Chapter

Vinpocetine and Ischemic Stroke

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Abstract

Vinpocetine (VPN) is a synthetic ethyl-ester derivative of the alkaloid apovincamine from *Vinca minor* leaves. VPN is a selective inhibitor of phosphodiesterase type 1 (PDE1) has potential neurological effects through inhibition of voltage gated sodium channel and reduction of neuronal calcium influx. VPN have noteworthy antioxidant, anti-inflammatory and anti-apoptotic effects with inhibitory effect on glial and astrocyte cells during and following ischemic stroke (IS). VPN is effective as an adjuvant therapy in the management of epilepsy; it reduces seizure frequency by 50% in a dose of 2 mg/kg/day. VPN improves psychomotor performances through modulation of brain monoamine pathway mainly on dopamine and serotonin, which play an integral role in attenuation of depressive symptoms. VPN recover cognitive functions and spatial memory through inhibition of hippocampal and cortical PDE-1with augmentation of cAMP/cGMP ratio, enhancement of cholinergic neurotransmission and inhibition of neuronal inflammatory mediators. Therefore, VPN is an effective agent in the management of ischemic stroke and plays an integral role in the prevention and attenuation of post-stroke epilepsy, depression and cognitive deficit through direct cAMP/cGMP-dependent pathway or indirectly through anti-inflammatory and anti-oxidant effects.

Keywords: vinpocetine, phosphodiesterase type 1, antioxidant, anti-inflammatory, stroke, post-stroke

1. Introduction

Vinpocetine (VPN) is a synthetic ethyl-ester derivative of the alkaloid apovincamine from *Vinca minor* leaves which is known as lesser periwinkle. A VPN has a specific chemical structure contains carboxylic acid ethyl ester which is soluble in alcohol, acetone and sulfoxide, **Figure 1** [1].

VPN is widely used in the treatment of different cerebro-vascular disorders, cognitive dysfunction, memory disorders, tinnitus, macular degeneration and glaucoma. In addition, VPN is effective in the management of acute kidney injury, renal stone, hair loss and peptic ulceration [2].

Nevertheless, this critical review only focused on the potential role of VPN in the management of ischemic stroke.

A multiplicity of search strategies was taken and assumed which included electronic database searches of Medline and Pubmed using MeSH terms, keywords and title words during the search. The terms used for these searches were as follows: [Vinpocetine OR apovincamine] AND [cognitive function OR stroke OR brain ischemia OR blood flow OR cerebral circulation OR oxidative stress OR blood

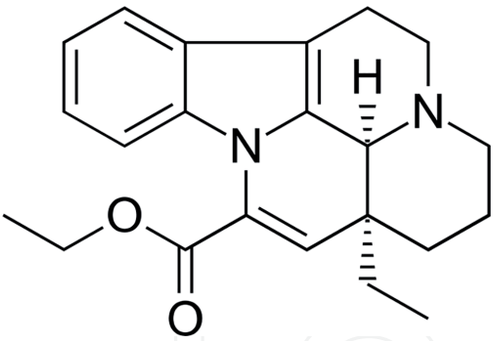

Figure 1.
Chemical structure of Vinpocetine.

viscosity OR cerebral blood flow]. [Vinpocetine OR apovincamine] AND [cerebral metabolism OR cerebral hypoxia OR ischemic degeneration OR minor stroke]. Reference lists of identified and notorious articles were reviewed. In addition, only English articles were considered and case reports were not concerned in the review. The key features of recognized applicable search studies were considered and the conclusions summarized in a critical review.

2. Pharmacology of vinpocetine

VPN is a selective inhibitor of phosphodiesterase type 1 (PDE1) which increasing of cAMP and cGMP leading to vasodilatation. Also, it inhibits the release of pro-inflammatory cytokines through inhibition of IKK/NF-kB activator protein-1 (AP-1) pathway which is involved in the propagation of inflammatory cytokines translocation and release [3]. Moreover, VPN has potential neurological effects through inhibition of voltage gated sodium channel, reduction of neuronal calcium influx and antioxidant effect with augmentation of dopamine metabolism since it increases 3, 4-dihydroxyphenylacetic acid (DOPAC) which is the breakdown metabolites of dopamine [4].

