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Updates of Recent Vinpocetine Research in Treating Cardiovascular Diseases

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Abstract

Vinpocetine is a derivative of vincamine. It has been used to prevent and treat cerebrovascular disorders such as stoke and dementia, and remains widely available in dietary supplements that often marketed as nootropics. Due to its excellent safety profile at therapeutic dose regimen, vinpocetine has raised research interest in its new applications in various experimental disease models. Here we review recent studies that uncovered novel functions of vinpocetine in cardiovascular diseases, including atherosclerosis, obesity, neointimal hyperplasia, vasoconstriction, pathological cardiac remodeling and ischemia stroke. Molecular mechanisms underlined the protective effects of vinpocetine are also discussed. These novel findings may suggest a broadened usage of vinpocetine against relevant cardiovascular diseases in human.

Keywords

Vinpocetine; Vascular disease; Cardiac remodeling; Stroke; Inflammation

Introduction

Vinpocetine was originally discovered and marketed under the trade name Cavinton around 1978. Vinpocetine is a synthetic derivative of the vincamine molecule which is an alkaloid extracted from the periwinkle plant, *Vinca minor* [1]. It has been clinically used in many Asian and Europe countries for preventing and treating neurological disorders, including stroke, senile dementia and memory disturbances. In the United States, it is commonly sold as a dietary supplement for the general population as a memory enhancer. The therapeutic dosage regimen may range from 5–10 mg orally, 3 times a day, due to a short half-life (1 to 2 hours) [2,3]. According to human studies, vinpocetine is readily absorbed from gastrointestinal tract [4] and has good blood–brain barrier penetration profile [5]. The peak plasma levels are reached at about one hour after oral administration [2,6]. The distribution volume is 3.2 ± 0.9 L/kg which reflects high distribution of the drug binding in tissue [3].

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Vinpocetine is rapidly and extensively metabolized mainly to its deesterified derivative, apovincaminic acid and other minor metabolites. The total plasma clearance of vinpocetine is 0.88 ± 0.20 L/hour per kg [4]. Vinpocetine showed linear pharmacokinetics at the therapeutic dose suggesting no drug accumulation [2]. To date, there have been no reports of significant side effects, toxicity, or contraindications at therapeutic doses of vinpocetine, therefore it is an interesting compound to explore novel therapeutic applications. This review summarizes the recent progress of vinpocetine research in treating cardiovascular diseases.

Molecular Targets of Vinpocetine

Vinpocetine has several cellular targets, including Ca^{2+}/calmodulin-stimulated cyclic nucleotide phosphodiesterase 1 (PDE1) [7–9], voltage-dependent Na^+ channel [10–14] and IκB kinase (IKK) [15]. PDEs are a superfamily of phosphohydrolases that catalyze the degradation of cAMP and cGMP. To date, there are over 60 PDE isoenzymes derived from 21 genes. The gene products are grouped into eleven broad families, PDE1–PDE11, based on their distinct kinetic properties, regulatory mechanisms and sensitivity to selective inhibitors [16]. *In vitro*, PDE1 catalytic activity can be stimulated by calcium and calmodulin to increase basal activity up to 10-fold or more [17]. This unique property allows PDE1 members to mediate the crosstalk between Ca^{2+} and cyclic nucleotide signaling [18]. PDE1 members are encoded by three distinct genes, PDE1A, 1B, and 1C. Different PDE1 isozymes differ in their regulatory properties, substrate affinity, tissue/cell distribution and Ca^{2+} sensitivity [16]. *In vitro*, PDE1A and PDE1B isoenzymes hydrolyze cGMP (PDE1A Km: ~5uM; PDE1B Km: ~3uM) with much higher affinities than cAMP (PDE1A Km: ~112uM; PDE1B Km: ~24uM), whereas PDE1C isoenzymes hydrolyze both cAMP and cGMP with equally high affinity (Km for cAMP: ~1uM; Km for cGMP: ~1uM) [19]. Vinpocetine inhibited PDE1A and PDE1B isozymes with similar potencies (IC_{50} ≈ 8–20 μM), which are about 3-fold higher than that for PDE1C isozymes (IC_{50} ≈ 40–50 μM) [7–9]. Vinpocetine has been widely used as a PDE1 inhibitor in researches [20–24]. Inhibition of PDE1 by vinpocetine have been implicated in the protective mechanism against pathological vascular and heart remodeling [25–29].

