

## Importance of the blood supply to the brain for a healthy memory function

By S. Busiguina, PhD. COVEX, S.A. Spain



*Vinca Minor, L.*

The advantages of medical science, change in lifestyle, and in eating habits during the last century leads to the extension of a lifespan. The average lifespan increased from 58,5 years in 1900 to 69,5 years in 1996<sup>1</sup>. Because of medical care, physical exercise, the improvement of health-related habits, and health education, one can gain and maintain a superior state of health. Ultimately one should focus on a healthy diet along with the use of dietary supplements, nutraceuticals, functional foods and beverages to maintain good health. We should not only be concerned about the health of the physical body, but also for the mind. It has been shown that human memory may start to decline at the age of 30 old<sup>2</sup>. The experimental findings have been confirmed by personal observations. With age, people begin to have some problems with memory. It was shown that cerebral circulation increased in specific areas of the brain with verbal task<sup>3</sup>, mental effort<sup>4</sup>, memorisation<sup>5</sup>, speech or reading<sup>6</sup> and was significantly different when compared to the resting CBF (cerebral blood flow) pattern<sup>7</sup>. The deficiency in cerebral blood supply may be one of the most important factors in the decline of memory capacity and cognitive impairment.

Health cerebral tissue can afford a little reduction in blood flow without important functional and morphological changes. The reason is that the oxygen deficit to the brain could be restored by increasing the utilization of oxygen from the blood and by other mechanisms. However, the reduction of cerebral perfusion below determinate level gives rise to changes in neuron function. The moderate reduction in cerebral perfusion does not result in immediate functional disorders. Although if it persists over a long period of time (weeks or months), it could lead to irreversible disturbances and morphological changes of nervous tissue<sup>8</sup>.

It is critical to maintain a supply of oxygen, glucose and other nutrients to brain tissue to prevent memory and cognitive impairment. Nutraceutical markets all over the world offer a variety of different types and forms of memory enhancer products. The products contain ingredients that have different mechanisms of

action to support the brain. Particular products, to improve cerebral circulation are called "Intelectol®", "Vinca Minor Extract" and "Oxopocetine" which contain vinpocetine or vincamine as active ingredients.

Natural alkaloid vincamine is extracted from a short evergreen perennial herb *Vinca Minor*, L (fam. Apocynaceae). The total contents of *Vinca* phytochemicals embrace 83 different substances. Just in the leaves are 10-15% of total alkaloids. Extracts of *Vinca Minor* have been used for centuries in Europe, India, China, and America for medical purposes. In Europe, and other countries, extracts of *Vinca Minor* were used to treat all kinds of diseases, from coughs and sore throats to eye and lung infections: Most interesting is that it was folk-use in treating diabetes. In the 20th century, researchers discovered the plant contains dozens of alkaloids; some of which lower blood sugar and blood pressure. In the 1950's, scientists discovered two alkaloids that are the source of anticancer drugs.

Vincamine and vinpocetine have been used clinically for over 25 years with minimal difference in their structural formula. Vinpocetine is a selective inhibitor of phosphodiesterase-1 (PDE-1) and has demonstrated its beneficial effects on brain circulation in many clinical studies.

In conditions of cerebral hypoperfusion, the oxygen and glucose entering brain tissue is diminished. As a consequence, the utilization of blood oxygen rises, deformability of blood forming elements is reduced, and the predisposition to thrombosis increases. The main biological action of *Vinca* alkaloids, vinpocetine and vincamine is that it improves brain circulation by the regulation of cerebral vascular resistance. In addition, it increases cardiac output of cerebral fraction without an effect on the systemic circulation. The transcranial Doppler and a near infrared spectroscopy study have shown that vinpocetine increases cerebral perfusion, transmembrane glucose transport and parenchymal oxygen extraction as well<sup>9, 10, 11, 12</sup>. The clinical studies have shown an increase of erythrocyte deformability by vinpocetine which improves cerebral microcirculation<sup>13,14</sup>.

In a state of hypoxia, the cells ATP content is reduced, which leads to a breakdown in cell membrane functions. As a result of membrane Na<sup>+</sup> K<sup>+</sup> pump failure, intracellular Na<sup>+</sup> levels and extracellular K<sup>+</sup> levels increase. The increase of intracellular Na<sup>+</sup> results in the release of activating amino acids and glutamate. This leads to the activation of Na<sup>+</sup> and Ca<sup>2+</sup> transmembrane channels by excitotoxic mechanisms and an increase in entry of intracellular Ca<sup>2+</sup> causing cell damage.

