EXPERIMENTAL MODELS FOR MEMORY IMPAIRMENT

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Abstract

Numerous animal models have been developed and have contributed to the exploration of the pathology of diseases and development of new drug therapies. Memory is the ability to record, retain and recall the data or event of life whenever needed. In the last years, the increasing number of neurological disorders raise a concern, for this, various investigations have been done to postulate the basic mechanisms and signalling molecules and steps involved in the process of the formation of memory and learning. Various neurotoxins have been utilized as an experimental model to study and develop new pathways and specific targets to treat the disorders, but none of them are able to predict all the characteristic features that are involved in the alteration of memory. Toxins being utilized for the different experimental models include scopolamine, ethanol, domoic acid, streptozotocin, okadaic acid, quinolinic acid, paraquat, rotenone, MPTP, methamphetamine, etc. The current study summarizes the toxins from a different sources that could support the investigation to explore the pathology and to develop the target drug delivery for memory impairment, impaired neurodevelopment, diminished intellectual power, and other cognitive disorders like AD, PD, HD, etc.

Introduction:

Memory is the capability of an individual to record and retain sensory stimuli, data and different events of life and to recall them whenever needed (Nadkarni, 1998). It is the process of coordinating mental and physical life together. Without memory, we cannot perform our everyday jobs, without this it would have become much difficult to manage the daily activities.

In the last few years, neurobiological studies of the brain have accomplished a common platform developing cell and molecular biology on one hand which is relating to the brain system and its psychology on the other hand (Kandel et al., 2014). The pathological reason behind the decrease in the cognition has always been a concern issue that has grabbed the attention of neurobiologists for decades. Though with the help of different prototypes in various organism models, we are able to recognize the molecular processes involved in cognition (Johansen et al., 2011, Dunning et al., 2003). The different in-vitro models analysing memory power and other impaired expressions of the brain, made it possible to understand the pathology of neurological disorders (Martin et al., 2000). Dementia is a brain disorder resulting in the depleted memory potential which alters the physiology of different region of the brain described by the diminished intellectual activity and loss of motor coordination and mental functioning.
A study confirms that about 4.5 million people would be suffering from dementia by the year 2050, which may upsurge to a 114 million (Plassman et al., 2007, Wimo et al., 2003, Tayeb et al., 2012). Dementia includes the manifestations like impaired motor functions (apraxia), executive functions, language (aphasia) and failure in recognition (agnosia) (Kidd et al., 2008). Various neurological disorders have diminished memory or low learning power as their characteristic feature (Worsley et al., 2006) include Lewy-body, vascular dementia, AD, PD, HD, etc. (Sodhi et al., 2011). There are many reasons behind the development of neurological disorders like drugs interrupting brain physiology, chronic diseases, toxins, etc., while, age and stress remain major and common reasons for it. Hence, animal prototypes are required to recognize all the aspects of learning and memory processes which further clarify the mechanism for normal and the damaged brain activities (Overmier et al., 2001), a contributing factor to dementia, and also helps to formulate new therapeutics which would aid in an improved understanding of the neurotoxicity and impairment (Nestler EJ et al., 2002, Kim JJ et al., 2001).

Animals-based research promote the understanding of the physiology existing in the regulation of memory and learning and also made possible to understand the different system involved in different forms of memory and how they coordinate with each other for maintaining a healthy life. With the increased frequency of neurodegenerative diseases, it is equally essential to develop more experimental models (Elder et al., 2010) to elucidate all the parameters governing cognitive and behavioural abnormalities (Tayebati et al., 2006).

### Chemical for inducing Memory Impairment

**Scopolamine**

The cholinergic implication in coordinating cognitive processes has been recognized decades ago, whereas their antagonists are being used for reducing the cognition power in different models, which are being used for studying memory processes (Von Linstow Roloff et al., 2007). Altered cholinergic physiology may lead to develop dementia-like state including diminished cognitive activities and disorientation, which is a common indication also seen in AD (Chen et al., 2014, Dhingra et al., 2003). It has been confirmed that interruption in the cholinergic transmission in the brain region is an indication of the disturbed learning and memory potential (Goverdhan et al., 2012). Disturbed cholinergic transmission and damaged neuronal network seems to be key indications in AD patients (Schiffliti et al., 2010).

Scopolamine, a well-known alkaloid used as an anticholinergic drug for the induction of memory deficit in experimental prototypes. It seems to occlude the binding of acetylcholine (Ach) in the brain’s cortex region, which unbalances the Ach level of the brain, damaging the neural functioning of the brain consequently causing loss of memory and learning power (Riedel et al., 2009). Scopolamine exerts its effect by blocking muscarinic receptors. Synaptic plasticity, occurred due to the modification in the NMDA receptors and chromatin by a chromatin-modifying enzyme in the hippocampal region (Singh et al., 2015), leading to the loss of memory. The alterations in various receptors like CREB, Homer-1, AMPA-R, enhanced activity of glycogen synthase kinase-3β, and disrupted activity of the spine are also scopolamine-induced effects (Wu et al., 2013). The effective dose of scopolamine for the assessment of learning and cognitive functioning was found to be 0.03 mg/kg (high dose).

Scopolamine is observed to affect the sort term memory as well. It is the most wide and expensive experimental model (Klinkenberg et al., 2010) and also a useful tool for the assessment of memory and cognition power.

### 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)

Dopamine can be seen as the principal neurotransmitter modulating synaptic changes affecting memory and also involves in the memory grid at the prefrontal cortex (Jay et al., 2003, Seamans et al., 2004). 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is a well-known toxin affecting the nervous system and has been used to explore the aetiology of PD (Dovero et al., 2016). Traditionally, PD was primarily described as decreased or disrupted motor functions (Caballol et al., 2007). However, the disturbed and interrupted non-motor aspects have also been a part of PD (Kehagia et al., 2010) to a greater extent, resulted from non-dopaminergic neuronal systems (Yarnall et al., 2013). Several studies confirm cognition alterations and also the presence of lesions on the pars compacta of Substantia Niagra, which occurred due to the MPTP (Da Cunha et al., 2002, Miyoshi et al., 2002). It forms a preliminary model for studying early PD amnesia. It was also observed that with the Intramigral injection of MPTP, the dopamine level tends to decrease in the prefrontal cortex and dorsal striatum whereas in the other memory regulating centres like the hippocampus, amygdala, and ventral striatum it remains unaffected (Gevaerd et al., 2001).

MPTP is a fat-soluble molecule that can easily cross the blood-brain barrier and bind with the astrocytes followed by the absorption into the neurons by the dopamine active transporter and deposition into the vesicles. It is known to...
interrupt the respiratory chain, which consequently increases the oxidative load and reduces the formation of ATP molecules within the neuron (Cui et al., 2009). Dopamine transporter deficient animals, are resistant to the MPTP due to the absence of the transporter. Accumulated MPTP into the vesicles decreases the chances of its toxicity. The degeneration of dopamine by induced free radicals is caused as MPTP present in the vesicles drives it intracellularly, involves the conversion of dopamine into 3,4-dihydroxyphenylacetaldehyde (Panneton et al., 2010). This deterioration of the dopaminergic neurons leads to the impairment in object recognition in rats can be considered as the marker of the neuro-inflammation in the Hippocampus. Also, it decreases the CaMK-II activity in the hippocampus can be linked with the cognition deficit in MPTP-treated animals (Moriguchi et al., 2012). Delayed response, slow recognition power, low recalling power, and attentional set-shifting test are the important parameters evaluated during the assessment of cognition deficit in primates. MPTP has been used specifically employed as an experimental model for evaluating cognitive dysfunction. Studies that evaluated the PD models have reported diminished response in the Y-maze (Magen et al., 2012) and T-maze (Itier et al., 2003) which confirms the altered learning ability, restoring and recalling power and object-recognition ability.