Vinpocetine inhibits voltage-dependent Na^+ channel. Previous studies using patch clamp approaches show that vinpocetine blocked voltage-gated Na^+ channels and decrease Na^+ currents at IC_{50} values 10–50 μM in rat cortical neurons [13,14] and isolated cortical nerve terminals [10–12]. Under anoxia there are excess Na^+ entry into neurons, which may trigger neuronal injury and death [30]. Many voltage-dependent Na^+ channels blockers have shown neuroprotective effects in experimental ischemia models, such as tetrodotoxin and anticonvulsants [31]. Therefore, antagonizing Na^+ load likely is involved in the neuroprotective mechanism of vinpocetine.

Vinpocetine has been shown to be an IKK inhibitor, and thus suppressing NF-κB-dependent inflammation [15]. The IC_{50} value of vinpocetine on IKK inhibition is around at 17.17 μM [15], which is similar to the affinities of vinpocetine on other targets. In response to external inflammatory stimuli, a set of intracellular IKK complex is activated. The activated IKK complex phosphorylates IκBα, leading to its ubiquitination and degradation. NF-κB is liberated due to IκB degradation and then enters the nucleus to activate the transcription of

inflammatory molecules. Therefore, IKK is an important mediator of the inflammatory signaling pathway. There are other IKK inhibitors that are effective to treat diseases with enhanced or inappropriate activation of NF-κB, such as arthritis, intestinal inflammation diseases and cancer, in preclinical animal studies and clinical trials, suggesting IKK inhibition as a promising therapy approach [32,33]. The anti-inflammation action of vinpocetine has been reported in various cell types, including endothelial cells [15], vascular smooth muscle cells [15], monocyte/macrophages [15], neutrophils [34], epithelial cells [35], brain microglial cells [36], astrocytes [37] and dendritic cells [38]. The anti-inflammation effect of vinpocetine is also demonstrated in experimental animal models *in vivo*, such as lipopolysaccharide (LPS) or TNF-α induced lung inflammation [15], LPS induced inflammatory pain [34] and S. pneumoniae caused otitis media [39]. Summary of the pharmacokinetic parameters and IC_{50} of vinpocetine are listed in Table 1.

Role of Vinpocetine in Vascular Diseases

Atherosclerosis

Vinpocetine has been reported to exhibit inhibitory effects on the animal models of atherosclerosis, which is likely mediated by multiple cellular and molecular mechanisms [27,28,40,41]. Vinpocetine has been shown to regulate lipid accumulation in macrophage [28], adipogenesis and lipolysis in fat cells [41], osteoblastic differentiation of vascular smooth muscle cells (SMC) [40] and macrophage inflammation [27], all of which are implicated in the development of atherosclerosis. In a high-fat diet induced atherosclerosis model in ApoE knockout mice, vinpocetine treatment significantly reduced atherosclerotic lesion in aorta [28]. This was accompanied with decreased oxidized low density lipoprotein (ox-LDL) uptake in macrophages *in vitro* and reduced expression of ox-LDL receptor 1 (LOX-1) in macrophages of atherosclerotic lesions [28]. Vinpocetine has also been reported to regulate adipogenesis and hyperlipidemia. Using 3T3-L1 cells differentiation as an adipogenesis cell model, vinpocetine treatment inhibited expression of adipogenesis master regulators, including PPARγ, C/EBPα, C/EBPβ, and reduced the phosphorylation of adipogenesis-associated signaling pathways, such as AKT, ERK, and JAK2-STAT3. Prompted expression of thermogenic UCP1 by vinpocetine suggest the induction of lipolysis pathway. *In vivo*, vinpocetine-treated mice had reduced white adipose tissue size and decreased adipogenesis-associated gene expression [41]. Vinpocetine also improved hyperlipidemia with lower serum level of triacylglycerol and improved glucose homeostasis [41]. Mechanistic study shows that vinpocetine increased cAMP level in adipocyte culture, which might suggest a PDE1 inhibition related mechanism against adipogenesis [41]. Vinpocetine might also play a role in suppression of vascular calcification. Early studies have reported an inhibitory effect of vinpocetine in calcium deposition in central nervous system, liver, kidneys of rabbits with atherosclerosis induced by a cholesterol-rich diet. Vinpocetine treated rabbits showed less atherosclerotic lesion and reduced serum peroxide lipid concentration [42,43]. A more recent study elaborates in more detail about inhibitory effect of vinpocetine in osteoblastic differentiation of vascular SMC. In a beta-glycerophosphate induced cell model, vinpocetine significantly reduced the osteoblast-like phenotypes including alkaline phosphatase activity, osteocalcin, collagen type I, Runx2 and BMP-2 expression as well as the formation of mineralized nodule [40]. Besides the above-

