogram

ERK ½ Extracellular Regulated Kinase

FBS Fetal Bovine Serum

FSH Follicle-Stimulating Hormone

GABA Gamma-Aminobutyric Acid

GADPH Glyceraldehyde 3-phosphate dehydrogenase

GEPRs Genetically Epilepsy Prone Rats

Glut Glutamate

GSH Glutathione

GSK3 Glycogen Synthase Kinase 3

HB Hydrogen Bounding

5-HIAA 5-Hydroxyindol Acetic Acid

H_2O_2 Hydrogen Peroxide

5-HT 5-Hydroxytryptamine (serotonin)

5-HTP 5-Hydroxytryptophan

HVA Homovanillic Acid

ILAE International League Against Epilepsy

IP_3 Inositol Triphosphate

IP Intraperitoneal

KA Kainic Acid

L-Dopa L-3,4-Dihydroxyphenylalanine

LH Luteinizing Hormone

MAO Monoamine Oxidase

MAPK Mitogen Activated Protein Kinase

MDA Malondialdehyde

MES Maximal Electroshock Seizure

MHPG 3-Methoxy-4-Hydroxyphenylglycol

MPP^+ 1-Methyl-4-Phenylpyridinium

MRI Magnetic Resonance Image

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

mRNA Messenger Ribonucleic Acid

MTLE Mesial Temporal Lope Epilepsy

3-MT 3-Methoxy Tyramine

NADH Nicotinamide Adenine Dinucleotide

NDRIs Norepinephrine Dopamine Reuptake Inhibitors

NE Norepinephrine

NETs Norepinephrine Transporters

NF-κB Nuclear Factor KappaB

NMDA N-Methyl-D-Aspartate

NMS Neuroleptic Malignant Syndrome

PBS Phosphate Buffer Saline

PD Parkinson Disease

PH Power of Hydrogen

PI3K Phosphatidylinositol-3 kinase

PKA Protein Kinase A

PKC Protein Kinase C

PLC Phospholipase C

PNS Peripheral Nervous System

PP1 Protein Phosphatase-1

PP2A Protein Phosphatase 2A

ROS Reactive Oxygen Species

SERTs Serotonin Transporters

SSRIs Selective Serotonin Reuptake Inhibitors

SUDEP Sudden Unexpected Death in Epilepsy

TBA Thiobarbituric Acid

TBARS Thiobarbituric Acid-Reactive Substances

TBST Tris Buffered Saline with Tween.

TCA Trichloroacetic Acid

TCI Tokyo Chemical Industry

TH Tyrosine Hydroxylase

TLE Temporal Lope Epilepsy

TPH Tryptophan Hydroxylase

Vit.B_6 Vitamine B_6

VMAT Vesicular Monoamine Transporter

1. Introduction

Neurotoxins are chemical compounds that cause destruction of the neurons/nerves in the central and peripheral nervous system. The neurotoxins can be classified into endogenous and exogenous neurotoxins. Examples of endogenous neurotoxins are glutamate, hydrogen peroxide, and nitric oxide. The exogenous neurotoxins include pesticides, insecticides, substances of abuse and various drugs. Dopaminergic neurotoxicity occurs due to insult of dopaminergic neurons in in the central and peripheral nervous system. The specific dopaminergic neurotoxins are 6-hydroxy dopamine, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone, and paraquat (J. Bove, Prou, Perier, & Przedborski, 2005). Investigating the effect of various toxins on dopaminergic neurons have significantly improved the understanding of the mechanisms and pathways affecting dopaminergic neurotransmission. Dopaminergic toxins exhibit their neurotoxicological effects by modulating various signaling mechanisms leading to reduced dopaminergic neuronal functions or neurodegeneration and eventually leading to death. MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) is a well-known neurotoxin and exerts its dopaminergic neurotoxicity due to its active metabolite, MPP^+ (1-methyl-4-phenylpyridinium). The conversion to the toxic metabolite (MPP^+) occurs by monoamine oxidase-B.

The common neurotoxic mechanisms include oxidative stress, mitochondrial dysfunction, apoptosis (programmed cell death), and excitotoxicity. Excitotoxicity is a neurological term used when the neurons/nerves are damaged because they were overactivated / excessively excited by glutamate. Glutamate exerts its action by acting on N-methyl-d-aspartate acid (NMDA), α-amino-3-hydroxy-5-methylisoxazole propionic acid (AMPA), or kainate receptors. Excitotoxicity occurs due to high calcium influx, generation of free radicals, reduced production of ATP, and increased caspase activity leading to DNA degradation. Excitotoxicity

can be caused by an imbalance between the inhibitory and excitatory neurotransmitters. Kainic acid is an established neurotoxin that binds to kainate receptors and has been mainly used to investigate the pathophysiology of seizures/epilepsy and exploring new/novel anti-epileptic effects of various compounds. Since excitotoxicity plays an important role in the etiology and pathogenesis of several movement, memory, and mental neurodegenerative / neurological disorders, it is essential to understand the role of kainate based excitatory neurotoxins effect on dopaminergic neuronal function.

Currently, the kainate receptor mediated dopaminergic toxicity is not well established. Therefore, in the current study, the comparative dopaminergic neurotoxic effects of kainic acid and 1-methyl-4-phenylpyridinium (MPP^+) was investigated. By undertaking this study, we can validate dopaminergic neurotoxic effects of kainate. Thus, to compare the dopaminergic neurotoxic effect of kainic acid, we used valid positive controls, such as glutamate, and MPP^+. The current study used accepted dopaminergic mammalian neuroblastoma cells, human M17 neuronal cells and rat dopaminergic N27 neuronal cells. M17 human neuronal cells and rat dopaminergic N27 neuronal cells expresses high level of tyrosine hydroxylase activity and other markers of oxidative stress, apoptosis, mitochondrial function, inflammation, and excitotoxicity.

Hypothesis:

Kainic acid bind to kainate receptors to induce oxidative stress(increase in pro-oxidants and lipid peroxide content), mitochondrial dysfunction (decrease in NADH content and depletion of ATP), apoptosis (increase in caspase 3 activity), and inflammation (increase in interleukin-1 activity) and/or kainic acid can cross the neuronal membrane to bind to tyrosine hydroxylase enzyme to reduce its expression or activity to cause dopaminergic neurotoxicity.

2. literature review

2.1 (a) Introduction to epilepsy

Epilepsy is a neurological disease in which the electrical activity of brain is being disrupted. Epilepsy is defined as an unprovoked seizures separated by more than one day (Fisher et al., 2005). The global as well as national burden of epilepsy is increasing. In the United States, 39 in 1000 people have developed epilepsy in their lifetime and about three millions have been diagnosed with epilepsy (I. o. M. Epilepsy, 2019). Globally, more than 60 million people are diagnosed with epilepsy (Baulac et al., 2015). Epilepsy affects all age groups and has similar prevalence among different socioeconomic and racial cohorts. However, its incidence is higher in pediatric and geriatric groups. It has been estimated that 75% of epilepsy cases affect children (Stafstrom & Carmant, 2015). It has also been reported that the entire direct cost for each patient affected with epilepsy is from $10,192 to $47,862 (Begley & Durgin, 2015). The life expectancy of epileptic patient is 10 years less than the normal peers (Gaitatzis, Johnson, Chadwick, Shorvon, & Sander, 2004).

Epilepsy is classified, according to the affected region, into a “focal” (partial) epilepsy in which affects a part of the brain hemisphere, or it could be “generalized” epilepsy in which affects the whole brain (Devinsky et al., 2018; Svob Strac et al., 2016). Epileptic seizures is categorized into generalized onset seizures that is categorized in to motor and non-motor seizures, focal onset seizure that is further classified in to aware or impaired awareness seizures and motor onset and non- motor onset seizures, and unknown seizures that is further classified in to motor and non-motor seizures. These categories of seizures are set by international league against epilepsy (ILAE) according to the different diagnostic characteristics that each seizure has (I. L. A. Epilepsy, 2019). There are different stages of seizures, beginning stage (prodrome

and aura), middle stage (ictal), and recovery stage (postictal). For the beginning stage (prodrome and aura) phases, they occur few seconds before the seizure starts, they warn the patient that the seizure is about to happen when the patients feels few symptoms depending on the seizure type he/she has. Middle stage (Ictal) phase when the actual seizure starts, and the electrical disturbance of the brain is continuing. Recovery stage (postictal) when the seizure is about to end, and the body starts to relax (Foundation, 2020).

Epilepsy is a disease that is triggered by certain factors called risk factors, such as inflammation, cerebral hemorrhage, and viral or bacterial infection in the brain. Epilepsy can be caused by external or internal factors. Head trauma including prenatal injury, brain tumors, brain infections, that could be viral or bacterial that alter the patient's neurological functions, are examples of external factors. While the internal factors include aging, gene mutation (SCN1A mutation), metabolic disorders (facilitated glucose transporter member 1 (GLUT1) deficiency), and autoimmune diseases like autoimmune encephalitis (Devinsky et al., 2018; Scheffer et al., 2017). Also, some of the cases have no specific cause. Abnormalities in ion channels conductance, such as blocking of sodium- potassium ATPase, imbalance between the inhibitory and excitatory neurotransmitters, disruption of the genes that regulate neurotransmitters functions, alterations in neuronal plasticity, electrolyte disturbance, and activation of NMDA receptor all induce epileptogenesis (Huff & Murr, 2020; J. Kapur, 2018; Scharfman, 2007; Svob Strac et al., 2016).

Epilepsy has wide range of symptoms and signs which depends on the type of epilepsy. The severity is more prominent in the generalized seizure. These range from no alteration in the consciousness to memory loss for the events of the attack. Furthermore, movement, controlling

voluntary as well as involuntary muscles are lost. Jerking, collapsing, and body stiffening are common in the generalized type (Mayo Foundation for Medical Education and Research, 2019b).

As other neurological disorders, the diagnosis of epilepsy is difficult because most of the attacks take place out of healthcare institutions as well as the witness of healthcare providers. However, several approaches are using to identify epilepsy like investigating patient's medical history, electroencephalogram (EEG), and neuroimaging (magnetic resonance image (MRI)). The early and accurate diagnosis is crucial in order to identify the appropriate treatment modality which can be reflected as improvement in patient's quality of life (Scheffer et al., 2017). Additional diagnostic tests can be performed to identify the epilepsy type and cause, such as positron emission tomography, single photon emission computed tomography, and magneto encephalogram (Hae Won Shin*, 2014).

Several treatment strategies are present to manage epilepsy. The corner stone of the current therapy is medications or called "anti-epileptic drugs" (AEDs). These drugs work by controlling the electrical activity in the brain that causes seizure. AEDs control more than two-thirds of epilepsy cases and usually the patients stop using them because they become seizure-free. More than one drug is usually added and replacing one by another is a common approach. Ketogenic diet, low-carbohydrate and high-fat diet is an option for children and adults who their epilepsy is not controlled by AEDs. Vagus nerve stimulation, surgery, and deep brain stimulation are also another treatment modalities but their use is limited to specific cases (Society, 2019).

Several hypotheses have been proposed to identify the physiological as well as the pathological changes associated with epilepsy. However, most of them are controversial because the diagnosis of epilepsy is complex. Monoamine neurotransmitters, such as serotonin, dopamine, and norepinephrine are bioactive substances that are characterized by an amino group connected to an aromatic ring and two carbon chain in their chemical structure. They control numerous body functions. Serotonin regulates mood and behavior, dopamine modulates movement activity, while noradrenaline controls cardiovascular functions and mental functions. It has been reported that monoamines play a major role in regulating epileptic seizures. At high concentration, they could evoke epilepsy and within certain concentration, they have a protective effect against epileptic seizures (Svob Strac et al., 2016). Association of psychological disorders, such as depression and anxiety with epilepsy support the role of monoamine in the epilepsy, at least in part, in the progression, complication and response to treatment. These influence patients' compliance to medications, sleep, and patients' quality of life. In some cases depression can be fatal in patients with epilepsy (Boylan et al., 2004; DiMatteo, Lepper, & Croghan, 2000; Helmstaedter et al., 2014; Shackleton, Kasteleijn-Nolst Trenite, de Craen, Vandenbroucke, & Westendorp, 2003). Epilepsy, depression and other neuropsychiatric abnormalities are caused by monoamines disturbance in the brain (Stafstrom & Carmant, 2015; Svob Strac et al., 2016). Here, this review aims to summaries the updates about the role of monoamines (serotonin, dopamine, and norepinephrine) in epilepsy, the pathophysiology, progression, complications, and response to treatment.

2.2 The role of serotonin in epilepsy

Serotonin is a monoamine neurotransmitter derived from the amino acid tryptophan. It is hydroxylated by tryptophan hydroxylase (TPH) which is the rate limiting enzyme in serotonin synthesis into 5-hydroxytryptophan (5-HTP) that is further decarboxylated by aromatic L-amino acid decarboxylase into serotonin or 5-hydroxytryptamine (5-HT). 5-HT is metabolized by monoamine oxidase into 5-hydroxyindol acetic acid (5-HIAA). Serotonin pathways project from raphe nuclei where the serotonin is synthesized to different parts of the brain, such as cortex, neostriatum, amygdala, substantia nigra, hippocampus, locus coeruleus, ventral tegmental area, hypothalamus (Merrill, 2017). Seven serotonergic receptors have been identified: 5-$HT_{1A, B, D, E, F}$; 5-$HT_{2A, B, C}$; 5-HT_3; 5-HT_4; 5-$HT_{5A, B}$; 5-HT_6; and 5-HT_7 (Reeves & Lummis, 2002). Serotonin can act as a hormone in the central nervous system and peripheral system to control mood, behavior, appetite, sleep, and sexual behavior (Mohammad-Zadeh, Moses, & Gwaltney-Brant, 2008). Serotonin has other functions that is linked to the peripheral system like platelet aggregation through the activation of 5-HT_2 receptors that is enhanced in the occurrence of thromboxane A and ADP (Cerrito, Lazzaro, Gaudio, Arminio, & Aloisi, 1993). It has been estimated that serotonin is associated with vasoconstriction in large arteries and veins contributed to hypertension. Moreover, serotonin has a prominent role in regulating gastrointestinal motility (Mohammad-Zadeh et al., 2008). All the serotonergic receptors are G proteins coupled receptors Gαi, Gαq/11, or Gαs except for 5-HT_3 which is a ligand gated ion channel (Sahu et al., 2018). Any alteration of serotonin levels in the brain is attributed to neurological disorders, such as depression, mania, and anxiety (Eric R. Kandel, 2011). It has been reported that serotonin plays a prominent role in controlling epilepsy. Coming to the essential amino acid tryptophan, the precursor of serotonin biosynthesis, it has been reported that low tryptophan dietary intake increases the susceptibility of convulsion in rats (Feria-Velasco et al., 2008). The serotonin synthesizing enzyme tryptophan hydroxylase (TPH)

expression has been reported to be decreased as well as serotonin transporters (SERTs) in sudden unexpected death in epilepsy (SUDEP) that is resulted in alteration of the serotonergic neurotransmission (Patodia et al., 2018). TPH expression has been reported to be significantly decreased in pilocarpine (cholinergic muscarinic agonist) induced seizure in rats (Lin et al., 2013). Regarding tryptophan hydroxylase (TPH) activity, 5- hydroxytryptophan, serotonin, and 5-HIAA levels, they have been reported to be decreased in a seizure model DBA/1 mice (Q. Chen et al., 2019). Aromatic L-amino acid decarboxylase has been revealed to be decreased in neonatal epileptic encephalopathy (Brautigam et al., 2002). Low levels of serotonin has been noted during seizures and epilepsy (Kurian, Gissen, Smith, Heales, & Clayton, 2011). According to low serotonin levels, any drug that works by increasing the level of serotonin, such as selective serotonin reuptake inhibitors (SSRIs) or 5-hydroxytryptophan is attributed to suppress focal and generalized seizures. Moreover, it has been reported that some antiepileptic drugs are exerting their pharmacological effect by increasing the serotonin level in the brain (Loscher, 1984; Prendiville & Gale, 1993; Yan, Jobe, Cheong, Ko, & Dailey, 1994). Different serotonergic receptors are present in the CNS and periphery, but it has been estimated that 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, and 5-HT_7 receptors are playing a role in epilepsy and evoking seizures (Bagdy, Kecskemeti, Riba, & Jakus, 2007). Serotonergic receptors 5-HT_{1A}, 5-HT_{2C}, and 5-HT_7 are containing glutamatergic or GABAergic neurons that are found on the hippocampus or cortex, so alteration in these receptors will result in imbalance between the excitatory and inhibitory neurotransmitters (Barnes & Sharp, 1999; Hoyer et al., 1994). However, 5-HT_3 is an ion channel receptor, that any change within this receptor will cause an alteration in the ions flow within the cells resulting in different de- and hyper polarization of neurons (Barnes & Sharp, 1999). 5-HT_3 agonist (SR 57227) and the selective serotonin reuptake inhibitor fluoxetine were effective in reducing seizure induced respiratory arrest in the DBA/1 mouse model; however, this protective effect was abolished by administration of 5-HT_3 antagonist

(ondansetron) (Faingold et al., 2016). Antiepileptic drugs, such as valproic acid, carbamazepine, and phenytoin work by blockage of voltage gated sodium channel and increasing GABA levels in the brain while lamotrigine blocks voltage gated sodium channel and decreases presynaptic glutamate release (Macdonald & Kelly, 1995). Zonisamide works by the blockage of voltage gated sodium channel and voltage gated T-type calcium channel (Okada et al., 1992). All these antiepileptic drugs are exerting their antiepileptic effect by increasing the level of serotonin, or enhancing its release (Ahmad, Fowler, & Whitton, 2005; Dailey et al., 1996; Okada et al., 1992).

It has been estimated that fluoxetine, which is a selective serotonin reuptake inhibitor, is effective against focal seizures in animal models that are injected with bicuculline ($GABA_A$ receptor antagonist) focally to induce seizures (Prendiville & Gale, 1993) or it could be injected directly into substantia nigra which is a part of the serotonergic tracts to enhance the serotonergic neurotransmission to prevent the generation of seizures (Pasini, Tortorella, & Gale, 1992). Interestingly, when fluoxetine is administered chronically, it would not have the anticonvulsant effect as the acute administration does (RAJU et al., 1999). Fluoxetine potentiates the action of some anti-epileptic drugs, such as carbamazepine, valproate, diphenylhydantoin, and phenobarbital in generalized epilepsy in maximal electroshock seizure (MES) model to provide a dose reduction in these anti-epileptic drugs into half (Borowicz, Stepien, & Czuczwar, 2006). 5-HT_{2C} receptor knock out mice are apt to audiogenic seizures that is induced by a sound in isolated acoustic chamber because 5-HT_{2C} receptor plays a role in epilepsy and regulating seizures (Applegate & Tecott, 1998; Bagdy et al., 2007; Brennan, Seeley, Kilgard, Schreiner, & Tecott, 1997; Tecott et al., 1995). 5-HT_{1A} knockout mice displayed lower seizure threshold when they are given kainic acid to induce seizure as compared to the control group because 5-HT_{1A} is involved in regulating epilepsy and seizures

(Bagdy et al., 2007; Parsons, Kerr, & Tecott, 2001; Sarnyai et al., 2000). There is a study that demonstrates that the depletion of serotonin by p-chlorophenylalanine (selective irreversible inhibitor of TPH) in kainic acid model rats displays more seizures than the control kainic acid model rats, which gives us a hint that serotonin could have an essential role in the regulation of seizures and preventing epilepsy (Maia, Brazete, Soares, Luz, & Lukoyanov, 2017).

