

Recent Advances on Piracetam

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Abstract: Piracetam, a derivative of the neurotransmitter gamma-aminobutyric acid (GABA), is responsible for the restoration of cell membrane fluidity. Piracetam modifies neurotransmission in a range of transmitter systems (including cholinergic and glutamatergic), has neuroprotective and anticonvulsant properties and improves neuroplasticity. At a vascular level, it appears to reduce erythrocyte adhesion to vascular endothelium, hinder vasospasm and facilitate microcirculation. It is useful in the treatment of cognitive disorders, dementia, vertigo, cortical myoclonus, dyslexia, sickle cell anemia. It improves learning, memory, brain metabolism and capacity. Piracetam acts by protecting the cell against hypoxia. Piracetam is an agent with antithrombotic, neuroprotective and rheological properties. Nowadays, there is increased use of nootropic drugs for the treatment of CNS disorders.

Key words: Alzheimer's disease • Gamma-aminobutyric acid • Membrane fluidity • Microcirculation

INTRODUCTION

Alzheimer's disease is a neurodegenerative disorder. The main features of Alzheimer's disease are presence of amyloid protein beta (A β) deposition in plaques and formation of neurofibrillary tangles. There may be various mechanisms of degeneration of neurons like oxidative stress, dysfunctioning of mitochondria, generation of free radicals, inflammatory response, cell death and other factors. All these factors lead to non-functioning of neurons which ultimately leads to cell death [1]. One of the important factors responsible for neuronal dysfunctioning in Alzheimer's disease is metal toxicity especially of aluminium. Aluminium causes neurotoxicity in mammals. The development of Alzheimer's disease may be due to the exposure of Aluminium. Both the senile plaques and neurofibrillary tangle bearing neurons in the brains of patients with Alzheimer's disease showed the presence of aluminium. It was depicted that neuropathological and neurobehavioral changes occur in animals when exposed to aluminium resulted in impaired learning and memory. Cholinesterase inhibitors enhance the acetylcholine level thereby improving the symptoms of Alzheimer's disease [1].

In past, improving memory was limited to only fiction or imagination. But it is possible in the present by using various neurotransmitters and smart drugs like piracetam. It has been reported that Serotonin transmission is responsible for depleting memory and learning processes. So, Serotonin inhibitors may be targeted to enhance memory and learning. Dementia is a syndrome due to progressive neuronal damage in the brain. Dementia can be characterized by improper functioning of the memory, orientation, language, calculation, learning capacity and judgment without alerting consciousness. Alzheimer's disease causes dementia and abnormal phosphorylation of the intracellular tau-proteins. It may lead to dysfunctioning of microtubule assembly and collapse of the cytoskeleton [2].

In experimental animals, atropine and scopolamine are used to induce impairment in memory. The amnesic action in animals can be produced by the administration of centrally acting muscarinic cholinergic antagonists, like scopolamine, has been a widely used model for the characterization of potential cognition-enhancing drugs. The cognitive impairment can be improved by herbal medicines. It has been reported that NONI juice is useful in the treatment of memory impairment. NONI juice was

prepared as a polyherbal formulation using *Morinda citrifolia* extract and *Garcinia cambogi*. Now-a-days polyherbal formulations are used widely for the cure of dementia [3].

Nootropic drugs are widely used for treating neurological disorders like (i) cognition/memory; (ii) epilepsy and seizure; (iii) neurodegenerative diseases; (iv) stroke /ischaemia; and (v) stress and anxiety [4].

Piracetam plays a crucial role to improve the function of acetylcholine by muscarinic cholinergic (ACh) receptors. These receptors are important in memory and learning. Piracetam exerts its action mainly by enhancing the cell membrane permeability. It also increases oxygen consumption in brain so the adenylate kinase activity has also been enhanced [1]. Piracetam was the first compound of nootropics (smart drugs) developed in 1967. It is a water-soluble pyrrolidone derivative and chemically similar to pyroglutamate. Its chemical name is 2-oxo-1-pyrrolidine acetamide and is also a cyclic derivative of gamma-aminobutyric acid. It is indicated for seizures, dementia, myoclonus or other neurological problems [5]. An Ayurvedic formulation was prepared from *Dioscorea batatas* for the enhancement of learning and memory. In the past, *Dioscorea batatas* was used as antioxidant, anti-inflammatory, angiotensin converting enzyme inhibitor, carbonic anhydrase and trypsin inhibitor [2]. Nootropics are the drugs used to cure memory impairment and also used to enhance intelligence. Nootropics are also called 'smart drugs' [2].

