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REVIEW

A Review on Synthesis and Pharmacological Activities of Piracetam and its Derivatives

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Piracetam is generally utilized as a nootropic drug, which is normally used in the treatment of CNS disorders. Piracetam is a cyclic compound and a derivative of γ-aminobutyric acid and improves learning, memory, brain metabolism, and ability. This drug belongs to the racetams group with the chemical name 2-oxo-1-pyrrolidine acetamide. The emphasis of this review article is to highlight different biological activities associated with piracetam and also some of its synthetic methodologies. Promising effects have been achieved in the management and treatment of several diseases for example alcoholism, Raynaud's phenomenon, deep vein thrombosis and brain injury.

Keywords: Cognitive disorders, Piracetam, GABA derivatives, CNS disorder, Nootropic drug.

INTRODUCTION

A γ-aminobutyric acid (GABA) derivative, piracetam contains a cyclic ring and was introduced in the market initially by drug manufacturer UCB Pharma in 1971. This was the first nootropic drug launched for the treatment of cognitive function by acting on vascular and neuronal functions and it does not lead to stimulation and sedation [1-3]. It's complete mechanism is not reported yet. Its uses are not limited to nootropic actions but go beyond that with its vascular effects are both central and peripheral and utilized for the treatment of cognitive disorders, which are age-dependent and other diseases like cortical myoclonus, vertigo and sickle cell anemia [4-6].

When one water molecule is lost subsequent to the formation of the ring, piracetam is obtained as shown in Fig. 1. Piracetam fits in the class of nootropic compounds in general, embodies a five-carbon atom oxo-pyrrolidone ring and is also known as racetams. Initially, nootrope word was used for it when a promising effect was established for cognitive improvement. Piracetam and its related compounds are required for modulating the functions of the cerebral and mainly utilized for the proper function of the brain and reinstating the memory of the brain in patients having disturbances in the brain [7-9].

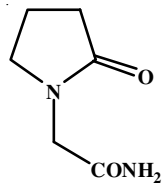


Fig. 1. Chemical structure of piracetam

To enhance the capacity of work and performance of the brain the drugs, which are utilized are known as nootropics. They are alternatively also called memory-enhancing substances, few examples of drugs belonging to this class are aniracetam, pramiracetam, piracetam and phenylpiracetam [10-12]. A few other compounds belonging to this category and extensively studied are rolziracetam, oxiracetam, etiracetam and nefiracetam. These compounds are categorized as piracetam analogs. Till now there is no worldwide recognized mechanism on how the racetam nootropics work has been established. Generally, they do not bind with the site of the receptor with one exception in this class of drugs is nefiracetam which has a high binding affinity to GABA receptor [13,14].

Various pharmacological applications of piracetam are discussed in this review. After an exhaustive literature survey

of the last three decades, it came to realize that there is a need for study in an exhaustive manner of this moiety.

Synthetic methodologies: Reyes *et al*. [15] synthesized 2,3-dihydro-1*H*-isoindol-1-one derivatives, which are related in structure with piracetam and executed its nootropic activity. Synthetic route of isoindolinone derivatives of (*R*,*S*)-3 and (*R*,*S*)-2, (*R*,*R*)-3 are presented in Fig. 2. After careful reduction of the racemic mixture of DL-5 with zinc in the presence of CH_3COOH and HCl, *N*-substituted isoindo-linone (*R*,*S*)-1 was obtained. Then NH_3 was allowed to react with (*R*,*S*)-1, leading to the formation of (*R*,*S*)-2.H, which on its reaction with (*R*)-α-phenyl ethylamine gives rise to (*R*,*S*)-3 and (*R*,*R*)-3 (Fig. 3)