Pathological changes in white matter, which consist from axons wrapped in myelin, astro-, oligo- and microglial cells. The changes are caused by hypoxic or anoxic conditions due to a rising entry of Ca<sup>2+</sup> in the axons. Diminished levels of ATP cannot supply enough energy to Na<sup>+</sup> transmembrane channels, so the influx of Na<sup>+</sup> is constant, and entry of Ca<sup>2+</sup> rises which results in myelin and axon damage.

Recent studies on vinpocetine's mechanism of action suggest that it is not limited only to vasodilation but, there is direct action on nervous tissue cells. The experimental electrophysiological studies

confirm alteration in electrical activity of neurons by vinpocetine. The results, showing similar effect of vinpocetine and cGMP, suggest that vinpocetine enhance potassium currents by not direct action on K<sup>+</sup> channels but through increasing cGMP levels. This information has confirmed that the scientific literature suggests about the capacity of vinpocetine to increase levels of cellular cGMP. The literature also suggests that vinpocetine inhibits PDE-1 and/or activate guanylate cyclase which is related to the NOS (nitric oxide synthase) - dependent vasodilation mechanism. On the other hand, it was observed that vincamine increases mitochondrial respiratory rate in mitochondrial fraction; this suggests that it increases the rate of ATP synthesis. Vinpocetine increases ATP availability for neuronal energy-dependent functions. 15, 16, 17, 18 by elevation of cortical cATP level.

Vinpocetine acts as neuronal and myelin protector, inhibiting the activity of Na<sup>+</sup>-channels and showing down excessive entry of Na<sup>+</sup> in cells. It has a specific activity on different types of transmembrane transport of Ca<sup>+</sup> but the exact mechanism of action has yet to be shown.

In response to cerebral hypoperfusion, protector mechanisms are activated. The neuroprotector effect of adenosine is one of these mechanisms, which prove very important. This effect assists in the inhibition of release of excitatory amino acids and reducing white matter damage.

Microglial activation is observed as a result of persistent hypoperfusion and astrogliosis as well. Free radical formation and other neurotoxic substances induce the astrocytes proliferation during this process. Astrocytes in normal conditions play an important role in maintaining ion balance in intracellular space. But in hypoxic conditions, reactivated astrocytes lose this ability and the mechanism for impediment of entry of excess of intracellular Ca<sup>2+</sup> is disrupted. Adenosine takes part in astroglial differentiation and in neuroglial activation and proliferation. Increased adenosine levels stimulate differentiation of neuroglia, which leads to reduce free radical production and restoration of ionic environment of neurons.

It was shown that vinpocetine could protect cultured neurons from hypoxic damage by improving adenosine metabolism.<sup>19</sup> Memory decline is directly related with neuronal changes and/or neuronal loss. The memory formation is integrative and complex process. It begins from the moment one receives external stimuli. The information received by the senses is transmitted to the brain by peripheral nerves as electrical signals. The nerve cells (neurons) do not have physical contact with each other. The transmission of electric signals from cell to cell occur by conversion of electrical impulses into a chemical signal. The neuron consists of a body of cells and extensions named axons and dendrites. The electric signal goes from a dendrite to the end of an axon (nerve terminal) which is situated close to another dendrite and the body of cells of the next neuron. The electric impulses trigger the release of specific chemicals (neurotransmitters), which are packed in vesicles, in the space between the nerve terminal and the surface of neighboring cells (post-synaptic membrane).

These three units, the surface of the nerve terminal, the post-synaptic membrane and the space between them, form the synapse. The synapse and neurotransmitters are very important in memory formation. Billions of neurons take part in transmitting and processing the received information and form a complex network. The neurotransmitters such as acetylcholine, dopamine, noradrenaline, and serotonin are released, and the synapses are modified while new ones are formed. The acetylcholine and noradrenaline are very important in learning, memory formation and movements; dopamine and serotonin take part in the state of human behavior, emotions, and mood. The memory formation, in scientific terms, consists in the modification of the synaptic

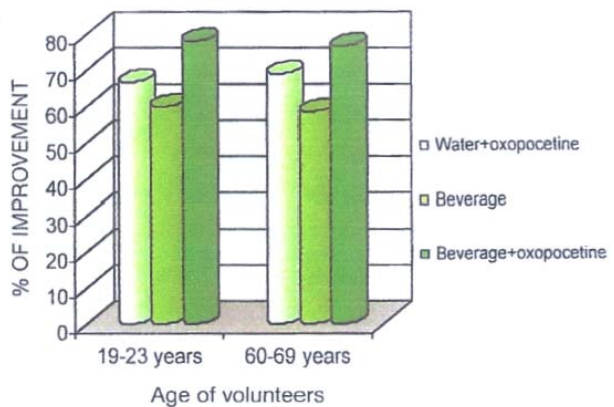
membrane and the synthesis of new proteins. All of these events can be correctly developed when the neurons have an adequate supply of oxygen, glucose and other factors for the proper functioning of the brain.