This review is done to investigate the possible pharmacological activities exhibited by Piracetam with respect to its mode of action. Various diseases which could be treated by piracetam is also been discussed in this review. Piracetam comes under the category of smart drugs, i.e. Nootropics. Piracetam has been also compared with the nootropic effect of herbal drugs.

Nootropics: It has been more than three decades since research on nootropic agents is going on. The research was done on their nootropic activity. Nootropics were also focused for their neuroprotective effect after stroke and their application in the treatment of epilepsy. C.E. Guirgea gave the concept of nootropic drug in 1972. He launched Piracetam and worked as Principal researcher for UCB Pharmaceutical Company of Belgium. C.E. Guirgea named "nootropic" from the italic words "noos" (mind) and "tropein" (to turn toward). Nootropics were developed to enhance the memory deficit. [11].

Characteristics of a Nootropic Drug:

- a) It should protect the brain from physical and chemical injuries.
- b) It should enhance the memory and learning processes.
- c) It should act against those agents which may impair memory and behavior.
- d) It should not produce harmful and toxic effects.
 - Piracetam has been licensed in India, Belgium, Austria, Germany and Switzerland. It is indicated in stroke, mild cognitive impairment.
 - Levetiracetam, another commonly used nootropic agent was developed in 1999 to cure epilepsy. It has been licensed in USA, Switzerland, Argentina and Norway.
 - There are many other drugs belonging to nootropics which are under research and clinical trials like Aniracetam, Fosracetam, Nefiracetam, Pramiracetam and Oxiracetam. These drugs are free from adverse drug reactions mainly on CNS. They are toxicologically safer drugs [4].

Pharmacological Properties of Nootropics: Nootropics influence cholinergic function. These drugs enhance the synthesis of acetylcholine by increasing high affinity choline uptake at muscarinic and nicotinic receptors. As the human beings age, a depletion of acetylcholine receptors has been observed. Piracetam acts by enhancing the number of acetylcholine receptors in frontal region of the brain. So, ultimately it increases the level of acetylcholine in the brain by 30-40 % [5].

In case of dementia or Alzheimer's disease the carbohydrate metabolism of our brain is declined.

Brain cells produce their own ATP from glucose and sugar as they cannot get it from any other source.

Piracetam acts by activating adenylate kinase enzyme that is responsible for the conversion of ADP into ATP and AMP. So, this compensates the deficiency of ATP in the brain cells. This may ultimately serve a crucial role in preventing and curing dementia by recovering the oxygen and energy demand in the brain.

- It also elevate the cerebral blood supply, oxygen supply, glucose metabolism rate in human brain functioning which was impaired from a long period like in the case of multi-infarct dementia, senile dementia, pseudo dementia, poor brain blood flow.
- It also acts by decreasing platelet aggregation and produces antithrombotic activity.

- It may alter the membrane characteristics by elevating the membrane fluidity by binding to membrane phospholipids.
- It enhances the synthesis of prostacyclin (PGI₂), phospholipids metabolism and protein synthesis.

Levetiracetam is one of the drugs used to cure epilepsy.

- It decreases calcium ion conductance.
- It antagonizes negative allosteric modulators of both GABA and glycine gated channels.
- It also protects the neurons.

Nefiracetam is also one of the drugs used to treat epilepsy.

Pramiracetam acts by elevating nitric oxide synthase activity. It is used in Italy to enhance memory.

Indications:

- Piracetam is indicated in the treatment of stroke, cognitive impairment, organic brain syndrome, multi-infarct dementia, senile dementia, Alzheimer's disease, post-concussion syndrome, post traumatic vertigo and coma, aphasia, alcoholism, alcohol withdrawal, head injury, sickle cell anemia, Raynaud's disease, Parkinson's disease, post anoxic myoclonus, primary generalized epilepsy with myoclonus, hypoxia, anoxia, cerebrovascular disorders.
- Levetiracetam: epilepsy, myoclonus [6]

Piracetam: Piracetam is chemically pyrrolidone acetamide. It is also termed as racetams which have a five-carbon oxopyrrolidone ring. Piracetam and piracetam-like drugs act by modulating the cerebral functions. Piracetam is useful in patients with encephalopathies due to cranial traumas, inflammation and stroke/ ischemia complications after bypass surgery as it enhances the memory and brain performance. It is also used for the treatment of seizures and neuromuscular convulsions [4]. Piracetam is a derivative of Gamma-aminobutyric acid (GABA), a neurotransmitter, marketed in 1971 by UCB Pharma. It enhances the cognitive function without causing adverse effects like sedation or stimulation [6].