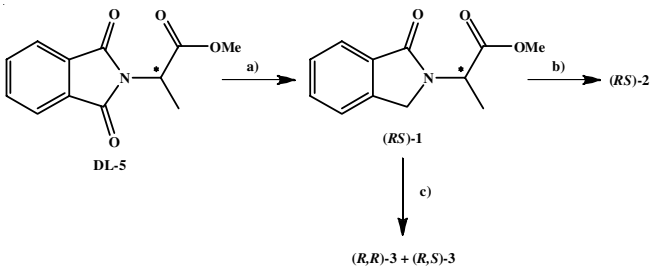


Fig. 2. Synthetic route of isoindolinone derivatives

For the establishment of the absolute configuration of (*R*,*S*)-3 and (*R*,*R*)-3 stereogenic carbon atoms, they were synthesized mainly in three steps in which the first step involves the reaction of phthalic anhydride with l-alanine to give (*S*)-6; in second step, the (*R*,*S*)-7 was obtained by the reaction of phthalic anhydride with l-alanine and the final step was the reduction as per the modified procedure given by Brewster [16]. By the structural modification of the piracetam, different drugs were synthesized namely pramiracetam, aniracetam and oxyracetam. The synthesis of piracetam derivatives in which the carbamide amine group is substituted and also thio variants were executed. Compound I was synthesized by reacting NH_4HS with l-cyanomethyl pyrrolidone-2 (III) embodying cyano group transformation. Compound II was difficult to synthesize, which can be easily prepared without any hindrance when the mixture of TP, II and acetal was allowed to react at 20 ºC in such a scenario *N*,*N*-dimethylaminomethylene derivative of TP was found appreciably more soluble as compare to II and hence take part in the reaction and can be segregated with ease. The shortcoming of the reaction of nitrile III thionization and later saponification and generation of TP, which were difficult to segregate [15] (Figs. 4 and 5).

Different pharmacological activity

Treatment of stroke: Piracetam has been established to increase the presence of blood in patients having an acute stroke.

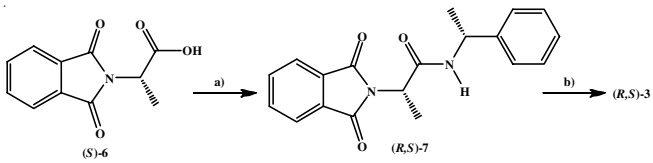


Fig. 4. Derivatives synthesized as per absolute configuration

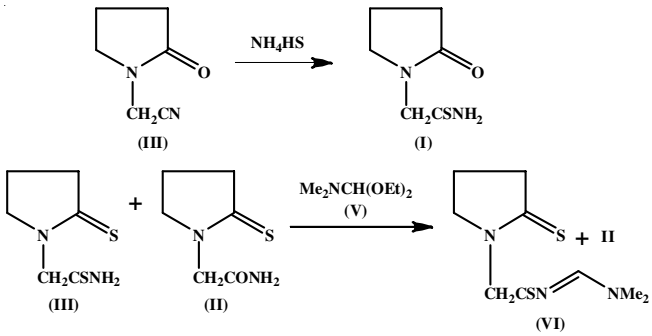
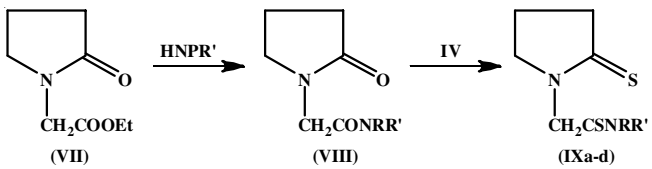


Fig. 5. Synthetic route of piracetam derivatives containing carbamide amine group is substituted and also sulfur variants

In another synthetic route of piracetam, l-ethoxycarbonylmethylpyrrolidone-2 (VII) was utilized as starting material for the synthesis of piracetam derivatives (Fig. 6). The ester VII was amidized with the help of the secondary and primary amines, which leads to the generation of analogs of piracetam in which there is a substitution in carbamide group nitrogen. Few more derivatives were synthesized with the utilization of Lawesson's reagent IV [15-18].



R = H, (a-c,f,g); R' = CH_2Ph (a), CH_2CH_2Ph (b), $CH(Me)CH_2Ph$ (c), $CH_2CH_2NEt_2$, adamantyl-1 (g); NRR' = morpholino (d), 4-methylpiperazino (e)

Fig. 6. Synthesis of piracetam derivatives using Lawesson's reagent

But after the analysis of data procured experimentally, it was realized that as compared to acetylsalicylic acid in terms of tolerance and utilized in patients, who do not get relief with acetylsalicylic acid [19]. The effectiveness of piracetam is supported by examining the findings of a meta-analysis of models in rats. This evidence is supported by the post-clinical findings and the beneficial effect of piracetam is well established. The verbal skills are found to be improved in patients with stroke. In another study, effects of piracetam were studied to counter stroke effects which occur due to the ischemic condi-

