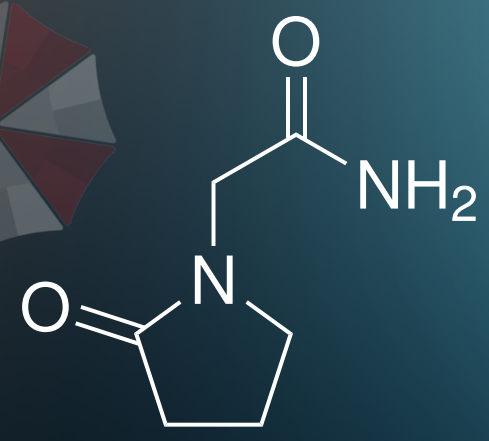

Piracetam - An Overview of Its Mechanisms and Research in Neurological Health

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History

Piracetam (also known as Nootropil or UCB-6215) was first synthesized around the year 1960 by the Romanian chemist Corneliu Giurgea in his lab at the Catholic University of Louvain. He also coined the term nootropic later in his career, using piracetam as one of the original compounds after which nootropics were defined, hence the name Nootropil. Piracetam entered the market in 1971 and was sold by UCB Pharma (Belgium). Today, piracetam is used as anti-dementia pharmaceutical and other applications in many countries.

Chemically, piracetam is a cyclic derivate of the neurotransmitter y-amino butyric acid (GABA). While the exact mechanism of action is not completely understood, it seems it does not directly affect neuronal function directly, in contrast to other drugs like amphetamines or SSRIs. It does also not lead to general sedation or excitation. Piracetam is a positive allosteric modulator of the AMPA receptor, although this action is very weak and its clinical effects may not necessarily be mediated by this action.[1] Interestingly, even though piracetam is structurally related to GABA, no effects on GABA receptors or GABA metabolism were found.[2]

The main action of piracetam seems to stem from its influence on the neurotransmitter acetylcholine, which is often the case for drugs with an anti-dementia role.[3] It is also thought influence ion channels, and oxygen consumption in the brain, probably due to its general increase in brain activity. It also possesses the ability to inhibit N-type calcium channels.[4] Other hypotheses about its mechanism of action point to its ability to regulate membrane fluidity, which is an important property of neurons and crucial for normal function.[5]

Other similar compounds of the same group include aniracetam, oxiracetam, and pramiracetam. In some countries like the Czech republic, piracetam is available as over-the counter drug. In the US. piracetam is an uncontrolled substance in the United States meaning it is legal to possess without a license or prescription.

Animal studies

Preclinical studies have shown that piracetam appears to offer neuroprotective benefits. Piracetam has been shown to reduce the incidence of animal deaths following barbiturate overdose, and to protect against morphological changes related to long-term alcohol use.[6] In alcohol-treated rats, piracetam administration is associated with

a decrease in lipofuscin, a marker of neuron membrane damage;[7] Piracetam administration initiated in rats 1 h after brain damage and continued twice daily for 3 weeks also reduced the extent of ischemic damage relative to placebo.[8] At the end of the treatment period, animals receiving piracetam showed a 30% smaller damaged brain area. Despite these promising preclinical findings, clinical studies have failed to demonstrate benefits of piracetam in individuals following acute stroke.[9]–[11] It is not clear why the effects in animals could not be reproduced in a clinical setting.

More preclinical research has found piracetam positively influenced neuroplasticity in rats. Neuroplasticity refers to the adaptation of neural circuitry through the modification and development of synaptic and neural connections. It is often used as a popular term to describe increased learning ability. Indeed, neuroplasticity is heavily involved in learning and memory but it can also limit the effects of ischemic damage. The neuroplastic effects of piracetam have been reported in two studies involving alcohol-treated rats .[12,6] Alcohol consumption is associated with neuronal loss, which may be exacerbated during a withdrawal period. In addition to reducing withdrawal-related neuronal loss, piracetam has been shown to increase the number of synapses in the hippocampus by up to 20% relative to alcohol-treated or alcohol-withdrawn rats.

In the 2000`s, it was discovered that piracetam has additional anti-inflammatory and anti-analgesic effects. For example, mice treated with piracetam showed lower levels of inflammatory markers and had a reduced reaction to pain compared to their control group.[13]

Further preclinical evidence also points to the conclusion neuroinflammatory diseases may be influenced positively by piracetam.[14],[15] Large clinical studies are still outstanding for this application however.

