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Iron Toxicity and Hypothalamic Dysfunction: The Central Role of Kisspeptin Signaling in Thalassemia-Associated Delayed Puberty

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ABSTRACT

Background: Delayed puberty is among the most prevalent endocrine complications in transfusion-dependent β-thalassemia, primarily resulting from chronic iron overload and its toxic effects on the hypothalamic–pituitary–gonadal axis. While pituitary dysfunction has historically been emphasized, accumulating evidence suggests that hypothalamic injury plays an earlier and potentially reversible role in pubertal failure. Iron accumulation within the central nervous system induces oxidative stress, mitochondrial dysfunction, neuroinflammation, and cellular apoptosis. These processes may selectively impair kisspeptin neurons in the arcuate nucleus, which are critical upstream regulators of gonadotropin-releasing hormone (GnRH) secretion and pubertal activation.

Aim: This review aims to examine the molecular and neuroendocrine mechanisms linking iron toxicity to hypothalamic dysfunction in β-thalassemia, with a specific focus on kisspeptin signaling pathways. We explore experimental, imaging, and clinical evidence supporting early hypothalamic involvement, analyze how iron-induced oxidative and inflammatory pathways may disrupt KISS1/KISS1R regulation, and discuss the translational implications for diagnosis and therapeutic targeting in adolescents with delayed puberty.

Conclusion: Emerging data indicate that iron deposition within the hypothalamus may precede overt pituitary damage, altering neuronal excitability, synaptic plasticity, and pulsatile GnRH release through disruption of kisspeptin networks. Reactive oxygen species generation, mitochondrial impairment, and activation of pro-inflammatory signaling cascades may downregulate kisspeptin expression or interfere with its receptor-mediated signaling. These mechanistic insights suggest that hypothalamic dysfunction represents a pivotal and potentially modifiable stage in thalassemia-associated hypogonadism. Understanding the interplay between iron metabolism and kisspeptin neurobiology may refine diagnostic strategies, identify early biomarkers of central dysfunction, and open avenues for targeted neuroprotective or modulatory therapies. Future research integrating neuroimaging, molecular profiling, and longitudinal endocrine assessment is essential to clarify reversibility thresholds and optimize reproductive outcomes in this vulnerable population.

Keywords β-thalassemia; iron overload; hypothalamic dysfunction; kisspeptin; KISS1; KISS1R; delayed puberty; hypogonadotropic hypogonadism; oxidative stress; neuroendocrinology

INTRODUCTION

Transfusion-dependent β-thalassemia has evolved from a fatal childhood disorder into a chronic condition compatible with long-term survival, owing to advances in transfusion strategies and iron chelation therapy. Nevertheless, chronic iron overload remains an inevitable consequence of repeated transfusions and continues to drive multisystem complications, particularly within endocrine organs. Among these, delayed puberty represents one of the earliest and most distressing manifestations in adolescents. While hypogonadotropic hypogonadism has traditionally been attributed to iron-induced pituitary damage, emerging evidence suggests that hypothalamic dysfunction may precede and contribute substantially to pubertal failure [1].

Iron is an essential micronutrient for neuronal metabolism, myelination, and neurotransmitter synthesis; however, excess iron is highly toxic to neural tissue. The central nervous system is particularly vulnerable to iron-mediated oxidative stress due to its high oxygen consumption, abundant lipid content, and relatively limited antioxidant defenses. In conditions of systemic iron overload, non–transferrin-bound iron can cross the blood–brain barrier, accumulate within specific brain regions, and catalyze the formation of reactive oxygen species. This process initiates lipid peroxidation, protein oxidation, mitochondrial damage, and ultimately neuronal dysfunction or apoptosis [2].

Neuroimaging and neuropathological studies in iron overload disorders have demonstrated iron deposition in multiple brain regions, including the basal ganglia, hippocampus, and pituitary gland. However, the hypothalamus—particularly the arcuate nucleus—has received comparatively less attention despite its central role in reproductive regulation. The arcuate nucleus houses kisspeptin-expressing neurons, which are critical upstream regulators of gonadotropin-releasing hormone (GnRH) pulsatility and pubertal onset. Disruption of these neurons can profoundly impair activation of the hypothalamic–pituitary–gonadal (HPG) axis [3].

