

Piracetam - The Original Nootropic

By James South MA

It was originally used to treat motion sickness. (1) Between 1968 and 1972, however, there was an explosion of piracetam (PIR) research which uncovered its ability to facilitate learning, prevent amnesia induced by hypoxia and electroshock, and accelerate EEG return to normal in hypoxic animals. (1) By 1972 700 papers were published on PIR. (1) Yet already by 1972 PIR's pharmacologic uniqueness led C.E. Giurgea, UCB's principal PIR researcher and research co-ordinator, to formulate an entirely new category of drugs to describe PIR: the nootropic drug. (2)

According to Giurgea, nootropic drugs should have the following characteristics: 1) they should enhance learning and memory. 2) They should enhance the resistance of learned behaviors/memories to conditions which tend to disrupt them (e.g. electroconvulsive shock, hypoxia). 3) They should protect the brain against various physical or chemical injuries (e.g. barbiturates, scopolamine). 5) They should "increase the efficacy of the tonic cortical/subcortical control mechanisms." 6) They should lack the usual pharmacology of other psychotropic drugs (e.g. sedation, motor stimulation) and possess very few side effects and extremely low toxicity. (3) As research into PIR and other nootropics (e.g. pyritinol, centrophenoquine, oxiracetam, idebenone) progressed over the past 30 years, section 5) of Giurgea's original definition has been gradually dropped by most researchers. (3) Nonetheless, the nootropic drugs represent a unique class of drugs, with their broad cognition enhancing, brain protecting and low toxicity/ side effect profiles. It is an interesting comment on the AMA/FDA stranglehold on American medicine that as of January 2001, not a single nootropic drug has ever been given FDA approval for use in the U.S.

PIR has been used experimentally or clinically to treat a wide range of diseases and conditions, primarily in Europe. (Although much of the research on PIR has been published in English, a large amount of PIR research has been published in German, French, Italian and Russian.)

PIR has been used successfully to treat alcoholism/ alcohol withdrawal syndrome in animals and man. (4,5,19) PIR has brought improvement, or slowed deterioration, in "senile involution" dementia and Alzheimer's disease. (6,7) PIR has improved recovery from aphasia (speech impairment) after stroke. (8) PIR has restored various functions (use of limbs, speech, EEG, state of consciousness) in people suffering from acute and chronic cerebral ischaemia (decreased brain blood flow). (9,10) PIR has improved alertness, co-operation, socialisation, and IQ in elderly psychiatric patients suffering from "mild diffuse cerebral impairment." (11)

PIR has increased reading comprehension and accuracy in dyslexic children. (8,12) PIR increased memory and verbal learning in dyslexic children, as well as speed and accuracy of reading, writing and spelling. (13,14) PIR potentiated the anticonvulsant action of various anti-epileptic drugs in both animals and man, while also eliminating cognitive deficits induced by anti-epileptic drugs in humans. (15,16) PIR has improved mental

performance in "aging, non-deteriorated individuals" suffering only from "middle-aged forgetfulness." (17) Elderly out-patients suffering from "age-associated memory impairment" given PIR showed significant improvement in memory consolidation and recall. (8) PIR reversed typical EEG slowing associated with "normal" and pathological human aging, increasing alpha and beta (fast) EEG activity and reducing delta and theta (slow) EEG activity, while simultaneously increasing vigilance, attention and memory. (17A)

PIR reduced the severity and occurrence of major symptoms of "post-concussional syndrome," such as headache, vertigo, fatigue and decreased alertness (18), while it also improved the state of consciousness in deeply comatose hospitalised patients following head injuries. (19) PIR has successfully treated motion sickness and vertigo. (1) PIR "is one of the best available drugs for treating...myoclonus [severe muscle spasms] of cortical origin." (20) PIR has successfully treated Raynaud's syndrome (severe vasospasm in hands and/or feet), with "a rapid and marked improvement.... The efficacy of piracetam has been maintained in several patients already followed for 2-3 years." (21) PIR has been used to inhibit sickle cell anemia, both clinically and experimentally. (11) PIR has improved Parkinson's disease, and may synergize with standard L-dopa treatment. (1)

