Casual Friday Series

# Melatonin: Beyond Sleep

## The Circadian Regulator of Gut, Immune, & Metabolic Health

A BIOGENETIX CLINICAL PRESENTATION

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# Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*

# How many times have we seen it?

- Patient's anxiety is rising… autoimmune flares are rising… metabolic numbers are stuck
- They "sleep" 7–8 hours but wake up exhausted
- They've tried every protocol — yet still plateau
- You've watched the CF's… L-Theanine helps the racing thoughts and somatic symptoms… but a few weeks later the anxiety, fatigue, or autoimmune flare comes roaring back.

**Why?** Because we are missing the "timer" and their circadian rhythm is broken

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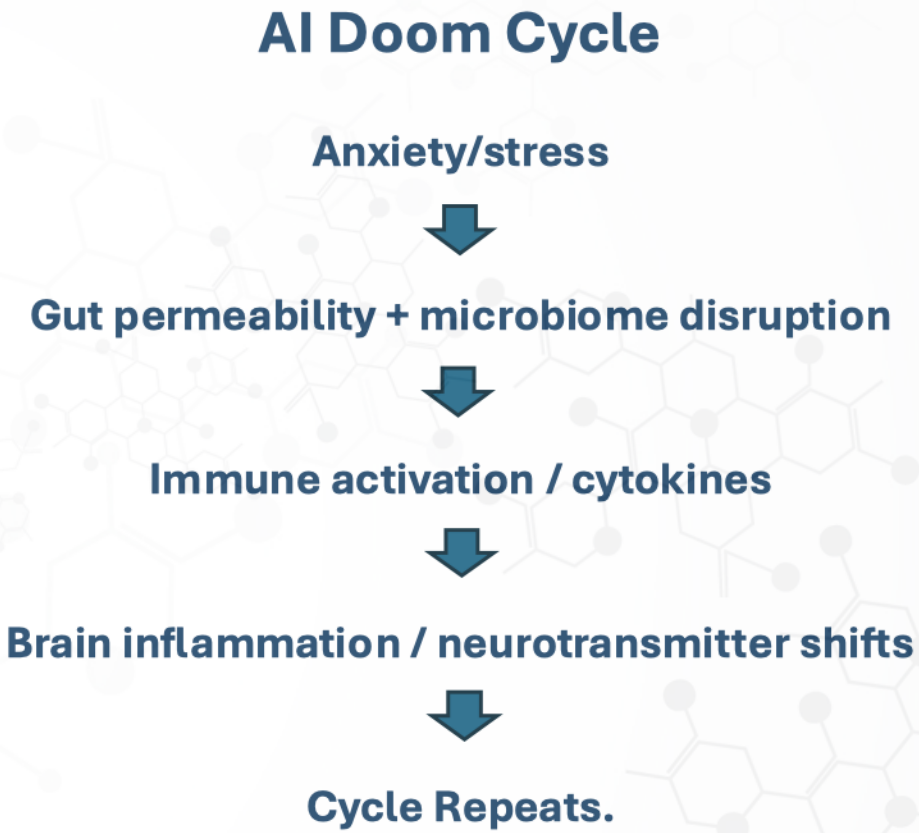
## Dr. Watts showed us the AI Doom Cycle

Today we're going to discuss an overlooked missing piece that has the potential to break that cycle at the source: The circadian rhythm and melatonin — the molecule that is *not* just a sleep aid, but the circadian regulator of gut, immunity, and metabolic health."

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# Melatonin Is NOT Just a Sleep Aid

- Melatonin is a mitochondrial, immune, metabolic, and gut signaling molecule
- Melatonin is produced in the…
  - Pineal gland
  - Gut mucosa
  - Immune cells
  - Mitochondria themselves

Most of the melatonin that actually matters in chronic disease is made right where the problem is — in the gut and the mitochondria.