**6-Hydroxy Dopamine-Induced Memory Impairment**

It has been a most widely used prototype for exploring the preclinical research of Parkinson. It is directly injected into the brain, as it cannot cross the BBB (Blesa et al., 2012). Under normal physical conditions, the 6-OHDA rapidly undergoes an auto oxidation to form free radicals such as hydrogen peroxides, hydroxyl radicals, super oxides and Quinones. 6-OHDA, exerts its toxic effects by the formation of free radicals (Hritcu et al., 2008). It also damages the neuronal bundle in the forebrain and striatal which is exerted via c-Jun N-terminal kinase signalling (Crocker et al., 2001).

It was reported that the cell destruction in both regions follows neuroglia activation in the SNpc and is also responsible for the hindered neurodegenerative phases (Harms et al., 2011), however the mechanism behind the neuronal death caused by the striatal administration is not clear to date, whereas the 6-hydroxydopamine intoxication in the medial forebrain disperses a protein called hsp60 which activates the neuroglia in a PD rat model (Feng et al., 2013). It is known to disrupt the functioning of Mitochondria within the SNpc lesions. The toxicant can be introduced via 3 methods striatum, Medial forebrain Bundles, and SNpc. Introduction of 6-OHDA into SNpc or the MFB causes fast and massive destruction of dopaminergic neurons, consequently adopting the nigrostriatal pathway for anterograde amelioration, whereas introduction of 6-OHDA in the striatum interrupts the nigrostriatal pathway and other protruding regions evolving retrograde progression (Tadaiesky et al., 2008). For studying cognition, a low concentration of 6-OHDA is injected into the brain which could develop the initial phase of Parkinson, manifested by the destruction of dopamine producing neurons.

For exploring the cognitive research, bilateral jab of low 6-OHDA concentration, causes loss of dopaminergic neural cells which is similar to the indicators of PD (Ferro et al., 2005). The use of 6-OHDA is a reproducible, and convincing prototype for exploring cognitive behaviour. The 6-OHDA model is the manageable, convincing, and reproducible tool for exploring cognitive manifestations like visuospatial defects, PD symptoms, low intellectual and execution power, and memory impairment (Lindgren et al., 2012)

**Amyloid Beta-Peptide (Aβ)**

Amyloid Beta-Peptide is a prominent and well-acknowledged prototype for the induction of memory loss and is also used to form the distinctive features of AD in various models (Lu et al., 2009). It is polypeptide obtained by the proteolysis of the Amyloid Beta-Peptide (Nunan et al., 2009). Two forms are obtained by the proteolysis based on the number of amino acid residues, the long-chain consists of 42-43 amino acid residues which easily gets accumulated then small chain which is a 40amino acid residue chain. The Aβ toxin gets deposited into the brain and is considered as the main cause for the advancement in neurological disorders (Small et al., 1999). There are many biological pathways suggesting the role of Aβ in the pathogenesis of AD and memory impairment. It is complicated to conclude the most involved and important pathway involved in the development of AD and their characteristics (Nunes et al., 2012). Inhibition of choline acetyltransferase impairing cholinergic neural response, increased hyperphosphorylation of tau protein further forming the neurofibrillary tangles in different prototypes, are the most involved mechanism insinuating the neurotoxic effects of Aβ (Götz et al., 2005, Hardy et al., 2002, Pennanen et al., 2005). Disturbed calcium regulation is the other most observed mechanism elicited by Aβ. Aβ oligomers are known to alter various channels like potassium channels, calcium channels, ion channels, receptors like nicotinic, and NMDA and also enhances the formation of calcium conducting pores further increasing the calcium level in the cytosol (Götz, J et al., 2001, Hardy et al., 2001). Aβ oligomers potentiate the inflammation in the brain regions by
increasing ROS in the brain cells. It is responsible for promoting pro-inflammatory responses, increasing ROS, and caspase-8, inducing neurotoxicity and detaining memory formation in the hippocampus. Majorly, it diminishes the synaptic activity via interfering signalling cascades directly. It predominantly interferes with the CAM-dependent protein kinase (Yamin et al., 2009). It inhibits the Ras/ERK and PI3K/AKT signalling, essential for the expression of CREB and BDNF (Tong et al., 2004). Aβ is known for inhibiting RACK1 distribution and also activates the MAPK cascade in the cortical and hippocampal region respectively, contributing towards neurodegeneration and memory impairment (Liu et al., 2011).

Okadaic Acid
It is one of the principal polyether marine microalgae toxins causing shellfish poisoning. Intracerebroventricular administration of Okadaic acid causes memory alterations and is used to screen drugs for dementia (Kamat et al., 2010). Its potency and selectivity for serine/threonine phosphatases 1and 2A makes it a useful model studying long and short-term memory alterations in rat models (Maidana et al., 2006). Some in-vivo and in-vitro studies reported the increased neural cell death and hyperphosphorylation of tau proteins in the toxin model (Cagnoli et al., 1996, He et al., 2001). It also prevent the initiation of synaptic plasticity, and thereby lowers synaptic transmission. It boosts the quantity of calcium in the hippocampus contributing to neural deterioration, diminishes the membrane potential of mitochondria, its activity with increase in the production of ROS in the hippocampus of rat brain (Fernández et al., 1993). It triggers heat expression, inhibits phosphatase inducing hyperphosphorylation, thus instigating neurodegeneration. Okadaic acid-induced cognition alteration in the animals, is linked with the enhanced cytokine, iNOS, IL-1β, TNF-α production and the total amount of nitrite in the cortical and hippocampus. Raised level of GFAP, enhanced p38MAPK protein, protein carbonylation, and lower level of GSH contribute to the spatial memory loss in the hippocampal region (Kamat et al., 2012). The phosphorylation of tau proteins by various protein kinases such as GSK-3, cyclin-dependent kinase 5, and mitogen-activated protein kinase, manifests for AD, while protein phosphatase 1, 2A, 2B, and 5, with PP2A as main constituents, dephosphorylates tau (Arendt et al., 1998, Liu et al., 2005). This imbalanced phosphorylation and dephosphorylation processes, is the reason behind the accumulation of tau proteins and developing risk for AD (Arendt et al., 1998). Some in-vitro and in –vivo studies, suggests the role of Okadaic acid in the accumulation and hyperphosphorylation of tau protein by blocking PP2A.

Administering the toxin via intra-hippocampal jab induces substantial neurological variations, involving hyperphosphorylation of tau, development of Aβ like plaque imposes arisk for neurodegeneration in the hippocampal region (Costa et al., 2012). It is an extraordinary tool for exploring the various cellular activities regulated by the dephosphorylation of proteins, as memory formation, signal transduction, and cell division (Fernandez et al., 2002). No drugs are available to date, which specifically act on the hyperphosphorylation of tau protein and inhibit it. Therefore, from the reported studies it is suggested that Okadaic acid-based models might be used as an auxiliary tool for the therapeutic exploration of AD tauopathy (Kamat et al., 2013).

Ethanol
A high dose of ethanol has been known to cause, retrograde amnesia, interrupted formation of memory, storage and retrieval power, and depleted cognition (Spinetta et al., 2008). It affects sensory and motor functions, disturbs focusing power, and interferes the emotional and motivational behaviour impairing learning and memory potential (Nader et al., 2006). It increases the oxidative load and lipid peroxidation which damages the cholinergic neural system and also diminishes the hippocampal-based learning end encoding processes (Rezayof et al., 2008). Ethanol causes loss in spatial memory due to the induced presynaptic dysfunction in dorsal hippocampal glutamatergic neurons(Shimizu et al., 1998).