It has been reported that VPN is a safe drug for long-term use and it well tolerated during the management of cerebrovascular disorders. Mild side effects such as headache, flushing, anxiety, dry mouth and nausea have been accounted during VPN uses. In spite of potent non-selective vasodilator effect it does not produce stealing effect on cerebral vasculatures due to the viscosity lowering effect and inhibition of platelet aggregations which together improve cerebral vessels rheological properties. Nevertheless, VPN does not reduce blood pressure and systemic circulation during acute and chronic uses [5].

VPN is well absorbed from small intestine, which increased by food, therefore, fasting bioavailability is 6.7% and non-fasting bioavailability is 60–100%. Similarly, VPN has no significant drug-drug interactions with different drugs such as oxazepam, imipramine, glibenclamide and other agents that are used in the management of ischemic stroke [6].

3. Vinpocetine in ischemic stroke

Ischemic stroke (IS) represents the main leading cause of death in the American Unite State and developed countries and regarded it as the main cause of long-term disability. IS represents 11.9% of annual total death and accounts for 90% of all

stroke cases [7]. Arboix study discussed briefly the risk factor of IS [8]. These risk factors are divided into non-modifiable risk factors (sex, age, inherited factors, ethicinity and low birth weight at birth) and modifiable risk factors (diabetes mellitus, hypertension, smoking, obesity, alcohol abuse, oral contraceptive and metabolic syndrome). [9] IS is mainly caused by arterial thrombosis on the atherosclerotic plaque of cerebral vessels, causing cerebral ischemia, infarction and induction of peri-infarct inflammation. Neuro-inflammations contribute into tissue repair and neuronal damage as well as retrograde and anterograde axonal degenerations [10]. IS leads to glucose and oxygen deprivation of neuronal cells which causing oxidative stress, excitotoxicity and calcium overload which eventually causing neuronal cell death and development of infarction core [11]. The infracted core and damaged neuronal cells due to induced oxidative stress, releasing of various inflammatory molecules that causing vasculitis and damage of blood brain barrier (BBB) [12]. Moreover, activated microglia and infiltrated macrophage during IS release neurotransmitters which are interact with neurons causing neuroinflammation and neuronal injury. As well, interleukin-8(IL-8), NF-kB and tumor necrosis factor (TNF-α) are over-expressed during IS which play a potential role in the initiation of inflammation and apoptosis [13]. In a similar way, vascular smooth muscle and endothelial cells of cerebral vasculature are activated by NF-kB pathway leading to further obstruction and thrombosis. Therefore, NF-kB pathway is an important pathway in the pathogeneses and development of neurological deficit thus; inhibition of NF-kB pathway by VPN is regarded as important and main mechanism of VPN neuroprotection [14].

In addition, activated microglia expresses cholesterol transporter protein (TSPO) which is over-expressed during brain injury and IS and inhibited by VPN [15].

During IS voltage gated sodium channels are activated causing intracellular accumulation of Na and Ca leading to neuronal cell damage, excitotoxicity, edema, acidosis and acute cellular dysfunctions. VPN inhibits voltage gated sodium channels leading to dose dependent reduction of intracellular concentrations of Na and Ca. Thus, the neuroprotective effect of VPN during IS is chiefly mediated by inhibition of neuronal voltage gated sensitive Na-channel [16].

Different studies illustrated that oxidative stress, excitotoxicity and impaired energy metabolism leading to neuronal death by both apoptosis and necrosis during IS. These events lead to reduction of cAMP system which is important in the expression and regulation of brain derived neurotrophic factor (BDNF), which improves neuronal survival. PDE1 is mainly localized in striatum and cortex which participating in the regulation of neuronal motor activity [17, 18].

Indeed, VPN increases neuronal cGMP through inhibition of calmodulin dependent phosphodiesterase which improves cerebral blood flow and oxygen consumption [19]. VPN improves cerebral metabolism through enhancing glucose and oxygen supply and ATP production by cerebral vasodilation. These effects prevent IS induced-memory and cognitive dysfunctions due to improvement of neurotransmitters such as serotonin, dopamine and noradrenaline, which are involved in the regulation of cognitive function [20].

3.1 Antioxidant effects of vinpocetine in ischemic stroke

In IS overproduction of free radicals and reactive oxygen and/or nitrogen species lead to neuro-pathological changes through complex interactions with cellular components such as proteins, DNA and lipids. Free radicals, mainly superoxide and non-radicals such as hydrogen peroxide may cause further neurological injury through depletion of endogenous antioxidant capacity. Therefore, drug with antioxidant potential may play a role in the prevention of cerebral injury during IS [21].

