ISSN No:-2456-2165

Animal Models for CNS Disorders: Current Perspectives and Future Directions

Tejesvi Mishra*
National Coordination Centre for Pharma covigilance Programme of India,
Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Ghaziabad, India

Abstract:- The numbers of probable neurotoxins are rising day by day and pose a perilous neuro-inflammation to the body. Currently, the evaluation of neurotoxicity is the most accomplished assessment in non-clinical as well as clinical studies. Mislaying memory, frailty in body, clouded vision, headache, and psychological un-certainty subsequently developing cognitive puzzlement are some of the major signs of progressive inflammation in brain. Asserted evidence in research states that the activated microglia, a major part of brain causes damage to the neurons present in central nervous system. The pattern of over-activated microglial cells followed by oxidative stress found to be the main pathway involved in neurotoxicity. Many studies support the involvement of reactive oxygen species (ROS) generation in hippocampus leading to toxic mediator's release and suggest excitotoxicity involving overload of Calcium ions in frontal cortex as a secondary damage. With the evolution of animal model, there has been research-based analysis which affirms that a developmental inflammatory symptom in brain can be induced by several drugs, chemicals, pesticides and can lead to neurodegenerative disorders. This study indulges with a descriptive remark on various rodent models related to neuronal inflammation.

Keywords:- *Heavy metals; Pesticides; ROS; Hippocampus; Neurotoxicity; Neurodegenerative diseases.*

I. INTRODUCTION

The Society of neuroscience, 2012 [1] states that the nervous system is a complex and highly specialized network and functioning. From vision to olfaction; walking to sleeping and speaking to thinking, our system of neurons organizes, explains and connects to perform actions. This nervous system comprises several parts including the brain, spinal cord and nerves to connect them. According to (National Institute of Neurological Disorder, 2018), any abrupt ingestion or exposure of toxins (natural, chemical, heavy metal, trauma, injury or certain drugs like cyclophosphamide and cefepime) may results in neuronal toxicity due to disruption of neurons. According to the study of [2] the first and foremost symptom of neurotoxicity targeted to the brain denotes headache. Headache is one of the most common neurological disorders that affect anyone at any age. Association of headache with fever, photo-sensitivity followed by stiffness of muscles predicts signs of meningitis. On the contrary, chronic pain in one portion of the head may signify migraine. As per (American Society of Microbiology, 2014) Multiple sclerosis (MS) is a kind of neuronal inflammatory disease characterised by disruption of blood brain barrier and demyelination. Ingestion of food contaminated with *Clostiridumperfrigens*, a spore forming bacterium potentiate chances of multiple sclerosis. Exposure to neurotoxins like dithiocarbamate (DTC) induces Parkinson disease (PD), also known as "shaking palsy"; which itself is a complex progressive neurodegenerative disorder leading to the degradation of dopaminergic neurons [3]. Alzheimer's disease denotes loss of memory due to imbalance in between acetylcholine and dopaminergic neurons. Although this disorder usually shows association with old age and genetic factors, exposure of microbial toxins such as bacteria, molds and viruses may contribute to cognitive declines [4]. An abnormal electrical activity in the brain that stimulates recurrent seizures is referred to as Epilepsy. [5] It was found that this induction of seizures is sometimes associated with exposure of certain pesticides including parathion and carbaryl. One of the evident motor neuron diseases (MND), frequently found in adults is Amyotrophic lateral sclerosis (ALS). It is progressive as well as fatal and shows its symptoms twitching of muscle, fatigue, difficulty in swallowing and shortness of breath, after the exposure of soil related fungal toxins [6]. As soon as chemicals like phenol and gases like hydrogen sulfite is exposed, there is a lack of blood flow in brain that results in stroke causes by formation of clot or direct blockage in arteries. Weakness followed by numbness in muscles, improper speech, imbalance and blurred vision are symptoms of stroke [4] and [7]. These neurological disorders are becoming much more vulnerable now a days. World wide data of world health organization (WHO) report, 2021 suggests that, across the globe 30 million people are suffering from neuronal diseases that are somehow subjected through neurotoxicity. In India, population survey summarizes the incidence and prevalence rate variation according to regions of the country. In a recent data it was found that, the cases of this neurological disease was found more in men as compare to women but women have high mortality rate [8]. When neurodegenerative disease comes into picture, neurotoxicity is claimed to be one of the major reasons. Neurotoxicity as the name itself suggests, it is toxicity associated with neuronal regions present in body [9]. The toxicity could be induced in brain or in the whole peripheral region of the body as neurons are present everywhere in the body [10]. The pathological changes such as oxidative stress, microglial activation followed by neuronal inflammation due to neurotoxicity can occur from exposure of several neurotoxins [11]. These neurotoxins (including heavy metals like arsenic, mercury and lead; chemicals like alcohol and phenol derivatives and carbofurans) are the particular agents that have ability to stimulate the inflammation in neurons [12]. The prognosis of brain toxicity is always known to be related to the length and degree of exposure in contrast to the severity of