Serotonergic marker	**Effect in epilepsy**	**Reference**
Tryptophan	Low tryptophan dietary intake is contributed to convulsion in rats.	(Feria-Velasco et al., 2008)
Tryptophan hydroxylase (TPH)	Tryptophan hydroxylase expression is reduced in SUDEP.	(Patodia et al., 2018)
	Tryptophan hydroxylase expression is significantly decreased in pilocarpine induced seizure in rats.	(Lin et al., 2013)
	Tryptophan hydroxylase activity is reduced in seizure induced respiratory arrest in DBA/1 mice.	(Q. Chen et al., 2019)
5-hydroxytryptophan (5- HTP)	Low levels of 5-hydroxy tryptophan reported in seizure induced respiratory arrest in DBA/1 mice.	(Q. Chen et al., 2019)
Aromatic L-amino Acid Decarboxylase (AADC)	Decreased in neonatal epileptic encephalopathy.	(Brautigam et al., 2002)
Serotonin (5-HT)	Serotonin levels is decreased during seizure.	(Kurian et al., 2011)
	Low levels of serotonin are reported in seizure induced respiratory arrest in DBA/1 mice.	(Q. Chen et al., 2019)
Serotonin metabolite (5-HIAA)	5-HIAA levels is reduced in pilocarpine induced epilepsy in rats.	(Lin et al., 2013)
	5-HIAA levels is decreased in seizure induced respiratory arrest in DBA/1 mice.	(Q. Chen et al., 2019)
Serotonin transporters (SERTs)	Serotonin transporters expression is reduced is SUDEP.	(Patodia et al., 2018)
Selective serotonin reuptake inhibitors (SSRIs)	Fluoxetine (SSRIs) suppress focal seizure in rats.	(Prendiville & Gale, 1993)
Serotonin agonists	5-HT_3 agonist (SR 57227) has a protective role to supress seizure in seizure induced respiratory arrest in DBA/1 mice.	(Faingold et al., 2016)
Serotonin antagonists	5-HT_3 antagonist (ondansetron) remove the protective effect of 5-HT_3 agonist (SR 57227) against seizure in seizure induced respiratory arrest in DBA/1 mice.	(Faingold et al., 2016)

Table 1: Different parameters affecting the serotonergic neurotransmission in epilepsy

Serotonergic neurotransmission plays a substantial role in regulating seizures and epilepsy. Any alteration in the serotonergic system (precursor, synthesizing enzyme, metabolites, receptors, reuptake) is attributed to lower seizure threshold and increase the brain susceptibility to seizures.

2.3 The role of dopamine in epilepsy

Dopamine is a neurotransmitter that is derived from the amino acid tyrosine that is present in the central nervous system as well as in the peripheral nervous system, such as kidney, adrenal gland, gut, heart, blood vessels, pancreas, and eye (Bucolo, Leggio, Drago, & Salomone, 2019; Klein et al., 2019). Dopamine is associated with different functions in the brain based on which pathway (major or minor) the dopamine belongs to (discussed in kainic acid review). Dopamine is present in the central nervous system and peripheral system where it regulates some functions there (discussed in kainic acid review). Dopamine synthesis is regulated by tyrosine hydroxylase which is the rate limiting enzyme in dopamine and other catecholamines synthesis (White & Thomas, 2012). Tyrosine is converted to L-DOPA by tyrosine hydroxylase with the help of tetrahydrobiopterin, oxygen, and iron as cofactors. L-DOPA is converted to dopamine by Aromatic L-amino acid decarboxylase by the help of the cofactor pyridoxal phosphate (Christenson, Dairman, & Udenfriend, 1970). Dopamine is transferred in to the synaptic vesicles with the help of vesicular monoamine transporter ($VMAT_2$) to be stored there in acidic environment to protect dopamine from oxidation (Eiden & Weihe, 2011; Guillot & Miller, 2009). Dopamine is released in to synaptic cleft to exert its action before this step, dopamine is susceptible to oxidation in the cytosol by MAO-B enzyme that metabolizes dopamine into DOPAC that is further metabolized by COMT enzyme into HVA (J. Chen et al., 2011; Eisenhofer, Kopin, & Goldstein, 2004). Once the dopamine is released from the

presynaptic neuron, it exerts its action through the activation of D_1 and D_2 like receptors, the excess dopamine on the post synaptic cleft is cleared by dopamine transporters (DATs) through the reuptake mechanism into the presynaptic neuron, where some drugs work by inhibiting this mechanism to increase the extracellular dopamine, such as amphetamine. D_1 and D_2 like receptors are G protein coupled receptors (metabotropic receptors) because their activation depends on the formation of the second messenger that stimulates or inhibits a specific intracellular pathway (Baik, 2013b; Beaulieu, Espinoza, & Gainetdinov, 2015) (dopaminergic intracellular signaling pathway is discussed in kainic acid review). Another pathway that is mediated by dopamine is the phosphatidylinositol-3 kinase PI3K-Akt– glycogen synthase kinase 3 (GSK3) signaling pathway (Beaulieu, Del'guidice, Sotnikova, Lemasson, & Gainetdinov, 2011; Beaulieu et al., 2004). This pathway has a prominent role in cell survival and differentiation (Liu, Cheng, Roberts, & Zhao, 2009; Martini, De Santis, Braccini, Gulluni, & Hirsch, 2014). In this pathway, dopamine mediates its action through D_2 receptor by inhibiting PI3K–Akt signaling pathway that leads to the activation of glycogen synthase kinase 3 (GSK3) (Beaulieu et al., 2011; Beaulieu, Gainetdinov, & Caron, 2009; Beaulieu, Tirotta, et al., 2007; Cross, Alessi, Cohen, Andjelkovich, & Hemmings, 1995; Gurevich, Benovic, & Gurevich, 2002; Kaidanovich-Beilin & Woodgett, 2011; Liu et al., 2009; Martelli et al., 2010). Moreover, D_1 and D_2 like receptors activate extracellular regulated kinase pathway ERK ½ that has a prominent role in cell apotosis and synaptic plasticity (Beom, Cheong, Torres, Caron, & Kim, 2004; Chang & Karin, 2001; J. Chen, Rusnak, Luedtke, & Sidhu, 2004; Thomas & Huganir, 2004). Interestingly, D_1 receptor activation will not regulate ERK phosphorylation unless glutamate is present to mediate MAPK signaling (Pascoli et al., 2011).

Any change in the dopamine levels will be contributed to a pathological disease, such as Parkinson disease, which is known as dopaminergic neurons loss in the nigrostriatal tract of

the brain, that could be treated by L-DOPA, dopamine agonists, and dopamine metabolism inhibitors, such as monoamine oxidase inhibitors and catechol-O-methyl transferase inhibitors that lead to increase the endogenous dopamine in the brain (Juarez Olguin, Calderon Guzman, Hernandez Garcia, & Barragan Mejia, 2016). Moreover, any increase in the dopamine content in the subcortical neurons is attributed to psychosis (Abi-Dargham et al., 2000; Abi-Dargham, van de Giessen, Slifstein, Kegeles, & Laruelle, 2009). Limbic striatum is associated with alterations of dopamine levels in patients with schizophrenia since the reward system in this particular area is compromised (S. Kapur, 2003). Huntington disease is another neurodegenerative disease that is associated with dopaminergic neuronal cell loss in the caudate and putamen region, where the dopamine receptors and dopamine signaling in this area are disrupted (Beaulieu & Gainetdinov, 2011; Cyr, Sotnikova, Gainetdinov, & Caron, 2006; Jakel & Maragos, 2000). Attention deficit hyperactivity disorder (ADHD) is another neurological disease that is associated with the impairment of dopamine signaling particularly dopamine transporters DATs, noradrenalin transporters NETs, D_4 and D_5 receptors (Faraone et al., 2005; Madras, Miller, & Fischman, 2005; Yang, Wang, Li, & Faraone, 2004). Addiction is another psychological disorder that is associated with the dysfunction of dopaminergic neurotransmission in the mesolimbic pathway that is resulted in the downregulation of dopaminergic D_2 receptors subsequently alters dopamine signaling (Baik, 2013a; Kenny, 2011).

It has been demonstrated that dopamine has a significant role to prevent limbic seizures (Clinckers et al., 2005; Starr, 1996). Any drug that increases the dopaminergic neurotransmission, such as L-DOPA, amphetamine, anti-parkinsonian drugs like pergolide and bromocriptine produce an anti-convulsant properties in the limbic area of the brain (Bozzi & Borrelli, 2013). Tyrosine, which is an amino acid precursor involved in the synthesis of

dopamine plays a role in regulating epilepsy (Kayacan et al., 2019; Suzuki & Mori, 1992). EI mice which are considered as a genetically prone mice that are easily induced to be convulsant by tossing or rocking, the level of tyrosine content is high in the epileptic EI (-) mice as compared to the epileptic EI (+) mice (Suzuki & Mori, 1992). Furthermore, the supplementation of L-tyrosine to penicillin induced epilepsy with some physical exercises in rats has an effect to reduce the epileptiform activity (Kayacan et al., 2019). Tyrosine hydroxylase activity, which is the rate limiting enzyme in dopamine synthesis, was not altered in patients with temporal cortex epilepsy (Pintor et al., 1990). However, tyrosine hydroxylase activity has been reported to be increased in focal seizures (Sherwin & van Gelder, 1986). One the other hand, tyrosine hydroxylase activity has been detected to be decreased In audiogenic seizure prone BALB/c mice (Vriend, Alexiuk, Green-Johnson, & Ryan, 1993). The level of tyrosine hydroxylase is elevated in patients with complex partial seizure in the mesial part of the temporal lope (Zhu, Armstrong, Grossman, & Hamilton, 1990). In kainic acid induced epilepsy in animal models, the expression of tyrosine hydroxylase is also increase in locus coeruleus (Bengzon, Hansson, Hoffman, & Lindvall, 1999). Interestingly, the level of tyrosine hydroxylase in genetically- epilepsy prone rates was low in in locus coeruleus and inferior colliculus and the repeated seizures will further reduce TH expression (Ryu et al., 2000). In pentylenetetrazol (non-competitive $GABA_A$ antagonist) induced seizure in rats, the expression of TH was elevated in substantia nigra pars compacta and ventral tegmental area for 3 days (Szot, White, & Veith, 1997). In genetically- epilepsy prone rat subtype 3 and 9; tyrosine hydroxylase expression was significantly increased in the dopaminergic neurons especially in the substantia nigra pars compacta and ventral tegmental area in GEPR-3 and GEPR-9 as compared to control. However, in the zona incerta region, the expression of tyrosine hydroxylase is significantly decreased in GEPR-3 as compared to control and GEPR-9 (Szot, Reigel, White, & Veith, 1996). Tetrahydrobiopterin (BH_4) can control seizures as well because

in a medical case of 9 year old girl demonstrated an abnormal EEG and focal spike had low levels of BH_4 suggesting that BH_4 could be used as a therapeutic agent to regulate epilepsy (Guttler, Lou, Lykkelund, & Niederwieser, 1984). Cortical injection of iron (ferrous) in rats induces recurrent seizures (Willmore, Sypert, & Munson, 1978) and focal epilepsy (Ronne Engstrom et al., 2001). However, In mesial temporal lope epilepsy, low levels of irons have been reported in subcortical structures of the brain, such as substantia nigra, basal ganglia, and red nucleus and the decrease of iron content in the subcortical structures of the brain is proportionally related to the progression of epilepsy (Z. Zhang et al., 2014). Suggesting that iron content could be used as an epileptic biomarker for the progression of the disease. In a medical case of 23-year- old girl, the deficiency of L-ferritin is attributed to idiopathic generalized seizures and a typical restless leg syndrome (Cozzi et al., 2013). Iron deficiency anemia is suggested to be associated with febrile seizure susceptibility in children (Naveed ur & Billoo, 2005). In contrast, in a patient with epileptic encephalopathy with WDR 45 mutation reported to have brain iron accumulation (Khoury, Kotagal, & Moosa, 2019) Administration of L-dopa in a medical case of 68-year- old woman suffering from Parkinson disease exhibited cortical myoclonus and seizures that is developed into generalized seizures suggesting that L-dopa has a role in the exacerbation of seizures in patients suffering from Parkinson disease (Yoshida, Moriwaka, Matsuura, Hamada, & Tashiro, 1993). Moreover, levodopa can induce myoclonic epilepsy (Menassa, Giroud, Gras, & Dumas, 1991). In contrast, in a medical case of three patients with a Parkinson disease receiving levodopa to manage their symptoms, no significant alteration in their EEG has been detected and no seizures have been evoked considering that L-dopa does not exacerbate a preexisting seizure in these patients (Newman, Tucker, & Kooi, 1973). In audiogenic seizure prone BALB/c mice, low levels of L-dopa has been detected (Vriend et al., 1993). Regarding aromatic L-amino acid decarboxylase, an interesting study that has been investigated in premature twins suffering from severe seizures,

myoclonus, and clonic contractions showed that they had low levels of AADC in their CSF and urine, subsequently, the level of L-dopa which is a substrate for AADC has been elevated in their CSF (Brautigam et al., 2002). In rats treated with cobalt to induce epilepsy , the level of aromatic L-amino acid decarboxylase enzyme was significantly reduced at 4-8 days then it returned to control levels at 24 days (Emson & Joseph, 1975). Moreover, aromatic L-amino acid decarboxylase has been decreased in epilepsy, generalized tonic seizures, involuntary non-epileptic movements (Ito et al., 2008), and neonatal epileptic encephalopathy (Clayton, Surtees, DeVile, Hyland, & Heales, 2003; Mills et al., 2005). Carbidopa which is considered as a dopa decarboxylase inhibitor used for the treatment of Parkinson disease has a role in epilepsy; in a medical case of two patients on a hemodialysis with a chronic renal failure reported a recurrent seizures with hallucination upon the administration of levodopa/carbidopa, one of the patients died and the other one showed an improvement by of vitamin B_6 supplementation (Bamford et al., 1990). Low levels of pyridoxal phosphate has been detected in epileptic encephalopathy (Clayton et al., 2003; Mills et al., 2005).

Dopamine has a strong role in regulating epilepsy and seizures and the level of dopamine and its metabolites are varied according to the type of epilepsy and the animal model used in the study (Starr, 1996). Interestingly, high levels of dopamine and dopaminergic neuronal firing are attributed to temporal lobe epilepsy (Cifelli & Grace, 2012; Meurs, Clinckers, Ebinger, Michotte, & Smolders, 2008). In different areas of the brain, such as brain hemispheres, cerebellum, , hypothalamus and truncus cerebri, the dopamine content has been reported to be increased in rats susceptible to audiogenic convulsion (Sergienko & Loginova, 1983). Glutamate interacts with dopamine, and the interaction between glutamate and dopamine occurs when protein kinase A (PKA) phosphorylates AMPA and NMDA glutamate receptors in the limbic area of the brain (Girault & Greengard, 2004; Starr, 1996). Moreover, glutamate

reduces the activity of protein kinase that phosphorylates DARPP-32 in striatal neurons which means that glutamate by itself can impact the D_1 receptor/PKA/ DARPP-32 dependent intracellular pathway by activating protein phosphatase 2A (PP2A) (Nishi et al., 2017). Moreover, dopamine abnormalities have been reported in epileptic patients with depression and anxiety comorbid conditions (Rocha et al., 2012). The expression of vesicular monoamine transporters (VMATs) is decreased in patients with temporal lope epilepsy. However, in pilocarpine (cholinergic muscarinic agonist) treated rats, the expression of VMATs is increased for 1 to 3 days then it is decreased after recurrent seizures (Jiang et al., 2013). An anti-convulsant Gabapentin and pregabalin reduce the calcium influx of the presynaptic terminal of dopamine, glutamate and other monoamines which means that during seizure the presynaptic calcium influx is enhanced to cause further release of dopamine (Dooley, Donovan, & Pugsley, 2000; Dooley, Mieske, & Borosky, 2000). Dopaminergic D_2 like receptors including D_2, D_3, D_4 receptors have an inhibitory effect on seizures upon stimulation and they elicit an anti-convulsant effect since they are Gi protein coupled receptors that lead to decrease the excitation of neurons in the hippocampus and prevent seizures from occurrence (Bozzi & Borrelli, 2013; Starr, 1996). According to this fact, antipsychotic drugs that act as dopaminergic D_2 antagonists exacerbate seizures; however, anti-parkinsonian drugs that stimulate dopaminergic D_2 receptor, such as pergolide and bromocriptine provide a neuroprotective effect against seizures and epilepsy (Starr, 1996). On the other hand, activation of dopaminergic D_1 like receptors by the administration of SKF 38393 produces convulsions (Starr, 1996). In mesial temporal lope epilepsy (MTLE) and temporal lope epilepsy secondary to brain tumor or lesion, the expression of D_1 receptor was high as compared to D_2 receptor (Rocha et al., 2012). According to the dopaminergic signaling pathway in epilepsy, Activation of D_1 like receptor (including D_1 and D_5) leads to activation of adenyl cyclase (AC) since D_1 like receptor is a Gs protein coupled receptor that increases the level of cyclic AMP (cAMP) and activate protein kinase A

(PKA) to phosphorylate dopamine regulated phosphoprotein (DARPP-32) to convert it to an inhibitor of protein phosphatase-1 (PP-1), this pathway has an outstanding role in seizures and regulating excitability (Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2011; Greengard, 2001; Greengard, Allen, & Nairn, 1999). Phosphorylated DARPP-32 and activated protein kinases including PKA and PKC lead to phosphorylation of other proteins, such as, glutamate receptors, GABA, and sodium and calcium channels (Greengard, 2001; Greengard et al., 1999). Extracellular regulated kinase (ERK) signaling pathway plays a crucial role in D_1 and D_2 like receptors regulating seizures, so in response to seizures by D_1 agonists, the ERK signaling pathway is upregulated that leads to phosphorylation of ERK targeted proteins (Gangarossa et al., 2011). However, activation of D_1 receptors that activates phospholipase C (PLC) not (AC) does not produce seizures (Clifford et al., 1999; O'Sullivan et al., 2008). Regarding D_5 receptors activation, it leads to hyperexcitability and increase in cyclic AMP as in D_1 receptor activation, but the effect was less noticeable and pronounced as compared to D_1 receptor activation (O'Sullivan et al., 2008). Activation of D_2 like receptor (including D_2, D_3, D_4) elicits a neuroprotective effect against seizures since D_2 like receptor is a Gi protein coupled receptor, and this effect is mediated by two pathways which are cyclic AMP dependent (canonical) and cyclic AMP independent pathways (Bozzi & Borrelli, 2013). Regarding cyclic AMP dependent (canonical) pathway, all the signals that are triggered by D_1 receptor activation: cyclic AMP-PKA- DARPP-32 pathway are down regulated by D_2 receptor activation that leads to decrease neuronal hyperexcitability and promote neuronal cell survival (Beaulieu & Gainetdinov, 2011). For the cyclic AMP independent pathway, $D_2R^{-/-}$ mice exhibit inhibition of Akt activity that leads to hyperactivation of glycogen synthase kinase3β (Beaulieu, Gainetdinov, & Caron, 2007; Beaulieu et al., 2005). Activation of D_3 receptors has a low inhibitory effect on limbic seizure as compared to D_2 agonists which gives us a hint that the anti-convulsant properties are mediated through D_2 receptors rather than D_3 receptors activation (Alam & Starr, 1994). D_3

agonists exert their minimal anti-convulsant effect through cyclic AMP independent pathway (Beaulieu, Tirotta, et al., 2007). D_4 agonists exhibit a maximal inhibitory effect on seizures that is induced by 4- aminopyridine or bicuculline ($GABA_A$ receptor antagonist) in animals and this can be shown in $D_4R^{-/-}$mice when they show high frequency of hyperexcitability (Rubinstein et al., 2001). Although some dopaminergic agonists exhibit anti-convulsive effect, no dopaminergic drug has been used to treat epilepsy (Beaulieu & Gainetdinov, 2011; Starr, 1996). The reason of not using DA agonists to treat epilepsy is due to their neurological and neuropsychiatric adverse effects, but some studies confirmed that D_2 receptor agonists, such as bromocriptine is effective in treating epilepsy and reducing hyperexcitability without producing adverse side effects (S. C. Chen, 2006; Clemens, 1988). It has been established that D_2 receptor agonists including bromocriptine elucidate a neuroprotective effect against kainic acid induced epilepsy (Micale et al., 2006). In patients with Temporal lope epilepsy (TLE), the expression of MAO enzymes was high especially MAO-B in the cerebral cortex that explains the low level of dopamine in the cerebral cortex in these patients (Kumlien et al., 1995), MAO-B activity has been studied to be increased too in temporal lope epilepsy (Kumlien, Hilton-Brown, Spannare, & Gillberg, 1992). Based on that, L-deprenyl (selegiline) which is considered as an irreversible MAO B inhibitor demonstrated to exert an anti-epileptic and anti-convulsant properties in amygdala kindled rats (Loscher & Honack, 1995). Moreover, L-deprenyl has been proposed to be efficacious against different types of seizures (Loscher & Lehmann, 1996). Interestingly, it has been studied that the inhibition of MAO A not MAO B produces an anti-convulsant properties in amygdala kindled rats that is elucidated by the administration of a MAO A inhibitor drug, such as (Esuprone) to elicit an anti-convulsant effect in kindled animal models. L-deprenyl inhibits MAO B but in higher doses, it is extended to inhibit MAO A, so the anti-convulsant properties of L-deprenyl is linked to MAO A inhibition not MAO B inhibition (Loscher, Lehmann, Teschendorf, Traut, & Gross, 1999). In audiogenic

seizure resistant mice (C57B1/6J mice), high of COMT activity has been reported while low COMT activity has been reported in (DBA/2J mice) susceptible to audiogenic seizure (Doyle & Sellinger, 1980; Schlesinger, Harkins, Deckard, & Paden, 1975). In patients with refractory epilepsy with neuropsychiatric conditions, COMT activity has been reported to be increased because of COMT genetic polymorphism in those patients (Doherty et al., 2019). The first generation COMT inhibitors, such as tolcapone and entacapone have been studied to induce convulsions as a side effect (Haasio, 2010; Kumlien & Lundberg, 2010). Entacapone causes convulsions as a symptom of neuroleptic malignant syndrome (NMS) (Mayo Foundation for Medical Education and Research, 2019a). Patients with mesial temporal lope epilepsy or temporal lope epilepsy secondary to brain tumor or lesion showed significant low content of dopamine, DOPAC, and HVA (Rocha et al., 2012). In neonatal epileptic encephalopathy, the level of HVA has been detected to be reduced (Brautigam et al., 2002; Clayton et al., 2003). Low levels of 3-methoxytyramine has been detected as well as significant low levels of dopamine, DOPAC, and HVA has been reported in striatum of audiogenic seizure prone BALB/c mice (Vriend et al., 1993). It has been proposed that dopamine transporters in the dopaminergic neurons can play a role in genetically epilepsy prone rats as well, since they have been reported to be significantly decreased in GEPR-3 as compared to control and GEPR-9 (Szot et al., 1996). Dopamine transporters (DATs) have been reported to be reduced in different forms of epilepsy, such as juvenile myoclonic epilepsy and epilepsy with tonic-clonic seizures (Ciumas, Wahlin, Espino, & Savic, 2010; Ciumas et al., 2008; Odano et al., 2012). Moreover, In pentylenetetrazol (non-competitive $GABA_A$ antagonist) induced seizure in rats, the expression of DATs has been reduced in substantia nigra pars compacta and ventral tegmental area for 1 day (Szot et al., 1997). Interestingly, bupropion, which is known as a norepinephrine dopamine reuptake inhibitor used for the treatment of depressive disorders and for the aid of smoking cessation is associated with generalized seizures in a case of 24-year-old woman (Wah