Recent study by Al-Kuraishy et al. reported that VPN is a potent antioxidant agent which improves antioxidant capacity and reduces of oxidative stress [22]. As well, Santos et al., study illustrated that VPN attenuates oxidative stress during IS through inhibition of lipid peroxidation and generation of free radical [23]. In addition, VPN has a potential neuroprotective effect, though antioxidant effect since it prevents oxidative stress injury and toxic demyelination in rat brain [24]. The antioxidant neuroprotective effect of VPN is mainly at low-moderate doses since; high doses of VPN lead to oxidative stress due to prooxidant and proinflammatory effects [25]. Deshmukh et al. reported that antioxidant potential of VPN contributes into the prevention of IS induced-neuronal injury through modulation of cholinergic neurons [26]. Therefore, antioxidant mechanisms of VPN are related to direct free radical scavenging effect, potentiating of endogenous antioxidant capacity and inhibition the generation of free radicals. The molecular antioxidant effect of VPN is linked to the suppression of ADP stimulated respiration, mitochondrial Na+/Ca+ exchange, mitochondrial swelling and regulation of mitochondrial membrane potentials [16, 27].

3.2 Anti-inflammatory effects of vinpocetine in ischemic stroke

IS induced-inflammatory changes and neuroinflammations lead to secondary brain damage. Toll-like receptors (TLRs) are over-expressed in IS, leading to the induction the release of pro-inflammatory mediators through myeloid differentiation factor-88 (MyD88) dependent pathway and Toll /IL-IR domain-containing adaptor factor protein inducing interferon-beta (TRIF) dependent pathway [28]. Therefore, inhibition of TLR4/MyD88 and NF-$_K$B pathways lead to noteworthy neuroprotection against IS. It has been noted that VPN inhibits TNF-α induced NF-$_K$B activation, pro-inflammatory releases and inflammatory biomarkers such as

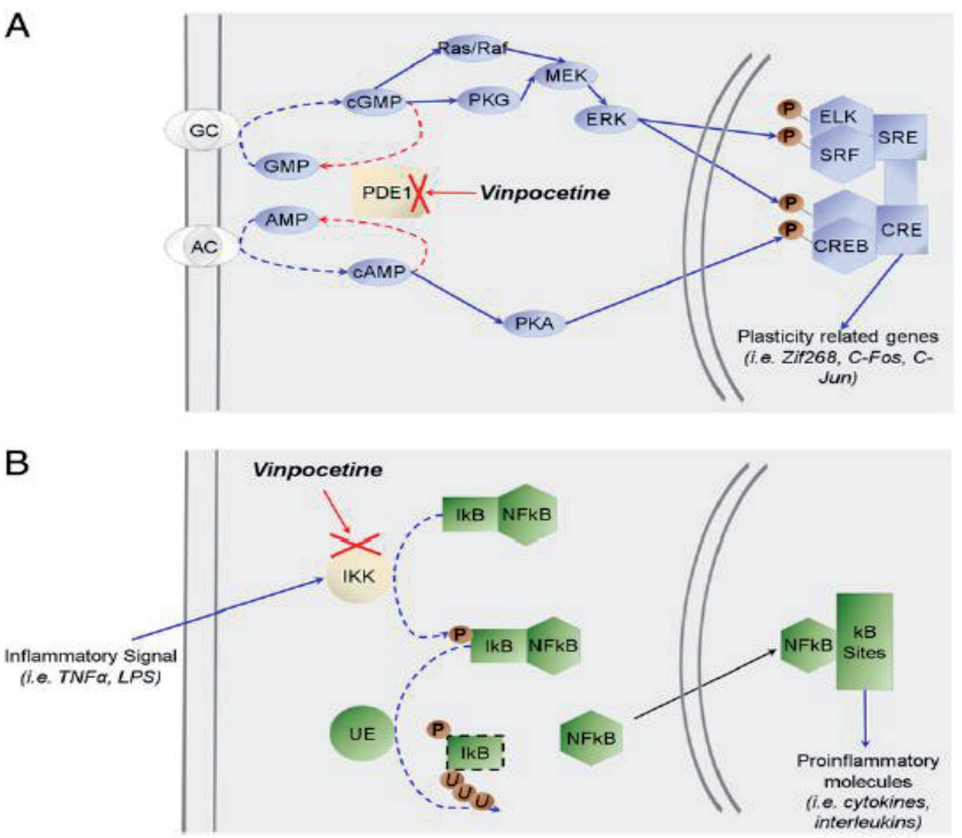

Figure 2.
Anti-inflammator effects of vinpocetine. (A) Basic effect, (B) Anti-inflammatory effect.

