ABSTRACT
Neuropsychiatric symptoms (NPS) like psychosis, depression and aggression are considered the main characteristics of Alzheimer’s disease (AD). Piracetam is a derivative of the neurotransmitter gamma-aminobutyric acid (GABA) which is mainly responsible for the restoration of cell membrane fluidity. Piracetam has antithrombotic, neuroprotective, rheological and anticonvulsant properties and also improves neuroplasticity. It has been reported that piracetam decreases erythrocyte adhesion to vascular endothelium, inhibit the vasospasm and stimulate microcirculation. It is useful in the treatment of vertigo, cognitive disorders, dementia, dyslexia and sickle cell anemia. It improves learning, memory, brain metabolism and capacity. Piracetam protects the cells against hypoxia. Nowadays, there is increased use of nootropic drugs for the treatment of CNS disorders.

KEYWORDS: Piracetam, Alzheimer’s disease, neurodegeneration, memory.

INTRODUCTION
Piracetam is a drug having nootropic activity. This drug functions as a transmitter through acetylcholine through neurotransmitter which is incorporated in the memory process (Pilch, H. et al., 1988). The main role of the drug piracetam is not only to enhance the mitochondrial function but as well as it protects against mitochondrial damages during the period of aging and dementia. The brain which is the main organ of the body is responsible for all voluntary and involuntary actions. The average weight of human brain is 1.34 Kg which is one fiftieth weight of the body present in cranial cavity. There are two types of cells which are generally seen in the brain i.e. neuronal and non-neuronal cells. Nerve signals are transmitted through neurons and non-neuronal cell gives protection to the neuron hence they are known as supporting cells of the nervous system. Neurotoxins are the toxin which directly acts on the membrane proteins. The activity of the toxins acting on neuron depends on the dose uptaken. There are several neurotoxins which are self prepared by the human body, such as glutamate which when gets accumulated around the neuron causes cell death. The impact of inflammation is investigated by most common inflammogen LPS on death of neuron (Li, X.L., et al, 2014). Reactive oxygen species are produced by pathological effect of neurotoxin on cell signaling pathways which underline the pathophysiology of the diseases like neurodegeneracy (Serrano-Pozo, A., et al., 2011). Reactive nitrogen species also results in the LPS induced neurotoxicity in the brain. (Singh, S., et al; 2005). In many neurodegenerative diseases neuronal damages were reported due to loss of cellular antioxidant system and oxidative stress (Venkateshappa, C., et al 2012).

Nervous System
Nervous system consists of network of nerves and cells which are known as neurons, which transmits signals throughout the body parts. Nervous system of vertebrates consist of peripheral nervous systems and central nervous system, in which central nervous system consists of brain, spinal cord and retina where as peripheral nervous systems consists of ganglia which is made up of clusters of neurons, sensory neurons and those nerves which connects to the central nervous system (Gupta, R., et al. 2003). Peripheral nervous system is bifurcated into Autonomic nervous systems and Somatic nervous system (Yossi, G.S., et al. 2001).

Learning and Memory
Brain consists of memory which is having an ability to recall, store information and to record sensory stimuli and this information can be retrieved after long period of time (Dhingra, D., et al, 2004). Nervous system can be modified in the fields of morphology, biochemistry and physiology which are associated with the learning and memory (Amlio, M., et al, 2004).

Neurodegeneration
The term “Neurodegeneration” means death of neurons. The main characteristics of the disease caused by death of neurons results in the molecular changes in different
parts of the brain regions which results in loss of function (Viana, R., et al., 2011). Neurodegenerative diseases includes a range of situation where neurons are affected resulting in death of neurons. As neurons play an important role in both central and peripheral nervous system, so the regeneration of the neurons is not possible and it also starts degrading with the time leading to neurodegenerative disease. Some of the examples of the age related neurodegenerative disease are Parkinson’s, Alzheimer’s, and Huntington’s which is due to the death of the specific neuronal population. The main causes of degeneration of neurons is decrease in the level of the antioxidant, increase in oxidative stress, impairment of the mitochondrial activity, protein modification, damage in DNA and apoptosis. The chances of neurodegeneration in aged person lies between 60-70% (Singh, S., et al., 2005). It is often seen that Proteosome inhibitor promotes degeneration in neurons in hippocampal region of the brain resulting in inflammation (Pintado et al., 2012). There are some drugs which are used for curing the disease like KP-546 which is administered orally for the prevention of chemotherapy based neuropathology and also in neurodegenerative diseases. EAAT-2 i.e Excitatory amino acid transporter-2 is also used as a stimulator for the treatment of neurodegeneration. In present scenario NA-571 Clorioquil is used as the drug for the treatment (Wu, G., et al., 2004). In parkinson’s disease 1-methyl4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is the neurotoxin which results in dopaminergic neurodegeneration (Julie, L., et al., 1996). Microglia releases glutamate which is taken up by astrocytic L-Glu transporter, GLAST (EAAT1 in human). Transporter like L-Glu helps to maintain the level of L-Glu below toxicity and if the level increases, it results in excitotoxicity. Impairment in L-Glu level can also cause neurodegenerative disease like Parkinson’s disease, Amyotrophic Lateral Sclerosis and Alzheimer disease (Fujimori, K., et al., 2015).