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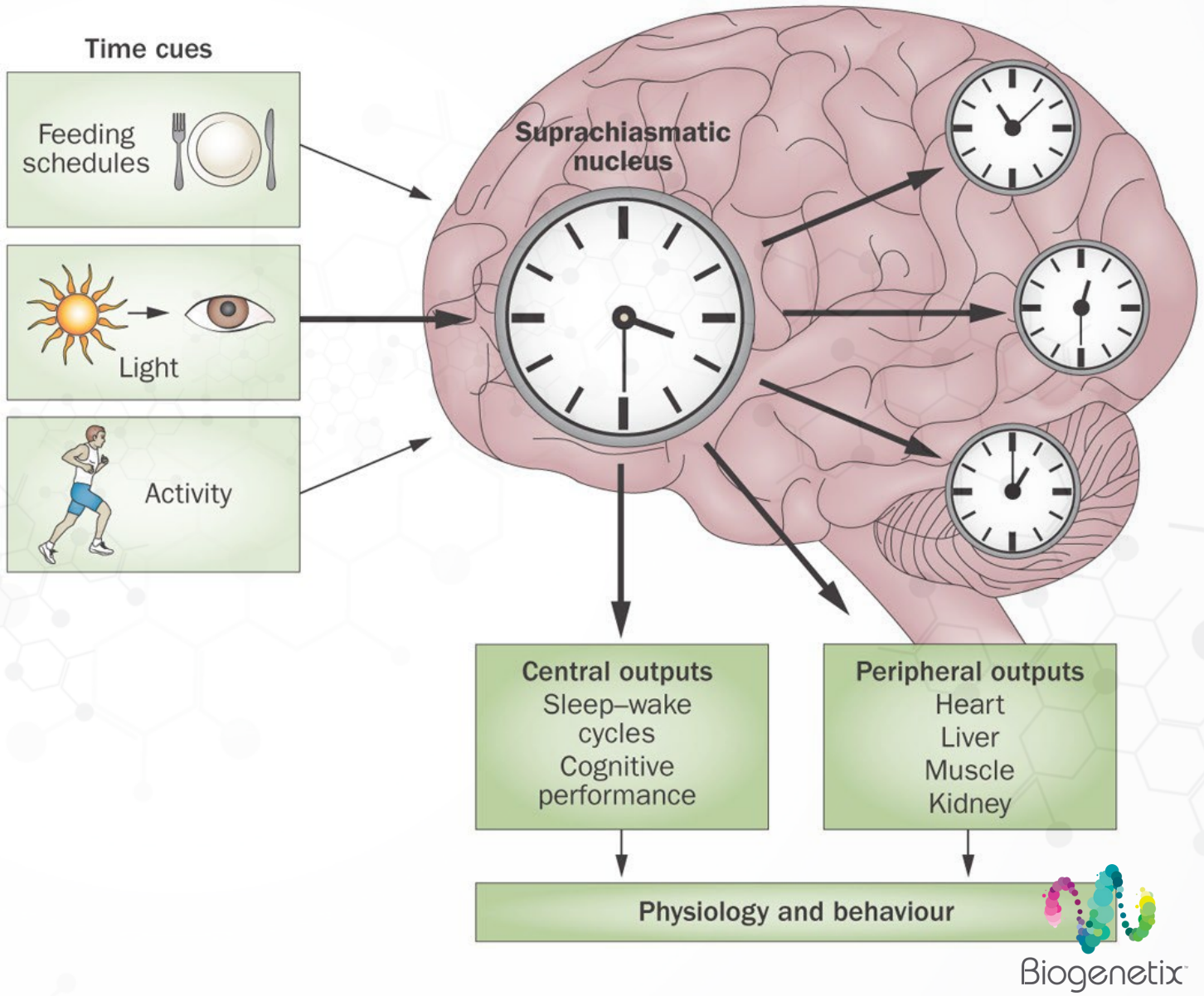
# Circadian Biology and Cortisol

**Suprachiasmatic nucleus (SCN) = master clock**

- Morning light → sets the rhythm
- Evening blue light / late eating → flattens the rhythm
- Melatonin rises as cortisol falls — they are inverse

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# When the Rhythm Breaks

- The Cortisol Curve Flattens… ie high night-time cortisol
  - This flattened cortisol curve = exactly what Dr. Watts showed in the high-inflammation and stress-sensitized subtypes
- Who is more prone: Shift workers, screen junkies, late-night eaters
- The Result ↑ anxiety, ↑ autoimmune flares, ↑ insulin resistance

Many of your “anxious” patients aren’t anxious — they’re circadian-misaligned.

