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VINPOCETINE: A SMART DRUG AND A SMART NUTRIENT: A REVIEW

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ABSTRACT

Vinpocetine, a semisynthetic derivative alkaloid of Vincamine, an extract from the periwinkle (plant) *Vinca minor* is the first full-fledged nootropic (a supplement positively affecting the mind). Vinpocetine is safe and non-toxic with an amazing array of functional and structural benefits for improved health. Vinpocetine appears to improve a person's ability to acquire new memories and to restore memories that have been lost. Vinpocetine has several pharmacologic and biochemical actions, including stimulating cerebral vasodilation, increasing tolerance of cerebral tissue to hypoxic and ischemic insults, anticonvulsant activity, inhibitory effects on phosphodiesterase (PDE), improving hematologic flow properties, and inhibiting thrombocyte aggregation. It also appears to provide direct neuroprotective effects under in vitro and in vivo conditions. In a sense, Vinpocetine is Viagra® for the brain. These effects appear to be related to the inhibition of voltage-dependent neuronal sodium channels, indirect inhibition of some molecular cascades initiated by the rise of intracellular calcium levels, and to a lesser extent, inhibition of adenosine reuptake. These neuroprotective effects might also be enhanced by vinpocetine's selective inhibition of calcium calmodulin–dependent cGMP-PDE. This inhibition may enhance intracellular cGMP levels in vascular smooth muscle, leading to reduced cerebrovascular resistance and increased cerebral blood flow.

INTRODUCTION: Vinpocetine (vinpocetine-ethyl apovincaminate) was synthesized in the late 1960s from the alkaloid vincamine, extracted from the leaf of the lesser periwinkle plant (*Vinca minor*) [1].

Vinpocetine was made available under the trade name Cavinton in 1978 and has since been used widely in Japan, Hungary, Germany, Poland, and Russia for the treatment of cerebrovascular-related pathologies [2]. **Figure 1** represents the Chemical Structure of Vinpocetine.

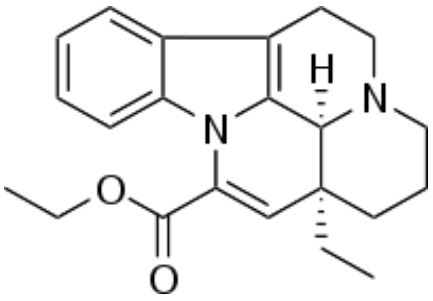

FIG. 1: CHEMICAL STRUCTURE OF VINPOCETINE

Systematic (IUPAC) name: (3α, 16α)-Eburnamenine-14-carboxylic acid ethyl ester. Formula: $C_{22}H_{26}N_2O_2$. Molecular Mass: 350.454 g/mol

The earliest investigations of Vinpocetine resulted in its utilization for the treatment of cerebrovascular dysfunctions. Since then it has become a reference compound in the pharmacological research of cognitive deficits caused by hypoxia (not getting enough oxygen) and ischemia (not getting enough blood, which carries oxygen and glucose). Experimental data indicates that Vinpocetine provides a considerable neuroprotective effect.

Vinpocetine is one of the few substances studied which can offer multiple cognitive benefits as well as a remarkable number of benefits for the body. It turns up our mind and keeps our lights bright at the same time that it helps our cardiovascular and GI systems, along with muscles, joints, and sensory organs to function better.

Vinpocetine, when taken on an empty stomach, has an absorption rate of 6.7 percent [3]. When taken with food, absorption increases 60-100 percent. Vinpocetine reaches the bloodstream approximately one hour after administration, whether taken with food or on an empty stomach [4]. The elimination half-life of the oral form is one to two hours and the majority of vinpocetine is eliminated from the body within eight hours [3].

Recent studies, either following i.v. infusion of vinpocetine in patients with cerebrovascular disorders or using positron emission tomography (PET) scans in animals, have shown that vinpocetine crosses the blood-brain barrier and is taken up by cerebral tissue [5, 6]. PET studies have also clearly shown in human subjects vinpocetine is preferentially absorbed in the central nervous system at twice the level that would be expected according to total body distribution. PET studies on the uptake and regional distribution of vinpocetine in human subjects. The highest uptake of vinpocetine is seen in the thalamus, putamen and neocortical regions.

