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Neurotoxicity and Reproductive Hormone Dysregulation: Oxidative Stress and Immunomodulatory Mechanisms Across the Gut-Brain-Gonadal Axis

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ABSTRACT

The gut–brain–gonadal (GBG) axis represents a complex bidirectional network integrating endocrine, neural, and immune signals to regulate homeostasis. Emerging evidence indicates that dysregulation of reproductive hormones, such as estrogens, progesterone, and androgens, intersects with oxidative stress and immune signaling to exacerbate neurotoxicity. Disturbances in the gut microbiota, altered hypothalamic–pituitary–gonadal (HPG) axis activity, and chronic systemic inflammation converge to disrupt neuronal survival, synaptic plasticity, and neuroendocrine balance. Reactive oxygen species (ROS) and reactive nitrogen species (RNS) promote DNA damage, mitochondrial dysfunction, and lipid peroxidation, while immune mediators including cytokines, Toll-like receptors, and microglial activation amplify neuroinflammatory cascades. Hormonal fluctuations-particularly hypoestrogenism, androgen deficiency, and altered gonadotropin secretion-further modulate oxidative and immune pathways, heightening susceptibility to neurodegeneration, mood disorders, and reproductive dysfunction. This review synthesizes mechanistic insights into the interplay of oxidative stress and immunomodulation within the GBG axis, highlighting their roles in neurotoxicity and endocrine disruption. It also discusses therapeutic implications, including microbiota-targeted strategies, antioxidants, and immunomodulatory agents that may restore axis homeostasis and mitigate disease progression.

Keywords: neurotoxicity, reproductive hormones, oxidative stress, immunomodulation, gut-brain-gonadal axis

INTRODUCTION

The gut–brain–gonadal (GBG) axis is an intricate regulatory network that interlinks reproductive hormones, neural circuits, immune mediators, and microbial metabolites to maintain physiological balance [1]. This axis not only orchestrates reproductive processes but also profoundly influences cognition, mood, stress responses, and neurodevelopment. Communication occurs through endocrine signaling via the hypothalamic–pituitary–gonadal (HPG) axis, neural pathways including the vagus nerve, and immunometabolic routes involving cytokines and microbial metabolites [2]. In health, these connections preserve homeostasis; however, disturbances in one component reverberate across the system, producing widespread dysfunction. Disruption of hormonal homeostasis is one of the most significant triggers of GBG axis imbalance [3]. Natural life transitions such as menopause and andropause, pathological conditions like polycystic ovary syndrome (PCOS) and hypogonadism, and environmental exposures to endocrine-disrupting chemicals can all disturb the delicate equilibrium of reproductive hormones [4]. Such disruptions alter neuronal excitability, redox balance, and immune tone, creating conditions favorable for neurotoxicity. Neurotoxicity within the GBG axis may arise from multiple factors, including chronic metabolic stress, accumulation of environmental toxins, and sustained systemic inflammation [5]. Central to this process is oxidative stress—an imbalance between the production of reactive oxygen and nitrogen species and the antioxidant systems that neutralize them. Excess oxidative burden damages DNA, proteins, and lipids, undermines mitochondrial efficiency, and destabilizes neuronal membranes [6]. In parallel, immune activation perpetuates inflammatory signaling, recruits microglia and astrocytes, and disrupts blood–brain barrier integrity [6]. The intersection of oxidative stress and immune dysregulation explains why individuals with reproductive hormone imbalance are particularly vulnerable to neurological decline. For example, women transitioning through

menopause often report cognitive impairment, mood instability, and sleep disturbances, which are increasingly attributed to estrogen deficiency and its downstream effects on mitochondrial and immune function [7]. Similarly, aging men experiencing andropause demonstrate increased rates of depression and cognitive decline, linked to androgen insufficiency and chronic low-grade inflammation [8]. This interplay between endocrine, oxidative, and immune mechanisms across the GBG axis connects systemic hormonal disturbances with major neurological disorders, including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and depression [9]. Importantly, these links extend beyond the brain to reproductive health, as neurotoxicity and oxidative–immune imbalance also impair gonadal function, fertility, and sexual behavior [9]. Understanding these integrated mechanisms is crucial for developing therapeutic strategies that address neurotoxicity not as an isolated phenomenon but as a consequence of whole-body dysregulation.

2. Reproductive Hormone Dysregulation and Neurotoxicity

Reproductive hormones shape neuronal development, synaptic activity, and brain plasticity throughout life. When their signaling is dysregulated-whether through natural aging, disease states, or environmental insults-neurological vulnerability increases substantially.

