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An update on Vinpocetine: New discoveries and clinical implications

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Abstract

Vinpocetine, a derivative of the alkaloid vincamine, has been clinically used in many countries for treatment of cerebrovascular disorders such as stroke and dementia for more than 30 years. Currently, vinpocetine is also available in the market as a dietary supplement to enhance cognition and memory. Due to its excellent safety profile, increasing efforts have been put into exploring the novel therapeutic effects and mechanism of actions of vinpocetine in various cell types and disease models. Recent studies have revealed a number of novel functions of vinpocetine, including anti-inflammation, antagonizing injury-induced vascular remodeling and high-fat-diet-induced atherosclerosis, as well as attenuating pathological cardiac remodeling. These novel findings may facilitate the repositioning of vinpocetine for preventing or treating relevant disorders in humans.

Keywords

1. Introduction

Vinpocetine (14-ethoxycarbonyl-(3a,16a-ethyl)-14,15-eburnamine) is a synthetic derivative of vinca alkaloid vincamine that is an alkaloid extracted from the periwinkle plant, *Vinca minor* (Fig. 1). Vinpocetine can pass the blood-brain barrier and enter the brain after oral or intravenous administration (Gulyas et al., 2002a, Gulyas et al., 2002b). The chemical structure, pharmacokinetics, metabolism, and distribution have been previously reviewed in detail (Bonoczk et al., 2000). Vinpocetine, trade name as Cavinton, was originally developed and marketed in Hungary around 1978. Vinpocetine has been clinically used in many Asian and European countries for the prevention and treatment of stroke, senile dementia, and

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memory disturbances. In addition, numerous brands of vinpocetine-containing memory pills or products are currently also available worldwide as dietary supplements (https://naturalmedicines.therapeuticresearch.com). No significant side effects and toxicity have been reported for vinpocetine at therapeutic doses and it is generally thought to be safe for long-term use. Vinpocetine has thus attracted considerable attention from academic and scientific community as well as pharmaceutical industries to characterize its novel therapeutic functions, mechanism of actions, and pharmacological targets. This review will summarize and update the recent progress in vinpocetine researches.

2. Pharmacological targets of vinpocetine

Vinpocetine has a number of different cellular targets (Bonoczk et al., 2000, Patyar et al., 2011) (Table 1). Cyclic nucleotide phosphodiesterase 1 (PDE1) is among the first pharmacological target reported for vinpocetine (Ahn et al., 1989, Chiu et al., 1988, Hagiwara et al., 1984, Souness et al., 1989). PDEs are a superfamily of enzymes that catalyze the degradation of cAMP and/or cGMP, which are grouped into eleven broad families, PDE1–PDE11, based on their distinct kinetic properties, regulatory mechanisms and sensitivity to selective inhibitors (Bender and Beavo, 2006). PDE1 family members are encoded by three distinct genes, *PDE1A*, *PDE1B* and *PDE1C* with multiple N-terminal and/or C-terminal splice variants (Chan and Yan, 2011). PDE1 catalytic activity can be stimulated by calcium in the presence of calmodulin, which is the reason that PDE1 is also referred to as Ca^{2+}/calmodulin-stimulated PDE. Ca^{2+}-dependent activation of PDE1 isozymes play critical roles in the crosstalk between Ca^{2+} and cyclic nucleotide signaling (Yan et al., 2003). Individual PDE1 isozymes differ in their substrate affinity, Ca^{2+} sensitivity and tissue/cell distribution. *In vitro*, PDE1A and PDE1B show much higher substrate affinities for cGMP than cAMP, while PDE1C is equally sensitive for both cGMP and cAMP (Chan and Yan, 2011). Vinpocetine have distinct inhibitory affinities for different PDE1 isoforms. For instances, vinpocetine inhibits PDE1A or PDE1B at $IC_{50} \approx 8$–20 μM, while PDE1C at $IC_{50} \approx 40$–50 μM (Loughney et al., 1996, Yan et al., 1996, Yu et al., 1997). Thus, vinpocetine has higher affinity for PDE1A/1B than for PDE1C. In addition, vinpocetine may also act as a blocker for voltage-dependent Na^+ channels. For example, previous studies through patch clamp approaches have shown that vinpocetine blocked voltage-dependent Na^+ channels at IC_{50} values 10–50 μM (Molnar and Erdo, 1995, Sitges et al., 2005, Sitges and Nekrassov, 1999, Zhou et al., 2003). More recently, vinpocetine was reported to be an inhibitor of IκB kinase (IKK), with an IC_{50} value around 17 μM (Jeon et al., 2010). IKK plays a critical role in mediating cellular inflammatory responses. In response to external inflammatory stimuli, a set of IKK complex is activated. The activated IKK complex phosphorylates IκBα, leading to its ubiquitination and degradation. IκB is an inhibitor of NF-κB that is a key transcriptional factor responsible for the expression of variety of proinflammatory mediators, including cytokines, chemokines and adhesion molecules. NF-κB is liberated due to IκB degradation and then enters the nucleus to activate the transcription of inflammatory molecules (Rothwarf and Karin, 1999). Thus, IKK-mediated phosphorylation of IκBα is the central point in regulating NF-κB-dependent inflammatory response. Therefore, vinpocetine, by inhibiting IKK activity, acts as a novel potent anti-inflammatory agent (Jeon et al., 2010, Medina, 2010).

