

# The Cyclical Effect of Stress, Sleep And Insomnia

Presented by Dr. Penny Kendall-Reed, ND  
On Demand Recording



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RA Approved  
January 2022



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**Dr. Penny Kendall-Reed, N.D.**

I am a paid advisor to Pure Encapsulations. I have no other conflicts of interest to disclose.

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# The Terrible Triad

- 30% of the population suffers from insomnia, and up to 60% of those over 60 years old have insomnia.
- The WHO has declared sleep loss an epidemic in industrialized nations.
- People sleep 20% less today than they did 100 years ago.
- Approximately 100 million people in the US use prescription sleeping pills.
- The number one cause of insomnia is stress/anxiety.
- 90% of visits to health care practitioners are due to stress or stress related pathologies.
- Cortisol can increase the production of inflammatory cytokines by 3-fold, even more so in those with genetic variants.

*Mental Health Commission of Canada  
Soc Sci Med 2010;71-1027  
J Clin Endocrinol Metab 2011;96:486-493  
Science Daily Mar 24 2010  
National Sleep Foundation  
Mayo clinic*



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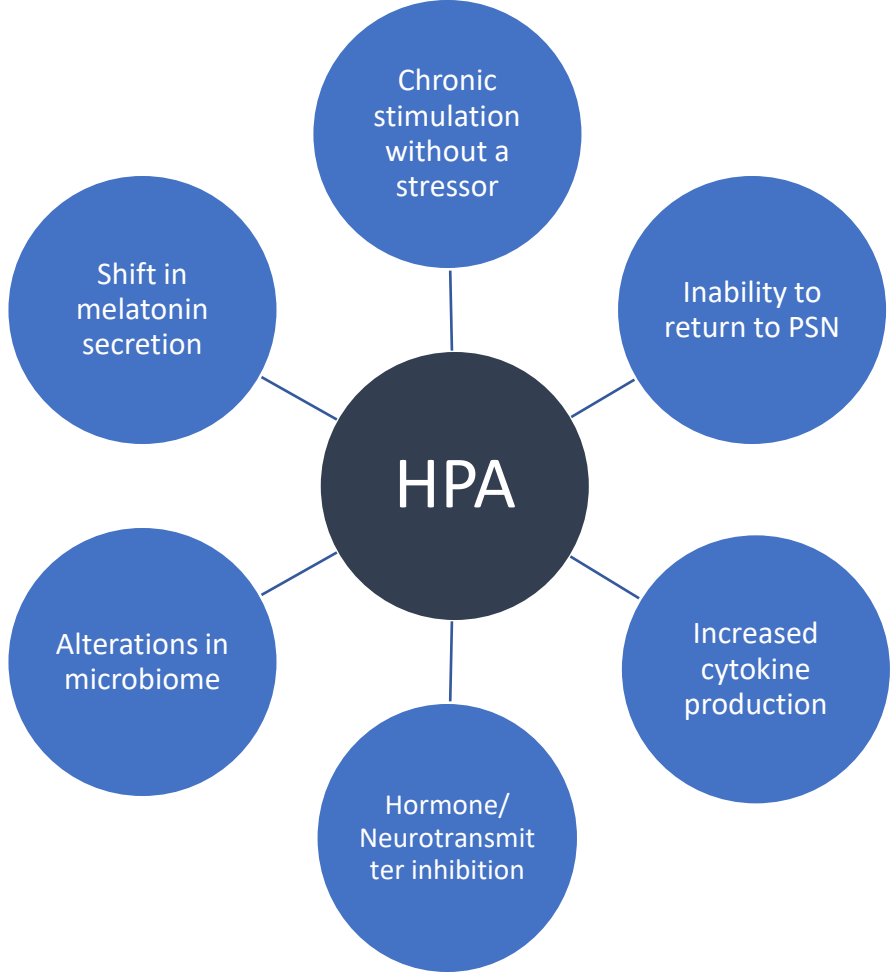


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# Loss of Negative Feedback in the HPA axis



*Australian Spinal Research Foundation June 2016  
Gen Psychiatry 2000 Aug 57(8):787-793*