ISSN No:-2456-2165

neurological injuries. As per study of [2], it has been found that at a specific level the exposure of neurotoxin can be fatal but in some cases patients may completely be able to recover after the required treatment [13]. Exposure of neurons to neurotoxins can also leadto cause progressive neurodegenerative diseases like Parkinson's disease, Alzheimer's disease, Huntington's disease and disorders like meningitis. In prognosis of such diseases, there is always involvement of neuronal inflammation and oxidative stress generation at neuronal site. These neurotoxic effects can be studied well with the help of various toxicological models [14]. Experimental studies explained below are helpful to analyse chronic outcomes on brain.

II. ELECTRIC SHOCK SEIZURES IN RODENTS

As per [15], An Electric shock induced seizures in mice and rat model signifies development of epilepsy. In this model seizures are potentiated by applying electric shock of 60 micro ampere, 60 hertz for 2 seconds on rat. On the contrary, 12 microampere with a frequency of 50 hertz is applied in case of mice for 0.2 seconds. Due to electro-convulsive shocks, inflammation followed by destruction of neurons occurs leading neurological disorders like epilepsy. This model predicts more accurate results but, physical instability of rodents become one of the demerit of this model. This study is more prone to brain traumatic injuries [16].

III. KINDLING RAT SEIZURE MODEL

This model summarizes repetitive administration of an initially sub convulsion electrical stimulation on rodents. Electrodes are re-implanted in right amygdala of brain by surgical method and stimulations are provided. Animal is then allowed to recover from surgery for at least 1-2 weeks. Daily electrical stimulations are applied via electrodes (400-500 micro ampere for 1 mili second). Animals are tested on the day, before and after the treatment of test compound [16]. Occurrence and degree of seizures are compared between control and test compounds. Kindling rat model provides effect of reoccurrence of electric shocks on brain. In comparison Electric shock model, this study has more chances to develop trauma in rodents as there is re-occurrence of electric shocks [17].

IV. RUN WAY AVOIDANCE IN RATS AND MICE

In this model analysis, animal is placed in the box with uniform illumination of light. One loud speaker is also mounted 50 cm above the start box. The animal is administered acoustic stimulus of 80db of 2000 hertz frequency. After 5 minutes animal is exposed to electric shock of 1 micro ampere for 1 second [19]. Thereafter, evaluation of time required to reach safe at door is noted in order to access the efficacy of drug. It is one of the simplest study for assessment of behavioural studies [20].

V. MORRIS WATER MAZE TEST

According to [21], this model helps to understand spatial learning ability of rats. Within a circular tank divided into 4 quadrants, filled with water in a depth of 20 cm rats are placed. Rats learn to swim in water tank to escape platform hidden under water. Rat has to find the platform to escape within 15 minutes. Trained rats and rats with good memory used to take time of less than 10 seconds. This test helps in assessment of memory as well as learning ability of rats. Complex procedure and handling assessment can be its demerit [22].

