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Role of vinpocetine in ischemic stroke and poststroke outcomes: A critical review

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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) that has potential neurological effects through inhibition of voltage-gated sodium channel and reduction of neuronal calcium influx. VPN has 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 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 PDE1 with augmentation of cyclic adenosin monophosphate and cyclic guanosin monophosphate ratio, enhancement of cholinergic neurotransmission, and inhibition of neuronal inflammatory mediators. Therefore, VPN is an effective agent in the management of IS and plays an integral role in the prevention and attenuation of poststroke epilepsy, depression, and cognitive deficit through direct cAMP/cGMP-dependent pathway or indirectly through anti-inflammatory and antioxidant effects.

Keywords:

Anti-inflammatory, antioxidant, phosphodiestrase type 1, poststroke, stroke, vinpocetine

Introduction

Vinpocetine (VPN) is a synthetic ethyl-ester derivative of the alkaloid apovincamine from Vinca minor leaves 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 cerebrovascular 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 (IS).

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: (VPN OR apovincamine) AND (cognitive function OR stroke OR brain ischemia OR blood flow OR cerebral circulation OR oxidative stress OR blood viscosity OR cerebral blood flow). (VPN 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

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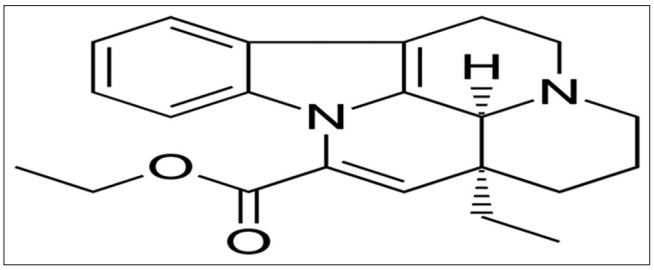

Figure 1: Chemical structure of vinpocetine

concerned in the review. The key features of recognized applicable search studies were considered and the conclusions summarized in a critical review.

Pharmacology of Vinpocetine

VPN is a selective inhibitor of phosphodiesterase type 1 (PDE1), which increasing cAMP and cGMP leading to vasodilatation. Furthermore, it inhibits the release of pro-inflammatory cytokines through inhibition of I kappa B kinase/nuclear factor kappa (IKK/NF-κB) activator protein-1 pathway which is involved in the propagation of inflammatory cytokines translocation and release.[3] 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 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 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 nonselective vasodilator effect, it does not produce stealing effect on the 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 the small intestine, which increased by food. Therefore, fasting bioavailability is 6.7% and nonfasting 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 IS.[6]

Vinpocetine in Ischemic Stroke

IS represents the main leading cause of death in the United States of America 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 factors of IS.[8] These risk factors are divided into nonmodifiable risk factors (sex, age, inherited factors, ethnicity, 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. Neuroinflammations contribute to tissue repair and neuronal damage as well as retrograde and anterograde axonal degenerations.[10] IS leads to glucose and oxygen deprivation of neuronal cells also which, causes oxidative stress, excitotoxicity, and calcium overload that eventually causing neuronal cell death and development of infarction core.[11] The infracted core and damaged neuronal cells due to induced oxidative stress, release various inflammatory molecules that causing vasculitis and damage of blood–brain barrier (BBB).[12] Moreover, activated microglia and infiltrated macrophage during IS release different neurotransmitters and interact with neurons causing neuroinflammation and neuronal injury. As well, interleukin-8 (IL-8), NF-κB, and tumor necrosis factor (TNF-α) are overexpressed during IS which plays 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-κB pathway leading to further obstruction and thrombosis. Therefore, NF-κB pathway is an important pathway in the pathogeneses and development of neurological deficit thus, inhibition of the NF-κB pathway by VPN is regarded as important and main mechanism of VPN neuroprotection.[14]

In addition, activated microglia expresses cholesterol transporter protein, which is overexpressed 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]