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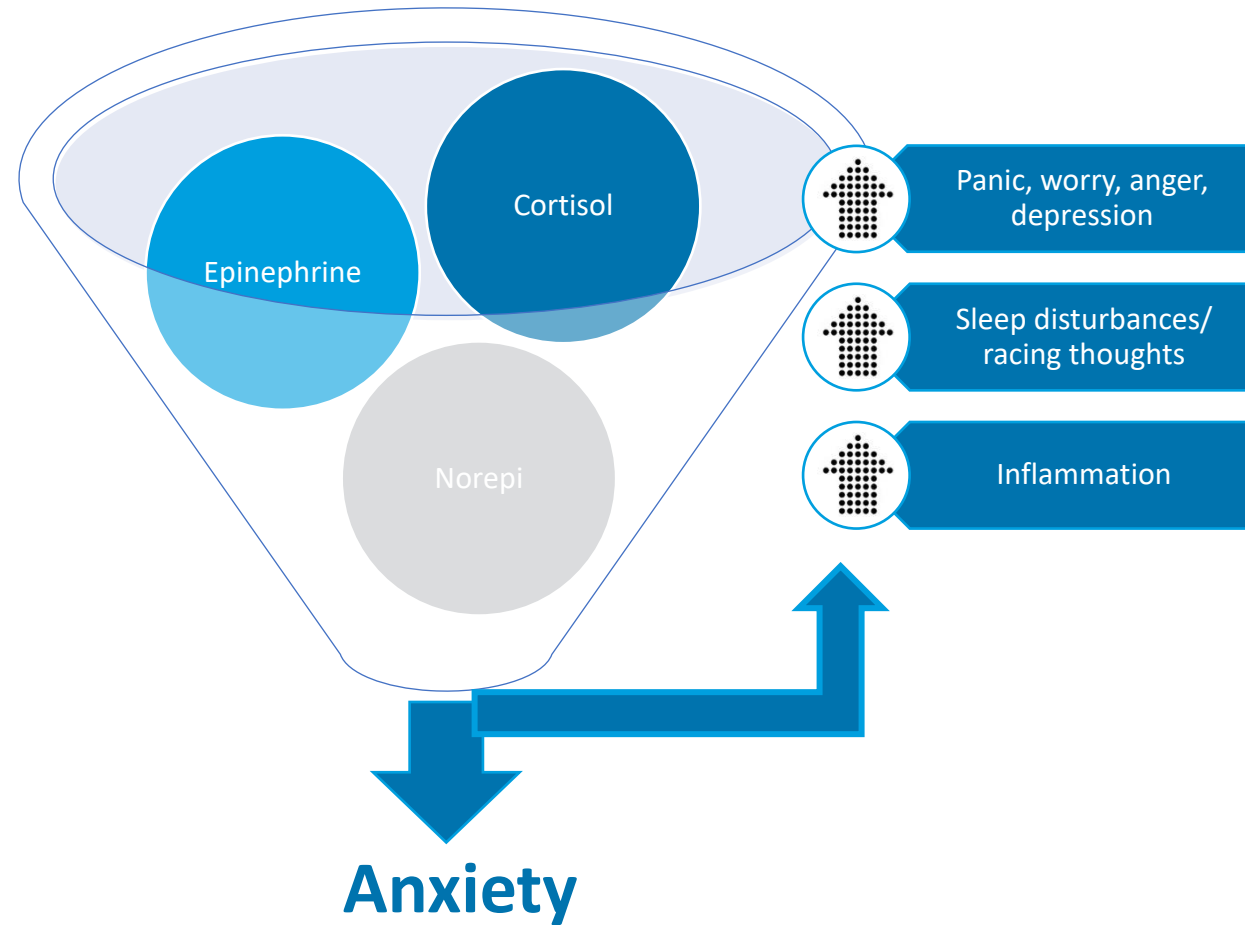
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# Stress and Anxiety



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# Effects of Early Childhood Stress



*National Academy of Sciences of the USA, vol 97, 2000*



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# Stress's Effect on the Microbiome



Golubeva et al., 2015 *Psychoneuroendocrinology*;60:58-74  
Bizzarebiology.com McMaster University  
National Academy of Sciences of the USA, vol 97, 2000



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# Stress and Inflammation

“While up to 90% of human disease is related to the activation of the stress system...evidence suggest that excessive inflammation plays critical roles in the pathophysiology of stress-related diseases.”