Kisspeptin, encoded by the *KISS1* gene and acting through the G-protein–coupled receptor *KISS1R*, has emerged as a master regulator of puberty. Genetic mutations affecting this signaling pathway result in congenital hypogonadotropic hypogonadism, underscoring its indispensable role in human reproductive maturation. Beyond genetic defects, environmental and metabolic stressors have been shown to modulate kisspeptin expression and neuronal excitability, suggesting that acquired insults such as iron toxicity may similarly disrupt this pathway [4].

Despite recognition of central hypogonadism in β-thalassemia for decades, most clinical investigations have focused on pituitary hormone secretion and structural pituitary changes on imaging. The possibility that iron-induced hypothalamic injury contributes to early pubertal arrest has not been comprehensively explored. Furthermore, the molecular mechanisms by which iron-mediated oxidative stress and neuroinflammation may alter kisspeptin signaling remain poorly characterized. This represents a critical gap in understanding the pathogenesis of delayed puberty in transfusion-dependent adolescents.

This review aims to summarize current knowledge on iron neurotoxicity and hypothalamic vulnerability, with particular emphasis on kisspeptin neuronal networks. By integrating insights from neurobiology, iron metabolism, and reproductive endocrinology, we seek to clarify how iron overload may disrupt central pubertal regulation at a molecular level. Identifying hypothalamic dysfunction as a potentially early and modifiable stage of endocrine injury could reshape both diagnostic strategies and therapeutic approaches in thalassemia-associated delayed puberty.

Brain Iron Homeostasis and Mechanisms of Iron Entry into the Hypothalamus

Iron homeostasis within the central nervous system is tightly regulated to balance essential metabolic requirements against the risk of oxidative injury. Under physiological conditions, circulating transferrin-bound iron crosses the blood–brain barrier (BBB) via transferrin receptor–mediated endocytosis on brain capillary endothelial cells. Following endosomal release and reduction to ferrous iron, iron is transported into the cytoplasm through divalent metal transporter 1 (DMT1) and subsequently distributed to neurons and glial cells for incorporation into enzymes, mitochondrial respiratory complexes, and myelin synthesis pathways [1]. This regulated system ensures adequate neuronal function while preventing excess accumulation.

In transfusion-dependent β-thalassemia, chronic systemic iron overload saturates transferrin-binding capacity, leading to the

generation of non–transferrin-bound iron (NTBI). NTBI is highly reactive and capable of crossing cellular membranes through unregulated pathways, including voltage-gated calcium channels and other divalent metal transporters. Unlike transferrin-bound iron, NTBI uptake bypasses physiological control mechanisms, predisposing tissues—including the brain—to toxic iron deposition [2]. This altered iron trafficking represents a central mechanism underlying iron-mediated neurotoxicity.

Experimental studies indicate that the BBB is not impermeable to iron overload states. Iron accumulation has been demonstrated in various brain regions in conditions such as hereditary hemochromatosis and transfusional siderosis. Animal models show that excess systemic iron can disrupt BBB integrity, increasing vascular permeability and facilitating further iron influx into the brain parenchyma. Oxidative stress at the endothelial interface may exacerbate this process, creating a feed-forward cycle of neurovascular injury [3]. These findings raise concern regarding similar mechanisms occurring in adolescents with chronic transfusion therapy.

The hypothalamus may be particularly vulnerable to iron deposition due to its unique anatomical and functional characteristics. Certain hypothalamic regions, including the median eminence and arcuate nucleus, possess a relatively fenestrated capillary network that facilitates hormone exchange between the brain and peripheral circulation. While this architecture supports neuroendocrine signaling, it may also render these nuclei more susceptible to circulating NTBI exposure during systemic iron overload [4]. Consequently, iron accumulation within hypothalamic neurons could occur earlier than previously appreciated.

At the cellular level, excess intracellular iron promotes formation of hydroxyl radicals via the Fenton reaction, leading to lipid peroxidation of neuronal membranes and oxidative modification of proteins and nucleic acids. Neurons are particularly sensitive to such oxidative damage because of their high metabolic demand and limited regenerative capacity. Moreover, mitochondrial iron accumulation disrupts oxidative phosphorylation, reduces ATP production, and triggers intrinsic apoptotic pathways, further compromising neuronal survival [5]. These mechanisms collectively contribute to functional impairment of neuroendocrine circuits.

Within the context of thalassemia-associated delayed puberty, iron entry into the hypothalamus represents a critical upstream event that may impair kisspeptin neuronal networks. If oxidative and inflammatory processes disrupt arcuate nucleus integrity, pulsatile gonadotropin-releasing hormone secretion may decline even before structural pituitary damage becomes evident. Understanding the molecular pathways governing iron transport and neuronal susceptibility in the hypothalamus is therefore fundamental to elucidating early stages of reproductive axis dysfunction in iron overload states [6].

