

Research Progress in Regulatory Mechanism of Valproic Acid on Inflammatory Responses to Burns and Trauma

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Abstract

Inflammation plays an important role in the defense of the human body. The inflammatory response can suppress the spread of pathogens, accelerate the removal of necrotic cells, and repair the damaged tissues and organs. However, an excessive inflammatory response can be fatal as it may lead to cellular apoptosis, necrosis of tissues and organs, and systemic dysfunction. An inflammatory response occurs when the skin is burned or injured, causing more severe and extensive pathological damage to the injured area. For example, inflammation can damage the coagulation system in the capillaries, resulting in the formation of small blood clots in the affected areas. In severe cases, inflammation can lead to necrosis of the injured area and may even affect other uninjured areas, causing hypoxia and inadequate blood supply. The role of valproic acid (VPA), a histone deacetylase inhibitor, has been increasingly recognized in recent years. Evidence suggests that VPA can effectively alleviate tissue and organ injuries secondary to ischemia and hypoxia, and improve the body's tolerance to ischemia-hypoxia and inflammatory insults, thus increasing the survival rates of the patients. This article reviews the latest research progress made in the mechanisms by which VPA regulates inflammatory response to burns.

Keywords

Trauma, burns, valproic acid, histone deacetylase inhibitors

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Introduction

The human body has three barriers to protect itself, of which the skin is the outermost one. Once the skin is injured, it increases the risk of wound infection, and local tissue damage will trigger an inflammatory response in the human body (Strudwick et al., 2020). As an innate immune response to burns and trauma, the human body will produce a large amount of pro-inflammatory cytokines that are secreted by monocytes and macrophages in the immune system, along with an increased accumulation of neutrophils within the wounded tissue, thereby manifesting an excessive inflammatory response. These cells are initially stimulated by lipopolysaccharide (LPS), which causes significant changes in the levels of some key pro-inflammatory cytokines, including tumor necrosis factor- α (TNF- α), IL-1, IL-6, and IL-8. TNF- α can also promote cell differentiation during inflammation. For example, it can trigger the production of more monocytes and macrophages to participate in the inflammatory response by influencing the differentiation of bone marrow cells. TNF- α , IL-1, and IL-8 can also affect the vasculature by increasing the vascular permeability, the

pro-coagulant activity of vascular endothelial cells (VECs), and the adhesion to neutrophils (Stone et al., 2018). The inflammatory response is an essential part of wound healing. A variety of immune cells (e.g., endothelial cells, macrophages, and neutrophils) and immune molecules participate in this process to remove pathogens and ultimately promote wound healing (Larouche et al., 2018; Salibian et al., 2016). Valproic acid (VPA) is a histone deacetylase inhibitor (HDACi) that has been shown to protect organs in the course of disease and treatment, thereby increasing survival rates in animal models of hemorrhagic shock or lethal burn injury (Kuai et al., 2016; Liu

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et al., 2022; Tang et al., 2018; Wakam et al., 2021). HDACi can effectively reduce tissue and organ damage secondary to ischemia and hypoxia, and it also has certain efficacy in alleviating the inflammatory response caused by ischemia and hypoxia, thereby improving survival in rat models of burn shock (Toppi et al., 2019). There is increasing research interest in the role of VPA in inhibiting anti-inflammatory response and anti-inflammatory factors and its underlying mechanism. This article reviews the latest research progress in the mechanisms by which VPA regulates the inflammatory response to burns and trauma.