*Front Hum NeuroSci. 2012;11:316*



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# Stress and Depression >>>>Inflammation

- Those diagnosed with depression and anxiety all have **significantly** higher levels of IL6, TNFa and CRP.
- Conversely depressive/anxious symptoms are more frequent in those with inflammatory conditions.

*Psychos3 Med 2009 71:171-186*

- One of the biggest predictors of a stress induced pro-inflammatory response (outside of genetics) is early childhood adversity or stress.
- Childhood stress induced neural inflammation causes physiological changes in the HPA axis and deregulation of the negative feedback loop.

*J Clin Child Adolesc Psychol 2018 47:142-156*



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# Inflammation>>>Stress and Depression

- Cytokines act upon GC receptors and upregulate the synthesis of CRH, ACTH and cortisol.
- Cytokines activate indoleamine-2, 3-dioxygenase (IDO), stealing tryptophan and lowering serotonin.
- Cytokines lowers the vagal response which in turn increases cortisol and further increases cytokine production.

*Biol Psychol 2010 84:290-295*

*Am J Psychiatry 2013 160:1554-1565*



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# Cortisol and Inflammation

- The peripheral immune system alters cytokine balance in the brain which can alter mood and behaviour.
- Increased brain cytokine production increases HPA activity and raises cortisol levels far beyond normal.
- The rise in cortisol, further stimulates cytokine production, particularly IL6, IL1B and TNF-a.

*Inter J of Molecular Sci., 2020: 21;1118*

*Acta Neuropsychiatry, 2003: 15;148-155*

*Neuron, 2009: 64;33-39*



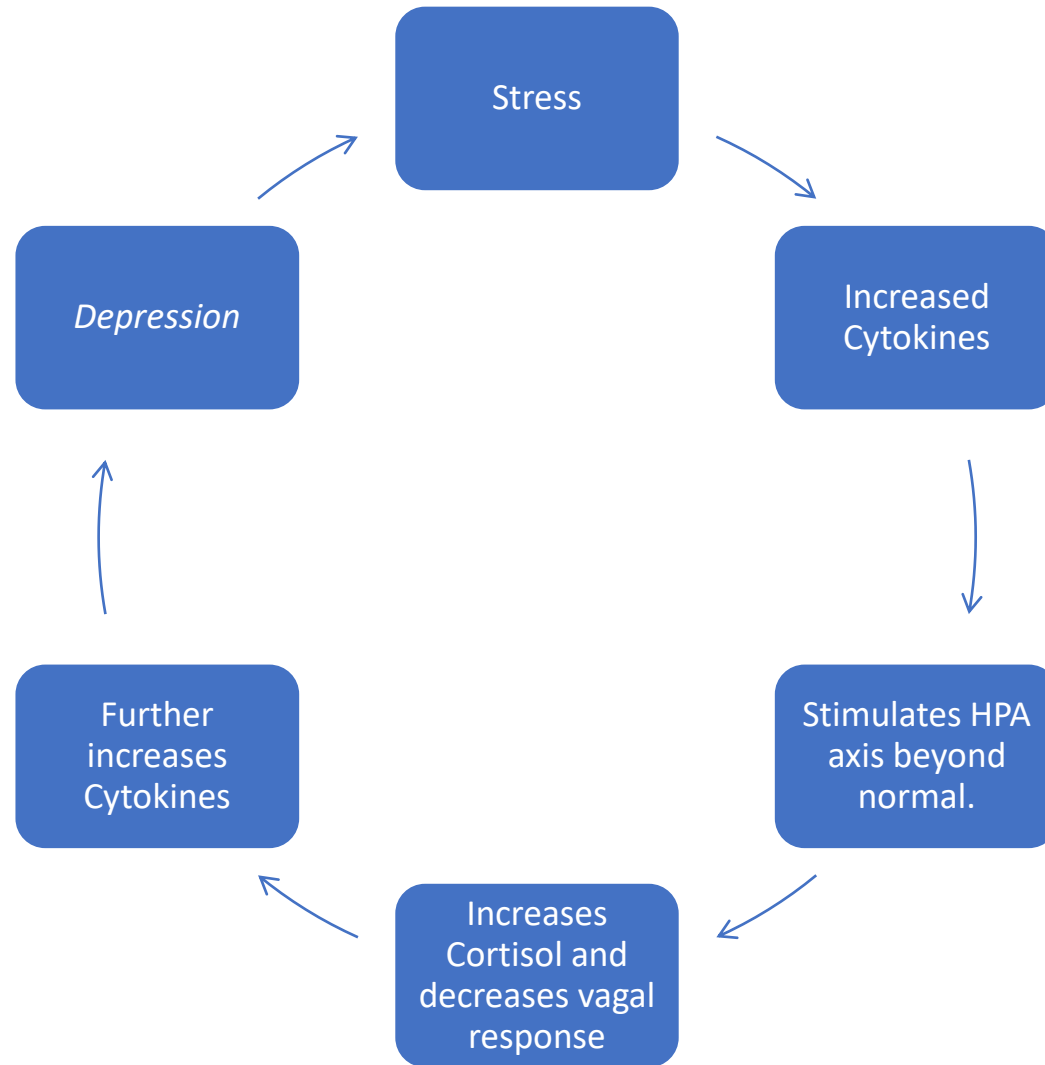
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*Inter J of Molecular Sci., 2020: 21;1118*  
*Acta Neuropsychiatry, 2003: 15;148-155*  
*Neuron, 2009: 64;33-39*



