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Gut–vascular axis: Mechanisms regulating erectile dysfunction

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INTRODUCTION: FROM THE GUT–TESTIS AXIS TO THE GUT–VASCULAR AXIS

Erectile dysfunction (ED) and oligoasthenospermia are urological disorders with increasing incidence. The gut microbiota has been shown to significantly influence testicular spermatogenic function and hormone secretion through pathways involving nutritional metabolism, immune regulation, hormonal balance, and microbe-derived extracellular vesicles. Concurrently, a growing body of evidence links ED to gut microbial dysbiosis.[1]

Male erectile function is highly dependent on vascular health. The core pathophysiology of ED is closely associated with vascular endothelial dysfunction and impairment of the nitric oxide (NO)-soluble guanylate cyclase (sGC)-cyclic guanosine monophosphate (cGMP) signaling pathway. The gut microbiota orchestrates vascular function through integrated metabolic, immune, and neuroendocrine pathways. Given the systemic influence of the gut microbiota and the predominant role of vascular mechanisms in ED, we propose the "gut–vascular axis" as a crucial conceptual framework for elucidating the core link between gut microbiota dysbiosis and ED.

VASCULAR ENDOTHELIAL DYSFUNCTION: THE CORE PATHOLOGICAL BASIS OF ERECTILE DYSFUNCTION

Normal erectile function relies on NO signaling and vascular integrity. Dysfunction in these systems is a key step in ED and serves as an early marker of systemic vascular disease. Specifically, NO produced by neuronal and endothelial nitric oxide synthase (nNOS and eNOS) activates sGC to generate cGMP. This, via protein kinase G (PKG), reduces intracellular Ca^{2+} and enhances myosin light chain phosphatase activity, leading to cavernosal smooth muscle relaxation and penile engorgement.

Vascular endothelial dysfunction decreases eNOS activity and NO production, directly restricting cGMP synthesis and impeding smooth muscle relaxation—a critical step in ED pathogenesis. In contrast, the RhoA/ROCK pathway maintains vascular contractility by increasing Ca^{2+} sensitivity. Conditions such as diabetes, hypertension, and aging upregulate RhoA/ROCK while inhibiting eNOS, thereby exacerbating ED. Reactive oxygen species (ROS) reduce NO bioavailability, induce inflammation, and disrupt endothelium-dependent dilation.

In erectile regulation, neuronal initiation of erection is tightly coupled with endothelial signals. Impairment of this neuro-endothelial coupling results in insufficient inflow and incomplete filling of the corpora cavernosa. Chronic ischemia and metabolic abnormalities further lead to apoptosis of smooth muscle cells, collagen deposition, reduced tissue compliance, and eventual venous leakage—a "venous" manifestation secondary to arterial insufficiency and tissue remodeling. Additionally, testosterone deficiency inhibits the NOS/NO/cGMP pathway, promotes oxidative stress, and facilitates fibrosis, thereby weakening erectile function at both vascular and tissue levels.

GUT MICROBIOTA DYSBIOSIS INDUCES VASCULAR ENDOTHELIAL DYSFUNCTION

Gut dysbiosis triggers systemic inflammatory cascades

Dysbiosis increases intestinal permeability, allowing bacterial metabolites such as lipopolysaccharide (LPS) to enter the circulation. LPS activates systemic immune responses via the Toll-like receptor 4 (TLR4)/MyD88 pathway, leading to a chronic low-grade inflammatory state. Pro-inflammatory cytokines suppress eNOS activity and expression, significantly reducing NO bioavailability and directly impairing vasodilation. Activation of TLR4 upregulates the activity of the NADPH oxidase complex, leading to the generation of a large amount of superoxide anions, which significantly reduces NO bioavailability. Concurrently, this oxidative stress induces an imbalance in the ratio of tetrahydrobiopterin (BH_4) to dihydrobiopterin (BH_2), ultimately resulting in eNOS uncoupling and exacerbating endothelial injury, thereby precipitating or worsening ED.

Concurrently, inflammation promotes monocyte/macrophage recruitment and activation, which produce more ROS and inflammatory factors, increasing endothelial apoptosis and reducing vascular responsiveness. Thus, dysbiosis-induced inflammation creates a self-reinforcing cycle of barrier disruption, immune activation, endothelial damage, and vascular impairment, collectively driving ED pathogenesis.