Inhibitory Effects of VPA on the Anti-inflammatory Response

Oncological research has shown that HDACi can, to some extent, inhibit the growth of tumor cells and promote their apoptosis (Bai et al., 2021; Wang et al., 2021). Further studies in animal models of degenerative lesions, burn shock, neurological lesions, hemorrhagic shock, septic shock, traumatic injury, or ischemia-reperfusion injury have revealed that HDACi does not cause apoptosis of parenchymal cells in various organs; rather, it increases cellular tolerance to harmful stimuli and thus helps to maintain cellular function and suppress inflammatory responses. Therefore, the potential value of HDACi in treating other diseases has received increasing attention, especially its inhibitory effects on pro-inflammatory cytokines. Some recent studies have demonstrated that HDACi can also increase the tolerance of cells to hypoxic inflammatory environments, thus protecting various organs. Li et al. (2010); Liu et al. (2013), Liu et al. (2014) and Zhao et al. (2013) showed that HDACi was important for maintaining histone acetylation homeostasis, especially in animals in hypovolemic or septic shock; in addition, HDACi could increase cellular tolerance to hypoxic inflammatory environments, thereby protecting organs and prolonging the life of animals. By causing microglia activation and promoting histone acetylation, VPA affects the MAPK and NF- κ B signaling pathways, regulates the expressions of inflammation-related genes, and alleviates the inflammatory response. Microglia are the resident immune cells of the central nervous system. When disease or injury occurs, the resting microglia are activated to become phagocytic and meanwhile secrete pro-inflammatory factors. VPA pretreatment of the primary rabbit microglia could reduce the expression of TNF- α induced by LPS. Dambach et al. (2014) found that high-level VPA caused severe damage to microglia and also stimulated the production of inflammatory factors by microglia. As an inhibitor of class I/II histone deacetylases (HDACs), VPA can also regulate gene expression by promoting histone deacetylation. Notably, VPA may enhance the activity of NF- κ B p65, which ultimately initiates transcriptional signaling to produce pro-inflammatory cytokines such as TNF- α and IL-1 β (Goodwin et al., 2018; Lamparter et al., 2017; Mitchell et al., 2016; Sugiura et al., 2011).

Regulatory Effects of VPA on Pro-inflammatory Cytokines

In a rat model of renal ischemia-reperfusion injury, Amirzargar et al. (2017) found that VPA enhanced the expression of anti-inflammatory cytokines and lowered their levels in renal tissue, thereby promoting the recovery of damaged kidney function by correcting the imbalanced immune response. Some experiments have confirmed that VPA pretreatment can down-regulate the expression of pro-inflammatory cytokines, antimicrobial peptides, and acute-phase proteins, inhibit apoptosis, and promote an autophagic response.

Regulation of MAPK and NF- κ B Signaling Pathways

The MAPK and NF- κ B signaling pathways play crucial roles in various inflammatory responses. NF- κ B can activate multiple downstream signaling pathways, controlling the transcription and expression of various factors. During an inflammatory response, the MAPK-mediated signaling pathways are mainly composed of p38, ERK, and JNK. MAPK activation mediates the inflammatory response mainly by activating gene expression. All the p38, ERK, and JNK signaling pathways can regulate the transcriptional-translational mechanisms after being activated, and exert a certain regulatory effect on the expression of various pro-inflammatory cytokines. By doing so, they can control the proliferation and differentiation of inflammatory cells, and regulate a range of inflammatory responses. Via multi-level cascade reaction, the MAPK signals alter the activities of pathway targets and therefore can also affect targets such as the NF- κ B pathway. Histone acetylation is a key link in the regulation of gene transcription. Activation of MAPK and NF- κ B can promote the expression of pro-inflammatory cytokines (including IL-6, IL-8, and TNF- α) and elicit immune responses. In both mouse models of LPS-induced acute lung injury and bovine mammary epithelial cells after LPS stimulation, mammary epithelial cells stimulated with LPS, NF- κ Bp65, ERK, JNK, and p38 in the MAPK and NF- κ B pathways were activated, and the expressions of pro-inflammatory cytokines TNF- α and IL-6 were significantly increased (Liu, Chen, et al., 2019; Liu, Chang, et al., 2019; Ma et al., 2019). VPA is an HDACi that can regulate histone acetylation, which is likely to lead to diversified biological functions. Targeting mainly class I HDACs (HDAC1 and HDAC3), VPA can affect cell survival and protect cells. Bambakidis et al. (2016) showed that VPA down-regulated the expression of pro-inflammatory cytokine IL-1 β and alleviated the inflammatory response in a porcine model of CNS injury. VPA can inhibit the transcription of the inflammasome by suppressing the LPS-induced activation of P-38, JNK, and NF- κ B pathways in mouse brain micro VECs. In addition, VPA may inhibit matrix metalloproteinase-9

(MMP9) activity, thereby reducing inflammatory responses and brain edema after brain injury (Li et al., 2015; Shi et al., 2019).