Piracetam has a pyrrolidone nucleus and its Molecular Formula is C₆H₁₀N₂O₂. It modulates the activity of neurotransmitters, like acetylcholine and glutamate. The racetams act as positive allosteric modulators for the AMPA receptor. Racetams reveal their activity by stimulating glutamate receptors that are colocalized with

cholinergic receptors. The racetams are able to enhance memory by similar way as the acetyl cholinesterase inhibitors. The nootropic efficacy of racetams is enhanced if choline or acetylcholine precursors are administered together [5].

Piracetam-Like Compounds: Piracetam-like compounds may be classified into three subgroups.

Subgroup 1 Drugs: Piracetam, oxiracetam, aniracetam, pramiracetam and phenylpiracetam belong to the first category of Piracetam –like drugs. These are used in humans and some as dietary supplements. The clinical use of Oxiracetam and Aniracetam has been restricted. The depletion of memory and learning caused by traumatic brain injuries may be managed by using Pramiracetam. Piracetam is used during coronary bypass surgery as a neuroprotective agent. Piracetam is also used to cure depression, anxiety, cognitive disorders, myoclonus epilepsy and tardive dyskinesia. Phenylpiracetam has a higher range of potency than piracetam and uses for many disorders.

Subgroup 2 Drugs: Levetiracetam, seletracetam and brivacetam belong to second category of Piracetam –like drugs. Clinically they are used for their antiepileptic activity.

Subgroup 3 Drugs: Piracetam derivatives like nefiracetam and rolipram belong to third category of Piracetam –like drugs. It has been reported that nefiracetam was unable to improve cognition in post-stroke patients. Rolipram is the upcoming therapy for depression [4].

Mechanism of Action of Piracetam:

The Membrane Hypothesis: Piracetam acts by restoring the membrane fluidity. Membrane fluidity is crucial for the regulation of membrane transport, enzyme activity, chemical secretion, receptor binding and stimulation. It has been reported that piracetam interacts with the cell membranes and prevented the appearance of alcohol-related changes in a synthetic phosphatylcholine monolayer.

It was observed that amyloid peptide gets aggregated on the neuronal membranes and causes lipid disorganization within the cell membranes. Piracetam reduces the destabilizing effects of the amyloid peptide. This could happen as a result when piracetam interacts with phospholipid head groups of the cell membranes.

Piracetam changes the membrane fluidity especially when the normal fluidity of the cell membrane is improper.

It was reported that piracetam not only affects the membrane fluidity of the brain but also the membrane of blood platelets [6].

Piracetam also plays an important role in energy metabolism by enhancing the utilization of oxygen in the brain and enhancing the cell permeability and also the permeability of mitochondrial membranes to the intermediate products of Krebs's cycle [4].

Piracetam also acts as an antioxidant/neurotonic. It also enhances the number of acetylcholine receptors.

The agents belonging to subgroup 1 like piracetam, oxiracetam and aniracetam stimulate AMPA type glutamate receptors.

Piracetam, oxiracetam belonging to subgroup 1 acts by stimulating amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA)-type glutamate receptors which enhances the number of receptor binding sites for AMPA and calcium uptake. This ultimately causes enhancement of intracellular calcium ions.

Levetiracetam belonging to subgroup 2 acts by reducing incoming ions in AMPA- and kainite-induced currents inside the cortical neurons. It inhibits the calcium ion channel in neurons acts shows antiepileptic activity [4].

Pharmacological Effects of Piracetam

Neuronal Effects on Neurotransmission: Piracetam plays a crucial role in neurotransmission by acting on various neurotransmitter systems like glutamatergic, cholinergic, serotonergic and noradrenergic systems. Piracetam acts by enhancing postsynaptic receptors or restart the receptor functions. The functions of neurotransmitters are altered by membrane fluidity according to the membrane hypothesis. Neurotransmitters bind to these proteins embedded within the membrane and alter the ions and other substances flow in and out of the cell. Due to the alteration in membrane fluidity, the action of neurotransmitters and cell signaling is also altered. The improper functioning of cholinergic and glutamatergic systems may be responsible for memory impairment. So, if Piracetam is used as a therapy for cognitive disorders, it may alter the acetylcholine levels in hippocampus and enhance the number of muscarinic cholinergic receptors in the frontal cortex of the brain. The treatment for the glutaminergic system with piracetam enhances the number of N-methyl-D-aspartate (NMDA) receptors in the prosencephalon[5].