Mechanism of Action: Vinpocetine appears to have several pharmacologic and biochemical actions, including stimulating cerebral vasodilation, increasing tolerance of cerebral tissue to hypoxic and ischemic insults, anticonvulsant activity, inhibitory effects on phosphodiesterase (PDE), improving hematologic flow properties, and inhibiting thrombocyte aggregation [2, 7, 8]. Vinpocetine also appears to provide direct neuroprotective effects under in vitro and in vivo conditions. These effects appear to be related to the inhibition of voltage-dependent neuronal sodium channels, indirect inhibition of some molecular cascades initiated by the rise of intracellular calcium levels, and to a lesser extent, inhibition of adenosine reuptake [7].

These neuroprotective effects might also be enhanced by vinpocetine's selective inhibition of calcium calmodulin–dependent cGMP-PDE [7]. This inhibition may enhance intracellular cGMP levels in vascular smooth muscle, leading to reduced cerebrovascular resistance and increased cerebral blood flow.

Highlights of the mechanism of action of Vinpocetine include:

- **Voltage-dependent Sodium Channel Inhibition:** It has been hypothesized that vinpocetine's application in ischemic stroke is secondary to its effect on voltage-dependant sodium channels in the brain. Inhibition of sodium channels in neural tissue is the primary mechanism of several different drugs reported to have neuroprotective effects in experimental ischemia [9]. This action, effectively blocking accumulation of sodium in neurons, decreases the damage of reperfusion injury and may be beneficial in lessening the toxic effects of oxidative stress resulting from anoxia [10].

  This in turn regulates calcium channel operations (Ca^{2+}) preventing abnormally high intracellular Ca^{2+} concentrations following oxygen or blood flow disruptions (hypoxia or ischemia) or both. This inhibition (of Na^{+} channels), and reduction (of intracellular Ca^{2+} levels) is thought to moderate the excitotoxicity of neurotransmitters such as glutamate, which are released due to the effect of ischemia or hypoxia. Vinpocetine may thus prevent the initiation of intracellular molecular cascades that may result in the irreversible damaging of neurons. In this way, vinpocetine produces neuro- and cerebro-protective effects.

- **Phosphodiesterase-1 Inhibition:** Vinpocetine inhibits Ca^{2+}/calmodulin- dependent phospho-diesterase (PDE) type 1 [11]. This effect would

theoretically lead to an increase of cyclic AMP over cyclic GMP and may be responsible for the benefits in cerebral circulation and decreased platelet aggregation observed after vinpocetine administration [12]. However, it is not yet clear how this mechanism is related to vinpocetine's cerebro- and neuro-protective effects.

- **Uptake-Inhibitory Action:** Vinpocetine inhibits adenosine uptake. Adenosine is an inhibiting neurotransmitter. Thus, especially in hypoxia and ischemia (when the large-scale declines of ATP can lead to the increase in extracellular adenosine concentration), adenosine reduces Ca2+ channel activity which can result in excitotoxic damage. At the same time, it can inhibit excessive release of glutamate which can have an excitotoxic effect (see **Figure 2**).

