

Methylene blue and thyroid health: exploring the intersections of mitochondrial function, redox biology, and endocrine adaptation

Abstract

Methylene blue (MB), a century-old compound historically used for methemoglobinemia and other medical applications, has re-emerged as a molecule of interest in mitochondrial medicine, neuroprotection, and longevity research. Beyond its established clinical uses, MB functions as a redox-active agent capable of modulating mitochondrial respiration, oxidative stress pathways, and cellular energetics. These mechanisms may hold particular relevance for endocrine and metabolic systems, especially the thyroid gland, which is highly dependent on mitochondrial activity and tightly linked to redox balance. Thyroid hormones regulate oxidative phosphorylation, thermogenesis, mitochondrial biogenesis, and metabolic flexibility, while thyroid hormone synthesis itself relies on tightly controlled reactive oxygen species signaling. Disruptions in mitochondrial function and redox homeostasis have increasingly been implicated in fatigue syndromes, chronic inflammatory states, neurocognitive dysfunction, and tissue-level hypothyroid symptoms, even in the setting of biochemically euthyroid laboratory profiles. Emerging evidence suggests that MB may influence several pathways relevant to thyroid physiology, including mitochondrial electron transport, nitric oxide signaling, neuroinflammation, and oxidative stress modulation. This review explores the mechanistic intersections between methylene blue, thyroid hormone signaling, mitochondrial biology, and redox regulation within the broader framework of precision endocrinology and longevity medicine. Potential implications for metabolic resilience, neuroendocrine function, inflammation, and ferroptosis-related pathways are discussed, alongside important safety considerations and current limitations in the clinical evidence base. While direct thyroid-specific clinical data remain limited, MB represents an intriguing candidate for future translational investigation at the intersection of mitochondrial and endocrine health.

Keywords: methylene blue, thyroid hormones, mitochondria redox signaling, oxidative stress, precision endocrinology, metabolic flexibility, ferroptosis

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Introduction

Methylene blue (MB), a synthetic thiazine dye first developed in the late nineteenth century, has historically been utilized for a variety of medical applications, including the treatment of methemoglobinemia, malaria, and vasoplegic states.¹⁻³ In recent years, however, MB has re-emerged as a molecule of growing interest in mitochondrial medicine, neuroprotection, and longevity research because of its unique redox properties and potential effects on cellular energetics.⁴⁻⁷ Acting as an alternative electron carrier within the mitochondrial electron transport chain (ETC), MB may enhance oxidative phosphorylation, support adenosine triphosphate (ATP) production, and modulate reactive oxygen species (ROS) signaling under certain physiologic conditions.⁴⁻⁸ These mechanisms have generated increasing interest in the possible translational applications of MB across metabolic, neurologic, and age-related disorders characterized by mitochondrial dysfunction and impaired redox balance.

The endocrine system, and particularly the thyroid gland, is highly dependent on mitochondrial integrity and tightly regulated oxidative signaling. Thyroid hormones play central roles in mitochondrial biogenesis, thermogenesis, oxygen consumption, and metabolic flexibility, influencing nearly every organ system through effects on cellular respiration and energy utilization.⁹⁻¹² Triiodothyronine (T3), the biologically active thyroid hormone, directly regulates genes involved in oxidative phosphorylation, mitochondrial turnover, and ATP synthesis.^{10,11} Conversely, mitochondrial dysfunction may impair

tissue-level thyroid hormone signaling and contribute to fatigue, cognitive dysfunction, metabolic inflexibility, and other symptoms commonly associated with hypothyroid states, even in the setting of biochemically euthyroid laboratory profiles.¹³⁻¹⁵

Redox biology also occupies a uniquely important position in thyroid physiology. Unlike many endocrine organs, the thyroid gland requires physiologic ROS generation for normal hormone synthesis, particularly through hydrogen peroxide-dependent iodination reactions mediated by thyroid peroxidase.^{16,17} At the same time, excessive oxidative stress may contribute to thyroid autoimmunity, inflammatory signaling, impaired deiodinase activity, and cellular injury.¹⁸⁻²⁰ Emerging evidence suggests that mitochondrial ROS production, nitric oxide (NO) signaling, iron metabolism, and inflammatory pathways may collectively influence thyroid function, metabolic adaptation, and neuroendocrine resilience.²¹⁻²⁴ These concepts have gained increasing relevance within modern precision endocrinology, particularly in patients with persistent fatigue syndromes, chronic inflammatory conditions, metabolic dysfunction, or non-thyroidal illness syndrome (NTIS), where standard biochemical assessments may incompletely reflect tissue-level energetics and metabolic health.^{14,15,25}

Against this backdrop, MB has emerged as a molecule of growing interest at the intersection of mitochondrial biology and endocrine physiology. Beyond its effects on mitochondrial respiration, MB has demonstrated potential influences on NO

pathways, neuroinflammation, oxidative stress modulation, and cellular resilience.^{4-8,26} These mechanisms overlap with pathways implicated in thyroid hormone signaling, metabolic adaptation, and aging biology. Additionally, emerging concepts involving ferroptosis, mitochondrial iron handling, and redox-mediated cellular injury may further expand the relevance of MB within endocrine and metabolic research.^{24,27}

This narrative review explores the mechanistic and translational intersections between MB, thyroid physiology, mitochondrial function, and redox biology within the broader framework of systems-based endocrine medicine and longevity science. Potential implications for metabolic adaptation, neuroendocrine function, inflammation, and thyroid-related symptomatology are discussed alongside current limitations in the evidence base and important clinical safety considerations. While direct thyroid-specific clinical data remain limited, MB represents an emerging area of interest in the evolving field of mitochondrial-endocrine medicine.

Historical and pharmacologic overview of methylene blue

Methylene blue is a synthetic phenothiazine derivative originally synthesized in 1876 by Heinrich Caro as a textile dye before rapidly gaining medical relevance because of its unique redox properties.²⁸ Early applications included its use as an antimalarial agent, histologic stain, and treatment for methemoglobinemia, a role for which it remains approved by the United States Food and Drug Administration (FDA).^{2,29,30} Over time, MB has also been investigated in septic vasoplegia, cyanide toxicity, neurodegenerative disorders, psychiatric disease, and mitochondrial dysfunction, reflecting its broad biologic activity across multiple organ systems.^{2,30-33} More recently, interest in MB has expanded within the fields of mitochondrial medicine, neuroprotection, and longevity research because of its potential effects on cellular energetics, oxidative stress modulation, and metabolic resilience.⁴⁻⁸

At the molecular level, MB functions as a redox-active compound capable of cycling between oxidized (methylene blue) and reduced (leucomethylene blue) forms.³⁴ This redox cycling ability allows MB to participate in electron transfer reactions within mitochondria, where it may serve as an alternative electron carrier under conditions of impaired ETC function.^{5,34,35} Experimental studies suggest that MB can accept electrons from nicotinamide adenine dinucleotide (NADH) and donate them directly to cytochrome c, thereby bypassing dysfunctional segments of the ETC and potentially improving mitochondrial respiration and ATP production.^{5,35} These effects may reduce electron leakage and excessive ROS generation while preserving oxidative phosphorylation efficiency under certain physiologic conditions.⁴⁻⁶

Importantly, the biologic effects of MB appear to be highly dose dependent. Low concentrations may support mitochondrial signaling, cellular respiration, and antioxidant defense systems, whereas higher concentrations can paradoxically impair mitochondrial function and increase oxidative stress.^{34,36} This biphasic or hormetic response has become an important consideration in translational and clinical discussions surrounding MB supplementation and therapeutic use. Similar hormetic principles have been observed in other metabolic and mitochondrial interventions, where mild physiologic stressors may promote adaptive cellular resilience while excessive exposure becomes detrimental.³⁷

