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Потенциальная роль ингибиторов PDE4 в лечении пептической язвы

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Аннотация

Актуальность. Пептическую язву, представляющую собой распространенное заболевание желудочно-кишечного тракта, чаще всего вызывают инфицирование *Helicobacter pylori*, прием нестероидных противовоспалительных препаратов и факторы образа жизни, в том числе употребление алкоголя и курение. Ирсогландин, неспецифический селективный ингибитор PDE4, продемонстрировал терапевтический потенциал в отношении язвы желудка – он способствовал заживлению слизистой оболочки, уменьшению воспаления и усилению антиоксидантной защиты. В настоящем обзоре рассмотрен терапевтический потенциал ирсогландина и ингибиторов PDE4B в лечении пептических язв.

Материалы и методы. Чтобы найти подходящее исследование для этой обзорной статьи, был проведен тщательный поиск литературы с использованием электронных баз данных, таких как Google Scholar и PubMed. В стратегии поиска использовались такие ключевые слова, как «peptic ulcer», «Phosphodiesterase-4 inhibitors», «irsogladine», «cAMP» и «mucosal healing». В поиск были включены только последние англоязычные публикации.

Заключение. Ингибиторы фосфодиэстеразы-4, в особенности воздействующие на фосфодиэстеразу-4B, играют значимую роль в модуляции иммунного ответа, снижении окислительного стресса и содействии ангиогенезу. Указанные свойства делают их многообещающим средством для лечения пептических язв. Дальнейшие исследования должны быть ориентированы на оптимизацию селективности ингибиторов фосфодиэстеразы-4, оценку их безопасности при длительном использовании и проведение широкомасштабных клинических исследований с целью определения их эффективности для лечения пептической язвы.

Ключевые слова: пептическая язва, фосфодиэстераза, циклический аденозинмонофосфат, ирсогландина малеат, селективные ингибиторы PDE4B.

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Potential Roles of PDE4 Inhibitors in Peptic Ulcer Treatment

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Abstract

Introduction. Peptic ulcer disease, a common gastrointestinal disorder, is mostly caused by Helicobacter pylori infection, non-steroidal anti-inflammatory drug usage, and lifestyle factors including alcohol use and smoking. Irsogladine, a non-specific selective PDE4 inhibitor, has demonstrated therapeutic potential in gastric ulcers by promoting mucosal healing, reducing inflammation, and enhancing antioxidant defenses. This review explores the therapeutic potential of irsogladine and PDE4B inhibitors in treating peptic ulcers.

Methods. To find appropriate research for this review article, a thorough literature search was carried out utilizing electronic databases such as Google Scholar and PubMed. Keywords such as “peptic ulcer”, “Phosphodiesterase-4 inhibitors”, “irsogladine”, “cAMP” and “mucosal healing” were used in the search strategy. Only recent, English-language publications were included in the search.

Conclusion. Phosphodiesterase-4 inhibitors, particularly those targeting phosphodiesterase -4B inhibitors, play a significant role in modulating immune responses, reducing oxidative stress, and supporting angiogenesis. These properties make them a promising therapeutic approach for peptic ulcer disease. Future research should focus on optimizing the selectivity of phosphodiesterase-4 inhibitors, evaluating their long-term safety, and conducting large-scale clinical trials to establish their efficacy in peptic ulcer management.

Keywords: peptic ulcer, phosphodiesterase, cyclic adenosine monophosphate, irsogladine maleate, selective PDE4B inhibitors.

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Introduction

Peptic ulcer disease (PUD) affects millions of individuals worldwide, posing a significant healthcare burden owing to its high prevalence, associated complications, and substantial impact on healthcare systems and quality of life. It is caused by Helicobacter pylori infection, long-term use of non-steroidal anti-inflammatory drugs, excessive alcohol consumption, stress, and smoking [1]. The disease is characterized by gastric and duodenal ulcers, causing symptoms like burning stomach pain, bloating, and heartburn. Untreated ulcers can lead to gastrointestinal bleeding, hematemesis, or melena, while chronic ulcers can cause perforation or peritonitis, potentially causing life-threatening infections [2].

