

Vinpocetine, The Superior Cerebral Enhancer And Protector By James South MA

Vincamine (VCM) is an alkaloid extracted from the Periwinkle plant, *Vinca minor*. Vinpocetine (VPC) is produced slightly altering the VCM molecule. VPC is more technically referred to as "ethyl apovincaminatate."

VCM and VPC have been widely researched and used clinically for over 25 years, in disorders ranging from cerebral arteriosclerosis and senile dementia, to Meniere's disease, tinnitus, and diabetic retinopathy.

Research has gradually shown VPC to be the superior *Vinca* alkaloid, usually having a few (and minor) if any side effects and a greater range of clinical and metabolic benefits than VCM.

Vinpocetine's actions

VPC has been shown to be a cerebral metabolic enhancer and a selective cerebral vasodilator (1,2). VPC has been shown to enhance oxygen and glucose uptake from blood by brain neurons, and to increase neuronal ATP bio-energy production, even under hypoxic (low oxygen) conditions (3,4).

VPC has been shown to reduce the cell death that normally occurs when a brain region is temporarily but severely deprived of blood flow (5).

The human brain and its energy

To fully appreciate the medical and life enhancement importance of these key aspects of VPC pharmacology, it is first necessary to review some basics of brain physiology and biochemistry.

The human brain typically weighs about 3 pounds (1-3% of total bodyweight). The brain is generally estimated to contain 10-100 billion neurons (electrically active nerve cells), and approximately 10 times as many glial cells, which are structural and nutritional support cells surrounding neurons. The brain normally receives 15-20% of the body's total blood supply, and uses 15-20% of the body's total inhaled oxygen.

The brain must use this oxygen, along with its chief fuel- glucose- to produce and use 15-20% of the body's total ATP energy.

Unlike most other cells, which can burn either fat or sugar (glucose) for their energy production needs, neurons can only burn glucose under normal, non-starvation conditions, and they typically consume 50% of the total blood sugar. Unlike liver and muscle cells, which can store large amounts of sugar as glycogen, neurons can only store at most a minute or two's worth of glucose, and so they are dependant upon a continuous and uninterrupted blood supply to maintain normal energy metabolism and avoid injury or death.

Most other cells (except heart and skeletal muscle cells) reproduce continually throughout a lifetime yet after the brain reaches a full complement of neurons (birth to 2 years of age), neurons never reproduce, they are an irreplaceable essential of life.

Under normal conditions of adequate oxygen supply, neurons convert glucose into energy (ATP) through a 3-phase process.

The first phase occurs in the cytoplasm of the cell (the gel-like stuff between the nucleus and outer cell membrane), and is called "aerobic [oxygen using] glycolysis." As each molecule of glucose is metabolized through aerobic glycolysis, two molecules of ATP are produced. In addition, two other by-products result which are used to make further ATP in the next two phases of energy production.

The "ash" from aerobically burning glucose is pyruvic acid, which is then converted to acetyl-coenzyme A (ACoA).

ACoA is then metabolized through the Krebs' or citric acid cycle to generate more ATP. The Krebs' cycle occurs inside the mitochondria, the "power plants" of the cell. The other energy-rich substance produced through aerobic glycolysis is NADH- the active coenzyme of vitamin B3.

Aerobic glycolysis produces two molecules of NADH for each molecule of glucose burned. The NADH is then transported to the mitochondria, where it serves as a fuel in the third phase of energy metabolism- the electron transport side chain (ETSC). Each NADH run through the ETSC, with adequate oxygen, produces 3 molecules of ATP. Eventually, through the successful interaction of aerobic glycolysis, the Krebs'/ citric acid cycle, and the ETSC, a single molecule of glucose can yield a maximum of 38 molecules of ATP bio-energy, assuming adequate oxygen for both glycolysis and mitochondrial "respiratory" metabolism.

When neurons are under-supplied with oxygen, however, different forms of sugar burning occurs- anaerobic (without oxygen) glycolysis.

For each molecule of glucose burned, anaerobic glycolysis yields two molecules of ATP. However, instead of producing the valuable Krebs' cycle fuel, pyruvic acid, anaerobic glycolysis produces the somewhat toxic waste product, lactic acid. And anaerobic glycolysis yields no bonus of NADH to be converted to ATP through the ETSC. And with inadequate oxygen, mitochondrial metabolism proceeds poorly, it at all.