Beyond mitochondrial respiration, MB exerts several additional biologic effects relevant to endocrine and metabolic physiology. MB

inhibits nitric oxide synthase (NOS) and soluble guanylate cyclase activity, thereby influencing NO-mediated vascular signaling and cellular oxygen utilization.^{38,39} These mechanisms have contributed to its use in vasoplegic syndromes but may also intersect with mitochondrial oxygen consumption, neurovascular coupling, and metabolic regulation. In experimental models, MB has additionally demonstrated potential neuroprotective, anti-inflammatory, and cognitive-enhancing properties, possibly through effects on mitochondrial function, synaptic activity, and oxidative stress modulation.^{6,26,40}

Pharmacokinetically, MB is well absorbed following oral administration and demonstrates broad tissue distribution, including penetration across the blood-brain barrier.⁴¹ Hepatic metabolism primarily occurs through reduction to leucomethylene blue, with renal excretion contributing to its characteristic blue-green urine discoloration.³ Clinically, dosing strategies vary substantially depending on indication, route of administration, and formulation. While intravenous MB remains standard for methemoglobinemia and vasoplegia, oral low-dose formulations have gained popularity in integrative, cognitive, and longevity-focused settings despite limited long-term clinical data.^{2,32,42}

Safety considerations remain essential when evaluating MB for translational endocrine or metabolic applications. MB acts as a monoamine oxidase inhibitor (MAOI) at higher doses and may precipitate serotonin syndrome when combined with serotonergic medications.⁴³ Additional contraindications include glucose-6-phosphate dehydrogenase (G6PD) deficiency, severe renal impairment, and pregnancy.^{2,43} Adverse effects may include nausea, dizziness, headache, hypertension, hemolysis in susceptible individuals, and dose-related neurotoxicity.^{2,44} Furthermore, variability in supplement quality and compounding practices has raised concerns regarding purity, dosing consistency, and potential contaminants in non-pharmaceutical preparations marketed for wellness or longevity purposes.⁴⁵

Taken together, MB represents a pharmacologically complex compound with multifaceted effects on mitochondrial respiration, redox signaling, vascular biology, and cellular energetics. These mechanisms provide a biologic rationale for exploring potential intersections between MB and endocrine physiology, particularly in systems highly dependent on mitochondrial integrity and oxidative balance such as the thyroid gland.

The principal mechanisms through which MB may influence endocrine and metabolic physiology are summarized in Table 1.

Methylene blue as a mitochondrial redox modulator

Mitochondria serve as the primary site of cellular energy production and play central roles in oxidative phosphorylation, redox signaling, apoptosis, calcium homeostasis, and metabolic adaptation.⁴⁶ Beyond ATP synthesis, mitochondria function as dynamic signaling organelles capable of integrating nutrient availability, inflammatory stress, oxygen utilization, and hormonal input to regulate cellular resilience and metabolic flexibility.^{47,48} Disruptions in mitochondrial function have increasingly been implicated in aging, neurodegeneration, chronic inflammatory states, metabolic disease, and endocrine dysfunction, including disorders involving altered thyroid hormone signaling.^{11,46,49} Within this context, MB has attracted growing scientific interest because of its unique ability to influence mitochondrial electron transport, oxidative stress pathways, and cellular energetics.

Electron transport chain support and cellular energetics: The mitochondrial ETC consists of a series of protein complexes responsible

for transferring electrons derived from NADH and flavin adenine dinucleotide (FADH₂) to molecular oxygen, ultimately generating the proton gradient necessary for ATP synthesis.⁵⁰ Dysfunction within

the ETC may result in impaired ATP production, excessive electron leakage, and increased ROS generation, contributing to cellular injury and metabolic inefficiency.^{46,50}

Table 1 Mechanisms of methylene blue relevant to endocrine and metabolic physiology

Mechanism	Proposed biologic effect	Potential endocrine / Metabolic relevance
Alternative electron transport chain (ETC) electron shuttling	Facilitates electron transfer between NADH and cytochrome c; may bypass dysfunctional ETC components	Supports mitochondrial respiration and cellular energetics relevant to thyroid hormone action
Enhancement of oxidative phosphorylation	Improves ATP production and mitochondrial efficiency under certain conditions	May influence fatigue, metabolic resilience, and tissue-level energy availability
Reduction in electron leakage	Decreases excessive superoxide and ROS generation	Potential relevance to oxidative stress-associated thyroid and metabolic disorders
Redox cycling activity	Modulates cellular redox balance and oxidative signaling pathways	Intersects with thyroid hormone synthesis, deiodinase activity, and antioxidant defense systems
Nitric oxide (NO) pathway modulation	Inhibits nitric oxide synthase and soluble guanylate cyclase activity	May influence vascular signaling, mitochondrial oxygen utilization, and neuroendocrine function
Neuroprotective and neurometabolic effects	Supports neuronal mitochondrial respiration and cerebral metabolic activity	Potential implications for brain fog, fatigue, mood, and neurocognitive symptoms associated with thyroid dysfunction
Mitohormetic signaling	Mild ROS modulation may activate adaptive cellular stress-response pathways	Possible relevance to metabolic flexibility, stress adaptation, and longevity pathways
Mitochondrial resilience and quality control	May support mitochondrial stability and resistance to oxidative injury	Potential role in aging biology, chronic inflammatory states, and endocrine resilience
Modulation of inflammatory signaling	Influences oxidative stress and inflammatory mediator pathways	Potential relevance to autoimmune thyroid disease and chronic low-grade inflammation
Interaction with iron-redox biology	May influence iron-mediated oxidative signaling and mitochondrial ROS dynamics	Emerging theoretical relevance to ferroptosis and thyroid oxidative biology
Blood-brain barrier penetration	Allows central nervous system bioenergetic effects	Potential relevance to neuroendocrine regulation and stress physiology
Dose-dependent biphasic activity	Low doses may support mitochondrial function, while higher doses may become pro-oxidative	Important consideration for safety, therapeutic window, and clinical translation

The mechanisms and physiologic effects summarized are derived primarily from preclinical, mechanistic, and translational studies. Direct thyroid-specific clinical evidence remains limited, and proposed endocrine applications of methylene blue remain investigational.

MB possesses the unusual capacity to function as an alternative redox cyler within the ETC. In its oxidized form, MB can accept electrons from NADH, while reduced leucomethylene blue may donate electrons directly to cytochrome c, partially bypassing complexes I and III under conditions of mitochondrial dysfunction.^{5,34,51} Experimental studies suggest that this mechanism may preserve oxidative phosphorylation efficiency, improve oxygen consumption, and reduce electron leakage during states of metabolic stress.^{5,35,51} By facilitating more efficient electron transfer, MB may support ATP generation while simultaneously limiting excessive ROS accumulation under certain physiologic conditions (Figure 1).⁴⁻⁶

These mitochondrial effects appear particularly relevant in tissues with high energetic demands, including the brain, skeletal muscle, myocardium, and endocrine organs.⁵² The thyroid gland itself is metabolically active and heavily dependent upon mitochondrial respiration for hormone synthesis, iodide transport, and maintenance of cellular homeostasis.^{10,11} Accordingly, interventions capable of modulating mitochondrial efficiency and redox balance may hold theoretical relevance for thyroid physiology and tissue-level metabolic function.

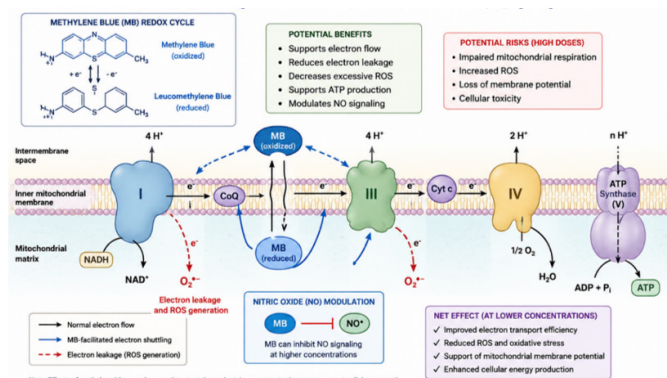


Figure 1 Methylene blue as a mitochondrial redox modulator.