Systemic review by Bereczki and Fekete showed that VPN decreases the size of cerebral infarction after middle cerebral artery occlusion in rats and mice. In controlled human studies, VPN increases cerebral perfusion and oxygen extraction and prevents the worsening of attention in patients with multiple cerebral infarcts so; VPN has been used to treat stroke in several countries in Europe. Therefore, there is no evidence to support the routine use of VPN in all patients with acute IS. Further trials are needed to decide if the routine application of VPN decreases case fatality and the proportion of dependent survivors in acute IS.[21] Besides, a previous clinical study involved 92 patients with acute IS treated with VPN and/or ganglioside illustrated that this combination can promote the neural functional reconstruction and inhibit the occurrence of cerebral hemorrhage and cerebral re-infarction in convalescents with acute cerebral infarction.[22] Therefore, these studies confirm the valuable role of VPN alone or in combination with other neuroprotective agents in acute IS.

Antioxidant effects of vinpocetine in ischemic stroke

In IS, overproduction of free radicals and reactive oxygen and/or nitrogen species leads to neuro-pathological changes through complex interactions with cellular components such as proteins, DNA, and lipids. Free radicals, mainly superoxide and nonradicals 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.[23]

A recent study by Al-Kuraishy *et al*. reported that VPN is a potent antioxidant agent improves antioxidant capacity and reduces oxidative stress.[24] As well, Santos *et al*. study illustrated that VPN attenuates oxidative stress during IS through inhibition of lipid peroxidation and generation of free radical.[25] In addition, VPN has a neuroprotective effect, through the antioxidant effect since it prevents oxidative stress injury and toxic demyelination in rat brain.[26] The antioxidant neuroprotective effect of VPN is mainly at low-moderate doses since high doses of VPN lead to oxidative stress due to pro-oxidant and pro-inflammatory effects.[27] Deshmukh *et al*. reported that antioxidant potential of VPN contributes to the prevention of IS induced-neuronal injury through modulation of cholinergic neurons.[28] Therefore, antioxidant mechanisms of VPN are related to direct free radical scavenging effect, potentiating 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.[29,30]

Anti-inflammatory effects of vinpocetine in ischemic stroke

IS-induced inflammatory changes and neuroinflammations lead to secondary brain damage. Toll-like receptors (TLRs) are overexpressed in IS, leading to the induction of 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.[31] Therefore, inhibition of TLR4/MyD88 and NF-KB pathways lead to noteworthy neuroprotection against IS. It has been noted that VPN inhibits TNF-α induced NF-κB activation, pro-inflammatory releases, and inflammatory biomarkers such as IL-1β and IL-33 in an experimental ischemic model.[32] 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-κB pathways in IS and associated atherosclerosis.[33] In a similar way, VNP leads to the significant neuroprotective effect and regulation of neuronal plasticity through the anti-inflammatory effect via suppression of IKK pathway in IS [Figure 2].[34,35]

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 neuroinflammatory reactions. Microglia improves brain homeostasis by 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).[36] It has been reported that VPN inhibits neuronal inflammation in IS via suppression of microglia activity.[37] Furthermore, VPN inhibits IS-induced inflammatory changes and reduces brain edema and