Thus anaerobic glycolysis produces a total of only two ATP's for each glucose burned. In other words, when glucose brain fuel is burned without adequate oxygen, it produces only 5% as much ATP energy as when glucose is burned with adequate oxygen!

There are 3 main uses for ATP inside neurons- the "housekeeping-maintenance," electrical and neurotransmitter functions. Since neurons don't reproduce and must last a

lifetime, they are continually expending energy to repair or replace various cell components- cell membrane segments, microtubules, mitochondria, etc.

Neurons also use ATP to produce, transport, package, secrete and reuptake neurotransmitters, which provide cell to cell communication. And massive amounts of ATP are necessary to facilitate the frequent discharges of electrical energy from the receiving end of the neuron- the dendrites- through the cell body, where signal processing occurs, and down the transmitting end- the axon. For this electrical process to occur there must be a rapid and continuous exchange of sodium and potassium ions back and forth across the neuronal membranes.

This exchange process depends on sodium-potassium pumps, powered by sodium-potassium ATPase enzyme systems.

Some physiologists estimate as much as 45% of a neuron's ATP may be used to power the sodium-potassium pumps.

Brain disorders

It should now be evident why unconsciousness rapidly occurs if breathing stops, or brain blood flow is interrupted even briefly.

As the delivery of oxygen to the brain halts, neurons rapidly shift from aerobic to anaerobic energy metabolism, with a consequent drop in energy production, up to 95%!

There will simply not be enough ATP energy to facilitate neuronal electrical activity and neurotransmitter discharge- the electrochemical basis for consciousness. And if aerobic metabolism ceases for too long, eventually either irreparable damage or even cell death may occur, as even the "housekeeping-maintenance" neuronal activities fall behind or fail due to energy shortage.

For most of us, falling unconscious or suffering brain death due to cessation of breathing or brain blood flow is not a regular problem to contend with! However, a more subtle, insidious, slow-developing form of brain energy crisis can and does occur in most people to some degree over a lifetime, in the form of cerebral arteriosclerosis, ministrokes, or transient ischaemic attacks (brief interruptions of brain blood supply, often due to blood vessel spasm).

In its early stages, this brain energy crisis may lead to only the slightest of symptoms- subtle memory impairment, occasional confusion or lapses in concentration, slightly more difficulty in learning etc.

At a more advanced stage the brain energy crisis may show itself as senility or senile dementia, and eventually may terminate in coma or death.

Thus as Branconnier notes "...the severity of the dementia is directly correlated to the loss of functional brain tissue, independent of the primary neuropathology. This view is consistent with evidence from studies of cerebral blood flow, oxygen uptake, and glucose

utilization that 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..." (6)

Orthomolecular psychiatry pioneer Abram Hoffer has suggested that when the brain oxygenation becomes chronically deficient enough, neurons switch to anaerobic glycolysis as their main energy source. This may provide (barely) enough energy for the neurons to survive, but it will not provide enough energy to power their functional roles as electrochemical signal processors/ transmitters. Then the affected neurons will be "off-line," in an electrically quiescent "idling" state.

However, if normal aerobic metabolism is restored before irreparable cell damage or death occurs, then the neurons and their functions can be restored (7).

Vinpocetine's clinical trials

Both animal experimental and human clinical research have shown VPC to restore impaired brain carbohydrate/ energy metabolism.

In 1976 Vamosi and colleagues reported their favorable results comparing VPC with Xanthinol Nicotinate in treating 143 patients with various cerebrovascular diseases.

They measured a large number of blood and cerebrospinal fluid variables before and after treatment, such as glucose, lactate, pyruvate, oxygen, pH, electrolyte levels, etc. They concluded from their study "Though not all the changes are significant statistically, yet connected with each other they prove that Cavinton [VPC] enhances both glycolytic and oxidative reactions of glucose breakdown in CNS [brain]. The changes in the concentration of K [potassium] and Mg [magnesium]... may be considered a sign of recovery of the energy metabolism of the nerve cells." (1)

Vamosi's study also demonstrated a superior clinical efficacy of VPC over Xanthinol Nicotinate.