A key part of PIR's specialness is its amazing lack of toxicity. PIR has been studied in a wide range of animals: goldfish, mice, rats, guinea pigs, rabbits, cats, dogs, marmosets, monkeys and humans. (1,19) In acute toxicity studies that attempted to determine PIR's "LD50" (the lethal dose which kills 50% of test animals), PIR failed to achieve an LD50 when given to rats intravenously at 8gm/kg bodyweight. (1) Similarly, oral LD50 studies in mice, rats, and dogs given 10gm PIR/kg bodyweight also produced no LD50! (1) This would be mathematically equivalent to giving a 70 kg (154 pound) person 700gm (1.54 pounds) of PIR! As Tacconi and Wurtman note, "Piracetam apparently is virtually non-toxic.... Rats treated chronically with 100 to 1,000 mg/kg orally for 6 months and dogs treated with as much as 10g/kg orally for 1 year did not show any toxic effect. No teratogenic [birth deformity] effects were found, nor was behavioral tolerance noted." (22) Thus, PIR must be considered one of the toxicologically safest drugs ever developed.

From the earliest days of PIR research, the ability of PIR to partly or completely prevent or reverse the toxic action of a broad array of chemicals and conditions has been repeatedly demonstrated. Paula-Barbosa and colleagues discovered that long-term (12 month) alcohol-feeding to rats significantly increased formation of lipofuscin (an age-related waste pigment) in brain cells. Giving high dose PIR to the alcohol-fed rats reduced their lipofuscin levels significantly below both the control and alcohol/no PIR rats' levels. (4) PIR antagonized the normally lethal neuromuscular blockade (which halts breathing) induced by mice by intravenous hemicholinium-3 (HC-3) (23), and PIR also blocked the lethal neuromuscular blockade induced in cats by d-tubocurarine. (1) PIR reversed learning and memory deficits in mice caused by the anti-cholinergic substance, HC-3. (23) When mice were given oxydipentonium, a short-acting curare-like agent which halts breathing, at a dose sufficient to kill 90% of one group and 100% of another

group of placebo-treated controls, the two groups of PIR-treated mice had a 90% and 100% survival rate. (19)

Rapid synthesis of new protein in brain cells is required for memory formation. PIR has ameliorated the amnesia induced by rodents by cycloheximide, a protein synthesis inhibitor. (1)

Hexachlorophene (HCP) is a toxic chemical that induces edema, membrane damage, and increased sodium /decreased potassium in brain cells. (HCP was used in shampoos, soaps and other personal care products until about a decade ago.) Rats were fed HCP orally for 3 weeks, then given PIR or one of 5 other drugs by injection for 6 days. HCP seriously disrupted the rats' ability to navigate a horizontal ladder without frequently falling off the rungs. PIR reduced the fall rate 75% compared to saline-injected controls on the first day of treatment. None of the other drugs came close to that improvement. (24)

PIR increases the survival rate of rats subjected to severe hypoxia. (1,25) When mice, rats and rabbits have been put under diverse experimental hypoxic (low oxygen) conditions, PIR has acted to attenuate or reverse the hypoxia-induced amnesia and learning difficulties, while speeding up post-hypoxic recovery time and reducing time to renormalize the EEG. (1,2,25) When a single 2400mg dose of PIR was given to humans tested under 10.5% O₂ (equivalent to 5300m./17,000 ft. altitude), eye movement reflexes were enhanced, while breathing rate and choice reaction time were reduced by PIR. (26)

Electroconvulsive shock (ECS) is a powerful disruptor of learning and memory. When a group of rats were taught to avoid a dark cubicle within their cage, there was 100% retention of the learned behavior 24 hours later.