VI. TREMORINE AND OXOTREMORINE ANTAGONISM

The rationale of this study is to reduce Parkinson's like symptoms (including tremor, ataxia, salivation, lacrimation, and spasticity) in rodents by administration of muscarinic antagonists (like tremorine and oxotremorine). Animals are administered with a dose of 5mg/kg benzatropine 1 hour prior administration of 0.5mg/kg oxotremorine via subcutaneous route. Score of tremors, salivation, and lacrimation is recorded under 3 observations. This model measures only central anti-cholinergic activity, and it is not used for assessment of dopaminergic drugs [23].

VII. RESERPINE ANTAGONISM

The purpose of this test is to analyse sedation in mice, as reserpine induces depletion of central catacholamines. Due to sedative effect, mice are observed with signs of eye lid pitosis, hypokinesia, rigidity, and immobility. In this study, preferably male mice are administered with reserpine (5mg/kg) intra-peritoneal route and tested after 24 hours. Before 30 minutes of observation, administration of test compound is done. Evaluation of loco motor activity such as rearing and grooming are scored. This model shows significance in assessment of loco motor activities as well as behavioural studies [24].

VIII. N-METHYL-4-PHENYL-1, 2, 3, 6-TETRAHYDROPYRIDINE (MPTP) MODEL FOR RODENTS

N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) itself act as a neurotoxin that usually destruct dopaminergic cells present in substantianigraof brain results occurrence of Parkinson's like symptoms. A dose of 5-9 mg/kg via intra peritoneal route is administered in mice for 5-8 days followed by test drug. Locomotion, sleep duration, balance and coordination are evaluated and scored [25]. MPTP model shows contribution in analysis of Parkinson like disorder in not only rodents but also in monkeys. This study can also be helpful in summarizing effect of neurotoxin in various CNS disorders including depression and anxiety in which dopamine plays vital role. Exposure to neurotoxin can also cause lethal effects in brain, sometimes can be fatal for animal [26].

ISSN No:-2456-2165

IX. VARIOUS ANIMAL MODELS FOR NEUROTOXICITY

A study at genetic level was conducted to analyse synucleinopathy induced neurotoxicity in rodent cells. Leucine-rich repeat kinase-2 (LRRK2) causes microglial cells to get stimulated in response to raised extracellular α-synuclein results in neurotoxicity [27]. Induction of sepsis in brain via cecal ligation and puncture (CLP) in rodents results in down-regulated expression of interleukins (IL-1β, IL-6), and tumor necrosis factor (TNF-α) followed by long-term cognitive impairment [18], [27]. In neonatal mice, high quantities of pain killers such as sevoflurane, isoflurane, and midazolam were reported to cause altered learning and memory abnormalities Parkinson's disease exacerbates α-synuclein in brain which directly indicates neuronal inflammation. As PD itself is a neurodegenerative disorder, therefore its lethal effects may summarize the key features of neurotoxic mediators like longterm memory deflects followed by improper release of motor hormones in rodent model [15], [28]. Ischemia is marked for decreased level of oxygen in the cell, but when the oxygen amount is less in brain cells it leads to generate acute ischemic stroke. Due to which there is decrease in brain water content followed by lipid peroxidation and inflammation [29]. Schizophrenia is a complex psychotic ailment with unidentified etiologies and inadequate treatment options. Recent developments in understanding both hereditary and hormonal impacts on risk for this condition have given rise to a lot of optimism in defining executable health risks and rectifiable Neuropathological processes &inflammated neuropathy in the brain, notably in the hippocampus region, was discovered to be a main cause of inflammated neuropathic pain in a mouse model where this psychotic disease was created. [22], [29]. AD is one of the well-known neurological disorders that can be specified by defienciency of dopaminergic neurons which is always marked for depletion of neuronal networks in brain. In a study AD was induced in rodents via intra-cerebroventricular implantation and cannulation in brain that leads to hyperactive neurons and altered functioning followed by inflammation [6], [29]. Anxiety is characterised by feelings of fear, dread, and uneasiness, as well as nervousness, restlessness, a sense of approaching danger, and panic. It can make you tired, feel uneasy and tight, and cause your heart to race. It's possible that it's a natural reaction to stress. Anxiety was produced in mice by exposing them to a dark room for two weeks in a murine model research. Rodents were shown to have a lower level of social interaction [14], [30]. Neuroinflammation can also be produced by induction of microelectrodes in brain via intra cortical implantation. In a pre-clinical study of similar model when the surgery was performed, there was a rise in inflammatory biomarkers, toll-like receptors (TLR) followed by neuronal astrocytes activation. [23], [31]. Excitotoxic Injury induction in mice also leads to cause lethal neurotoxicity in hippocampus and frontal cortex of brain.