A study reported that intoxication to the infant mice on PD7 causes caspase-mediated neurodegeneration in the developing brain of mice, following with the spatial memory alterations which gets severe at PD30 and becomes less severe with the increasing days and get normal to later adulthood (Wozniak et al., 2004). Spatial memory alterations were also established, due to the activated κ-opioid and activated dynorphins and CA3 hippocampal region (Kuzmin et al., 2013). The acute ethanol usage exerts its effects via GABAergic transmission, stimulates the activity of NOS due to the enhanced NO production, is related to the impaired memory in the memory associated regions (Ryabinin et al., 1998). It hindersthe glutaminergic activity, NMDA receptors, and kainite receptors and stimulate the GABAergic transmission in memory-related regions of the brain (White et al., 2000). The limitation of this model is that it is very lengthy and time taking as it requires pregnant female rats.
Colchicine
It is a powerful cytotoxic substance that depolymerizes the microtubules by invariably binding with them. Microtubules are considered as an important fibres in the formation of the cytoskeleton of cells. It also plays a crucial role in the cell division, cell growth, and axonal and dendritic communication. It has been established that the central administration of the toxin depletes memory in the rats due to the degeneration of the cholinergic neurons and increased superoxidants load (Kumar et al., 2007, Yu et al., 1997). It forms lesions on the hippocampus causing interrupted cholinergic transmission, proving an appropriate prototype for exploring AD pathology (Nakagawa et al., 1987). Colchicine can also augment neurotoxicity and loss in cognition power due to the extensive destruction of the cholinergic neuron and its pathway and low cholinergic transmission in the hippocampus (Evrard et al., 1999). It is also found that colchicine cause a fall in the level of serotonin, norepinephrine, and dopamine in the cortical, hippocampal, and caudate nucleus region (Ganguly et al., 2008).

Colchicine, increase the expression of COX-1 and COX -2 (Subbaramiah et al., 2000) and the level of ROS in the rat brain (Kumar et al., 2010). It also raises the glutamate/GABA level in the brain, hyperactivates NMDA receptors, resulting in the high influx of calcium further stimulating calcium-dependent enzymes like protein kinases, cyclooxygenase, protease, phospholipase A2, and xanthine oxidase. ICV administration of the toxin at a dose of 7.5 µg in 10 µL causes memory loss in the rodents (Sharma et al., 2010). Intracerebral jab of the toxin (3 µg/mice) cause alterations in the spatial memory. The chief advantage of this model is it produces definite characters for sporadic dementia. The model requires more animals due to the high mortality rate and also it is a time-consuming model.

Trimethyltin
It is a powerful neurotoxin, causing neural cell death in the hippocampus of animals as well as of humans. In several animal-based prototypes (Besser et al., 1987, Earley et al., 1992). Trimethyltin leads to the impaired memory, related to the injured neural cells of the hippocampus. It is considered as a valuable model for studying cognition impairment and seizures (Balaban et al., 1988, Ishikawa et al., 1997). Toxin-induced destruction of the cerebral cortex, hippocampus, and neocortical region are the contributing factors for depleted cognition power in the trimethyltin intoxicated rodents (Nommeman et al., 2013). Accidental trimethyltin exposure in humans develops a syndrome featuring disorientation, confusion, seizures, aggression, low intellectual power, and impaired memory. Trimethyltin-induced neurodegeneration, is primarily due to the generated oxidative load (Feldman et al., 1993). Targeted delivery of trimethyltin leads to neural cell death and ultimately contributing to neurotoxicity. Several investigations confirmed that different pro-inflammatory cytokines and different protein signalling are stimulated by trimethyltin which gives the indications for the mechanism involved in the trimethyltin mediated brain damage (Harry et al., 2002, Ogita et al., 2004, Shirakawa et al., 2007, et al., Kuramoto et al., 2011). Current reports suggest the role of the phosphoinositol 3-kinase/ Akt can be a target for neuroprotection against trimethyltin-induced neurotoxicity. It can be considered as an important model for studying various neurodegenerative diseases and dysfunctional hippocampus (Kim et al., 2013). Currently, GSK-3 signalling is found to be involved in trimethyltin mediated neurotoxicity in rodents. Therefore, various novel signalling pathways have been discovered that reveal the mechanism involving trimethyltin mediated neurotoxicity.

Streptozotocin(STZ)
Streptozotocin is a naturally occurring substance, isolated from the bacteria present in the soil. Earlier, it was used as an antibiotic and formerly used as an anticancer agent for treating neuroendocrine tumors. Investigations revealed that administration of Streptozotocin at a dose of 3 mg/kg results in decrease brain weight, increased tau level, increased Aβ plaque, and diminished cognition (Lannert et al., 1998). Studies also confirm that STZ jab causes altered neurochemicals and loss of memory (Mayer et al., 1990). Several studies reported that damage caused by the streptozotocin is limited to the areas comprising axons and myelin of the fornix, periventricular arrangements and anterior hippocampus which is involved in the regulation of cognition power (Salkovic-Petrisic et al., 2014). Studies also demonstrated that the dynamics of the damage to the brain depends on the administered dose of the toxin in rodents (Biessels et al., 1996).

Methamphetaminne
Methamphetamine causes a significant neurotoxic effect causing both structural as well as functional discrepancies. Many investigations reported that toxin administered at high dose, destroys serotonergic and dopaminergic nerve endings causing neural loss in rodents. Although, this is not a reliable method to demonstrate memory impairment (Trulson MEet al., 1998).
192 IgG-Saporin

192IgG-saporin is an in-vivo immunotoxin that kills neurons. It is composed of a saporin protein (a ribosome-inactivating protein), that prevents protein synthesis and stimulates apoptosis by catalytically damaging ribosomal RNA (Wrennet al., 1998). Nerve growth factor (NGF), regulates the function of the cholinergic neurons in the caudal forebrain by acting on NGF receptors. These neurons have p75-neurotrophin receptor (p75NGFR) components (Thomas et al., 1994). The 192 IgG-saporin has a low affinity against p75NGFR. Systemic administration of toxin bind to the p75-neurons, suppressed by endocytosis. This method is a perfect way to target the basal forebrain CBF neurons since only the cholinergic neurons can express p75. The p75 protein is bound to the surface of the neuron and then internalized by endocytosis. The saporin component of the toxin inactivates ribosomal subunit, inhibiting protein synthesis, causing cell death (Wiley et al., 1992).

ICV and direct injection of the toxin into the basal forebrain, form lesions of the cholinergic cells, ensuring the loss of cholinergic transmission, cholinesterase activity, and cholinergic filaments in the CBF (Kostrzewa, 2014). Purkinje cells of the cerebellum are also affected by the ICV injection. Toxin at a high dose of 4-10mg causes impairment in the passive avoidance test in rodents. The toxin impairs working memory as well as spatial memory. The advantage of this model over others is the specificity of killing cholinergic neurons (Garcia-Alloza et al., 2006, Berger-Sweeney et al., 1994).

Quinolinic Acid (QA)

QA is a well-identified NMDA receptor agonist, commonly used to induce Huntington's disease (HD). It produces various neurochemicals and histopathological changes in HD neuropathology with a decrease in cognition ability (Bealet al., 1985). It is a neuroactive metabolite, usually present in the human brain and CSF, responsible for the occurrence of a wide range of neurological diseases. Being an NMDA receptor agonist, it has more in-vivo effectiveness as an antitoxin (Lugo-Huitrón et al., 2013). Certain regions of the brain such as the striatum, neocortex, and hippocampus are more sensitive to QA than any other region. This sensitivity of the regions has related to the presence of NMDA receptors. It has been documented that, by using three NMDA receptor antagonists, the QA-induced toxicity can be fully reversed (Chen et al., 2011).