3. Vinpocetine and neurological diseases

Vinpocetine has been initially developed for the treatment of neurological diseases associated with cerebrovascular disorders such as stroke and dementia that are often caused by ischemia or other cognitive deficits. A number of studies have reported the protective effects of vinpocetine after ischemic injury of the brain in rodents (Jincai et al., 2014, Rischke and Krieglstein, 1991, Sauer et al., 1988) and humans (Bonoczk et al., 2002, Szilagyi et al., 2005, Szobor and Klein, 1976, Vas and Gulyas, 2005, Vas et al., 2002, Zhang et al., 2016). In addition, vinpocetine appears to be also beneficial for degenerative neuronal disorders such as Parkinson's disease (PD) (Medina, 2011, Sharma and Deshmukh, 2015), Huntington's disease (HD) (Gupta and Sharma, 2014), and Alzheimer's disease (AD) (Heckman et al., 2015, Medina, 2011). In the brain, vinpocetine improves brain blood flow by acting as a cerebral vasodilator (Bonoczk et al., 2000, Bonoczk et al., 2002, Patyar et al., 2011, Szilagyi et al., Vas et al., 2002, Zhang and Yang, 2015); and enhances cerebral metabolism by increasing oxygen and glucose uptake and stimulating neuronal ATP production (Bonoczk et al., 2000, Bonoczk et al., 2002, Patyar et al., 2011, Szilagyi et al., 2005, Zhang and Yang, 2015). In a number of neuronal cells or nerve terminals, vinpocetine has also been shown to function as an antioxidant (Deshmukh et al., 2009, Herrera-Mundo and Sitges, 2013, Horvath et al., 2002, Pereira et al., 2000, Santos et al., 2000, Solanki et al., 2011), and prevent neurotoxic calcium and sodium elevation (Sitges et al., 2005, Sitges and Nekrassov, 1999, Tretter and Adam-Vizi, 1998). It is thus evident that multiple mechanistic actions of vinpocetine through different molecular targets contribute to the neuroprotective effects of vinpocetine. In addition, vinpocetine also elicits protective effects in other ischemia-related conditions, such as retina (Nivison-Smith et al., 2014, Nivison-Smith et al., 2017, Nivison-Smith et al., 2015), liver (Abdel Salam et al., 2007, Zaki and Abdelsalam, 2013), kidney (Fattori et al., 2017), and skin (Xiao-Xiao et al., 2013).

4. Vinpocetine and inflammation

Recently, vinpocetine has been demonstrated as a potent anti-inflammatory agent in a variety of *in vitro* cultured cells such as vascular endothelial cells (ECs) (Jeon et al., 2010), vascular smooth muscle cells (SMCs) (Jeon et al., 2010), monocytes/macrophages (Jeon et al., 2010), neutrophils (Ruiz-Miyazawa et al., 2015), epithelial cells (Jeon et al., 2010, Liu et al., 2014), brain microglial cells (Zhao et al., 2011), and dendritic cells (Feng et al., 2017). Through directly inhibiting IKK activity, vinpocetine attenuates IKK-mediated phosphorylation of IκB and increases the stability of IκB, which leads to binding of IκB with NF-κB and subsequent suppression of NF-κB-dependent inflammatory molecule expression. The effect of vinpocetine on antagonizing NF-κB-dependent transcriptional activity is unlikely mediated by targeting PDE1 or Na$^+$ channels as PDE1-selective inhibitor IC86340 and Na$^+$ channel blocker tetrodotoxin had no effect on NF-κB transcriptional activity (Jeon et al., 2010). The anti-inflammatory effects of vinpocetine have also been revealed in various animal models *in vivo*. In a rat cerebral ischemia-reperfusion injury model, NF-κB and TNFα levels were found to be associated with changes in brain edema and infarct volume. Vinpocetine inhibited NF-κB and TNFα expression and decreased the inflammatory response after cerebral ischemia-reperfusion (Wang et al., 2014a). More importantly, the anti-inflammatory effect of vinpocetine was recently reported a multi-center