Table 1: Disorders of CNS caused by neurotoxicity

CNS disorder caused by neurotoxicity	Species	Dose and route	Duration	Observations	References
Sepsis	Old Sprague-Dawley rats	Intracerebral implantation	Treatment drug 14 days	Down regulation of IL-1β, IL-6, and TNF-α.	[18]
Parkinson's disease	C57BL/6 mice	2.5 mg/kg by intracerebroventricular injection	36 days	Microglial activation Dopaminergic neuro-degeneration	[15]
Acute ischemic stroke	Mice	Middle Cerebral Artery Occlusion-Reperfusion (MCAO/R) surgery		Astrocyte-mediated inflammation ROS generation Lipid peroxidation	[21]
Over dose of Anaesthesia in mice	C57Bl/6 neonatal mice	3% isoflurane: 2 hr/day	3 days	Cognitive defects altered memory	[6]
Oxidative injury induced neurotoxicity	C57BL/6 mice	Surgery of cortex		Release of inflammatory bio-markers	[42]
Schizophrenia	Transgenic mice	Induction of 22q11 deletion syndrome (22q11DS)	2 weeks	Hippocampal hyperactivity and Psychosis-related behaviour	[22]
AD induced neurotoxicity	APP/PS1-Stat3WT	Surgical Intracerebroventricular	6 weeks	Astrocyte-specific deletion of Stat3	[6]

	mice	implantation		Dystrophic neuritis Inflammation in frontal cortex of brain which is responsible for learning and memory.	
Anxiety induced neurotoxicity	Mice	Dark exposure to mice	2 weeks	Reduced social interaction Hippocampal oxidative stress	[14]
Implanted microelectrodes induced neurotoxicity	C57-BL6 mice	Surgical implantation Intracortical microelectrode		Up-regulation of toll-like receptor (TLR-4) and catalase Activated macrophages CD68 Neuronal nuclei damage	[23]

A. Pesticide induced neurotoxicity

Pesticides are designed to kill bugs, but they can be harmful to the brain. In addition to CNS impacts, their exposure can cause a variety of neurological problems by acting on synapses, such as a sodium/potassium mismatch, which prevents normal nerve impulse transmission. They disrupt neurological signals by sinus inflammation, disorientation, and chest pain, followed by severe muscle aches [32]. Organophosphorus (OP) cholinesterase inhibitor intoxication can cause convulsions that can result in long consequences. A preclinical paradigm in which acute di-isopropylfluorophosphate (DFP) intoxication results in tremors, ongoing cytokine production, death, and cognitive problems due to neuronal injury and neuro-inflammation caused by gliosis which is known for enlargement of glial cells. As glial cell plays a key role in adapting inflammation in the neuronal region by direct stimulation of cellular responses in neurons, astrocytes and blood brain barrier followed by T-cells infiltration [33]. Organophosphates (OP) are a group of compounds that are phosphoric, phosphonic, and phosphinic acid derivatives. The severe effects of OP can lead to severe problems such as aerotoxic illness, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis), long-term neuropsychiatric effects of acute and repeated exposures such as acetylcholine receptors inhibition, astrocyte deficits, oxidative stress and neuroinflammation, and autoimmunity, and long-term neuropsychiatric effects of acute toxicity [34]. Numerous neurological illnesses have been linked to exposure to the fungicide ziram (zinc dimethyldithiocarbamate). In rodents, ziram administered intranasally produces neurochemical changes. In findings of [35], Inflammatory mediators including TNF-α causes cellular damage in brain that provokes the release of 4-hydroxynonenal (4-HNE) and 3-nitrotyrosine (3-NTS) in the striatum region. Carbofuran is a chemical pesticide that is widely used to manage insects as well as nematodes during crop production due to its biological activity. It also acts as a neurotoxin that induces neurotoxicity by generating free radicals and depletion of critical antioxidant enzymes, as per World Health Organization (WHO). The modification of acetylcholine-esterase (AChE) and other transporters has been linked to carbamate-induced cytotoxicity.