Clinical Trials

Piracetam has a long history of use in humans.

Memory function

The benefits of piracetam in a range of cognitive disorders in the elderly have been re- ported in several studies and reviews.[16]–[18] In one study, 162 patients with age-associated memory impairment received piracetam 2.4 g/day, piracetam 4.8 g/day, or placebo for 3 months.[18] All patients were also enrolled in a memory training program. The improvement with piracetam 4.8 g/day was significantly greater than with placebo alone on a range of memory tests. Piracetam 2.4 g/day seemed to be less effective but still produced a significant effect in some tests.

In 2002, a meta-analysis of 19 double blind placebo controlled studies on 1488 patients suffering from dementia or cognitive impairment in the elderly. The results show a definite statistical superiority of piracetam over placebo on a global measure of clinically meaningful change. These results provide compelling evidence for the global clinical efficacy of piracetam in a diverse group of older subjects with cognitive impairment.[19]

A second review from 2004 included 24 studies with almost 12000 participants. Statistical analysis of the respective results revealed that treatment with piracetam did increase the chance of improvement in neurological condition by 3 fold compared to placebo.[20]

Long-term and high-dose treatment of Alzheimer's disease symptoms with piracetam (8g per day orally for 1 year). No improvement occurred, but results support the hypothesis that long-term administration of high doses of piracetam might slow the progression of cognitive deterioration in patients with AD. Even at this high dose, the drug was well-tolerated.[21]

Besides the treatment of dementia, piracetam has also been trailed to treat other neurological conditions such as epilepsy. Results from animal studies had previously given reason to believe that piracetam had a positive effect on epileptic individuals.[22] One study in humans from 1992 found that not only could piracetam increase cognitive function in patients with epilepsy (cognitive decline is often observed in epileptic individuals), but also improved seizure protection in patients receiving carbamazepine, a common anti-epileptic drug.[23] Further studies also showed anti-convulsant effects.[24]

Vascular Effects

There have been a variety of studies suggesting that beneficial effects of piracetam on memory are at least partially due to a facilitation of blood flow in the brain. For example, some studies suggest that piracetam exerts several effects on erythrocytes, such as decreased adhesion to the walls of blood vessels.[25] There also seems to be a direct effect on the diameter of blood vessels at high doses.[26] A single dose of piracetam (3.2 to 9.6 g) reduced plasma levels of fibrinogen and von Willebrand factor in a dose-dependent manner by up to 40%. Both substances are needed for blood coagulation, a decrease will result in a reduced ability to form blood cloths. A direct ability to enhance blood flow to the brain was shown in cats and humans with acute cerebral ischemia.[27],[28] Other studies reported increased blood flow in the kidneys and the inner ear.[29],[30]

Vertigo

Piracetams positive effects on blood flow and neural activity can be useful in a variety of disorders. For example, patients suffering from vertigo often have problems either with blood circulation in the inner ear or neuronal transmission. Hence piracetam was trailed for this indication.

In a double-blind study of 143 elderly patients with chronic vertigo piracetam 2.4 g/day was compared with placebo.[31] Following 8 weeks of treatment, the number of episodes of vertigo had decreased by approximately nine with piracetam compared with an increase of approximately three with placebo. There was no difference between the treatments in attack severity. However, between attacks, piracetam had a significantly greater beneficial effect on severity of malaise and severity of imbalance than placebo. Several other studies indicated the efficacy of piracetam on vertigo.[32],[33]

Dyslexia

Several double-blind studies have investigated piracetam in the treatment of dyslexia, and, while the findings are not entirely consistent, most report a significant effect of piracetam relative to placebo on reading speed and accuracy.[34] In one study, 225 children with dyslexia, between 7 and 12 years of age, received piracetam 3.3 g/day or placebo for 36 weeks.[35] At the end of treatment, piracetam significantly improved reading, compared with placebo. The improvement of dyslexia with piracetam is modest, however, and may take months to manifest.