Vascular damage leads to tissue necrosis, ischemia, hypoxia, and free radical production. The resulting inflammatory response involves gastric mucosal damage, neutrophil infiltration, reactive oxygen species (ROS) release, prostaglandin formation, and cytokine imbalance favoring pro-inflammatory cytokines [3]. Peptic ulcer disease arises from an imbalance between protective factors – such as the mucus barrier, normal mucosal blood flow, bicarbonate secretion, prostaglandins, and endogenous antioxidants – and aggressive factors, including gastric acid, pepsin, ROS,

and stress [4]. Inflammation, immune dysregulation, [1], and oxidative stress [2] play pivotal roles in the pathogenesis of peptic ulcers by disrupting the balance between protective and aggressive factors in the gastric mucosa, leading to tissue damage and impaired healing [3]. Given the role of inflammation and oxidative stress in peptic ulcer pathogenesis, targeting, a key regulator of these processes, has emerged as a promising therapeutic strategy.

Given the central role of inflammation and oxidative stress in the pathogenesis of PUD, targeting phosphodiesterase-4 (PDE4) – a key regulator of these processes – has emerged as a promising therapeutic strategy.

PDE is an enzyme that breaks phosphodiester bonds and degrades cyclic nucleotide second messengers like cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) [5]. PDEs can be classified into 11 groups that can be divided into three groups: PDEs 4,7, 8 are specific for cAMP, PDEs 5, 6, 9 are specific for cGMP, and the other PDEs can hydrolyze both cAMP and cGMP5 [6].

A PDE inhibitor is a drug that blocks one or more PDE subtypes, preventing the inactivation of intracellular cAMP and cGMP second messengers. There are two types of PDE inhibitors; non-selective such as methylated xanthines and derivatives and selective PDE [5].

PDE4 selective inhibitors prevent the breakdown of cAMP by the PDE4 enzyme, leading to increased intracellular cAMP levels. This activates the protein kinase A signaling pathway, which regulates smooth muscle relaxation, neural plasticity, and inflammatory responses. PDE4 is highly expressed in immune cells, making it a target for anti-inflammatory therapies [7]. These inhibitors reduce ROS production by suppressing nicotinamide adenine dinucleotide phosphate oxidase activity and mitochondrial dysfunction. They also decrease the release of pro-inflammatory cytokines (such as tumor necrosis factor (TNF-α), interleukins (IL) -6 & -8) and mediators (such as prostaglandins, leukotrienes) by inhibiting nuclear factor kappa-B cells and mitogen-activated protein signaling pathways. These mechanisms have been demonstrated in inflammatory conditions such as asthma, chronic obstructive pulmonary disease (COPD), rhinitis, and rheumatoid arthritis [5].

The PDE4 subfamily has four subtypes: PDE4A, PDE4B, PDE4C, and PDE4D, each with unique tissue distribution and physiological roles. Non-specific selective PDE4 inhibitors that bind all four PDE4 subtypes simultaneously, such as roflumilast, cilomilast, crisaborole, apremilast, and irsogladine have many therapeutic benefits [6]. The Food and Drug Administration has approved roflumilast and cilomilast for the treatment of chronic obstructive pulmonary disease; however, roflumilast is more effective than cilomilast at inhibiting PDE4B in inflammatory cells. Additionally, it approved crisaborole and apremilast for the treatment of atopic dermatitis and psoriatic arthritis, respectively [8].

Irsogladine maleate (4,4'-Dihydroxy-2,2'-dimethoxy-5,5'-dimethyl-diphenylmethane) is one of non-specific selective PDE4 inhibitors. It is used in the treating and preventing of the various forms of gastric peptic ulcer. Additionally, it is more beneficial than famotidine for people who smoke and consume alcohol [9]. Despite its ability to inhibit PDE4, irsogladine generally causes only mild to moderate nausea and rarely induces emesis. This makes it better tolerated than other non-specific selective PDE4 inhibitors. Due to dose-limiting adverse effects like nausea and vomiting, other non-specific selective PDE4 inhibitors such roflumilast, cilomilast, crisaborole, and apremilast are not widely used [6].

Specific selective PDE4B inhibitors, such as PF-07038124, PF-04880594 D-159687, D-159404, and D-145, exhibit potent anti-inflammatory and immunomodulatory effects [10].