Oxidative Stress, Mitochondrial Dysfunction, and Neuronal Injury in the Hypothalamus

Iron-induced oxidative stress represents the principal molecular mechanism underlying neuronal injury in systemic iron overload states. Excess intracellular ferrous iron catalyzes the conversion of hydrogen peroxide into highly reactive hydroxyl radicals via the Fenton reaction, generating a cascade of lipid peroxidation and protein oxidation. In neuronal cells, oxidative damage preferentially affects polyunsaturated fatty acids within cell membranes, compromising membrane integrity and synaptic function. Because hypothalamic neurons are metabolically active and highly interconnected, they are particularly susceptible to such oxidative perturbations [7].

Mitochondria serve as both targets and amplifiers of iron-mediated injury. Iron accumulation within mitochondrial matrices disrupts electron transport chain function, increases superoxide generation, and impairs ATP synthesis. This bioenergetic failure compromises neuronal excitability and neurotransmitter release, including pathways essential for pulsatile gonadotropin-releasing hormone (GnRH) secretion. Furthermore, mitochondrial permeability transition pore opening can trigger cytochrome c release and activation of intrinsic apoptotic cascades, resulting in progressive neuronal loss [8]. Such mitochondrial dysfunction may critically affect arcuate nucleus kisspeptin neurons.

Oxidative stress also activates redox-sensitive transcription factors such as nuclear factor kappa B (NF-κB) and activator protein-1 (AP-1), which regulate inflammatory gene expression. Activation of these pathways promotes the production of pro-inflammatory cytokines, including interleukin-1β and tumor necrosis factor-α, within the hypothalamic microenvironment. Chronic neuroinflammation can further suppress neuronal firing rates, alter synaptic plasticity, and impair neuropeptide synthesis, thereby compounding reproductive axis dysfunction [9]. This inflammatory milieu may directly influence kisspeptin gene expression.

Emerging data suggest that oxidative stress can modulate epigenetic regulatory mechanisms in neuronal tissue. Reactive oxygen

species have been shown to alter DNA methylation patterns and histone modifications, leading to persistent changes in gene transcription. In the context of kisspeptin signaling, oxidative stress–induced epigenetic repression of the *KISS1* promoter region could theoretically reduce peptide synthesis and downstream GnRH stimulation [10]. Such mechanisms may explain prolonged pubertal arrest even after partial correction of systemic iron levels.

In addition to direct neuronal toxicity, iron overload may impair astrocyte and microglial function within the hypothalamus. Glial cells play essential roles in maintaining synaptic homeostasis and modulating neuroendocrine signaling. Activated microglia release inflammatory mediators that can inhibit GnRH neuronal activity, while dysfunctional astrocytes may disrupt metabolic support to adjacent kisspeptin neurons. This glial-neuronal crosstalk further amplifies central reproductive suppression in iron overload conditions [11].

Collectively, oxidative stress, mitochondrial dysfunction, neuroinflammation, and epigenetic dysregulation converge to create a hostile microenvironment within hypothalamic nuclei. These processes compromise neuronal viability and functional output, potentially diminishing kisspeptin-mediated stimulation of GnRH neurons. In transfusion-dependent β-thalassemia, such molecular events may precede overt structural pituitary damage, underscoring the importance of recognizing hypothalamic injury as an early driver of delayed puberty [12].

Kisspeptin Neuronal Networks Under Iron Stress — Molecular and Cellular Disruption

Kisspeptin neurons located primarily within the arcuate nucleus function as central regulators of pulsatile gonadotropin-releasing hormone secretion and pubertal initiation. These neurons co-express neurokinin B and dynorphin, forming the KNDy neuronal network responsible for generating rhythmic GnRH pulses. The integrity of this network depends on tightly regulated intracellular signaling, mitochondrial function, and synaptic plasticity. Any disturbance in cellular homeostasis, particularly oxidative or inflammatory stress, may disrupt oscillatory firing patterns and impair downstream reproductive signaling [13].

Iron-induced oxidative stress may directly influence kisspeptin neuronal excitability. Reactive oxygen species can modify ion channel activity, including voltage-gated calcium and potassium channels, altering membrane depolarization thresholds. Since kisspeptin neuronal activity depends on coordinated excitatory and inhibitory inputs, even subtle redox-mediated alterations in ion channel kinetics may suppress pulse frequency or amplitude. Such electrophysiological changes could translate into reduced GnRH pulsatility and delayed pubertal activation [14].