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# Stress and Inflammation

- Glucocorticoids increase the production of the inflammasome NLRP3 which increases IL-1B and IL-18 as well as PGE2 series.
- A loss of negative feedback in the HPA axis stimulates the inflammatory genes (IL6 and TNF-a) and inhibits anti-inflammatory genes (GSH genes).

*Brain Behav. Immune. 2007; 21:901-912*

*Biol. Psychiatry. 2009; 65:732-741*



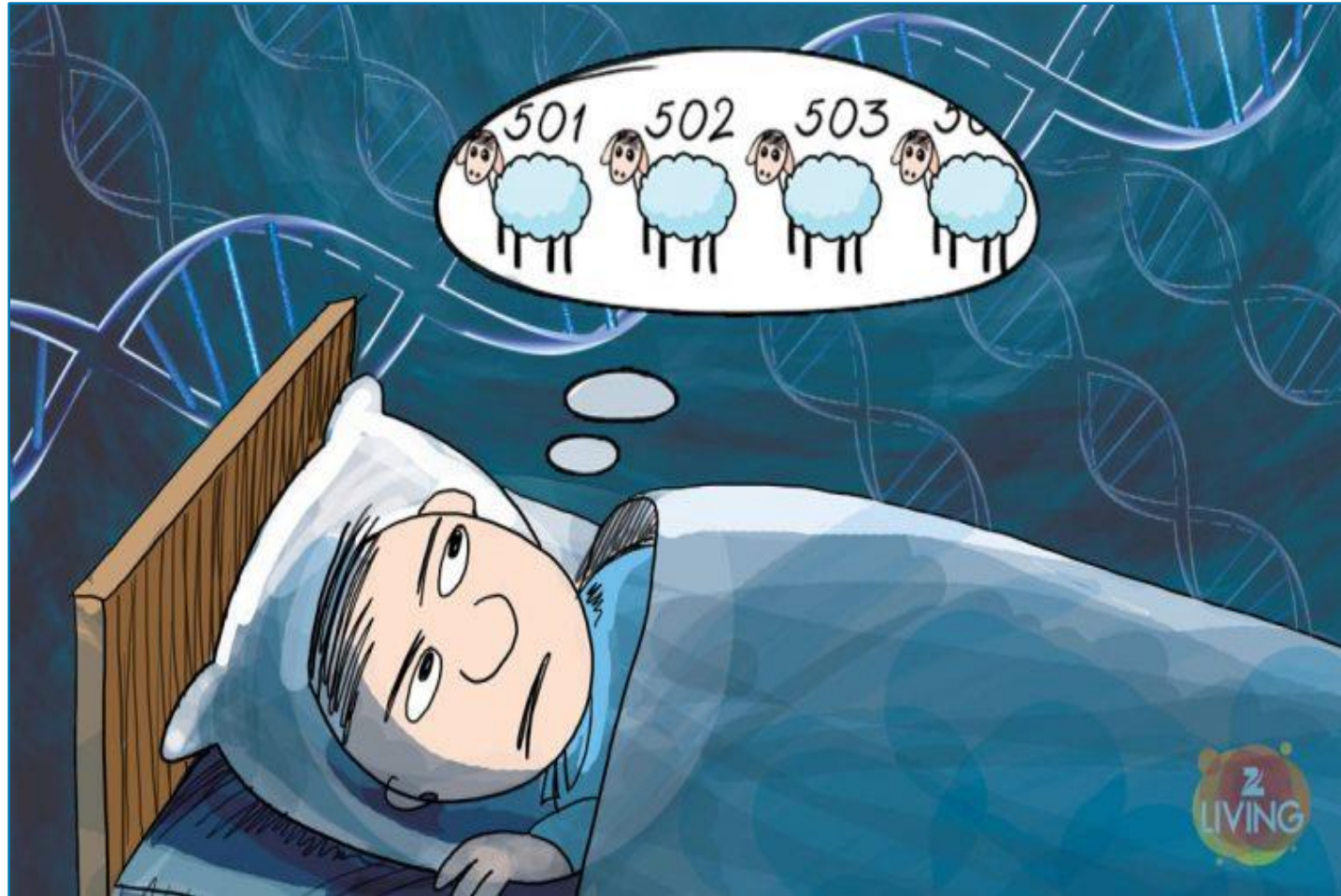
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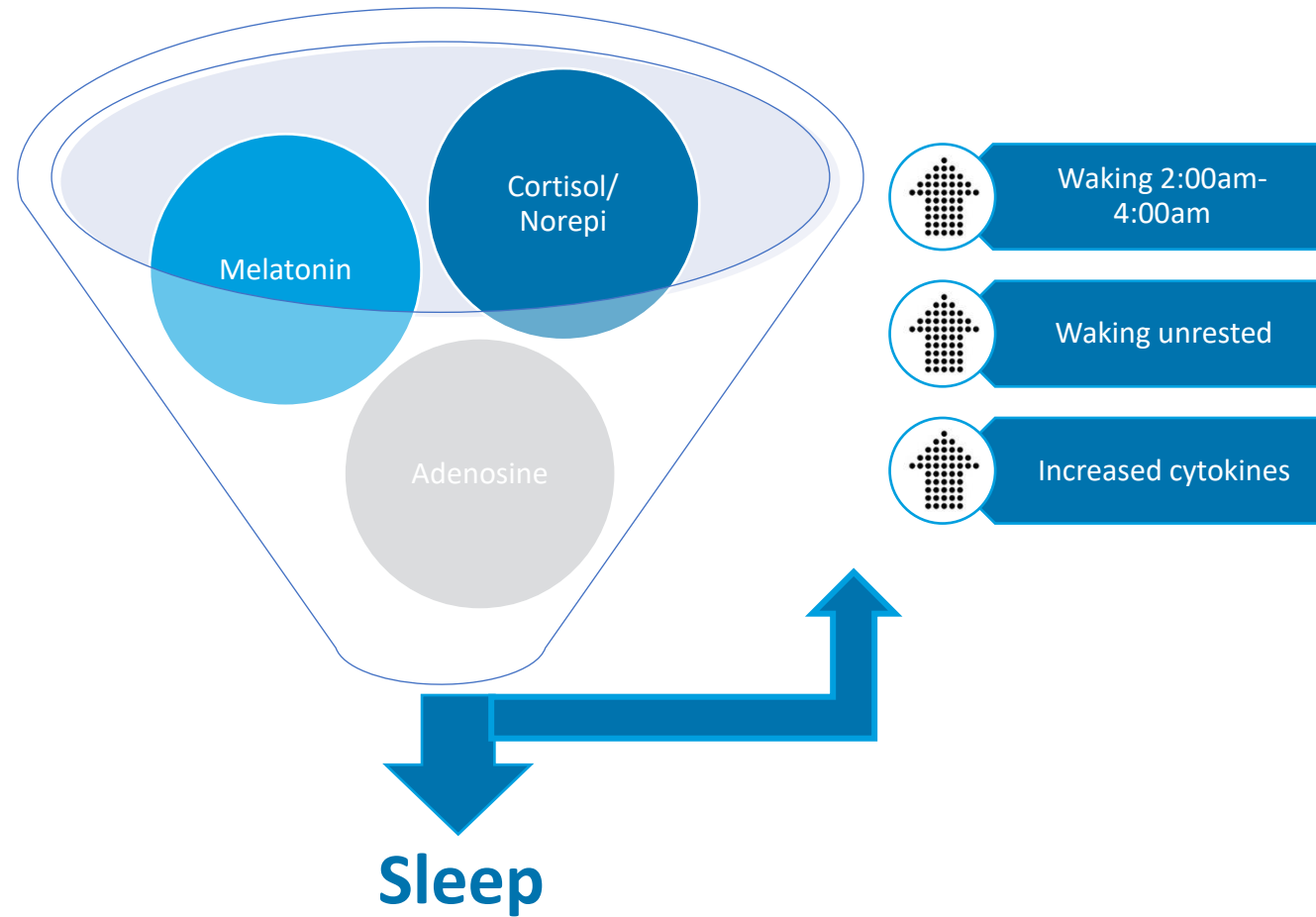