Methylene blue (MB) functions as a redox-active compound capable of cycling between oxidized and reduced forms within the mitochondrial electron transport chain (ETC). Under certain physiologic conditions, MB may facilitate electron transfer between nicotinamide adenine dinucleotide (NADH) and cytochrome c, partially bypassing dysfunctional ETC components and reducing electron leakage associated with reactive oxygen species (ROS) generation. MB has additionally been shown to influence nitric oxide (NO) signaling and mitochondrial oxygen utilization. At lower concentrations, these mechanisms

may support oxidative phosphorylation, ATP production, and cellular energetics, whereas higher concentrations may exert pro-oxidative or toxic effects. The biologic effects of MB are dose- and context-dependent, and its endocrine applications remain investigational.

Reactive oxygen species, redox balance, and mitohormesis: Reactive oxygen species were historically viewed primarily as harmful byproducts of oxidative metabolism; however, contemporary understanding recognizes ROS as critical signaling molecules involved in cellular adaptation, immune regulation, mitochondrial biogenesis, and stress response pathways.⁵³ Physiologic ROS generation participates in hormetic signaling processes that may promote resilience and adaptive metabolic responses, whereas excessive or uncontrolled ROS accumulation contributes to oxidative damage and inflammation.^{37,53}

MB appears capable of modulating ROS dynamics in a context-dependent manner. By improving electron flow through the ETC, MB may reduce electron leakage and attenuate excessive superoxide generation under certain conditions of mitochondrial dysfunction.⁴⁻⁶ Conversely, mild ROS generation induced by MB may activate adaptive antioxidant and stress-response pathways consistent with the concept of mitohormesis.^{36,37} This biphasic relationship likely contributes to the dose-dependent nature of MB's biologic effects, where low concentrations may enhance cellular resilience while excessive exposure becomes pro-oxidative or toxic.^{34,36} These concepts may be particularly relevant in thyroid physiology, where tightly regulated oxidative signaling is essential for normal hormone synthesis but excessive oxidative stress may contribute to autoimmunity, impaired deiodinase activity, mitochondrial dysfunction, and tissue injury.¹⁶⁻²⁰ Thyroid hormone signaling itself influences mitochondrial ROS production, oxygen consumption, and antioxidant defense systems, further highlighting the close interplay between redox biology and endocrine regulation.^{11,19}

Nitric oxide signaling and mitochondrial oxygen utilization: Nitric oxide serves as an important regulator of vascular tone, mitochondrial respiration, neurotransmission, and immune signaling.⁵⁴ Within mitochondria, NO may reversibly inhibit cytochrome c oxidase, thereby influencing oxygen utilization and oxidative phosphorylation efficiency.⁵⁵ While physiologic NO signaling contributes to vascular and metabolic homeostasis, excessive NO production may impair mitochondrial respiration and promote nitrosative stress under inflammatory conditions.^{54,55}

MB exerts inhibitory effects on NO synthase and soluble guanylate cyclase pathways, mechanisms that have contributed to its clinical use in vasoplegic syndromes and distributive shock states.^{38,39} Through modulation of NO signaling, MB may influence mitochondrial oxygen consumption, vascular perfusion, and cellular energetics. Experimental evidence additionally suggests potential interactions between MB, cerebral blood flow, neurovascular coupling, and neuronal metabolic activity.^{6,40} These pathways may hold broader relevance in endocrine and metabolic conditions characterized by fatigue, autonomic dysfunction, inflammatory stress, or impaired tissue oxygen utilization.

Emerging interest in NO signaling has also extended to thyroid physiology and metabolic adaptation. Altered NO production has been implicated in autoimmune thyroid disease, inflammatory signaling, endothelial dysfunction, and changes in peripheral thyroid hormone metabolism.^{56,57} Moreover, chronic stress states, inflammatory cytokine activation, and mitochondrial dysfunction may collectively contribute to impaired cellular oxygen utilization and "hypometabolic" phenotypes despite normal circulating thyroid

hormone concentrations.^{23,58} These observations further support the potential relevance of mitochondrial-redox modulators such as MB within precision endocrine frameworks focused on tissue-level energetics and metabolic resilience.

Neuroprotection, cellular resilience, and aging biology: In addition to its bioenergetic effects, MB has demonstrated neuroprotective and cytoprotective properties across multiple experimental models. Proposed mechanisms include enhancement of mitochondrial respiration, reduction of oxidative injury, stabilization of cellular membranes, modulation of neuroinflammation, and support of synaptic function.^{6,26,40,59} Experimental studies have additionally reported improvements in memory retention, cerebral metabolic activity, and resistance to oxidative stress following low-dose MB exposure.^{6,35,40}

These findings have generated growing interest in MB within the broader fields of aging biology and longevity medicine. Mitochondrial dysfunction, oxidative stress, impaired metabolic flexibility, and chronic low-grade inflammation ("inflammaging") are increasingly recognized as central features of biologic aging and endocrine decline.^{60,61} Thyroid hormone signaling intersects closely with these pathways through effects on mitochondrial turnover, thermogenesis, nutrient sensing, and energy metabolism.⁹⁻¹¹ Consequently, MB may represent an intriguing investigational compound at the interface of mitochondrial medicine, neuroendocrine resilience, and metabolic aging.

Collectively, the ability of MB to influence mitochondrial electron transport, ROS signaling, NO pathways, and cellular energetics provides a biologically plausible framework for examining potential endocrine and thyroid-related applications. Although much of the current evidence remains preclinical or mechanistic in nature, these mitochondrial-redox interactions form the foundation for exploring how MB may intersect with thyroid physiology, metabolic adaptation, and tissue-level endocrine signaling.

Thyroid hormones, mitochondria, and cellular energetics

Thyroid hormones are among the body's most important regulators of energy metabolism and mitochondrial function. Through genomic and non-genomic mechanisms, thyroid hormones influence oxygen consumption, thermogenesis, ATP production, lipid metabolism, glucose utilization, mitochondrial turnover, and cellular adaptation to energetic stress.⁹⁻¹² The intimate relationship between thyroid physiology and mitochondrial biology has become increasingly recognized within endocrinology, particularly as growing evidence suggests that mitochondrial dysfunction may contribute to fatigue, metabolic inflexibility, neurocognitive symptoms, and impaired tissue-level thyroid hormone responsiveness.^{11,49,62} These concepts provide an important biologic framework for understanding how mitochondrial-redox modulators such as MB may intersect with endocrine and metabolic health.

Thyroid hormones as regulators of mitochondrial function: Thyroid hormones exert profound effects on mitochondrial respiration and oxidative phosphorylation. Triiodothyronine (T3), the active thyroid hormone, regulates the transcription of numerous nuclear and mitochondrial genes involved in ETC activity, ATP synthesis, fatty acid oxidation, mitochondrial biogenesis, and thermogenesis.^{10,11,65} T3 additionally influences mitochondrial membrane potential, oxygen consumption, uncoupling protein expression, and reactive oxygen species dynamics, thereby coordinating cellular energy production with metabolic demand.^{11,63,64}

These mitochondrial effects are particularly evident in metabolically active tissues such as skeletal muscle, liver, heart, and brain.^{9,21,65} In hypothyroid states, reductions in mitochondrial oxidative capacity and ATP production may contribute to fatigue, cold intolerance, impaired exercise tolerance, cognitive slowing, and metabolic dysfunction.⁶⁶ Conversely, hyperthyroid states are associated with increased oxygen consumption, accelerated mitochondrial activity, and elevated ROS generation, which may promote oxidative stress and tissue injury when excessive or prolonged.^{19,67}

Thyroid hormones also regulate mitochondrial turnover through effects on mitochondrial biogenesis and mitophagy.⁶⁸ Proper mitochondrial quality control is essential for maintaining cellular energetics and preventing accumulation of dysfunctional mitochondria capable of generating excessive oxidative stress and inflammatory signaling.^{68,69} Emerging evidence suggests that impaired mitochondrial turnover may contribute to aging-related endocrine decline, metabolic disease, and chronic inflammatory conditions.^{60,61} These observations further reinforce the central role of thyroid hormones in maintaining mitochondrial integrity and metabolic resilience.