Table 2: Pesticides induced neurotoxicity in rodents

Name	**Species**	**Dose and route of adm.**	**Duration of experiment**	**Findings**	**References**
Acute diisopropylfluorophosphate (DFP) neurotoxicity	Sprague Dawley rats	9 mg/kg	14 days	Acute DFP intoxication causes persistent neuronal damage and neuroinflammation, cognitive deficits	[17]
sodium dimethyldithiocarbamate induced neurotoxicity	Swiss albinoMice	Intranasal 10 µL, 100 mg/mL	7days	Depression like behavioral alterations Activated astrocytes	[8]

carbofuran-induced neurotoxicity	Swiss albino mice	5 mg/kg b.wt/ day	90 days	Change in antioxidant markers	[21]

From the above explained table; Acute-diisopropylfluorophosphate (DFP) neurotoxicity model can be utilized for neurodegenerative disorders like Alzheimer disease, Parkinson's disease while sodium dimethyldithiocarbamate can be utilized in models for depression.

B. Chemicals induced neurotoxicty

There are various chemicals those have deleterious effects to central nervous system (CNS) such as alcohol based products and phenolic compunds. Acute ethanol treatment to postnatal pups causes significant neurodegeneration, and studies have demonstrated that the neurotoxicity generated in the neurodevelopment can last for a lot longer, even into adulthood. Upon administration of high dose of ethanol in rats, the cellular level findings of [36] indicated induction of the MAPK p-P38/p-JNK pathway, triggered gliosis, productive p-NF-KB/p-IKK, apoptosis, and neuro degeneration. The NF-kB/Nrf/HO-1 propagation pathway was discovered to be involved in stress and alcohol-exposed rodents in a study. Chronic immobility and alcohol intake can result in harmful consequences in the hippocampus area of the brain, which can lead to cognitive impairment [37]. Due to administration of 3-nitro propionic acid (3-NP), lipid peroxidation and alteration in motor activity was noted [38]. When it comes to neurotoxicity, hydrogen sulphite is the most common neurotoxic gas, and its exposure results in changes in neurotransmitter like dopamine levels in brain which leads to altered behaviour of rodents [39].

Table 3: Chemical-induced neurotoxicity in rodents

Name	**Species**	**Dose and route of adm.**	**Duration of experiment**	**Findings**	**References**
Ethanol induced neurotoxicity	Sprague dawley rats pups	single dose of acute ethanol (5 g/kg, subcutaneous (s.c.)	7 days	Activation of the MAPK p-P38/p-JNK pathway, activated gliosis, and neuronal degeneration	[24]
Alcohol induced neurotoxicity	Swiss albino mice	15% v/v oral	28 days	Activated p-NF-KB/ p-IKKβ, apoptosis	[12]
3-nitropropionic acid induced neurotoxicity	Wistar rats	30 mg/kg, i.p.	22 days	Stratum damage in brain	[11]

From the above explained table; ethanol induced neurotoxicity can serve as model for neuro-degenerative diseases like Alzheimer disease, Parkinson disease and epilepsy. As rising evidence shows that depression may results in neurodegenerative disorders, therefore ethanol exposure at 5mg/kg via subcutaneous route may provoke neuronal destructive diseases.