& Wah, 2004). Numerous seizure reports have been published in patients receiving bupropion suggesting that this drug should be restricted in patients with seizures or patients who have a history of seizures (Wooltorton, 2002). The seizure induced by bupropion is determined by two factors: the dose and the formulation of the drug; high doses of bupropion is associated with seizures and the immediate release form of the drug causes seizure more than the sustained release one (Dobek, Blumberger, Downar, Daskalakis, & Vila-Rodriguez, 2015).

During epilepsy and seizures, the dopaminergic pathways are affected, for example, the mesolimbic D_2 receptors density in nucleus accumbens has been found to be significantly increased in hippocampal kindling rats (Csernansky, Kerr, Pruthi, & Prosser, 1988; Csernansky, Mellentin, Beauclair, & Lombrozo, 1988). The mesocortical pathway is also affected since high mesocortical dopaminergic innervation is caused by Otx2 gene hyper-expression in transgenic mice that leads to induction of seizure genes and susceptibility (Tripathi et al., 2014). For the nigrostriatal pathway, the genetically audiogenic seizure prone rats (KM rats) reported high ERK1/2 activity (Dorofeeva et al., 2015), suggesting that the inhibition of ERK1/2 activity in the nigrostriatal system in these rats leads to the inhibition of seizures (Dorofeeva et al., 2017). According to the tuberoinfundibular pathway, high levels of prolactin has been counted in some pathological diseases including epilepsy (Petty, 1999). Chemoreceptor trigger zone pathway is stimulated by dopamine in epilepsy and other neurological disorders to induce nausea and vomiting (Johns, 1995). Regarding the incerto-hypothalamic pathway, Hypothalamic (gelastic) epilepsy is a well-known disease that is caused by Hypothalamic hamartomas, a tumor on the hypothalamus, that causes gelastic seizures and developed to be generalized epileptic encephalopathy (Panayiotopoulos, 2006). Zona incerta shows a vulnerability to generalized epilepsy (Brudzynski, Cruickshank, & McLachlan, 1995) as a stimulation of zona incerta has been investigated to halt spike wave discharges in rats (S.

F. Liang et al., 2011). For the medullary periventricular pathway, the pathway associated with eating behavior, seizures are accompanied with eating disorders, such as anorexia nervosa (Patchell, Fellows, & Humphries, 1994) suggesting that this pathway is compromised in seizure disorders. Interestingly, antiepileptic drugs alleviate the symptoms of anorexia nervosa associated with epilepsy with un-known mechanism of action (Tachibana, Sugita, Teshima, & Hishikawa, 1989). As the medullary periventricular pathway is located on the vagus nerve, vagus nerve stimulation is considered as a therapeutic approach to treat pharmacoresistant epilepsy (Wheless, Gienapp, & Ryvlin, 2018).

Dopaminergic marker	Effect in epilepsy
Tyrosine content	✓ high in epileptic EI (-) mice than ddy mice and epileptic EI (+) mice (Suzuki & Mori, 1992) ✓ L-tyrosine with physical exercises reduces epileptogenesis (Kayacan et al., 2019).
Tyrosine hydroxylase (TH) (activity/expression)	✓ Tyrosine hydroxylase activity has been decreased in audiogenic seizure prone BALB/c mice (Vriend et al., 1993). ✓ Tyrosine hydroxylase activity is increased in human focal epilepsy (Sherwin & van Gelder, 1986). ✓ Tyrosine hydroxylase expression is significantly decreased in zona incerta in genetically epilepsy prone rat subtype 3 (GEPR-3) (Szot et al., 1996). ✓ Tyrosine hydroxylase expression is elevated in substantia nigra pars compacta and ventral tegmental area of the brain in genetically epilepsy prone rat (GEPR-3 and 9) (Szot et al., 1996). ✓ In pentylenetetrazol induced seizure in rats, the expression of TH was elevated in substantia nigra pars compacta and ventral tegmental area for 3 days (Szot et al., 1997).
Tetrahydrobiopterin (BH_4) content	✓ Low levels of biopterin has been detected in seizures (Guttler et al., 1984).
Iron content	✓ Cortical injection of iron (ferrous) in rats induces recurrent seizures (Willmore et al., 1978) and focal epilepsy (Ronne Engstrom et al., 2001). ✓ Low levels of irons have been reported in mesial temporal lope epilepsy (Z. Zhang et al., 2014). ✓ Deficiency of L-ferritin is attributed to idiopathic generalized seizures (Cozzi et al., 2013). ✓ Low levels of irons have been reported with febrile seizure susceptibility in children (Naveed ur & Billoo, 2005) . ✓ WDR 45 mutation in patients with epileptic encephalopathy reported to have brain iron accumulation (Khoury et al., 2019)
L-Dopa content	✓ L-dopa is decreased in audiogenic seizure prone BALB/c mice in striatum (Vriend et al., 1993). ✓ Administration of levodopa can induce generalized seizure in patients suffering from Parkinson disease (Yoshida et al., 1993). ✓ Levodopa can induce myoclonus epilepsy (Menassa et al., 1991). ✓ Levodopa had no significant alteration on EEG of a preexisting seizure (Newman et al., 1973).
Dopa decarboxylase (activity/expression)	✓ Aromatic L-amino acid decarboxylase deficiency has been reported in epilepsy and seizures (Ito et al., 2008). ✓ Aromatic L-amino acid decarboxylase levels has been significantly reduced in cobalt induced epilepsy in rats (Emson & Joseph, 1975) ✓ Aromatic L- amino acid decarboxylase activity has been decreased in neonatal epileptic encephalopathy (Clayton et al., 2003; Mills et al., 2005)

	✓ Aromatic L amino acid decarboxylase deficiency has been detected in premature twins with epileptic encephalopathy (Brautigam et al., 2002)
Role of carbidopa	✓ Recurrent seizures have been reported by the administration of the combination therapy levodopa/carbidopa (Bamford et al., 1990)
Pyridoxal phosphate (Vitamin B6) content	✓ Pyridoxal phosphate has been reduced in neonatal epileptic encephalopathy (Clayton et al., 2003; Mills et al., 2005)
Dopamine content	✓ Significant decrease of dopamine in striatum in audiogenic seizure prone BALB/c mice (Vriend et al., 1993). ✓ Significant decrease of dopamine in mesial temporal lope epilepsy and temporal lope epilepsy secondary to brain tumor or lesion (Rocha et al., 2012). ✓ Increased levels of dopamine has been demonstrated in rats susceptible to audiogenic seizures (Sergienko & Loginova, 1983).
Effect of dopamine agonists	✓ Anti-Parkinsonian drugs (dopaminergic D_2 agonists), such as pergolide and bromocriptine provide a neuroprotective effect against epilepsy (Starr, 1996).
Effect of dopamine antagonists	✓ Anti-psychotic drugs (dopaminergic D_2 antagonists) exacerbate seizure (Starr, 1996).
Vesicular monoamine transporters (VMATs) expression	✓ Reduced in TLE, but in pilocarpine treated rats, it is increased for 1 to 3 days (Jiang et al., 2013).
Dopaminergic presynaptic Calcium influx	✓ Dopaminergic presynaptic calcium influx is increased during seizure because anti-convulsant drugs, such as gabapentin and pregabalin work by decreasing the calcium influx of the presynaptic neurons of dopamine, to reduce seizures (Dooley, Donovan, et al., 2000; Dooley, Mieske, et al., 2000)
Dopaminergic D_1 receptor expression	✓ High protein expression of D_1 receptor is detected in mesial temporal lope epilepsy and temporal lope epilepsy secondary to brain tumor or lesion (Rocha et al., 2012)
Dopaminergic D_2 receptor expression	✓ Less protein expression of D_2 receptor as compared to D_1 receptor is reported in mesial temporal lope epilepsy and temporal lope epilepsy secondary to brain tumor or lesion (Rocha et al., 2012)
Adenyl cyclase activity	✓ Mediated by D_1 like receptor activation to be activated in seizure and inhibited by D_2 like receptor activation in non-seizure conditions (Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2011; Greengard, 2001; Greengard et al., 1999).
Cyclic AMP	✓ Increased in seizure by activation of D_1 like receptor while decreased in non-seizure condition by D_2 like receptor activation (Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2011; Greengard, 2001; Greengard et al., 1999).
Protein Kinase activity	✓ Activated in seizure by D_1 like receptor activation and inactivated in non- seizure conditions by D_2 like

	receptor activation (Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2011; Greengard, 2001; Greengard et al., 1999)
Dopamine regulated phosphoprotein (DARPP-32)	✓ Activated in seizure and inactivated in non-seizure conditions (Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2011; Greengard, 2001; Greengard et al., 1999).
Extra cellular regulated kinase ERK ½ activity	✓ Activated in seizure and inactivated in non- seizure conditions (Gangarossa et al., 2011)
Protein phosphatase PP-1 activity	✓ Inhibited in seizure to phosphorylate DARPP-32 (Beaulieu & Gainetdinov, 2011; Gangarossa et al., 2011; Greengard, 2001; Greengard et al., 1999)
Akt activity	✓ Akt phosphorylation is reduced in $D_2R^{-/-}$ mice (Beaulieu, Gainetdinov, et al., 2007)
Glycogen synthase kinase (GSK-3β) activity	✓ Hyperactivation of (GSK-3β) in $D_2R^{-/-}$ mice
MAO (activity/expression)	✓ The expression of MAO-B is high in the cerebral cortex in patients with temporal lope epilepsy (Kumlien et al., 1995). ✓ MAO-B activity has been detected to be increased in patients with temporal lope epilepsy (Kumlien et al., 1992).
Effect of MAO inhibitors	✓ L-deprenyl (selegiline) which is a MAO B inhibitor, exerts an anti-epileptic and anti-convulsant effect in amygdala kindled rats (Loscher & Honack, 1995). ✓ L-deprenyl is effective against different types of seizures in mice (Loscher & Lehmann, 1996).
Difference between MAO A and MAO B inhibitors in epilepsy	✓ Inhibition of MAO A elicits anti-convulsant properties more than MAO B in amygdala kindled rat. L-deprenyl (selegiline) is a MAO B inhibitor but in high doses, it becomes a MAO A inhibitor to produce the anti-convulsant effect (Loscher et al., 1999).
COMT (activity/expression)	✓ Increased COMT activity has been reported in audiogenic seizure resistant mice (C57B1/6J mice) while low COMT activity has been reported in sound induced seizure susceptible mice (DBA/2J mice) (Doyle & Sellinger, 1980; Schlesinger et al., 1975) ✓ COMT gene polymorphism that codes for high COMT enzyme activity has been reported in neuro psychiatric conditions in patients with refractory epilepsy (Doherty et al., 2019).
Effect of COMT inhibitors	✓ The first generation COMT inhibitors, such as tolcapone and entacapone induce convulsions as a side effect (Haasio, 2010; Kumlien & Lundberg, 2010) ✓ Entacapone causes convulsions as a symptom of a neuroleptic malignant syndrome (Mayo Foundation for Medical Education and Research, 2019a).
Effect of norepinephrine dopamine reuptake inhibitors (NDRIs)	✓ Bupropion which is a NDRI has been reported to cause generalized seizures (Dobek et al., 2015; Wah & Wah, 2004; Wooltorton, 2002)
Dopamine transporters DATs expression	✓ DATs expression is significantly reduced in substantia nigra pars compacta, ventral tegmental area, and zona

	incerta regions in genetically epilepsy prone rat subtype 3 (GEPR-3) (Szot et al., 1996). ✓ DATs expression has been reduced in substantia nigra pars compacta and ventral tegmental area in pentylenetetrazol induced seizure in rats (Szot et al., 1997). ✓ DATs expression has been reduced in juvenile myoclonic epilepsy and epilepsy with tonic-clonic seizures (Ciumas et al., 2010; Ciumas et al., 2008; Odano et al., 2012)
DOPAC content	✓ Significant decrease of DOPAC content in audiogenic seizure prone BALB/c mice (Vriend et al., 1993). ✓ Significant decrease of DOPAC content in mesial temporal lope epilepsy and temporal lope epilepsy secondary to brain tumor or lesion (Rocha et al., 2012).
HVA content	✓ Significant decrease of HVA in audiogenic seizure prone BALB/c mice (Vriend et al., 1993). ✓ Significant decrease of HVA in mesial temporal lope epilepsy and temporal lope epilepsy secondary to brain tumor or lesion (Rocha et al., 2012). ✓ HVA has been reported to be decreased in neonatal epileptic encephalopathy (Brautigam et al., 2002; Clayton et al., 2003).
3-methoxy tyramine (3-MT) content	✓ 3-MT is decreased in audiogenic seizure prone BALB/c mice (Vriend et al., 1993).
Mesolimbic pathway	✓ Hippocampal kindling in rats causes significant increase of the mesolimbic D_2 receptor density in nucleus accumbens (Csernansky, Kerr, et al., 1988; Csernansky, Mellentin, et al., 1988).
Mesocortical pathway	✓ Otx2 gene overexpression in transgenic mice is associated with high mesocortical dopaminergic innervation that leads to induction of seizure genes and susceptibility (Tripathi et al., 2014).
Nigrostriatal pathway	✓ In genetically audiogenic seizure prone rats (KM rats), increased activity of ERK ½ has been reported in the nigrostriatal tract (Dorofeeva et al., 2015). Consequently, blockage of ERK ½ in the nigrostriatal system leads to inhibition of seizures (Dorofeeva et al., 2017)
Tuberoinfundibular pathway	✓ High levels of prolactin is associated with epileptic seizures (Petty, 1999).
Incerto-hypothalamic pathway	✓ Hypothalamic (gelastic) epilepsy causes gelastic seizures and developed to be generalized epileptic encephalopathy (Panayiotopoulos, 2006). ✓ Zona incerta plays a role in generalized epilepsy susceptibility (Brudzynski et al., 1995) since the stimulation of zona incerta stops spike wave discharges in rats (S. F. Liang et al., 2011).

Medullary periventricular pathway	✓ Since medullary periventricular pathway is associated with eating behaviour (Prasad, 2010). Seizures have been linked to eating disorders, such as anorexia nervosa (Patchell et al., 1994). Suggesting that medullary periventricular pathway in epilepsy is compromised. ✓ Since medullary periventricular pathway is located in the vagus nerve, vagus nerve stimulation is considered as a therapeutic approach to treat pharmacoresistant epilepsy (Wheless et al., 2018)
Chemoreceptor trigger zone pathway	✓ Dopamine Stimulates chemoreceptor trigger zone to induce vomiting in epilepsy (Johns, 1995).

Table 2: Different parameters affecting the dopaminergic neurotransmission in epilepsy

Dopaminergic neurotransmission (precursor, synthesizing enzymes, metabolite, receptors, reuptake) are playing a role in regulating seizures and epilepsy as discussed in the review. Dopamine abnormalities is associated with different types of epilepsy. Dopaminergic D_1 receptor is a proconvulsant receptor that exacerbate seizure while D_2 is an anticonvulsant receptor that elicits a protective effect against seizure suggesting that D_2 agonists, such as bromocriptine could be used as special targets to treat epilepsy.