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# Melatonin as Immune Modulator

This should sound familiar…

- Down-regulates NF-κB
- Lowers IL-6, TNF-α
- Supports regulatory T-cells
- Dual role: can be stimulatory or calming depending on dose & timing

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# Melatonin as the Missing Link Between Sleep Deprivation and Immune Dysregulation: A Narrative Review

PMCID: PMC12296019 PMID: 40724980

Sleep deprivation impairs immune function, and melatonin has emerged as a key mediator in this process. This narrative review analyzes 50 studies published between 2000 and 2025 to determine the extent to which reduced melatonin synthesis contributes to immune dysregulation. Consistent sleep loss lowers melatonin levels, which correlates with elevated proinflammatory cytokines (e.g., IL-6 and TNF-α), increased oxidative stress, and reduced immune cell activity, including that of natural killer (NK) cells and CD4+ lymphocytes. Melatonin regulates immune pathways, including NF-κB signaling. It also supports mitochondrial health and helps maintain gut barrier integrity. These effects are particularly relevant in vulnerable populations, including older adults and shift workers. Experimental findings also highlight melatonin's therapeutic potential in infections like SARS-CoV-2, where it modulates inflammatory responses and viral entry mechanisms. Despite the heterogeneity of study methodologies, a consistent correlation emerges between circadian disruption, melatonin suppression, and immune imbalance. These findings underscore melatonin's dual role as a chronobiotic and immunomodulator. Addressing sleep loss and considering melatonin-based interventions may help restore immune homeostasis. More clinical trials are needed to determine the best dosing, long-term efficacy, and population-specific strategies for supplementation. Promoting healthy sleep is crucial for preventing chronic inflammation and diseases associated with immune dysfunction.

# The Gut–Melatonin Connection

- Gut produces far more melatonin than the pineal gland… about 400× more melatonin than pineal gland
- Regulates motility, tight junctions, microbiome balance
- Reduces intestinal permeability
- Protects against the stress “bulldozer”
- Food-responsive (late eating = gut melatonin chaos)

Clinically we can see IBS, SIBO, IBD, nighttime reflux, and leaky gut

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# Gastrointestinal melatonin: localization, function, and clinical relevance

PMID: 12395907 DOI: 10.1023/a:1020107915919

The gastrointestinal tract of vertebrate species is a rich source of extrapineal melatonin. The concentration of melatonin in the gastrointestinal tissues surpasses blood levels by 10-100 times and there is at least 400x more melatonin in the gastrointestinal tract than in the pineal gland. The gastrointestinal tract contributes significantly to circulating concentrations of melatonin, especially during the daytime and melatonin may serve as an endocrine, paracrine, or autocrine hormone influencing the regeneration and function of epithelium, enhancing the immune system of the gut, and reducing the tone of gastrointestinal muscles. As binding sites for melatonin exhibit circadian variation in various species, it has been hypothesized that some melatonin found in the gastrointestinal tract might be of pineal origin. Unlike the photoperiodically regulated production of melatonin in the pineal, the release of gastrointestinal melatonin seems to be related to the periodicity of food intake. Phylogenetically, melatonin and its binding sites were detected in the

Review

# Gut microbiota in neurological diseases: Melatonin plays an important regulatory role

Biomedicine & Pharmacotherapy
Volume 174, May 2024, 116487

Somayeh Ahmadi [a b], Mohammad Taghizadieh [c], Elham Mehdizadehfar [d], Alka Hasani [b e], Javad Khalili Fard [f], Hadi Feizi [b g], Hammed Hamishehkar [f], Masood Ansarin [f], Mina Yekani [h i] ✉, Mohammad Yousef Memar [j] ✉

## Highlights

- The gut microbiota contributes to the production of melatonin from tryptophan.
- Melatonin has a beneficial effect on intestinal barrier function and microbial populations.
- The potential connection is between melatonin and the microbiome-gut-brain axis.
- Enteric microbiota play an important role in brain-related diseases through melatonin modulation in the gut.