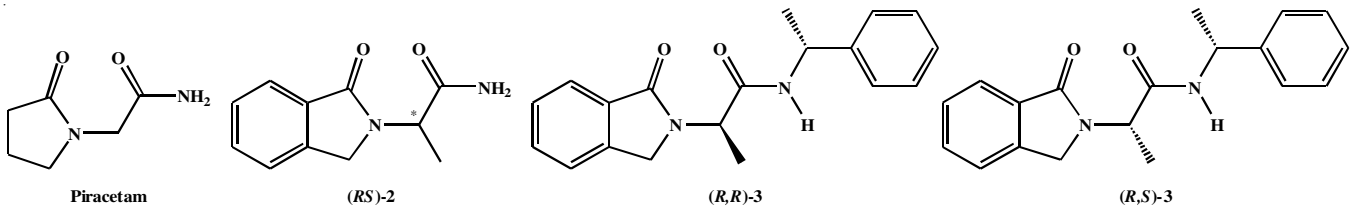


Fig. 3. Chemical structures of different piracetam derivatives

tions. To examine the trials of patients under controlled conditions group strategy of cochrane stroke was utilized and the functional outcome was utilized to evaluate the endpoints of the study. The patients were examined in the interval of 48 h and 501 patients were given piracetam and control. Although routine administration of piracetam is not recommended in ischemic stroke, its major benefits on stroke cannot be underscored [20-24].

Cortical myoclonus: In the sensorimotor cortex region when any unusual activity is termed as cortical myoclonus, which includes an array of motor conditions. This condition sometimes occurs together with generalized seizures and generally consists of muscle movements which are uncontrollable. It affects speech and several works of daily life and hence it is debilitating. Drugs already used for the treatment of convulsion manage only the seizures, but less efficient in the supervision of muscle movements which are involuntary. Hence, piracetam is utilized for the management of various categories of cortical myoclonus and gives effective results when other drug therapy failed. As far as the myoclonic conditions are concerned, it can give promising results either alone or with other anticonvulsants as evident by the reports, trials and studied (Fig. 7).

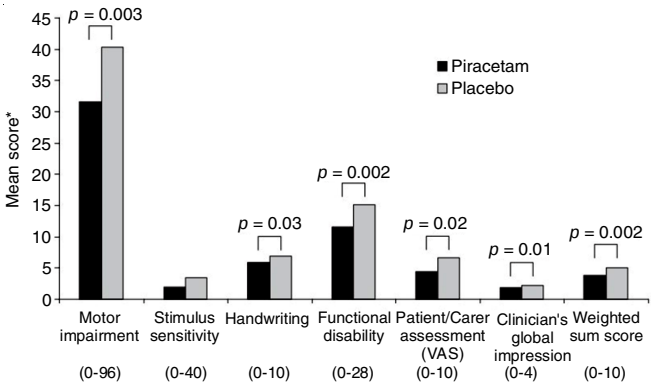


Fig. 7. Influence of placebo and piracetam on cortical myoclonus. In this better outcome is indicated by lower scores

Sometimes piracetam gives far better results as compared to the other treatment given at the same time for the treatment of cortical myoclonus. A study was conducted on 24 patients by double-blind method to identify the cortical myoclonus and the patients were administered piracetam to determine the effective dose. After analyzing the administered dose along with the placebo it was observed that piracetam has considerably helpful in the management of myoclonus [1,25-27].

Treatment of Alzheimer's disease: Dementia is a major outcome of Alzheimer's disease and the piracetam is a drug of choice in the management of dementia, which cures Alzheimer's disease by avoiding the accumulation of peptides of β-amyloid nature, whose accumulation lead to a serious damage. The continual use of piracetam has a major effect on Alzheimer's disease, which is sought to be affected by the membrane fluidity restoration [28].

Cognitive benefits of piracetam have been established by the research studies but specific benefits concerning the Alzheimer's disease are not fully established [29]. To support the evidence of prevention of Alzheimer's disease a study was conducted in 33 patients and the study was controlled by placebo. A high dose of piracetam was administered initially, improvement was not observed, however subsequent long term high dose administration of piracetam was able to control the cognitive disorder in Alzheimer's disease [30].