Vinpocetine improves turnover and increases the concentration of noradrenaline, dopamine, acetylcholine and serotonin involved in complex integrative processes of memory formation. It has been shown that the little brain area, Locus coeruleus is involved in fine mechanisms of behavior such as regulation, learning, memory, emotions, awakesness and autonomic regulation. Vinpocetine is a potent activator of Locus coeruleus neurons. It is known that the quantity of these neurons is reduced with age and more in men than in women. This reduction affects the concentration capacity, thinking, memory and speed of processing of information. Vinpocetine has the capacity to improve the vigor of these noradrenergic neurons to gain the name, "brain enhancer". Experimental work on animals provides direct electrophysiological evidence that vinpocetine has the capacity to increase the functionality of Locus coeruleus neurons and the activity of the noradrenergic system. The noradrenergic system is responsible for learning and memory function. Vinpocetine increases the level of dopamine. In the prefrontal brain area, vinpocetine modulates working memory. A functional disorder in this area is associated with schizophrenia and a low level of dopamine with Parkinson's disease. 20-26

A clinical study was performed on 199 clinically healthy volunteers by COVEX, S.A. (Covex S.A. is proprietary of this data). Volunteers were divided into two groups by their age: The first group included individuals that were 19-23 years old, and the second group individuals who were 60-69 years old. The results of the study clearly demonstrated the beneficial effects of "Oxopocetine" and "Vinca Minor Extract" on memory function and cognitive capacity when taken with different beverages such as tea, coffee or cola beverages (Graph 1). "Oxopocetine's" active ingredient is vinpocetine citrate, which is a soluble salt of vinpocetine. It has all of the properties of vinpocetine. The patented technology permits the mixture of beverages containing the combination of caffeine or theobromine with vinpocetine citrate (US Patent, Eurasian Patent, and Norwegian Patent).

Vinpocetine has also been clinically shown to have a high safety profile with only minor and rare side effects.

#### References on next page



% of improvement assessed according to the to the subjective criteria in compliance with individual surveys and their subsequent medical evaluation. MMSE and SCAG tests were used.