At the transcriptional level, iron-mediated oxidative injury may downregulate *KISS1* gene expression. Experimental models have demonstrated that cellular stress pathways, including activation of NF-κB and p38 MAP kinase signaling, can interfere with neuropeptide gene transcription. Chronic inflammatory signaling within the hypothalamus may therefore suppress kisspeptin synthesis, diminishing its stimulatory input to GnRH neurons. Reduced peptide availability would compromise physiological activation of the hypothalamic–pituitary–gonadal axis [15].

Iron overload may also disrupt receptor-mediated signaling through KISS1R. This G-protein–coupled receptor activates phospholipase C, inositol triphosphate production, and intracellular calcium mobilization upon ligand binding. Oxidative modifications of receptor proteins or downstream signaling molecules could impair this cascade, attenuating GnRH neuronal activation even in the presence of adequate kisspeptin levels. Such post-receptor signaling defects may represent an underrecognized mechanism of central hypogonadism in chronic systemic disease [16].

Neuroinflammation secondary to iron deposition further alters synaptic connectivity within the arcuate nucleus. Activated microglia release cytokines that inhibit synaptic plasticity and reduce dendritic spine density. Kisspeptin neurons rely on dynamic synaptic remodeling during pubertal transition, integrating metabolic and hormonal cues. Disruption of this structural plasticity may blunt the normal pubertal increase in kisspeptin neuronal activity, delaying or preventing reproductive axis activation [17].

Additionally, metabolic dysregulation commonly observed in thalassemia, including altered leptin signaling and chronic systemic stress, may synergize with iron toxicity to suppress kisspeptin output. Leptin is a known permissive factor for pubertal initiation and acts partly through kisspeptin neurons. Iron-induced hypothalamic injury may impair leptin receptor signaling pathways, further compounding central reproductive suppression and creating a multifactorial inhibitory environment [18].

Together, these molecular and cellular disturbances suggest that kisspeptin neuronal networks are highly vulnerable to iron-mediated injury. Disruption at the level of peptide synthesis, receptor signaling, electrophysiological function, and synaptic architecture may converge to impair GnRH pulsatility. Recognizing this vulnerability provides mechanistic insight into early

hypothalamic dysfunction in β-thalassemia–associated delayed puberty and underscores the need for targeted neuroprotective strategies [19].

Neuroinflammation, Microglial Activation, and Reproductive Axis Suppression

Neuroinflammation is increasingly recognized as a central mediator of hypothalamic dysfunction in systemic disease states, including iron overload conditions. Excess iron promotes activation of microglia, the resident immune cells of the central nervous system, through oxidative stress–dependent pathways. Activated microglia adopt a pro-inflammatory phenotype characterized by release of cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α. These mediators can directly impair neuronal firing and synaptic transmission within hypothalamic nuclei critical for reproductive regulation [20].

Microglial-derived cytokines exert inhibitory effects on gonadotropin-releasing hormone neurons both directly and indirectly. Experimental studies have demonstrated that inflammatory cytokines reduce GnRH mRNA expression and suppress pulsatile secretion patterns. Additionally, cytokine signaling may alter upstream kisspeptin neuronal activity, thereby attenuating excitatory input to GnRH neurons. Inflammatory suppression of the reproductive axis is thought to represent an adaptive response during systemic illness; however, chronic activation can lead to persistent hypogonadotropic states [21].

Iron accumulation amplifies neuroinflammation through activation of redox-sensitive signaling pathways, including nuclear factor kappa B and inflammasome complexes. Iron-induced reactive oxygen species enhance transcription of pro-inflammatory genes and promote assembly of the NLRP3 inflammasome, leading to sustained interleukin-1β production. This inflammatory cascade creates a self-perpetuating cycle of neuronal stress and cytokine release, further compromising hypothalamic network integrity [22].

Within the arcuate nucleus, microglial activation may disrupt the delicate balance of excitatory and inhibitory inputs governing KNDy neuron oscillatory behavior. Kisspeptin neurons depend on coordinated signaling with neurokinin B and dynorphin to generate rhythmic output. Inflammatory signaling can alter neuropeptide synthesis and synaptic connectivity within this network, leading to irregular or diminished GnRH pulse generation. Such alterations may be sufficient to prevent the pubertal rise in gonadotropin secretion [23].