Regulation of Autophagy

Autophagy is a self-clearance process that enables the removal of damaged organelles or pathogens by lysosomes to maintain homeostasis. Autophagy also protects the body by reducing the number of inflammasomes. Autophagy is involved in the regulation of many diseases, particularly traumatic diseases, and acts in the entire process of recovery. In a mouse model of traumatic brain injury, VPA significantly inhibited the elevation of the p62 level to increase the autophagic capacity (Zheng et al., 2019). In both spinal cord injury and myocardial dysfunction, VPA can ameliorate (Zheng et al., 2019) injury by inducing autophagy.

Regulation of Pro-inflammatory Cytokines

VPA can also inhibit PREP, a protease that is primarily used to break down serine and is widely distributed in the body. Its main role in the body is to regulate inflammation and lipid accumulation and to hydrolyze proline residues (Zhou et al., 2016). Research has demonstrated that PREP activity can be inhibited during the treatment of neutrophil-induced inflammation, which is thought to be due to a reduction in the production of the neutrophil chemokine proline-glycine-proline (PGP); in addition, PREP can hydrolyze collagen by synergizing with MMPs-8/9, and the PGP produced by hydrolysis can also bind to the CXC receptors (CXCR1 and CXCR2) on the surface of neutrophils, thus enriching the neutrophils (Abdul Roda et al., 2014). Therefore, the inhibition of PREP, MMP, or PGP can be used for therapeutic purposes. Some HDACi can modulate inflammatory responses by affecting the expression of pro-inflammatory cytokines. VAP can reduce the neuroinflammatory response after traumatic brain injury by modulating oxidative stress and autophagy induced by the Nrf2/ARE pathway and downregulating the expressions of IL-1 β , IL-6, and TNF- α (Leoni et al., 2022). It has been shown that VPA can effectively inhibit the expression of pro-inflammatory factors such as nitric oxide, prostaglandins, and cytokines. Clinically, the use of VPA in combination with levetiracetam significantly reduced the blood TNF- α and IL-6 levels and alleviated the inflammatory response in patients with stroke-related epilepsy.

Protection of Cellular Barriers

VPA can restore the balance of histone acetylation, increase cellular tolerance to inflammation, suppress cell differentiation, and improve cellular function in response to stressful stimuli such as ischemia and hypoxia (Liu, Chen, et al., 2019; Liu,

Chang, et al., 2019; Luo et al., 2017; Tang et al., 2018; Zhou et al., 2021). Burns and trauma can stimulate the body, resulting in the release of large amounts of pro-inflammatory mediators and the increase in the histone deacetylation level, which induces changes in endothelial cell conformation and disruption of cellular barriers, finally leading to increased permeability (Claesson-Welsh et al., 2021). The increased levels of oxidative stress and pro-inflammatory mediators after burns and trauma damage the endothelium and disrupt cellular barriers. For example, the release of IL-6 and TNF can cause apoptosis (Nielson et al., 2017). Meanwhile, excessive expression of hypoxia-inducible factor 1 (HIF-1) occurs after burns and trauma. By regulating key downstream genes such as MLCK and VEGF, HIF-1 leads to the redistribution of tight junctions and cytoskeleton and thus disrupts cellular barriers. Many HDACi, including VPA, can regulate cellular transcription and chromosomal modifications by inhibiting the expression of HIFs (especially HIF-1 α), affecting the permeability and normal physiological functions of cells. In addition, the HIF-1 α subunit has two transactivation domains (TAD): NH 2-terminal (N-TAD or NAD) and COOH-terminal (C-TAD or CAD). HIF-1 α may be regulated by both NDA and CAD, among which the trans-activating activity of CAD is dependent on the binding of the activator p300/CREB-binding protein (CBP). The CBP and p300 are two acetyltransferases, and many of their structural domains are rich in lysine residues that can be modified by their acetylation (Usui-Ouchi et al., 2020).

