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GENERAL

PIRACETAM – AN OLD DRUG WITH NOVEL PROPERTIES?

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Abstract: Piracetam (2-oxo-1-pyrrolidine-acetamide), the most common of the nootropic drugs, is a cyclic derivative of gamma-aminobutyric acid. The treatment with piracetam improves learning, memory, brain metabolism, and capacity. Piracetam has been shown to alter the physical properties of the plasma membrane by increasing its fluidity and by protecting the cell against hypoxia. It increases red cell deformability and normalizes aggregation of hyperactive platelets. Piracetam is an agent with antithrombotic, neuroprotective and rheological properties. The interaction of this molecule with the membrane phospholipids restores membrane fluidity and could explain the efficacy of piracetam in various disorders ranging from dementia and vertigo to myoclonus and stroke.

Keywords: piracetam, nootropic drugs, platelet inhibitors, rheology

Piracetam (2-oxo-1-pyrrolidineacetamide) (Figure 1) is a cyclic derivative of gamma-aminobutyric acid (GABA), obtained after the loss of one molecule of water followed by ring formation (1). It is the first representative of the "*nootropic*" drugs (2).

The term *nootropic* comes from a Greek word meaning "acting on the mind". Piracetam was synthesized by Giurgea in UCB Laboratories in Belgium. It has been in clinical use since 1972. Since then other pharmaceutical companies have been scrambling to develop their own nootropics (e.g. vinpocetine, aniracetam, pramiracetam, oxiracetam).

Piracetam might be successfully used to treat senile dementia, vertigo, sickle cell anemia, and numerous other health problems like Alzheimer's disease or stroke (3–6). Piracetam might increase reading comprehension and accuracy in dyslexic children (7). It has improved alertness, socialization and IQ in elderly psychiatric patients. Piracetam has also been used to treat alcoholism. In 1991 Paula-Barbosa and colleagues discovered that long-term (12 months) alcohol-feeding to rats significantly increased the formation of lipofuscin (an age-related waste pigment) in brain cells. Giving high doses of piracetam to the alcohol-fed rats reduced their lipofuscin levels significantly below the control levels (8). In 1997 it was demonstrated that piracetam might reduce the neuronal loss following chronic alcohol consumption (9).

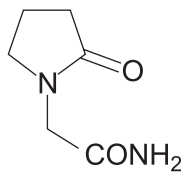

Figure 1. Structure of piracetam (2-oxo-1-pyrrolidineacetamide) – prototypical nootropic; a cyclic derivative of GABA.

Piracetam enhances cognition under conditions of hypoxia, and also enhances memory and learning (10). When piracetam is taken with choline, there is a synergistic effect that causes a greater improvement in memory.

The specific pharmacological properties of piracetam were reported almost 30 years ago but its mechanism of action was unknown for a long time. Piracetam was firstly tested in a model of "*central nystagmus*" which was sensitive only to anticholinergic and antihistaminic drugs (2, 11). The current use of piracetam in vertigo might be related to this property. The subsequent research, however, revealed that piracetam was without anticholinergic or antihistaminic properties (5, 10, 12).

Although piracetam is a derivative of the inhibitory neurotransmitter GABA, the mechanism of its action is not related to that of GABA. Piracetam has little affinity for glutamate receptors, yet it does have various effects on glutamate neurotransmission. One subtype of glutamate receptor is the AMPA receptor. Micromolar amounts (levels which are achieved through oral piracetam intake) of piracetam enhance the efficacy of AMPA-induced calcium influx in brain cells. Piracetam also

increases the maximal density of AMPA receptors in synaptic membranes from rat cortex due to the recruitment of a subset of AMPA receptors which do not normally contribute to synaptic transmission (12). At micromolar levels piracetam potentiates potassium-induced release of glutamate from rat hippocampal nerves (12).

Piracetam is generally reported to have minimal or no side effects. It is interesting to note, however, that piracetam's occasionally reported side effects of anxiety, insomnia, agitation, irritability and tremor are identical to the symptoms of excessive acetylcholine/glutamate neuroactivity. In spite of these effects, piracetam is generally not considered to be a significant agonist or inhibitor of the synaptic action of most neurotransmitters. The piracetam-type nootropic drugs might exert their effect on some species of molecules present in the plasma membrane. It would seem that they act as potentiators of an already present activity, rather than possessing any neurotransmitter-like activity of their own (12). Thus, piracetam is not prone to the often serious side effects of drugs which directly amplify or inhibit neurotransmitter action, e.g. MAO inhibitors, selective serotonin reuptake inhibitors, tricyclic antidepressants, or amphetamines.