It promotes the release of glutamate, minimizes its uptake by astrocytes, and confines the activity of glutamine synthetase, which unbalance the glutamate level and develops neurotoxicity (Ting et al., 2009). Lipid peroxidation is the other mechanism for QA neurotoxicity (Santamaria et al., 2001). Few investigations report that QA binds with the iron to form a complex which leads to the formation of free radicals. Few studies suggest that QA can alter the integrity of BBB (Sípek et al., 1997). Interestingly, some areas of the hippocampus and striatum are more sensitive to QA. It activates nitric oxide synthase and nitric oxide synthase, contributing towards a large NO production (Braidy et al., 2010). Current studies suggest the role of QA in phosphorylating cellular protein which destabilizes the cytoskeleton filaments (Pieroza et al., 2010). QA at the therapeutic dose intermediates the expression of pro-inflammatory cytokines and chemokines (Guillemin et al., 2003).

Domoic Acid

It is a kinate receptor agonist and is structurally analogous to glutamic acid and kainic acid. Introduction of the toxin into the hippocampus of rodents causes degeneration of dentate gyrus, CA1, and CA3 pyramidal cells (Perez-Gomez et al., 2014). The toxin induces working memory deficit, mediated by inhibition of adenylate cyclase stimulated by CAM and raisesthe level of calcium (Nijjare et al., 2014). The stimulated AMPA/KA pathway raises the calcium intracellularly, which releases glutamate and ultimately activating NMDA receptors (Berman et al., 1997). The stimulation of AMPA/KA receptor induces apoptosis and necrosis in the neural cells, which is a dose-dependent phenomenon. High concentration (10 µM) activates NMDA receptors, whereas low concentration (0.1 µM) induces apoptosis via AMPA/KA pathway (Giordano et al., 2006). Additionally, the degree of neurotoxicity caused by domoic acid also depends upon the exposure time. Few reports documented the role of glial cells facilitating domoic acid neurotoxicity (Mayer et al., 2001). IP jab of the toxin into the rodents causes lesions in the cortical region, thalamus, amygdala, and olfactory cortex, but the highly injured area is septal nuclei and hippocampus (Strain et al., 1991). The damages caused by the toxin can also be seen in the hippocampal region of primates and the human brain (Schmued et al., 1995, Perez-Gomez et al., 2014). Direct injection of the toxin into the hippocampus induces spatial memory loss as compared to non-spatial memory. Individuals who had a domoic acid exposure are incapable of forming new memory sufficiently (Teitelbaum et al., 1990). Domoic acid has been documented as a potent and efficient tool for studying neurotoxicology and neuroscience (Perez-Gomez et al., 2014).
Pesticide/Herbicide for Memory Impairment

Paraquat
It is a plant-based chemical widely used for agriculture purposes, chemically named as N, N-dimethyl-4-4-bipiridinium. Structurally, similar to MPP+, but biologically increasing the oxidative stress facilitated by redox cycling, a contributor of ROS. Few researches demonstrated the effect of toxins in the nigrostriatal region reducing motor activity, and a dose-dependent striatal fibres deficit, while some later investigations refuted no alterations (Thiruchelvam M et al., 2000). PD researchers confirms the enhanced synuclein in the SNpc and Lewy-like bodies describing the manifestation of PD.

Rotenone
It is used as an insecticide as well as herbicide, which is highly fat-soluble in nature and can easily distort the BBB. The toxin is capable of manifesting similar characteristics to PD (Thiruchelvam M et al., 2000). It is reported that rotenone is able to cause synuclein aggregation and Lewy-like body formation. The model is used to explore PD in that enhances DA oxidation but due to limited evidence the reliability of this model is low (Wu YNet al., 2000). Further, there are no available reports have been documented suggesting its use as a human model (Greenamyre JT et al., 2010).

Metals-Inducing Memory Impairment
Several reports have been done, confirming the role of metal toxins such as aluminum, chromium, cobalt, lead, iron, arsenic, copper, and zinc increasing oxidative load and are one of the principal contributors for impairing memory and developing neurotoxicity (Bonda et al., 2011, Jellinger et al., 2013). Metals like arsenic, cadmium, and lead exert their effect via depletion of glutathione (Jomovaet al., 2011). Currently, a study investigated that Arsenic (As) exposure can cause endothelial dysfunction and memory loss in rodents. Few studies revealed the dysregulation of the serine/threonine protein phosphatases stimulated the activity of microglia and enhanced pro-inflammatory cytokines, which occurred due to the exposure to lead (Pb) (Rahmanet al., 2011). Zinc (Zn) has been related with the increased risk for AD due to the enhanced Aβ plague formation and aluminium (Al) is found to interfere with the Aβ metabolism and promote the accretion of tau protein, further imposes a risk for neurological disorders like AD (Kozinet al., 2011, Brewer et al., 2013). There are several other mechanisms identified which are involved in the pathology of AD-like manifestation include inhibiting degradation of Aβ peptide, affecting oxidative phosphorylation, impairing mitochondrial functioning, and inhibiting cAMP-PKA-CREB signalling.

Conclusions:-
Animal models are the closest to the human system and are therefore being used to explore the pathology of memory impairment, related disorders and also the brain functions on molecular, biochemical, and morphological level. The toxin either of natural source or synthetic source used as an experimental prototypes on different animals by the researchers by moderating dose of the toxins. With the above summarized study we came to know that toxins are being used for years and they are known to interfere the various processes of the brain such as alteration of synaptic plasticity, neural damage in striatal, hippocampus, nigrostriatal, pre-frontal cortex, disruption of the mitochondrial functioning, storage and release of neurotransmitters, excessive production of ROS in the brain cells, building up of the plague like Aβ which is responsible for the development of AD and related manifestations. But none of the model can mimic the histopathological, behavioural and biochemical anomalies described by depleted cognition. Use of genetic models, are the secondary option to study the disease pathology closely.