Piracetam effect on platelets: Piracetam acts by inhibiting the accumulation of platelet and hence modify the function of the platelet and it is known for this uses for more than 20 years. There is still a controversy on the utilization of this drug, however, the mode of its action is still debated. The dose required for antiplatelet action is about 2-4 times higher as compared to the produce nootropic effects. It is utilized in various types of conditions such as diabetes mellitus, acute stroke, attacks due to cerebral ischemia and Raynaud's phenomenon. This drug has also been established to produce its effect on the vascular wall by the stimulation of the production of prostacyclin in the endothelium [17] (Fig. 8).

Platelet-inhibitory effects have been suggested to be due to reduced responsiveness to ADP or inhibition of thromboxane A2 synthesis. Piracetam was also reported to have a direct effect on the vascular wall, stimulating production in endothelium with an associated decline of the release of Willebrand's factor through the Weibel-Palade bodies [31-34].

Potential mechanism of action of piracetam through the membrane hypothesis: Piracetam which is a derivative of neurotransmitter present inside the body called GABA, however, the mechanism is not related to the neurotransmitter properties. There is a huge speculation regarding the exact mechanism of action but has been extensively proved that it acts by restoring the fluidity of cell membrane which is neither organ-specific and/or cell-specific. Piracetam has a variety of physiological effects that results from cell membrane fluidity restoration. The interaction between the cell membrane and piracetam has come into existence in which piracetam to some extent prohibited the modifications caused due to alcoholic group present in the monolayer of synthetic phosphatidylcholine (Fig. 9). This interaction is also dealt with in another study in which the toxic effect aggregates the amyloid peptide studied on the neuronal membranes [32,33].

Effects on neuroplasticity: Neuroplasticity term is generally applied to the neural circuitry adaptation by the means of neural and synaptic connections development and adjustment. It was observed that piracetam stimulates neuroplasticity when there is a possibility of the neuronal circuits being recovered. Piracetam neuroplastic effects were identified in two separate examinations, which involve rats when treated with alcohol. Neuronal loss was observed with the administration of alcohol but become heightened when alcohol is withdrawn. Piracetam along with the withdrawal symptoms associated with alcohol also increases in the hippocampus the number of synapses by 20% as compared to treated with alcohol and without rats [34,35].

Piracetam by its action on the microcirculation and nerve transmission helps in avoiding the vertigo, a kind of dizziness which perceived that everything is moving in nature includes environment and self, a type of illusion. The disorders in the vestibular system centrally or peripherally or both can be a major