IL-1β and IL-33 in an experimental ischemic model [5]. In intriguing way, Zhang and Yang reported that VPN inhibits the release of chemokines and inflammatory cytokines from microglia, macrophage and endothelial cells in IS through inhibition of NF-$_K$B pathways in IS and associated atherosclerosis [29]. In a similar way, VNP leads to the significant neuroprotective effect and regulation of neuronal plasticity through the anti-inflammatory effect which is mediated by suppression of IB-Kinase (IKK) pathway in IS, **Figure 2** [30, 31].

Usually, microglia cells are resident macrophages in the brain and act as an active immune defense against cerebral injury and infection through induction and regulation of neuro-inflammatory reactions. Microglia improves brain homeostasis through removal of tissue debris, dead cells, and induction of neurogenesis and preservation of myelin sheath with secretion of neuroprotective factors such as insulin-like growth factor. On the other hand, activated microglia leads to neuronal injury during IS through the release of TNF-α, IL-6, IL1β and nitric oxide (NO) [32]. It has been reported that VPN inhibits neuronal inflammation in IS through suppression of microglia activity [33]. Also, VPN inhibits IS induced-inflammatory changes and reduces brain edema and infarction size mainly through inhibition the expression of NF-$_K$B and TNF-α in the activated microglia which is PDE1 independent pathway [34].

3.3 Effects of vinpocetine on ischemic reperfusion injury in ischemic stroke

Ischemic-reperfusion (I/R) injury in IS leads to activations of perivascular macrophages, which play a role in the progression of neuronal damage through the release of proinflammatory biomarkers which also participate in the injury to blood brain barrier. Furthermore, activate macrophages, microglia, T-cells and dendritic cells infiltrate the infarct site following I/R injury causing further damage through the release of monocyte chemoattracting protein (MCP-1) which attracts circulating neutrophils into the injury site. VPN inhibits TNF-α induced-IKKα/β activation with reduction of target genes activations and reduction of various forms of proinflammatory cytokines and mediator following I/R injury in IS, **Figure 3** [35, 36].

In addition, injured neurons in IS release specific proteins called danger associated molecular patterns including; heat shock protein (HSP), high mobility group-box 1 protein (HMGB-1), ATP and nicotinamide adenine dinucleotide (NAD) which activate TLR4 receptors on perivascular macrophage, microglia and endothelial cells. Therefore, TLR4 antagonist reduces infarct size attenuates IS-induced inflammatory changes and I/R injury [37, 38]. Different in *vitro* and in *vivo* studies illustrated that VPN inhibits I/R injury in IS through suppression of TLR4 receptors and NF-$_K$B signaling pathway in animal model studies [39].

Neuronal mitochondrial reactive oxygen species (ROS) contribute into the pathogenesis of I/R injury in IS as well as neurodegeneration and glutamate excitotoxicity [40]. VPN activates peripheral benzodiazepine receptors (BBRs) which regulate mitochondrial outer cell membrane and prevent the opening of mitochondrial permeability transition pore (MPTP). Furthermore, VPN prevents mitochondrial dysfunction through the prevention of mitochondrial depolarization, inhibition of mitochondrial Na^+/Ca^{2+} exchange, prevention of mitochondrial Ca^{+2} release, MPTP opening and the release of free radicals from outer mitochondrial membrane during neuronal injury [41]. Therefore, VPN regulates mitochondrial redox homeostasis through induction of ATP hydrolysis, inhibition of mitochondrial respiration and regulation of ATP synthesis. Thus, VPN preserves mitochondrial integrity and attenuates inflammatory and oxidative damage following I/R injury in IS. Moreover, Qiu et al., illustrated that VPN is effective in reducing the volume of cerebral infarct and