mentioned actions by vinpocetine, the anti-inflammatory role of vinpocetine in atherosclerosis has also been evaluated in the animal model of atherosclerosis. In ApoE knockout mice fed with high cholesterol diet, vinpocetine markedly decreased atherosclerotic lesion area and stabilized plaque in aortic sinus which was associated with enhanced collagen content, thickened fibrous cap and decreased TNF-α expression [27]. *In vitro*, vinpocetine reduced monocyte adhesion to ox-LDL stimulated endothelium. ox-LDL-induced oxidative stress and proinflammatory cytokines, such as TNF-α, IL-6 in macrophages were also inhibited by vinpocetine treatment [27]. In line with previous report [15], vinpocetine antagonized ox-LDL induced inflammation in macrophage via inhibition of IκBα phosphorylation and NF-κB activity [27].

Thrombosis

Vinpocetine has been suggested for a role against platelet aggregation. In a human study, patients who had atherosclerosis and symptoms of chronic ischemic coronary heart disease and cerebrovascular disorders were administrated with single dose of vinpocetine [44]. Blood was collected immediately before and 3 hours after the dose for platelet aggregation test using aggregator ADP, adrenaline, collagen individually or in combination [44]. It was shown that vinpocetine reduced platelet aggregability in response to single aggregator, but not combination of aggregators, suggesting the complexity of anti-thrombosis effect *in vivo* [44]. In a mouse model of carotid artery ligation injury *in vivo*, it was shown that vinpocetine treatment reduced thrombosis occurrence and intra-plaque hemorrhage [25]. It is yet unknown whether vinpocetine plays a role in thrombosis resolution in stroke.

Injury-induced neointima hyperplasia

Vinpocetine has been demonstrated to suppresses pathological vascular remodeling by inhibiting vascular SMC proliferation and migration. In the study by Cai et al., vinpocetine reduced neointimal formation induced by carotid artery ligation injury and decreased spontaneous human saphenous vein remodeling *ex vivo*, which both were associated with decreased vascular SMC proliferation [25]. In cultured SMC, vinpocetine suppressed G1/S transition, decreased cyclin D1 expression and increased $p27^{Kip1}$ level [25]. Vinpocetine also inhibited platelet-derived growth factor (PDGF)-stimulated SMC migration and ECM synthesis, such as type I collagen and fibronectin [25]. Mechanistic studies further showed that vinpocetine suppressed PDGF-BB-induced reactive oxidative stress (ROS) production in SMC, which largely mediated the inhibitory effects of vinpocetine on ERK1/2 activation and SMC growth [25]. Vinpocetine has also been reported to inhibit hyperglycemia-facilitated neointimal hyperplasia induced by carotid artery balloon injury in diabetic rats [26]. *In vitro*, high glucose induced vascular SMC proliferation, migration, ROS generation and apoptotic resistance were ameliorated by vinpocetine treatment, which were associated with decreased phosphorylation of AKT and JNK1/2, as well as reduced expression of cyclin D1 and Bcl-2 [26]. The inhibitory effects of vinpocetine on SMC growth and vascular remodeling is consistent with loss of function of PDE1A or PDE1C. PDE1C was highly induced in synthetic SMC culture and SMC-like cells in rodent and human disease vessels, but not in contractile SMC freshly isolated from vessel media layers [45,46]. Using PDE1C knockout mice or specific PDE1 inhibitor IC86340 attenuated neointimal hyperplasia induced by carotid artery ligation injury *in vivo* and vascular remodeling of human