Redox biology and oxidative signaling in thyroid physiology:

The thyroid gland possesses a uniquely complex relationship with oxidative biology. Unlike many endocrine tissues in which ROS are primarily viewed as potentially harmful byproducts, physiologic ROS generation is essential for normal thyroid hormone synthesis.^{16,17} Hydrogen peroxide (H₂O₂), produced largely through dual oxidase (DUOX) enzymes, serves as a required substrate for thyroid peroxidase-mediated iodination of thyroglobulin during thyroid hormone biosynthesis.^{6,17} As a result, thyroid tissue is continuously exposed to oxidative reactions that require precise regulatory balance to avoid cellular injury.

Under physiologic conditions, antioxidant defense systems including glutathione peroxidases, catalase, superoxide dismutase, and selenium-dependent enzymes help maintain redox homeostasis within the thyroid gland.^{18,70} Selenium is particularly important because deiodinases responsible for peripheral thyroid hormone activation and inactivation are selenoproteins highly sensitive to oxidative stress and micronutrient status.^{3,70} Disruptions in redox balance may therefore impair thyroid hormone conversion, alter tissue-level thyroid signaling, and contribute to inflammatory or autoimmune processes.

Oxidative stress has increasingly been implicated in the pathogenesis of Hashimoto's thyroiditis, Graves' disease, thyroid nodules, and other thyroid disorders.^{18–20} Excess ROS generation may promote inflammatory cytokine signaling, DNA damage, lipid peroxidation, and immune dysregulation within thyroid tissue.⁷¹ Chronic oxidative stress may additionally impair mitochondrial function, contributing to reduced cellular energetics and persistent symptomatology even after biochemical normalization of thyroid hormone levels.^{19,20} These mechanisms have contributed to growing interest in antioxidant and mitochondrial-targeted strategies within integrative and precision endocrine medicine.

Tissue-level thyroid hormone signaling and metabolic adaptation:

Although serum TSH and circulating thyroid hormone concentrations remain central to conventional thyroid assessment, increasing recognition has been given to the complexity of tissue-level thyroid hormone signaling and metabolic adaptation.^{13,14} Local deiodinase activity, transporter expression, mitochondrial function, inflammatory signaling, nutrient availability, and cellular redox state may all influence thyroid hormone action at the tissue level independent of serum laboratory values.^{13,15,72}

These concepts are particularly relevant in conditions such as non-thyroidal illness syndrome (NTIS), chronic inflammatory disease, obesity, caloric restriction, aging, and chronic stress states, where alterations in thyroid hormone metabolism may reflect adaptive shifts in energy conservation and mitochondrial regulation.^{14,15,73} Reduced peripheral conversion of T₄ to T₃, elevated reverse T₃ production, altered transporter activity, and changes in cellular thyroid hormone responsiveness have all been described in these settings.^{14,15} While some adaptive responses may initially preserve survival under acute stress, persistent alterations in mitochondrial energetics and thyroid signaling may contribute to fatigue, impaired metabolic flexibility, neurocognitive dysfunction, and reduced physiologic resilience over time.^{23,58}

Mitochondrial dysfunction itself may further impair tissue responsiveness to thyroid hormones. Because thyroid hormone action is fundamentally linked to mitochondrial respiration and ATP production, disrupted cellular energetics may create a state in which adequate circulating hormone levels fail to translate into optimal metabolic function at the tissue level.^{11,49,62} This concept has generated increasing discussion surrounding “cellular hypothyroidism,” metabolic inefficiency, and persistent symptomatology in some patients despite biochemically euthyroid profiles.⁷⁴ Although these models remain incompletely understood and occasionally controversial, they highlight the growing need for more nuanced approaches to endocrine and metabolic assessment.

Mitochondrial dysfunction, neuroendocrine symptoms, and metabolic resilience:

Mitochondrial dysfunction has increasingly been implicated in fatigue syndromes, neurocognitive impairment, mood disorders, autonomic dysfunction, and chronic inflammatory states frequently encountered in endocrine practice.^{47,58,75} Because thyroid hormones strongly influence cerebral metabolism, mitochondrial respiration, and neurotransmitter regulation, disruptions in thyroid-mitochondrial signaling may contribute to symptoms such as brain fog, reduced stress tolerance, impaired concentration, and diminished exercise capacity.^{21,65}

Additionally, chronic stress and inflammatory signaling may further impair mitochondrial function through activation of glucocorticoid pathways, inflammatory cytokines, oxidative stress, and alterations in cellular danger response signaling.^{23,58} These overlapping pathways suggest that mitochondrial dysfunction may represent an important mechanistic intersection linking endocrine dysregulation, inflammation, neurocognitive symptoms, and metabolic decline.

Within this framework, compounds capable of modulating mitochondrial respiration, oxidative signaling, and cellular energetics have attracted growing interest in translational endocrinology and longevity medicine. The unique mitochondrial-redox effects of MB therefore provide a biologically plausible rationale for investigating potential applications in metabolic resilience, neuroendocrine function, and tissue-level thyroid physiology.

Potential intersections between methylene blue and thyroid health

The overlap between mitochondrial biology, redox regulation, neuroendocrine signaling, and metabolic adaptation provides a useful framework for exploring potential intersections between MB and thyroid physiology. Although direct thyroid-specific clinical evidence remains limited, many of the pathways influenced by MB—including mitochondrial respiration, oxidative signaling, nitric oxide regulation, and cellular energetics—are also central to thyroid hormone action and metabolic health.^{4–8,11,19} As a result, MB has generated growing

interest as a potential tool for investigating mitochondrial-endocrine interactions within systems-based models of metabolic health. The major mechanistic domains through which MB may intersect with thyroid physiology, metabolic adaptation, and endocrine health are summarized in Figure 2.

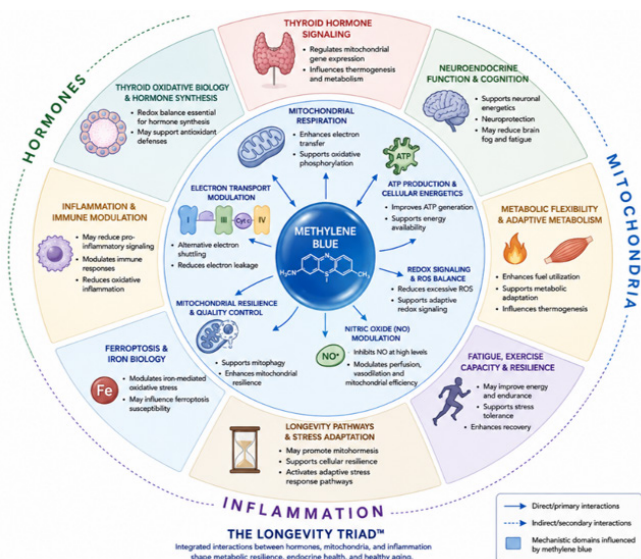


Figure 2 Systems-based intersections between methylene blue, thyroid physiology, and metabolic resilience.