It was found that piracetam instead facilitates interhemispheric transfer, enhances the cerebral resistance to noxious stimuli like hypoxia and improves learning and other cognitive functions under normal conditions (13, 14). However, the improvement of these functions is much more pronounced when brain function is impaired by a variety of noxious stimuli (e.g. hypoxia, aging, cerebral injuries). The *in vivo* experiments indicate that the cognition-enhancing properties of piracetam are usually more significant in older animals (15, 16). It suggests that the mechanism of action of the nootropic drugs is associated with biochemical alterations in the aged brain. Therefore nootropics might probably restore or counteract these biochemical changes. Reduced fluidity of brain cell membranes (probably caused by higher membrane concentrations of saturated fatty acids) represents mechanism associated with functional alterations in the aged brain (17) and might be responsible for deficits or dysfunctions of mechanisms of signal transduction (18,19).

Piracetam in aphasia

Most patients after the ischemic stroke regain some of the lost functions. The improvement of sensorimotor function is accompanied by an increased blood flow in impaired brain regions. Whereas the effect of physiotherapy for the improvement of sensorimotor deficits is unchallenged, the efficacy of speech therapy is still questionable/unclear. Whether the rehabilitation can be enhanced by adjuvant pharmacotherapy in patients with cerebral disorders is also a matter of speculation (20–22). First trials were started in the 1940s and concerned various agents in various neurological disorders (23–25). Since piracetam improves learning and memory, Kessler et al. investigated in a double-blind, placebo-controlled study whether piracetam improves language recovery in poststroke aphasia (26). They found that piracetam significantly improves activated blood flow and facilitates rehabilitation of poststroke aphasic patients (26). Piracetam as an adjuvant to speech therapy improves recovery of various language functions, and this effect is accompanied by a significant increase of task-related flow activation in eloquent areas of the left hemisphere (26). However, the mechanism by which piracetam enhances recovery from aphasia is still a matter of speculation. Since infracted tissue cannot regenerate, recovery from postroke aphasia must involve regions outside the morphologically damaged area that probably take over language functions lost in acute stroke.

Levetiracetam – derivative of piracetam with antiepileptic properpies

Levetiracetam is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidineacetamide (Figure 2).

Although piracetam might be useful in myoclonus and potentiates anticonvulsant action of various antiepileptic drugs (28,29), it was not previously used *per se* in epilepsy. Levetiracetam, however, was approved for the add on treatment of partial epilepsy, both in United States and in Europe (27). Levetiracetam has antiepileptogenic and neu-

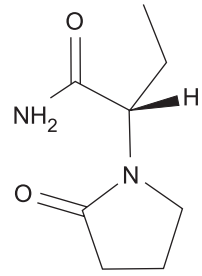

Figure 2. Levetiracetam is a pyrrolidone derivative and is chemically designated as (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide (27).

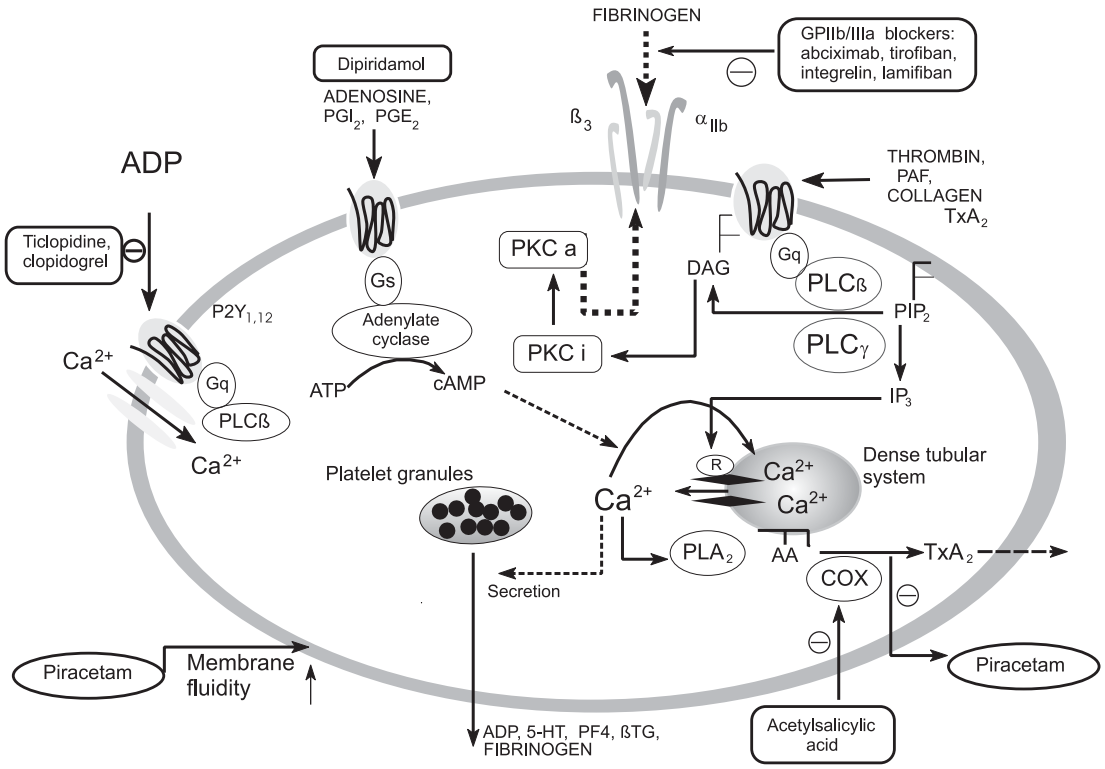

Figure 3. Molecular mechanisms of the inhibition of platelet responses by piracetam, acetylsalicylic acid, ticlopidine, dipiridamol and GPIIb/IIIa blockers.