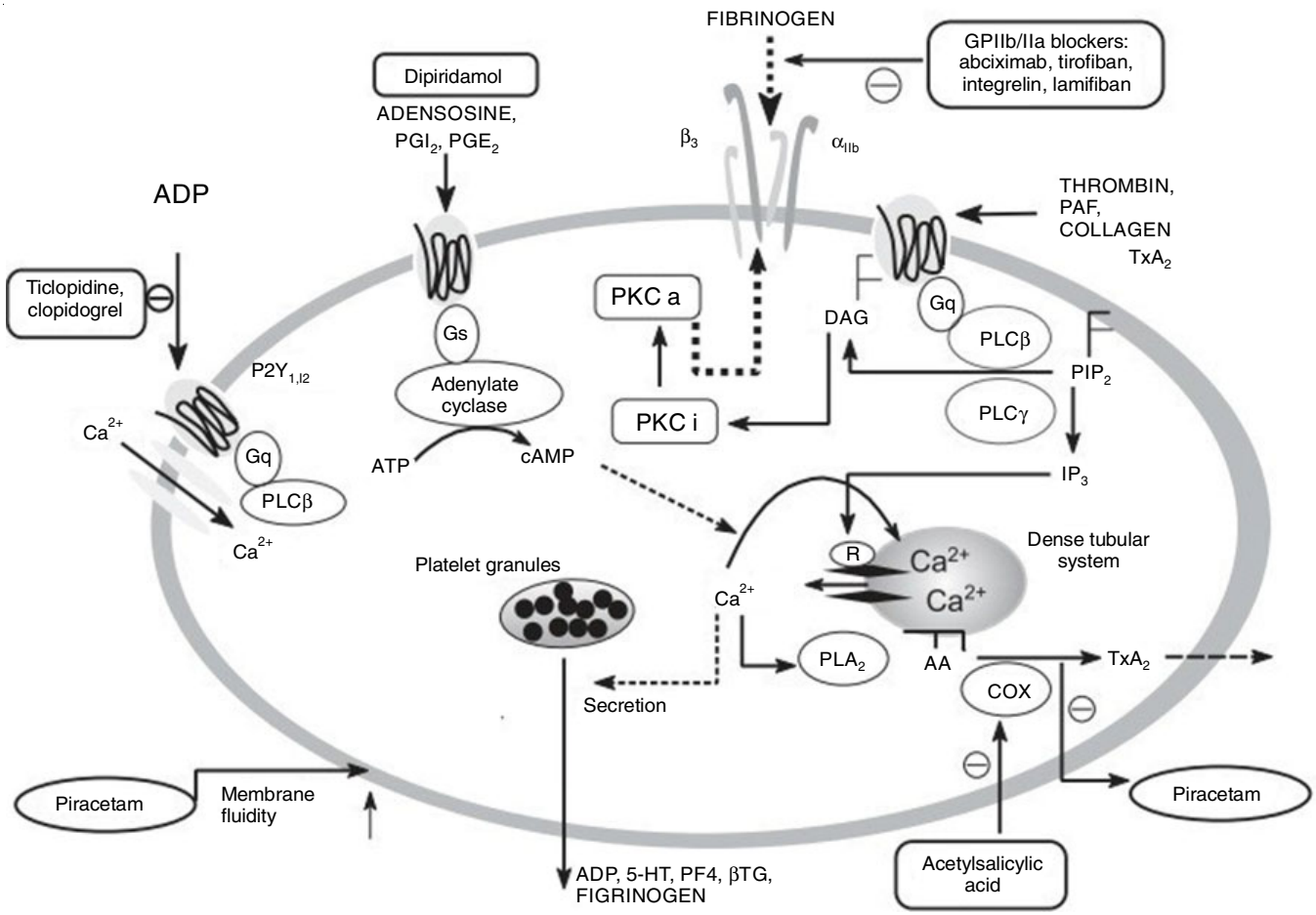


Fig. 8. Inhibition of responses of platelet by piracetam

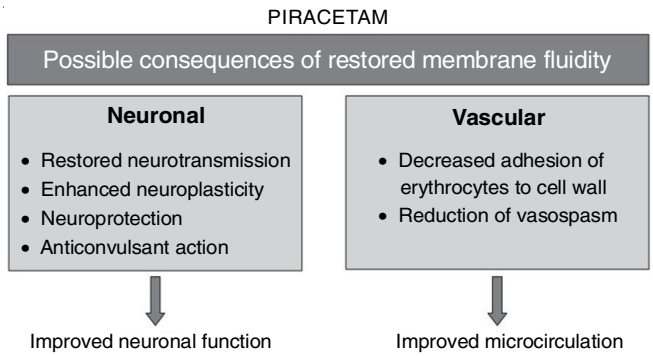


Fig. 9. Membrane fluidity which is restored has numerous physiological consequences

factor in causing the vertigo. A study was conducted by taking 143 old age patients suffering from the chronic vertigo and the dosage regimen was compared between placebo and piracetam. After nearly 8 weeks of continuous treatment, it was observed that vertigo episodes were managed [36].

Effects on aphasia: In 1940s, the trial concerning the disorders of cerebral was primarily started for the establishment of newer drugs. A double-blind examination was executed by Kessler *et al*. [22] in which piracetam was found to improve the memory and learning capabilities in patients having post-stroke aphasia by increasing the blood supply and hence rehabilitate the patient. It leads to the enhancement of the sensorimotor function leading to a surplus supply of blood in different impaired parts of the brain. However, there is still a huge uncertainty in the mechanism of action of piracetam against aphasia, the exact mechanism is still unknown. As far as utilization of this drug in speech therapy is concerned, it is still shrouded in mystery. Piracetam is also used along with speech therapy aids in the recovery of language functions [37].

Effects on drug abuse by cocaine: The biogenesis of mitochondria is affected by the misuse of cocaine and this affected biogenesis leads to affect the normal function of the neuronal part. If cocaine is taken in an unscrupulous way, it has a major factor in the modification of methylation of DNA, which can adversely affect the proper function of the central nervous system [38-40] (Fig.10).