saphenous vein explants *ex vivo* [46]. *In vitro*, PDE1C deficiency by knockout or shRNA antagonize SMC proliferation and migration, inhibited ERK1/2 and AKT activation, and negatively regulated the stability of growth factor receptors, such as PDGF-receptor-beta known to be important in pathological vascular remodeling [46,47]. PDE1A has also been reported to regulate SMC growth and survival. In the study by Nagel et al., nuclear PDE1A was found to be associated with SMC "synthetic" phenotype. In subcultured SMC, reducing PDE1A function using shRNA or IC86340 significantly attenuated SMC growth via G1 arrest and induced apoptosis, leading to intracellular cGMP elevation, $p27^{Kip1}$ upregulation, cyclin D1 downregulation, and p53 activation [48]. PDE1A was also reported for regulation of SMC growth by promoting nuclear β-catenin protein stability via GSK3β–β-catenin/T-cell factor signaling [49]. It is unknown whether the inhibitory effect of vinpocetine on ROS production in SMC is PDE1 dependent [25].

Vascular relaxation

Vinpocetine has been demonstrated a vasorelaxation effect. Nitroglycerin (NTG), as a treatment of angina pectoris, has potent vasodilation effect by releasing NO, which activates soluble guanylyl cyclase, produce cGMP and relax smooth muscle cell. It was shown that PDE1 activity and PDE1A expression was upregulated in NTG tolerant rat aorta which was associated with decreased cGMP and reduced vasorelaxation after chronic NTG stimuli [20]. Vinpocetine treatment enhanced the decreased cGMP by chronic NTG and partially restored vasorelaxation to subsequent NTG exposure [20]. In cultured rat aortic SMC, Angiotensin II (Ang II) increased PDE1A1 activity and vinpocetine blocked the inhibitory effect of Ang II on ANP induced cGMP accumulation [20]. Therefore, induction of PDE1A in SMC may be one mechanism by which NO/cGMP-mediated vasodilation was tolerant, and vasorelaxation effect of vinpocetine may be mediated through inhibition of PDE1A activity. Vinpocetine also enhanced pulmonary vasodilation and transpulmonary cGMP induced by NO inhalation in lambs in an acute pulmonary hypertension model, likely through PDE1 inhibition [50]. This effect has been demonstrated in other species, such as pulmonary artery of piglet [51], aorta and small mesenteric artery of hypertensive rat [52], and AngII induced elevation of systolic blood pressure in mouse [29]. Consistently, other selective PDE1 inhibitors such as IC86340 or Lu AF41228/Lu AF58027 have been found to induce vasodilation or lower blood pressure in rodents [53,54]. Also, it is reported that PDE1A activity null mice had lower aortic blood pressure which further supports the role of PDE1A in blood pressure regulation [55]. Taken together, these observations indicate that the effect of vinpocetine on vascular relaxation is likely mediated by PDE1A inhibition.

Role of Vinpocetine in Cardiac Diseases

A recent study revealed a cardioprotective effect of vinpocetine in a rat myocardial infarction (MI) model induced by acute treatment with isoproterenol (ISO) [56]. ISO treatment in rats caused cardiomyopathy reflected by increased serum markers of MI (such as serum creatine kinase-MB, lactate dehydrogenase, glutamic oxaloacetic transaminase, and Troponin-T) as well as histopathological features of MI (such as myocardial necrosis, edema, infiltration of macrophages and lymphocytes). Vinpocetine pretreatment significantly restored these changes by ISO [56]. The cardiac damage induced by ISO

