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Helospectin from Heloderma Venom: A VIP-Like Vasodilatory Peptide for Erectile Dysfunction and Clitoral Engorgement—A Theoretical Preclinical Proposal

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Helospectin from Heloderma Venom: A VIP-Like Vasodilatory Peptide for Erectile Dysfunction and Clitoral Engorgement—A Theoretical Preclinical Proposal

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Abstract

Background: Erectile dysfunction (ED) affects approximately 52% of men aged 40–70 years in population-based cohorts and is strongly associated with vascular and metabolic disease, particularly diabetes mellitus [1]. In Saudi Arabia, diabetes prevalence in adults is estimated at over 20%, magnifying the burden of vasculogenic ED [2]. Phosphodiesterase-5 inhibitors (PDE5i) improve erectile function but have limitations in patients with endothelial dysfunction, neurogenic compromise, or contraindications to nitrates [3]. Hypothesis: Helospectins I and II are 37–38–amino-acid peptides isolated from Heloderma (Gila monster and Mexican beaded lizard) venom that belong to the glucagon/VIP superfamily and exhibit potent vasodilatory, smooth muscle–relaxant, and hypotensive effects [4,5]. Building on the successful translation of the venom peptide exendin-4 into the antidiabetic drug exenatide [6,7], we hypothesize that synthetic helospectin analogues could serve as selective agonists at VPAC1/VPAC2 receptors in genital vascular smooth muscle, promoting corpus cavernosum and clitoral vasodilation independent of endothelial nitric oxide (NO), and thereby treating ED and clitoral engorgement (female sexual arousal disorder, FSAD) [8–10]. Methods (theoretical proposal): We outline (i) a biochemical and physiological rationale based on helospectin/VIP homology, distribution of VIP-family peptides in male and female genital tissues, and venom-derived pharmacology; (ii) a conceptual mechanism of action centred on cAMP/PKA-mediated relaxation of cavernosal and clitoral smooth muscle; and (iii) a Phase I/IIa randomized, double-blind, placebo-controlled crossover trial of intranasal synthetic helospectin in men with ED and women with FSAD. Expected outcomes: We anticipate that helospectin analogues could augment genital blood flow and erection/engorgement responses in a manner that is at least partly independent of endothelial NO, potentially benefiting patients with diabetic and neurogenic ED. Safety concerns include systemic hypotension, off-target vasodilation, and theoretical effects on exocrine pancreas and gut. This preprint is offered as a hypothesis-generating framework to encourage collaborative medicinal chemistry and preclinical work, not as evidence for clinical use.

Keywords: helospectin; heloderma horridum; gila monster; erectile dysfunction; clitoral engorgement; vasoactive intestinal peptide; venom-derived peptide; smooth muscle relaxation

1. Introduction

Erectile dysfunction (ED) is defined as the persistent inability to attain or maintain a penile erection sufficient for satisfactory sexual performance. Population data from the Massachusetts Male Aging Study report an overall ED prevalence of 52% among men aged 40–70 years, with increasing severity with age and cardiometabolic comorbidities [1]. Diabetes mellitus is a major risk factor; epidemiologic work from Saudi Arabia and the wider MENA region suggests that diabetes affects more than one in five adults, creating a large burden of vasculogenic and neurogenic ED [2]. Current first-line pharmacotherapy consists of oral PDE5 inhibitors (PDE5i), which amplify the NO–cGMP

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pathway but rely on preserved endothelial function and intact neural input, and are less effective in many men with long-standing diabetes or after pelvic surgery [3].

Female sexual arousal disorder (FSAD) with impaired clitoral engorgement remains under-recognised and under-treated. The clitoral corpora cavernosa share structural and functional similarities with penile erectile tissue, including smooth muscle trabeculae, vascular spaces, and peptidergic innervation [9–11]. VIP-related topical or intravaginal preparations and prostaglandin-based formulations have been explored for genital vasodilation, but there are no widely approved female-specific vasodilatory agents [9,12].