Neurodegenerative diseases are caused due to the modification of methyl group of DNA aided by cocaine were studied and treatment of it employing piracetam was also examined. This type of disease is more prone to genomic instability owing to unwanted activation of the gene. In this method, colorimetric estimation was executed for the quantification of DNA methylation denoted as 5-mC and the cells were allowed to treat with or without piracetam and cocaine in the concentration of 10 μM and 1 μM for about 1 day. During the course of the study, it was realized that piracetam in the concentration of 16% was found to stop the DNA hypomethylation affected by cocaine in astrocytes [41-43].

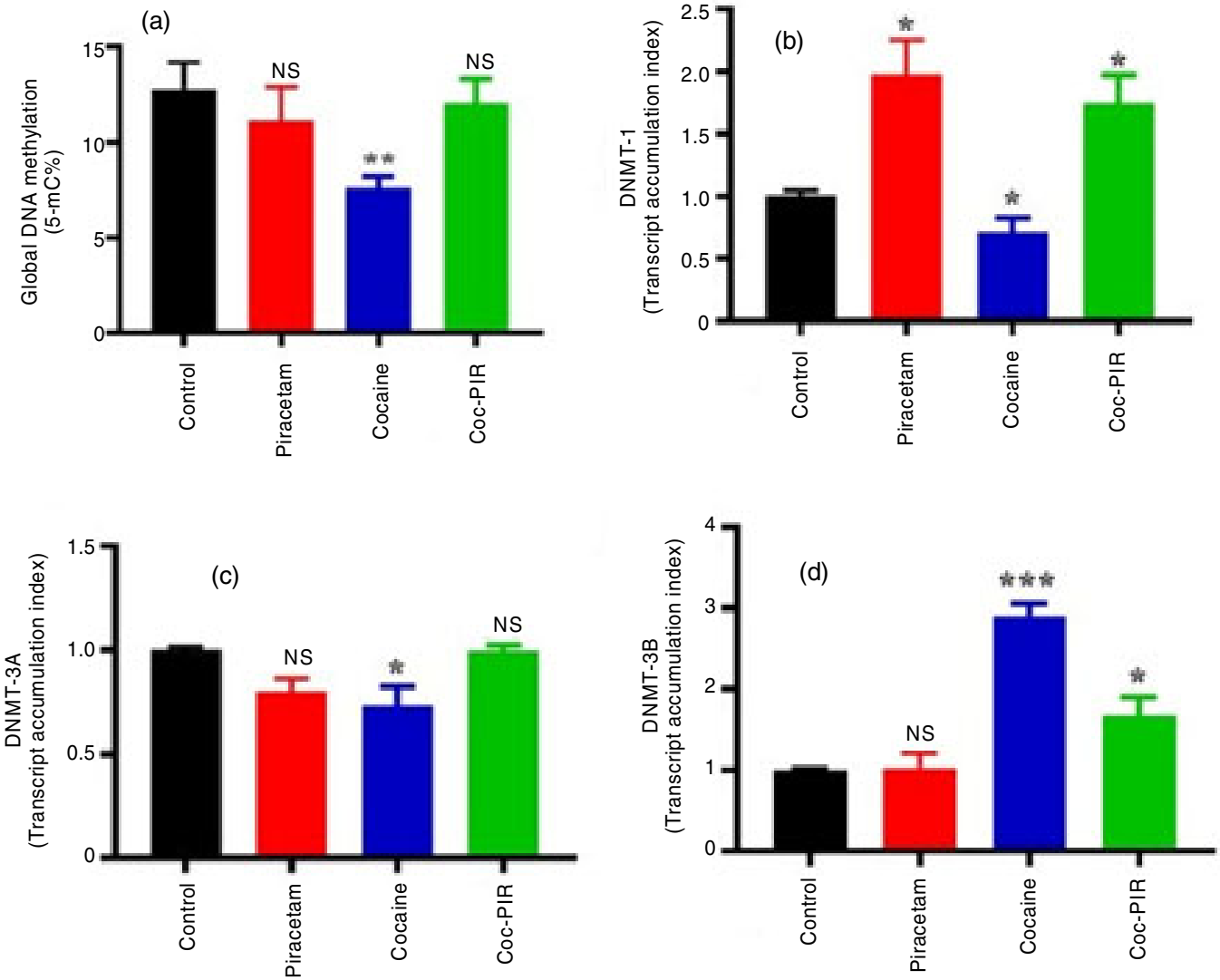


Fig. 10. Impact of cocaine-induced DNA methyltransferases (DNMT's) gene expression and DNA methylation (5-mc) and was reversed by the drug piracetam