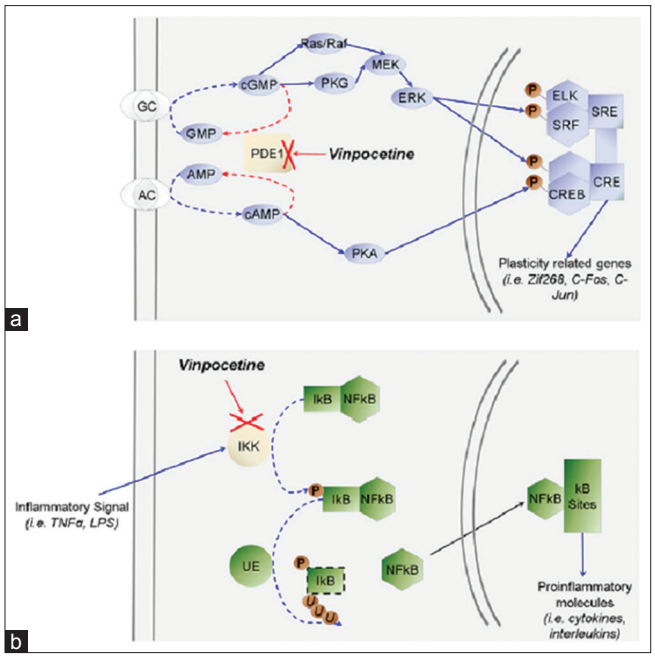

Figure 2: Anti-inflammatory effects of vinpocetine, (a) PDEI-dependent (b) PDE1-independent

infarction size mainly through inhibition the expression of NF-κB and TNF-α in the activated microglia which is PDE1-independent pathway.[38] Animal model studies showed that after 4-6 h of ischemia, circulating leukocytes adhere to the vessel walls, leading to migration and accumulation in the ischemic brain lesion, which results in secondary injury. Neutrophils are highly associated with the neuronal damage so, inhibiting the adhesion molecules that facilitate neutrophil entry into the injured brain will improves neurological outcomes. This can be accomplished by VPN's inhibition of IKK/NF-κB in endothelial cells and macrophages. The protective effect seen in lymphocyte-deficient mice, or caused by blocking postischemic trafficking of T-cells into the ischemic brain, occurs 24–48 h after ischemia.[39,40] As a consequence, VPN acts as an anti-inflammatory agent by ameliorating cerebral ischemia/reperfusion injury *in vitro* and *in vivo*. VPN inhibits inflammatory responses through the TLR4/MyD88/NF-κB signaling pathway that are independent of TRIF-mediated inflammatory responses. As a result, VPN may be an attractive therapeutic candidate for the treatment of cerebral ischemic injuries and inflammatory diseases.

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 pro-inflammatory biomarkers which also participate in the injury to BBB. 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-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 pro-inflammatory cytokines and mediator following I/R injury in IS [Figure 3].[40,41]

In addition, injured neurons in IS release specific proteins called danger-associated molecular patterns including heat shock protein, high mobility group-box 1 protein, adenosin triphosphate (ATP), and nicotinamide adenine dinucleotide which activate TLR4 receptors on perivascular macrophage, microglia, and endothelial cells. Therefore, TLR4 antagonist reduces the infarct size, attenuates IS-induced inflammatory changes, and I/R injury.[42,43] Different *in vitro* and *in vivo* studies illustrated that VPN inhibits I/R injury in IS through suppression of TLR4 receptors and NF-κB signaling pathway in animal model studies.[44]

Neuronal mitochondrial reactive oxygen species contribute to the pathogenesis of I/R injury in IS as well as neurodegeneration and glutamate excitotoxicity.[45] VPN activates peripheral benzodiazepine receptors which regulate mitochondrial outer cell membrane and prevent the opening of mitochondrial permeability transition pore (MPTP). Furthermore, VPN prevents mitochondrial dysfunction through prevention of mitochondrial depolarization, inhibition of mitochondrial Na^+/Ca^{2+} exchange, anticipation of mitochondrial Ca^{2+} release, MPTP opening, and the release of free radicals from outer mitochondrial membrane during neuronal injury.[46] Furthermore, VPN regulates mitochondrial redox homeostasis through induction of ATP hydrolysis, inhibition of mitochondrial respiration and regulation of ATP synthesis. As a result, 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 attenuation I/R injury through downregulation of NF-κB p65 and cyclo-oxygenase 2 with upregulation of neuroprotective mediator called peroxisome proliferator-activator receptor γ during IS.[47]

Vinpocetine and postischemic stroke

Immunological and inflammatory reactions in postischemic stroke

In the brain, there are multiple communications between the glial cell and other immune cells, which together participate in the immune reactions during ischemic events. In the post-IS (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 such as transforming growth factor-β and IL-10 which promote the resolution of inflammations.[48]

