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Therapeutic Potential of SH-HP (His-D-Trp-Ala-Trp-D-Phe-Lys) in Helicobacter Pylori Infection and Acute Gastric Intoxication

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Therapeutic Potential of SH-HP (His-D-Trp-Ala-Trp-D-Phe-Lys) in Helicobacter Pylori Infection and Acute Gastric Intoxication

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Abstract

***Helicobacter pylori* is a highly prevalent gastric pathogen (colonizing ∼50% of people worldwide) that causes chronic gastritis, peptic ulcer disease, MALT lymphoma, and gastric cancer. Rising antibiotic resistance (e.g. >15% clarithromycin resistance) has compromised standard eradication regimens, necessitating novel therapies. SH-HP (His-D-Trp-Ala-Trp-D-Phe-Lys) is a synthetic hexapeptide analogue of the endogenous hormone ghrelin/GHRP-6, originally developed as a growth hormone secretagogue. Preclinical studies reveal that SH-HP/GHRP-6 has potent gastroprotective and anti-inflammatory effects: it prevents stress-induced gastric mucosal lesions and mitigates multiorgan damage in ischemia/reperfusion models. Given that ghrelin receptor signaling plays a key role in gut mucosal defense (via nitric oxide and prostaglandins) and gut–brain homeostasis, we hypothesize that SH-HP may improve outcomes in H. pylori infection and acute gastric injury. This paper reviews the background and rationale for SH-HP therapy, including its effects on mucosal integrity, systemic inflammation, and the gut–brain axis. We propose a randomized, placebo-controlled clinical trial (see Table 1) to evaluate SH-HP as an adjunct to standard H. pylori eradication therapy. If effective, SH-HP could represent a new adjunctive treatment to protect the gastric mucosa, counteract inflammation, and restore neuroendocrine balance in infected patients.**

Keywords: Helicobacter pylori, Gastric ulcers, Ghrelin, Growth hormone secretagogues, Gut–brain axis, Clinical trial

1. Introduction

Helicobacter pylori infection is a major global health problem, with roughly half of the world's population harboring the bacterium. Infection rates exceed 50% in many developing regions and still approach 30–40% in developed countries. Although most carriers are asymptomatic, H. pylori is the primary cause of chronic gastritis and peptic ulceration, and a leading risk factor for gastric cancer and MALT lymphoma. In fact, virtually all duodenal ulcer patients and the majority of gastric ulcer patients are H. pylori-positive. Eradication of the organism typically requires multi-drug antibiotic regimens; however, rising antibiotic resistance (e.g. clarithromycin resistance >15% worldwide) has made H. pylori difficult to eliminate. New acid-blocking drugs and probiotics are being explored, but unmet needs remain for therapies that protect the stomach lining and modulate host response.

H. pylori infection also perturbs the *gut–brain axis*, altering appetite hormones (ghrelin, leptin) and neuroimmune signaling. Infected patients often show reduced ghrelin levels and dysregulated hunger signals, which may contribute to dyspeptic symptoms and mood changes. Recent reviews highlight that H. pylori can induce changes in cognitive function, appetite, and immune activation via the brain–gut axis. Thus, an ideal new therapy would not only aid in bacterial clearance but also protect the gastric mucosa and restore gut–brain homeostasis. In this context, we focus on **(His-D-Trp-Ala-Trp-D-Phe-Lys)**, a synthetic GHRP-6 analogue with promising gastroprotective properties.

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2. SH-HP (GHRP-6) and mechanism of action

SH-HP is chemically identical to **GHRP-6** (His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2), a small synthetic peptide originally developed to stimulate growth hormone (GH) release. It binds the ghrelin/GH secretagogue receptor (GHS-R) in the stomach, pituitary, and other tissues. In cell culture, GHRP-6 induces GH secretion in a dose-dependent manneracting synergistically with endogenous GH-releasing factor. However, beyond its endocrine effects, GHRP-6 has been found to exert powerful *cytoprotective and anti-inflammatory* actions via GH-independent pathways. For example, GHRP-6 and related GHS analogues protect cardiac and liver cells from ischemic injury through anti-oxidative and anti-apoptotic mechanisms. Notably, SH-HP can be administered safely even at high doses, and it is effective orally or via injection.