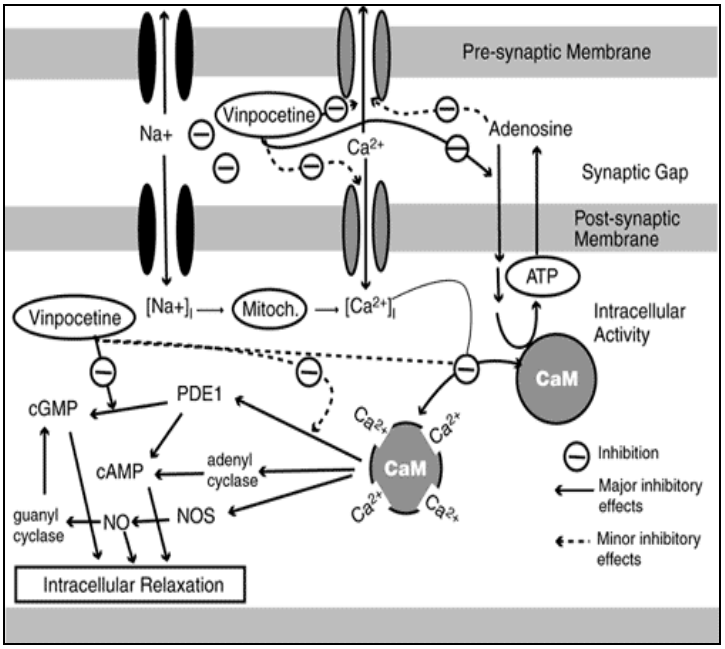

FIG. 2: PRESUMABLE MECHANISMS OF ACTION OF VINPOCETINE

Vinpocetine blocks the sodium channel (Na+) operation at the neuronal level, which regulates calcium channel (Ca^{2+}) operations preventing high intracellular Ca^{2+} concentrations.

Lessening neurotransmitter excitotoxicity may result, lowering ischemic or hypoxic damage and providing cerebro-protective effects. Vinpocetine also inhibits uptake of the neurotransmitter adenosine. This reduces Ca^{2+} channel activity preventing excitotoxic damage. Also shown is vinpocetine's inhibition of the enzyme phosphodiesterase type I (PDE1) lessening cGMP and relaxing blood vessel muscles and increasing cAMP. PDE1 is dependent on calmodulin (CaM), a calcium binding protein, which is weakly inhibited by vinpocetine. CaM is weakly inhibited by Ca^{2+}. Vinpocetine may weakly inhibit the effect of CaM on PDE1 either through inhibition of calmodulin or its effect on Ca^{2+}. CaM increases nitric oxide's relaxation effect by increasing cGMP.

- **Antioxidant Effects:** Like vitamin E, vinpocetine is an effective scavenger of hydroxyl radicals. It has also been shown to inhibit lipid peroxidation in synaptosomes of murine brain tissue and to protect against global anoxia and hypoxia in animals. Vinpocetine has decreased areas of neuronal necrosis in animal models up to 60 percent in experimentally- induced ischemia [10].

- **Other Neuroprotective Effects:** Vinpocetine has been shown to protect neurons from the toxicity of glutamate and Nmethyl- d-aspartate (NMDA). Vinpocetine lowers blood viscosity in patients with cerebrovascular disease, has significant vasodilating properties [16], decreases platelet aggregation and increases and maintains erythrocyte flexibility under oxidative stress all of which are potentially beneficial in cerebrovascular disease. Vinpocetine causes a selective increase in cerebral blood flow and increases cerebral metabolic rate.

Pharmacokinetic of Vinpocetine: Vinpocetine is eliminated with a mean half-life of 2.12 +/- 0.51 h. Total plasma clearance (CL) and distribution coefficient of the parent drug is found 2.2 +/- 0.9 l/kg/h and 6.7 +/- 3.7 l/kg, respectively. The CL and distribution coefficient of vinpocetine differs significantly from young subjects but the elimination half-life is not found altered [13]. The Bioavailability of Vinpocetine is generally found to be 56.6 +/- 8.9%. It is metabolised extensively to inactive apovincaminic acid in liver and is eliminated through the renal route of excretion. It appears to be better absorbed with meals. It is absorbed 60% with food and about 7% without.

Clinical Indications:

Chronic Cerebral Vascular Ischemia: Two PET studies in chronic stroke patients have shown that vinpocetine has a significant effect in increasing glucose uptake and metabolism in the healthy cortical and subcortical regions of the brain, particularly in the area surrounding the region of the stroke [14]. A study in fifteen chronic ischemic stroke patients found that a two-week vinpocetine trial significantly increased cerebral blood flow in the non-symptomatic hemisphere. Ten Recent studies using Doppler sonography and near infrared spectroscopy have shown increased perfusion of the middle cerebral artery in patients with chronic cerebrovascular disease given a single infusion of vinpocetine [10].

Acute Ischemic Stroke: Although small studies have shown that vinpocetine has an immediate vasodilating effect in cerebrovascular circulation[10] a meta-analysis of the existing studies examining short- and longterm fatality rates with vinpocetine was unable to assess efficacy [2]. In the analysis of eight studies in acute stroke patients (vinpocetine was administered within two weeks of event), only one study met the meta-analysis criteria. In the selected trial, three weeks after onset of i.v. vinpocetine therapy, 8 of 17 vinpocetine patients and 12 of 16 placebo patients were determined “dependent” (unable to live without assistance), and all were still alive. The meta-analysis authors were unable to determine a beneficial effect of vinpocetine, but did state that considering the *in vitro* studies and animal data, vinpocetine has potential to be effective in acute stroke. Properly designed studies have not yet been conducted.