Giving a maximal ECS right after learning caused the learning-retention rate to drop to 20% 24 hours later in the control group, while PIR-treated ECS rats still had a 100% retention of the avoidance behavior 24 hours later. (2) Other experiments with mice and rats show PIR's ability to attenuate or reverse ECS-induced amnesia. (19,27)

When given the fast acting barbiturate secobarbital (SEC), combined with PIR injected 1 hour before the SEC, 10/10 rabbits survived, with only minimal abnormalities in their EEG records. The EEG records the electrical activity of large groups of cortical neurons, and also reflects cerebral oxygen/glucose metabolism and blood flow. (25)

Only 3/10 rabbits given SEC with saline injection survived, and most of that groups' EEG records showed rapid onset of electrical silence, followed quickly by death. When SEC was given to rabbits combined with oral PIR, 8/9 survived, with only 3/9 saline-fed controls surviving. The EEG records of both groups were similar to those of the rabbits given i.v. PIR and saline. (28)

By the 1980s neuroscientists had discovered that brain cholinergic neural networks, especially in the cortex and hippocampus, are intimately involved in memory and learning. Normal and pathological brain aging, as well as Alzheimer's type dementia,

were also discovered to involve degeneration of both the structure and function of cholinergic nerves, with consequent impairment of memory and learning ability. (29)

During this same period a growing body of evidence began to show that PIR works in part through a multimodal cholinergic activity. Studies with both aged rats and humans which combined PIR with either choline or lecithin (phosphatidyl choline), found radically enhanced learning abilities in rats, and produced significant improvement in memory in Alzheimer's patients. (30-35)

Yet giving choline or lecithin alone (they are precursors for the neurotransmitter acetylcholine) in these studies provided little or no benefit, while PIR alone provided only modest benefit.

Animal research has also shown that PIR increases high-affinity choline uptake (HACU), a process that occurs in cholinergic nerve endings which facilitates acetylcholine (ACH) formation. (23,29) "HACU rate has been shown to be directly coupled to the impulse flow through the cholinergic nerve endings and it is a good indicator of ... ACH utilization nootropic drugs [including PIR] activate brain cholinergic neurons" (29) HC-3 induces both amnesia and death through blocking HACU in the brain and in peripheral nerves that control breathing. Since PIR blocks HC-3 asphyxiation death and amnesia, this is further evidence of PIR's pro-HACU actions. (23,29)

Scopolamine (SCO) is a drug that blockades ACH receptors and disrupts energy metabolism in cholinergic nerves. When rats were given SCO, it prevented the learning of a passive avoidance task, and reduced glucose utilization in key cholinergic brain areas. When rats given SCO were pretreated with 100mg/kg PIR, their learning performance became almost identical to rats not given SCO. (36) The PIR treatment also reduced the SCO depression of glucose-energy metabolism in the rats' hippocampus and anterior cingulate cortex, key areas of nerve damage and glucose metabolism reduction in Alzheimer's disease. (36)

German researchers added to the picture of PIR's cholinergic effects in 1988 and 1991. Treatment for 2 weeks with high dose oral PIR in aged mice elevated the density of frontal cortex ACh receptors 30-40%, restoring the levels to those of healthy young mice. A similar decline in cortex ACh receptors occurs in "normal" aging in humans. (37) The same group of researchers then discovered that there is a serious decline in the functional activity of ACh receptors in aged mice; with many receptors becoming "desensitized" and inactive. Oral treatment with high dose PIR also partially restored the activity of ACh cortex nerves, as measured by the release of their "second messenger," inositol-1-phosphate. (38)

