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Review

Role of vinpocetine in cerebrovascular diseases

Sazal Patyar, Ajay Prakash, Manish Modi, Bikash Medhi

Department of Pharmacology & Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, Chandigarh, India

Correspondence: Bikash Medhi, e-mail: drbikashus@yahoo.com

Abstract:
A cerebrovascular accident, or stroke, is defined as the abrupt onset of a neurological deficit, which can be due to ischemia. Cerebral ischemia is caused by a reduction in blood flow that thereby decreases cerebral metabolism. Chronic cerebral hypoperfusion leads to irreversible brain damage and plays an important role in the development of certain types of dementia. Vinpocetine, chemically known as ethyl apovincaminate, is a vinca alkaloid that exhibits cerebral blood-flow enhancing and neuroprotective effects. Non-clinical and clinical studies have suggested multiple mechanisms responsible for the beneficial neuroprotective effects of vinpocetine. As no significant side effects related to vinpocetine treatment have been reported, it is considered to be safe for long-term use. This vasoactive alkaloid is widely marketed as a supplement for vasodilation and as a nootropic for the improvement of memory. The present review focuses on studies investigating the role of vinpocetine in cerebrovascular diseases.

Key words:
vinpocetine, cerebrovascular, neuroprotection, ischemia, nootropic, positron emission tomography

Abbreviations: Aβ – amyloid β-peptides, AD – Alzheimer's disease, AEDs – antiepileptic drugs, AICVD – asymptomatic ischemic cerebrovascular disorders, ATP – adenosine triphosphate, CGI – Clinical Global Impression, cGMP – cyclic guanosine monophosphate, DOPAC – 3,4-dihydroxyphenylacetic acid, DPG – 2,3-diphosphoglycerate, GABA – γ-aminobutyric acid, LC – locus coeruleus, MMSQ – mini-mental status questionnaire, NMDA – N-methyl-D-aspartic acid, PET – positron emission tomography, PSNHL – progressive sensorineural hearing loss, PTZ – pentylenetetrazole, RBC – red blood cell, rCBF – regional cerebral blood flow, ROS – reactive oxygen species, RR – relative risk, SCAG – Sandoz clinical assessment geriatric scale

Introduction

Cerebrovascular diseases include a group of brain disorders associated with cerebral vascularization. The most common disorders include ischemic stroke, hemorrhagic stroke and cerebrovascular anomalies, such as intracranial aneurysms and arteriovenous malformations. Other disorders of cerebrovascular origin include memory problems, aphasia, apraxia, motor disorders, dizziness, hearing dysfunction (tinnitus and progressive sensorineural hearing loss) and headache. As per a study conducted by the World Health Organization (WHO), cerebrovascular disease is the second leading cause of death worldwide. The study estimated that cerebrovascular disease (stroke) accounted for 9.6% of all deaths. Furthermore, these diseases are the leading cause of disability in adults [82]. Various clinical studies have indicated that the incidence and high mortality of cerebrovascular diseases can be prevented to a large extent. Antiplatelet therapy and carotid endarterectomy are effective for secondary stroke prevention. However, with the exception of aspirin, the medical and surgical therapies used to treat

acute ischemic stroke have very limited efficacy [3]. Thus, there is a pressing demand for the development of newer, safer and more effective drugs.

Vinpocetine is a synthetic ethyl ester of the alkaloid apovincamine, which is isolated from the leaves of *Vinca minor*, commonly known as the lesser periwinkle. The chemical name for vinpocetine is ethyl apovincaminate [35]. Since its synthesis in the late 1960s, vinpocetine has been widely used for the treatment of cerebrovascular disorders, as it has shown cerebral blood-flow enhancing and neuroprotective effects [3]. Vinpocetine has also been marketed as a nootropic agent for the improvement of memory. Other indications for vinpocetine exist in the fields of geriatry, neuropsychiatry, ophthalmology and otolaryngology [19, 53, 72]. In addition, vinpocetine has shown promising results in the treatment of tinnitus and progressive sensorineural hearing loss (PSNHL) [46, 53]. It has been used to alleviate macular degeneration, certain glaucoma-related problems and other vision disorders of vascular origin [26]. Animal studies have demonstrated its effectiveness in preventing gastric mucosal damage [43]. Some studies have reported potential uses for this compound in the treatment of kidney stones, as its application removed tumoral calcinosis in kidney dialysis patients with renal failure [41]. Vinpocetine is also being studied for the treatment of hair loss. However, for the purpose of the current review, we will only focus on the cerebrovascular and neuropsychiatric indications of this compound.

Chemistry

The active drug substance of vinpocetine is (3α,16α)-eburnamenine-14-carboxylic acid ethyl ester (Fig. 1). It is a solid, white powder with a molecular weight of 350.5 g/mol and is soluble in 100% ethanol, dimethyl sulfoxide and acetone [35].

Pharmacology

Mechanism of action

Several different mechanisms have been implicated in the action of vinpocetine. Studies have reported that vinpocetine selectively inhibits voltage-sensitive sodium (Na^+) channels, causing a dose-dependent decrease in evoked extracellular calcium (Ca^{2+}) ions in striatal nerve endings [60]. It has been shown that increases in intracellular Na^+ and Ca^{2+} concentrations are responsible for the cell damage induced by ischemia/reperfusion and the development of other acute dysfunctions, including acidosis, cytotoxic edema and glutamate excitotoxicity. Thus, the Na^+ channel-inhibiting properties of vinpocetine are thought to be responsible for its neuroprotective and anticonvulsant activities [1]. A recent study has revealed that the neuroprotective action of vinpocetine involves additional drug targets along with the neuronal peripheral-type benzodiazepine receptors (PBRs) involved in the mitochondrial transition pore complex [74]. Another mechanism responsible for the neuroprotection exhibited by vinpocetine is its marked antioxidant activity due to the scavenging of hydroxyl radicals [65]. Vinpocetine selectively inhibits Ca^{2+}-calmodulin-dependent cGMP-phosphodiesterase, thereby enhancing intracellular cGMP levels in the vascular smooth muscle leading to reduced resistance in cerebral vessels and an increase of cerebral blood flow. This property is also responsible for neuroprotection [17, 20, 78]. Recent studies have shown that vinpocetine has potent anti-inflammatory actions that are caused by a direct inhibition of the IκB kinase complex (IKK) rather than phosphodiesterase blockade. This finding indicates that the anti-inflammatory action of vinpocetine can be exploited for the treatment of cerebrovascular diseases because chronic inflammation results in endothelial dysfunction and atherosclerosis, which further enhance the risk of stroke. The anti-inflammatory role of vinpocetine, in addition to its cognitive improvement properties, makes it a potential candidate

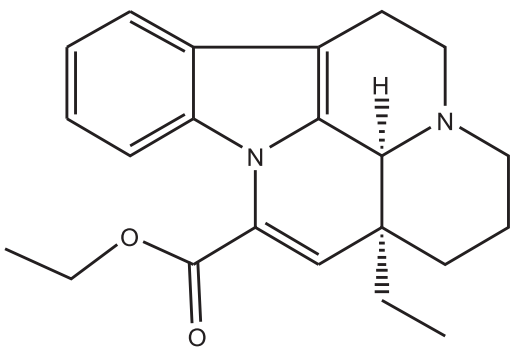

Fig. 1. Chemical structure of vinpocetine ($C_{22}H_{26}N_2O_2$)