Neuroprotective Effects: Membrane fusion may be prevented by reaction between piracetam and membrane lipids. It was reported that if piracetam is administered to alcohol-treated rats then it abolishes the secretion of lipofuscin which shows that there is reduced damage in the neuron membrane.

Effects on Neuroplasticity: The regulation of neural circuitry by altering and developing the synaptic and neural connections is termed as Neuroplasticity. It has been reported that piracetam produces neuroplasticity which means that it enhances memory and learning processes thereby preventing lesions and ischemic damage. The adverse effects of alcohol can be compensated by using piracetam.

Anticonvulsant Effects: It has been reported that piracetam process anticonvulsant activity. If piracetam is administered with carbamazepine and diazepam, then it further enhances their anticonvulsant activity.

Vascular Effects

Effects on Erythrocytes: Piracetam acts by diminishing the adhesion of erythrocytes on the endothelium so, the erythrocytes are able to move through the blood circulation.

Effects on Blood Vessels: Piracetam acts by enhancing the synthesis of prostacyclin which causes vasodilation platelet aggregation inhibition.

Effects on Blood Coagulation: Piracetam acts by decreasing the fibrinogen and von Willebrand factor level which is responsible for hemostasis. Thus, it may reduce the blood coagulation.

Effects on Microcirculation: It has been reported that piracetam increases the blood flow to the brain so can be used as a therapy of cerebral ischemia. Piracetam also acts by enhancing the microcirculation by acting on red blood cells, blood vessels and blood coagulation [7].

Piracetam (2-oxo-1-pyrrolidine acetamide) is used to cure seizures, Alzheimer's and senile dementia and other neurological problems. Doxapram (1-ethyl-4-(2-morpholin-4-ylethyl)-3, 3-diphenyl-pyrrolidin-2-one) is used for the treatment of respiratory failure [8].

The nootropic activity of piracetam was found in 1967. Piracetam-like nootropics acted to rectify the amnesia induced by scopolamine and other amnesic drugs, electroconvulsive shock and hypoxia. They act by modifying the acetylcholine and glutamate actions [9].

Pharmacology

Antiamnesic Test (Passive-Avoidance Test): The test was performed according to the step-through method described by Jarvik and Kopp [12]. The apparatus consists of a two-compartment acrylic box with a lighted compartment connected to a darkened one by a guillotine door. In the original method, mice received a punishing electrical shock as soon as they entered the dark compartment, while in the newer method, after entry into the dark compartment, mice receive a non-painful punishment consisting of a fall (from 40 cm) into a cold water bath (10°C). For this purpose, the dark chamber was constructed with a pitfall floor. The latency times for entering the dark compartment were measured in the training test (first day) and after 24 h in the retention test (second day). Mice that did not enter after 60 s latency were excluded from the experiment. For memory disruption, mice were i.p. injected with the amnesic drugs (scopolamine). All investigated drugs were given i.p. (dissolved in saline solution) or p.o. (dispersed in 1% carboxymethylcellulose) 20 min before the training session, while amnesic drugs were injected immediately after termination of the training session. The maximum entry latency allowed in the retention session was 120 s. The degree of received punishment memory (fall into cold water) was expressed as the increase in seconds between training and retention latencies [9].

Vision: Piracetam cured the color discrimination in patients (aged 19–24 years) suffering from traumatic brain injuries.

Stroke/Ischemia: Piracetam is also useful for the treatment of stroke and ischemia conditions.

Neurodegenerative Disorders:

Ataxia: Piracetam is also useful for curing posture and gait abnormalities.

Epilepsy, Convulsion, Seizure: Piracetam can be used for the treatment of Epilepsy, Convulsion and Seizure if given in combination with valproate or clonazepam.

Memory, Cognition, Attention and Depression: Phenylpiracetam is used for the treatment of cognitive deficits and/or depression after encephalopathy and brain injuries [4].

It has been reported that Piracetam has very less or no adverse effects. Sometimes, it may show some adverse effects like anxiety, insomnia, agitation and tremor.

Pharmacokinetics: Piracetam is orally rapidly absorbed. Its absorption is not affected by food. The peak plasma concentrations after oral administration in fasting subjects are achieved in about 30 min. The bioavailability of oral dose of piracetam is nearly 100%. Piracetam does not form any metabolites. Its excretion takes place through urine. Piracetam may penetrate the blood-brain and placental barriers. The plasma half-life of piracetam is about 5 hours [6].