References:-
1. Arendt, T.; Holzer, M.; Bruckner, M.K.; Janke, C.; Gartner, U. The use of okadaic acid in vivo and the induction of molecular changes typical for Alzheimer’s disease. Neuroscience 1998, 85, 1337–1340.
2. Balaban, C.D.; O’Callaghan, J.P.; Billingsley, M.L. Trimethyltin-induced neuronal damage in the rat brain: Comparative studies using silver degeneration stains, immunocytochemistry and immunoassay for neuronotypic and gliotytic proteins. Neuroscience 1988, 26, 337–361.
3. Beal, M.F.; Kowall, N.W.; Ellison, D.W.; Mazurek, M.F.; Swartz, K.J.; Martin, J.B. Replication of the neurochemical characteristics of huntington’s disease by quinolinic acid. Nature 1985, 321, 168–171.
4. Berger-Sweeney, J.; Heckers, S.; Mesulam, M.-M.; Wiley, R.G.; Lappi, D.A.; Sharma, M. Differential effects on spatial navigation of immunotoxin-induced cholinergic lesions of the medial septal area and nucleus basalis magnocellularis. J. Neurosci. 1994, 14, 4507–4519.
5. Berman, F.W.; Murray, T.F. Domoic acid neurotoxicity in cultured cerebellar granule neurons is mediated predominantly by NMDA receptors that are activated as a consequence of excitatory amino acid release. J. Neurochem. 1997, 69, 693–703.
6. Besser, R.; Krämer, G.; Thümler, R.; Bohl, J.; Gutmann, L.; Hopf, H. Acute trimethyltin limbic-cerebellar syndrome. Neurology 1987, 37, 945.
7. Biessels, G.J.; Kamal, A.; Ramakers, G.M.; Urban, I.J.; Spruijt, B.M.; Erkelens, D.W.; Gispen, W.H. Place learning and hippocampal synaptic plasticity in streptozotocin-induced diabetic rats. Diabetes 1996, 45, 1259–1266.
8. Blesa, J.; Phani, S.; Jackson-Lewis, V.; Przedborski, S. Classic and new animal models of Parkinson’s disease. BioMed Res. Int. 2012, 2012.
9. Bonda, D.J.; Lee, H.-G.; Blair, J.A.; Zhu, X.; Perry, G.; Smith, M.A. Role of metal dyshomeostasis in Alzheimer’s disease. Metallomics 2011, 3, 267–270.
10. Braidy, N.; Grant, R.; Adams, S.; Guillemin, G.J. Neuroprotective effects of naturally occurring polyphenols on quinolinic acid-induced excitotoxicity in human neurons. FEBS J. 2010, 277, 368–382.
11. Brewer, G.J.; Kaur, S. Zinc deficiency and zinc therapy efficacy with reduction of serum free copper in Alzheimer’s disease. Int. J. Alzheimers Dis. 2013, 2013.
12. Caballol, N.; Martí, M.J.; Tolosa, E. Cognitive dysfunction and dementia in Parkinson disease. Mov. Disord. 2007, 22, S358–S366.
13. Cagnoli, C.M.; Khramchov, E.; Atabay, C.; Uz, T.; Manev, H. Apoptosis induced in neuronal cultures by either the phophatase inhibitor okadaic acid or the kinase inhibitor staurosporine is attenuated by isoquinolinesulfonamides H-7, H-8, and H-9. J. Mol. Neurosci. 1996, 7, 65–76.
14. Chen, C.; Li, X.-H.; Zhang, S.; Tu, Y.; Wang, Y.-M.; Sun, H.-T. 7,8-dihydroxyflavone ameliorates scopolamine-induced Alzheimer-like pathologic dysfunction. Rejuvenation Res. 2014, 17, 249–254.
15. Chen, Y.; Brew, B.J.; Guillemin, G.J. Characterization of the kynurenine pathway in NSC-34 cell line: Implications for amyotrophic lateral sclerosis. J. Neurochem. 2011, 118, 816–825.
16. Costa, A.P.; Tramontina, A.C.; Biasibetti, R.; Batassini, C.; Lopes, M.W.; Wartchow, K.M.; Bernardi, C.; Tortorelli, L.S.; Leal, R.B.; Gonçalves, C.-A. Neurological alterations in rats submitted to the okadaic acid-induced model of dementia. Behav. Brain Res. 2012, 226, 420–427.
17. Crocker, S.; Lamba, W.; Smith, P.; Callaghan, S.; Slack, R.; Anisman, H.; Park, D. C-jun mediates axotomy-induced dopamine neuron death in vivo. Proc. Natl. Acad. Sci. USA 2001, 98, 13385–13390.
18. Cui, M.; Aras, R.; Christian, W.V.; Rappold, P.M.; Hatwar, M.; Panza, J.; Jackson-Lewis, V.; Javitch, J.A.; Ballatori, N.; Przedborski, S. The organic cation transporter-3 is a pivotal modulator of neurodegeneration in the nigrostriatal dopaminergic pathway. Proc. Natl. Acad. Sci. USA 2003, 109, 8043–8048.
19. Da Cunha, C.; Angelucci, M.E.M.; Caneras, N.S.; Wonnacott, S.; Takahashi, R.N. The lesion of the rat substantia nigra pars compacta dopaminergic neurons as a model for Parkinson’s disease memory disabilities. Cell. Mol. Neurobiol. 2002, 22, 227–237.
20. Dhingra, D.; Parle, M.; Kulkarni, S. Effect of combination of insulin with dextrose, D(-) fructose and diet on learning and memory in mice. Indian J. Pharmacol. 2003, 35, 151–156.
21. Dovero, S.; Gross, C.; Bezard, E. Unexpected toxicity of very low dose MPTP in mice: A clue to the etiology of Parkinson’s disease? Synapse 2016, 70, 49–81.
22. Dunning, J.; During, M.J. Molecular mechanisms of learning and memory. Expert Rev. Mol. Med. 2003, 5, 1–11.
23. Earley, B.; Burke, M.; Leonard, B.E. Behavioural, biochemical and histological effects of trimethyltin (TMT) induced brain damage in the rat. Int. Neurochem. 1992, 21, 351–366.
24. Elder, G.A.; Gama Sosa, M.A.; De Gasperi, R. Transgenic mouse models of Alzheimer’s disease. Mount Sinai J. Med. 2010, 77, 69–81.
25. Evrard, P.A.; Ragusi, C.; Boschi, G.; Verbeek, R.K.; Scherrmann, J.-M. Simultaneous microdialysis in brain and blood of the mouse: Extracellular and intracellular brain colchicine disposition. Brain Res. 1998, 786, 122–127.
26. Feldman, R.G.; White, R.F.; Eriator, I.I. Trimethyltin encephalopathy. Arch. Neurol. 1993, 50, 1320–1324.
27. Feng, M.J.; Zhang, L.; Liu, Z.; Zhou, P.; Lu, X. The expression and release of Hsp60 in 6-OHDA induced in vivo and in vitro models of Parkinson’s disease. Neurochem. Res. 2013, 38, 2180–2189.
28. Fernandez, J.; Candenas, M.; Souto, M.; Trujillo, M.; Norte, M. Okadaic acid, useful tool for studying cellular processes. Curr. Med. Chem. 2002, 9, 229–262.
29. Fernández, M.T.; Zitko, V.; Gascón, S.; Torreblanca, A.; Novelli, A. Neurotoxic effect of okadaic acid, a seafood-related toxin, on cultured cerebellar neurons. Ann. N. Y. Acad. Sci. 1993, 679, 260–269.
30. Ferro, M.M.; Bellissimo, M.I.; Anselmo-Franci, J.A.; Angellucci, M.E.M.; Canteras, N.S.; Da Cunha, C. Comparison of bilaterally 6-OHDA-and MPTP-lesioned rats as models of the early phase of Parkinson’s disease: Histological, neurochemical, motor and memory alterations. J. Neurosci. Methods 2005, 148, 78–87.

31. Ganguly, R.; Guha, D. Alteration of brain monoamines & EEG wave pattern in rat model of Alzheimer’s disease & protection by moringa oleifera. Indian J. Med. Res. 2008, 128, 744–751.

32. Garcia-Alloza, M.; Zaldúa, N.; Diez-Ariza, M.; Marcos, B.; Lashezas, B.; Gil-Bea, F.J.; Ramirez, M.J. Effect of selective cholinergic denervation on the serotonergic system: Implications for learning and memory. J. Neuropathol. Exp. Neurol. 2006, 65, 1074–1081.

33. Gevaerd, M.S.; Miyoshi, E.; Silveira, R.; Canteras, N.S.; Takahashi, R.N.; Da Cunha, C. L-Dopa restores striatal dopamine level but fails to reverse MPTP-induced memory deficits in rats. Int. J. Neuropsychopharmacol. 2001, 4, 361–370.

34. Giordano, G.; White, C.C.; McConnachie, L.A.; Fernandez, C.; Kavanagh, T.J.; Costa, L.G. Neurotoxicity of domoic acid in cerebellar granule neurons in a genetic model of glutathione deficiency. Mol. Pharmacol. 2006, 70, 2116–2126.

35. Götz, J.; Chen, F.; Van Dorpe, J.; Nitsch, R. Formation of neurofibrillary tangles in P301L tau transgenic mice induced by Aβ42 fibrils. Science 2001, 293, 1491–1495.

36. Götz, J.; Pennanen, L.; Different tau epitopes define Aβ42-mediated tau insolubility. Biochem. Biophys. Res. Commun. 2005, 337, 1097–1101.

37. Goverdhan, P.; Sravanthi, A.; Mamatha, T. Neuroprotective effects of meloxicam and selegiline in scopolamine-induced cognitive impairment and oxidative stress. Int. J. Alzheimers Dis. 2012, 2012, 974013.

38. Greenamyre JT, Cannon JR, Drolet R, Mastroberardino PG. Lessons from the rotenone model of Parkinson’s disease. Trends Pharmacol Sci 2010; 31:141–2; author reply: 142–3.