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# Blood Sugar & Metabolic Regulation

- MT1 & MT2 receptors on pancreatic beta cells sense melatonin
- At night, high melatonin, decreases insulin secretion (protective)
- Inhibits cAMP pathway: prevents excess insulin during fasting/rest
- Keeps glucose steady for brain overnight without over-insulinizing
- Late-night eating while melatonin high → overrides protection
- Carbs + elevated melatonin = blunted insulin response
- Result: worse glucose tolerance, higher spikes, prolonged elevation
- Shift workers & late eaters fight natural rhythm → higher diabetes/metabolic risk
- Misaligned timing disrupts the protective nightly "insulin brake"

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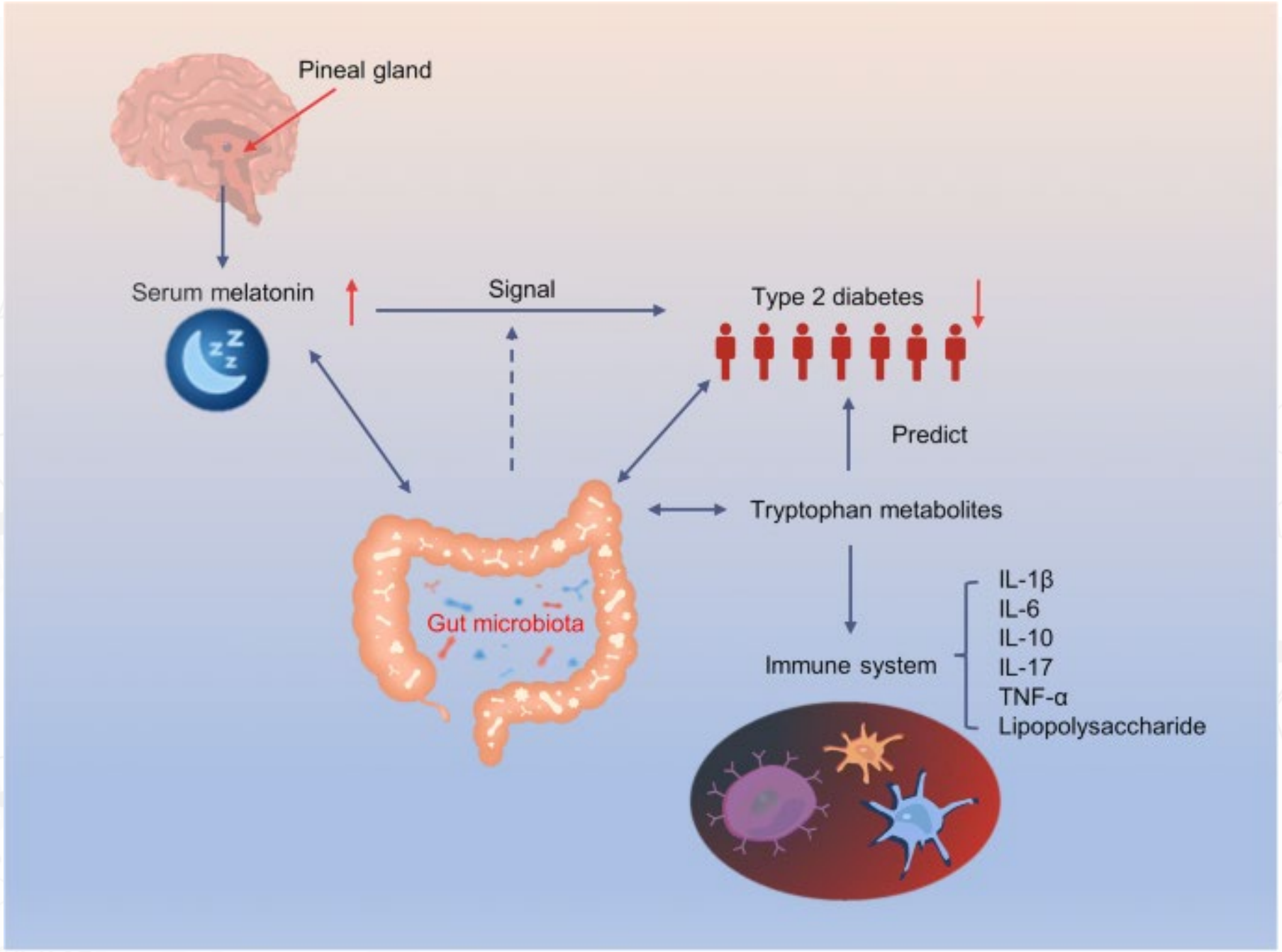
Pineal gland
Serum melatonin
Signal
Type 2 diabetes
Predict
Tryptophan metabolites
Gut microbiota
Immune system
IL-1β
IL-6
IL-10
IL-17
TNF-α
Lipopolysaccharide