Causes of Neurodegeneration: Oxidative stress
The main cause of Alzheimer’s disease is oxidative stress (Wu, G.,et al 2004). The state of oxidative stress arises when there is rise in the concentration of ROS and RNS or there is decrease in the concentration of antioxidant level. This stage may arise when the tissue damages by physical, chemical and psychological factor leading injury and inflammation in tissue. Alzheimer’s disease does not only results by the high concentration of the ROS and RNS but also due to change in the level of the metabolism of the gluthathione and through peroxidation of lipid which destroys the structure of cell including lipids, nucleic acid and protein. ROS and RNS also cause damage to the cell membrane by releasing cell’s intracellular components. Under oxidative stress condition free radicals formation takes place mainly during cerebral ischemia. After the onset of reperfusion of cerebral ischemia there is the bursting of free radicals which are generated. Brain is the only organ in the body which is susceptible to damage as neurons are rich in polyunsaturated fatty acids and the antioxidant enzymes level is low which leads to neuronal cell death under oxidative stress condition (Goswami, P., et al 2014). Oxidative stress can cause damages like cell death as reactive oxygen species (ROS) oxidizes components of cell like DNA, proteins, lipids. The exposure of brain is mainly to the amino acid like glutamate whose metabolism produces ROS which promotes excitotoxicity. Antioxidant protection mechanism removes oxygen by scavenging reactive oxygen as well as nitrogen species and also inhibition of ROS formation takes place (Tyagi, E., et al 2010). In lipids, proteins and in DNA reactive oxygen species results in oxidative damage as ROS consumes 20% oxygen through the brain and it also contains polyunsaturated fatty acids with low level of endogenous antioxidant activity in comparison to other tissues. (Tincer, G., et al 2016).

Neurodegenerative Diseases
1. Alzheimer’s Disease (AD)
This type of disease is very slow growing disease which starts depleting the neurons present in brain resulting in the impairment of the memory as well as disturbances in the reasoning, learning, planning, understanding language and perception. This type of disease is often seen when there is the accumulation of protein (β-amyloid protein) in the brain, which may also results in death of nerve cells when the concentration increases in the brain. This process takes place when there is deposition of neurotoxic beta amyloid peptides derived from proteolytic processing of precursor protein which results in increase of the voltage gated potassium ion channel which finally results in the apoptosis of neurons. The accumulation takes place at the age of 70’s. This disease is not an ordinary part of aging, it is something which is unavoidable and happens in the later stage of life span (Tyagi, E., et al., 2010). Our nervous system consists of substance P (SP) which is present in those parts which acts as neurotransmitter, neuromodulator, and neurotransmitter. It is observed that patients showing symptoms of neurodegeneration results in the reduction of level of SP in brain as well as in spinal fluids as this substance P shows stimulation of non amyloidogenic precursor protein which reduces the possibility of toxic generation in the brain (Severini et al., 2016).

Pathology of Alzheimer’s Disease
The death of brain cells results in neurodegenerative diseases giving rise to Alzheimer’s disease which shows drastic death of cells over a period of time. This disease results in shrinkage of brain with very few nerve cells and their connections. Damaged neuronal cells shows plaques and tangles which are as follows:-
- Plaques- Plaques are formed in brain when the protein β- amyloid gets accumulated in brain.
- Tangles- Tangles are formed in neurons through degeneration of protein known as tau.
Parkinson’s Disease (PD)

Parkinson’s disease (PD) is also a neurodegenerative disease caused by depletion of nigral dopaminergic neurons which decreases in dopamine neurotransmitter. The main cause of this disease is decrease in the level of the nigrostriatal dopaminergic neurons and presence of intraneuronal proteinacious cytoplasmic inclusions which are also known as “Lewy Bodies”. Hyperkinetic features which are seen in this disease is due to inhibition of glutamate-induced calcium signaling, mainly caused by striatal depletion of the dopamine (Tyagi, E., et al., 2010). The neurotoxin which participate in dopaminergic neurodegeneration in parkinson’s diseases (PD) is 1-methyl-4-phenyl-1, 2, 3, 6- tetrahydropyridine (MPTP) (Sarika et al., 2005). The age associated neurodegenerative disorder i.e. Parkinson’s disease results in loss of the dopaminergic neurons in the substantia nigra (SN), which further results in the dysfunctioning of the mitochondria and oxidative stress. Mutation may also lead to Parkinson’s disease which shows alterations in the nicotinamide adenine dinucleotide NAD salvage metabolism. NAD acts as a co-factor for energy generation in mitochondria as well as in DNA repair mechanism by consuming poly (ADP-ribose) polymerases (PARPs) (Lehmann, S., et al., 2016). A calcium binding protein i.e CaV1.3 is a therapeutic target for neurodegeneration in the Parkinson’s disease. The function of CaV1.3 is to render the neurons which are very much susceptible to excitotoxicity and oxidative stress. Early parkinson’s disease takes place when there is a change in the calcium binding protein (Michael et al., 2013). For the treatment of parkinson’s disease precursors like L-DOPA (L-3,4 dihydroxyphenylalanine), compounds like catechol-O-methyltransferase inhibitors (COMT) are used. This disease can also be treated with inhibitors of monoaminoxidase type B and also through glutaminergic receptors amantadine (Cieslak, M., et al., 2008). The Parkinson’s disease is also caused by the conversion of MPTP to MPP+, which is facilitated by glial cells (Cali, T., et al., 2011).Neurotrophins which are released by astrocytes plays an important role in protection of neurons (Venkateshappa, C., et al., 2012).