2.4 The role of norepinephrine in epilepsy

Norepinephrine is a neurotransmitter derived from dopamine when the dopamine is converted to norepinephrine by dopamine beta hydroxylase with oxygen and ascorbic acid as cofactors. Norepinephrine is existed in the central nervous system as well as in the peripheral nervous system, and it is associated with two brain regions, the locus coeruleus and the lateral tegmental area where the noradrenergic neurons can be found there (Weinshenker & Szot, 2002). The noradrenergic tract originates from locus coeruleus to different regions of the brain including cerebral cortex, limbic system, and spinal cord. Fight and flight responses are attributed to the physiological action of norepinephrine where it can increase the blood pressure and cardiac output through acting on adrenergic alpha and beta receptors. Regarding the noradrenergic signalling, three distinct noradrenergic receptors are linked to different G- protein coupled

receptors. alpha-1 adrenoreceptor is linked to Go/Gq that activates phospholipase C and intracellular calcium release. Alpha-2 adrenoreceptor is linked to Gi that inhibits adenyl cyclase. Beta 1 and 2 adrenoreceptors that is linked to Gs that activates adenyl cyclase (Hussain, Reddy, & Maani, 2020). Norepinephrine is metabolized by monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) to give 3-methoxy-4-hydroxyphenylglycol (MHPG) that is further oxidized into 3-methoxy-4-hydroxymandelic acid (Eisenhofer et al., 2004). Many studies have shown that norepinephrine can play a role in modulating seizure; for example, the expression of TH enzyme and NE transporters are elevated in the locus coeruleus in KA induced epilepsy in animals (Bengzon et al., 1999). To proof that norepinephrine is acting as an endogenous anticonvulsant, it has been reported that dopamine beta hydroxylase, which is the enzyme that converts DA to NE, knockout mice showed lower response to the antiepileptic agent valproic acid. Suggesting that NE is producing some anticonvulsant effect by valproic acid (Schank, Liles, & Weinshenker, 2005). Interestingly, disulfiram, which is an anti-alcoholism drug acting by the inhibition of dopamine beta hydroxylase showed more seizures that are induced by cocaine because of the inhibition of DBH; moreover, DBH knockout mice reported more seizure susceptibility (Gaval-Cruz, Schroeder, Liles, Javors, & Weinshenker, 2008). More confirmative studies proofed that the activity of DBH in epileptic patients is lower than the normal people (Warter, Coquillat, & Kurtz, 1975). Regarding the cofactors, ascorbic acid has been studied to attenuate seizure in pilocarpine induced seizures in rats suggesting that ascorbic acid could be used as a therapeutic agent to treat seizures (Dong et al., 2013). Oxygen plays a role in epilepsy since hypoxia and reduction of oxygen concentrations can induce epileptiform activity (Ingram et al., 2014; Wei, Ullah, Ingram, & Schiff, 2014). It has been proofed that using reserpine, which is a monoamine depleting agent can exacerbate seizure since reserpine depletes 5-HT, DA, and NE (Arnold, Racine, & Wise, 1973; Blank, 1976). Reserpine lacks specificity to determine which monoamine is responsible

for the anticonvulsant effect, so 6-hydroxydopamine has been injected directly to locus coeruleus to deplete NE to show more epileptiform activity in penicillin induced epilepsy in rats suggesting that NE is an endogenous anticonvulsant (Sullivan & Osorio, 1991). In genetically epilepsy prone rats (GEPRs), the steady state of NE levels has been reduced and the reuptake of NE has been reported to be significantly reduced in cortex, hippocampus, amygdala, and hypothalamus as well as DBH activity has been studied to be decreased in these brain regions (Browning, Wade, Marcinczyk, Long, & Jobe, 1989). The release of NE has been reported in generalized and focal seizures to be significantly increased in rat hippocampus of kindled model (Bengzon, Kikvadze, Kokaia, & Lindvall, 1992; Shouse, Staba, Ko, Saquib, & Farber, 2001). Noradrenergic agonists drugs, St 587 and clonidine that are classified as alpha-1 and alpha-2 adrenoreceptors agonists respectively have been studied to produce an anticonvulsant effect in kindled rats (Loscher & Czuczwar, 1987). Clonidine, which is an alpha-2 receptor agonist at high doses can produce an anticonvulsant effect but at lower doses it produced proconvulsant properties where it can act in the presynaptic terminal to decrease NE release in audiogenic seizures (Tacke & Kolonen, 1984) Interestingly, in GEPRs pre-treated with alpha-1 adrenoreceptor antagonist (prazosin) inhibits the anticonvulsant effect of alpha-1 adrenoreceptor agonists methoxamine and nisoxetine in superior colliculus of the brain (Yan, Dailey, Steenbergen, & Jobe, 1998). Alpha-1 adrenoreceptor density has been reported to be decreased in GEPRs and audiogenic seizure- sensitive DBA/2J mouse strain indicating that NE eliciting its partial anticonvulsive properties through this receptor subtype (Jazrawi & Horton, 1986; Nicoletti, Barbaccia, Iadarola, Pozzi, & Laird, 1986). Regarding the norepinephrine transporters (NETs) inhibitors, the antideppressant reboxetine produced both proconvulsant and anticonvulsant properties in flurothyl-induced seizures in mice suggesting that selective NETs inhibitors might not be safe to be used in seizure prone population because the prolonged inactivation of NETs leads to downregulation of adrenergic receptors and

increasing seizure sucesiptibility (Ahern et al., 2006). In amygdaloid kindled rats, the levels of NE were increased in cortex but its metabolite (MHPG) was not altered. However, in the cerebellum the levels of NE and its metabolite (MHPG) were increased (Berzaghi, Naffah-Mazzacoratti, Amado, & Cavalheiro, 1990). In a medical case of twins suffering from neonatal epileptic encephalopathy, the level of NE metabolite (MHPG) has been reported to be decreased in the cerebrospinal fluid of these patients (Brautigam et al., 2002). Suprisingly, ketogenic diet that is considered as a non-pharmacological therapy of epilepsy and some antiepileptic drugs such as phenytoin, carbamazapine, and valproic acid increase the central NE levels as a part of their anticonvulsant effect (Baf, Subhash, Lakshmana, & Rao, 1994a, 1994b; Meshkibaf, Subhash, Lakshmana, & Rao, 1995; Sands, Guerra, & Morilak, 2000). All these findings indicate that NE acts as an endogenous anticonvulsant because NE induces the presynaptic release of GABA (Ferraro et al., 1993; Pittaluga & Raiteri, 1987) and GABA facilitates the release of NE from the noreadrenergic terminal (Bonanno & Raiteri, 1987; Fassio, Rossi, Bonanno, & Raiteri, 1999). Interstingly, stimulation of NMDA receptors (subtype of ionotropic glutamate receptors) decresed the NE levels in rat hippocampus (Dazzi, Matzeu, & Biggio, 2011). So these findings demonstrates that the anticonvulsant properities of NE is due to its interaction with GABAergic and glutamergic meurotransmission.

Noradrenergic Marker	Effect in epilepsy	Reference
Dopamine beta hydroxylase (DBH) (enzyme)	Inhibition of DBH and DBH knockout mice showed more seizure susceptibility.	(Gaval-Cruz et al., 2008)
	DBH enzyme activity is reduced in epileptic patients as compared to normal people.	(Warter et al., 1975)
	DBH activity has been reported to be decreased in GEPRs.	(Browning et al., 1989)
Ascorbic acid (cofactor)	Ascorbic acid can mitigate seizure susceptibility in pilocarpine induced seizures in rats.	(Dong et al., 2013)
Oxygen (cofactor)	Reduced oxygen levels can induce seizures.	(Ingram et al., 2014; Wei et al., 2014)
Norepinephrine	Decreased in GEPRs.	(Browning et al., 1989)
	In amygdaloid kindled rats, the level of NE is increased in cortex and cerebellum.	(Berzaghi et al., 1990)
Norepinephrine metabolite (MHPG) levels	In amygdaloid kindled rats, the levels of MHPG was not altered in the cortex but it is increased in the cerebellum.	(Berzaghi et al., 1990)
	MHPG levels has been reported to be decreased in neonatal epileptic encephalopathy.	(Brautigam et al., 2002)
Norepinephrine release	Significantly increased in rat hippocampus kindled model.	(Bengzon et al., 1992; Shouse et al., 2001)
Noradrenergic agonists	Noradrenergic agonists produced an anticonvulsant effect in kindled rats.	(Loscher & Czuczwar, 1987)
Noradrenergic antagonists	Alpha-1 adrenoreceptor antagonist (prazosin) inhibits the anticonvulsant properties of alpha-1 adrenoreceptor agonists in GEPRs.	(Yan et al., 1998)
Adrenoreceptor density	Alpha-1 adrenoreceptor density is decreased in GEPRs and audiogenic seizure- sensitive DBA/2J mouse strain.	(Jazrawi & Horton, 1986; Nicoletti et al., 1986)
NE transporters expression	Elevated in the locus coeruleus in KA animal model.	(Bengzon et al., 1999)
Norepinephrine reuptake	Significantly decreased in GEPRs.	(Browning et al., 1989)
Norepinephrine transporters (NETs) inhibitors	Both proconvulsant and anticonvulsant properties are produced by NETs inhibitor (reboxetine) in flurothyl-induced seizures in mice.	(Ahern et al., 2006)

Table 3: Different parameters affecting the noradrenergic neurotransmission in epilepsy

Noradrenergic neurotransmission (precursor, synthesizing enzyme, metabolites, receptors, reuptake) plays a significant role in controlling epilepsy and seizure. Any alterations in the noradrenergic neurotransmission is contributed to epilepsy suggesting NE could act as an endogenous anticonvulsant.

2.5 (b) Effect of Kainic acid on Dopaminergic Neurotransmission

Dopaminergic neurotransmission occurs both in the central nervous system (CNS) and peripheral nervous system (PNS). The major/minor dopaminergic pathways in the CNS are the following:

The major pathways are

- ✓ Mesolimbic pathway
- ✓ Mesocortical pathway
- ✓ Nigrostriatal pathway
- ✓ Tuberoinfundibular pathway

The dopaminergic minor pathways are the following:

- ✓ Incerto-hypothalamic pathway
- ✓ Medullary periventricular pathway
- ✓ Chemoreceptor trigger zone pathway

The major dopaminergic pathways in the CNS:

In the mesolimbic pathway, the dopaminergic neurons project from ventral tegmental area, a region of the brain plays a role in rewarding and aversion mechanisms (Bariselli, Glangetas, Tzanoulinou, & Bellone, 2016) to nucleus accumbens, hippocampus, amygdala, and prefrontal cortex to mediate pleasure and reward functions (Adinoff, 2004; Dingman, n.d). In the Mesocortical pathway, the dopaminergic neurons originate form ventral tegmental area into prefrontal cortex to control cognition and decision making (Guzmán, n.d). With regard to the nigrostriatal pathway, the dopaminergic neurons arise from substantia nigra and project to the striatum, any alteration in this dopaminergic pathway is associated with movement disorders (Guzmán, n.d). In the tuberoinfundibular pathway, the dopaminergic neurons project from the

hypothalamus exactly from arcuate and periventricular nuclei to the infundibular region to regulate lactation and sexual functions through the suppression of prolactin release from the anterior pituitary gland (Guzmán, n.d).

The innervation and functions of the minor dopaminergic pathways are:

Incerto-hypothalamic pathway that is divided into a rostral and a caudal part. For the rostral part, the dopaminergic neurons originate from the rostral periventricular nucleus into the preopticosuprachiasmatic and medial preoptic nuclei. For the caudal part, the dopaminergic neurons project from the medial zona incerta into the dorsomedial and anterior hypothalamic nuclei (Lookingland & Moore, 1984). The function of the incerto-hypothalamic pathway is to stimulate the release of luteinizing hormones (MacKenzie, James, & Wilson, 1988) and suppression of gonadotrophin release (Bjorklund, Lindvall, & Nobin, 1975; Sita, Elias, & Bittencourt, 2007). Medullary periventricular pathway is located in the nucleus of the vagus nerve, tractus solitarius, and tegmentum of the periaqueductal gray matter; this pathway is linked to food intake and eating behaviors (Brain, n,d; Prasad, 2010). Chemoreceptor trigger zone pathway that is present in the medulla oblongata particularly located in the area postrema outside the blood brain barrier. Activation of the dopaminergic D_2 receptors in this pathway induces emesis (MacDougall & Sharma, 2019). However, antagonizing D_2 receptor in this particular pathway by using different D_2 antagonists, such as metoclopramide inhibits emesis (Becker, 2010).

Similarly, the peripheral dopaminergic neurotransmission mainly occurs in ophthalmic tract, respiratory tract, cardiovascular system, gastrointestinal tract, urinary tract, liver, genital tract, skin, and muscles. Dopamine in the eye controls visual functions and regulates glaucoma through reducing the intraocular pressure (Bucolo et al., 2019; Zhou, Pardue, Iuvone, & Qu,

2017). In the respiratory tract, dopamine promotes bronchodilation through D_1 receptor activation (Mizuta et al., 2013). In the cardiovascular system, dopamine at low doses can cause peripheral vasodilation through the activation of D_1 receptor while the intermediate doses can stimulate D_1 and beta 1 adrenoreceptors to increase cardiac output, and the high doses of dopamine can have an extra alpha adrenoreceptor stimulation to cause vasoconstriction in the peripheral arteries (Debaveye & Van den Berghe, 2004; Holmes & Walley, 2003). In the gastrointestinal tract, dopamine inhibits gastric smooth muscles contraction and regulates its motility through D_2 receptor activation (C. Bove, Anselmi, & Travagli, 2019; Li, Schmauss, Cuenca, Ratcliffe, & Gershon, 2006; Thompson & de Carle, 1982). In the urinary tract, dopamine promotes renal vasodilation to induce diuresis through D_1 receptor stimulation (Bucolo et al., 2019; Shigetomi & Fukuchi, 1994). In the liver, dopamine increases hepatic perfusion and minimizes liver function loss through D_1 receptor stimulation (Mitchell, Pollock, & Jamieson, 1995). In the genital tract, dopamine induces genital arousal through D_1 and D_2 receptors activation (Giuliano & Allard, 2001). In the skin, dopamine promotes healthy skin appearance and texture through D_1 receptor activation since D1 agonists , such as fenoldopam are used to treat psoriasis (Keren et al., 2019; Shigetomi & Fukuchi, 1994). In the skeletal muscles, dopamine promotes skeletal muscles contraction by acting on the postsynaptic nigrostriatal dopamine D_1 and D_2 receptors to regulate movement (Korchounov, Meyer, & Krasnianski, 2010). In the stomach smooth muscles, dopamine causes contraction in the circular muscles through alpha adrenoreceptors stimulation and relaxation in the longitudinal muscles through D1 receptor stimulation (Kurosawa, Hasler, Torres, Wiley, & Owyang, 1991). Few studies have clearly shown the effect of kainic acid on the dopaminergic neurotransmission. In this review, we will evaluate the dopaminergic effect of kainic acid on dopamine synthesis, storage, release, receptor binding, enzymatic degradation, reuptake, and presynaptic D_2 receptor stimulation.

2.6 Dopamine synthesis:

The precursor (s), cofactor (s) and synthesizing enzymes associated with dopamine synthesis are the following: Tyrosine, tyrosine hydroxylase, tetrahydrobiopterin, iron, L-3,4-dihydroxyphenylalanine, aromatic amino acid decarboxylase, and pyridoxal phosphate.

Tyrosine is a precursor for dopamine synthesis hydroxylated by tyrosine hydroxylase in the presence of tetrahydrobiopterin (BH_4), iron as cofactors to produce L-3,4-dihydroxyphenylalanine (L-dopa) that is decarboxylated by aromatic amino acid decarboxylase and in the presence of pyridoxal phosphate as a cofactor to dopamine. There are several *in vitro* and *in vivo* studies that has evaluated the effect of kainic acid on the synthesis of dopamine. kainic acid (50uM) incubated with substantia nigra from the rat brain increases the damage of dopaminergic neurons and decreases tyrosine hydroxylase expression (the rate limiting enzyme in dopamine synthesis) (Johnson, Luo, & Bywood, 1997). Moreover *in vivo* study, IP injection of kainic acid causes loss of tyrosine hydroxylase expression and damage of the substantia nigra and in rats (Bywood & Johnson, 2000).

Stereotaxic injection of kainic acid into striatum is associated with a significant increase in tyrosine hydroxylase activity that has been demonstrated within two days (Schwarcz & Coyle, 1977). However, within 40 to 150 days of intrastriatal injection of kainic acid, tyrosine hydroxylase activity is decreased that leads to decrease dopamine synthesis (Tissari & Onali, 1982). Long term (two weeks) intranigral injection of kainic acid is associated with decreased tyrosine hydroxylase activity (Nagy, Vincent, Lehmann, Fibiger, & McGeer, 1978).

So based on these studies, short term effect of intrastriatal kainic acid (hours) is associated with increased tyrosine hydroxylase activity; however, long term effect of intranigral and intrastriatal kainic acid (weeks and months) respectively is associated with decreased tyrosine

hydroxylase activity. Intrastriatal injection of kainic acid for one week is followed by high levels of (Tetrahydrobiopterin BH_4) in the striatal astrocytes (Foster, Christopherson, & Levine, 2002). Kainic acid induced status epilepsy has a role to increase mitochondrial iron in rat hippocampus to cause oxidative stress and hippocampal brain damage (L. P. Liang, Jarrett, & Patel, 2008). Degeneration of dopaminergic neurons by intrastriatal kainic acid injection leads to decrease dopamine synthesis by significantly decreasing aromatic L- amino acid decarboxylase activity in the striatum (Melamed, Hefti, Pettibone, Liebman, & Wurtman, 1981). Based on the decrease of aromatic L- amino acid decarboxylase activity , L-dopa will not be converted to dopamine and L-dopa will be accumalated in the striatum (Melamed, Hefti, & Wurtman, 1980). All kainic acid lesions have been done in the substantia nigra or the striatum because they are considerd as a two major components of the nigrostriatal dopaminergic pathway that play a role in the central dopaminergic neurotransmission in the brain. Pyridoxal phosphate (pyridoxine) is a cofactor of aromatic L-amino acid decarboxylase enzyme. Pyridoxal phosphate has a protective role in attenuating seizures by increasing the levels of gamma-aminobutyric acid (GABA) since pyridoxal phosphate is considered as a cofactor of glutamate decarboxylase that converts glutamate into GABA (Stephens, Havlicek, & Dakshinamurti, 1971; Wilson, Plecko, Mills, & Clayton, 2019). Moreover, pyridoxal phosphate when it is given with sodium valproate that increases GABA brain levels can reduce the high levels of glutamate and calcium influx in the cerebral cortex of mice induced by domoic acid that is considered as an analogue of kainic acid (Dakshinamurti, Sharma, & Geiger, 2003). Both pyridoxal phosphate and sodium valporate increase GABA brain levels to inhibit further seizures. Due to the above effect on the synthesizing enzymes and cofactors, Long term effect of kainic acid (weeks) is associated with DA depletion in the substantia nigra and striatum (Friedle, Kelly, & Moore, 1978). However, short term effect of acute intrastriatal

kainic acid (hours) is associated with DA level increase in the striatum (Braszko, Bannon, Bunney, & Roth, 1981).

2.7 Dopamine metabolite levels:

Dopamine is metabolized by monoamine oxidase B and catechol-O-methyl transferase into 3,4-dihydroxyphenyl acetic acid (DOPAC), 3-methoxy tyramine (3-MT), and homovanillic acid (HVA). There are several *in vivo* studies elucidating the effect of kainic acid on dopamine metabolites. Levels of dopamine metabolite DOPAC (3,4-dihydrophenylacetic acid) and dopamine turnover which refers to (the ratio of dopamine metabolite to the dopamine itself) are elevated in the striatum and the contralateral (opposite) side of substantia nigra after two days of unilateral intrastriatal kainic acid injection (Sperk, Berger, Hortnagl, & Hornykiewicz, 1981). Moreover, DOPAC and HVA levels are increased after direct injection of kainic acid into the striatum (Guevara, Hoffmann, & Cubeddu, 1997). However, long term intrastriatal kainic acid injection is followed by DOPAC content reduction (Tissari & Onali, 1982). Regarding 3-MT, its levels is significantly decreased after two days of intrastriatal kainic acid injection (Naudon, Dourmap, Leroux-Nicollet, & Costentin, 1992).

Parameters affecting neurotransmission	Dopaminergic neurotransmission	Kainic acid effect	Reference
Precursor	**Tyrosine**	Not altered in striatum.	(Korf & Venema, 1983)
	L-dopa	Increased in striatum.	(Melamed et al., 1980)
Cofactors	**Tetrahydrobiopterin BH_4**	Its levels are elevated In striatum.	(Foster et al., 2002)
	Irons	Increased in hippocampus	(L. P. Liang et al., 2008)
	Pyridoxal phosphate	Exogenous Vit.B_6 attenuated seizures induced by domoic acid in the cerebral cortex	(Dakshinamurti et al., 2003; Stephens et al., 1971; Wilson et al., 2019)
Synthesizing enzymes	**Tyrosine hydroxylase (Expression and activity)**	Tyrosine hydroxylase expression is reduced in substantia nigra	(Johnson et al., 1997)
		Short term effect of kainic is associated with increased TH activity in striatum	(Schwarcz & Coyle, 1977)
		Long term effect of kainic acid is associated with decreased TH activity in striatum and substantia nigra	(Nagy et al., 1978; Tissari & Onali, 1982)
	Aromatic L- amino acid decarboxylase activity	Decreased in striatum	(Melamed et al., 1981)
Neurotransmitter	**Dopamine**	Short term effect of KA is associated with dopamine increase in striatum	(Braszko et al., 1981)
		Long term effect of KA is associated with dopamine decrease in striatum	(Friedle et al., 1978)
Metabolites	**3,4- Dihydrophenylacetic acid (DOPAC)**	Increased (short term effect) in striatum, substantia nigra, and caudate putamen	(Guevara et al., 1997; Sperk et al., 1981)
		Decreased (long term effect) in striatum	(Tissari & Onali, 1982)
	Homovanillic acid (HVA)	Increased in caudate putamen	(Guevara et al., 1997)
	3-Methoxy tyramine	Decreased in striatum	(Naudon, Dourmap, et al., 1992)

Table 4: The effect of kainic acid on parameters affecting dopaminergic synthesis

2.8 Dopamine storage:

Once a neurotransmitter (dopamine, noradrenaline, or serotonin) is synthesized, it has to be stored in a vesicle with the help of vesicular monoamine transporter (VMAT) before exocytotic release (Bernstein, Stout, & Miller, 2014). It is classified into VMAT1 and VMAT2 where VMAT1 is present in the peripheral nervous system and VMAT2 is present in both peripheral and central nervous system (Weihe, Schafer, Erickson, & Eiden, 1994). Neurotoxins like pesticides (polychlorinated biphenyls, brominated flame retardants) and psychostimulants, such as dopamine releasing agents (methamphetamine) and dopamine reuptake inhibitors (cocaine) can decrease the vascular uptake of dopamine (Bernstein et al., 2014; Fleckenstein & Hanson, 2003). Severely lesioned subregions in the striatum by kainic acid in male sprague-dawley rats will cause a significant reduction in vascular monoamine transporters (VMAT) densities in 15 days post kainic acid lesion. Once the density of VMAT is reduced, the reuptake of monoamines from the cytosol to vesicles to be stored is reduced, so dopamine will be metabolized in the cytosol to cause oxidative stress and neurodegeneration (Naudon, Leroux-Nicollet, Boulay, & Costentin, 2001). The decrease of VMATs after intrastriatal kainic acid lesion were more prominent in 30 and 60 days, which means that the destruction of VMAT by striatal kainic acid lesion is time dependent (Naudon, Leroux-Nicollet, & Costentin, 1992). Regarding the storage vesicles, after one month injection of kainic acid into thalamus, the synaptic vesicles are less expressed in afferent fibers of the lesioned thalamus which is considered as a part of the dopaminergic mesolimbic pathway (Weil-Fugazza, Peschanski, Godefroy, Manceau, & Besson, 1988).