It has been noticed that IS activates neuroinflammations which increase the permeability of BBB due to activation of mast cells and macrophages which release histamine and pro-inflammatory cytokines, respectively. These mediators recruit immune cells to the site of injury leading to the progression of ischemic injury.[49] Therefore, the relationship between immune cells and neurons during IS is such an 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 the classical pathway (M1) and alternative pathway (M2). M1 activation leads to induction of inducible NO synthase and TNF-α causing neuronal damage, while M2 activation leads to induction the release of pro-inflammatory cytokines and arginase leading to neuroprotection.[50] Aging is associated with impaired M2 activation and thus; M1 activation overriding M2 causing more inflammatory changes in elderly patients with IS.[51]

Similarly, astrocyte which is another type of glial cell contributes to the formation of BBB and is activated following IS. Reactive astrocyte subdivided into A1 which plays a role in the neuronal damage through upregulation of complement genes, and A2 which plays a role in the neuroprotection through upregulation of neurotrophic factors.[52] One month following IS, astrocyte undergoes morphological and functional changes leading to reactive gliosis and activation of T-cell at ischemic regions.[53]

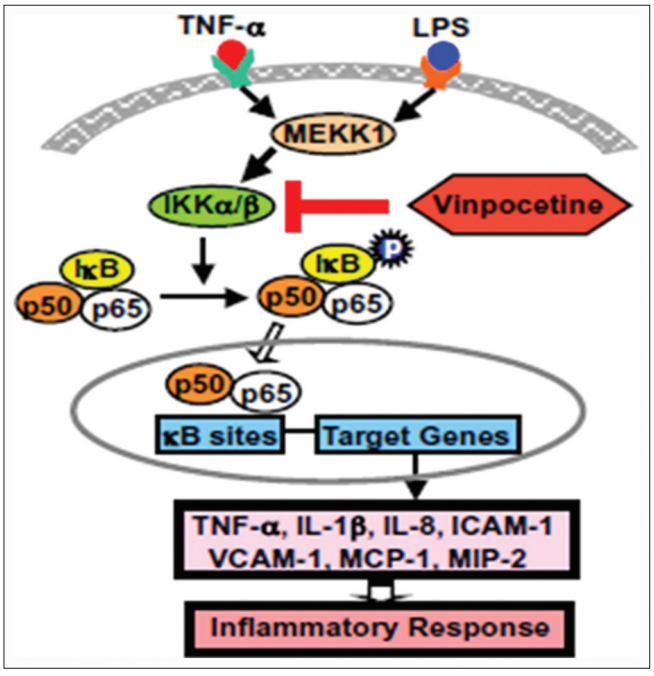

Figure 3: Effects of vinpocetine on pro-inflammatory mediators during ischemic-reperfusion injury in ischemic stroke

Therefore, astrocyte and glial cells act as bridge for interaction between neurons and immune system through different pro-inflammatory cytokines [Figure 4].[54] It has been shown that inflammatory changes, glial and astrocyte activations at poststroke period participating together in the induction of different poststroke complications such as depression, epilepsy, dementia, and cognitive dysfunctions.[55] Vardian study illustrated that VPN has noteworthy antioxidant, anti-inflammatory, and antiapoptotic effects with inhibitory effect on glial and astrocyte cells during and following IS. Furthermore, VPN reduces astrocyte edema and excitability through cAMP-dependent PKA pathway.[56]

As well, experimental studies observed that VPN inhibits lipopolysaccharides-induced NF-κB activation and TNF-α, IL-1β, and IL-33 production by macrophages. When these cytokines activate endothelial cells, they upregulate the expression of adhesion molecules promoting neutrophil recruitment to the infracted tissues. Hence, VPN reduces neutrophil recruitment and the activity of myeloperoxidase in mice.[40] Therefore, VPN is an effective agent in the prevention of CNS inflammation following acute IS and can be used to attenuate poststroke inflammatory reactions.[57]