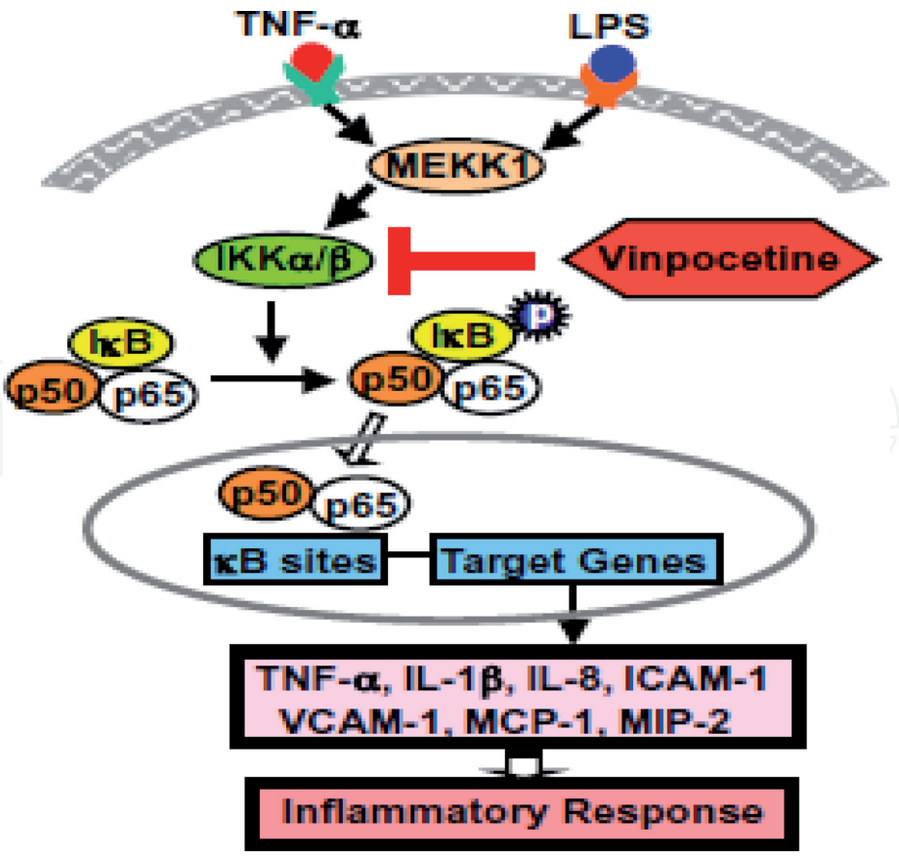

Figure 3.
Effects of vinpocetine on proiinflammatory mediators during ischemic-reperfusion (I/R) injury in ischemic stroke.

attenuation I/R injury through down-regulation of NF-KB p65 and cyclo-oxygenase 2(COX-2) with up-regulation of peroxisome proliferator-activator receptor γ(PPARγ) which is neuroprotective mediator during IS [42].

3.4 Vinpocetine and post-ischemic stroke

3.4.1 Immunological and inflammatory reactions in post-ischemic stroke

In the brain, there is multiple communications between glial cell and other immune cells, which together participate in the immune reactions during ischemic events. In the post-ischemic stroke (PIS), B-cell, T-cell, macrophage and neutrophils enter the brain to connect and engage glial cells in immune interactions. This interaction maintains homeostasis and prevents further neuronal damage through generation of pro-survival factors like transforming growth factor-β and IL-10 which promote the resolution of inflammations [43].

It has been noticed, that IS activates neuro-inflammations which increase the permeability of BBB leading to activation of mast cells and macrophages which release histamine and pro-inflammatory cytokines respectively which recruit immune cell to the site of injury leading to progression of ischemic injury [44].

Therefore, the relationship between immune cells and neurons during IS is so intricate relationship.

Microglia is regarded as a first line defense mechanism of innate immunity against ischemic injury which activated within hours following IS. There are two activation pathways for microglia, which are classical pathway (M1) and alternative pathway (M2). M1 activation leads to induction of inducible nitric oxide synthase