A review has found that stroke patients also had an improved ability to write after piracetam treatment. The number of studies in this review was small though, hence the validity of such a claim is questionable. [36]

Cortical Myoclonus

Cortical myoclonus refers to a range of motor conditions that result from abnormal electrical activity in the sensorimotor cortex. These conditions are characterized by uncontrollable muscle movements, which may be entirely spontaneous or occur in response to certain sensory stimulants or movement. Piracetam is useful in several types of cortical myoclonus, sometimes causing marked improvements when other therapies have failed.[37] Its success in treating myoclonic conditions alone or in combination with other anticonvulsants has been reported in several case reports and open trials and in two double-blind studies.[38]–[41] In the first of the double- blind studies, 24 patients with cortical myoclonus were included in an open-label run-in period to identify responders to piracetam and to establish clinically effective doses.[42]

Sickle Cell Anaemia

In individuals suffering from sickle cell anaemia, erythrocytes are deformed and adhere more readily to the endothelial wall relative to healthy subjects. This erythrocyte adherence tends to occlude capillary blood flow resulting in local tissue damage and periods of pain, known as sickle cell crises. Piracetam exerts several effects on erythrocytes making it a potential candidate for treatment of this disease, and indeed, studies have shown its efficacy in prophylaxis and during crises.[43]–[45]

Distribution and Metabolism

Following oral administration, peak plasma concentrations in fasting subjects are achieved in approximately 30 min.[46] Following a single oral dose of 3.2 g, peak concentration is typically 84 µg/mL. Oral formulations of piracetam are extensively absorbed with a bioavailability close to 100%. No metabolites of piracetam are known and the

drug is excreted unchanged in the urine by glomerular filtration.[47] While food does not affect the extent of absorption of piracetam, it does decrease the maximal plasma concentration of the drug by 17% and prolongs the elimination time. Piracetam crosses blood–brain and placental barriers and is found in all tissues, except adipose tissue. The uptake into the brain is less rapid than into the circulation, and, at nearly 8 h, half-life in cerebrospinal fluid is longer than in plasma (about 5 h).

Piracetam is remarkably well tolerated. In preclinical trials, no irreversible toxicity was reported in mice, rats and dogs receiving single oral doses of up to 10 g/kg. In a pooled analysis of 91 double-blind, placebo-controlled studies (piracetam n = 3017, placebo n = 2850), hyperkinesia, weight gain, nervousness, somnolence, depression and asthenia were slightly increased with piracetam, although the incidence of each of these events was less than 2%. It is one of the few pharmacologically active substances wich can be seen as practically non-toxic.

Clinical Use

Due to its positive effects in several conditions, piracetam is either used as a prescription or over the counter drug, depending on the legal status in a given country. The indications for which piracetam are used for include:

- Dementia
- Vertigo
- Cortical Myoclonus
- Dyslexia
- Sickle cell anemia

Contraindication for its use are

- Hyper irritability against similar compounds
- Cerebral bleeding
- Chronic kidney disease
- Pregnancy & breastfeeding

Dosing

The dosing of piracetam varies according to indication. For cognitive disorders and vertigo it is 2.4–4.8 g daily, for dyslexia it is 3.2 g daily, for cortical myoclonus it is 7.2–24.0 g daily, for prophylaxis of vaso-occlusive crises in sickle cell anaemia it is 160 mg/kg/day, all doses are for oral consumption. In acute vaso-occlusive crises, it is given at a total dose of 300 mg/kg/day intravenously in several smaller packages.

Conclusion

It is clear that piracetam can improve the symptoms of memory, concentration, and thinking disorders, lack of drive and motivation as well as fatigue in dementia sufferers, especially as part of an overall therapeutic concept. At a symposium organized by the manufacturer UCB, five years after its market launch, researchers presented numerous studies that suggested a "general improvement in the cerebral aging process" or were intended to demonstrate "a clinically relevant improvement in memory function." Seniors in need of care improved their activities of daily living and were less in need of help. It stimulates cellular sugar metabolism and oxygen utilization in the brain and is used for the symptomatic treatment of chronic organic brain-related performance disorders like dementia and other disorders discussed above.

Recently, preclinical evidence has shown that piracetam may be useful to treat neuroinflammatory disorders like multiple sclerosis, which may lead to a broadening of its clinical use. However first, large scale studies in patients need to be performed to confirm the preclinical observations.

Most studies with piracetam are designed to find positive effects in clinical disease management, but very limited evidence exist on the matter of performance in healthy subjects. There is one study in 18 aging, healthy individuals for two 4-week periods of piracetam and placebo administration. They performed conventional and computerized perceptual-motor tasks. In a majority of these tasks, the subjects did significantly better when on piracetam than on placebo, a finding consistent with ratings completed by independent observers.[48] This suggests piracetam has positive effects on the mental performance of healthy individuals, although the study subjects in this study were of advanced age (median age was 56).

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