Several key mechanisms have been described for SH-HP/GHRP-6 that could benefit H. pylori–infected stomachs:

- **Gastroprotection and mucosal defense:** Ghrelin (the natural GHS-R ligand) strongly promotes gastric mucosal blood flow and integrity via nitric oxide and prostaglandins. Exogenous ghrelin or GHRP-6 markedly reduces ethanol-, NSAID-, and stress-induced ulcers in rodents In rat models of acute stress (water-immersion restraint), GHRP-6 given intravenously completely prevented gastric erosions. Thus SH-HP likely enhances mucosal defense and repair. This includes stimulation of growth factors (e.g. EGF) and anti-oxidative pathways in the gastric epithelium, improving ulcer healing.
- **Anti-inflammatory and immunomodulatory effects:** GHS-R agonists modulate immune cell function directly. In animal studies, GHRP-6 reduced systemic inflammatory markers and multi-organ injury in ischemia/reperfusion shock. It activates the PI3K/Akt and HIF-1α pathways to promote cell survival. By blunting pro-inflammatory cytokine release, SH-HP could mitigate the immune-mediated component of H. pylori gastritis. Furthermore, ghrelin signaling has been shown to inhibit inflammatory pathways in gastric mucosa; thus SH-HP may down-regulate the chronic gastritis induced by H. pylori.
- **Gut–brain axis and neuroendocrine regulation:** As a ghrelin analog, SH-HP likely influences hypothalamic and vagal circuits. Ghrelin stimulates appetite and exerts anxiolytic effects. H. pylori infection is known to lower ghrelin levels and is associated with higher rates of anxiety and visceral hypersensitivity. By activating GHS-R, SH-HP may restore normal appetite signaling and reduce dyspeptic symptoms via neural pathways. Importantly, ghrelin can act centrally by crossing the blood–brain barrier or via vagal afferents; thus SH-HP may also help rebalance the disturbed brain–gut signaling seen in H. pylori infection.

In summary, SH-HP couples gastrointestinal protection with systemic regulation. Its dual action on the stomach lining and on host neuroimmune circuits makes it an attractive candidate for H. pylori–associated diseases.

3. Evidence of gastroprotective effects

Preclinical data support SH-HP's potential benefit in gastric injury models. In rats subjected to water-immersion stress, GHRP-6 dramatically prevented the formation of gastric ulcers. This protection was shown to be mediated via peripheral (not central) mechanisms, likely involving vagal pathways and reduced acid secretion. In various ulcer models, ghrelin or its agonists preserved mucosal integrity: for example, endogenous ghrelin rises after acute stress or ethanol injury, suggesting a feedback protection mechanism. If SH-HP mimics these effects, it could protect the stomach during acute insults ("gastric intoxication") as well as chronic infection.

In addition, SH-HP may cooperate with standard eradication therapy to improve outcomes. By improving mucosal healing and reducing inflammation, it could enhance antibiotic efficacy and symptom relief. Its growth hormone–releasing action might also improve nutritional status in malnourished patients. Finally, the systemic anti-inflammatory actions demonstrated in diverse models suggest SH-HP could help prevent extra-gastric consequences of H. pylori infection, such as anemia or autoimmune effects.

4. Proposed clinical trial design

H. pylori's impact on the nervous system is increasingly recognized. Infection alters hypothalamic–pituitary–adrenal and autonomic regulation, leading to changes in mood and gut sensation. Studies indicate that eradicating H. pylori normalizes ghrelin and leptin levels and can improve depressive symptoms Because SH-HP is a potent ghrelin agonist, it may help correct the hormonal and neural dysregulation caused by H. pylori. In other words, SH-HP could modulate the gut–brain axis to improve both gastrointestinal and psychological well-being in infected

Table 1. Proposed study design for a clinical trial of SH-HP in H. pylori infection.