study involving 60 patients with anterior cerebral circulation occlusion and onset of stroke (Zhang et al., 2017). Patients treated with vinpocetine not only had a better recovery of neurological function and improved clinical outcomes, but also had reduced NF-κB signaling activation and pro-inflammatory mediator expression. Moreover, vinpocetine is also effective in other animal inflammatory disease models, such as lipopolysaccharide (LPS)-induced inflammatory pain (Ruiz-Miyazawa et al., 2015), LPS-induced lung inflammation (Jeon et al., 2010), mouse otitis media (Lee et al., 2015), and acute kidney injury (Fattori et al., 2017).

5. Vinpocetine and vascular diseases

The vasorelaxing effect of vinpocetine has also been shown in peripheral vessels from different species, which is likely mediated by inhibiting PDE1 that preferentially hydrolyzes cGMP with high affinities (Ahn et al., 1989, Chiu et al., 1988, Giachini et al., 2011, Hagiwara et al., 1984, Souness et al., 1989). It has been previously shown that PDE1A was upregulated in a rat model of nitroglycerin (NTG) tolerance, and vinpocetine partially restored the sensitivity of the tolerant vasculature to subsequent NTG exposure (Kim et al., 2001). PDE1A activation can decrease cGMP levels. Thus, induction of PDE1A in nitrate-tolerant vessels may be one mechanism by which NO/cGMP-mediated vasodilation is desensitized and Ca^{2+}-mediated vasoconstriction is supersensitized. Inhibition of PDE1A activity could be effective to limit nitrate tolerance. Other PDE1-selective inhibitors such as IC86340 (Miller et al., 2009) and Lu AF41228/Lu AF58027 (Laursen et al., 2017) have been reported to cause vasodilation and/or lower blood pressure in rodents. The role of PDE1A in blood pressure regulation has been more specifically confirmed by the recent finding that PDE1A activity null mice had lower aortic blood pressure (Wang et al., 2017). Human genetic studies have revealed the association of *PDE1A* single nucleotide polymorphisms (SNP) with diastolic blood pressure (Bautista Nino et al., 2015, Yan, 2015). Moreover, vinpocetine also augmented the cGMP levels and pulmonary vasodilatory response after NO inhalation in lambs with acute pulmonary hypertension, likely through inhibiting PDE1 (Evgenov et al., 2006). Genome-wide association analysis has identified PDE1A locus associated with idiopathic pulmonary artery hypertension in a Japanese population (Kimura et al., 2017).

In addition to vasodilation, recent studies have also revealed the novel functions of vinpocetine in other chronic vascular diseases associated with vascular structural remodeling. For example, a recent study by Cai et al. indicated that vinpocetine significantly attenuated vessel wall thickening and neointimal formation in mouse carotid arteries after ligation injury, and markedly suppressed spontaneous remodeling of human saphenous vein explants in an *ex vivo* culture model (Cai et al., 2012). A similar study also reported that vinpocetine attenuated balloon injury-induced carotid artery neointimal hyperplasia in diabetic rats (Wang et al., 2014b). In cultured SMCs, vinpocetine inhibited SMC growth through antagonizing reactive oxygen species (ROS) production (Cai et al., 2012, Wang et al., 2014b). The inhibitory effects of vinpocetine on SMC growth and vascular remodeling appear to be in line with the consequences of specific suppression of PDE1A or PDE1C. Genetically knocking down PDE1A expression through specific RNA interference attenuated vascular SMCs growth and promoted SMC death (Nagel et al., 2006). PDE1C