Effects on sickle cell anemia: Piracetam effects on the erythrocytes have high potential in the management and treatment of sickle cell anemia, which is a genetically acquired disease where the hemoglobin becomes sickle in shape or lost its normal shape and size leading to the erythrocytes rigidity sticks to the endothelial wall thereby stopping the blood flow resulting in the damage of tissue. Piracetam exerts its numerous effects on erythrocytes and found to be a promising drug during the time of crisis. A study conducted broadly on 101 children ranging in age between 3 to 12 years in a double-blind mode results in a conclusion that piracetam considerably reduced the number of crises, severity index and the number of blood transfusions [44-48].

Effects on depression: Drug piracetam after long use is established to be lacking in high toxicity and severe adverse effects. It helps in the cognitive maladies by modulating the improper function in the glutamatergic transmission. It also increases the neuron excitation to supports in the long period potentiation. It has been proved to be a positive modulator of glutamate receptors of AMPA type. It increases the neurotropin secretion which is helpful in the neurite growth. These effects of piracetam are helpful in cases of depression and disorders of mood [49,50].

Effects on seizure: Piracetam derivative levetiracetam is its structural analog and used along with carbamazepine for the treatment of epilepsy [51].

Effect on analgesia: A prior study providing an evidence of analgesic effects of piracetam is the writhing test of acetic acid. Pain due to inflammation occurs as a result of migration of neutrophils and oxidative stress and release of prostanoids. The anti-inflammatory and analgesic activity of piracetam was discovered in contemporary examinations. By the inhibition of IL-1β, released as a result of stimulation of TNF-α, reduction in the activity of myeloperoxidase activity (MPO) and carrageenin inhibition its analgesic activity. Acetic acid, formalin and phenyl-*p*-benzoquinone induced pain can be managed by the treatment with piracetam [52]. It has also been observed that the mechanical hyperalgesia is caused by TNF-α, while thermal and mechanical hyperalgesia are caused due to carrageenin, which can be treated with piracetam [53]. The data

related to the research of analgesic activity of piracetam is found in various models and hence it has major benefits in the treatment of analgesia in patients suffering from pain [52].

Piracetam reduces the licking response caused by formalin in phase first, which gives the neuronal effect. Piracetam mainly reduces the release of serotonin and its subsequent action on the nociceptors. To summarize pain of inflammation can be reduced by piracetam associated with oxidative stress, decreased production of cytokine and MPO activity [54].

Management of agenesis concerning corpus callosum: In the cerebral cortex of brain is present a bundle of fibers called the corpus callosum, whose absence results in the agenesis of corpus callosum, which is a inherited defect. Piracetam acts by enhancing the blood supply in the brain thereby increasing the utilization of oxygen. It serves its action by enhancing the brain and neuronal actions by means of modulating nerve signal transmission and neurotransmitters functions. It has produced no side effects and major toxicity in the clinical investigations and found to be well-tolerated. The LD_{50} in mice was observed to be 20 g/kg and in rats found to be 5.6 g/kg, which clearly reflects that it does not produce a high toxicity. Several illnesses of neurological origin such as brain atrophy, mental retardation have been found to be cured by piracetam which has been reported by several research articles [55-58].

Management of dysfunction of mitochondria after the oxidative stress: A decrease in the synthesis of ATP and reduction in the potential across the membrane of the mitochondria leads to the ageing and hypoxia, which is mainly due to the lack of proper function of mitochondria. The role of piracetam was examined on the improper function of mitochondria with the help of PC12 cells after the oxidative stress because of the improvement of cognition by piracetam in the said pathological state. Oxidative stress was stimulated with help of sodium nitroprusside (SNP) and lack of serum. At a concentration range from 100 to1000 mM, piracetam was found to improve the potential of the membrane of mitochondria and the production of ATP in PC12 cells. In older patients, these effects on mitochondria give an idea of the probable mechanism of its benefits [59]. A marked improvement was observed in the function of mitochondria cells of the brain in the old animals as compared to younger ones when the mice are treated with a dose of 100-500 mg/kg of piracetam. If a similar treatment is given to older mice, only it leads to the reduction of the antioxidant enzymes. The properties of radical scavenging were not found in piracetam [60].