Methylene blue (MB) interacts with multiple mitochondrial and redox-regulating pathways that may influence endocrine and metabolic physiology. Central mitochondrial effects of MB include modulation of electron transport chain activity, support of oxidative phosphorylation and ATP production, regulation of reactive oxygen species (ROS) signaling, and interactions with nitric oxide (NO)-mediated pathways. These mitochondrial-redox mechanisms may intersect with broader physiologic domains relevant to thyroid health and metabolic resilience, including thyroid hormone signaling, neuroendocrine function, inflammation, metabolic flexibility, fatigue syndromes, oxidative biology, and iron/ferroptosis-related pathways. The outer framework reflects the Longevity Triad™ model integrating hormones, mitochondria, and inflammation as interconnected determinants of endocrine and metabolic health. The pathways illustrated represent proposed mechanistic and translational relationships derived primarily from preclinical, mechanistic, and emerging evidence; direct thyroid-specific clinical applications of MB remain investigational.

Mitochondrial dysfunction and hypometabolic states: Persistent fatigue, impaired exercise tolerance, cognitive dysfunction, cold intolerance, and reduced metabolic resilience are common clinical features associated with hypothyroid states and other disorders involving impaired mitochondrial energetics.^{66,75} Increasing evidence suggests that mitochondrial dysfunction may contribute to these symptom clusters even in individuals with biochemically euthyroid laboratory profiles.^{11,49,62} Disruptions in oxidative phosphorylation, ATP generation, mitochondrial turnover, and redox balance may impair cellular energy availability and contribute to “hypometabolic” phenotypes characterized by reduced physiologic adaptability and diminished stress tolerance.⁵⁸

Because MB may enhance electron transfer efficiency and support mitochondrial respiration under certain conditions of ETC dysfunction, interest has grown regarding its potential role in disorders associated with impaired bioenergetics.^{5,34,51} Experimental studies have demonstrated that MB may improve mitochondrial oxygen consumption, ATP production, and neuronal metabolic activity while reducing excessive ROS accumulation.^{4-6,40} These effects raise the

possibility that MB could theoretically support metabolic efficiency and cellular energetics in states characterized by mitochondrial impairment or altered thyroid hormone responsiveness.

Additionally, thyroid hormones themselves exert major regulatory effects on mitochondrial respiration and thermogenesis.⁹⁻¹¹ Consequently, mitochondrial-targeted interventions such as MB may indirectly influence pathways associated with thyroid-mediated energy metabolism and tissue-level metabolic function. While clinical applications remain speculative, these overlapping mechanisms support continued investigation of MB in conditions characterized by impaired bioenergetics, altered metabolic adaptation, and reduced physiologic resilience.

Neuroendocrine function, cognition, and fatigue: Neurocognitive symptoms are frequently encountered in patients with thyroid dysfunction and may include brain fog, impaired concentration, mood disturbances, slowed information processing, and fatigue.⁶⁵ Thyroid hormones strongly influence cerebral metabolism, mitochondrial activity, neurotransmitter signaling, and neuronal plasticity, particularly within regions involved in cognition, mood regulation, and autonomic control.^{65,75} Mitochondrial dysfunction and neuroinflammation may therefore represent important mechanistic contributors to persistent neuroendocrine symptoms in endocrine and metabolic disorders.

MB has demonstrated several neuroprotective and neurometabolic effects in experimental models. Proposed mechanisms include enhancement of mitochondrial respiration, increased cerebral oxygen utilization, modulation of oxidative stress pathways, and support of synaptic activity.^{6,26,40,59} Animal studies have reported improvements in memory retention, neuronal metabolic efficiency, and resistance to oxidative injury following low-dose MB administration.^{6,35,40} Additionally, MB readily crosses the blood-brain barrier, allowing direct effects on central nervous system energetics and signaling pathways.⁴¹

These observations may hold relevance for conditions characterized by fatigue, neurocognitive dysfunction, chronic stress physiology, and altered neuroendocrine resilience. Emerging evidence suggests that chronic inflammatory signaling, glucocorticoid dysregulation, impaired mitochondrial function, and cellular danger response activation may collectively contribute to persistent fatigue syndromes and impaired metabolic adaptation.^{23,58} Given the close relationship between thyroid hormone signaling and cerebral metabolism, MB may offer a useful model for exploring how mitochondrial function influences cognition, fatigue, and neuroendocrine resilience in endocrine and metabolic disorders.

Oxidative stress, autoimmunity, and thyroid inflammation: Oxidative stress plays a central role in thyroid physiology and pathology.¹⁸⁻²⁰ The thyroid gland continuously generates ROS during hormone synthesis, rendering thyroid tissue particularly susceptible to oxidative injury when antioxidant defenses become overwhelmed.^{16,17} Excessive ROS accumulation has been implicated in autoimmune thyroid disease, inflammatory signaling, mitochondrial dysfunction, and progressive tissue injury.¹⁸⁻²⁰

Hashimoto’s thyroiditis, the most common cause of hypothyroidism in iodine-sufficient regions, has been associated with increased oxidative stress markers, impaired antioxidant capacity, inflammatory cytokine activation, and mitochondrial dysfunction.¹⁸⁻²⁰ Similar mechanisms have been implicated in Graves’ disease and thyroid nodular disease.^{19,71} Emerging evidence additionally suggests that chronic inflammation and oxidative injury may impair deiodinase

activity and alter peripheral thyroid hormone metabolism, potentially contributing to tissue-level hypothyroid symptoms despite normalized serum hormone levels.^{13,70}

Because MB may influence mitochondrial ROS production and redox signaling, interest has emerged regarding its potential interactions with inflammatory and oxidative pathways relevant to thyroid disease.⁴⁻⁶ At lower concentrations, MB may help reduce excessive electron leakage within mitochondria while supporting adaptive redox signaling pathways.^{34,36} However, these effects appear highly context dependent, and excessive MB exposure may itself become pro-oxidative.³⁶ Consequently, careful consideration of dose, physiologic context, and redox balance remains essential when evaluating potential endocrine applications.

At present, direct evidence supporting MB in autoimmune thyroid disease remains limited and largely theoretical. Although direct evidence remains limited, the convergence of oxidative stress, mitochondrial dysfunction, and immune activation highlights an area worthy of further investigation within thyroid and endocrine medicine.

Metabolic flexibility, longevity pathways, and adaptive energetics:

Metabolic flexibility refers to the ability of cells and organisms to appropriately adapt fuel utilization, energy expenditure, and mitochondrial activity in response to environmental and physiologic demands.⁷⁶ Impaired metabolic flexibility has increasingly been implicated in obesity, insulin resistance, aging, chronic inflammatory disease, and endocrine dysfunction.^{76,77} Thyroid hormones serve as critical regulators of these adaptive metabolic processes through effects on mitochondrial respiration, thermogenesis, nutrient sensing, and substrate utilization.⁹⁻¹²

Interest in MB has expanded within longevity and metabolic medicine because of its potential influence on mitochondrial resilience, oxidative stress modulation, and cellular adaptation pathways.⁴⁻⁷ Experimental evidence suggests that MB may support mitochondrial efficiency and promote resistance to oxidative injury under certain conditions of metabolic stress.^{4,36} These mechanisms overlap conceptually with broader longevity frameworks involving mitohormesis, caloric restriction signaling, and adaptive stress-response pathways.^{37,60}

Such concepts may hold particular relevance in modern endocrine contexts characterized by altered energy availability, including chronic caloric restriction, overtraining, inflammatory stress states, and glucagon-like peptide-1 (GLP-1) receptor agonist-associated weight loss.⁷⁸ Adaptive reductions in T3 levels and metabolic rate observed during prolonged energy restriction may reflect coordinated mitochondrial-endocrine responses aimed at preserving survival during perceived energy scarcity.^{14,73} Understanding how mitochondrial modulators such as MB interact with these adaptive pathways represents an emerging area of translational interest.