Bidirectional regulation by gut microbial metabolites

Gut microbial metabolites bidirectionally regulate vascular endothelial function. Harmful metabolites, such as trimethylamine N-oxide (TMAO), induce endothelial oxidative stress, promote adhesion molecule expression (ICAM-1/VCAM-1), and facilitate foam cell formation, directly damaging vascular structure. As a competitive inhibitor of L-arginine, TMAO blocks nitric oxide synthesis at the substrate-binding level. Concurrently, TMAO induces eNOS uncoupling and inhibits the Ca^{2+}/calmodulin-dependent eNOS activation pathway. At the level of phosphorylation regulation, TMAO increases the phosphorylation of Thr495 while decreasing the phosphorylation of Ser1177, thereby directly inhibiting eNOS enzymatic activity. At the cellular level, TMAO accelerates cellular senescence by disrupting endoplasmic reticulum integrity and the mitochondrial unfolded protein response, and it establishes a sustained pro-inflammatory state via the endoplasmic reticulum stress/mitochondrial reactive oxygen species/glycolysis pathway. Ultimately, TMAO impairs endothelial function through these synergistic actions.In contrast, protective short-chain fatty acids (SCFAs) maintain endothelial homeostasis by activating GPR41/43 receptors and inhibiting histone deacetylase (HDAC) and NADPH oxidase, thereby enhancing NO bioavailability and alleviating oxidative stress.[2] Butyrate specifically activates GPR43 and GPR41 receptors. Activation of GPR43 can inhibit the nuclear translocation of NF-κB via a β-arrestin-2-dependent pathway, thereby effectively downregulating the expression of inflammatory cytokines. Meanwhile, as a natural inhibitor of class I and class II HDACs, butyrate significantly increases the acetylation level of histone H3 lysine 9 in $CD4^+$ T cells of the intestinal lamina propria, further promoting immunomodulation. In addition, butyrate not only serves as a primary energy source for colonic epithelial cells but also maintains intestinal barrier integrity by upregulating the expression of tight-junction proteins and stimulating mucus secretion.

Integrated neuro–hormonal–vascular pathways

The gut microbiota influences erectile function through interconnected hormonal, neural, and vascular pathways, forming complex functional and vicious cycles. Specifically, the "steroid microbiome" affects testosterone metabolism and circulation. A decline in testosterone not only reduces libido but also impairs vascular endothelial function and NO production, forming a functional microbiota–testosterone–vascular loop.[3]

Simultaneously, the gut microbiota modulates brain regions involved in emotion, stress, and sexual arousal by affecting neurotransmitter balance (e.g., serotonin, dopamine), resulting anxiety-related ED may exacerbate microbial dysbiosis, creating a psyche–microbiota–neuro–vascular vicious cycle. Furthermore, microbial metabolites can directly activate central pathways controlling sexual arousal, with this neural regulation ultimately reflected in the control of penile vascular relaxation.[4]

Thus, as shown in Figure 1, the gut microbiota orchestrates a network spanning hormonal regulation, neurotransmitter balance, central neural control, and vascular function. Disruptions in this network manifest as ED and feed back into the system through functional loops and self-perpetuating cycles.[5]