appeared to involve ROS and vinpocetine treatment increased the activity of a number of antioxidant enzymes [56]. Another study by Wu et al. also showed a protective effect of vinpocetine against pathological cardiac remodeling in a chronic mouse model [29]. It was shown that chronic Angiotensin II (Ang II) infusion induced cardiac hypertrophy and cardiac fibrosis, which were markedly attenuated by systemic administration of vinpocetine *in vivo*. Furthermore, in isolated adult mouse cardiomyocytes (CMs), vinpocetine suppressed Ang II-stimulated CM hypertrophic growth. In cultured cardiac fibroblasts (CFs), vinpocetine suppressed TGFβ-induced fibroblast activation and matrix gene expression, such as smooth muscle alpha-actin, type I collagen and fibronectin [29].

The effects of vinpocetine on CM hypertrophy and CF activation are very likely mediated through targeting PDE1. PDE1 selective inhibitor IC86340 exhibit similar protective effect as vinpocetine against cardiac hypertrophy [53] and fibrosis [57] induced by chronic ISO infusion. Both PDE1A and PDE1C have been reported in mouse CMs [53,58]. PDE1A expression is upregulated in the ventricular myocardium of diseased heart induced by ISO infusion, Ang II infusion, transverse aortic constriction (TAC), as well as in isolated CMs stimulated by ISO or Ang II *in vitro* [53]. Blocking PDE1A function with PDE1A selective shRNA inhibited phenylephrine (PE)-mediated hypertrophy and hypertrophic gene expression in neonatal rat CMs [53]. PDE1C expression was also up-regulated in mouse and human failing hearts, and was predominantly expressed in CMs [59]. PDE1C knockout ameliorated TAC-induced myocardial hypertrophy, cardiac fibrosis, and contractile dysfunction. PDE1C deficiency also attenuated isolated CM hypertrophic growth stimulated with Ang II or ISO *in vitro* [59]. In CFs, PDE1A and PDE1C are different -PDE1A but not PDE1C is expressed in CFs [57,58]. PDE1A expression is induced in activated CFs (myofibroblasts) stimulated by Ang II and TGF-β *in vitro* as well as within fibrotic scar regions of mouse, rat, and human diseased hearts [57]. Inhibition of PDE1A function via PDE1A shRNA or PDE1 inhibitor IC86340 significantly reduced Ang II or TGF-β-induced CF activation, ECM synthesis, and profibrotic gene expression *in vitro* [57]. The facts that PDE1C is important in cardiac fibrosis but PDE1C is not expressed in CFs suggest a critical role of PDE1C in the crosstalk of CMs and CFs. Indeed, it has been shown that the conditioned medium from PDE1C deficient CMs significantly reduced TGF- β stimulated CF activation compared to the conditioned medium from wild-type CMs [58]. Together these studies support a critical role for PDE1 in cardiac hypertrophy and fibrosis. The findings that IC86340 together with different doses of vinpocetine exhibited no additional effect in CM hypertrophy and CF activation [29], suggesting that IC86340 and vinpocetine act on the same molecular target, perhaps PDE1, in CMs and CFs.

Role of Vinpocetine in Ischemic Stroke

Vinpocetine has been long used to treat cerebrovascular disorders including ischemic stroke. Ischemic stroke is often caused by reduced cerebral blood flow due to a blood clot blocking an artery of brain. Many reports have suggested a protective effect of vinpocetine against brain injury associated with ischemia. In animal models of cerebral ischemia, vinpocetine reduced hypoxia-induced lethality [60], hippocampal neuron damage [37,61–65], infarct size [66] and motor behavior restoration [63]. In clinical studies, vinpocetine treatment in ischemic stroke patients was associated with increased cerebral blood flow, improved

glucose uptake and parenchymal oxygen utilization [67,68], better recovery of neurological function, smaller growth of infarct lesions volume, and improved cognitive skill during the acute phase and several months follow-up [69–72].