Therapeutic Applications of Citicoline and Piracetam

Combination: Piracetam can be used in combination with citicoline for the treatment of cognitive disorders. This combination rapidly enters the cerebrospinal fluid as it crosses the blood-brain barrier. This combination is widely used for the Memory enhancement, Parkinsonism disorder, Neurological and cognitive disorder, Depression, anxiety, stroke, Alzheimer's disorder and vasospastic disorders.

Piracetam affects the neuronal, vascular functions as well as cognitive function. It does not behave like a sedative or any stimulant. It is utilized therapeutically to cure nerve degeneration, coagulation, alcoholism, Alzheimer's and senile dementia with its starting dose of about 4.8 to 9.6 grams divided into three daily doses at 8 hours [5].

It has been reported that piracetam is used in the treatment of children suffering from Down's syndrome (DS) by enhancing the cognitive function [7].

Tolerability: Piracetam is a well-tolerated drug. There was no severe toxicity noticed in preclinical trials done on mice, rats or dogs in single oral doses of about 10g/kg. It was reported that in a pooled study; hyperkinesia, weight gain, somnolence, depression and nervousness were slightly increased with piracetam in 2% cases only [6].

Contraindications and Drug Interactions: Piracetam should not be administered in patients with renal disorder and it is strictly contraindicated in patients with end-stage renal disease. It is also contraindicated in patients with cerebral hemorrhage. Piracetam cannot be safely used in pregnant and lactating women as no study on human is done although no risk to fetus has been observed yet.

Piracetam is not metabolized in the liver. It is not plasma protein bound. So, there are very less chances of drug–drug interactions.

Piracetam has been observed to increase the anticonvulsant activity of carbamazepine. But, there are no interactions of any other drugs with piracetam [6].

Therapeutic Dose Range: The dose of piracetam may vary with respect to its application:

- 2.4–4.8 g daily p.o. in case of cognitive disorders and vertigo.
- 3.2 g daily p.o. in case of dyslexia.
- 7.2–24.0 g daily p.o. in case of cortical myoclonus.
- 160 mg/kg/day p.o. in case of vaso-occlusive crises in sickle cell anemia [9].

Marketed Products:

- Piracetam and levetiracetam were developed by UCB Pharma, Belgium.
- Oxiracetam by ISF, Italy.
- Aniracetam by Roche Pharmaceuticals, Switzerland.
- Pramiracetam by Warner-Lambert, USA [2].
- Phenylpiracetam by the Medical-Biological Institute of the Russian Academy of Sciences (manufactured by Valenta Pharmaceuticals, Russia).

Pharmacological Committee of Russia approved phenylpiracetam as a drug for treating cerebrovascular deficiency, depression, apathy, attention and memory decline [4].

Levetiracetam was approved in the US in 1999 as adjunctive therapy of myoclonic epilepsy. The European Medicines Agency recently approved it as monotherapy for partial seizures and as adjunctive therapy for tonic-clonic seizures [4].

CONCLUSIONS

Nowadays, piracetam and piracetam-like compounds are analyzed for the treatment of new ailments. For most of the indications, piracetam has proved to be very efficacious. The neuroprotective and neuroregenerative effects of piracetam are yet to be identified. Piracetam and some piracetam-like drugs are safer to use in different diseases as they do not cause adverse effects like that of GABA-mimetic drugs. Improvements in the design of newer chemical moieties can ultimately lead to good clinical effectiveness [4].

Nutraceuticals are effective ways of treating Memory impairment especially in elderly patients. Many such agents can be established for the treatment of dementia, neurological disorders depending on their pharmacological, biochemical and physical compatibility. Nutraceutical combinations like combination of Citicoline and piracetam are available in the market to prevent and cure the neuronal degeneration and memory impairment.

Citicoline and piracetam is therapeutically useful in the cure of various disorders like alcoholism, clotting, coagulation, vasospastic disorders Alzheimer's and senile dementia, depression and anxiety stroke, ischemia, dyspraxia and dysgraphia, closed craniocerebral trauma[5]. Piracetam is a well-tolerated drug and useful in treatment of age-related cognitive disorders, vertigo, cortical myoclonus, dyslexia and sickle cell anemia. It restores the membrane fluidity. Detailed study on piracetam should be performed in order to elucidate its significance in treatment of other disorders [6].

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