Vinpocetin for postischemic stroke epilepsy

Kim *et al*. reported that PIS predisposes for early- and late-onset epilepsy which called poststroke seizure (PSS) due to the disturbances in the neuronal metabolic homeostasis, reactive gliosis, glutamate release, and neuronal hyperexcitability.[58] Recently, Garza-Morales

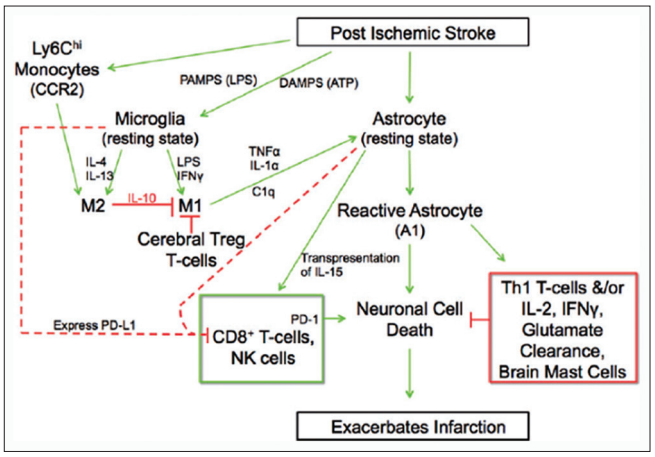

Figure 4: Microglial and astrocyte activations in postischemic stroke.CCR2: chemokine receptor 2, PAMPs: pathogen-associated molecular patterns, LPS: lipopolysaccharides, PD-1: programmed death-ligand 1, NK: natural killer, CD: cluster of differentiation

et al. found that VPN is effective as 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.[59] The antiepileptic mechanisms of VPN are through blockade of presynaptic Na-channel-mediated glutamate release, inhibition of TNF-α and IL-1 β which play a role in the augmentation of presynaptic Ca and Na permeability.[60,61] The site of stroke lesions has been reported as a chief clinical factor enduring tendency to generate further and additional seizures. Several studies have established that early PSS is an independent risk factor for the development of late and repeated seizures.[62] Early seizure control is important because uncontrolled repetitive seizures may affect patients not only through potential physical injuries but also throughout the harmful effects on the brain with stroke lesion and degenerative changes. It is also probable that recurrent peri-infarct depolarization might be injurious to already susceptible tissues because the additional metabolic stress could cause further neuronal injuries.[63,64] Even though, seizures after stroke are known to be related to increased resource utilization and length of hospital stay as well as decreased survival at 30-day and 1-year time points.[65] In view of lower volume of cortical gray matter and decreased excitability due to degenerative changes, it is easy to assume that younger patients might develop seizures more often.[66] Herein, VPN may be used to control PSS alone or in combination with other antiseizure medications through improvement of the neuronal plasticity and reduction of poststroke inflammation and oxidative stress-induced neuronal excitability.[67]

Vinpocetin for poststroke depression

Poststroke depression (PSD) is a critical psychiatric complication of IS characterized by psychomotor disturbances, fatigue, and sleep disorders with the prevalence of 33% following IS.[68] PSD is developed due to inflammatory reaction-induced neuroplasticity and imbalance of pro-inflammatory/anti-inflammatory ratio which causing glutamate excitotoxicity and intracellular Ca dysregulation.[69] Different studies illustrated that inflammatory cytokines induced-PSD lead to a reduction in the synthesis of serotonin, BDNF, and fibroblast growth factor-2 (FGF-2), which are important in the regulation of mood and neurotransmission.[70,71]