Inflammation response is an important element contributing to the pathogenesis of stroke [36,37,64,72]. An anti-inflammatory effect of vinpocetine in ischemic stroke has been recently investigated in human. For example, the clinical trial by Zhang et al., show that in isolated peripheral blood mononuclear cells of acute ischemic stroke patients with vinpocetine treatment, there was increased IκBα mRNA as well as reduced IκBα phosphorylation and degradation [72]. These effects were associated with decreased activation of microglial cells (macrophages in the brain) within peri-infarct region and reduced inflammatory cytokines in plasma [72]. In cell models induced by inflammatory or oxygen-glucose deprivation stimuli, vinpocetine was reported to suppress inflammation in various brain cell types, such as plasmacytoid dendritic cells [38], astrocytes [37], microglial cells [36]. Conditioned microglial medium by vinpocetine also exerted protection against primary neuron death [36]. In cerebral ischemia animals, it was also shown that vinpocetine treatment attenuated NF-κB level and nucleus translocation and inflammatory molecules in brain [36,37,64]. Besides inflammation, vinpocetine also have important roles against ROS and cell apoptosis in astrocytes, neurons and glial cells [37,73].

Conclusions

Preclinical and clinical studies have suggested multiple functions of vinpocetine, including vasodilation, anti-oxidation, anti-inflammation, anti-remodeling in vessel and heart, and anti-lipid uptake, through multiple pharmacological targets to exert synergistic therapeutic benefits. Summary of the reported findings are listed in Table 2. Cardiovascular diseases are complex processed, involving in a variety of cell types and inter-cellular communications. The multiple actions of vinpocetine in different cell types may permit synergistic beneficial effects. For example, vinpocetine may hamper atherosclerosis progression by antagonizing lipid uptake, hyperlipidemia, oxidative stress and inflammation synergistically due to its multi-action mechanisms. There are still some limitations remained in previous studies. The molecular mechanisms responsible for some novel functions of vinpocetine were not fully understood mechanistically, e.g. anti-oxidation and anti-lipid accumulation. Specific genetic and pharmacological approaches in cell models, as well as gene knockout mice/transgenic mice of PDE1 isoforms, IKK, Na+ channels might facilitate a precise understanding of some of the mechanisms. Also, to reposition vinpocetine for its novel functions against cardiovascular diseases, the findings from animal studies need to be further validated for effectiveness in clinical human studies.

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Table 1:

Pharmacokinetic parameters and IC_{50} of vinpocetine.

Volume of distribution	3.2 ± 0.9 L/kg	Intravenous single bolus injection of 10mg in young healthy human subjects	[3,4]
Total plasma clearance	0.88 ± 0.20 L/hour/kg		
Elimination half-life ($t_{1/2}$)	1–2 hours	Intravenous single bolus injection of 10mg in young healthy human subjects	[3]
		3X5 and 3X10 mg tablet daily doses for seven days in young healthy human subjects	[2]
IC_{50}	PDE1A, PDE1B	8–20 uM	[7–9]
	PDE1C	40–50 uM	[7,8]
	Voltage-gated Na^+ channel	10–50 uM	[10–14]
	IKK	17.17 uM	[15]

Table 2:

Vinpocetine is a multi-action drug regulates multiple pathophysiological events implicated in cardiovascular disease.

Regulated pathophysiology	Disease	Reference
Lipid uptake in macrophage	Atherosclerosis	[27, 28, 40]
Osteoblastic differentiation of smooth muscle cell		
Adipogenesis, hyperlipidemia	Obesity	[41]
Platelet aggregation	Thrombosis	[44] [25]
Smooth muscle cell growth and migration	Injury induced neointimal hyperplasia and atherosclerosis	[25, 26]
Vasoconstriction	Tolerance of vasorelaxation treatment	[20, 50–52, 54]
Cardiomyocyte hypertrophic growth	Pathological cardiac remodeling	[29, 56]
Cardiac fibroblast activation		
Neuron injury and death, inflammation, thrombosis	Ischemia stroke	[10–14]
Inflammation	Multiple cardiovascular diseases	[15, 34, 36–38, 72]
Oxidative stress	Multiple cardiovascular diseases	[25, 37, 56]

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