C. Drug induced neurotoxicity

Docetaxel (DTX) is a chemotherapeutic drug that is used to treat a variety of cancers. However, it causes CNS deficits. In DTX-induced rodent models, abnormal levels of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) were discovered. Other findings include decreased c-Jun N-terminal kinase (JNK) expression in the sciatic nerve and higher cyclic AMP response element binding protein (CREB) expression in the brain, most of which were stimulated by DTX [40]. Over-stimulating the CNS with medications has always resulted in a significant increase in neurotransmission signalling in the brain. According to a recent study, CNS stimulants produce a rise in serum and brain levels of lipopolysaccharide (LPS) and brain cyclooxygenase-2 (COX-2). Studies have reported that regular administration of Methamphetamine caused dopamine and serotonin in the brain striatum, there is a shortage of dopamine and serotonin in the striatum, along with serotonin in the prefrontal cortex, due to regular administration of methamphetamine [41]. 2C (2C-x) , one of the most common chemicals from the family of phenethylamines with two methoxy groups 2 and 5 positions in benzene ring have potential to produce neurotoxic effects. Activated microgliosis, increased both Iba-1 and GFAP expression levels in the striatum were also noted [42]. In Pentylenetetrazol (PTZ)-kindled model; mice were acclimatised and confronted to an electroconvulsive shock of 12 micro ampere, 50 hertz of frequency for 0.2 seconds,

2-3 times per week for a duration of 28 days; then studied for excitotoxicity and inflammation in central nervous system [43]. An administration of 5-FU in rodents at a high dose can lead to convulsions, tremors, confusion and memory memory impairments. Vincristine (VCR) is a medicine that is routinely used to treat a variety of haematological malignancies; nevertheless, neurotoxicity in rodents is a typical repercussion. Vincristine was discovered to have the potential to cause ganglionic and neurological abnormalities in a recent pre-clinical research [44].

Table 4: Drug-induced neurotoxicity in rodents

Name	Species	Dose and route of adm.	Duration of experiment	Findings	References
Vincristine-induced neurotoxicity	C57BL/6 J mice	0.1mg/kg ip	14days	Hyperalgesia neurite damage ganglionic damage	[26]
5-FU induced neurotoxicity	Swiss albino mice	200 and 400 mg/kg, i.p.	14 days	Convulsions Tremors confusion	[17]
PTZ (pentylenetetrazol) induced neurotoxicity	Swiss albino mice	PTZ (40 mg/kg, i.p.),	5 days per week for 13 days	Generation of reactive nitrogen species (RNS) and inflammosomes	[18]
Phenethylamines induced neurotoxicity	C57BL/6 J mice	10 mg/kg i.p.	7 days	Reduced motor activity induce memory defcits	[19]
Methamphetamine induced neurotoxicity	Sprague Dawley rats	10 mg/kg, once every 2 hr via i.p.	28 days	Raised level of Calcium, glutamate-mediated excitotoxicity	[25]
Docetaxel-induced neurotoxicity	Sprague Dawley rats	a single dose of DTX (30 mg/kg, b. w.) i.p. on 1st day	7 days	Reduced level of glutathione (GSH), superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPx) Altered expression of nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1 (HO-1) and B-cell lymphoma-2 (Bcl-2) and downregulated the expression of Bcl-2 associated X protein (Bax)	[2]
Cefepime induced neurotoxicity	Swiss albino mice	250 and 500mg/kg i.v.	14 days	Raised level of inflammatory biomarkers in brain like IL-8 and IL-12	[26]

From the above explained table; 5-FU induced neurotoxicity and Methamphetamine induced neurotoxicity can be treated as models for epilepsy. Phenethylamines induced neurotoxicity, Cefepime induced neurotoxicity and PTZ (pentylenetetrazol) induced neurotoxicity can serve as models for Alzheimer's disease and Parkinson disease. Docetaxel-induced neurotoxicity and Vincristine-induced neurotoxicity can be utilised as models for other neurological disorders including Amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS) and Huntington's disease.