In his review on the use of Vinca alkaloids in dementia, Nicholson observed that "...vincamine increases mitochondrial respiratory rate in mitochondrial suspensions..., indicating that vinca alkaloids can increase the rate of ATP synthesis... In addition, elevation of cortical cyclic AMP levels may increase ATP availability... and this may contribute to the metabolic activity of vinpocetine." (8)

Karpati and Szporny resulted favorable results of VPC used to treat anaesthetized dogs. Anesthetics reduce brain aerobic metabolism and ATP production- this is a key aspect of their ability to produce unconsciousness. Based on their experiments they note that "Increase of cerebral arterial-venous oxygen difference, cerebral metabolic rate for oxygen and cerebral oxygen utilization indicate that RGH-4405 [vinpocetine] affects cerebral metabolism, with a dose-dependant rise in endogenous respiration of cerebral tissue... Our results indicate that rate of cerebral [energy production] metabolism is increased by [vinpocetine]."

Karpati and Szporny conducted a study with cats that were subjected to repeated episodes of brain hypoxia. They reported that "... transitory and partial interference even with normal cerebral circulation caused an increase of Neurochemical disturbances due to hypoxia... deficient formation of intermediaries in the Krebs cycle was observed, mainly due to shortage of oxygen.

These and cytological studies refer to a selective failure of mitochondrial metabolism... RGH-4405 [VPC] had favorable effects on these parameters... It seems probable that the effect of RGH-4405 [VPC] is even more pronounced in vascular insufficiency..." (9)
These are just a few of the many reports indicating the ability of VPC to safely and effectively restore failing neuronal energy metabolism, even under hypoxic or ischaemic (poor blood flow) conditions.

Vinpocetine's unique and selective affects

VPC has also been shown to be a unique, selective cerebral vasodilator. Solti and co-workers reported their results using VPC with 10 men suffering from cerebrovascular disorders (average age: 49). They conclude; "Cavinton [VPC] belongs to the rather few drugs which exert a potent, favorable effect on the cerebral circulation. The effect of Cavinton [VPC] on the cerebral circulation has two main features;

1. It strongly reduces cerebral vascular resistance, which is typically high in cerebral vascular disease;
2. Cerebral fraction of cardiac output is increased. No marked effect on systemic circulation, blood pressure and total vascular resistance decreased very slightly on acute Cavinton effect. Since the drug, far from increasing RATHER reduces effort of the heart, its effects may be assumed to be favorable in cerebral alterations associated with heart disease and hypertension." (2)

Hadjiev and Yancheva also reported favorable clinical results with 50 patients suffering cerebral circulation impairment. They noted that VPC does not elicit the "steal effect" that occurs with non-selective vasodilators. (The "steal effect" occurs when a vasodilator opens up blood vessels in brain regions that do not suffer from reduced circulation even more than it opens up blood vessels in regions suffering damaged circulation. This causes a net shift of cerebral blood flow away from the injured area, causing even further damage to the already blood starved part). (10)

Vinpocetine and the eyes

In another study with 100 patients suffering from poor blood circulation to the eye, Kahan and Olah note VPC's inhibition of platelet aggregation. The microvessels that feed neurons in the brain and retina are smaller in diameter than a single red blood cell- they are easily "clogged up" by clumps of platelets, impairing local microcirculation. This provides another mechanism of action for VPC's ability to enhance cerebral blood flow- inhibition of unnecessary platelet aggregation, which may be triggered by a high fat diet, magnesium deficiency, and stress hormones, among other factors (11).

Vinpocetine and brain aging

Another key benefit from VPC derives from its activating effect on the noradrenaline nerve cluster in the reticular activating system called the "locus coeruleus." Olpe and co-workers have shown that VCM and some of its derivatives (VPC) to be some of the most effective activators of locus coeruleus (LC) neurons. This small group of neurons extends its noradrenaline-secreting nerve fibers diffusely throughout the cerebral cortex (the thinking, planning, integrative brain).