Glutamic acid (glutamate) is the chief excitatory neurotransmitter in the mammalian brain. PIR has little affinity for glutamate (GLU) receptors, yet it does have various effects on GLU neurotransmission. One subtype of GLU receptor is the AMPA receptor. "Micromolar amounts [levels which are achieved through oral PIR intake] of piracetam enhance the efficacy ... of AMPA-induced calcium influx [which "excites" nerve cells to

fire] in cerebellar [brain] cells Piracetam also increases the maximal density of [AMPA GLU 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." (1) Further support for involvement of the GLU system in PIR's action is provided by a Chinese study which showed that the memory improving properties of PIR can be inhibited by ketamine, an NMDA (another major subtype of GLU receptor) channel blocker. (1) Furthermore, high dose injected PIR decreases mouse brain GLU content and the GLU/GABA ratio, indicating an increase in excitatory nerve activity. (1) At micromolar levels, PIR potentiates potassium-induced release of GLU from rat hippocampal nerves. (1)

Given that ACh and GLU are two of the most central "activating" neurotransmitters, and the facilitatory effects of ACh/GLU neural systems on alertness, focus, attention, memory and learning, PIR's effects on ACh/GLU neurotransmission must be presumed to play a major role in its demonstrated ability to improve mental performance and memory. Although PIR is generally reported to have minimal or no side effects, it is interesting to note that PIR's occasionally reported side effects of anxiety, insomnia, agitation, irritability and tremor (18) are identical to the symptoms of excess ACh/GLU neuroactivity.

In spite of the many and diverse neurological/psychological effects PIR has shown in human, animal and cell studies, PIR is generally NOT considered to be a significant agonist (direct activator) or inhibitor of the synaptic action of most neurotransmitters. Thus, major nootropic researchers Pepeu and Spignoli report that "... the pyrrolidinone derivatives [PIR and other racetams] show little or no affinity for CNS receptors for dopamine, glutamate, serotonin, GABA or benzodiazepine." (23) They also note however that "... a number of investigations on the electrophysiological actions of nootropic drugs have been carried out.... Taken together, these findings indicate that the nootropic drugs of the [PIR-type] enhance neuronal excitability [electrical activity] within specific neuronal pathways." (23)

Grau and colleagues note that "... there exist papers giving data of bioelectric activity as affected by Piracetam, and suggesting that it acts as a non-specific activator of the excitability. [i.e. brain electrical activity] thus optimizing the functional state of the brain." (25)

Gouliarov and Senning similarly state "... we think that the racetams exert their effect on some species [of molecule] present in the cell membrane of all excitable cells, i.e. the ion carriers or ion channels and that they somehow accomplish an increase in the excitatory [electrical] response.... It would therefore seem that the racetams act as potentiators of an already present activity (also causing the increase in glucose utilization observed), rather than possessing any [neurotransmitter-like] activity of their own, in keeping with their very low toxicity and lack of serious side effects. The result of their action is therefore an increase in general neuronal sensitivity toward stimulation." (1)

Thus PIR is NOT prone to the often serious side effects of drugs which directly amplify or inhibit neurotransmitter action - e.g. MAO inhibitors, Prozac® - style "selective serotonin reuptake inhibitors," tricyclic antidepressants, amphetamines, Ritalin® benzodiazepines (Valium®), etc.

A key finding on PIR in various studies is its ability to enhance brain energy, especially under deficit conditions. Energy (ATP) is critical to the brain's very survival - it typically uses 15-20% of the body's total ATP production, while weighing only 2-3% or so of bodyweight. Brain cells must produce all their own ATP from glucose (sugar) and oxygen - they cannot "borrow" ATP from other cells. Branconnier has observed that "... evidence from studies of cerebral blood flow, oxygen uptake and glucose utilization have shown that brain carbohydrate metabolism (BCM) is impaired in a variety of dementias and that the degree of reduction in BCM is correlated with the severity of the dementia." (39) In a 1987 study, Grau and co-workers gave saline or PIR i.v. to rats who were also fed i.v. radioactive deoxyglucose to help measure brain metabolism. Compared to saline controls, PIR rats had a 22% increase in whole brain glucose metabolism, while the increase in 12 different brain regions ranged from 16 to 28%. (25) This increase in brain energy metabolism occurred under normal oxygen conditions.