X. HEAVY METALS INDUCED NEUROTOXICITY

Heavy metals are well known for their deleterious effects in the body. Although the effect of heavy metal has studied well on vital organs like liver, kidney and gastro-intestinal tract (GIT), though some studies like [45] have reported about their effect on the central nervous system (CNS). Lead poisoning causes not only perinatal toxicity but also brain diseases, including learning and memory impairment. In aged rats, lead exposure causes cognitive impairment by altering intracellular calcium signalling via RyR. There is a promotion of inflammation and cell oxidation buildup of lead in tissues [46]. In mice, mercury sulphite causes chronic neuro inflammation, which is followed by impaired body movements, increased microglia activation, and consequently death of dopaminergic neurons.Aside from that, the alteration of the gut

microbiome utilising real-time PCR with 16S rRNA primers was also noted [47]. From years, arsenic has been utilised as a homicidal agent. It produces toxic results in brain via reduction of glutathione through methylated oxidation mechanism [48]. On the other hand, arsenic also reduces level of acetyl cholinesterase in brain due to which neurodegenerative disorders like Alzheimer's disease get more triggered. Cisplatin as a first platinum-derived molecule which is used in cancer therapy causes hyperexcitability of neurons in brain which results in chronic neurotoxicity [49]. Manganese (Mn) overdose affects the central nervous system, primarily impacting nigrostriatal cortical connectivity and resulting in behavioural and motor disorders due to protein misfolding which including -synuclein and amyloid [50].

Name	Species	Dose and route of adm.	Duration of experiment	Findings	References
Pb induced neurotoxicity	Old Sprague Dawley (SD) rats	0.05% lead acetate p.o.	3 weeks	Cell apoptosis, calcium overload in cells	[21]
hydrogen sulfide–induced neurotoxicity	Mice	765 ppm H2S for 15 min/day	1 week	Activation of cytochrome oxidase enzyme changes in dopamine (DA) and its metabolites, Altered GABA/Glutamate	[11]
Mercury sulphide induced neurotoxicity	C57BL/6 mice	0.6g/kg oral feeding	35 days	LPS aggravated MPTP neurotoxicity Loss of dopaminergic neurons	[28]
Arsenic induced neurotoxicity	Male Mice	2 mg/kg	12 days	Mitochondrial dysfunction Lipid Peroxidation increased Calpain Decreased Acetylcholinesterase Activity	[27]
Platinum induced neurotoxicity	Mice	16 to 80 mg/kg ip	30 days	Exaggerated neurons Rise in malonaldehyde (MDA)	[16]
Oxaliplatin induced neurotoxicity	Wistar rats	5mg/kg, was administered i.v.	8 days	Destructed α-synuclein and amyloid protein	[16]

Table 5: Heavy metal-induced neurotoxicity in rodents

XI. CONCLUSION

Toxicity in neurons is not new chore for researchers to stick on, as it's one of well-known dose-limiting adverse effect of many first line chemotherapeutic drugs. Due to its high prevalence in patients, it is now clenched highlights for core competency. The association of neurotoxicity is not only with neurological stress but it also alters the electrophysiology of the brain. Although, we have well established models including kindled model, Morris water model, Reserpine antagonist model and MPTP induced model for rodents to understand neurological disorders. But, to analyse CNS disorders in a broader manner with reference to neurotoxins; the explained models can be utilized. As per many pre-clinical studies, induction of neurotoxicity can be seen in rodents by the help of pesticides, chemicals and heavy metals. This whole study sums up various models and their mechanisms involved in studying neuronal diseases in a wider way to establish pre-clinical studies.

- **Conflicts of Interest**: Author declares no conflict of interest

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