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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.

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, 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 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} ≈ 8–20 μM, while PDE1C at IC_{50} ≈ 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

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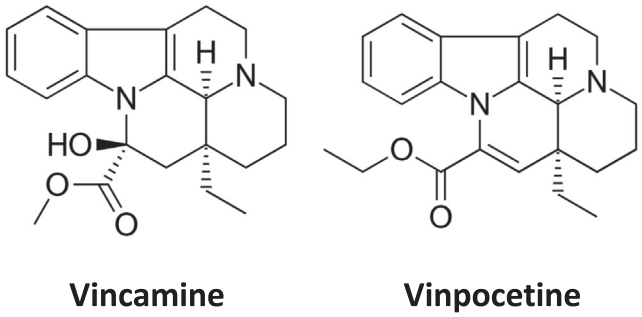

Fig. 1. Chemical structures of vincamine and vinpocetine. The chemical structures are derived from Wikipedia.

Table 1
Multiple molecular targets of vinpocetine.

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

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, 2002; Patyar et al., 2011, Szilagyi et al., 2005; 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, 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, 2017, 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