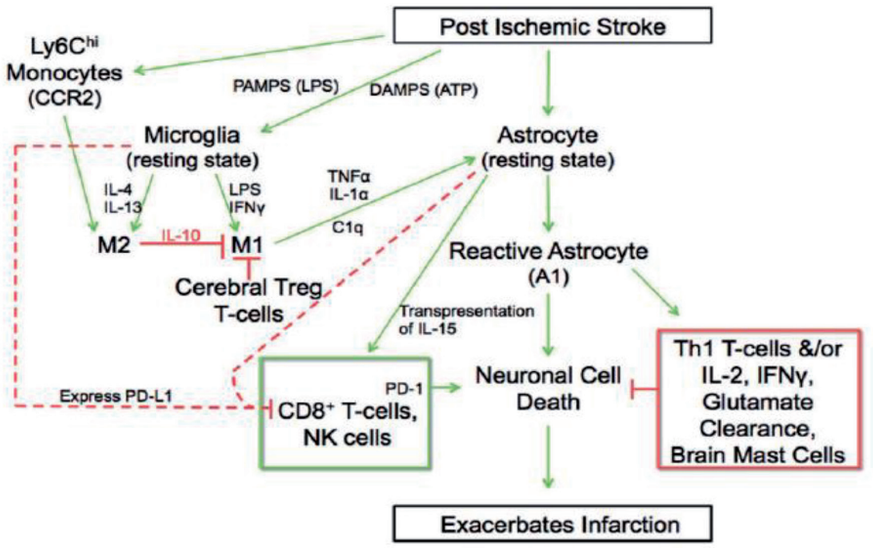

Figure 4.
Microglial and astrocyte activations in post-ischemic stroke. CCR2: chemokine receptor 2; PAMPs: pathogen-associated molecular patterns; LPS: lipopolysaccharides; PD-1: programmed death-ligand 1; NK: natural killer; CD: cluster of differentiation.

(iNOS) and TNF-α causing neuronal damage while; M2 activation leads to induction the release of pro-inflammatory cytokines and arginase leading to neuroprotection [45]. Aging is associated with impaired M2 activation and thus; M1 activation overriding M2 causing more inflammatory changes in elderly patients with IS [46].

Similarly, astrocyte which is another type of glial cell contributes in the formation of BBB and activated following IS. Reactive astrocyte subdivided into A1plays a role in the neuronal damage through upregulation of complement genes, and A2 plays a role in the neuroprotection through up-regulation of neurotrophic factors [47]. One month following PIS, astrocyte undergoes morphological and functional changes leading to reactive gliosis and activation of T-cell at ischemic regions [48].

Therefore, astrocyte and glial cells act as bridge interaction between neurons and immune system through different pro-inflammatory cytokines, **Figure 4** [49]. It has been shown that inflammatory changes, glial and astrocyte activations at post-stroke period participating together in the induction of different PIS complications such as depression, epilepsy, dementia and cognitive dysfunctions [50]. Vardian study illustrated that VPN have noteworthy antioxidant, anti-inflammatory and anti-apoptotic effects with inhibitory effect on glial and astrocyte cells during and following IS. Also, VPN reduces astrocyte edema and excitability through cAMP dependent-PKA pathway [51].

3.4.2 Vinpocetin for post-ischemic stroke epilepsy

Kim et al. reported that PIS predisposes for early and late onset epilepsy which called post-stroke seizure (PSS) due to the disturbances in the neuronal metabolic homeostasis, reactive gliosis, glutamate release and neuronal hyper-excitability [52]. Recently, Garza-Morales et al., found that VPN is effective as an adjuvant therapy in the management of epilepsy, it reduces seizure frequency by 50% in a dose of 2 mg/kg/day as compared with placebo [53]. The anti-epileptic mechanisms of VPN are through blockade of presynaptic Na-channels mediated glutamate release, inhibition of TNF-α and IL-1β which play a role in the augmentation of presynaptic Ca and Na permeability [54, 55].

3.4.3 Vinpocetin for post-stroke depression

Post-stroke depression (PSD) is a critical psychiatric complication of IS characterized by psychomotor disturbances, fatigue and sleep disorders with a prevalence of 33% following IS [56]. PSD is developed due to inflammatory reactions induced-neuroplasticity and imbalance of pro-inflammatory/anti-inflammatory ratio which causing glutamate excitotoxicity and intracellular Ca dysregulation [57]. Different studies illustrated that inflammatory cytokines induced-PSD lead to a reduction in the synthesis of serotonin, brain derived neurotrophic factor and fibroblast growth factor-2 which are important in the regulation of mood and neurotransmission [58, 59].

Inflammatory cytokines are implicated in the induction of PSD through activation of indolamine-2,3-dioxygenase at the marginal zone of the infracted area leading to depletion of serotonin and initiation of depression [60]. Furthermore, Wierner et al. found that nerve growth factor (NGF) which important secretory protein inhibits apoptosis and improves neuronal differentiations was low in PSD [61]. On the other hand, calcitonin gene-related peptide (CGRP) which is a neuroprotective peptide is elevated in patients with PSD and thus; CGRP antagonist could improve depressive symptoms [62].