Astrocytes also contribute to inflammatory modulation of reproductive signaling. Under oxidative stress conditions, astrocytes may undergo reactive gliosis, characterized by morphological changes and altered metabolic support functions. Astrocytic release of prostaglandins and cytokines can influence GnRH neuron excitability and modify local extracellular glutamate concentrations. Disruption of astrocyte–neuron communication further destabilizes hypothalamic microcircuitry essential for pubertal initiation [24].

Importantly, chronic neuroinflammation may induce long-term structural remodeling within hypothalamic nuclei. Prolonged cytokine exposure can reduce dendritic spine density, impair axonal projections, and promote apoptotic pathways in susceptible neurons. In adolescents with transfusion-dependent β-thalassemia, sustained iron-driven inflammation may therefore produce cumulative damage to kisspeptin and GnRH neuronal populations, shifting potentially reversible functional suppression toward permanent neuroendocrine failure [25].

These findings highlight neuroinflammation as a pivotal intermediary between systemic iron overload and central reproductive axis suppression. By disrupting neuronal signaling, synaptic plasticity, and neuropeptide expression, inflammatory processes may critically impair kisspeptin-mediated activation of puberty. Targeting inflammatory pathways may thus represent a promising adjunct strategy in preventing or mitigating thalassemia-associated delayed puberty [26].

Epigenetic Regulation and Long-Term Neuroendocrine Reprogramming Under Iron Overload

Epigenetic mechanisms play a central role in regulating pubertal timing by modulating gene expression within hypothalamic neuronal networks. The transition from prepubertal quiescence to pubertal activation requires coordinated changes in DNA methylation, histone modification, and chromatin remodeling at promoters of key neuroendocrine genes, including *KISS1* and *GNRH1*. Disruption of these tightly controlled epigenetic processes may alter the developmental trajectory of reproductive maturation [27].

Iron-induced oxidative stress has been shown to influence DNA methyltransferase activity and histone-modifying enzymes, leading to aberrant methylation patterns and chromatin structural changes. Reactive oxygen species can oxidize guanine residues

within CpG islands, interfering with normal methylation dynamics and potentially repressing gene transcription. In the context of hypothalamic neurons, such epigenetic alterations could suppress *KISS1* expression, thereby diminishing excitatory input to GnRH neurons [28].

Experimental data suggest that the polycomb group (PcG) proteins, which maintain transcriptional repression of pubertal genes during childhood, must be downregulated for normal pubertal onset. Environmental stressors have been shown to sustain PcG-mediated repression of *KISS1*, delaying activation of the reproductive axis. Chronic iron toxicity may similarly perpetuate repressive chromatin states, preventing the epigenetic switch required for pubertal progression [29].

Histone acetylation is another critical regulator of neuropeptide gene expression. Oxidative stress can alter histone acetyltransferase and deacetylase activity, leading to reduced acetylation at promoter regions of genes involved in reproductive signaling. Hypoacetylation of the *KISS1* promoter may limit transcriptional accessibility, resulting in decreased peptide synthesis even in the absence of overt neuronal loss. Such epigenetic silencing mechanisms could contribute to prolonged or incomplete pubertal development [30].

MicroRNAs (miRNAs) further modulate gene expression at the post-transcriptional level and are increasingly implicated in hypothalamic regulation of puberty. Oxidative and inflammatory stress can alter miRNA expression profiles within neuronal tissue. Dysregulated miRNAs targeting components of the kisspeptin–GnRH signaling pathway may suppress translation of critical proteins, compounding transcriptional repression and weakening neuroendocrine output [31].

Importantly, epigenetic changes may persist even after partial correction of systemic iron levels, raising concerns regarding long-term neuroendocrine reprogramming. Adolescents exposed to prolonged iron overload during critical developmental windows may experience sustained alterations in hypothalamic gene expression patterns. This concept of iron-induced epigenetic imprinting could explain incomplete recovery of pubertal function despite aggressive chelation therapy [32].

Collectively, these findings suggest that iron toxicity may not only cause acute oxidative injury but also induce durable epigenetic modifications within kisspeptin neuronal networks. Such molecular reprogramming may delay or blunt activation of the hypothalamic–pituitary–gonadal axis, contributing to persistent hypogonadotropic hypogonadism in β-thalassemia. Understanding these mechanisms is essential for identifying therapeutic windows and designing interventions aimed at reversing central reproductive suppression [33].