Regulation of Nutrient Metabolism

The intense post-burn stress response results in altered metabolism of the three major nutrients, with a substantial increase in catabolism and a relative inhibition of anabolism (Deng et al., 2021). In the presence of stress hormones and pro-inflammatory mediators, reduced total body protein mass further exacerbates malnutrition. The mechanistic target of rapamycin (mTOR), a component of the AKT signaling pathway, promotes the growth and proliferation of eukaryotic cells (Ilha et al., 2018). It is a central regulator of cell metabolism, proliferation, growth, and survival. AKT promotes cell survival and growth as well as biosynthesis of a variety of anabolic factors by directly or indirectly phosphorylating its target proteins (Hoxhaj & Manning, 2020). VPA regulates nutrient metabolism by promoting anabolism through its regulatory effects on inflammatory factors and active mTOR signaling pathways.

Problems and Prospects

VPA is a short-chain fatty acid that was first synthesized by Beverley Burton, an American chemist, in 1882. With anti-convulsant properties, it was initially used in the treatment of epilepsy; later, VPA was shown to have neuroprotective and nutritional properties and was used to treat bipolar disorder. VPA

has a simple structure, consisting only of C atoms and branched chain fatty acids. This makes it somewhat lipophilic. The absorption rate of VPA in the gastrointestinal tract is influenced by the route of administration and the formulation. Oral administration may result in high absorption rates, with a bioavailability of up to 100%. VPA can bind to plasma proteins and cross the blood-brain barrier, and thus the blood concentration of VPA will reach its peak within 1–3 hours. Therefore, this agent constitutes a rapid, simple, and effective strategy in the early treatment of burns and trauma. Recent studies have shown that VPA can defend against pathogens and protect the body *in vitro* and *in vivo* by inhibiting inflammatory responses, reducing apoptosis, suppressing cancer cells, and regulating autophagy. HDACi can attenuate the inflammatory response by promoting histone acetylation, affecting the MAPK and NF- κ B signaling pathways, and regulating the expression of inflammation-related genes. VPA, a class I/II HDACi, inhibits the activity of HDACs, promotes histone deacetylation, and thereby regulates gene transcription and expression to suppress inflammatory responses. Damaged skin leads to the activation of the coagulation system inside and outside the cells, thus triggering an inflammatory response in the body. The skin is the first barrier to protect the body; once it is damaged, pathogens can easily enter the body and trigger inflammation. Injury to the tissues can lead to inadequate blood and oxygen supply, resulting in ischemia-reperfusion injury, which can lead to the production of large numbers of free radicals and inflammation. In addition, tissue necrosis and infection following skin trauma can trigger an immune response, resulting in the release of large amounts of catecholamines and other substances that regulate the inflammatory responses. While the therapeutic effect of VPA on the inflammatory response to burns and trauma has been demonstrated in many studies, further animal experiments and clinical trials are still required to verify this finding. The standard therapeutic dose remains unclear, and overdosing may exacerbate the inflammatory response. Furthermore, the effective half-life of the drug is poorly defined. Therefore, further research is needed to determine the optimal dose, frequency, and route of administration of VPA in alleviating inflammation and its synergistic effect with other drugs, so as to optimize the treatment of post-burn and post-traumatic inflammatory responses.

Abbreviations

C-TAD or CAD: COOH-terminal; CXCR1 and CXCR2: CXC receptors; HDAC: Histone deacetylase; HDACi: Histone deacetylase inhibitor; LPS: Lipopolysaccharide; MMP9: Matrix metalloproteinase-9; mTOR: Mechanistic target of rapamycin; N-TAD or NAD: NH₂-terminal; PGP: Proline-glycine-proline; TAD: Transactivation domains; VECs: Vascular endothelial cells; VPA: Valproic acid.

Author Contributions

Meidi Zhu: Provision of study materials or patients, collection and assembly of data, manuscript writing, final approval of manuscript. Shu-Ming Wang: Conception and design, administrative support, data analysis and interpretation, manuscript writing, final approval

of manuscript. Rui Liu: Conception and design, administrative support, provision of study materials or patients, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Approved by the Medical Ethics Committee of Heilongjiang Provincial Hospital [batch number (2021)099].

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