Olpe notes that LC neurons decline in number with increasing age, with degeneration advancing slightly faster in men than women. The lessening number and activity of LC neurons that occurs with aging is known to play a significant role in the reduction of concentration, alertness, and information processing speed and ability that occurs with aging. Thus VPC's ability to improve the cerebral cortical activating power of remaining LC neurons makes it a true "cognition enhancing" agent (12).

Vinpocetine, EEG and aging

Saletu and Grunberger have published considerable pioneering research on EEG correlates of vigilance, and the effects of various drugs on EEG recordings. They report that "Human brain function as measured by... electroencephalogram (EEG) shows significant alterations in normal and pathological aging characterized by an increase of [slow wave] delta and theta activity and a decrease of alpha and ... beta activity [fast wave] as well as by slowing of the dominant [EEG] frequency.

These changes are indicative of deficits in the vigilance regulatory systems, [which includes the LC neurons]. By the term vigilance we [mean] the... dynamic state of total neural activity... Elderly subjects with bad memory exhibit slower [EEG] activity and less alpha and alpha-adjacent beta activity than those with good memory... Antihypoxidotic/nootropic drugs such as... vincamine-alkaloids [VCM and VPC] induce interestingly just oppositional changes [to the age related slowing of EEG waves] in human brain function, thereby improving vigilance." (13)

Vinpocetine's side effects

VPC thus possesses a unique profile; Potent metabolic enhancer; selective (non "steal effect") cerebral blood flow enhancer; neural oxygenator; anti-platelet aggregation blood thinner; locus coeruleus activator; EEG normalizing vigilance enhancer. And yet human and animal studies consistently show a remarkable safety profile and freedom from side effects. Thus, in a study on VPC's ability to improve sensorineural hearing disorders, Ribari and colleagues note that "The drug [VPC] has no side effects." (14) In their extremely detailed examination of VPC use in 100 patients with neuro-vascular diseases Szobor and Klein report that "Laboratory tests, urinalysis, blood picture, blood sugar, liver function, SGOT, SGPT, CN, electrolytes, cholesterol and total [lipids] did not change... The glucose tolerance did not deteriorate in the diabetic patients." (4)

In a highly successful double-blind placebo study of VPC with 84 elderly patients suffering from chronic vascular senile brain dysfunction, Balestreri et al, found only 12 adverse effect reports in the VPC group (mostly digestive complaints) versus 17 in the

placebo group! No significant adverse laboratory findings were found in either group (15). A major Japanese study by Otomo and colleagues with 207 patients suffering various cerebral disorders found only a 2% incidence of mild adverse side effects- anorexia in 2 patients, hives and stomach pain in 1 and hot flashes in 1. No significant adverse laboratory findings occurred in the 207 VPC patients (16).

In their summary of various animal safety tests, Cholnoky and Domok found the oral LD50 for VPC (the dose lethal for 50% of the test animals) to be 534mg/ Kg of bodyweight for mice, 503 mg/Kg of bodyweight for rats.

This would equate to approximately 35,000mg for a 150 pound human. The usual therapeutic dose for VPC for humans is 15-30mg per day!

Because of side effects at high doses when used with pregnant rats (uterine bleeding in some), Cholnoky and Domok caution against using VPC in pregnant women, or those trying or expecting to get pregnant (17).

Overall, VPC side effects reported in the literature are rare, usually minor, frequently disappear with prolonged use, and rarely require discontinuance of the drug. Stomach/ GI upset; dry mouth, rapid heart beat, low blood pressure, and rash/ hives are the main (rarely occurring) reported side effects.

Who might benefit from Vinpocetine?

1. Anyone over 40, cerebral arteriosclerosis is less well known to the public than heart disease, but it is just as common, and develops gradually over a lifetime. By the time serious symptoms develop, as with heart disease, the blood vessel occlusion is usually well advanced. VPC can minimize the structural/ functional damage to brain neurons that may accompany gradually developing cerebral arteriosclerosis.

2. Anyone who has noticed a decrease in memory, alertness, concentration, learning speed/ ability, neuro-muscular co-ordination and reaction time, vision, hearing, or who suffers from tinnitus.

3. Anyone who suffers from, or is known to be at risk for, various cerebral disorders- cerebral hemorrhage, stroke, senile dementia, transient ischaemic attacks, chronic cerebral circulatory insufficiency, etc.