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# Mitochondria, Oxidative Stress & Brain Drainage

- Direct free-radical scavenger (better than glutathione in some tissues)
- Upregulates glutathione & superoxide dismutase (SOD)
- Protects mitochondrial DNA
- Deep sleep = glymphatic clearance (brain's lymphatic drainage)

Deep sleep = glymphatic clearance. Without it, the brain inflammation and Doom Cycle never clears.

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# Melatonin: A Versatile Protector against Oxidative DNA Damage

PMID: 29495460 PMCID: PMC6017920 DOI: 10.3390/molecules23030530

Oxidative damage to DNA has important implications for human health and has been identified as a key factor in the onset and development of numerous diseases. Thus, it is evident that preventing DNA from oxidative damage is crucial for humans and for any living organism. Melatonin is an astonishingly versatile molecule in this context. It can offer both direct and indirect protection against a wide variety of damaging agents and through multiple pathways, which may (or may not) take place simultaneously. They include direct antioxidative protection, which is mediated by melatonin's free radical scavenging activity, and also indirect ways of action. The latter include, at least: (i) inhibition of metal-induced DNA damage; (ii) protection against non-radical triggers of oxidative DNA damage; (iii) continuous protection after being metabolized; (iv) activation of antioxidative enzymes; (v) inhibition of pro-oxidative enzymes; and (vi) boosting of the DNA repair machinery. The rather unique capability of melatonin to exhibit multiple neutralizing actions against diverse threatening factors, together with its low toxicity and its ability to cross biological barriers, are all significant to its efficiency for preventing oxidative damage to DNA.

# Protective Effects of Melatonin and Mitochondria-targeted Antioxidants Against Oxidative Stress: A Review

PMID: 26087763 DOI: 10.2174/0929867322666150619104143

Oxidative damage is related to aging and a wide range of human disorders. Mitochondria are in large part responsible for free radical production and they are also main targets of the attack of these toxic molecules. The resulting deleterious effects of the damage to mitochondria can be prevented by antioxidants. Melatonin is an endogenously-produced indoleamine that modulates numerous functions, including mitochondria-related functions; this result from its capacity to penetrate all morphophysiological barriers and to enter all subcellular compartments due to its amphiphilic nature. Furthermore, this indoleamine and its metabolites are powerful antioxidants and scavengers of free radicals, protecting cellular membranes, the electron transport chain and mitochondrial DNA from oxidative damage. These properties may make melatonin a potent protector against a variety of free radical-related diseases. By comparison, other conventional antioxidants have less efficacy due to their limited access to the mitochondria. In recent years, research has focused on the advancement of mitochondria-targeted antioxidants, such as MitoQ (composed by the lipophilic triphenylphosphonium cation conjugated to the endogenous antioxidant coenzyme Q10) and MitoE (composed by the triphenylphosphonium cation attached to the antioxidant α-tocopherol). Mitochondria-targeted antioxidants accumulate in several hundred-fold greater concentrations within mitochondria and protect these critical organelles from oxidative damage. Melatonin also seems to be a mitochondria-targeted antioxidant and has similar protective actions as the synthetic antioxidants. Further work is required to determine the therapeutic properties of these antioxidants in ameliorating diseases related to mitochondrial dysfunction.