2.1 Estrogens and Neuroprotection

Estrogens are among the most potent neuroprotective hormones. They enhance synaptic plasticity by increasing dendritic spine density, regulate neurotransmitter release, and improve cerebral blood flow [10]. At the mitochondrial level, estrogens optimize oxidative phosphorylation, limit ROS generation, and activate antioxidant response pathways such as Nrf2 [11]. During menopause, declining estrogen levels weaken these protective mechanisms, leading to greater susceptibility to oxidative stress and neuroinflammation [12]. Clinically, this is reflected in higher risks of dementia, depression, and mood disorders among postmenopausal women.

2.2 Androgens and Cognitive Health

Androgens such as testosterone play a key role in regulating hippocampal neurogenesis, modulating dopaminergic pathways, and supporting memory and learning [13]. Deficiency, which commonly occurs in aging men or in hypogonadism, contributes to oxidative stress, increases microglial activation, and accelerates neuronal degeneration [14]. On the other hand, excessive androgen exposure seen in certain endocrine disorders or anabolic steroid misuse can disrupt neuronal excitability and exacerbate excitotoxicity and inflammatory processes, underscoring the importance of hormonal balance [14].

2.3 Progesterone and Neuroimmune Modulation

Progesterone exerts neuroprotective actions by supporting oligodendrocyte function, enhancing myelination, and modulating neuroinflammatory responses [15]. It dampens microglial activation and promotes the release of anti-inflammatory cytokines, thereby limiting secondary injury in conditions such as traumatic brain injury. When progesterone signaling is dysregulated, these protective effects are lost, predisposing to demyelination, impaired repair mechanisms, and heightened vulnerability to neurodegenerative diseases [16].

2.4 Gonadotropins and Neural Stress

Although traditionally associated with reproduction, gonadotropins such as luteinizing hormone (LH) and follicle-stimulating hormone (FSH) also exert direct effects on the brain [17]. Their receptors are expressed in hippocampal and cortical neurons, where they influence synaptic activity and survival pathways. Dysregulated gonadotropin levels, commonly observed with aging or infertility, activate oxidative cascades and inflammatory signaling that impair neuronal resilience [18]. Elevated LH, for example, has been associated with amyloid accumulation and Alzheimer's pathology, while altered FSH contributes to oxidative stress and glial activation [19].

3. Oxidative Stress Across the Gut–Brain–Gonadal Axis

Oxidative stress serves as a central mediator connecting reproductive hormone dysregulation to neurotoxicity within the gut–brain–gonadal (GBG) axis [20]. Under physiological conditions, reactive oxygen species (ROS) and reactive nitrogen species (RNS) act as signaling molecules regulating synaptic plasticity, hormone synthesis, and immune communication [21]. However, when their production surpasses antioxidant capacity, cellular integrity is compromised, leading to mitochondrial dysfunction, DNA damage, and lipid peroxidation [22]. In the brain, neurons are particularly vulnerable to oxidative damage because of their high oxygen consumption, abundant polyunsaturated fatty acids in membranes, and relatively modest antioxidant reserves [23]. Estrogen deficiency, as occurs during menopause, diminishes antioxidant enzyme activity, including superoxide dismutase and glutathione peroxidase. This reduces resilience to ROS, permitting accumulation of oxidative lesions that impair neurotransmission and synaptic integrity [24]. Similarly, androgen deficiency in aging men alters nitric oxide signaling and heightens mitochondrial dysfunction, accelerating oxidative injury in hippocampal and cortical neurons [25].

The gut microbiota also plays a pivotal role in modulating oxidative stress across the axis. Dysbiosis leads to increased production of pro-oxidant metabolites such as trimethylamine N-oxide (TMAO) and decreased levels of short-chain fatty acids (SCFAs) like butyrate, which normally enhance antioxidant defenses and maintain gut barrier

integrity [26]. Barrier disruption allows translocation of bacterial products, including lipopolysaccharide (LPS), which triggers systemic ROS production and primes neuroinflammatory pathways [27]. This oxidative spillover damages the blood–brain barrier (BBB), facilitating neurotoxic insults [27]. The gonads are both targets and sources of oxidative stress [27]. Excessive ROS disrupt spermatogenesis, oocyte maturation, and steroidogenesis, resulting in abnormal reproductive hormone secretion [27]. This in turn alters neuronal redox balance, creating a feedback loop of dysfunction. For example, oxidative stress-induced impairment of Leydig cells reduces testosterone output, which diminishes neuronal antioxidant defenses, perpetuating neuronal injury [28].