Parameters affecting dopamine storage	**Kainic acid effect**	**Reference**
VMAT	VMAT densities decrease in striatum	(Naudon et al., 2001; Naudon, Leroux-Nicollet, et al., 1992)
Storage Vesicles	The synaptic vesicles are less expressed in the thalamus	(Weil-Fugazza et al., 1988)

Table 5: The effect of kainic acid on parameters affecting dopamine storage

2.9 Dopamine release:

Once the neurotransmitter is stored in a synaptic vesicle, the action potential that is defined as an electrical stimulus that is generated by influx of sodium ions to depolarizes the presynaptic axon terminal to cause calcium (Ca^{++}) release that facilitates synaptic vesicle diffusion to release dopamine into synaptic cleft. Dopamine release is mainly based on the content of dopamine stored in the vesicle and the influx of calcium through the presynaptic calcium channel. Intrastriatal injection of kainic acid in rats induces the release of dopamine and aspartate (Jacobsson, Cassel, Karlsson, Sellstrom, & Persson, 1997). Dopamine neurons firing which means more dopamine release that can alter the synaptic plasticity is increased in one-hour post injection of kainic acid; however, in 12 hours, dopamine neuron firing is significantly decreased (Braszko et al., 1981). A presynaptic calcium influx is induced by intrastriatal kainic acid to cause high dopamine release (Carrozza, Ferraro, Golden, Reyes, & Hare, 1991).

Parameters affecting dopamine release	**Kainic acid effect**	**Reference**
Presynaptic calcium channel influx	Induces calcium influx	(Carrozza et al., 1991)
Dopamine release	Enhances dopamine release	(Braszko et al., 1981; Jacobsson et al., 1997)

Table 6: The effect of kainic acid on parameters affecting dopamine release

2.10 Dopamine Receptor binding:

Dopamine receptors are classified into D_1 and D_2 like receptors. The D_1 like receptors are D_1 and D_5 receptors. The D_2 like receptors are D_2, D_3, and D_4 receptors. Dopamine receptors are widely expressed in the CNS and peripheral nervous system (Missale, Nash, Robinson, Jaber, & Caron, 1998). D_1 and D_2 like receptors are both G protein coupled receptors; D_1 like receptors are coupled to Gs protein that is considered as a stimulatory protein to stimulate adenyl cyclase, but D_2 like receptors are coupled to Gi protein that is an inhibitory protein to

inhibit adenyl cyclase (Missale et al., 1998). D_1 and D_5 receptors are located in the postsynaptic dopamine cells while D_2 and D_3 receptors are located in the presynaptic and postsynaptic dopaminergic neurons (Baik, 2013b; Beaulieu & Gainetdinov, 2011). D_1 receptor activation will stimulate adenyl cyclase and increases cyclic adenosine monophosphate (cAMP) to activate protein kinase A (PKA) that activates dopamine regulated neuronal phosphoprotein (DARPP-32) that mediates the inhibitory effect of protein phosphatase-1 (PP1) to regulate excitation of smooth muscles. Protein phosphatase-1 plays a role in the central nervous system to dephosphorylate many phosphoproteins to regulate synaptic plasticity; it is important as well in learning and memory (Mansuy & Shenolikar, 2006). In D_2 like receptor activation, an inhibitory response would occur by inhibiting adenyl cyclase and decreasing (cAMP) to inhibit protein kinase and DARPP-32 to allow protein phosphatase to dephosphorylate any excitable protein resulting in zero excitation of smooth muscles (Bateup et al., 2008; Hemmings, Greengard, Tung, & Cohen, 1984; Kebabian & Calne, 1979; Kebabian & Greengard, 1971; Missale et al., 1998; Svenningsson et al., 2004). There are several *in vivo* and *in vitro* studies that elucidated the effect of kainic acid on dopamine receptors and dopamine signalling transduction. Unilateral injection of kainic acid into hippocampus produced a significant hippocampal damage of D_1-like and D_2 like receptor binding that leads to desensitization of dopamine receptors present in the post synaptic cleft. However, the dopamine receptor density, which means the number of dopamine receptor present, has not been altered in striatum (Tarazi, Campbell, & Baldessarini, 1998). Dopamine D_1 and D_2 receptor binding in the striatum is relatively reduced after kainic acid lesion in young rats than old rats. D_1 receptor binding is decreased more than D_2 in both age groups after kainic acid injection (L. Zhang, Joseph, & Roth, 1997). However, one study has shown that the susceptibility of striatal D_2 receptor in the presence of kainic acid is becoming more vulnerable than striatal D_1 receptor (Mesco, Joseph, & Roth, 1992). Acute kainic acid administration is resulting in 2 fold reduction of

dopamine D_2 receptor affinity and 2 fold increase in dopamine D_2 densities in brain regions, such as cerebellum, cortex, hippocampus, medulla and pons, midbrain and hypothalamus except striatum (Ridd, Kitchen, & Fosbraey, 1998). The activity of dopamine-sensitive adenylate cyclase was decreased by 85% by stereotaxic injection of kainic acid into striatum (Schwarcz & Coyle, 1977). Injection of kainic acid into rat neostriatum is associated with adenylate cyclase activity reduction up to 56%, and the activity of cyclic nucleotide phosphodiesterase that hydrolyses cAMP or cGMP is diminished up to 84%. However, intrastriatal kainic acid injection did not alter the steady state levels of cyclic AMP *in vivo* and in *vitro* studies (Minneman, Quik, & Emson, 1978). On the other hand, dopamine-sensitive adenylate cyclase was not reduced in substantia nigra after kainic acid lesion (Nagy et al., 1978). Kainic acid did not alter cyclic AMP levels when it was incubated with tissue slice preparation of caudate putamen and accumbens (de Barioglio & Brito, 1996). 32K phosphoprotein is considered as a substrate for the cAMP dependent protein kinase. It is present in the dopaminergic neurons to inhibit protein phosphatase-1 to modulate dopaminergic signaling pathway. It has been found that 32K phosphoprotein is less expressed in the rostal part of striatum and decreased in substantia nigra after kainic acid injection. Interestingly, 32K phosphoprotein has not been altered in neither substantia nigra nor striatum after 6-hydroxydopamine lesion (Lemos, Barberis, Tassin, & Bockaert, 1984). Injection of kainic acid into neostriatum is associated with DARPP-32 and phosphatase inhibitor-1 levels decrease, but the activity of protein phosphatase-1 has not been changed by kainic acid injection in neostriatum (Nairn, Hemmings, Walaas, & Greengard, 1988). Both striatum and neostriatum share the same anatomical structure since both are made up by caudate nucleus and putamen. Based on these studies, kainic acid caused a deleterious effect on dopamine D_1 and D_2 like receptors that affect the dopaminergic intracellular pathway.

Parameters affecting dopamine receptor	Kainic acid effect	Reference
Dopamine receptor binding	Dopamine D_1 and D_2 like receptors loss in hippocampus	(Tarazi et al., 1998)
	Ligand binding to D_1 and D_2 dopamine receptors are reduced in striatum	(Mesco et al., 1992; L. Zhang et al., 1997)
	2fold reduction in D_2 receptors affinities in cerebellum, cortex, hippocampus, medulla and pons, midbrain and hypothalamus	(Ridd et al., 1998)
Dopamine receptor density (dopamine D_1 like and D_2 like receptors)	Not altered (D_1 like and D_2 like receptors) in striatum	(Tarazi et al., 1998)
	2 folds increase in D_2 receptors densities in cerebellum, cortex, hippocampus, medulla and pons, midbrain and hypothalamus	(Ridd et al., 1998)
Dopamine sensitive adenyl cyclase activity	Decreased in striatum	(Schwarcz & Coyle, 1977)
	Not altered in substantia nigra	(Nagy et al., 1978)
	Decreased in neostriatum	(Minneman et al., 1978)
Cyclic AMP	Not altered in neostriatum	(Minneman et al., 1978)
	Not altered in Caudate putamen and accumbens.	(de Barioglio & Brito, 1996)
32K phosphoprotein	Less expressed in Rostal part of striatum	(Lemos et al., 1984)
	Decreased in substantia nigra	(Lemos et al., 1984)
	Decreased in neostriatum	(Nairn et al., 1988)
protein phosphatase-1 levels	Decreased in neostriatum	(Nairn et al., 1988)

Table 7: The effect of kainic acid on parameters affecting dopamine receptors

2.11 Termination of dopaminergic neurotransmission:

Dopaminergic neurotransmission is terminated by the following process:

- ✓ Enzyme degradation by monoamine oxidase B or catechol-O-methyl transferase.
- ✓ Reuptake by dopamine transporters.
- ✓ Pre-synaptic receptor activation of D_2 receptor.

2.11 (a) Enzyme degradation by monoamine oxidase (MAO):

Monoamine oxidase is an enzyme that exists in the central and peripheral nervous system to oxidize monoamines, such as dopamine, serotonin, and norepinephrine into their relative metabolites. There are two forms of monoamine oxidase: MAO A and MAO B (Fowler et al., 2015). MAO inhibitors is a class of drugs used when there is low levels of neurotransmitters (dopamine, norepinephrine, and serotonin) to increase the level of monoamines in the postsynaptic cleft to target neuropsychiatric conditions where there is low levels of monoamines (Kumar, Gupta, & Kumar, 2017). Several studies have shown the effect of kainic acid on MAO enzymes activity. Injection of kainic acid (2 ug) to adult male Sprague-dawley rats caused a significant decrease in MAO-A activity where 90% of dopamine deamination was performed by MAO-A enzyme. This study was performed in the glial cells of the striatum and the decrease was observed within two days of injection and remained in the same level up to 12 days (Schoepp & Azzaro, 1983).

	Kainic acid effect	**Reference**
MAO A activity	Decreased in striatum	(Schoepp & Azzaro, 1983)

Table 8: The effect of kainic acid on MAO activity

2.11 (b) Enzyme degradation by catechol-O-methyl transferase (COMT):

Catechol-O-methyl transferase is an enzyme that metabolizes catecholamines in the central and peripheral nervous system into their metabolites. COMT expression is high in the peripheral tissues, such kidney and liver and low in the brain (Myohanen, Schendzielorz, & Mannisto, 2010). There are two forms of COMT: soluble and membrane bound enzymes, both isoforms are equally distributed in tissues; however, the membrane bound COMT is preferably located in brain tissues especially hippocampus, hypothalamus, and cerebral cortex, also it has been reported that both isoforms are present in microglial and astroglial cells (Myohanen et al., 2010). Soluble and membrane bound COMT have distinct roles, the membrane bound COMT is responsible for the O-methylation of the dopaminergic and noradrenergic neurotransmitters (Roth, 1992). However, the soluble COMT isoform is responsible for the elimination of the toxic biological catechol, so the soluble COMT form could be classified as a detoxifying agent (Kaakkola, Gordin, & Mannisto, 1994; Mannisto et al., 1992). COMT inhibitors beside MAO B inhibitors can be used in the treatment of Parkinson disease (Finberg, 2019). Based on published studies, kainic acid had effect on COMT activity for both isoforms. Intrastriatal injection of kainic acid in rats caused a significant increase of soluble COMT activity but not in the membrane bound COMT since the membrane bound COMT activity is decreased in some extent (Espinoza, Manago, Leo, Sotnikova, & Gainetdinov, 2012). Soluble COMT has been reported to be found in the striatal glial cells, while striatal membrane bound COMT might be present in the postsynaptic neuronal and extra neuronal cells (Kaakkola, Mannisto, & Nissinen, 1987; Rivett, Francis, & Roth, 1983).

	Kainic acid effect	**Reference**
Soluble COMT activity	increased	(Kaakkola et al., 1987)
Membrane bound COMT activity	decreased	(Kaakkola et al., 1987)

Table 9: The effect of kainic acid on COMT activity

2.11 (c) Reuptake by dopamine transporters (DATs)

Dopamine transporters are plasma membrane proteins that exists in the presynaptic neuron to pump the dopamine from the synaptic cleft into cytosol. Since Parkinson disease, attention deficit hyperactivity syndrome, and bipolar disorder depressive phase are attributed to low dopamine levels, DATs can be used to target these disorders to improve dopamine signaling by inhibiting its reuptake back to cytosol (Vaughan & Foster, 2013). DATs density is significantly reduced in severely kainic acid lesioned male sprague- dawley rats in the striatum in 15 days after kainic acid injection. Once the density of DAT is reduced, the reuptake of dopamine from the postsynaptic cleft to the presynaptic neurons where these transporters are present is decreased that leads to increase the dopamine concentration in the post synaptic cleft that causes the desensitization of the dopaminergic receptors and dysregulation of monoaminergic transmission, as well as damaging the monoaminergic terminal (Naudon et al., 2001).

	Kainic acid effect	**Reference**
Dopamine transporters densities	Decreased	(Naudon et al., 2001)

Table 10: The effect of kainic acid on dopamine transporters densities

2.11 (d) Presynaptic dopamine receptors activation

Presynaptic dopaminergic receptors (D_2 receptors) were unaffected by intrastriatal kainic acid injection for 5-6 days (Bannon, Bunney, Zigun, Skirboll, & Roth, 1980).

	Kainic acid effect	**Reference**
Presynaptic dopaminergic D_2 receptors	Unaffected	(Bannon et al., 1980)

Table 11: The effect of kainic acid on presynaptic dopamine D_2 receptor

Based on the literature review, kainic acid affects the dopaminergic neurotransmission synthesis by increasing the dopamine levels in the short term and decreasing its levels in the long term. Kainic acid lesion is associated with a reduction in the number of synaptic vesicle and enhancing the dopamine release. Based on high dopamine release, D_1 and D_2 like receptors binding affinities are significantly reduced due to desensitization. The reuptake of dopamine by DATs is decreased by kainic acid lesion as well as MAO A activity. However, COMT activity is increased for the soluble form and decreased for the membrane bound form by kainic acid lesion. Pre-synaptic D_2 was not affected by kainic acid .Interestingly, the toxic effect of kainic acid is not restricted to be involved in the CNS, it is extended to affect the PNS, such as heart, kidney, gastrointestinal tract, and sexual organs.

2.12 Effect of kainic acid on dopaminergic pathways and peripheral organs

Dopaminergic Neuronal Tracts in the CNS	Physiological function (s) of dopamine	Effect of Kainic Acid
1. Mesolimbic pathway	Pleasure and reward function	Bilateral injection of KA to the hippocampus induced Spontaneous locomotor activity (Wilkinson et al., 1993)
2. Mesocortical pathway	Cognition and decision making	15 days after KA injection showed a reduction in the number of the inhibited and excited cortical neurons in the mesocortical pathway (Ferron, Thierry, Le Douarin, & Glowinski, 1984)
3. Nigrostriatal pathway	Locomotor activity	KA has been used to restore the nigrostriatal dopaminergic tract in PD model rats (Weng et al., 2017)
4. Tuberoinfundibular pathway	Suppression of prolactin release	KA increases of dopamine release that causes a suppression of prolactin secretion in male rats (Pinilla, Gonzalez, Tena-Sempere, Aguilar, & Aguilar, 1996b) and prepubertal female rats (Pinilla, Gonzalez, Tena-Sempere, Aguilar, & Aguilar, 1996a)
5. Incerto-hypothalamic pathway	Suppression of gonadotrophin release	Luteinizing hormone release is enhanced after KA injection, but the LH hormone response is decreased with repetitive injection of KA (Abbud & Smith, 1991)
6. Medullary periventricular pathway	Modulation of eating behaviors	Injection of kainic acid into a dorsal motor nucleus of the vagus nerve (medullary periventricular pathway connections) caused gastric lesion in rats (Okumura et al., 1989)
7. Chemoreceptor trigger zone (CTZ)	Emesis	IP injection of domoic acid that is considered as an analogue of kainic acid is associated with area postrema damage, where the CTZ is located there (Bruni, Bose, Pinsky, & Glavin, 1991)
8. cortico-striato-pallido-thalamo-cortical circuitry (Alexander and others 1986).	Cognitive control and emotion (Peters, Dunlop, & Downar, 2016)	Alterations of lipid levels in the cerebral cortex, thalamus, and striatum has been reported after acute administration of KA to induce seizure (Lerner, Post, Loch, Lutz, & Bindila, 2017)
9. Pyramidal tract	Controls voluntary movement (AbuHasan & Munakomi, 2020)	Significant increase of cholecystokinin expression has been reported in the cerebral cortex after kainic acid injection (Gruber, Greber, & Sperk, 1993)
10. Extrapyramidal tract	Controlling involuntary movement and maintaining posture (Lee & Muzio, 2020)	In the extrapyramidal system, intracerebral injection of KA is associated with GABA-ergic neurons alterations that is responsible for movement abnormalities in rats (Kurihara, Kuriyama, & Yoneda, 1980)

Table 12: The effect of kainic acid on dopaminergic pathways

System / Organ	Physiological function (s) of dopamine	Effect of Kainic Acid
Ophthalmic	Regulation of visual functions, refractive development, glaucoma, and stimulation of eye growth (Bucolo et al., 2019; Zhou et al., 2017)	Kainic acid induces enlargement of the eye in chickens (Wildsoet & Pettigrew, 1988)also it has been reported that kainic acid induces retinal synapse damage in chickens as well (Fleming et al., 2018)
Respiratory	Bronchodilation through the activation of D_1 like receptors (Mizuta et al., 2013)	Obstructive apnea has been showed after intrahippocampal injection of KA (Jefferys, Arafat, Irazoqui, & Lovick, 2019)
Cardiovascular **Heart** **Blood vessel**	Increasing cardiac output to target congestive heart failure (Rajfer, Borow, Lang, Neumann, & Carroll, 1988) and regulation of blood pressure since the post synaptic D_2 like receptors increase blood pressure and the presynaptic D_2 like receptors produce the reverse effect (Jose, Eisner, & Felder, 1999)	Heart histological damage has been studied in the form of myofibril lysis and mitochondrial damage after intraperitoneal injection of domoic acid that is considered as an analogue of kainic acid (Vieira et al., 2016). Moreover, heart rate and blood pressure are elevated by KA injected into hypothalamus (Soltis & DiMicco, 1991)
Gastrointestinal	Inhibitory effect on gastric smooth muscle contraction (Thompson & de Carle, 1982)and modulation of gastric motility(C. Bove et al., 2019)	Kainic acid induces acid reflex that has been recorded by low PH levels in the esophagus that is considered as a reason for sudden death in seizures induced by kainic acid in rats (Budde et al., 2018)
Urinary	Vasodilation and natriuresis (Shigetomi & Fukuchi, 1994)	Domoic acid (kainic acid analogue) has been studied to cause renal damage (nephrotoxicity) due its accumulation in the kidney (Funk et al., 2014)
Liver	Regulation of glucose metabolism (Ter Horst et al., 2018). Hepatic encephalopathy has been reported in patients with Parkinson disease (Junker, Als-Nielsen, Gluud, & Gluud, 2014)	KA has been reported to increase oxidative stress markers by decreasing the activity of catalase, glutathione peroxidase, and superoxide dismutase in the liver, but the effect was less significant as compared to brain (Szaroma, Dziubek, Gren, Kreczmer, & Kapusta, 2012), also hepatic CYP3A microsomal enzyme is elevated by KA (Runtz et al., 2018)
Sexual Organs	Sexual function motivation and genital arousal (Giuliano & Allard, 2001)	Sexual activity disfunction is followed by KA lesion in the septal area of the limbic system in a female rat (Nance & Myatt, 1987)
Endocrine System	Suppression of gonadotrophin release and prolactin release (Henderson, Townsend, & Tortonese, 2008)	KA at low concentrations induced gonadotrophin release LH and FSH from the anterior pituitary gland (Zanisi, Galbiati, Messi, & Martini, 1994)
Immune	Dopamine regulates the immunity through the production of cytokines and antibodies, apoptosis, and chemotaxis (Arreola et al., 2016)	Kainic acid lesion in the lateral septal area is followed by inhibition of humoral immunity in female rats but not male rats (Wetmore & Nance, 1991)
Smooth Muscle	In circular muscles, dopamine promotes contraction through acting on alpha adrenoreceptors; however, in longitudinal muscles, dopamine induces relaxation through acting on D_1 receptors (Kurosawa et al., 1991).	KA produced contraction of the rat isolated gastric fundus and rectum (Jankovic, Milovanovic, Matovic, & Iric-Cupic, 1999). Moreover, in vivo injection of kainic acid, gastric contractility has been induced (Heymann-Monnikes, Tache, Trauner, Weiner, & Garrick, 1991)
Skeletal Muscle	Dopamine controls movement through the regulation of skeletal muscles tone by D_1 like receptor activation (Schwarz & Peever, 2011)	Chronic lesion of KA for 28 days in the mouse spinal cord caused skeletal muscles degeneration (Blizzard, Lee, & Dickson, 2016)
Skin	Healthy and proper skin appearance (Shigetomi & Fukuchi, 1994). Promotion of skin barrier recovery (Fuziwara, Suzuki, Inoue, & Denda, 2005).	KA is associated with an increase in the nociceptor activity in normal and inflamed rat skin (Du, Zhou, & Carlton, 2006)