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# Spotting Circadian Disruption in Practice (no fancy labs needed)

- Wakes between 2–4 a.m. → night-time cortisol spike
- Can’t fall asleep before 11 p.m. despite exhaustion
- Morning grogginess that lasts >30 min
- Nighttime reflux or sugar cravings
- Poor response to otherwise good protocols
- Poor sleep + somatic symptoms + autoimmune comorbidity = high-inflammation subtype from Dr. Watts

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# Dosing & Timing

**Lifestyle First — Always**

- Morning sunlight (10–30 min)
- Evening darkness / blue-light block after sunset
- Stop eating 3 hrs before bed
- Consistent sleep/wake times

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# Dosing & Timing

**Physiologic Dosing** (Circadian + Gut/Mito Support)

- 0.3 – 1 mg
- 60–90 min before desired bedtime (or up to 3 hrs for stronger circadian shift)
- Immediate-release preferred — mimics natural rise

**Standard Clinical Dosing** (Most Patients)

- Start 0.5 – 3 mg
- Titrate to 5 mg max if needed
- 30–60 min before bed (immediate for onset, extended for maintenance)

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# Dosing & Timing

**Research / Targeted Dosing** (Autoimmune, Metabolic, Oxidative Stress)

- Hashimoto's, IBD, MS: 3–6 mg nightly (bedtime)
- RA & metabolic support: 6–10 mg nightly
- Higher mito/antioxidant contexts (elderly/comorbid): 10–40+ mg (well-tolerated in studies up to 200 mg)

**Key Takeaway**

Lower physiologic doses timed correctly support the local gut + mitochondrial melatonin that actually drives immune and metabolic benefits. We don't need to flood the system — we support the rhythm.

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# Cautions & When NOT to Use

- Short term usage is preferred
- Pregnancy
- Severe depression (can worsen in some)
- Autoimmune patients on high-dose immunosuppression
- Kids — use lowest effective dose
  - 0.5–3 mg max

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# Clinical Integration

1. **Considerations from other CFs**
   - Root To Fruit (stress, gut, antigenic cloud)
   - Calm the anxious brain/gut with L-Theanine
   - Repair leaky gut & cytokines (high-inflammation subtype focus)

2. **Restore Circadian Capacity**
   - Morning sunlight 10–30 min
   - Evening darkness / blue-light block
   - Stop eating 3 hrs before bed (protect gut melatonin pool)
   - Consistent sleep/wake times

3. **Add Timed Melatonin if Needed**
   - Physiologic: 0.3–1 mg (60–90 min before bed) for local gut/mito support
   - Clinical: 1–3 mg (or 3–6 mg for autoimmune/IBD/MS overlap)
   - Immediate for onset; extended for maintenance
   - Melatonin supports the rhythm, doesn’t replace it

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# How Biogenetix Supports the Foundation

- **Hypaax Balance:** restores healthy HPA-axis & cortisol rhythm
- **BioG-Max GABA:** calms evening nervous system tone, supports parasympathetic wind-down
- **BioG-Max GSH + CoQ10:** mitochondrial antioxidant protection & energy production (synergizes with local mitochondrial melatonin)
- **Binder Pro:** binds LPS & gut-derived toxins, supports barrier integrity (protects the gut melatonin factory)
- **Metabolic Clearing Kit:** full-system inflammation reset & drainage capacity (liver, lymph, gut)

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You can not fix the inflammation without fixing the timing.
Melatonin isn’t the hero… the Circadian Rhythm is!

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