Degenerative Senile Cerebral:

Dysfunction: A meta-analysis of six randomized, controlled trials involving 731 patients with degenerative senile cerebral dysfunction showed that vinpocetine was highly effective in the treatment of senile cerebral dysfunction. Using several psychometric testing scales in addition to physical symptoms (speech and movement capacity, muscular coordination and strength, sensory-perceptual ability) the researchers were able to show a highly significant effect of vinpocetine on both cognitive and motor functions[15].

Alzheimer’s disease: Although evidence has been limited to one small study, the results suggest that vinpocetine supplementation may not be effective as a therapy for Alzheimer’s disease. A double-blind, placebo controlled study of vinpocetine in 15 Alzheimer patients, treated with increasing doses of vinpocetine (30, 45, and 60 mg per day) in an open label pilot trial during a one-year period, resulted in no improvement [16].

Tinnitus/ Meniere’s Disease/Visual:

Impairment: Vinpocetine has been used in the treatment of acoustic trauma with subsequent hearing loss and tinnitus [17]. Disappearance of tinnitus occurred in 50 percent of those who started vinpocetine within one week of the trauma. Regardless of the time since the incident, 79 percent of patients had improved hearing and 66 percent had a significant decrease in the severity of the tinnitus. Vinpocetine has also been found to be effective in treating Meniere’s disease and in visual impairment secondary to arteriosclerosis[18]**.**

Dr. Ward Dean, a cognitive investigator and noted nootropic gourmand said this about vinpocetine, "It's one of the few cognitive enhancers that I actually notice a [positive] difference when I take it." [19]. The word nootropics was coined in 1964 by Dr. Corneliu E. Giurgea. He created this word to refer to substances that enhanced memory and cognition without harming the brain. These nootropics could be smart drugs, supplements, nutraceuticals, or even foods purported to have medicinal brain boosting qualities.

For sure, Vinpocetine has some extraordinary characteristics. Here, at last, is something for everyone. There is strong evidence indicating that Vinpocetine can help;

You Feel Smarter:

- Improve long and short term memory
- Enhance alertness
- Serve as a neuroprotector
- Improve the delivery and utilization of glucose and oxygen to your brain
- Improve blood flow in your brain

- Act to enhance dopaminergic, serotonergic, noradrenergic functions
- Prevent ischemic damage in the brain, muscle tissue, liver and elsewhere
- Prevent epileptic seizures
- Diminish senile cerebral dysfunction
- Prevent excitotoxic (excessive receptor excitement) cell death in the brain
- Reduce cerebral anoxic (absence of oxygen) damage

Protect Heart Function:

- Diminish atherosclerotic plaque
- Improve cardiac output and nutritive blood flow to various organs
- Improve vasodilation
- Enhance lipoprotein structure in the blood
- Increase red-blood cell flexibility
- Scavenge toxic metals in the body such as aluminium and lead

Improve Visual Function:

- Protects and enhances eye functions
- Decrease retinal degeneration by increasing blood circulation in the retina and the optic nerve

Improve Hearing Function:

- Prevent or relieve dizziness (vertigo)
- Lessen space motion sickness

And Much More:

- Prevent high altitude sickness
- Improve joint function
- Relieve arthritic discomfort
- Alleviate asthma
- Ameliorate climacteric conditions
- Improve GI functions by operating as a gastroprotective agent
- Operate as a high level antioxidant scavenging hydroxyl free radicals
- Act as a muscle relaxant
- Enhance mood

Safety Issues: Vinpocetine is generally well tolerated, and no significant adverse effects have been seen in clinical trials. There is one case report of vinpocetine apparently causing reversible agranulocytosis [20]**.** In addition, vinpocetine reportedly impairs platelet aggregation [21]**.** Maximum safe dosages in individuals with severe hepatic or renal disease are not known.

Drug Interactions: If Vinpocetine does in fact impair platelet aggregation, potentiation of anticoagulant or antiplatelet agents might be expected. However, one study found that Vinpocetine marginally impairs the anticoagulant effect of warfarin [22].