In 1976 Nickolson and Wolthuis discovered that PIR increased the activity of adenylate kinase (AK) in rat brain. AK is a key energy metabolism enzyme that converts ADP into ATP and AMP and vice versa. It comes into play especially when low brain oxygen begins to reduce mitochondrial ATP production. As existing ATP is used up, ADP is formed. Under the influence of AK, 2ADP becomes ATP plus AMP. Thus PIR-activated AK can slow down the drop in ATP in oxygen compromised brains. This helps explain PIR's ability to prevent abnormalities in animals subjected to hypoxia or barbiturates. When oxygen levels return toward normal, AK can convert AMP into ADP, which can then be used in the reactivated mitochondria to make more ATP. This accounts for the ability of PIR to speed up recovery from hypoxia seen in animal studies. (40)

In their 1987 study with rats, Piercey and colleagues found that PIR could restore scopalamine depressed energy metabolism modestly in many brain areas, and significantly in the hippocampus and anterior cingulate cortex. (36)

PIR has also been shown to increase synthesis and turnover of cytochrome b5, a key component of the electron transport chain, wherein most ATP energy is produced in mitochondria. (22) PIR also increases permeability of mitochondrial membranes for certain intermediaries of the Krebs cycle, a further plus for brain ATP production. (25) In his 1989 paper on cerebral ischaemia in humans, Herrschaft notes that the German Federal Health Office has conducted controlled studies that indicate a "significant positive" effect of PIR (4.8 - 6gm/day) to increase cerebral blood flow, cerebral oxygen usage metabolic rate and cerebral glucose metabolic rate in chronic impaired human brain function - i.e. ***multi-infarct dementia, senile dementia of the Alzheimer type, and pseudo-dementia. (9)

The cerebral cortex in humans and animals is divided into two hemispheres - the left and right cortex. In most humans the left hemisphere (which controls the right side of the body) is the language center, as well as the dominant hemisphere. The left cortex will tend to be logical, analytical, linguistic and sequential in its information processing, while the right cortex will usually be intuitive, holistic, picture-oriented and simultaneous in its information processing.

Research has shown that most people favor one hemisphere over the other, with the dominant hemisphere being more electrically active and the non-dominant hemisphere relatively more electrically silent, when a person is being tested or asked to solve problems or respond to information. The two cortical hemispheres are linked by a bundle of nerve fibres: the corpus callosum and the anterior commissure. In theory these two structures should unite the function of the two hemispheres. In practice they act more like a wall separating them.

From a neurological perspective, the cerebral basis for a well-functioning mind would be the effective, complementary, simultaneous integrated function of both cortical hemispheres, with neither hemisphere being automatically or permanently dominant. This in turn would require the corpus callosum and cerebral commissure to optimize information flow between the two hemispheres. Research has shown PIR to facilitate such inter-cerebral information transfer-indeed, it's part of the definition of a "nootropic drug."

Giurgea and Moyersoons reported in 1972 that PIR increased by 25 to 100% the transcallosal evoked responses elicited in cats by stimulation of one hemisphere and recorded from a symmetrical region of the other hemisphere. (41) Buresova and Bures, in a complex series of experiments involving monocular (one-eye) learning in rats, demonstrated that "...Piracetam enhances transcommissural encoding mechanisms... and some forms of inter-hemispheric transfer..." (42)

Dimond and co-workers used a technique called "dichotic listening" to verify the ability of PIR to promote interhemispheric transfer in humans. In a dichotic listening test, different words are transmitted simultaneously into each ear by headphone. In most people the speech centre is the left cortex. Because the nerves from the ears cross over to the opposite side of the brain, most people will recall more of the words presented to the right ear than the left ear. This occurs because words received by the right ear directly reach the left cortex speech centre, while words presented to the left ear must reach the left cortex speech centre indirectly, by crossing the corpus callosum from the right cortex. Dimond's research with healthy young volunteers showed that PIR significantly improved left ear word recall, indicating PIR increased interhemispheric transfer. (43)