39. Guillemin, G.J.; Croitoru-Lamoury, J.; Dormont, D.; Armati, P.J.; Brew, B.J. Quinolinic acid upregulates chemokine production and chemokine receptor expression in astrocytes. Glia 2003, 41, 371–381.

40. Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer’s disease: Progress and problems on the road to therapeutics. Science 2002, 297, 353–356.

41. Hardy, J.; Selkoe, D.J. The amyloid hypothesis of Alzheimer’s disease: Progress and problems on the road to therapeutics. Science 2002, 297, 353–356. [CrossRef] [PubMed] 121.

42. Harms, A.S.; Barnum, C.J.; Ruhn, K.A.; Vargashe, S.; Treviño, I.; Blesch, A.; Tansey, M.G. Delayed dominant-negative TNF gene therapy halts progressive loss of nigral dopaminergic neurons in a rat model of Parkinson’s disease. Mol. Ther. 2011, 19, 46–52.

43. Harry, G.J.; Tyler, K.; d’Hellencourt, C.L.; Tilson, H.A.; Brew, B.J. Quinolinic acid upregulates chemokine production and chemokine receptor expression in astrocytes. Glia 2003, 41, 371–381.

44. He, J.; Yamada, K.; Zou, L.B.; Nabeshima, T. Spatial memory deficit and neurodegeneration induced by the direct injection of okadaic acid into the hippocampus in rats. J. Neural. Transm. 2001, 108, 1435–1443.

45. Hriteu, L.; Ciobica, A.; Artemie, V. Effects of right-unilaterial 6-hydroxydopamine infusion-induced memory impairment and oxidative stress: Relevance for Parkinson’s disease. Open Life Sci. 2008, 3, 250–257.

46. Husband, A.; Worley, A. Different types of dementia. Pharm. J. 2006, 277, 579–582.

47. Ishikawa, K.; Kubo, T.; Shibanoki, S.; Matumoto, A.; Hata, H.; Asai, S. Hippocampal degeneration inducing impairment of learning in rats: Model of dementia? Behav. Brain Res. 1997, 83, 39–44.

48. Itier, J.-M.; Ibáñez, P.; Mena, M.A.; Abbas, N.; Cohen-Salmon, C.; Bohne, G.A.; Laville, M.; Pratt, J.; Corti, O.; Pradier, L. Parkin gene inactivation alters behaviour and dopamine neurotransmission in the mouse. Hum. Mol. Genet. 2003, 12, 2277–2291.

49. Jay, T.M. Dopamine: A potential substrate for synaptic plasticity and memory mechanisms. Prog. Neurobiol. 2003, 69, 375–390.

50. Jellinger, K.A. The relevance of metals in the pathophysiology of neurodegeneration, pathological considerations. Int. Rev. Neurobiol. 2013, 110, 1–47.

51. Johansen, J.P.; Cain, C.K.; Ostroff, L.E.; LeDoux, J.E. Molecular mechanisms of fear learning and memory. Cell 2011, 147, 509–524.

