Vinpocetine as a potent antiinflammatory agent

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Chronic inflammatory processes are related to conditions as distinct as atherosclerosis, amyotrophic lateral sclerosis, asthma, systemic lupus, Alzheimer's disease, and Parkinson's disease. The continuous use of antiinflammatory agents is required to treat these conditions. However, the long-term use of these drugs creates an additional challenge: the high frequency of severe side effects. For instance, the long-term use of corticosteroids and cyclooxigenase (COX) inhibitors can dramatically increase the risk for cardiovascular problems and diabetes (1). Currently, there are great efforts to discover antiinflammatory drugs that can be used for long periods with minimal side effects. In PNAS, Jeon et al. (2) show that vinpocetine, a phosphodiesterase (PDE) inhibitor known for its minimal side effects (3, 4) and great potential in cognitive enhancement (5–8), also has potent antiinflammatory action. Surprisingly, the antiinflammatory action of vinpocetine is caused by a direct inhibition of the IκB kinase complex (IKK) rather than PDE blockade.

Vinpocetine Improves Neuronal Plasticity

Vinpocetine is an alkaloid extracted from the periwinkle plant and has been tested as a neuronal plasticity enhancer and marketed as a "memory booster." Vinpocetine treatment has been shown to facilitate long-term potentiation (9), improve spatial memory in animal models (6, 7), and enhance performance on cognitive tests in humans (10). The cognitive enhancement function of vinpocetine comes from its inhibition of PDE type 1, which leads to an increase in cAMP and cGMP levels. These cyclic nucleotides can in turn activate a series of kinases that phosphorylate the transcription factors cAMP response element binding protein (CREB) and serum response factor (SRF), leading to the expression of plasticity-related genes (11) (Fig. 1*A*).

Vinpocetine Reduces Inflammation by IKK Inhibition

Recently, it was shown that the modulation of cAMP by PDE type 4 inhibitors can be effective in reducing inflammation by reducing cytokine release in a variety of cell types, and these drugs are being tested in chronic obstructive pulmonary disease and bowel disease (12–14). However, most PDE type 4 inhibitors can produce nausea and vomiting, and active research for more tolerable agents is ongoing (12).