There is some evidence that piracetam acts on platelets as an antagonist of thromboxane A_2 or as an inhibitor of thromboxane A_2 synthetase together with a reduction in the plasma level of von Willebrand's factor (36). Piracetam also possesses a rheological effect related to its action on cell membrane deformability (37).

AA – Arachidonic acid; AC – Adenylyl cyclase; ADP – Adenosine diphosphate; βTG – β-thromboglobulin; COX – Cyclooxygenase; DAG – Diacylglycerol; GPIIb/IIIa – Glycoprotein IIb/IIIa; Gq, Gs – G-proteins; 5-HT – Serotonin; IP_3 – Inositol-1,4,5-triphosphate; $P2Y_{1,12}$ – ADP-receptor; PAF – Platelet activating factor; PF4 – Platelet factor 4; PG G_2, PG H_2, PG I_2, PG E_2 – Prostaglandins G_2, H_2, I_2, E_2; PIP_2 – Phosphatidylinositol-4,5-diphosphate; PKC_a, PKC_i – Protein kinase C (active and inactive, respectively); PLA_2 – Phospholipase A_2; $PLC_{\beta,\gamma}$ – Phospholipase $C_{\beta,\gamma}$; TxA_2 – Thromboxane A_2

roprotective effects, with the potential to slow or arrest disease progression (30). It may benefit myoclonus in progressive myoclonic epilepsy (31). Although the mechanism of action of levetiracetam is not completely understood, it is suggested that a reduction of potassium currents in neurons may contribute to its antiepileptic effect(s) (32).

Piracetam in Alzheimer's disease

Hippocampal membranes of patients with Alzheimer's disease show decreased fluidity which differ from age-specific membrane alterations. Clinical data suggest that long-term piracetam treatment appears to slow the progression of Alzheimer's disease, which was proposed to be explained by restoration of membrane fluidity (19).

Piracetam in stroke

Piracetam has been reported to increase compromised regional cerebral blood flow in patients with acute stroke and, given soon after onset, to improve clinical outcome (33, 34). It could be due to the modification of rheological properties of circulating blood by changing platelet responses (aggregation and adhesion) and beneficial effect on red blood cell deformability leading to a putative reduction of ADP release by damaged erythrocytes (35–37). Experimental data suggest that the efficacy of piracetam in secondary stroke prophylaxis is not as good as that of acetylsalicylic acid (ASA) but that piracetam is better tolerated (38). Therefore, piracetam might be an alternative for secondary stroke prophylaxis in patients who

cannot be treated by ASA or other antiplatelet drugs.

Piracetam and platelets

Modification of platelet function including inhibition of platelet aggregation by piracetam is known for over 20 years (35). However, the mode of its action is still debated (36–39).

Piracetam normalizes hyperactive platelets in various disorders including acute stroke (33, 34), transient cerebral ischemic attacks, Raynaud's phenomenon and diabetes mellitus (36). Platelet-inhibitory effects have been suggested to be due to a reduced responsiveness to ADP or to inhibition of thromboxane A_2 synthesis (37, 40). Piracetam was also reported to have a direct effect on the vascular wall, stimulating prostacyclin production in endothelium with an concomitant reduction of von Willebrand's factor release from Weibel–Palade bodies (37).

The doses necessary to achieve rheological and/or antiplatelet effects are about 2–4 times higher than the doses required to obtain nootropic effects (35). However, even at these elevated doses, piracetam is well tolerated and only few adverse effects have been recorded in human subjects (5, 10).

The rheological properties of piracetam are thought to be related to plasma membrane alterations such as lipid structure (37). Piracetam incorporates within membranes at the level of the polar heads of the phospholipids. This interaction with the membrane phospholipids restores membrane fluidity and could explain the pharmacological properties of piracetam. The observation that piracetam binds to the polar head groups of membrane bilayers and induces changes in membrane structure can explain that this drug works not only in the brain but also at the level of blood cells (19). Its activity is much more pronounced when membranes are impaired (e.g. in aging).

Since changes at the level of the platelet membrane seem to be involved into the cascade of events leading to platelet adhesion and aggregation, this membrane-modifying effect might be the primary mechanism of action of piracetam (Figure 3). This mechanism would differentiate piracetam from other drugs used to inhibit platelet aggregation such as ASA, ticlopidine or tirofiban. Ticlopidine, however, as a lipophilic drug might also alter the fluidity of platelet membrane.

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