Therefore, anti-inflammatory drugs with rehabilitation therapy enhance neuronal plasticity and functional recovery after IS [63]. VPN reduces the inflammatory processes and improves neuronal plasticity through inhibition the releases of inflammatory cytokines and chemokines from macrophage, microglia, and vascular smooth and endothelial cells with restoration of synaptic neurotransmissions [64]. As well, VPN improves psychomotor performances through modulation of brain monoamine pathway mainly on dopamine and serotonin, which play an integral role in attenuation of depressive symptoms [65]. Chen et al. reported that VPN improves neuronal functions and neurotransmission through modulation of NGF levels following IS [66]. Similarly, VPN improves neuronal transmission and inhibits induced pain pathway in PSD through down-regulation of CGRP [67]. Herewith, VPN attenuates PSD through different pathways either directly by activation of neuronal cAMP/cGMP pathway or indirectly through anti-oxidant, anti-inflammatory and modulation of brain peptides and neurotransmitters. Since, hippocampal cAMP-PKA response element of BDNF signaling pathway is decreased in patients with PSD. So, improvement of neuronal cAMP could interestingly prevent PSD [68].

3.4.4 Vinpocetin for post-stroke cognitive deficit

Post-stroke cognitive deficit (PSCD) is defined as global cognitive disability within 6 months after stroke regardless of presumptive causes according to American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorder. As well, 30% of stroke survivor found to have a noteworthy degree of cognitive decline within the first month after the stroke [69]. It has been noticed that some cognitive disorders may also develop subsequent to transient ischemic attack (TIA) suggesting that PSCD used in this way does not propose underlying neuro-pathological changes. Therefore, PSCD seems to be suitable for dementia, which associated with vascular insult and neuro-degenerative processes [70]. Various cross-sectional and longitudinal studies illustrated a link between high levels of inflammatory biomarkers in stroke survivors and risk of PSCD. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), IL-12 and IL-6 sera levels are elevated in patients with PSD and regarded as predictor factors [71, 72].

The inflammatory mechanism of PSCD is related to the dysregulation in inflammatory and immune factors since; reduction of IL-8 and IL-6 are associated with changes in both white and gray matters, suggesting a role in the pathogenesis of

PSCD. As well, IL-1, IL-10, TNF-α and α-synuclien are increased in PSCD [73]. Shen and Gao study reported that high somatostatin and low neuron specific enolase in patients with PSCD compared to the healthy controls [74].

Other mechanisms of PSCD are cerebral hypoperfusion, reduction in cerebrovascular reserve capacity, impairment of cerebral vasoreactivity and autoregulatory ability which together initiate abnormal neuronal cell membrane phosphorylation and amyloid beta formation [75]. In addition, irreversibly injured astrocytes are converted to clasmatodendrosis which leads to disruption of gliovascular association at BBB in the white matter. Clasmatodendrosis is associated with cognitive disorders in patients with PSCD [76]. From these points, the mechanisms of PSCD remain obscure due to overlapping between neuro-pathological data and findings of PSCD and Alzheimer disease [77]. VPN improves cognitive functions and spatial memory through inhibition of hippocampal and cortical PDE-1with augmentation of cAMP/cGMP ratio, enhancement of cholinergic neurotransmission and inhibition of neuronal IKK/NF-kB [78, 79]. It has been noticed by Bitner study that both cAMP and cGMP activate PKA and cAMP-response element-binding protein (CREP) which improves synaptic plasticity and neurogenesis through up-regulation of BDNF. cAMP/cGMP/CREP pathway increases early and late long-term potentiation of memory [80] Besides, other PDE inhibitors like sildenafil (PDE-5 inhibitors) and cilostazol (PDE-3 inhibitor) also improve cognitive function and PSCD [81]. Recently, McQuown et al. illustrated that VPN improves memory function mainly through inhibition of PDE-1B isoform as it mainly located in regions with high dopaminergic neurotransmission such as the prefrontal cortex, striatum and dentate gyrus [78]. Therefore, VPN is an effective therapy in rehabilitation of cognitive, memory deficit and PSCD through modulation of inflammatory changes and enhancement of neuronal cAMP/cGMP in post-stroke survivors [82].

4. Conclusions

VPN is an effective agent in the management of ischemic stroke and plays an integral role in the prevention and attenuation of post-stroke epilepsy, depression and cognitive deficit through direct cAMP/cGMP-dependent pathway or indirectly through anti-inflammatory and anti-oxidant effects.

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