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REVIEW ARTICLE

EXPERMENTAL 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

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(Sharma et al., 2010).A study confirms that about 4.5 million people would be suffering from dementia by the year 2050, which may upsurge to a 114million (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 (Worsleyet 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 animproved 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 neuroal network seems to be key indications in AD patients (Schifilliti 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 chromatinmodifying 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-3 β, 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 Intranigral 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, whereasthe 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 thedestruction 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 and CREB pathways (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 reasonbehind the accumulation of tau proteins and developing risk forAD (Arendt et al., 1998). Some in-vitro and in –vivo studies, suggests the role of Okadaic acid in the accumulation and hyperphosphorylationof tau protein by blocking PP2A.

Administering the toxin via intra-hippocampal jab induces substantial neurological variations, involving hyperphosporylation 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 toxindepletes memoryin 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 hippocampuscausing 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 (Subbaramaiahet 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 (Nonneman 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 revealthe 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 plague, 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-Petrisicet 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).

Methamphetamine

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 (p75NGFFR) components(Thomaset al., 1991).The 192 IgG-saporin has a low affinity against p75NGFFR. 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 neurons and then internalized by endocytosis. The saporin component of the toxin inactivates ribosomal subunit, inhibiting protein synthesis, causing cell death(Wileyet 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-Sweeneyet 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 (Santamaría 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(S típek 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 (Pierozan 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 CAMand raisesthe level of calcium(Nijjaret 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). I.P 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-dimethyl4–4–4-bipiridinium. Structurally, similar to MPP+, but biologically increasing the oxidative stress facilitated by redox cycling, a contributor of ROS. Few researchesdemonstrated the effect of toxins in the nigrostriatal regionreducing motor activity, and a dose-dependent striatal fibres deficit, while some later investigations refuted noalterations (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 aluminum (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, negrostriatal, 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.

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