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.[72] Furthermore, different clinical studies revealed a relationship between different cytokines and molecules with PSD, Wiener *et al*. found that nerve growth factor (NGF) which important secretory protein inhibits apoptosis and improves neuronal differentiations was low in PSD.[73] 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.[66] Similarly, reduced dopamine concentrations in ischemic striatum have been demonstrated in a mouse model of chronic PSD.[74] In addition to monoamine neurotransmitters, a low plasma glutamate has also been reported to be associated with early-onset PSD. This study found that the levels of IL-6 and TNF-α significantly higher in the PSD group than in the non-PSD group. Thus, inflammatory cytokines are implicated in the pathogenesis of PSD.[75]

Therefore, anti-inflammatory drugs with rehabilitation therapy enhance neuronal plasticity and functional recovery after IS.[76] VPN reduces the inflammatory processes and improves neuronal plasticity through inhibition of the releases of inflammatory cytokines and chemokines from macrophage, microglia, and vascular smooth and endothelial cells with restoration of synaptic neurotransmissions.[77] 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.[78] Chen *et al*. reported that VPN improves neuronal functions and neurotransmission through modulation of NGF levels following IS.[22] Similarly, VPN improves neuronal transmission and inhibits induced pain pathways in PSD through downregulation of CGRP.[79] Herewith, VPN attenuates PSD through different pathways either directly by activation of neuronal cAMP/cGMP pathway or indirectly through antioxidant, 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. Hence, improvement of neuronal cAMP could interestingly prevent PSD.[80]

Vinpocetin for poststroke cognitive deficit

Poststroke cognitive deficit (PSCD) is defined as a global cognitive disability within 6 months after stroke regardless of presumptive causes according to the American Psychiatric Associations Diagnostic and Statistical Manual of Mental Disorder. As well, 30% of stroke survivors found to have a noteworthy degree of cognitive decline within the 1st month after the stroke.[81] It has been noticed that some cognitive disorders may also develop subsequent to transient ischemic attack suggesting that PSCD used in this way does not propose underlying neuropathological changes. Therefore, PSCD seems to be suitable for dementia, which associated with vascular insult and neurodegenerative processes.[82] 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, IL-12, and IL-6 sera levels are elevated in patients with PSCD and regarded as predictor factors.[83,84]

The inflammatory mechanism of PSCD is related to the dysregulation in inflammatory and immune factors since reduction of IL-8 and IL-6 is 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-synuclein are increased in PSCD.[85] Shen and Gao study reported that high somatostatin and low neuron-specific enolase in patients with PSCD compared to the healthy controls.[86]

Other mechanisms of PSCD are cerebral hypoperfusion, reduction in the cerebrovascular reserve capacity, impairment of cerebral vasoreactivity and autoregulatory ability, which together initiate abnormal neuronal cell membrane phosphorylation and amyloid-beta formation.[87] 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.[88] From these points, the mechanisms of PSCD remain obscure due to overlapping between neuropathological data and findings of PSCD and Alzheimer's disease.[89] VPN improves cognitive functions and spatial memory through inhibition of hippocampal and cortical PDE-1 with augmentation of cAMP/cGMP ratio, enhancement of cholinergic neurotransmission, and inhibition of neuronal IKK/NF-κB.[90,91] It has been perceived by Bitner study that both cAMP and cGMP activate PKA-response element-binding protein (CREP) improves synaptic plasticity and neurogenesis through upregulation of BDNF. cAMP/cGMP/CREP pathway increases early and late long-term potentiation of memory.[92] Besides, other PDE inhibitors such as sildenafil (PDE-5 inhibitors) and cilotazol (PDE-3 inhibitor) also improve cognitive function and PSCD.[93] 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.[90] 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 poststroke survivors.[94]

Conclusions

Animal model, preclinical, and clinical studies confirmed that VPN is an effective agent in the management of IS and early poststroke complications. VPN plays an integral role in the prevention and attenuation of late poststroke complications such as epilepsy, depression, and cognitive deficit through direct cAMP/cGMP-dependent pathway or indirectly through anti-inflammatory and antioxidant effects. Further studies are recommended to observe and confirm the specific effect of VPN on stroke outcomes and complications.

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Conflicts of interest

There are no conflicts of interest.

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