Okuyama and Aihara tested the effect of aniracetam, a PIR analogue, on the transcallosal response of anaesthetised rats. The transcallosal response was recorded from the surface of the frontal cortex following stimulation of the corresponding site on the opposite cortical hemisphere. The researchers reported that "... the present results indicate that aniracetam...increased the amplitude of the negative wave, thereby facilitating inter-

hemispheric transfer.... Thus, it is considered that the functional increase in interhemispheric neuro-transmission by nootropic drugs may be related to the improvement of the cognitive function [that nootropics such as PIR and aniracetam promote]." (44)

The notable absence of biochemical, physiological, neurological or psychological side effects, even with high dose and/or long-term PIR use, is routinely attested to in the PIR literature. Thus in their 1977 review Giurgea and Salama point out: "Piracetam...is devoid of usual (routine) pharmacologic activities [negative side effects] even in high doses.... In normal subjects... no side effects or (doping) effects were ever observed. Nor did Piracetam induce any sedation, tranquillisation, locomotor stimulation or psychodysleptic symptomatology." (19) Wilshen and colleagues, in their study on 225 dyslexic children, note that "Piracetam was well tolerated, with no serious adverse clinical or laboratory effects reported." (12) In this particular study (as in many others), the incidence of (mild) side effects was higher in the placebo group than in the PIR group! In his 1972 8 week study on 196 patients with "senile involution" dementia, Stegink reported that "No adverse side effects of Piracetam [2.4gm/day] were reported." (6) In their study of 30 patients treated for one year with 8gm PIR/day, Croisile and colleagues observed that "Few side effects occurred during the course of the study - one case of constipation in the Piracetam group.... Piracetam had no effect on vital signs, and routine tests of renal, hepatic and hematological functions remained normal. No significant changes in weight, heart rate, or blood pressure occurred...." (7)

Yet as noted in the section on glutamate, because PIR is a cholinergic/glutamatergic activator, there is the potential for symptoms related to cholinergic/glutamatergic excess to occur, especially in those unusually sensitive to PIR. Such symptoms - anxiety, insomnia, irritability, headache, agitation, nervousness and tremor - are occasionally reported in some people taking PIR. (11,18) Reducing dosage, or taking magnesium supplements (300-500mg/day), which reduce neural activity, will frequently alleviate such "over-stimulation" effects. Persons consuming large amounts of MSG (monosodium glutamate) and/or aspartame in their diet should be cautious in using PIR, as should those who are highly sensitive to MSG-laden food (the "Chinese restaurant syndrome"). Caffeine also potentiates PIR's effects, as do other nootropics such as deprenyl, idebenone, vinpocetine and centrophenoxine, and it may be necessary to use PIR in a lower dosage range if also using any of these drugs regularly. Those wishing to augment PIR's cholinergic effects may wish to combine it with cyprodenate or centrophenoxine, which are much more powerful Ach enhancers than choline or lecithin.

B complex vitamins, NADH, lipoic acid, CoQ10 or idebenone, and magnesium will enhance PIR's brain energy effects. In the clinical literature on PIR, dosages have ranged from 2.4 gm/day (6,11) up to 8gm/day (7,21), continued for years (7,21). PIR has a relatively short half-life in the blood, although there is some short-term bioaccumulation in the brain. (1,22) PIR is therefore usually taken 3-4 times daily. 1.6 gm, 3 times daily, or 1.2 gm 3-4 times daily is a fairly typical PIR dosage, although some people report noticeable improvement in memory and cognition from just 1.2 gm twice daily.

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Last Updated: Tuesday, April 10, 2001
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