52. Jomova, K.; Valko, M. Advances in metal-induced oxidative stress and human disease. Toxicology 2011, 283, 65–87.

53. Kamat, P.K.; Rai, S.; Nath, C. Okadaic acid induced neurotoxicity: An emerging tool to study Alzheimer’s disease pathology. Neurotoxicology 2013, 37, 163–172.
54. Kamat, P.K.; Tota, S.; Rai, S.; Swarnkar, S.; Shukla, R.; Nath, C. A study on neuroinflammatory marker in brain areas of okadaic acid (ICV) induced memory impaired rats. Life Sci. 2012, 90, 713–720.
55. Kamat, P.K.; Tota, S.; Saxena, G.; Shukla, R.; Nath, C. Okadaic acid (ICV) induced memory impairment in rats: A suitable experimental model to test anti-dementia activity. Brain Res. 2010, 1309, 66–74.
56. Kandel, E.R.; Dudai, Y.; Mayford, M.R. The molecular and systems biology of memory. Cell 2014, 157, 163–186.
57. Kehagia, A.A.; Barker, R.A.; Robbins, T.W. Neuropsychological and clinical heterogeneity of cognitive impairment and dementia in patients with Parkinson's disease. Lancet Neurol. 2010, 9, 1200–1213.
58. Kidd, P.M. Alzheimer's disease, amnestic mild cognitive impairment, and age-associated memory impairment: Current understanding and progress toward integrative prevention. Altern. Med. Rev. 2008, 13, 85–115.
59. Kim JJ, Baxter MG. Multiple brain-memory systems: the whole does not equal the sum of its parts. Trends in neurosciences. 2001, 24(6), 324-30.
60. Kim, J.; Yang, M.; Kim, S.-H.; Kim, J.-C.; Wang, H.; Shin, T.; Moon, C. Possible role of the glycogen synthase kinase-3 signalling pathway in trimethyltin-induced hippocampal neurodegeneration in mice. PLoS ONE 2013, 8, e70356.
61. Klinkenberg, I.; Blokland, A. The validity of scopolamine as a pharmacological model for cognitive impairment: A review of animal behavioral studies. Neurosci. Biobehav. Rev. 2010, 34, 1307–1350.
62. Kostrzewa, R.M. Handbook of Neurotoxicity; Springer: New York, NY, USA, 2014.
63. Kozin, S.A.; Mezentsev, Y.V.; Kulikova, A.A.; Indeykina, M.I.; Golovin, A.V.; Ivanov, A.S.; Tsvetkov, P.O.; Makarov, A.A. Zinc-induced dimerization of the amyloid-β metal-binding domain 1–16 is mediated by residues 11–14. Mol. BioSyst. 2011, 7, 1053–1055.
64. Kumar, A.; Dogra, S.; Prakash, A. Protective effect of naringin, a citrus flavonoid, against colchicine-induced cognitive dysfunction and oxidative damage in rats. J. Med. Food 2010, 13, 976–984.
65. Kumar, A.; Seghal, N.; Naidu, P.S.; Padi, S.S.; Goyal, R. Colchicine-induced neurotoxicity as an animal model of sporadic dementia of Alzheimer’s type. Pharmacol. Rep. 2007, 59, 274–283.
66. Kuramoto, N.; Seko, K.; Sugiyama, C.; Shuto, M.; Ogita, K. Trimethyltin initially activates the caspase 8/caspase 3 pathway for damaging the primary cultured cortical neurons derived from embryonic mice. J. Neurosci. Res. 2011, 89, 552–561.
67. Kuzmin, A.; Chefer, V.; Bazov, I.; Mei, J.; Ögren, S.; Shippenberg, T.; Bakalkin, G. Upregulated dynorphin opioid peptides mediate alcohol-induced learning and memory impairment. Transl. Psychiatry 2013, 3.
68. Lannert, H.; Hoyer, S. Intracerebroventricular administration of streptozotocin causes long-term diminutions in learning and memory abilities and in cerebral energy metabolism in adult rats. Behav. Neurosci. 1998, 112, 1199–1208.
69. Lindgren, H.S.; Dunnett, S.B. Cognitive dysfunction and depression in Parkinson’s disease: What can be learned from rodent models? Eur. J. Neurosci. 2012, 35, 1894–1907.
70. Liu, F.; Grundke-Iqbal, I.; Iqbal, K.; Gong, C.X. Contributions of protein phosphatases pp1, pp2a, pp2b and pp5 to the regulation of tau phosphorylation. Eur. J. Neurosci. 2005, 22, 1942–1950.
71. Liu, W.; Dou, F.; Feng, J.; Yan, Z. Rack1 is involved in β-amyloid impairment of muscarinic regulation of gabaergic transmission. Neurobiol. Aging 2011, 32, 1818–1826.
72. Lu, P.; Mamiya, T.; Lu, L.; Mouri, A.; Zou, L.; Nagai, T.; Hiramatsu, M.; Ikejima, T.; Nabeshima, T. Silibinin prevents amyloid β peptide-induced memory impairment and oxidative stress in mice. Br. J. Pharmacol. 2009, 157, 1270–1277.
73. Lugo-Huitrón, R.; Ugalde Muñiz, P.; Pineda, B.; Pedraza-Chaverri, J.; Ríos, C.; Pérez-de la Cruz, V. Quinolinic acid: An endogenous neurotoxin with multiple targets. Oxidat. Med. Cell. Longev. 2013, 2013.
74. Magen, I.; Fleming, S.M.; Zhu, C.; Garcia, E.C.; Cardiff, K.M.; Dinh, D.; De La Rosa, K.; Sanchez, M.; Torres, E.R.; Masliah, E. Cognitive deficits in a mouse model of pre-manifest Parkinson’s disease. Eur. J. Neurosci. 2012, 35, 870–882.
75. Maidana, M.; Carlis, V.; Galhardi, F.G.; Yunes, J.S.; Geracitano, L.; Monserrat, J.M.; Barros, D.M. Effects of microcystins over short-and long-term memory and oxidative stress generation in hippocampus of rats. Chem. Biol. Interact. 2006, 159, 223–234.
76. Martin, S.; Grimwood, P.; Morris, R. Synaptic plasticity and memory: An evaluation of the hypothesis. Annu. Rev. Neurosci. 2000, 23, 649–711.
77. Mayer, A.M.; Hall, M.; Fay, M.J.; Lamar, P.; Pearson, C.; Prozialeck, W.C.; Lehmann, V.K.; Jacobson, P.B.; Romanic, A.M.; Uz, T. Effect of a short-term in vitro exposure to the marine toxin domoic acid on viability, tumor necrosis factor-α, matrix metalloproteinase-9 and superoxide anion release by rat neonatal microglia. BMC Pharmacol. 2001, 1.
78. Mayer, G.; Nitsch, R.; Hoyer, S. Effects of changes in peripheral and cerebral glucose metabolism on locomotor activity, learning and memory in adult male rats. Brain Res. 1990, 532, 95–100.
79. Miyoshi, E.; Wietzikoski, S.; Camplessi, M.; Silveira, R.; Takahashi, R.N.; Da Cunha, C. Impaired learning in a spatial working memory version and in a cued version of the water maze in rats with MPTP-induced mesencephalic dopaminergic lesions. Brain Res. Bull. 2002, 58, 41–47.
80. Moriguchi, S.; Yabuki, Y.; Fukunaga, K. Reduced calcium/calmodulin-dependent protein kinase II activity in the hippocampus is associated with cognitive impairment in MPTP-treated mice. J. Neurochem. 2012, 120, 541–551.
81. Nader, K.; Wang, S.H. Fading in. Learn. Mem. 2006, 13, 530–535.
82. Nadkarni AK. Indian materia medica. Bombay: Popular Prakashan; 1998.
83. Nakagawa, Y.; Nakamura, S.; Ka’se, Y.; Noguchi, T.; Ishihara, T. Chelamine lesions in the rat hippocampus mimic the alterations of several markers in Alzheimer’s disease. Brain Res. 1987, 408, 57–64.
84. Nestler EJ, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. Neuron. 2002, 34(1), 13-25.
85. Nijjar, M.; Nijjar, S.S. Domoic acid-induced neurodegeneration resulting in memory loss is mediated by Ca2+ overload and inhibition of Ca2+-calmodulin-stimulated adenylate cyclase in rat brain. Int. J. Mol. Med. 2000, 6, 377–466.
86. Nonneman, A.J.; Woodruff, M.L. Toxin-Induced Models of Neurological Disorders; Springer Science & Business Media: New York, NY, USA, 2013.
87. Nunan, J.; Small, D.H. Regulation of app cleavage by α-, β- and γ-secretases. FEBS Lett. 2000, 483, 6–10.
88. Nunes-Tavares, N.; Santos, L.E.; Stutz, B.; Brito-Moreira, J.; Klein, W.L.; Ferreira, S.T.; de Mello, F.G. Inhibition of choline acetyltransferase as a mechanism for cholinergic dysfunction induced by amyloid-β peptide oligomers. J. Biol. Chem. 2012, 287, 19377–19385.
89. Ogita, K.; Nitta, Y.; Watanabe, M.; Nakatani, Y.; Nishiyama, N.; Sugiyama, C.; Yoneda, Y. In vivo activation of c-Jun N-terminal kinase signalling cascade prior to granule cell death induced by trimethyltin in the dentate gyrus of mice. Neuropharmacology 2014, 97, 149–160.
90. Overmier, J. Bruce, and Marilyn E. Carroll., Basic issues in the use of animals in health research, 2001.
91. Panneton, W.M.; Kumar, V.; Gan, Q.; Burke, W.J.; Galvin, J.E. The neurotoxicity of dopal: Behavioral and stereological evidence for its role in Parkinson disease pathogenesis. PLoS ONE 2010, 5, e15251.
92. Pennanen, L.; Götz, J. Different tau epitopes define Aβ42-mediated tau insolubility. Biochem. Biophys. Res. Commun. 2005, 337, 1097–1101.
93. Perez-Gomez, A.; Tasker, R.A. Domoic acid as a neurotoxin. In Handbook of Neurotoxicity; Springer: New York, NY, USA, 2014; pp. 399–419.
94. Pierozan, P.; Zamoner, A.; SOSka, A.K.; Silvestrin, R.B.; Loureiro, S.O.; Heimfarth, L.; Souza, T.M.K.; Wajner, M.; Pessoa-Pureur, R. Acute intrastriatal administration of quinolinic acid provokes hyperphosphorylation of cytoskeletal intermediate filament proteins in astrocytes and neurons of rats. Exp. Neurol. 2010, 225, 188–196.
95. Plassman, B.L.; Langa, K.M.; Fisher, G.G.; Heeringa, S.G.; Weir, D.R.; Ofstedal, M.B.; Burke, J.R.; Hurd, M.D.; Poter, G.G.; Rodgers, W.L. Prevalence of dementia in the united states: The aging, demographics, and memory study. Neuroepidemiology 2007, 29, 125–132.
96. Rahman, A.; Brew, B.J.; Guillemin, G.J. Lead dysregulates serine/threonine protein phosphatases in human neurons. Neurochem. Res. 2011, 36, 195–204.
97. Rezayof, A.; Alijanpour, S.; Zarrindast, M.-R.; Rassouli, Y. Ethanol state-dependent memory: Involvement of dorsal hippocampal muscarinic and nicotinic receptors. Neurobiol. Learn. Mem. 2008, 89, 441–447.
98. Riedel, G.; Kang, S.; Choi, D.; Platt, B. Scopolamine-induced deficits in social memory in mice: Reversal by donepezil. Behav. Brain Res. 2009, 204, 217–225.
99. Ryabinin, A.E. Role of hippocampus in alcohol-induced memory impairment: Implications from behavioral and immediate early gene studies. Psychopharmacology 1998, 139, 34–43.
100. S’tipek, S.; S’taštný, F.E.; Pláteník, J.; Crkovská, J.; Zima, T. The effect of quinolinate on rat brain lipid peroxidation is dependent on iron. Neurochem. Int. 1997, 30, 233–237.
101. Salkovic-Petricic, M.; Osmanovic-Barilar, J.; Knezovic, A.; Hoyer, S.; Mosetter, K.; Reutter, W. Long-term oral galactose treatment prevents cognitive deficits in male wistar rats treated intracerebroventricularly with streptozotocin. Neuropharmacology 2014, 77, 68–80.
102. Santamaría, A.; Galván-Arzate, S.; Lisý, V.; Ali, S.F.; Duhart, H.M.; Osorio-Rico, L.; Ríos, C.; Sut’aštný, F. Quinolinic acid induces oxidative stress in rat brain synaptosomes. Neuroreport 2001, 12, 871–874.
103. Schifflitti, D.; Santamaría, L.B.; Rosa, G.; Di Nino, G.; Mandal, P.K.; Fodale, V.Cholinergic central system, Alzheimer’s disease, and anesthetics liaison: A vicious circle? J. Alzheimers Dis. 2010, 22, 35–41.
104. Schmued, L.C.; Scallet, A.C.; Slikker, W., Jr. Domoic acid-induced neuronal degeneration in the primate forebrain revealed by degeneration specific histochemistry. Brain Res. 1995, 695, 64–70.