Ferroptosis, iron biology, and redox signaling: Ferroptosis is a recently characterized form of regulated cell death driven by iron-dependent lipid peroxidation and oxidative injury.²⁴ Increasing evidence implicates ferroptosis in aging, neurodegeneration, inflammatory disease, mitochondrial dysfunction, and endocrine pathology.^{24,79} Because iron metabolism, ROS generation, glutathione depletion, and mitochondrial injury are closely interconnected, ferroptosis has emerged as a potentially important mechanistic bridge linking metabolic dysfunction and cellular decline.

The thyroid gland may be particularly vulnerable to ferroptosis-related injury because of its reliance on oxidative reactions for

hormone synthesis and its sensitivity to redox imbalance.¹⁶⁻²⁰ Emerging data suggest that iron dysregulation, mitochondrial ROS production, inflammatory signaling, and impaired antioxidant defenses may collectively contribute to thyroid dysfunction and autoimmune disease.^{85,86} Additionally, iron deficiency itself may impair thyroid hormone synthesis, deiodinase activity, mitochondrial respiration, and metabolic resilience.^{80,81}

Although direct evidence linking MB to ferroptosis modulation remains preliminary, its ability to influence mitochondrial redox cycling and oxidative signaling raises intriguing mechanistic questions.^{24,34} Depending on physiologic context, MB could theoretically influence pathways related to mitochondrial ROS balance, iron-mediated oxidative stress, and cellular resilience. However, these interactions remain incompletely understood and should presently be considered hypothesis-generating rather than clinically established.

Taken together, these pathways illustrate how MB intersects with broader mechanisms involved in thyroid physiology, adaptive metabolism, and cellular resilience. Whether these mechanistic observations translate into meaningful clinical applications remains unknown, but they provide a foundation for future translational research. While clinical evidence remains limited, these interconnected pathways may help inform future translational research aimed at understanding tissue-level energetics, metabolic resilience, and precision endocrine therapeutics.

The principal thyroid-related pathways through which MB may intersect with endocrine and metabolic physiology, along with the current level of supporting evidence, are summarized in Table 2.

Clinical considerations, safety, and translational challenges

Despite growing interest in MB within mitochondrial medicine, neuroprotection, and longevity research, important limitations and safety considerations must be acknowledged before translating mechanistic findings into endocrine or thyroid-related clinical applications. Much of the current evidence surrounding MB remains preclinical, observational, or extrapolated from non-endocrine contexts.^{4-8,26} Consequently, enthusiasm regarding potential metabolic or thyroid-related benefits should be balanced with careful consideration of dosing variability, pharmacologic complexity, contraindications, and the absence of robust thyroid-specific clinical trials.

Limitations of the current evidence base: At present, there are no large randomized controlled trials evaluating MB specifically for hypothyroidism, autoimmune thyroid disease, tissue-level thyroid dysfunction, or endocrine fatigue syndromes. Existing literature largely consists of mechanistic studies, animal models, neuroprotective investigations, and broader mitochondrial research.^{4-8,26} Although these data provide biologic plausibility for endocrine applications, they do not establish clinical efficacy or long-term safety in thyroid-related disorders.

Additionally, many proposed benefits of MB within wellness and longevity communities have outpaced the available scientific evidence. Claims related to enhanced metabolism, cognitive optimization, mitochondrial “boosting,” or reversal of chronic fatigue often rely on anecdotal experience or extrapolation from experimental models rather than rigorously controlled endocrine studies.⁸² This disconnect underscores the importance of maintaining a cautious, evidence-aware approach when discussing MB in clinical practice or precision medicine frameworks.

Table 2 Potential intersections between methylene blue and thyroid physiology

Thyroid-related pathway / Clinical domain	Proposed interaction of methylene blue (MB)	Potential clinical relevance	Current evidence level
Mitochondrial oxidative phosphorylation	Supports electron transport and ATP generation	Cellular energetics, fatigue, metabolic efficiency	Preclinical / mechanistic
Thyroid hormone-mediated mitochondrial activity	May influence pathways regulated by T3-dependent mitochondrial signaling	Tissue-level metabolic function and thermogenesis	Theoretical / mechanistic
Reactive oxygen species (ROS) balance	Reduces excessive electron leakage and modulates redox signaling	Oxidative stress regulation in thyroid tissue	Preclinical
Thyroid oxidative biology	Intersects with H ₂ O ₂ -dependent thyroid hormone synthesis pathways	Redox homeostasis in thyroid physiology	Theoretical
Deiodinase and selenium-dependent pathways	Redox modulation may indirectly influence deiodinase activity	Peripheral thyroid hormone conversion and tissue signaling	Theoretical
Neurocognitive symptoms associated with thyroid dysfunction	Enhances neuronal mitochondrial respiration and cerebral energetics	Brain fog, fatigue, cognitive dysfunction	Preclinical / translational
Chronic fatigue and “hypometabolic” phenotypes	Supports mitochondrial respiration and adaptive energetics	Fatigue syndromes and reduced metabolic resilience	Translational / theoretical
Nitric oxide (NO) signaling	Modulates NO pathways and mitochondrial oxygen utilization	Vascular function, tissue oxygen delivery, neuroendocrine regulation	Mechanistic
Autoimmune thyroid inflammation	May influence oxidative stress and inflammatory signaling pathways	Hashimoto’s thyroiditis and chronic inflammatory states	Theoretical / emerging
Metabolic flexibility and adaptive thermogenesis	Influences mitochondrial efficiency and stress-response signaling	Weight regulation, caloric restriction adaptation, GLP-1-associated metabolic adaptation	Translational
Ferroptosis and iron-redox biology	May interact with iron-mediated oxidative signaling and mitochondrial ROS pathways	Emerging relevance to thyroid oxidative injury and cellular resilience	Emerging / hypothesis-generating
Longevity and mitochondrial resilience	Supports mitochondrial function and adaptive stress-response pathways	Healthy aging and endocrine resilience	Preclinical / translational
Neuroendocrine stress adaptation	May influence mitochondrial responses to chronic stress signaling	HPA axis interactions and metabolic adaptation	Theoretical

The proposed interactions summarized above are based primarily on mechanistic, preclinical, and translational evidence. Direct thyroid-specific clinical studies evaluating methylene blue are currently lacking, and endocrine applications remain investigational. Evidence classifications reflect the current state of available literature and should not be interpreted as established therapeutic efficacy.

Another challenge involves the heterogeneity of conditions characterized by fatigue, cognitive dysfunction, or impaired metabolic resilience. Symptoms commonly attributed to mitochondrial dysfunction may arise from numerous overlapping contributors including inflammatory disease, micronutrient deficiencies, chronic stress physiology, sleep disruption, autonomic dysfunction, medication effects, mood disorders, and endocrine imbalance.^{23,75} As a result, identifying patient populations most likely to benefit from mitochondrial-targeted interventions remains difficult and highlights the need for improved biomarker-driven approaches within translational endocrinology.

Dose-dependent and biphasic effects: One of the most important pharmacologic features of MB is its dose-dependent biphasic activity.^{34,36} At low concentrations, MB may support mitochondrial electron transport, adaptive redox signaling, and cellular energetics.⁴⁻⁶ However, higher concentrations may impair mitochondrial respiration, increase oxidative stress, disrupt membrane potential, and promote cellular toxicity.^{34,36} This hormetic relationship complicates both clinical interpretation and therapeutic application.

Optimal dosing parameters for metabolic, cognitive, or endocrine purposes remain poorly defined. Oral preparations marketed for

wellness or longevity vary substantially in concentration, formulation, purity, and bioavailability.^{42,45} Furthermore, the pharmacodynamic effects of MB may differ depending on individual mitochondrial status, oxidative burden, inflammatory state, medication use, and underlying metabolic health. These variables raise concerns regarding both underdosing and unintended overstimulation or oxidative injury.