## References

- American Academy of Anti-aging Medicine. World Aging Report, 2000-2001.
- Smith, A.D. & Earles, J.L. (1996) Memory changes in normal aging. in T.Hess & F.Blanchard-Fields (Eds.), Cognitive changes in adulthood and aging. p.p. 192-220. New York: McGraw-Hill.
- Gur RC, Gur RE, Obrist WD, Skolnick BE, Reivich M. Age and regional cerebral blood flow at rest and during cognitive activity. Arch Gen Psychiatry 1987; 44:617-621.
- Ingvar DH, Risberg J. Increase of regional cerebral blood flow during mental effort in normals and in patients with focal brain disorders. Exp Brain Res 1967; 3:195-211.
- Risberg J, Ingvar DH. Patterns of activation in the grey matter of the dominant hemisphere during memorisation and reasoning. Brain 1973; 96: 737-756.
- Ingvar DH, Schwartz MS. Blood flow patterns induced in the dominant hemisphere by speech and reading. Brain 1974; 97:274288.
- Lassen NA, Ingvar DH, Skinhoj E. Brain function and blood flow. Sci Am 1978: 239:62-71.
- Miyazaki M.-- Correlation between cerebral circulation and intellectual impairment in patients with "aging brain" and the effect of vinpocetine on cerebral circulation / Drug Dev. Res. - 1988 - Vol.14 - .199-204.
- Matkovics B., Szabo L., Kiss B., et al.: Effect of ethyl apovincamate on the utilization of 14C-glucoses by rat brain in vitro / Arzneim. Forsch. - 1991 - Vol.41(2) - -107-108.
- B Gulyás, C Halldin, J Sandell, P Kar1sson, J SÓVÁGÓ, E KÁRPÁTI, B Kiss, A Vas, Z Cselényi, I-Farde PET studies on the brain uptake and regional distribution of [11C]vinpocetine in human subjects Acta Neurologica Scandinavica 2002. Vol.106 Is. 6 p.325
- Vas A, Gulyas B, Szabo Z, Bonocz P, Csiba L, Kiss B, Karpati E, Panczel G, Nagy Z. Clinical and non-Clinical investigations using positron emission tomography, near infrared spectroscopy and transcranial Doppler methods on the neuroprotective drug vinpocetine: a summary of evidences. J Neurol Sej 2002 Nov 15;203-204:25962
- Gulyas B, Halklin C, Sovago J, Sandell J, Cselenyi Z, Vas A, Kiss B, Karpati E, Farde L. Drug distribution in man: a positron emission tomography study after oral administration of the labelled neuroprotective drug vinpocetine. Eur J Nucl Med Mol Imaging 2002 Aug;29(8):1031-8
- Hayakawa M.Effect of vinpocetine on red blood cell deformability in stroke patients.Arzneimittelforschung. 1992 Apr;42(4):425-7.
- Hayakawa M. Effect of vinpocetine on red blood cell deformability in vivo measured by a new centrifugation method. Arzneimittelforschung. 1992 Mar;42(3):281-3.
- Bukanova JV, Solntseva EI, Skrebitsky VG. Selective suppression of the slow-inactivating potassium currents by nootropics in molluscan neurons. Int J Neuropsychopharmacol 2002 Sep;5(3):229-237
- Zelles T, Franklin L, Koncz I, Lendvai B, Zsilla G. The nootropic drug vinpocetine inhibits veratridine-induced [Ca<sup>2+</sup>]<sub>i</sub> increase in rat hippocampal CA1 pyramidal cells. Neurochem Res 2001 Sep;26(8-9):1095-100
- van Staveren WC, Markerink-van Ittersum M, Steinbusch HW, de Vente J.The effects of phosphodiesterase inhibition on cyclic GMP and cyclic AMP accumulation in the hippocampus of the rat. Brain Res 2001 Jan 12;888(2):275-286
- Bonocz P, Gulyas B, Adam-Vizi V, Nemes A, Karpati E, Kiss B, Kapas M, Szantay C, Koncz I, Zelles T, Vas A. Role of sodium channel inhibition in neuroprotection: effect of vinpocetine. Brain Res Bull 2000 Oct;53(3):245-54
- Kriegelstein J, Rischke R.Vinpocetine increases the neuroprotective effect of adenosine in vitro. EurJ Pharmacol 1991 Nov 19;205(1):7-10
- Olpe H., et al. Locus coeruleus as a target for psychogeriatric agents. Ann. N.Y. Acad. Sci.1985. Vol.4444.p.399-405.
- Jacobs B.L., Fomal C.A.: Activity of serotonergic neurons in behaving animals / N. J. Neuropsychopharmacol. - 1999 - Vol.21(Suppl2) - p.9S15S.
- Matsukawa M., Ogawa M., Nakadate K., et al.: Serotonin and acetylcholine are crucial to maintain hippocampal synapses and memory acquisition in rats / Neurosci. Lett. - 1997 - Vol.230(1) - p.13-16.
- Paulo T., Toth P.T., Thinguyen TT., et al.. (3H)Noradrenaline-releasing action of vinpocetine in the isolated main pulmonary artery of the rabbit / J. Pharm. Pharmacol. - 1986 - Vol.38 - .668-673.
- Pepeu G.; Spignoli G.: Nootropic drugs and brain cholinergic mechanisms / Progr. Neuropsychopharm. Biol. Psychiatry - 1989Vol.13(Suppl.) - --77-88.
- Shibuya T., Sato K.: Effects of vinpocetine on experimental brain ischemia, histochemical study of brain monoamines / Igaki No Ayumi - 1986 - Vol.139(3) - --217-219.
- Stancampiano R., et al.: Serotonin and acetylcholine release response in the rat hippocampus during a spatial memory task / Neuroscience - 1999 - Vo1.89(4) - p.135-143.

**Memory**  
Concentration  
Eyesight Hearing  
Attention

New Ingredient for  
improvement of brain functions

**VINCA MINOR EXTRACT**

Improvement of cerebral metabolism

Improvement of production - consumption of ATP

Improvement of cerebral circulation - Supplying neurons with oxygen and glucose

Improvement of neurotransmission

**Vinca Minor**  
Vinca Minor is a perennial plant indigenous to the Southern Europe. It has been scientifically proven that the extract of Vinca Minor supports regular cerebral circulation and improves cerebral metabolism. In Europe, this plant traditionally has been used as tea by elderly people who suffer mental disorders like loss of memory or lack of concentration. Presently Vinca Minor Extract is also used as a dietary supplement in form of capsules, syrup, etc.

**COVEX**  
Covex S.A.  
Avenida 25, Pol. Ind. Sur Colmenar Viejo, 28770 Madrid • Spain  
Tel: +34 91 804 4545 Fax: +34 91 804 3030  
Email: vinpocetin@covex.es - Web: www.covex.com