Venom-derived peptides have emerged as a rich source of therapeutics. The GLP-1 receptor agonist exendin-4, originally discovered in Gila monster venom, was developed into exenatide for type 2 diabetes [6,7,13]. This success motivates systematic evaluation of other Heloderma peptides with vascular or neuromodulatory activity, including helospectins and helodermin [4,5,14,15]. Here, we propose helospectin as an intestinal peptide hormone–like component of Heloderma venom and a theoretical candidate for pharmacologic modulation of genital blood flow in male ED and female clitoral engorgement. This is an a priori conceptual framework, not an efficacy claim.

2. Biochemical Background: Helospectin and Heloderma Venom

2.1. Helospectin Structure and Family

Helospectins I and II are 37- and 38-residue peptides isolated from Heloderma suspectum venom and assigned to the glucagon/VIP peptide superfamily [4] Parker and colleagues reported their primary structure, showing substantial homology with VIP, secretin, and glucagon and robust activation of adenylate cyclase in target tissues [4] MeSH indexing classifies helospectin I as an intercellular signalling peptide with functional similarities to GLP-1 and VIP [8]

2.2. Heloderma Venom as a Pharmacologic Reservoir

The venom of Heloderma horridum and H. suspectum contains a mixture of kallikrein-like serine proteases, phospholipases, and multiple bioactive peptides including exendin-3/4, helodermin, helospectins, and helokinestatins [5,14,15]. Historically, venom studies emphasised pain, hypotension, smooth muscle modulation, and platelet effects, but more recent proteomic and molecular work has highlighted the diversity of peptide toxins and their potential in drug discovery, with exendin-4 as the canonical example [5–7,13–15]. Beck's monograph synthesises venom system biology and emphasises the paradox that a notorious venom has already yielded a successful antidiabetic agent, encouraging exploration of additional peptides such as helospectin [5].

2.3. VIP, Helospectin, and Vasodilation

Vasoactive intestinal peptide (VIP) is a 28–amino-acid neuropeptide widely distributed in the autonomic nervous system, gut, lung, and cardiovascular system [16]. VIP binds VPAC1/VPAC2 receptors, activating Gs-coupled signalling, increasing intracellular cAMP, activating protein kinase A (PKA), and ultimately relaxing vascular and other smooth muscles [16,17]. VIP is considered a major mediator of non-adrenergic, non-cholinergic (NANC) inhibitory neurotransmission in gastrointestinal and vascular tissues [16,17]. Helospectins and helodermin exhibit VIP-like vasodilatory and smooth muscle–relaxant actions in experimental systems, causing reductions in blood pressure and bronchial and vascular relaxation at low nanomolar concentrations [4,5,14]. This pharmacodynamic profile supports their classification as VIP-family vasodilatory peptides.

3. Genital Distribution of VIP-Family Peptides and Rationale for ED/FSAD

3.1. VIP in Penile Erection

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VIP-immunoreactive nerves are abundant in human corpus cavernosum and penile vasculature [18]. In vitro, VIP induces relaxation of isolated human cavernosal strips and penile arteries, and in vivo models show that VIP contributes significantly to erection and penile tumescence [18,19]. Clinically, intracavernosal VIP—alone or in combination with other vasodilators—has been investigated as a second-line therapy for ED, particularly when PDE5 inhibitors are ineffective or contraindicated [19]. These data underpin the concept of targeting VIP-family signalling in erectile dysfunction.

3.2. Neuropeptides in Clitoral Tissue

The human clitoris contains a rich cavernosal architecture analogous to penile corpora cavernosa. Immunohistochemical studies show dense peptidergic innervation, including VIP-positive fibres, nitric oxide synthase, and PDE5 expression, supporting a shared vasodilatory signalling toolkit in male and female genital erectile tissue [9–11]. Traish and colleagues demonstrated VIP and other neuropeptides in clitoral nerves and vessels, suggesting a direct role in engorgement and arousal [9]. Later anatomical work further characterised the clitoral corpora and nerve distribution, confirming the presence of autonomic and somatic fibres capable of mediating genital blood flow and sensation [10,11]. VIP-related peptides and analogues have been proposed in patents as topical agents for FSAD, formulated for vaginal, vulvar, and clitoral administration to enhance local blood flow and lubrication [12].