Importantly, mitochondrial interventions should not necessarily be viewed as universally beneficial. In certain physiologic contexts, suppression of adaptive stress responses or inappropriate manipulation of redox signaling may theoretically impair endogenous resilience pathways.³⁷ Accordingly, future endocrine applications of MB will likely require greater understanding of patient-specific metabolic phenotypes, mitochondrial function, and redox balance.

Drug interactions and contraindications: MB possesses clinically important pharmacologic interactions that warrant careful consideration. Most notably, MB functions as MAOI, particularly at higher doses, and may precipitate serotonin syndrome when combined with serotonergic medications such as SSRIs, serotonin-norepinephrine reuptake inhibitors (SNRIs), MAOIs, and certain analgesics or supplements.^{43,83} Serotonin syndrome may present with autonomic instability, hyperthermia, neuromuscular abnormalities,

altered mental status, and potentially life-threatening complications.⁸³

Additional contraindications include G6PD deficiency, in which MB may precipitate hemolytic anemia because of impaired redox handling within erythrocytes.² Caution is also warranted in pregnancy, severe renal impairment, and certain pulmonary conditions.^{2,84} Adverse effects may include nausea, dizziness, headache, hypertension, urinary discoloration, gastrointestinal symptoms, paresthesias, and dose-related neurotoxicity.^{2,44}

Because many patients seeking integrative or longevity-focused therapies may already be using multiple supplements, hormones, or neuroactive medications, thorough medication reconciliation and risk assessment become particularly important when considering MB exposure. Additionally, compounded or non-pharmaceutical MB products may carry risks related to contamination, inaccurate dosing, or industrial-grade formulations not intended for human consumption.⁴⁵

Considerations in thyroid and endocrine practice: Within endocrine practice, interest in MB may arise in patients with persistent fatigue, cognitive symptoms, chronic inflammatory states, metabolic dysfunction, or perceived “low energy” phenotypes despite conventional biochemical management. However, clinicians should exercise caution in attributing these complex symptom patterns solely to mitochondrial dysfunction or presumed tissue hypothyroidism without comprehensive evaluation. Many endocrine symptoms are multifactorial and require careful assessment of thyroid status, iron metabolism, nutrient deficiencies, sleep quality, inflammatory burden, autonomic balance, mental health, and lifestyle factors.

Moreover, while mitochondrial dysfunction may contribute to persistent symptomatology in some individuals, evidence supporting MB as a treatment for hypothyroidism or autoimmune thyroid disease remains insufficient.^{13–15,74} Current thyroid management should continue to prioritize evidence-based diagnostic evaluation and individualized hormone optimization strategies while recognizing the growing importance of mitochondrial and metabolic health in endocrine physiology.

Importantly, MB may ultimately prove most relevant not as a “thyroid therapy” per se, but rather as a mitochondrial-redox modulator potentially influencing broader pathways related to cellular energetics, neuroendocrine resilience, and metabolic adaptation. This distinction is critical for maintaining scientific accuracy and avoiding overstated therapeutic claims.

Translational challenges and future research needs: Several important questions remain unanswered regarding the role of MB in endocrine and metabolic medicine. These include:

- I. Which patient populations may derive the greatest benefit from mitochondrial-redox interventions?
- II. How mitochondrial function or tissue-level energetics should be objectively assessed in clinical practice?
- III. What biomarkers best reflect adaptive versus maladaptive thyroid-metabolic responses?
- IV. How do factors such as aging, inflammation, caloric restriction, GLP-1 therapy, and chronic stress alter mitochondrial responsiveness to MB?
- V. What are the long-term safety implications of chronic low-dose MB exposure?

Future research will likely require integration of mitochondrial physiology, redox biology, metabolomics, endocrine signaling, and precision medicine approaches.⁸⁵ Improved understanding of tissue-level energetics and metabolic adaptation may ultimately help bridge the gap between conventional biochemical assessment and persistent symptomatology encountered in endocrine practice.

At present, MB should be regarded as an intriguing but still investigational compound within thyroid and endocrine medicine. While mechanistic evidence suggests substantial overlap between MB pathways and thyroid-mitochondrial biology, rigorous clinical studies are needed before meaningful therapeutic conclusions can be drawn.

Future directions in precision endocrinology and mitochondrial medicine

Growing recognition of the interconnected roles of mitochondrial function, redox biology, inflammation, and endocrine signaling has contributed to increasing interest in systems-based approaches to metabolic and thyroid health.^{47,48,60} Traditional endocrine models have largely focused on circulating hormone concentrations and glandular pathology; however, emerging evidence suggests that cellular energetics, mitochondrial resilience, inflammatory signaling, nutrient sensing, and tissue responsiveness may substantially influence clinical outcomes and symptom expression.^{13–15,72} Within this evolving framework, MB provides a useful lens through which to examine the relationship between mitochondrial biology and endocrine regulation.

Toward a more integrated model of thyroid physiology: Contemporary thyroid management has traditionally centered around serum TSH and circulating thyroid hormone measurements. While these biomarkers remain clinically essential, they may not fully capture the complexity of tissue-level thyroid hormone action, mitochondrial energetics, or adaptive metabolic responses.^{13,72} Increasing recognition has been given to the influence of deiodinase activity, transporter expression, nutrient status, inflammation, oxidative stress, and mitochondrial function on thyroid hormone signaling at the cellular level.^{13–15,70}

These concepts may help explain why some individuals continue to experience fatigue, cognitive dysfunction, impaired stress tolerance, or metabolic inflexibility despite biochemical euthyroidism.⁷⁴ Although such symptom patterns are multifactorial and should not automatically be attributed to “cellular hypothyroidism,” they highlight important limitations in reductionist endocrine models focused exclusively on serum biomarkers. Future precision endocrine frameworks may increasingly incorporate assessments of mitochondrial function, inflammatory burden, autonomic balance, metabolic flexibility, and tissue energetics alongside conventional hormonal evaluation.

Within this context, MB offers a unique mechanistic lens through which to examine mitochondrial-endocrine interactions. By modulating electron transport, redox signaling, NO pathways, and cellular energetics, MB may help illuminate broader physiologic relationships between thyroid hormone action, metabolic adaptation, and mitochondrial resilience.

Mitochondrial biomarkers and tissue-level energetics: One of the major challenges facing translational mitochondrial medicine is the absence of standardized clinical biomarkers capable of accurately assessing mitochondrial health and tissue-level energetics in routine practice. Current endocrine evaluation relies heavily on serum hormone concentrations, which may not adequately reflect intracellular energy production, oxidative stress burden, or adaptive metabolic signaling.

Future research may increasingly explore biomarkers related to:

- I. Mitochondrial respiration and ATP production
- II. Oxidative stress and antioxidant capacity
- III. Redox balance
- IV. Inflammatory signaling
- V. Metabolomics and substrate utilization
- VI. Autonomic nervous system function
- VII. Mitochondrial DNA integrity
- VIII. Cellular stress-response pathways

Advances in metabolomics, mitochondrial phenotyping, transcriptomics, and systems biology may eventually allow more individualized assessment of metabolic resilience and endocrine adaptation. Such approaches could prove particularly valuable in complex conditions characterized by chronic fatigue, neurocognitive symptoms, inflammatory stress, metabolic dysfunction, or altered thyroid hormone responsiveness.

Importantly, MB may serve not only as a potential therapeutic candidate but also as a physiologic probe for studying mitochondrial-endocrine interactions and adaptive bioenergetic responses in human disease.