Table 13: The effect of kainic acid on peripheral organs

3. Materials and Methods

3.1 Chemicals and Reagents

Thiazolyl blue tetrazolium bromide (MTT) reagent was purchased from Tokyo Chemical Industry (TCI). Trypsin-EDTA solution, penicillin-streptomycin solution, Fetal Bovine Serum (FBS), Dulbecco's Modified Eagle Medium (DMEM), and RPMI-1640 were purchased from Corning (Manassas, VA). Kainic acid was purchased from hello bio (Princeton, NJ). 1-methyl-4-phenylpyridinium (MPP^+), phosphate buffer saline (PBS), dimethyl sulfoxide (DMSO), nicotinamide adenine dinucleotide (NADH), trichloroacetic acid, and thiobarbituric acid, were purchased from sigma Aldrich (St. Louis, MO). For protein quantification, thermo scientific pierce 660 nm protein Assay reagent kit was purchased (Pierce, Rockford, IL). AC-YVAD-AMC (interleukin- 1 converting enzyme substrate), AC-DEVD-AMC (caspase 3 substrate), and Griess reagent were purchased from Enzo life science (Farmingdale, NY). Cell lysis buffer, secondary anti rabbit/ mouse anti bodies, tyrosine hydroxylase, GADPH, primary anti bodies were purchased from cell signalling technology (Cell Signalling Technology, Inc., Danvers, MA). Glutamate was purchased from Alfa Aesar (Haverhill, MA).

3.2 Rat dopaminergic neuronal cells (N27)

N27 rat dopaminergic cells were cultured in DMEM medium supplemented with 10% FBS and 1% Penicillin-Streptomycin Solution. To perform the cell viability assay, N27 cells were grown in 75 cm^2 flask and incubated at 37 °C supplemented with 5% CO_2. When the cells reached confluency, they were detached by trypsinization and seeded in 96 well plate at a density of 1 x 10^5 cells/well (Majrashi et al., 2018).

3.3 Human neuroblastoma neuronal cells (M17)

M17 neuroblastoma cells were cultured in RPMI medium supplemented with 10% FBS and 1% Penicillin-Streptomycin Solution. M17 cells were grown in 75 cm^2 flask and incubated at 37 °C supplemented with 5% CO_2 until they reached confluency. After that, cells were detached by trypsinization and seeded in 96 well plate at a density of 1 x 10^5 cells/well to perform the cell viability assay.

3.4 Treatment design

Kainic acid was freshly prepared prior to each experiment and diluted in sterile water. To elucidate the dopaminergic neurotoxicity of kainic acid, different concentrations (100uM, 250uM, 500uM, 1mM, 2.5mM) of kainic acid were exposed to N27 and M17 neuronal cells for 24, 48, and 72 hours. To establish the neurotoxicity of kainic acid on oxidative stress and apoptosis, M17 neuronal cells were selected. The various groups were control, kainic acid (100uM), kainic acid (2.5mM), glutamate (10mM), glutamate (100mM), and MPP^+ (500uM) exposed to M17 neuronal cells for 48 hours in serum free medium then collected via trypsinization and centrifugation with serum-fed media. The serum-fed media was removed, and the pellet was kept for each group. Cold PBS was added to pellet with sonication under ice and centrifugation at 4°C to have the supernatant layer and to be kept at -80. MPP^+ and glutamate were used to validate the dopaminergic neurotoxicity of kainic acid as positive controls.

3.5 Cytotoxicity assay

MTT cell viability assay was used to evaluate the neurotoxicity of KA on N27 rat dopaminergic neuronal cells and M17 human neuroblastoma cells. The principle behind this assay is MTT (tetrazolium bromide) is reduced into insoluble purple crystal formazan

dye by mitochondrial succinate dehydrogenase, and the formed formazan is measured colorimetry at 544nm using Synergy HT (Winooski, VT, USA) Bio-Tek microtiter plate reader Inc (Berridge, Herst, & Tan, 2005; Katz et al., 2018; Mosmann, 1983; Ramesh et al., 2018). After 48 and 72 hours of incubation with KA, MPP^+ and glutamate in serum free medium, 0.5% w/v MTT reagent was added to each well and incubated for 2 hours. Then the medium was aspirated and DMSO was added to solubilize the formazan crystals and kept for 10 minutes. Results were expressed as a percentage change as compared to control.

3.6 Protein quantification

Thermo scientific pierce 660nm Protein Assay reagent kit (Pierce, Rockford, IL) was used for protein quantification and bovine serum albumin was used as a standard for protein measurement.

3.7 Western Blot analysis of Tyrosine hydroxylase expression

Tyrosine hydroxylase expression was assayed for treated cells by using western blot. Human neuroblastoma M17 neuronal cells were lysed by using lysis buffer and equal protein amounts of cell lysates were analyzed by western blot. The samples were heated to denature the protein at 95℃ for 5minutes and centrifuged for 1 minute before loading on 10% SDS-PAGE gel for protein separation. The separated proteins on SDS-PAGE were transferred onto nitrocellulose membrane and blocked with 5% BSA in Tris-buffered saline plus 0.1% Tween-20 (TBST) at pH 7.4. The membrane blot was incubated overnight at 4℃ with tyrosine hydroxylase antibody constituted in 5% BSA in TBST. Primary antibodies used in this study were anti-GAPDH and anti- tyrosine hydroxylase primary antibodies. The membrane was washed with TBST (3X, each for 5 min) and incubated with species dependent anti-rabbit IgG HRP- linked antibody as a secondary antibody for 60

min at room temperature. Membrane was again washed three times for 5 minutes with TBST. After washing, membrane was analyzed in ChemiDoc^{TM} MP Imaging system.

3.8 Hydrogen peroxide estimation

Control and treated cell homogenates were read fluorometrically using an excitation wavelength 335nm and emission wavelength 390nm. Hydrogen peroxide standard curve was used to estimate hydrogen peroxide content in each sample.

3.9 NADH estimation

Cell homogenates of the control and treated groups were read spectrofluorometrically at 340nm. NADH standard curve was used to estimate NADH content in each sample.

3.10 Nitrite content

Nitrite assay was measured by using Griess reagent. Nitric oxide reacts with sulfanilamide moiety under acidic condition to form diazonium ion. This ion is coupled to N-(1-naphthyl) ethylenediamine to form chromophoric azo product that can be measured spectrophotometrically at 545nm (Giustarini, Dalle-Donne, Colombo, Milzani, & Rossi, 2008).

3.11 Lipid peroxide content

Lipid peroxidation occurs due to degradation of the lipids when free radicals attack the polyunsaturated fatty acid of the cell membrane. Lipid peroxide content was estimated by measuring malondialdehyde (MDA) content in the form of thiobarbituric acid-reactive substances (TBARS) (Ohkawa, Ohishi, & Yagi, 1979). Control and treated cell homogenates were added to trichloroacetic acid (TCA, 20 % w/v), thiobarbituric acid (TBA, 0.5 % w/v), and deionized water and to be placed in water bath at 80ºC for 15

minutes. Then the samples were cooled in ice for 5 minutes and centrifuged at 10,000 rpm. The supernatant was read at 532nm. MDA levels was measured as TBARS per mg protein (Dhanasekaran et al., 2007).

3.12 Interleukin- 1 converting enzyme activity

Interleukin- 1 converting enzyme activity in cell homogenates is detected by the cleavage of (AC-YVAD-AMC) to liberate a fluorescent AMC by Interleukin- 1 converting enzyme to induce inflammation, so the amount of the liberated AMC is proportional to Interleukin-1 converting enzyme activity. Cell homogenate was mixed with AC-YVAD-AMC (10uM) to be measured fluorometrically at excitation wavelength 360nm and emission wavelength 460nm.

3.13Caspase 3 activity

Caspase 3 activity in cell homogenates is detected by the cleavage of (AC-DEVD-AMC) to liberate a fluorescent AMC by caspase 3 in apoptotic cells, so the amount of the liberated AMC is proportional to caspase 3 activity.

Cell homogenate was mixed with AC-DEVD-AMC (10uM) to be measured fluorometrically at excitation wavelength 360nm and emission wavelength 460nm.

3.14 Statistical Analysis

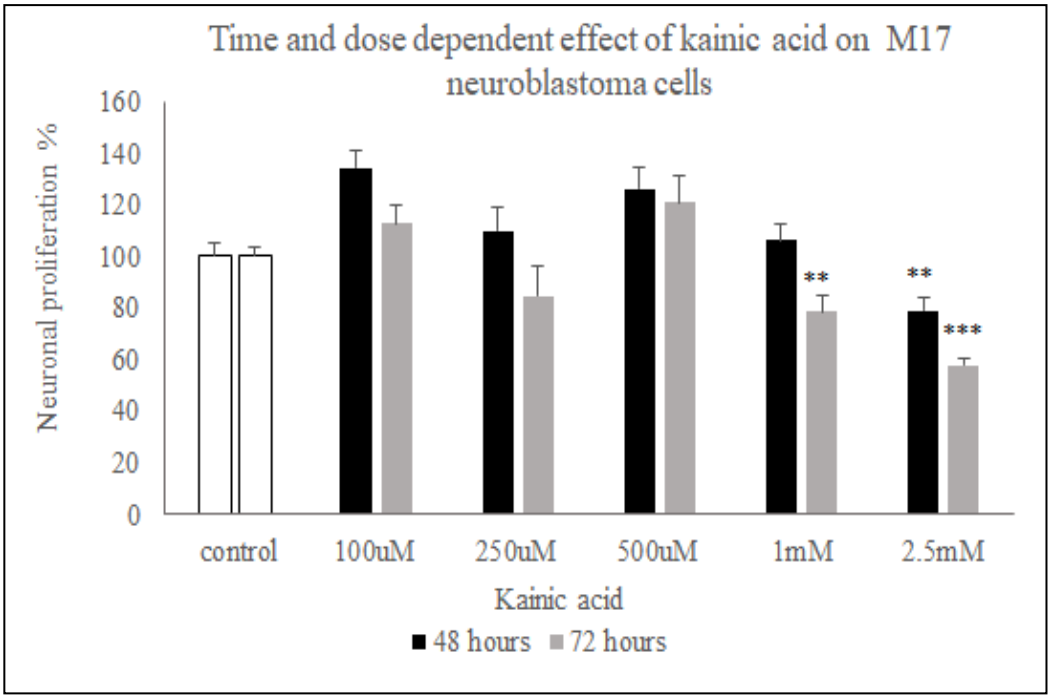
Data were reported as mean ± SEM. Statistical analysis was accomplished using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparison test. $p < 0.05$ was considered to be statistically significant. Statistical analysis was performed using Prism-V software (La Jolla, CA, USA).

4. Results

4.1 Kainic acid induced dose and time dependent reduction of neuroblastoma M17 and dopaminergic N27 neuronal cells based on cell viability assay.

Human neuroblastoma M17 cells and N27 rat dopaminergic neuronal cells were treated with different concentrations (100uM, 250uM, 500uM, 1mM, 2.5mM) of kainic acid for 24, 48 and 72 hours. M17 and N27 neuronal cells treated for 24 hours had no significant neurotoxicity (data not shown). The endogenous neurotoxin glutamate and the exogenous neurotoxin MPP^+ were used as positive controls for validation. Kainic acid caused a significant reduction in M17 and N27 neuronal cell viability in a dose and time dependent manner as compared to control ($n=20$, $p<0.0001$, figure 4.1(a) and (b)). For the positive controls MPP^+ and glutamate, a significant reduction in neuronal cell viability has been elucidated in a dose and time dependent manner in both neuronal cell lines as compared to control. Interestingly, the neurotoxic effect of MPP^+ and glutamate was more pronounced than the neurotoxic effect of kainic acid in both neuronal cell lines ($n=20$, $p<0.0001$, figure 4.1(c), (d), (e), (f)).

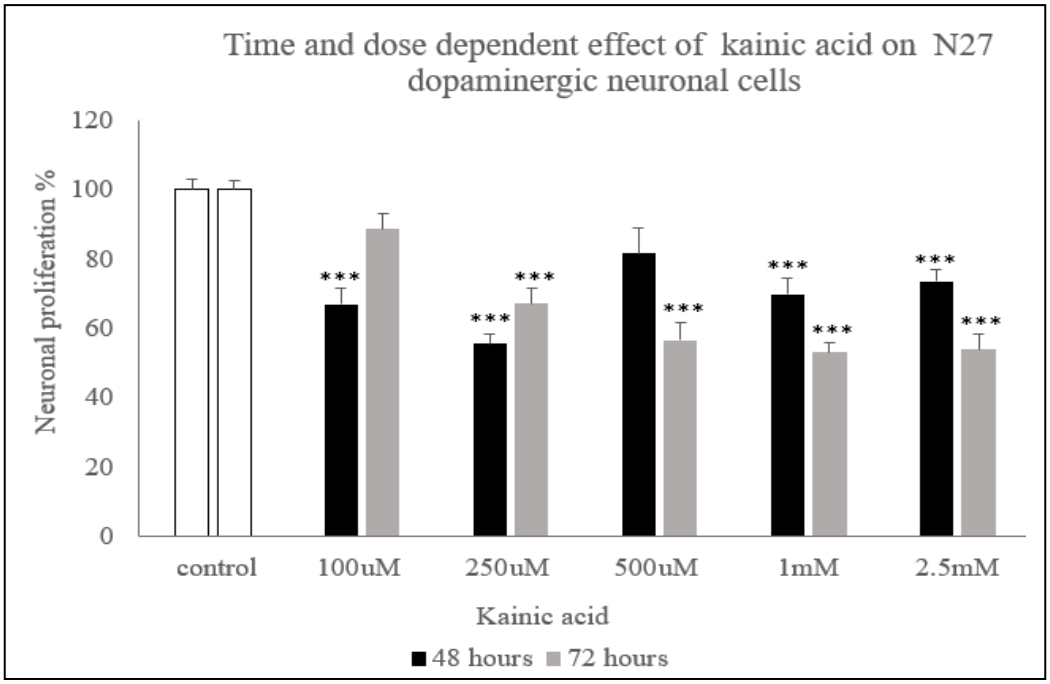
Figure 4 .1 (a) Effect of kainic acid on M17 neuroblastoma cells viability



4.1(a): M17 neuroblastoma cells were treated with different doses of kainic acid for 48and 72 hours

Neuronal viability was evaluated by using the MTT reduction assay. Results were expressed as percentage control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test. Note (*) indicates a statistically significant difference when compared to controls ($p < 0.0001$).

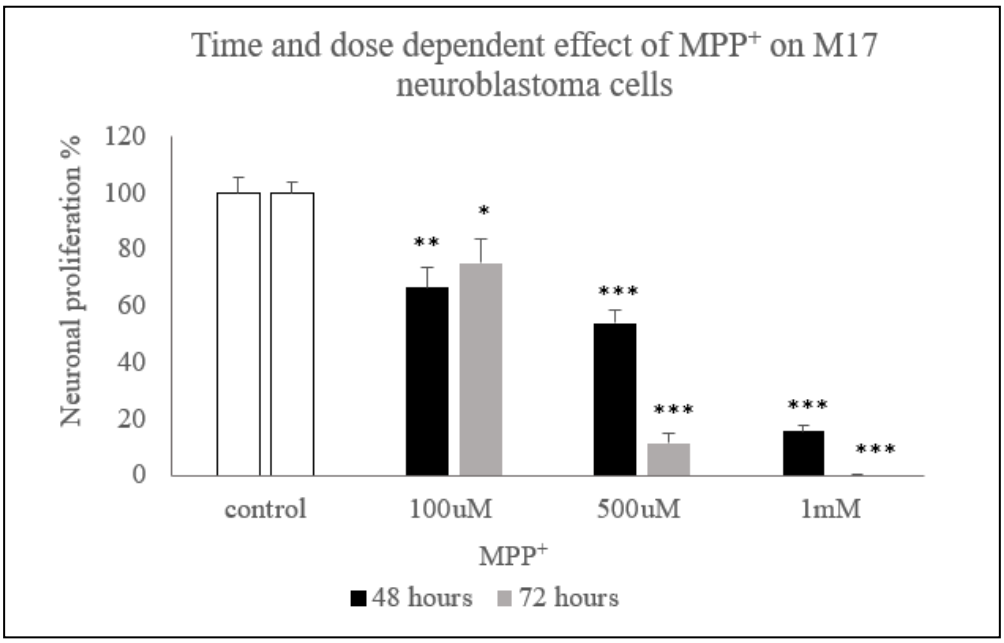
Figure 4.1 (b) Effect of kainic acid on dopaminergic N27 neuronal viability



4.1 (b): N27 dopaminergic neuronal cells were treated with different doses of kainic acid for 48 and 72 hours.

Neuronal viability was evaluated by using the MTT reduction assay. Results were expressed as percentage control ± SEM. Statistical comparisons were made using one- way ANOVA/ Tukey's Multiple Comparison Test. Note (*) indicates a statistically significant difference when compared to controls ($p < 0.0001$).

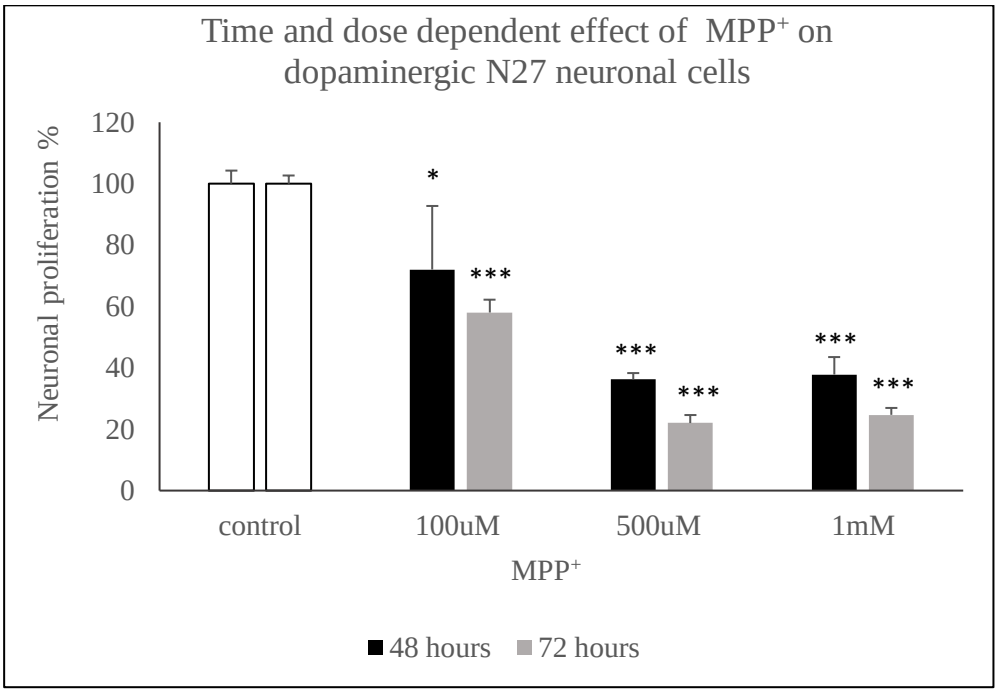
Figure 4.1 (c) Effect of MPP^+ on neuroblastoma M17 neuronal viability



4.1 (c): M17 neuroblastoma cells were treated with different doses of MPP^+ for 48 and 72 hours

Neuronal viability was evaluated by using the MTT reduction assay. Results were expressed as percentage control ± SEM. Statistical comparisons were made using one- way ANOVA/ Tukey's Multiple Comparison Test. Note (*) indicates a statistically significant difference when compared to controls ($p < 0.0001$).