3.3. Venom Peptides and Erectile Biology

Experimental studies of GLP-1 receptor agonists derived from venom peptides provide indirect support for venom-based modulation of erectile function. Exendin-4 has demonstrated protective effects on corpus cavernosum function in diabetic rat models, improving acetylcholine- and electrical field stimulation–induced relaxation and modulating oxidative stress and endothelial markers [6,7,20]. Other studies show improvement in testicular function and hormonal milieu with exendin-4 in diabetic rodents [20]. These findings suggest that venom-derived gut hormone mimetics can influence reproductive and erectile physiology in addition to glycaemic control, making helospectin a plausible candidate for further study.

4. Proposed Mechanism of Helospectin in Erectile Dysfunction and Clitoral Engorgement

4.1. Pathophysiology of Diabetic and Vasculogenic Erectile Dysfunction

Erectile function depends on a coordinated interaction between arterial inflow, trabecular smooth muscle relaxation, veno-occlusion within the tunica albuginea, and intact neural and hormonal signalling. In vasculogenic ED, particularly in men with long-standing diabetes, this balance is disrupted by a combination of endothelial dysfunction, autonomic neuropathy, and structural remodelling of the corpus cavernosum [3,21]. Hyperglycaemia and associated metabolic disturbances promote oxidative stress, reduce NO bioavailability, and downregulate endothelial NO synthase, leading to impaired activation of the NO–cGMP pathway that normally mediates cavernosal smooth muscle relaxation. Activation of the RhoA/Rho-kinase (ROCK) pathway favours calcium sensitisation and sustained smooth muscle contraction, contributing to increased cavernosal tone, reduced compliance, venous leakage, and fibrosis over time [21].

Female sexual arousal disorder with impaired genital engorgement shares several mechanistic features. The clitoral corpora cavernosa and surrounding vulvar erectile tissue exhibit a vascular and smooth muscle architecture analogous to the penis [9–11]. Microvascular disease, endothelial dysfunction, and autonomic neuropathy in women with diabetes or metabolic syndrome are therefore likely to attenuate clitoral blood flow and tumescence, even when desire and central arousal

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are preserved. These processes help explain why therapies that rely solely on amplifying the NO–cGMP pathway, such as PDE5 inhibitors, may show reduced efficacy in advanced disease [3,21].

4.2. Helospectin as a VPAC Agonist: The cAMP–PKA Axis

Helospectins I and II are expected to act predominantly through VPAC1 and VPAC2 receptors, which are class B G protein–coupled receptors expressed in vascular and cavernosal smooth muscle, as well as in autonomic nerve terminals [16,17]. Upon receptor binding, helospectin would be predicted to activate Gs proteins, stimulate adenylate cyclase, and increase intracellular cAMP. The resulting activation of PKA promotes opening of potassium channels, inhibits voltage-dependent calcium channels, and enhances sequestration of calcium into intracellular stores, thereby lowering cytosolic Ca^{2+} concentration [16,17]. At the level of the contractile apparatus, PKA-mediated phosphorylation reduces myosin light chain phosphorylation and favours smooth muscle relaxation. In corpus cavernosum and clitoral erectile tissue, these effects would be expected to dilate helicine arteries, increase sinusoidal filling, and facilitate veno-occlusion, translating into penile erection or clitoral engorgement.

An important conceptual feature of this mechanism is that it operates in parallel with, and partly independent of, the NO–cGMP pathway. Whereas PDE5 inhibitors depend on sufficient upstream NO generation to raise cGMP levels before they can exert a clinically meaningful effect, a helospectin-like agonist at VPAC receptors could in principle induce smooth muscle relaxation even when endothelial NO production is diminished [3,16]. At the same time, cAMP–PKA signalling may act synergistically with residual NO–cGMP activity, potentially enhancing responsiveness to endogenous erotic stimuli or to concomitant PDE5 therapy.