Aging, longevity, and adaptive metabolism: Mitochondrial dysfunction, oxidative stress, inflammaging, and impaired metabolic flexibility are increasingly recognized as hallmarks of biologic aging.^{60,61,86} Thyroid hormones intersect closely with these processes through regulation of thermogenesis, nutrient sensing, mitochondrial turnover, oxygen consumption, and energy expenditure.^{9–12} Aging-related changes in thyroid physiology may therefore represent not simply glandular decline but broader alterations in mitochondrial-endocrine communication and adaptive metabolism.

Interest in MB within longevity medicine has largely centered on its potential ability to support mitochondrial respiration, improve redox balance, and enhance cellular resilience under conditions of metabolic stress.^{4–7} Experimental models suggest possible neuroprotective and cytoprotective effects; however, whether these findings translate into meaningful clinical benefits in aging populations remains uncertain.^{6,59}

Additionally, modern metabolic environments characterized by chronic stress, sleep disruption, sedentary behavior, environmental toxicant exposure, energy dense nutrient deficient diets, and fluctuating caloric availability may place persistent demands on mitochondrial adaptability and endocrine signaling.^{23,58} These pressures may contribute to altered thyroid hormone metabolism, impaired mitochondrial efficiency, inflammatory activation, and reduced physiologic resilience over time. Understanding how mitochondrial-redox modulators interact with these adaptive systems represents an important future direction in longevity-focused endocrine research.

GLP-1 therapy, energy conservation, and metabolic adaptation: The rapid expansion of GLP-1 receptor agonist use has renewed interest in adaptive energy regulation, metabolic flexibility, and thyroid hormone physiology during caloric restriction and weight loss.⁸⁷ Significant reductions in caloric intake and body mass may induce compensatory decreases in T3 levels, resting energy expenditure, and thermogenesis as part of coordinated energy-conservation responses.^{78,87} Similar physiologic adaptations are observed in fasting states, chronic illness, and non-thyroidal illness syndrome.^{14,15}

These adaptive responses likely involve integrated signaling between thyroid hormones, mitochondrial energetics, nutrient sensing pathways, inflammatory mediators, and central neuroendocrine regulation.⁷³ Understanding how compounds such as MB interact with these pathways may offer future insights into metabolic resilience, adaptive thermogenesis, and tissue-level energetics during intentional or pathologic weight loss states.

Importantly, these concepts should not be interpreted as justification for indiscriminate metabolic “enhancement” or inappropriate suppression of adaptive physiology. Rather, they underscore the complexity of endocrine-mitochondrial signaling and the need for nuanced approaches to metabolic medicine that respect the body’s inherent adaptive mechanisms.

The emerging role of systems-based precision endocrinology: The future of endocrine medicine will likely increasingly incorporate systems biology approaches integrating hormonal signaling, mitochondrial function, inflammation, metabolism, environmental exposures, and individualized physiologic variability.⁸⁸ Rather than viewing endocrine disorders solely through isolated laboratory abnormalities, precision endocrinology may evolve toward a more dynamic understanding of interconnected biologic networks governing resilience, adaptation, and energy regulation.

Within this broader paradigm, MB may ultimately prove valuable not because it “treats” thyroid disease directly, but because it intersects with fundamental pathways influencing mitochondrial respiration, oxidative signaling, neuroendocrine function, and metabolic flexibility. These mechanisms align closely with emerging models of endocrine aging and systems-based metabolic health.

The future of endocrine medicine will likely involve greater integration of hormonal signaling, mitochondrial physiology, inflammation, metabolism, environmental exposures, and individualized biologic variability [88]. Rather than viewing endocrine disorders solely through isolated laboratory measurements, systems-based approaches may provide a more complete understanding of resilience, adaptation, and energy regulation. Within this context, MB may prove valuable not because it directly treats thyroid disease, but because it helps illuminate fundamental pathways connecting cellular energetics, metabolic flexibility, and endocrine function. At present, however, MB remains an investigational and incompletely understood compound within endocrine medicine. Future progress will require rigorous translational research, carefully designed clinical trials, improved biomarker development, and thoughtful integration of mitochondrial biology into endocrine science.

Conclusion

Methylene blue has re-emerged as a molecule of growing scientific interest because of its multifaceted effects on mitochondrial respiration, redox signaling, cellular energetics, and neuroprotection. Historically recognized for its role in methemoglobinemia and other acute medical conditions, MB is increasingly being explored within the broader contexts of mitochondrial medicine, metabolic health, and longevity science.

These mechanisms intersect closely with thyroid physiology. Thyroid hormones regulate mitochondrial function, oxidative phosphorylation, thermogenesis, and metabolic flexibility, while thyroid hormone synthesis itself depends upon tightly controlled redox signaling. Increasing evidence suggests that mitochondrial dysfunction, oxidative stress, inflammatory signaling, and altered tissue responsiveness may contribute to fatigue syndromes, neurocognitive symptoms, metabolic dysfunction, and changes in

thyroid hormone action across a variety of endocrine and chronic disease states.

Within this framework, MB offers a unique model through which to explore broader questions surrounding mitochondrial-endocrine communication and adaptive metabolism. Potential mechanistic overlaps involving mitochondrial electron transport, oxidative stress modulation, nitric oxide signaling, neuroendocrine function, ferroptosis-related pathways, and cellular resilience provide biologic plausibility for continued investigation. At the same time, direct thyroid-specific clinical evidence remains limited, and many proposed applications of MB exceed the currently available scientific data.

Importantly, MB should not presently be viewed as a treatment for hypothyroidism or autoimmune thyroid disease. Rather, its greatest value may lie in what it reveals about the interconnected nature of mitochondrial function, redox biology, and endocrine adaptation. As systems-based approaches continue to shape the future of endocrinology, greater integration of mitochondrial biology, inflammation, metabolic flexibility, and tissue energetics may help refine our understanding of complex symptom patterns not fully explained by conventional biochemical assessment alone.

Future research will require rigorous mechanistic investigation, biomarker development, and carefully designed clinical studies to determine whether mitochondrial-redox modulators such as MB can meaningfully influence endocrine and metabolic outcomes in human disease. Nevertheless, the convergence of thyroid physiology, mitochondrial function, oxidative biology, and adaptive metabolism represents an important and rapidly evolving frontier in modern endocrinology and longevity medicine.

Key takeaways

- I. Methylene blue (MB) is a redox-active compound with emerging relevance in mitochondrial medicine, neuroprotection, and metabolic health.
- II. Thyroid hormones are major regulators of mitochondrial respiration, oxidative phosphorylation, thermogenesis, and cellular energetics, creating important biologic overlap between thyroid physiology and mitochondrial function.
- III. MB may influence pathways relevant to endocrine and thyroid health, including mitochondrial electron transport, oxidative stress modulation, nitric oxide signaling, neuroinflammation, and adaptive metabolism.
- IV. The thyroid gland is uniquely dependent on tightly regulated redox signaling for normal hormone synthesis, making oxidative balance central to thyroid physiology and pathology.
- V. Mitochondrial dysfunction and impaired metabolic flexibility may contribute to fatigue, neurocognitive symptoms, and persistent “hypometabolic” phenotypes even in some biochemically euthyroid individuals.
- VI. Emerging concepts involving ferroptosis, mitochondrial ROS signaling, and tissue-level energetics may further expand understanding of thyroid-metabolic interactions.
- VII. Current evidence supporting MB in thyroid disease remains limited, and no robust clinical trials currently support its use as a treatment for hypothyroidism or autoimmune thyroid disease.
- VIII. Important safety considerations include dose-dependent biphasic effects, serotonin syndrome risk, G6PD deficiency, drug interactions, and variability in supplement quality.

- IX. Future precision endocrine models may increasingly integrate mitochondrial biology, redox signaling, metabolic resilience, and tissue-level energetics alongside conventional hormonal assessment.
- X. MB represents an intriguing investigational compound for future translational research at the intersection of thyroid physiology, mitochondrial medicine, and longevity science.

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None.

Conflicts of interest

None to declare.

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