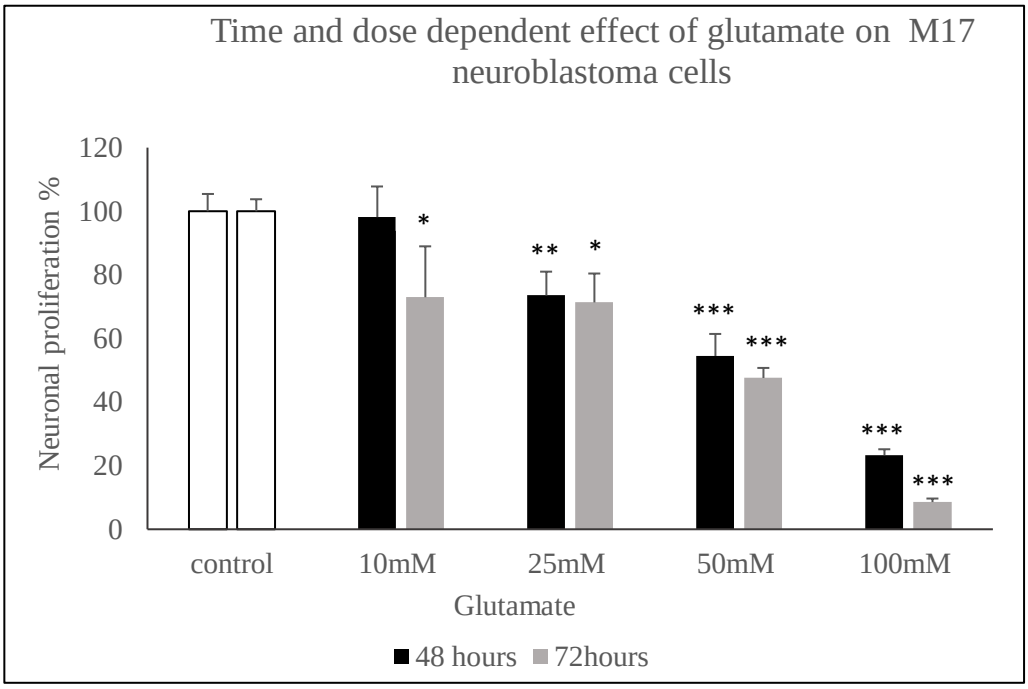
Figure 4.1 (d) Effect of MPP^+ on dopaminergic N27 neuronal viability



4.1 (d): N27 dopaminergic neuronal cells were treated with different doses of MPP^+ for 48 and 72 hours

Neuronal viability was evaluated by using the MTT reduction assay. Results were expressed as percentage control ± SEM. Statistical comparisons were made using one- way ANOVA/ Tukey's Multiple Comparison Test. Note (*) indicates a statistically significant difference when compared to controls ($p < 0.0001$).

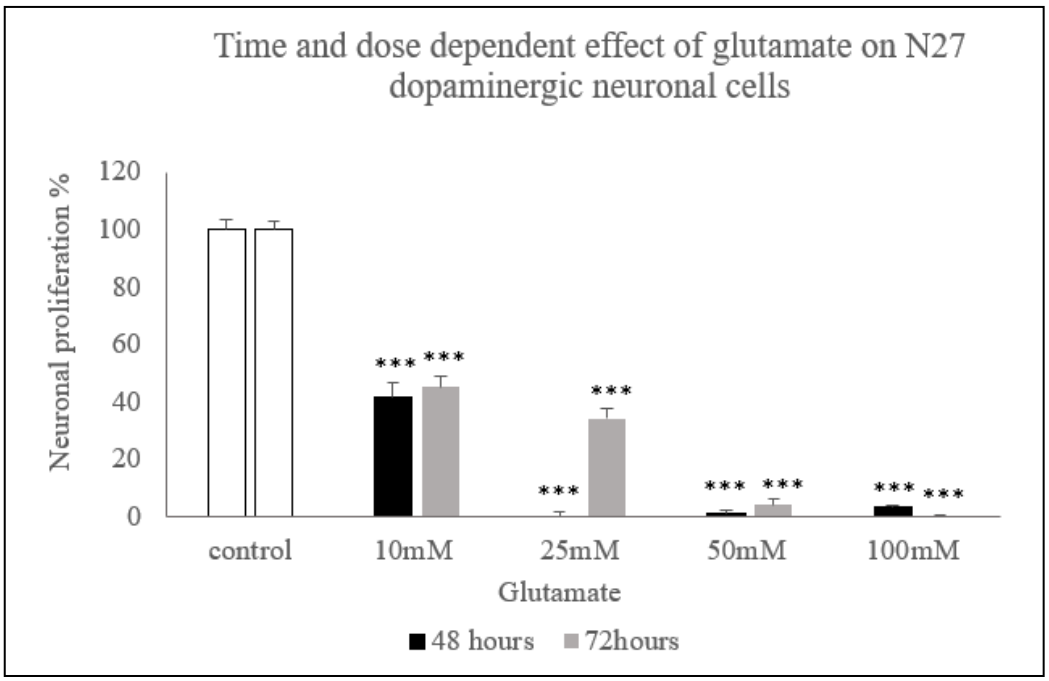
Figure 4.1 (e) Effect of glutamate on neuroblastoma M17 neuronal viability



4.1(e): M17 neuroblastoma cells were treated with different doses of glutamate for 48 and 72 hours

Neuronal viability was evaluated by using the MTT reduction assay. Results were expressed as percentage control ± SEM. Statistical comparisons were made using one- way ANOVA/ Tukey's Multiple Comparison Test. Note (*) indicates a statistically significant difference when compared to controls ($p < 0.0001$).

Figure 4.1 (f) Effect of glutamate on dopaminergic N27 neuronal viability



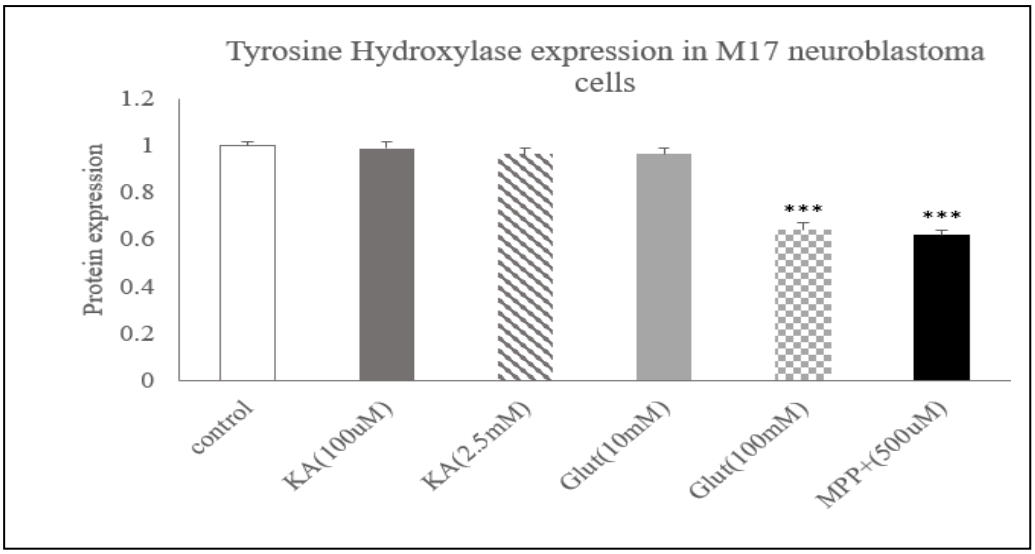
4.1 (f): N27 dopaminergic neuronal cells were treated with different doses of glutamate for 48 and 72 hours

Neuronal viability was evaluated by using the MTT reduction assay. Results were expressed as percentage control ± SEM. Statistical comparisons were made using one- way ANOVA/ Tukey's Multiple Comparison Test. Note (*) indicates a statistically significant difference when compared to controls ($p < 0.0001$).

4.2 Effect of kainic acid, MPP^+, and glutamate on tyrosine hydroxylase expression in M17 neuroblastoma cells.

Tyrosine hydroxylase is the rate limiting enzyme in dopamine synthesis. Any drug that decreases tyrosine hydroxylase expression or activity is considered as a dopaminergic neurotoxin. MPP^+ is a valid dopaminergic neurotoxin, so it is hypothesized that it causes a significant dopaminergic neuronal cell death as compared to control. MPP^+ (500uM) and glutamate (100mM) caused a significant reduction in tyrosine hydroxylase expression in M17 neuroblastoma cells because MPP^+ is a valid dopaminergic neurotoxin as compared to kainic acid and glutamate ($n=3$, $p<0.05$; figure 4.2 (a, b).

a)



b)

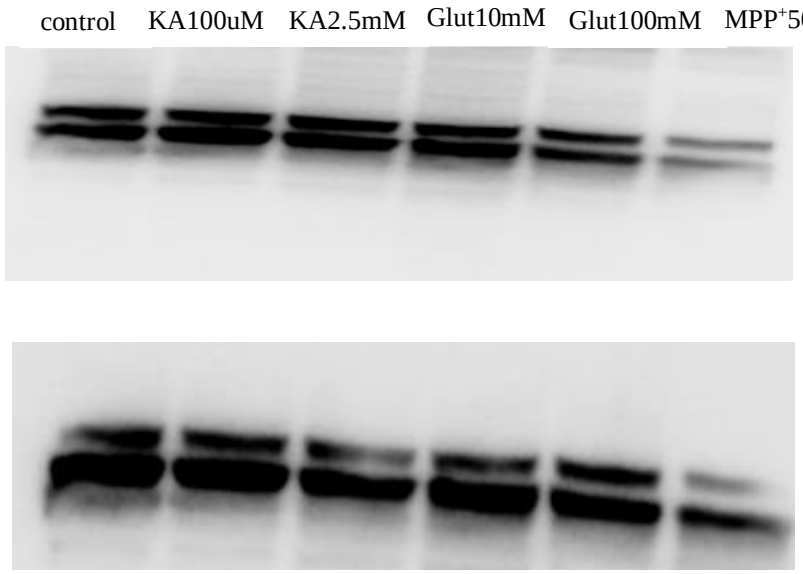


Figure 4.2 (a, b): The effect of kainic acid, MPP^+, and glutamate on Tyrosine hydroxylase expression in M17 neuroblastoma cells.

Glutamate (100mM) and MPP^+ (500uM) caused a significant decrease in tyrosine hydroxylase expression in M17 neuroblastoma cells (n=3, $p<0.05$). blots were prepared by using 1:1000 dilution with primary antibodies. GADPH (1:1000) was used as a loading control. Band densities for each sample were normalized to their respective GAPDH signal and reported as a fold change as compared to control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.3 Effect of kainic acid, MPP^+, and glutamate on H_2O_2 production in M17 neuroblastoma cells.

Generation of hydrogen peroxide is associated with neurodegeneration and oxidative stress. MPP^+ (500μM) caused a significant increase in hydrogen peroxide formation in M17 neuronal cells (n=5, $p<0.05$; figure 4.3).

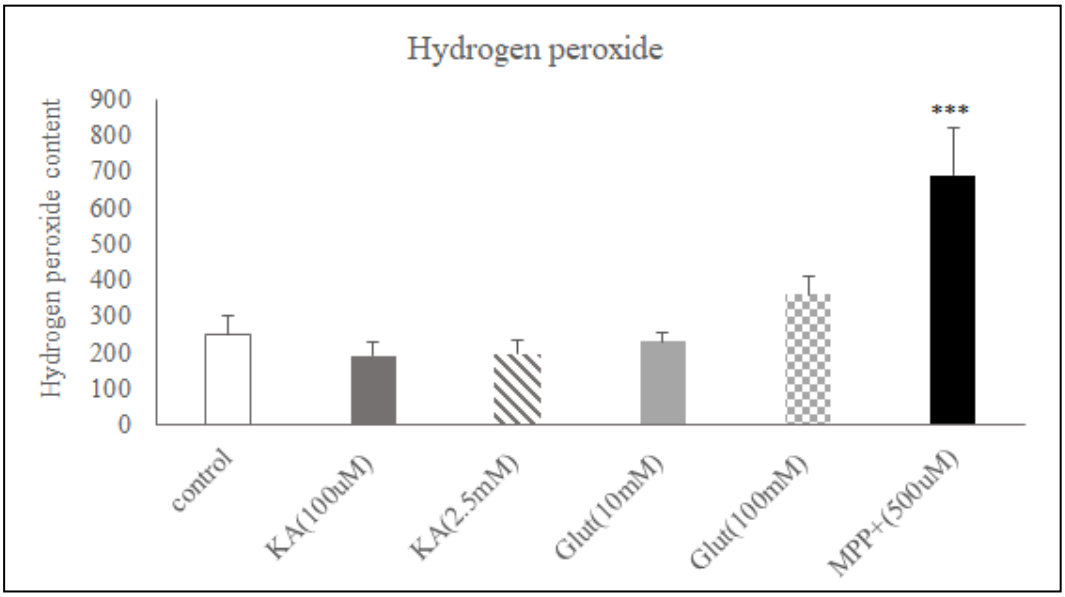


Figure 4.3: The effect of kainic acid, MPP^+, and glutamate on H_2O_2 production in M17 neuroblastoma cells.

MPP^+ (500μM) caused a significant increase in hydrogen peroxide production in M17 neuroblastoma cells (n=5, $p<0.05$). Hydrogen peroxide production was determined spectrofluorometrically at excitation 335/emission 390nm. Results were expressed as control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.4 Effect of kainic acid, MPP^+, and glutamate on NADH production in M17 neuroblastoma cells.

NADH is a cofactor that plays a central role in cellular energy production and metabolism. MPP^+ (500μM) caused a significant reduction in NADH content in M17 neuronal cells (n=5, $p<0.05$; table 14).

Doses	NADH content (uM/ mg protein)
Control	5620.73 ± 686.3
Kainic acid (100uM)	5643.76 ± 640.7
Kainic acid (2.5mM)	4509.56 ± 225.4
Glutamate (10mM)	4219.29 ± 377.1
Glutamate (100mM)	6072.88 ± 457
MPP^+	1432.02 ± 490.4 (***)

Table 14: The effect of kainic acid, MPP^+, and glutamate on NADH content in M17 neuroblastoma cells.

MPP^+ (500μM) caused a significant reduction in NADH content in M17 neuroblastoma cells (n=5, $p<0.05$). NADH content was determined spectrofluorometrically at 340nm. Results were expressed as control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.5 Effect of kainic acid, MPP^+, and glutamate on nitrite production in M17 neuroblastoma cells.

Nitrite production leads to oxidative stress that is associated with neurodegenerative diseases, such as Parkinson disease (Qureshi et al., 1995). MPP^+ (500µM), kainic acid (100uM, 2.5mM), and glutamate (10,100mM) caused an increase in nitrite production in M17 neuronal cells (n=5, $p<0.05$; figure 4.5) but the effect was not statically significant.

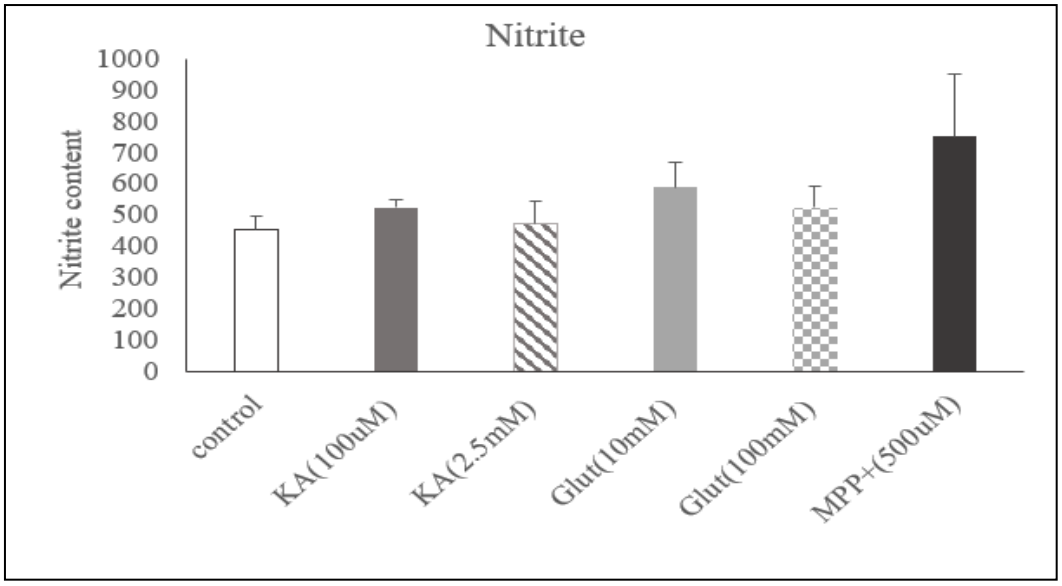


Figure 4.5: The effect of kainic acid, MPP^+, and glutamate on nitrite production in M17 neuroblastoma cells.

MPP^+ (500µM), kainic acid (100uM, 2.5mM), and glutamate (10, 100mM) caused an increase in nitrite content in M17 neuroblastoma cells (n=5, $p<0.05$) but the effect was not statically significant. Nitrite content was determined colorimetrically at 540 nm. Results were expressed as control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.6 Effect of kainic acid, MPP^+, and glutamate on lipid peroxide content in M17 neuroblastoma cells.

MPP^+ (500uM) significantly induced lipid peroxide content in M17 neuronal cells (n=5, $p<0.05$; figure 4.6).

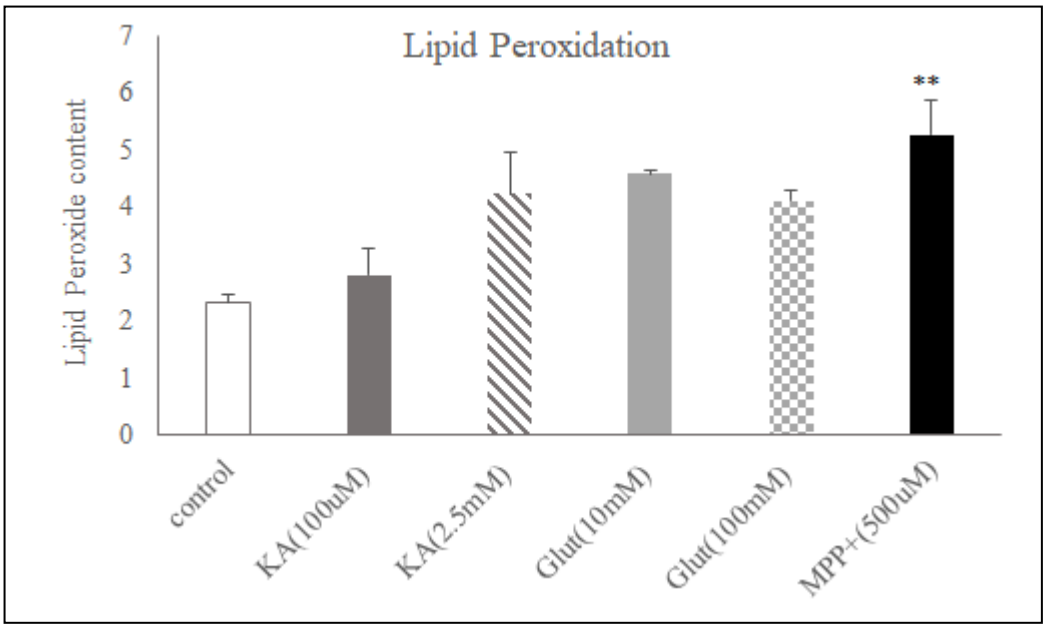


Figure 4.6: The effect of kainic acid, MPP^+, and glutamate on lipid peroxide content in M17 neuroblastoma cells.