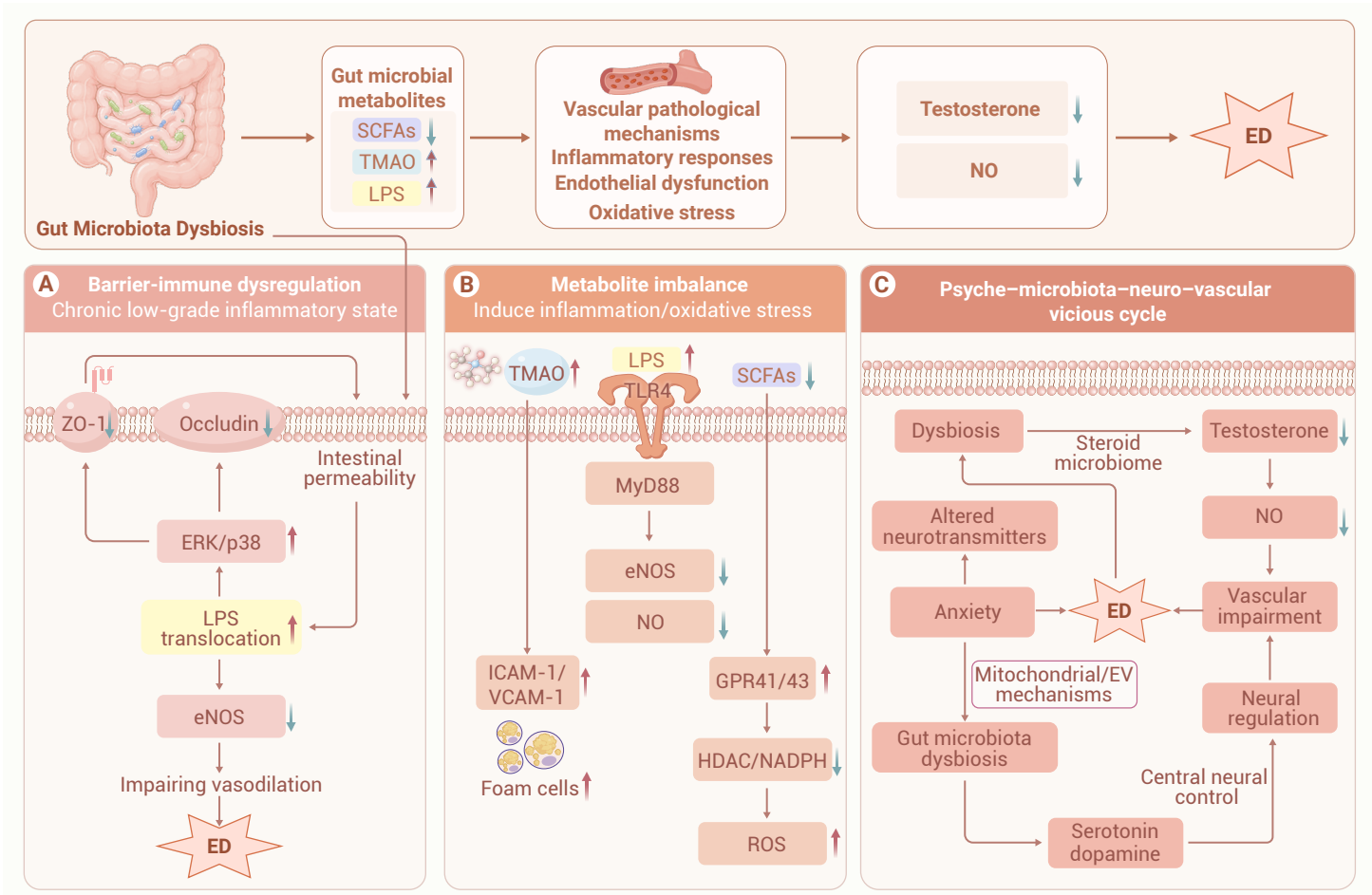

Figure 1. Multidimensional pathological mechanisms of gut dysbiosis-mediated ED This schematic illustrates three major pathways through which gut dysbiosis contributes to ED pathogenesis. (A) Gut dysbiosis increases intestinal permeability, leading to LPS translocation and downregulation of tight junction proteins. This activates ERK/p38 signaling pathways, suppresses eNOS expression, and triggers chronic low-grade inflammation, ultimately impairing vasodilation. (B) Elevated TMAO and LPS activate the TLR4/MyD88 pathway, promoting expression of adhesion molecules and foam cell formation. Reduced SCFAs impair GPR41/43 receptor signaling, increasing ROS production and inducing oxidative stress and endothelial dysfunction. (C) Dysbiosis alters steroid metabolism, reducing testosterone levels, and disrupts neurotransmitter balance, promoting anxiety and further exacerbating vascular damage. All three pathways converge on decreased NO synthesis and reduced testosterone levels, collectively contributing to ED development.

CONCLUSION AND PROSPECTS

In summary, the gut–vascular axis elucidates a core pathogenic mechanism through which gut microbiota dysbiosis drives erectile dysfunction, by systemically impairing vascular endothelial function via intertwined metabolic, inflammatory, and neurohormonal pathways. This integrative framework not only reframes our understanding of ED but also opens promising avenues for future research and intervention. Moving forward, it is imperative to shift from correlation to causation by identifying specific microbial strains and key metabolites with direct causal links, leveraging advanced approaches such as Mendelian randomization and gene editing. Concurrently, the integration of multi-omics technologies with sophisticated physiological models—such as organ-on-chip systems—will be essential to construct a precise and dynamic "gut–vascular–sexual function" network. On the translational front, these mechanistic insights should catalyze the development of targeted microbiota-modulating strategies, including next-generation probiotics, prebiotics tailored to enhance beneficial metabolites like SCFAs, and optimized fecal microbiota transplantation protocols. The gut–vascular axis not only provides a novel etiological perspective on ED but also charts a course toward mechanism-based, personalized therapeutic solutions.

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AUTHOR CONTRIBUTIONS

Yulin Zong and Yanying Li drafted the manuscript. Wenlong Sun and Lingru Li revised the article. Wenlong Sun and Yanfei Zheng contributed to the conceptualization of the article. All authors contributed to and approved the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.