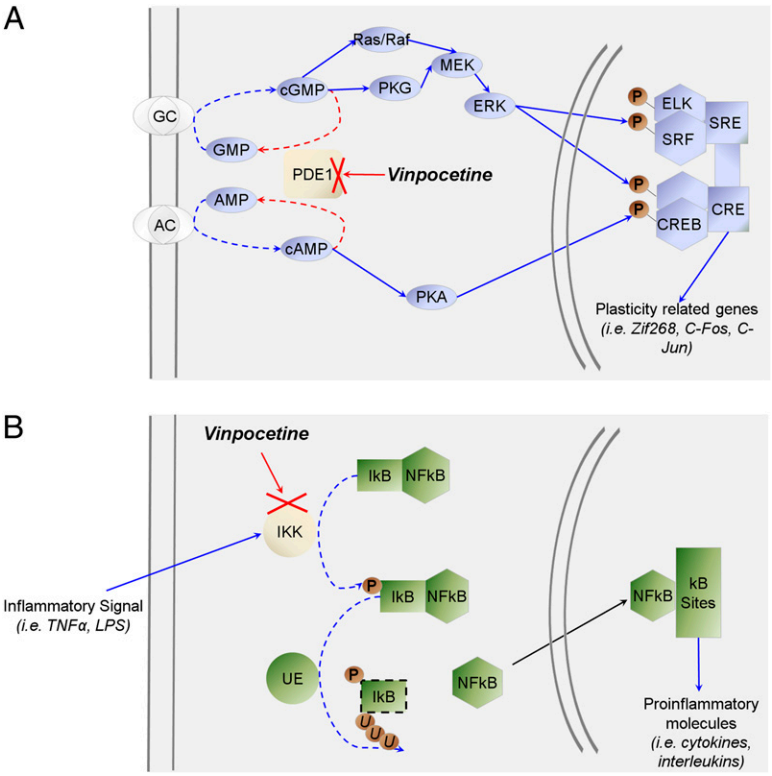

Fig. 1. Mechanisms of vinpocetine action. (*A*) Adenylyl cyclase activity increases cAMP levels, activating PKA. Active forms of PKA may translocate to the nucleus and phosphorylate CREB. Similarly, guanylyl cyclase activity increases cGMP levels, activating the Ras/Raf pathway either directly or through PKG. This leads to the activation of ERK and the phosphorylation of both CREB and SRF. Because PDE1 catalyzes the hydrolysis of cAMP and cGMP, its inhibition by vinpocetine increases the level of these cyclic nucleotides, ultimately leading to the expression of plasticity-related genes. (*B*) In its inactive state, NFκB is located in the cytoplasm attached to its inhibitory subunit IκB. Inflammatory signals activate the IKK complex, which in turn phosphorylates IκB. IκB phosphorylation leads to its ubiquitination (and eventual degradation) by ubiquitin enzymes (UE). Without IκB, NFκB translocates to the nucleus, where it phosphorylates κB sites in many genes, which results in the expression of many proinflammatory molecules. Vinpocetine blocks IKK activity, preventing NFκB-triggered protein expression.

Because vinpocetine is a PDE inhibitor that has minimal side effects, Jeon et al. investigated whether this drug could be efficient in reducing NFκB transcription after stimulation by TNFα (one of the hallmarks of the inflammatory process). Remarkably, in vitro tests showed that vinpocetine prevented the up-regulation of NFκB by TNFα in vascular smooth cells, human umbilical vein endothelial cells, lung epithelial A549 cells, and a macrophage cell line. In addition, RT-PCR analysis showed that vinpocetine also reduced the TNFα-induced expression of the mRNA of proinflammatory molecules such as interleukin-1β, monocyte chemoattractant protein-1 (MCP-1), and vascular cell adhesion molecule-1 (VCAM-1). To confirm the antiinflammatory properties of vinpocetine in an in vivo preparation, the authors used a lipopolysaccharide and TNFα intratracheal inoculation in the mouse. Remarkably, i.p. administered vinpocetine was able to significantly reduce polymorphonuclear neutrophil infiltration in lung tissues.

What are the mechanisms that underlie the antiinflammatory properties of

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vinpocetine? Using multiple assays, Jeon et al. showed that vinpocetine inhibits IKK, preventing IκB degradation and the consequent translocation of NFκB to the nucleus (Fig. 1*B*). Surprisingly, this mechanism is independent of vinpocetine action on PDE1.

An important question that arises from this work is whether vinpocetine's effect can be maintained during long-term treatment. Would IKK blockade show tolerance? Would feedback mechanisms cancel the initial effect? Answering these questions would be important to evaluate vinpocetine's potential for clinical use.

Could Vinpocetine Reduce Inflammation and Enhance Cognition in Neurodegenerative Diseases?

The antiinflammatory role of vinpocetine in tandem with its cognitive improvement properties could be of particular interest in neurodegenerative conditions such as Parkinson's disease (PD) and Alzheimer's disease (AD) (see refs. 15 and 16 for reviews). For instance, in PD, TNFα is increased in the striatum and substantia nigra and probably contributes to the neuroinflammatory processes that culminate in neuronal death (17, 18). Supporting this view, it has also been shown that genetic alterations of TNFα can significantly increase the risk of developing PD (19, 20). In AD, there is growing evidence showing that the accumulation of the amyloid-β protein leads to an up-regulation of interleukins and TNFα that contributes to the neurodegeneration seen in many brain regions (21). In fact, prolonged treatment with antiinflammatory drugs can reduce the risk for AD (16, 21). It would be interesting to test whether vinpocetine's antiinflammatory properties would have a protective effect in models of neurodegenerative conditions such as AD and PD.

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