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# Sleep



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# Fatal Familial Insomnia

- A rare genetic disorder that prevents people from sleeping
- A homozygote variant condition of the PRNP gene
- This gene codes for the production of the prion protein - PrP

The disease has 4 stages:

1. Increasing insomnia resulting in panic attacks, paranoia and phobias (4 months)
2. Hallucinations and panic attacks (5 months)
3. Complete inability to sleep (3 months)
4. Dementia, unresponsiveness and then death (last final 6 months)



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# Sleep Biomechanics

## Sleep is divided into 2 forms:

- Non REM sleep: stages 1-4, slower deeper sleep
- REM sleep: paradoxal sleep or wakefulness

A cycle from stage 1 through REM lasts roughly 90 mins (up to 120 mins); the first few hours of sleep are dominated by Non REM sleep.

## The Sleep cycle is controlled by 2 main mechanisms:

- Sleep Pressure
- Sleep Rhythm



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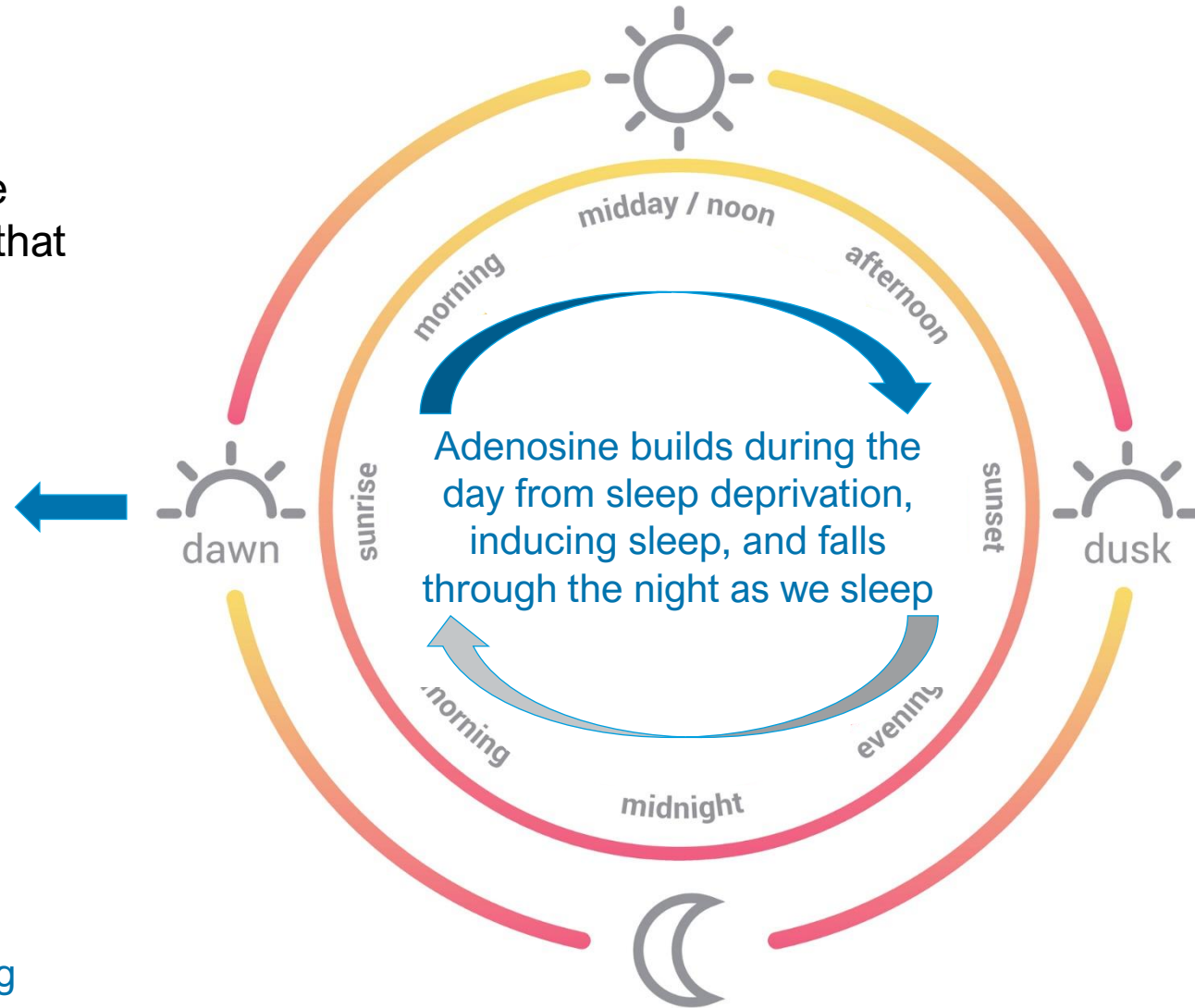
# Sleep Pressure