4. Anyone wishing to use a generally very safe, low side effect, brain metabolism enhancing, vigilance enhancing, cognition activating "smart drug."

Vinpocetine's doses and uses

VPC is normally taken orally, 5-10mg, two or three times daily. Some people report feeling "over-revved" from higher/ more frequent dosing, and report as little as 2.5mg once or twice daily to be useful but not over-stimulating. Mild and transient nausea, though rare, is more likely to occur when VPC is taken on an empty stomach.

Sublingually VPC may allow lower dose (2.5mg) use, with quicker and sometimes more noticeable effect.

While VPC may need to be used for weeks or months before seeing major improvement in medical situations, the cognitive enhancement benefits may be noticeable from even a single dose, or within the first several days' use. Improvements in cerebral disorders and in hearing and vision problems may last only as long as the drug continues to be taken.

Because VPC enhances cerebral blood flow, it may potentate other nootropic/ cerebro-active drugs taken simultaneously, thus allowing/ requiring then to be taken in lower doses.

References

- (1). B. Vamosi et al (1976) "Comparative study of the effect of Ethyl Apovincamate and Xanthinol Nicotinate in cerebrovascular diseases" *Arzneim Forsch (drug research)* 28, 1980-84. Hereafter abbreviated "AF (DR)")
- (2). F. Solti et al (1976) "Effect of Ethyl Apovincamate on the cerebral circulation" *AF(DR)* 28, 1945-47.
- (3). E. Karpaty & L. Szporny (1976) "General and cerebral haemodynamic activity of Ethyl Apovincamate" *AF(DR)*28, 1908-12.
- (4). A. Szobor and M. Klein (1976) "Ethyl Apovincamate therapy in neurovascular disease" *AF(DR)* 28, 1984-89.
- (5). D. Sauer et al (1988) "Vinpocetine prevents ischaemic cell damage in rat hippocampus" *Life Sci.* 43, 1733-39.
- (6). R. Branconnier (1983) "The efficacy of the cerebral metabolic enhancers in the treatment of senile dementia." *Psychopharm Bull* 19, 212-19.
- (7). A. Hoffer & M. Walker, *Smart Nutrients*, Garden City Park, NY: Avery, 1994.
- (8). C. Nicholson (1990) "Pharmacology of nootropics and metabolically active compounds in relation to their use in dementia." *Psychopharm* 101, 147-59.
- (9). K. Biro et al (1976) "protective activity of Ethyl Apovincamate on ischaemic anoxia of the brain" *AF(DR)*28, 1918-20.
- (10). D. Hadjiev & S. Yancheva (1976) "Rheoencephalographic and psychological studies with Ethyl Apovincamate in cerebral vascular insufficiency" *AF(DR)*28, 1947-50.
- (11). A. Kaham & M. Olah (1976) "Use of Ethyl Apovincamate in ophthalmological therapy" *AF(DR)*28, 1969-72.
- (12). H. Olpe et al (1985) "Locus Coeruleus as a target for psychogeriatric agents" *Ann NY Acad Sci* 444, 399-405.
- (13). B. Saletu & J. Grunberger (1985) "Memory dysfunction and vigilance; neurophysiological and psychopharmacological aspects" *Ann NY Acad Sci* 444, 406-27.
- (14). O. Ribari et al (1976) "Ethyl Apovincamate in the treatment of sensorineuronal impairment of hearing" *AF(DR)*28, 1977-80.
- (15). R. Balestreri et al (1987) "A double blind placebo controlled evaluation of the safety and efficacy of vinpocetine in the treatment of patients with chronic vascular senile cerebral dysfunction." *J. Am Geriatr Soc* 35, 525-30.

(16). E. Otomo et al (1985) "Comparison of vinpocetine with Ifenprodil Tartrate and Dihydroergotoxine Mesylate treatment and results of long term treatment with vinpocetine." Curr Ther Res 37, 811-21.

(17). E. Chohnoky & L. Domok (1976) "Summary of safety tests of Ethyl Apovincamate" AF(DR)28, 1938-44.

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Last Updated: Wednesday, March 21, 2001

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