Tolerability: Numerous clinical studies indicated that Vinpocetine is safe during long-term administration. No serious side effects related to the treatment have been found [23, 24, 25]**.** Szobor and Klein, (1976) [26] established that Vinpocetine (10-30 mg daily at combined oral and i.m. administration, or 30-45 mg daily orally) did not change laboratory tests, blood pictures, blood sugar, liver functions, did not cumulate and did not produce allergic symptoms). There are few reports about side effects of Vinpocetine after i.v. administration. Some patients had a passing sensation of warmth after injection of the drug [18, 26, 27, 28].

Safety/Toxicity: Some studies have noted flushing, rashes, or minor gastrointestinal problems in some subjects; however, these side effects did not warrant discontinuation of the medication [15]. In one study no significant side effects were reported, even in larger doses of 20 mg three times daily [16].

Dosage: It is found that all of the studies used either 10 mg Vinpocetine 3 times daily orally or i.v. Vinpocetine. Patients with chronic cerebrovascular disorders that were included in the meta-analysis [15] had been on an oral dosage of 10 mg three times daily. It is recommended that first-time users ingest only 2–5 mg of Vinpocetine with meals to make sure they are not hypersensitive to it. Users may then increase the dosage to 10-40 mg a day (which may, although very rarely, cause some light side-effects). Vinpocetine is available in 10 mg capsules, usually taken 3 times per day.

Research Progress for Vinpocetine: Vinpocetine increases the brain's blood circulation. Animal studies have shown Vinpocetine can reduce the loss of neurons due to decreased blood flow. In three studies of older humans with memory problems associated with poor brain circulation or dementia-related disease, Vinpocetine produced significantly more improvement than a placebo in attention, concentration, and memory [29].

In a 2003 review of double-blind, randomized Vinpocetine studies, researchers assessed vinpocetine's efficacy and safety in the treatment of patients with cognitive impairment due to vascular disease, Alzheimer's disease, mixed (vascular and Alzheimer's disease) and other dementias [30].

The three studies included in the review- all performed before the 1990s- involved 583 people with dementia treated with Vinpocetine or placebo. The results showed that Vinpocetine treatment did exert some benefits at 30 mg per day and 60 mg per day compared with placebo. Because the number of patients treated for 6 months or more was small, and only one study extended treatment to one year, the reviewers stated that they would like to see longer term, larger studies to validate Vinpocetine's potential benefit.

Vinpocetine's ability to protect neurons is well researched. In Hungary, Vinpocetine has become a reference compound in the pharmacological research of cognitive deficits caused by low oxygen (hypoxia) and ischemia. Early experiments with Vinpocetine indicated five main actions: (1) selective enhancement of brain circulation and oxygen use without significant alteration in systemic circulation, (2) increasing the brain's tolerance toward hypoxia and ischemia, (3) anticonvulsant activity, (4) inhibitory effect on phosphodiesterase, an enzyme critical for the breakdown of cyclic adenosine monophosphate, a nucleotide important in a variety of metabolic responses to cell stimuli and (5) improvement of blood properties and inhibition of "sticky" platelets.

Later studies in various laboratories confirmed the above effects; suggested Vinpocetine also works by influencing sodium and calcium-dependent communication between neurons and clearly demonstrated that Vinpocetine offers significant and direct neuroprotection both under in vitro and in vivo conditions [21]. Research into nootropics, smart nutrients, smart drugs, and related brain boosters is an exciting and promising area of scientific studies. The future of smart drugs is wide open. We will see incredible advances in the science of mental performance enhancement over the next few decades.

SUMMARY: Vinpocetine is a supplement with a wide variety of biological effects. It causes relaxation of smooth muscle, dilation of blood vessels, and improved blood flow, all of which have beneficial health effects. It also provides protection for nerve cells deprived of oxygen and nutrients, and further protects those cells from oxidative stress when blood flow is restored. The supplement has had its greatest proven clinical benefit in patients with chronic cerebral vascular ischemia, and evidence is growing for its potential usefulness in acute stroke, various forms of dementia, and urinary incontinence. Even after more than two decades of extensive use in Europe and Asia, side effects and adverse events are rarely reported among people taking Vinpocetine supplements.

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