105. Seamans, J.K.; Yang, C.R. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Prog. Neurobiol. 2004, 74, 1–58.

106. Sharma, B.; Singh, N. Pitavastatin and 40 -hydroxy-30 -methoxyacetophenone (HMAP) reduce cognitive dysfunction in vascular dementia during experimental diabetes. Curr. Neurovasc. Res. 2010, 7, 180–191.

107. Shimizu, K.; Matsubara, K.; Uezono, T.; Kimura, K.; Shiono, H. Reduced dorsal hippocampal glutamate release significantly correlates with the spatial memory deficits produced by benzodiazepines and ethanol. Neuroscience 1998, 83, 701–706.

108. Shirakawa, T.; Nakano, K.; Hachiya, N.S.; Kato, N.; Kaneko, K. Temporospatial patterns of COX-2 expression and pyramidal cell degeneration in the rat hippocampus after trimethyltin administration. Neurosci. Res. 2007, 59, 117–123.

109. Singh, P.; Konar, A.; Kumar, A.; Srivas, S.; Thakur, M.K. Hippocampal chromatin-modifying enzymes are pivotal for scopolamine-induced synaptic plasticity gene expression changes and memory impairment. J. Neurochem. 2015, 134, 642–651.

110. Small, D.H.; McLean, C.A. Alzheimer’s disease and the amyloid β protein. J. Neurochem. 1999, 73, 443–449.

111. Sodhi, R.K.; Singh, N.; Jaggi, A.S. Neuroprotective mechanisms of peroxisome proliferator-activated receptor agonists in Alzheimer’s disease. Naunyn Schmiedeberg Arch. Pharmacol. 2011, 384, 115–124.

112. Spinetta, M.J.; Woodlee, M.T.; Feinberg, L.M.; Stroud, C.; Schallert, K.; Cormack, L.K.; Schallert, T. Alcohol-induced retrograde memory impairment in rats: Prevention by caffeine. Psychopharmacology 2008, 201, 361–371.

113. Strain, S.M.; Tasker, R.A. Hippocampal damage produced by systemic injections of domoic acid in mice. Neuroscience 1991, 44, 343–352.

114. Subbaramaiah, K.; Hart, J.C.; Norton, L.; Dannenberg, A.J. Microtubule-interfering agents stimulate the transcription of cyclooxygenase-2 evidence for involvement of ERK1/2 and p38 mitogen-activated protein kinase pathways. J. Biol. Chem. 2000, 275, 14838–14845.

115. Tadaiesky, M.; Dombrowski, P.; Figueiredo, C.; Cargnin-Ferreira, E.; Da Cunha, C.; Takahashi, R. Emotional, cognitive and neurochemical alterations in a premotor stage model of Parkinson’s disease. Neuroscience 2008, 156, 830–840.

116. Tayeb, H.O.; Yang, H.D.; Price, B.H.; Tarazi, F.I. Pharmacotherapies for Alzheimer’s disease: Beyond cholinesterase inhibitors. Pharmacol. Ther. 2012, 134, 8–25.

117. Tayebati, S.K. Animal models of cognitive dysfunction. Mech. Ageing Dev. 2006, 127, 100–108.

118. Teitelbaum, J.S.; Zatorre, R.J.; Carpenter, S.; Gendron, D.; Evans, A.C.; Gjedde, A.; Cashman, N.R. Neurologic sequelae of domoic acid intoxication due to the ingestion of contaminated mussels. N. Engl. J. Med. 1990, 322, 1781–1787.

119. Thiruchelvam M, Brockel BJ, Richfield EK, Bagger RB, Cory-Slechta DA. Potentiated and preferential effects of combined paraguat and mane on nigrostriatal dopamine systems: environmental risk factors for Parkinson’s disease? Brain Res 2000; 873:225–34.

120. Thomas, L.B.; Book, A.A.; Schweitzer, J.B. Immunohistochemical detection of a monoclonal antibody directed against the NGF receptor in basal forebrain neurons following intraventricular injection. J. Neurosci. Methods 1991, 37, 37–45.

121. Ting, K.K.; Brew, B.J.; Guillemin, G.J. Effect of quinolinic acid on human astrocytes morphology and functions: Implications in Alzheimer’s disease. J. Neuroinflamm. 2009, 6

122. Tong, L.; Balazs, R.; Thornton, P.L.; Cotman, C.W. β-amylloid peptide at sublethal concentrations downregulates brain-derived neurotrophic factor functions in cultured cortical neurons. J. Neurosci. 2004, 24, 6799–6809.

123. Trulson ME, Cannon MS, Faegg TS, Raese JD. Effects of chronic methamphetamine on the nigral-striatal dopamine system in rat brain: tyrosine hydroxylase immunohistochemistry and quantitative light microscopic studies. Brain Res Bull 1985;15:569–77

124. Von Linstow Roloff, E.; Harbaran, D.; Micheau, J.; Platt, B.; Riedel, G. Dissociation of cholinergic function in spatial and procedural learning in rats. Neuroscience 2007, 146, 875–889.

125. White, A.M.; Matthews, D.B.; Best, P.J. Ethanol, memory, and hippocampal function: A review of recent findings. Hippocampus 2000, 10, 88–93.

126. Wiley, R.G. Neural lesioning with ribosome-inactivating proteins: Suicide transport and immunolesioning. Trends Neurosci. 1992, 15, 285–290.
127. Wimo, A.; Winblad, B.; Aguero-Torres, H.; von Strauss, E. The magnitude of dementia occurrence in the world. Alzheimer Dis. Assoc. Disord. 2003, 17, 63–67.
128. Wozniak, D.F.; Hartman, R.E.; Boyle, M.P.; Vogt, S.K.; Brooks, A.R.; Tenkova, T.; Young, C.; Olney, J.W.; Muglia, L.J. Apoptotic neurodegeneration induced by ethanol in neonatal mice is associated with profound learning/memory deficits in juveniles followed by progressive functional recovery in adults. Neurobiol. Dis. 2004, 17, 403–414.
129. Wrenn, C.C.; Wiley, R.G. The behavioral functions of the cholinergic basalforebrain: Lessons from 192 IgG-saporin. Int. J. Dev. Neurosci. 1998, 16, 595–602.
130. Wu YN, Johnson SW. Dopamine oxidation facilitates rotenone-dependent potentiation of N-methyl-D-aspartate currents in rat substantia nigra dopamine neurons. Neuroscience 2011.
131. Wu, Y.-Y.; Wang, X.; Tan, L.; Liu, D.; Liu, X.-H.; Wang, Q.; Wang, J.-Z.; Zhu, L.-Q. Lithium attenuates scopolamine-induced memory deficits with inhibition of GSK-3β and preservation of postsynaptic components. J. Alzheimers Dis. 2013, 37, 515–527.
132. Yamin, G. NMDA receptor-dependent signalling pathways that underlie amyloid β-protein disruption of LTP in the hippocampus. J. Neurosci. Res. 2009, 87, 1729–1736.
133. Yarnall, A.J.; Rochester, L.; Burn, D.J. Mild cognitive impairment in Parkinson’s disease. Age Aging 2013, 42, 567–576.
134. Yu, Z.; Cheng, G.; Hu, B. Mechanism of colchicine impairment on learning and memory, and protective effect of CGP 36742 in mice. Brain Res. 1997, 750, 53–58.