depletion also significantly suppressed SMC growth and migration *in vitro* (Cai et al., 2015). In global PDE1C knockout mice that have normal growth rates, feeding patterns, normal nursing and mating behaviors, neointimal formation induced by carotid ligation injury was suppressed ≈75% compared to wild-type control mice (Cai et al., 2015). However, it remains unknown whether the antioxidant effect of vinpocetine in SMCs is mediated by inhibiting PDE1. Human genetic studies have defined significant associations of *PDE1A* SNP with carotid intima–media thickness (Bautista Nino et al., 2015, Yan, 2015). Interestingly, vinpocetine also reduced vascular thrombosis after vascular injury in mice (Cai et al., 2012), which is consistent with previously reported effect of vinpocetine on antagonizing platelet aggregation (Akopov and Gabrielian, 1992). Furthermore, vinpocetine has been shown to attenuate high-fat diet-induced atherosclerosis in ApoE-deficient mice (Cai et al., 2013, Zhuang et al., 2013), as well as prevent atherosclerosis and calcification in rabbit atherosclerosis models (Yasui et al., 1989, Yasui et al., 1990). Vinpocetine was shown to suppress lipid accumulation in macrophages (Cai et al., 2013) and osteoblastic differentiation of SMCs (Ma et al., 2016), the key events in human vascular atherogenesis. Thus, vinpocetine may represent as a promising drug or supplement for clinical therapy of vascular atherosclerosis and calcification.

6. Vinpocetine and cardiac diseases

Recent study by Wu et al. investigated the roles of vinpocetine in cardiac hypertrophy, fibrosis, and pathological cardiac remodeling *in vitro* and *in vivo* (Wu et al., 2017). It was shown that vinpocetine significantly suppressed mouse myocardial hypertrophy and cardiac fibrosis *in vivo* induced by chronic angiotensin (Ang II)-infusion. Mechanistic studies further showed that vinpocetine directly attenuated mouse adult cardiomyocyte hypertrophic growth and cardiac fibroblast activation *in vitro*, likely in a PDE1-dependent manner. The finding from this study is consistent with previous reports on PDE1A and PDE1C function in cardiac remodeling with specific genetic approaches. For example, PDE1A and 1C have been shown to be up-regulated in animal hypertrophic hearts induced by isoproterenol (ISO)- or Ang II-infusion and/or failing hearts induced by chronic pressure overload or myocardial infarction, as well as in human failing hearts (Knight et al., 2016, Miller et al., 2011, Miller et al., 2009). Specific knockdown of PDE1A reduced cardiomyocyte hypertrophy (Miller et al., 2009), and fibroblast activation and extracellular matrix production (Miller et al., 2011). Similarly, genetic depletion of PDE1C attenuated cardiomyocyte hypertrophy, death, and fibrosis both *in vitro* and *in vivo* (Knight et al., 2016). In addition, vinpocetine also elicited inhibitory effects on sodium currents in cardiomyocytes, which may be protective for the heart (Ver Donck et al., 1993, Wei et al., 1997). However, the role of vinpocetine in cardiomyocyte death remains unknown. Massive cardiomyocyte death is associated with cardiac ischemia/reperfusion injury. Given the anti-apoptotic effects of vinpocetine in various other tissues (Lakics et al., 1995a, Onishchenko et al., 2008, Sonmez et al., 2017) and cell types (Bora et al., 2016, Chen et al., 2007, Erdo et al., 1990, Gabryel et al., 2002, Lakics et al., 1995b, Miyamoto et al., 1989), the protective effects of vinpocetine on cardiomyocyte death and cardiac I/R-injury remain to be investigated. A recent study found that PDE1A is highly expressed in rabbit cardiac

sinoatrial nodal cells and regulates pacemaker function. Therefore, the function of vinpocetine in regulating heart rate deserves to be further investigated.