Parameter	Description
Study design	Phase II randomized, double-blind, placebo-controlled trial
Participants	Adults (18–65) with active H. pylori infection (confirmed by urea breath or stool antigen test) and dyspeptic symptoms
Interventions	Intervention: Standard H. pylori eradication therapy + SH-HP (e.g. 100–300 μg SC daily for 4–8 weeks). Control: Standard therapy + placebo SC.
Primary endpoints	H. pylori eradication rate (4–6 wk post-therapy) and change in gastric symptom scores (e.g. GSRS)
Secondary endpoints	Endoscopic inflammation score; serum ghrelin level; inflammatory cytokines (IL-6, TNF-α); patient quality-of-life; incidence of adverse events
Sample size	~100 patients (50 per arm) to detect clinically meaningful differences (power calculations TBD)
Duration	8-week treatment period, with 3- and 6-month follow-up for recurrence or late effects
Analysis	Intention-to-treat analysis; comparison of eradication rates by chi-square; symptom scores by ANOVA; safety by incidence tables

patients. Its action on the vagus nerve (as shown in stress ulcer models) further underscores its neuromodulatory role.

5. Gut–Brain axis implications

To translate these findings, we propose a pilot clinical trial of SH-HP in H. pylori–infected patients. Table 1 outlines a suggested randomized, double-blind, placebo-controlled study. Adult patients with confirmed H. pylori gastritis would receive either subcutaneous SH-HP or placebo in addition to standard triple therapy. The primary endpoint would be H. pylori eradication rate (by urea breath test) and symptom score at 8 weeks. Secondary outcomes include endoscopic healing of gastritis, serum ghrelin and inflammation markers, and patient-reported quality of life. Safety assessments would focus on potential side effects (metabolic, cardiovascular) known from prior GHRP-6 trials.

- We anticipate that adjunctive SH-HP will enhance mucosal healing and reduce gastritis symptoms beyond antibiotic therapy alone.
- Exploratory analyses could compare results to historical controls or evaluate SH-HP in patients with NSAID-induced gastritis (acute gastric "intoxication").

In this model trial, a significant increase in eradication rate or a reduction in gastritis severity with SH-HP would justify larger studies. By including measures of gut–brain and metabolic hormones, the study could also shed light on the systemic effects of SH-HP.

6. Discussion and Conclusion

SH-HP (GHRP-6) represents a novel approach to treating H. pylori and gastric injury. Its known pharmacology suggests multiple synergistic benefits: enhancement of mucosal defense, suppression of excessive inflammation, and modulation of neurohormonal signaling. These are complementary to antibiotic and acid-blocking therapies. Importantly, SH-HP acts peripherally to protect the stomach lining, as well as centrally through the vagus nerve and brain–gut peptides.

Compared to current treatments, SH-HP could reduce the incidence of bleeding ulcers and speed healing of gastritis. Its potential to normalize appetite hormones might improve nutrition and quality-of-life in chronically infected patients. Moreover, by intervening in the gut–brain axis, SH-HP could mitigate functional dyspepsia symptoms that often persist after eradication. The safety profile of GHRP-6 is well-established in humans, and no significant systemic toxicity has been reported at pharmacologic doses.

In conclusion, the multifaceted actions of SH-HP justify its evaluation in clinical trials for H. pylori infection and acute gastric injury. We recommend initiating a controlled study as outlined above. If successful, SH-HP would offer a first-in-class gastroprotective therapy that works alongside antibiotics to treat this common infection. This strategy could also be extended to other forms of acute gastritis ("gastric intoxication") or as a preventive measure in high-risk patients. Further research on SH-HP in Helicobacter-related disease is warranted.

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