Antioxidant Enzymes Acting on Brain

Glutathione (GSH)

Glutathione is one of the major group having thiol group the metalloproteinases (PARPs) which finally get cleaved by thioredoxin to give GSH and NO which with NO to form nitrosoglutathione. Glutathione-S-transferase initiates the reaction to form mercapturates when GSH reacts with electrophiles, physiological metabolites and xenobiotics. As GSH gets conjugated with NO to form S-nitroso-glutathione which is further cleaved by thioredoxin to give GSH and NO. The targeting of NO is mediated by intracellular GSH which is very much necessary for hepatic action which regulates lipid, glucose, and amino acid utilization. Formaldehyde and GSH gets converted into S-formyl-glutathione as GSH acts as a substrate for formaldehyde dehydrogenase. Hence, GSH is required in the metabolism for conversion of prostaglandin H2 to prostaglandins D2 and E2 by endoperoxide isomerase (Galloway, S.M., et al, 1990).

Malondialdehyde

The organic compound Malondialdehyde is having formula CH3(CHO)2. This is one of the reactive species which occurs naturally and is involved in processing of oxidative stress. Malondialdehyde is also used as an indicator for lipid peroxidation (Nielsen, F, et al., 1997). Malondialdehyde (MDA) is one of the major polyunsaturated fatty acid peroxidation as this molecule is also named for its high toxic level and interaction with DNA and protein is known to be highly mutagenic and atherogenic (Pathan, A.B., 2012).

Neuroprotective Compound

1. Piracetam

The most effective drug which is used in present scenario is piracetam which affects brain’s mental function as it is also involved in the process of learning and memory. It is also known as “smart drug” (Ebrahimia, K., et al., 2017). The role of piracetam is to protect physical and chemical stress, which an important role in aging resulting in some diseases like Alzheimer’s disease, Parkinson’s disease, liver disease, cystic fibrosis, sickle cell anemia, kwashiorkor, seizure, HIV, AIDS, cancer, heart attack, stroke, and diabetes) (Severini, et al., 2016).
damages which are caused to brain. The drug piracetam enhances the efficacy of central nervous system i.e. cholinergic neurotransmission.

**Pharmacological properties of Piracetam**

The drug named piracetam is a derivative of γ amino butyric acid (GABA), which is also known as “Nootropic drug” which came from Greek word “acting on the mind”. This drug is having psychotropic activity. This drug is effective in enhancement of memory as it increases microcirculation and decreasing the activity of platelets circulating in that area of brain. It also decreases the activity of erythrocyte deformability which decreases the contact between the erythrocytes which are damaged and to the endothelium.

**Pharmacokinetics studies**

Piracetam is the drug which completely assimilates through the oral route. After 40-45 minutes of oral drug assimilation there is a rise in a concentration in plasma which is mainly seen in old people having multiple disease. The importance of this drug is that it reaches rapidly to the organ as half life of this drug is higher than plasma half life. This drug crosses blood brain barrier and reaches gray matter in cerebrum, cerebellum and gets excreted out through urine (Suelen, A., et al., 2013). This drug is also known as 2-oxo-1-pyrrolidone acetamide which is mainly derived from GABA (Morgenthaler, T.I., et al., 2007). Racetam drug has very low toxicity with less side effects, while piracetam blocks catecholamine receptor (CA) which proves that it is a neuroleptic drug (Amiraslani, B., et al., 2012). This drug is mainly prescribed by doctors for some conditions like myoclonus. Piracetam is well known for its boosting capacity for intelligence and also known as a stimulant for Central nervous system with no toxicity and addictive properties. This drug also helps children who are suffering from Down Syndrome (DS).

**CONCLUSION**

In present scenario the effect of Piracetam drug shows different effects on different parts of brain. This drug protects LPS induced DNA fragmentation. Piracetam often offers protection against LPS induced oxidative stress in mid brain, hippocampus and frontal cortex and also found in striatum regions of brain. As this drug reflects property of antioxidant in some region specific manner which can be further used in clinical applications.

**REFERENCES**


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