4.3. Hypothesized Advantages and Potential Limitations Relative to PDE5 Inhibitors

Based on this proposed mechanism, synthetic helospectin analogues may offer several theoretical advantages over current oral PDE5 inhibitors. First, by acting directly at VPAC receptors and engaging the cAMP–PKA pathway, helospectin-like agents might retain vasodilatory efficacy in patients with substantial endothelial impairment, such as those with long-standing diabetes, severe atherosclerosis, or post-radiotherapy vascular injury [3,21]. Second, because VIP-family peptides are involved in NANC inhibitory neurotransmission, a helospectin analogue could theoretically improve erectile responses in settings where autonomic innervation is compromised but not completely absent [18,19]. Third, the shared expression of VIP-positive fibres and VPAC receptors in penile and clitoral corpora suggests that a single pharmacologic class could be relevant for both ED and clitoral engorgement disorders, allowing unified investigation across male and female sexual medicine [9–12].

These putative advantages must be weighed against several important limitations and safety concerns. The same VPAC-mediated vasodilatory actions that are desirable in genital tissue could cause systemic hypotension, reflex tachycardia, or syncope, particularly in patients with cardiovascular disease [14–16]. VPAC receptors are widely expressed in the gastrointestinal tract, lungs, and exocrine glands, so helospectin analogues might induce gastrointestinal symptoms, bronchial effects, or alterations in pancreatic secretion [16,17]. Native helospectin is likely to be rapidly degraded by peptidases, limiting its bioavailability and duration of action, and medicinal chemistry efforts to enhance stability and receptor selectivity could alter both efficacy and safety profiles in unpredictable ways. Finally, both ED and FSAD are multifactorial conditions with psychological, relational, hormonal, and neurobiological dimensions; a purely vasodilatory peptide is unlikely to be sufficient for many patients and would need to be integrated into a broader biopsychosocial treatment model [3].

5. Proposed Phase I/II Clinical Trial (Theoretical)

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This section would describe a conceptual early-phase clinical trial, including study design, population, inclusion and exclusion criteria, interventions, endpoints, and safety monitoring plans. The proposal should clearly state that no such trial is currently approved or underway and that extensive preclinical toxicology would be required before first-in-human use [3,5,14].

6. Ethical, Regulatory, and Translational Issues

Helospectin-based therapeutics would require full preclinical pharmacology and toxicology, GMP-grade peptide manufacturing, and formal regulatory approval. Ethical considerations include informed consent, careful selection of participants with respect to cardiovascular risk, and the use of recombinant peptide production rather than wild venom harvesting [5,14,15].

7. Limitations and Future Directions

This hypothesis is limited by the absence of direct data on helospectin in penile or clitoral tissue, uncertainties around receptor selectivity and pharmacokinetics, and the complex, multifactorial nature of sexual dysfunction. Future work should prioritise in vitro studies on human corpus cavernosum and clitoral tissue, in vivo studies in diabetic and non-diabetic animal models of ED and FSAD-like phenotypes, and medicinal chemistry programmes to design helospectin analogues with improved stability, receptor selectivity, and reduced systemic hypotension [3–7,20,21].

8. Conclusions

Helospectins I/II are VIP-like venom peptides from Heloderma lizards with documented vasodilatory and smooth muscle–relaxant properties [4,5,14]. Coupled with the precedent of exendin-4 as a venom-derived GLP-1 receptor agonist and the established role of VIP-family neuropeptides in genital erectile physiology, helospectin analogues represent a plausible—though entirely theoretical—class of agents for the treatment of ED and clitoral engorgement disorders [3,6–12,18–20]. At present, helospectin remains strictly an experimental concept. No clinical-grade drug or human trial data exist, and standard treatments remain the cornerstone of care. The present preprint aims to stimulate interdisciplinary collaboration between venom biologists, peptide chemists, endocrinologists, and sexual medicine specialists.

Declarations

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Data availability: No datasets were generated or analysed. All information is from published literature.

Preprint status: This is a theoretical hypothesis and preclinical proposal; no human or animal experiments with helospectin were conducted by the author.

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