Effects of Vinpocetine in Ischemic Stroke

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Introduction

- Stroke is the 2nd most common cause of death worldwide. (Ischemic stroke - 80%–90%)
- Atherosclerosis is a common condition that increases the risk of stroke.
- It is a chronic inflammatory process affecting the large- and medium-size arteries, including those in the brain.

Pathogenesis of atherosclerosis:

Accumulation of lipids within artery walls

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Stimulation of endothelial cells

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Attraction of T lymphocytes & monocytes

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Transformation into macrophages & ingestion of oxidized LDL(ox-LDL) (foam cells)

Plaque (subendothelial lipid + increased extracellular matrix proteins + immune cells) formation

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Migration & proliferation of

vascular smooth muscle cells (VSMCs)-cap of the plaque

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Disruption of the cap

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Accumulation of platelets & coagulation proteins to form a thrombus

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Thrombotic stroke / traveling of an embolus to the brain (embolic stroke)

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Ischemia in the area supplied by the affected artery

Inflammatory pathophysiology of ischemic stroke

- Oxygen and glucose deprivation causes excitotoxicity, calcium overload & oxidative stress - cell death in the infarct core.
- Oxidative stress , creation of inflammatory cells & release of cytokines that together cause cellular damage in the infarct and peri-infarct area.

- Activated microglia release neurotransmitters and interact with neurons contributing to post-ischemic inflammation.

- Key protein complex in the inflammatory response is the transcription factor nuclear factor κ-light-chain-enhancer of activated B cells κB (NF-κB)
- It is activated by inflammatory molecules such as interleukin (IL)-6, IL-8 and tumor necrosis factor (TNF)-α.
- NF-κB initiates the expression of inflammatory cytokines and regulators of apoptosis.

- NF-κB pathway includes NF-κB, the inhibitor κB (IκB), and IκB kinase (IKK).

- Ox-LDL, activation of endothelial cells & proliferation of VSMCs are regulated via the NF-κB pathway in atherosclerosis.

Vinpocetin

- An alkaloid extracted from the periwinkle plant & derivative of the alkaloid vincamine.
- Inhibitor of phosphodiesterase type 1 (PDE1) & leads to increases in cAMP and cGMP, initiating plasticity-related gene expression.
- Suppresses release of proinflammatory molecules by inhibiting the inhibitor of the IKK/NF-κB pathway after TNF-α stimulation.

Anti-Inflammatory Effects of Vinpocetine in Atherosclerosis

Inhibition of Progression of Atherosclerosis

- Increase in the expression of vascular cell adhesion molecule-1 (VCAM-1) and P-selectin occurs in endothelial cells in the presence of ox-LDL by NF-kB pathway.

- By targeting the NF-κB pathways, vinpocetine inhibits the transcription of adhesion molecules, selectins, and proinflammatory cytokines, thus inhibits monocyte adhesion.
- Monocyte chemoattractant protein-1 (MCP-1) is pivotal in the transformation of monocytes into macrophages and through NF-κB, vinpocetine can indirectly impact this process.

- Various proinflammatory cytokines (such as IL-6, TNF-α)released by macrophage are also inhibited by vinpocetine through NF-κB.
- Vinpocetine enhances the collagen content and significantly increases fibrous cap thickness, thus stabilizing the atherosclerotic plaque.

- Vinpocetine relaxes cerebral VSMCs, thus enhancing cerebral blood flow.

Anti-Inflammatory Effects of Vinpocetine in Ischemic Stroke

Inhibition of Early Inflammation in Ischemic Stroke

- Vinpocetine selectively affects cerebral blood flow without influencing systemic circulation.
- Acts on IKK, upstream of NF-κB, and inhibits TNF-α-induced NF-κB activation and the subsequent induction of proinflammatory mediators in VSMCs and endothelial cells.

- Selectively inhibits voltage-sensitive sodium (Na+) channels, thus inhibiting Ca2+ accumulation in the cells, and consequently inhibits neuronal damage.
- Also elicits an antioxidant effect in neurons.

Inhibition of the Proliferation of Microglia

- Microglia produce inflammatory mediators and proteases, which exacerbate the ischemic damages in the brain.
- Vinpocetine inhibits the proliferation of microglia through NF-κB/AP-1 and suppresses the release of inflammatory factors.

Adaptive Immune Response after Ischemic Stroke

- NF-κB is a major transcription factor that regulates the genes responsible for both the innate and adaptive immune responses.
- Vinpocetine can reduce the level of disability during the early phase of stroke, and can improve quality of life and cognitive ability after stroke.

- It influences IKK/NF-κB in many cell types, thus reducing the release of inflammatory factors.
- However, vinpocetine’s impact on the adaptive immune response and its mechanism of action in adaptive immunity require further study.

Conclusion

- Inflammation and immunity are involved in lesion formation in both atherosclerosis and ischemic stroke.
- NF-κB pathway plays an important role in their progression.
- Vinpocetine influences release of many inflammatory mediators by suppressing the IKK/NF-κB pathway & exerts a neuroprotective effect.
- However, it's effect on adaptive immunity and immune response requires further study.

Thank you all.