7. Conclusion and perspective

Evidently, vinpocetine is a multi-action agent with a variety of pharmacological targets. Its multi-actions, including vasodilation, anti-oxidation, anti-inflammation, anti-thrombosis, and anti-remodeling, may act together to elicit synergistic therapeutic effects, thereby providing significant benefits to those multifactorial cerebrovascular and cardiovascular diseases. In addition, vinpocetine is effective for a wide range of pathological conditions. The explanation could be that many diseases share common pathologies that can be improved by vinpocetine, such as antagonizing inflammation in a variety of cell types, protecting different cells from death during ischemia injuries, and stimulating vasodilation to increase blood flow in diverse tissues. It should be noted that recent findings aimed to explore novel functions of vinpocetine are largely dependent on animal models. Clinical studies in humans are necessary to validate the effectiveness of vinpocetine in preventing pathological vascular and cardiac remodeling as well as in various inflammatory diseases. Molecular mechanisms underlying some of pharmacological effects of vinpocetine, including metabolic enhancement, anti-oxidation and anti-thrombosis, still remain unclear and need to be further investigated. Successful development of genetic modified animals including gene knockout mice or transgenic mice of PDE1 isoforms, IKK, and the sodium channels would facilitate the elucidation of more precise mechanistic action of vinpocetine.

Acknowledgments

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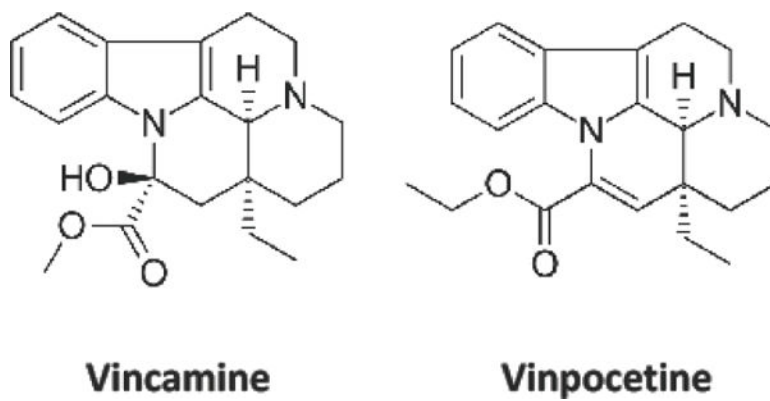
Figure 1. Chemical structures of vincamine and vinpocetine
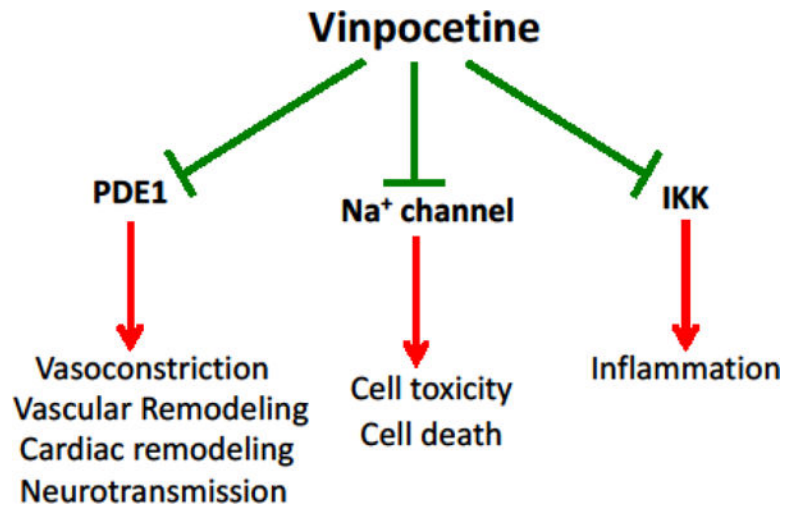The chemical structures are derived from Wikipedia.

Figure 2. Vinpocetine is a multi-action agent with a number of pharmacological targets
Vinpocetine has three major molecule targets including PDE1, voltage-gated Na^+ channel, and IKK. PDE1 has been shown to regulate vasoconstriction, vascular and cardiac structure remodeling, and neurotransmission. The Na^+ channel is involved in cell toxicity and cell death. IKK plays a critical role in mediating cellular inflammatory response.

Table 1

Multiple Molecular Targets of Vinpocetine

Targets	IC$_{50}$ Values	Tissue/Cell Expression
PDE1 isoforms	PDE1A/1B: 8–20 μM	Brain: PDE1A, 1B, &1C; Contractile SMCs:
	PDE1C: 40–50 μM	PDE1A; Proliferating SMCs: PDE1A&1C; Heart: PDE1A%1C; Macrophages: PDE1B
Na$^+$ channel	10–50 μM	Brain, Heart, vessels
IKK	≈ 17 μM	Most cell types