MPP^+ (500µM) caused a significant increase in lipid peroxide content in M17 neuroblastoma cells (n=5, $p<0.05$). Lipid peroxidation was measured colorimetrically at 532nm as TBARS, a marker of cellular membrane damage. Results were expressed as control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.7 Effect of kainic acid, MPP^+, and glutamate on interleukin-1 converting enzyme activity in M17 neuroblastoma cells.

Interleukin-1 converting enzyme is an enzyme of cysteine proteases family. It has a role to produce interleukin-1 beta that is considered as a mediator of inflammation (Thornberry & Molineaux, 1995). MPP^+ (500µM) caused a significant increase in interleukin-1 converting enzyme activity in M17 neuronal cells ($n=5$, $p<0.05$; Figure 4.7).

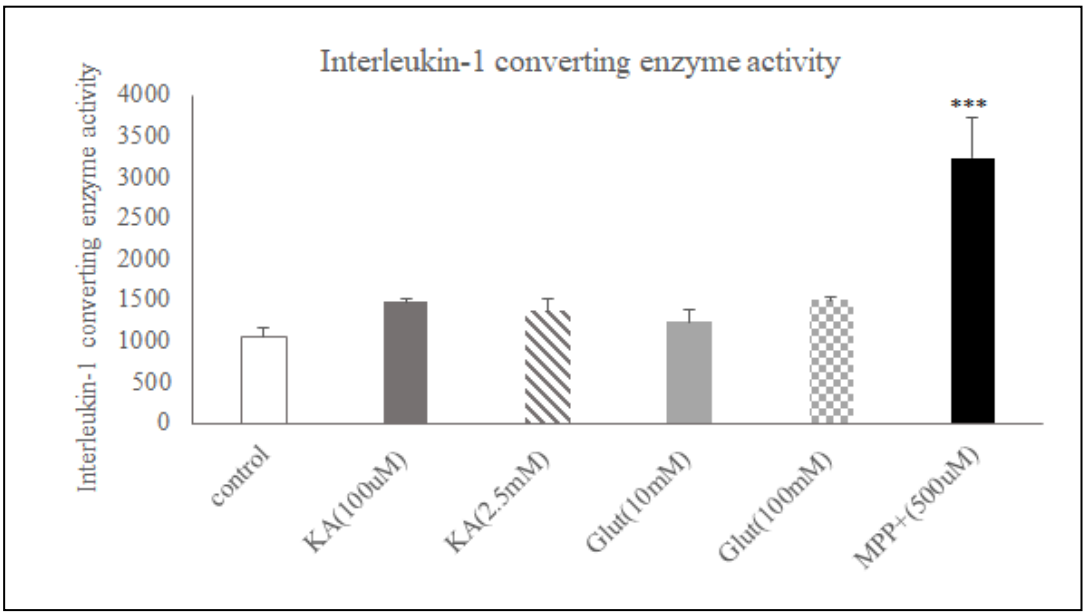


Figure 4.7: The effect of kainic acid, MPP^+, and glutamate on interleukin-1 converting enzyme activity in M17 neuroblastoma cells.

MPP^+ (500µM) caused a significant increase in interleukin-1 converting enzyme activity in M17 neuroblastoma cells ($n=5$, $p<0.05$). Interleukin-1 converting enzyme activity was determined spectrofluorometrically at excitation 360/emission 460 nm. Results were expressed as control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.8 Effect of kainic acid, MPP^+, and glutamate on caspase 3 activity in M17 neuroblastoma cells.

Caspase 3 is an enzyme that mediates programmed cell death (apoptosis) also it plays a major role in normal brain development (Porter & Janicke, 1999). MPP^+ (500µM) caused a significant increase in caspase 3 activity in M17 neuronal cells (n=5, $p<0.05$; Figure 4.8).

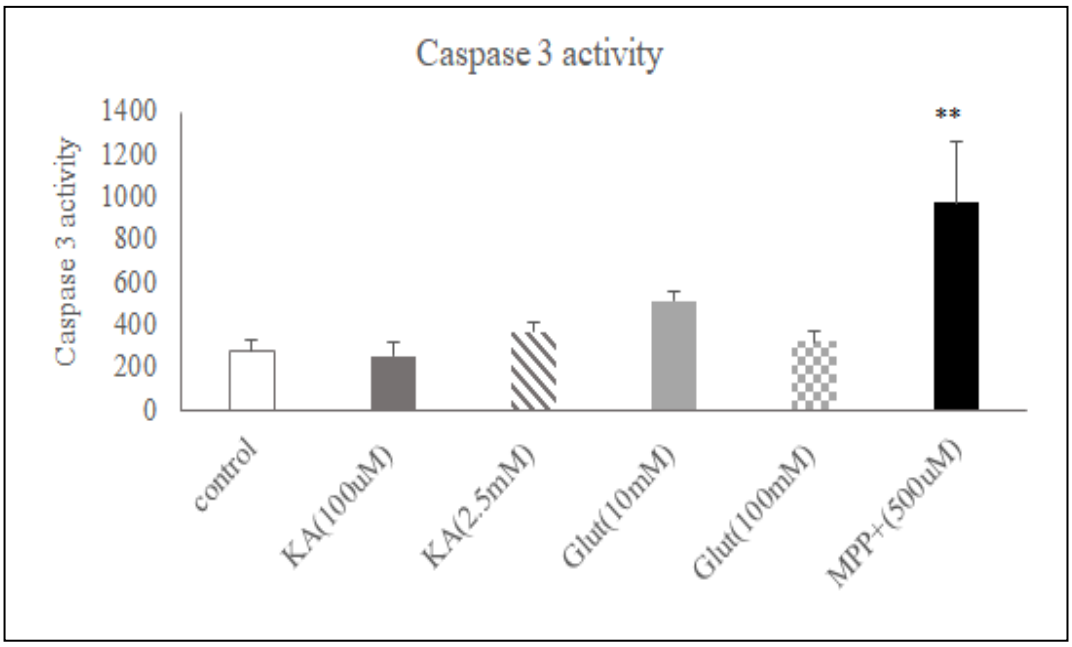


Figure 4.8: The effect of kainic acid, MPP^+, and glutamate on caspase 3 activity in M17 neuroblastoma cells.

MPP^+ (500µM) caused a significant increase in caspase 3 activity in M17 neuroblastoma cells (n=5, $p<0.05$). Caspase 3 activity was determined spectrofluorometrically at excitation 360/emission 460 nm. Results were expressed as control ± SEM. Statistical comparisons were made using one-way ANOVA/ Tukey's Multiple Comparison Test.

4.9 Computational analysis of kainic acid, glutamic acid, and MPTP.

We looked to the structural features of MPTP, glutamate, and kainic acid using quikpro scientific software. Based on log P value (table 15), MPTP is more lipophilic that gives it the capability to cross blood brain barrier to elicit significant dopaminergic neurotoxicity as compared to glutamate and kainic acid (table 16).

Compound	**Molecular weight**	**Donor HB**	**Accept HB**	**Log P**	**% Human oral absorption**	**Rule of 5**
Kainic acid	213.233	3	5.5	-1.3	24.1	0
Glutamic acid	147.13	4	5	-3.02	4.981	0
MPTP	173.257	0	2	2.5	100	0

Table 15: The permissible ranges are as follows: Mol wt: (130–725), Donor HB: (0.0–6.0), Accept HB: (2.0–20.0), LogP: (−2.0 to 6.5), % Human oral absorption: >80% high, <25% low, Rule of five (maximum 4).

Compound	**SASA(Å)**	**FOSA(Å)**	**FISA (Å)**	**PISA (Å)**	**#metab**	**CNS**	**QPlog BB**
Kainic acid	417.089	188.398	201.083	27.608	4	-1	-0.854
Glutamic acid	338.401	81.462	256.939	0	4	-2	-1.3
MPTP	422	199.911	5.935	216.153	3	2	0.9

Table 16: The permissible ranges are as follows: Area are (300–1000), FOSA: Hydrophobic components of the SASA (0.0–750.0), FISA: Hydrophilic components of the SASA (7.0–330.0), PISA: π (carbon and attached hydrogen) components of the SASA (0.0–450.0), #metab: Number of likely metabolic reactions (1 – 8) CNS: −2 (inactive) to +2 (active), QPlog BB: (−3.0 to −1.2) polar compounds have large negative values

5. Discussion

Kainic acid is a dicarboxylic acid, a pyrrolidine carboxylic acid, a L-proline derivative and a non-proteinogenic L-alpha-amino acid. Kainic acid exerts its pharmacological and toxicological effect by acting as a kainate receptor (ionotropic glutamate receptor agonist). Pharmacologically, it has been considered as an antihelminth drug to remove worms from the gastrointestinal tract and as an excitatory amino acid (glutamate) agonist. Kainate receptors are highly expressed in the brain with the greatest expression in the CA3 region of the hippocampus, and in the amygdala, perirhinal and entorhinal cortex (Miller et al., 1990). It is mainly used as an animal model to induce seizures model of epileptogenesis. Other glutamate analogue structurally related to kainic acid is domoic acid. In this study, Both M17 human neuroblastoma cells and rat N27 rat dopaminergic neuronal cells were used because both express high tyrosine hydroxylase activity (rate limiting enzyme in dopamine synthesis). Moreover, M17 human neuroblastoma cells express moderate dopamine-beta- hydroxylase activity (the enzyme that converts dopamine into norepinephrine) which gives it the capability to express both dopamine and norepinephrine. For rat N27 dopaminergic neuronal cells, they express DATs, MAO transporters, and VMATs that make both dopaminergic N27 and M17 neuronal cells good in vitro models to study dopaminergic neurotoxicity of various neurotoxin.

Glutamic acid is the main excitatory neurotransmitter that binds to a ligand gated ion channel, such as NMDA, AMPA, and kainate receptors to cause depolarization under normal conditions (Monaghan, Bridges, & Cotman, 1989). Normal endogenous levels of glutamate in the brain are ranged between 0.5-2µM in the extracellular fluid of the brain which is required to maintain normal functions of neurons, astrocytes and blood brain barrier (Hawkins, 2009). In rats, basal glutamate levels in hippocampus is 25nM and 0-2 µM in the whole brain (Blaker, Moore, &

Yamamoto, 2019; Herman & Jahr, 2007). If glutamate levels exceed normal levels, neuronal death can occur. Similarly, in our study low doses of glutamate did not induce any neurotoxicity, however, at high doses 10,25,50, and 100mM glutamate caused significant dopaminergic neuronal death.

Excitotoxicity occurs when the neurons are activated / excited by glutamate to induce depolarization. However, prolonged activation of glutamate receptors leads to excitotoxicity and neuronal cell death that is linked to neurodegenerative diseases, such as Parkinson's disease, Huntington's disease, and Alzheimer's disease (Doble, 1999). Excitatory amino acids are classified into endogenous excitatory amino acids, such as glutamate and exogenous excitatory amino acids, such as quisqualic, kainic, and domoic acids (Doble, 1999). Excitatory amino acid receptors are classified into NMDA, AMPA/kainate recptors, and metabotropic receptors and each type of these receptors has different subtypes (Monaghan et al., 1989). The mechanism of excitotoxicity undergoes to the impairment of calcium homeostasis, activation of nitric oxide synthesis, generation of free radicals and apoptosis (Wong, Cai, Borchelt, & Price, 2002). Impairment of calcium homeostasis is caused by prolonged depolarization of neurons to cause subsequent high calcium influx overload that leads to the activation of enzymes that breakdown proteins, membranes, and nucleic acid leading to cell death (Berliocchi, Bano, & Nicotera, 2005). In cerebrovascular disease, nitric oxide synthesis is activated by glutamate release and inhibition of its removal leading to overactivation of NMDA receptors and high calcium influx leading to excitotoxicity and cell death (Law, Gauthier, & Quirion, 2001). Free radicals or reactive oxygen species (ROS) are harmful products that are resulted by oxygen metabolism to induce cell death and mitochondrial dysfunction (Berman & Hastings, 1999). Excitotoxicity has a significant role in neurodegenerative diseases. In Huntington's disease, insoluble nuclear aggregates are formed in the brain that activate NMDA receptors to cause alteration of calcium signalling leading to cell death (H. Zhang et al., 2008).

Interestingly, intrastriatal injection of KA leads to excitotoxicity in striatum in Huntington's disease (Coyle & Schwarcz, 1976) suggesting that both KA and NMDA receptor agonists, such as quinolinic acid cause neuronal cell apoptosis by the activation of NF-κB and other proapoptotic proteins in rat striatum (Nakai, Qin, Chen, Wang, & Chase, 2000; Qin et al., 1999). In Alzheimer's disease, which is characterized by a memory loss and cholinergic neurons deficits in the hippocampus, is linked to excitotoxicity. Amyloid beta aggregates and intracellular neurofibrillary tangles which are considered as the two main biomarkers of the pathophysiology of Alzheimer's disease play significant role in excitotoxicity, oxidative stress and apoptosis (Robinson & Bishop, 2002). Interestingly, the glutamatergic signalling is compromised by amyloid beta aggregation that is parallel to cognitive deficits in Alzheimer's disease (Parameshwaran, Dhanasekaran, & Suppiramaniam, 2008). Furthermore, amyloid beta aggregation in Alzheimer's disease is linked to overactivation of NMDA receptors suggesting that NMDA antagonists, such as memantine produced a neuroprotective effect against excitotoxicity in Alzheimer's disease (Miguel-Hidalgo, Alvarez, Cacabelos, & Quack, 2002). Amyloid beta aggregation causes excessive generation of ROS by overactivation of NMDA receptors leading to dysregulation of NMDA receptors and oxidative stress (De Felice et al., 2007). In Parkinson's disease which is defined as a massive depletion of dopamine in the striatum to cause a loss of locomotion activity is linked to excitotoxicity and cell death. Dopaminergic neuronal loss is attributed to glutamate induced excitotoxicity (Muddapu, Mandali, Chakravarthy, & Ramaswamy, 2019). It has been demonstrated that parkin encoded by PARK2 gene regulates protein breakdown in the brain and a mutation of this gene is attributed to protein aggregation and misfolding in PD (Miklya, Goltl, Hafenscher, & Pencz, 2014). Parkin regulates the stability of glutamatergic synapses, so the expression of parkin in the postsynaptic terminal supress the excitatory glutamatergic transmission in hippocampal neurons. In PD, PARK2 gene is mutated to form misfunctioning parkin that increases

glutamatergic synapses and induces excitotoxicity (Helton, Otsuka, Lee, Mu, & Ehlers, 2008). Interestingly, some studies showed that NMDA antagonists can prevent parkinsonian symptoms or they can produce a synergistic effect when they are combined with L-dopa in PD animal model (Dauer & Przedborski, 2003). The excitotoxicity induced in dopaminergic neurons by MPTP has been alleviated by using NMDA antagonist MK-801 (dizocilpine) suggesting that MK-801 produced a neuroprotective effect against excitotoxicity induced by MPTP in dopaminergic neurons (Moring, Niego, Ganley, Trumbore, & Herbette, 1994). It has been published that dopamine has a neuroprotective effect against excitotoxicity induced by glutamate because it modulates calcium signalling in cortical hippocampal and midbrain neurons. The protective effect of dopamine against excitotoxicity induced by glutamate is mediated by using DA agonists especially D_2 agonists and exacerbated by using D_2 antagonists (Vaarmann, Kovac, Holmstrom, Gandhi, & Abramov, 2013). Interestingly, it has been demonstrated that DA and D_2 or D_4 receptor agonists significantly supress NMDA receptor activation (Higley & Sabatini, 2010; Wang, Zhong, Gu, & Yan, 2003). To wrap up, glutamate excitotoxicity plays a significant role in the pathogenesis and progression of neurodegenerative diseases suggesting that glutamate antagonists, such as NMDA antagonist can be used to alleviate the symptoms of neurodegenerative diseases beside the conventional treatment.

Thus, there are abundant evidence of NMDA mediated excitotoxicity playing a vital role in neurodegeneration. Kainic acid by acting on the kainate receptor also has shown to exhibit signal transduction mechanisms like the effect of glutamate binding to NMDA receptors.

The rationale behind the study is Tyrosine hydroxylase is the rate limiting enzyme in the synthesis of dopamine. Based on the quikpro and receptor binding study, kainic acid can cross the neuronal membrane and bind to tyrosine hydroxylase which can result in decreased expression or activity. Thus, kainic acid can cause decreased dopamine formation and significant dopaminergic neurotoxicity.

This study hypothesized that kainic acid would elicit dopaminergic neurotoxicity as compared to the established and accepted dopaminergic neurotoxin, MPP^+. However, the study contradicts the hypothesis, as kainic acid exerted weak dopaminergic neurotoxicity as compared to MPP^+. Moreover, kainic acid did not induce oxidative stress (increase pro-oxidants to induce lipid peroxidation), mitochondrial dysfunction (decrease in NADH content leading to ATP depletion), inflammation (increase in interleukin-1 activity), and apoptosis (increase in caspase-3 activity).

To sum up kainic acid failed to induce oxidative stress, apoptosis, inflammation and had no effect on tyrosine hydroxylase expression as compared to the exogenous dopaminergic neurotoxin MPP^+ that makes it a weak dopaminergic neurotoxin figure 5.1.

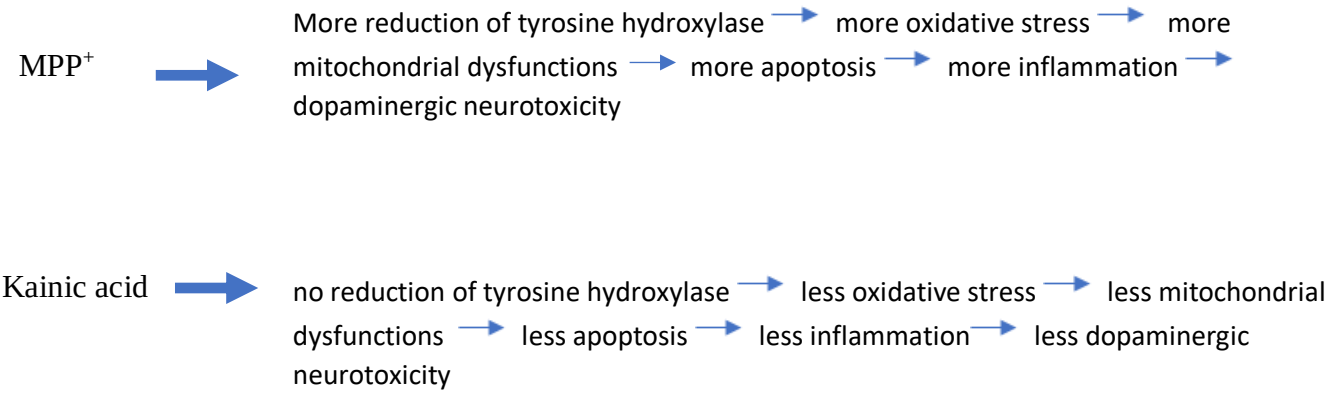


Figure 5.1: Comparison of the dopaminergic neurotoxic effect and mechanisms between kainic acid and MPP^+.

6. Conclusion

Kainic acid, even at high doses and after prolonged incubation did not exhibit complete dopaminergic neuronal cell death in both human dopaminergic M17 neuronal cells and rat dopaminergic N27 neuronal cells. The dopaminergic neurotoxicity of kainic acid is not as potent as compared to the dopaminergic neurotoxin MPP^+. The lack of potent dopaminergic neurotoxicity can be due to its ability not to affect the tyrosine hydroxylase expression, hydrogen peroxide content, nitrite content, lipid peroxide content, NADH content, interleukin-1 converting enzyme activity, and capase-3 activity in human dopaminergic M17 neuronal cells.

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