Translational Implications and Potential Neuroprotective Strategies

Recognition of hypothalamic vulnerability in transfusion-dependent β-thalassemia has important translational implications for early intervention. If iron deposition disrupts kisspeptin neuronal networks before irreversible pituitary damage occurs, timely therapeutic strategies targeting central iron accumulation and oxidative stress may preserve reproductive function. Advanced neuroimaging modalities, including T2*-weighted magnetic resonance imaging, have demonstrated utility in quantifying brain iron deposition and may offer a noninvasive method for identifying adolescents at risk of central neuroendocrine dysfunction [34].

Optimization of iron chelation therapy remains the cornerstone of preventing systemic and central iron toxicity. Chelators such as deferoxamine, deferiprone, and deferasirox differ in their capacity to penetrate the blood–brain barrier and mobilize intracellular iron pools. Emerging data suggest that lipophilic chelators may more effectively reduce neural iron accumulation, potentially mitigating hypothalamic injury. Early intensification of chelation in patients demonstrating biochemical or imaging evidence of central iron overload may improve long-term endocrine outcomes [35].

Beyond iron removal, antioxidant strategies represent a promising adjunctive approach. Agents targeting mitochondrial oxidative stress, including N-acetylcysteine and coenzyme Q10, have shown neuroprotective effects in experimental models of iron-induced injury. By reducing reactive oxygen species generation and stabilizing mitochondrial membranes, such therapies may preserve neuronal viability within the arcuate nucleus and support maintenance of kisspeptin signaling pathways [36].

Modulation of neuroinflammation also warrants investigation. Pharmacologic inhibition of inflammatory mediators or microglial activation has demonstrated protective effects on hypothalamic function in preclinical studies. Suppression of pro-inflammatory cytokine production may restore synaptic plasticity and normalize neuropeptide expression within reproductive regulatory circuits. Although clinical data in thalassemia are limited, targeting inflammatory pathways could complement iron chelation in preventing central hypogonadism [37].

Emerging research into kisspeptin-based therapeutic interventions further expands translational possibilities. Exogenous kisspeptin administration has been shown to stimulate gonadotropin secretion in individuals with functional hypothalamic suppression, indicating preserved GnRH neuronal responsiveness. In carefully selected adolescents with thalassemia-associated delayed puberty and evidence of hypothalamic dysfunction, intermittent kisspeptin therapy could theoretically serve as both a diagnostic probe and a therapeutic stimulus to promote pubertal progression [38].

Future strategies may also incorporate epigenetic-modifying agents aimed at reversing repressive chromatin states affecting pubertal genes. Histone deacetylase inhibitors and other chromatin-targeting compounds have shown potential in restoring gene expression in experimental neuroendocrine models. Although still investigational, such approaches underscore the importance of understanding iron-induced epigenetic alterations in hypothalamic neurons [39].

Ultimately, a precision medicine framework integrating neuroimaging, molecular biomarkers, endocrine testing, and individualized chelation regimens may offer the most effective approach to preserving reproductive health in β-thalassemia. Early identification of hypothalamic dysfunction and implementation of neuroprotective interventions could shift management from reactive hormone replacement to proactive preservation of endogenous pubertal capacity [40].

Conclusion

Iron overload in transfusion-dependent β-thalassemia exerts profound effects on the central nervous system, extending beyond classical pituitary injury to involve critical hypothalamic regulatory networks. Accumulating mechanistic evidence suggests that oxidative stress, mitochondrial dysfunction, neuroinflammation, and epigenetic alterations converge within the arcuate nucleus to impair kisspeptin neuronal activity. Because kisspeptin serves as the principal upstream activator of gonadotropin-releasing hormone secretion, disruption of this pathway represents a pivotal mechanism underlying delayed puberty and central hypogonadism in affected adolescents. These insights shift the paradigm from a predominantly pituitary-centered model toward a more comprehensive neuroendocrine framework that recognizes early hypothalamic vulnerability.

Understanding the molecular interplay between iron toxicity and kisspeptin signaling has significant diagnostic and therapeutic implications. Early identification of hypothalamic dysfunction through advanced imaging, molecular profiling, or dynamic neuroendocrine testing may enable timely optimization of iron chelation and implementation of adjunct neuroprotective strategies. Furthermore, targeted modulation of oxidative stress, inflammatory cascades, or epigenetic repression may offer future avenues for preserving endogenous pubertal activation. As survival improves in β-thalassemia, protecting reproductive health becomes an increasingly important component of long-term care. Continued translational research integrating neurobiology and clinical endocrinology is essential to define reversible thresholds of injury and to develop precision-based interventions that safeguard pubertal development in this vulnerable population.

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