In mammals, the PDE4B gene encodes five variants: PDE4B1, PDE4B2, PDE4B3, PDE4B4 and PDE4B5. The most widely expressed of these variants in immune cells, such as neutrophils, B cells, macrophages, and microglia, is PDE4B2, which also seems to be the main isoform involved in modifying inflammatory responses [5].

They represent a promising therapeutic approach, maximizing therapeutic effects while minimizing gastrointestinal tract (GIT) side effects. Its potential use in the management of peptic ulcers is a potentially useful concept. These inhibitors are currently in preclinical development and are expected to be used in clinical trials [11]. The clinical evidence regarding irsogladine and specific selective PDE4B inhibitors and their potential applications in PUD is the main topic of this review.

Mechanisms of Irsogladine Action in the treatment of peptic ulcer

The therapeutic potential of irsogladine in the prevention and management of peptic ulcers can be attributed to several mechanisms. It enhances GIT mucosal protection, exerts anti-inflammatory effects, and possesses antioxidant properties [12], while also increasing blood flow and angiogenesis, and modulating immune responses [13].

Irsogladine increases cAMP levels by inhibiting its breakdown, leading to the activation of protein kinase A. This cascade inhibits inflammatory mediators (e.g., nuclear factor kappa B, cyclooxygenase-2) and pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-8, IL-1β) while stimulating anti-inflammatory cytokines (e.g., IL-10) and T cell suppression [14].

It also reduces neutrophil chemotaxis, adhesion, degranulation, and phagocytosis, alleviating gastric mucosal inflammation. Additionally, by modulating immune responses, it mitigates immune-mediated gastric damage and enhances the clearance of Helicobacter pylori, improving antibiotic therapy effectiveness [9].

Irsogladine directly protects the GIT mucosa by stimulating mucus and bicarbonate production, glycoprotein synthesis, epithelial cell proliferation, and tissue repair, while also strengthening tight junctions between epithelial cells [13]. By upregulating connexin-32 and -26 proteins, it supports mucosal integrity and repair [15].

It reduces aggressive factors like gastric acid and pepsin while enhancing mucosal defense mechanisms such as the mucus barrier, bicarbonate secretion, and prostaglandins. A healthy gut barrier limits pathogenic microbe translocation, reducing ulcer risk. It also enhances gastric microcirculation, ensuring optimal tissue perfusion [12, 13].

Irsogladine promotes ulcer healing through re-epithelialization, angiogenesis, and improved gap junction function. It stimulates angiopoietin-1 production and matrix metalloproteinase activity, supporting vessel stabilization and tissue repair [12, 9]. Its antioxidant effects involve reducing ROS and increasing antioxidant enzymes [13].

PDE4B Inhibitors: Future Expectations

Selective PDE4B inhibitors, such as PF-07038124, PF-04880594D-159687, D-159404, and D-145, represent a promising future avenue for managing peptic ulcers due to their targeted mechanisms of action [6]. They elevate cAMP levels by inhibiting PDE4B, enhancing mucosal defenses, reducing oxidative stress, and modulating immune responses [17].

PDE4B inhibitors suppress lipopolysaccharide-induced nuclear factor kappa B activation, ROS generation, and neutrophil infiltration. Elevated cAMP suppresses pro-inflammatory cytokines (e.g., TNF-α, IL-6, IL-8) while enhancing anti-inflammatory mediators like IL-10, which stimulates angiogenesis [16].

These inhibitors also enhance epithelial repair mechanisms and suppress aggressive factors like gastric acid and pepsin. By improving mucosal defenses and reducing inflammation, PDE4B inhibitors show great potential as future therapeutic agents [17].

Conclusion

For irsogladine, the focus should be on optimizing its use in combination with existing therapies, such as proton pump inhibitors and antibiotics for Helicobacter pylori eradication, while monitoring for rare adverse effects such as liver enzyme elevation or allergic reactions. The future of PDE4 inhibitors in the treatment of peptic ulcers should prioritize improving selectivity, minimizing systemic side effects, and evaluating long-term safety in diverse patient populations. Additionally, addressing economic and accessibility challenges will be crucial for ensuring these therapies reach a broad patient base. By addressing these challenges, irsogladine and PDE4 inhibitors can be better positioned to fulfill their potential as effective, well-tolerated, and accessible treatments for peptic ulcers.

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