Effects on cognition: Piracetam was primarily acknowledged for its memory enhancing and brain concentration improving effects. Piracetam through modulating the nervous system, by maintaining the nerve receptor and nerve impulse helps in the management of several disorders and diseases like dementia and Alzheimer's disease. It also maintains the transmission of nerve impulses through neurotransmission and helps the neurons to get rid of toxins [61-63].

Effect on the behavioural and neuronal changes: A major health effecting condition among the general public is major depressive disorder (MDD), which is not completely managed by the current treatment regimen. Even the WHO warns the general public regarding the disability associated with it, which affects the economic aspect of life in general [64]. The current treatment scenario embodies weekly to monthly treatment which did not give promising results and even cases of suicides are also noticed. This condition can be cured by ketamine owing to its antidepressant activity, which maintains for a longer time. But treatment with ketamine can be fatal also as it has psychosis as its side effects along with producing the antidepressant effect [65,66]. Ketamine has a chance to be misused and hence complete monitoring is essential in its usage [67].

It was revealed in a pre-clinical trial that drugs concerning the protection of brain *e.g*. piracetam strengthen the imipramine effects on depression, which is observed due to swimming stress in rats. Using piracetam, a similar antidepressant effect can be achieved with a partial dose of imipramine as compare to its full dose. And hence by doing this the adverse effects of some drugs can be decreased [68-72].

Synaptic transmission at the CA1 area of hippocampal at a concentration of 5 to 20 μM is potentiated by ketamine. Ketamine by acting on only postsynaptic junction improves the synaptic transmission at reduced concentrations, but at higher concentrations, it acts on both post and presynaptic junction to improve the synaptic transmission [73,74]. Synaptic transmission of a lesser amount is obtained with piracetam at the concentration of 5 μM. When taken simultaneously with pira-cetam, ketamine at a concentration of 5 μM gives a similar effect as achieved with concentration at 20 μM owing to the postsynaptic action. Hence, it realized that piracetam meaningful potentiates the ketamine antidepressant effect [75,76].

Effects on passive avoidance response (PAC): In order to examine the several factors affecting memory and learning capacity, PAC is utilized. Mainly the novel synthesized nootropics were utilized which have several merits for example reduced time in grasping and probability of dissimilar effects in memory of dissimilar levels. In this study, the influence of piracetam on rats was observed in the three-compartment model on PAC [77]. Piracetam helps in modulating the avoidance response and makes it reproducible during its functional impairment and also helps in managing the emotional tension. Piracetam does not elevate the latency but only increases the priority for the safe compartment and hence PAC is mainly dependent on the conditioning of fear, the memory where the shock is exposed [78,79].

Effect on depression caused as a result of depression induced by acetylcholine: A study was conducted to assess the piracetam effect on depression caused by acetylcholine in neurons of the snail [80]. It was found that depression level and acquisition rate were lowered when the depression was induced by acetylcholine in comparison to control. A clear agreement is obtained of calculated in relation to experimental depression curves of acetylcholine when the drug piracetam is exposed with the help of computation results. In this, the exocytosis and endocytosis rates were decreased to half as compared to the control curve [81].

In neurons of snail, the depression mediated by acetylcholine was lowered with piracetam taken at a concentration of 1 mM. The mechanism behind this activity is modifications

in the actions of protein phosphatase, protein phosphatase, and myosin chain kinase [82,83].

Conclusion

Piracetam has various pharmacological activities and utilized for the treatment of various diseases. Few derivatives of piracetam drug have been prepared for the drug piracetam and there is a huge potential for research to be developed. The possible mechanism by how this drug act is in ambiguity since its research started as a cognitive enhancer, its other pharmacological benefits gives an idea whose moiety can be designed further to develop more pharmacological actions and treatments, as its other benefits in several treatments has been established.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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