Overall, oxidative stress acts as a unifying mechanism through which gut dysbiosis, hormone imbalance, and neural vulnerability converge [29]. By compromising mitochondrial health, altering neurotransmitter signaling, and impairing hormone synthesis, ROS and RNS create a permissive environment for neurotoxicity within the GBG axis [30,31].

4. Immunomodulatory Pathways in Neurotoxicity

Immune regulation is another cornerstone of GBG axis function, and its disruption strongly contributes to neurotoxicity. Under normal circumstances, immune mediators facilitate communication between the gut microbiota, reproductive system, and central nervous system [32]. However, chronic immune activation leads to persistent inflammation, which is increasingly recognized as a driver of neurodegenerative and neuropsychiatric disorders [33]. Cytokines such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are upregulated during reproductive hormone dysregulation [34]. For instance, estrogen deficiency promotes proinflammatory cytokine production, while androgen insufficiency skews immune cells toward inflammatory phenotypes [35]. These mediators cross the BBB or act locally within the CNS, activating microglia and astrocytes. Prolonged activation shifts glial cells into proinflammatory states, releasing further ROS and perpetuating neuronal injury.

The gut is a key initiator of these immune signals. Dysbiosis enhances microbial product leakage, activating Toll-like receptors (TLRs) on immune and neural cells [36]. TLR activation triggers NF-κB signaling, leading to sustained cytokine expression and chronic neuroinflammation [37]. At the same time, reproductive hormone fluctuations directly affect microglial reactivity: estrogens typically suppress microglial activation, while androgen deficiency enhances inflammatory signaling [38].

Adaptive immunity further amplifies neurotoxicity. Skewing toward Th1 and Th17 T-cell responses sustains chronic CNS inflammation, while impaired regulatory T-cell (Treg) function diminishes immune tolerance [39]. This imbalance affects not only the brain but also gonadal tissues, where local inflammation disrupts gametogenesis and hormone production. Importantly, oxidative stress and immune activation reinforce one another. ROS activate redox-sensitive transcription factors such as NF-κB and AP-1, amplifying cytokine production, while cytokines stimulate further ROS generation through NOX enzymes [40]. This vicious cycle links immune dysregulation and oxidative imbalance as co-drivers of neurotoxicity.

5. Gut Microbiota as a Mediator of GBG Axis Neurotoxicity

The gut microbiota is a central regulator of the gut–brain–gonadal (GBG) axis, shaping host physiology through the production of metabolites that influence reproductive hormones, oxidative balance, and immune responses [41]. In a healthy state, microbial-derived short-chain fatty acids (SCFAs) such as butyrate enhance antioxidant defenses, support intestinal barrier integrity, and exert anti-inflammatory effects [42]. However, microbial dysbiosis disrupts these protective mechanisms [43]. One key alteration involves increased activity of β-glucuronidase-producing bacteria, which interfere with estrogen metabolism and circulation, thereby disturbing hypothalamic–pituitary–gonadal (HPG) axis regulation [44]. Reduced SCFA production further diminishes antioxidant capacity and tight-junction stability, increasing systemic oxidative burden. At the same time, dysbiosis promotes endotoxemia by enhancing lipopolysaccharide (LPS) translocation across the weakened gut barrier [45]. Circulating LPS activates Toll-like receptor signaling, fueling chronic inflammation, blood–brain barrier (BBB) disruption, and microglial activation [46]. These effects amplify neuroinflammation and heighten neuronal vulnerability to oxidative stress. Importantly, reproductive hormone imbalances-such as hypoestrogenism or androgen deficiency—also reshape gut microbial composition, reinforcing the cycle of dysbiosis and systemic inflammation [47]. Thus, the gut microbiota functions as both a mediator and amplifier of neurotoxic processes in the GBG axis. Targeting microbial communities and their metabolites may provide novel strategies to mitigate hormone-driven oxidative stress and neuroinflammation.

CONCLUSION

Neurotoxicity arising from reproductive hormone dysregulation is deeply rooted in oxidative stress and immune dysregulation across the gut–brain–gonadal axis. Dysbiosis, redox imbalance, and chronic inflammation reinforce each other, amplifying neuronal and reproductive dysfunction. Therapeutic strategies that integrate hormonal, antioxidant, immune, and microbiota-focused interventions may offer the most effective approach to restoring axis

balance and reducing neurotoxic risk. Future research should prioritize biomarker discovery and clinical trials that assess multi-modal therapies targeting this intricate system.

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