Sleep pressure is controlled by the neuromodulator called adenosine that promotes sleep and suppresses arousal.

A rapid fall occurs in the morning, along side with cortisol rising to stimulate waking



Too much caffeine, cortisol, norepinephrine and/or sugar block adenosine production and inhibiting receptor binding



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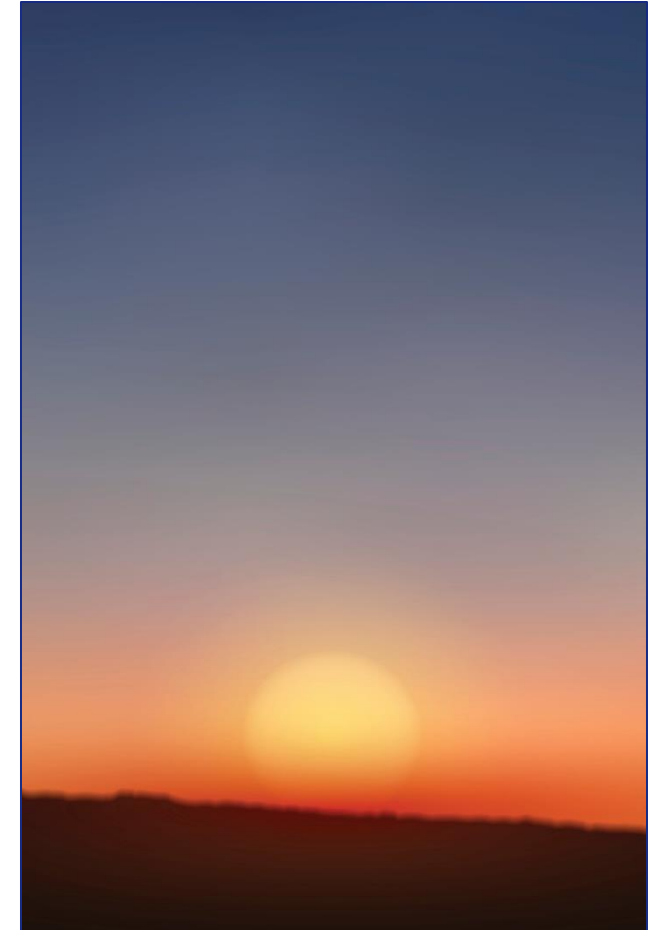
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# Sleep Rhythm - our circadian rhythm

- Studies on plants and humans both show that when deprived of all sunlight, the body retains its natural 24-26 wake/sleep cycle.
- The SCN stimulates the release of melatonin from the pineal gland after dusk, regulating the timing of sleep, but not the onset of sleep.
- As we begin to sleep, melatonin rises until approximately 2:00 am, and then begins to rapidly fall.



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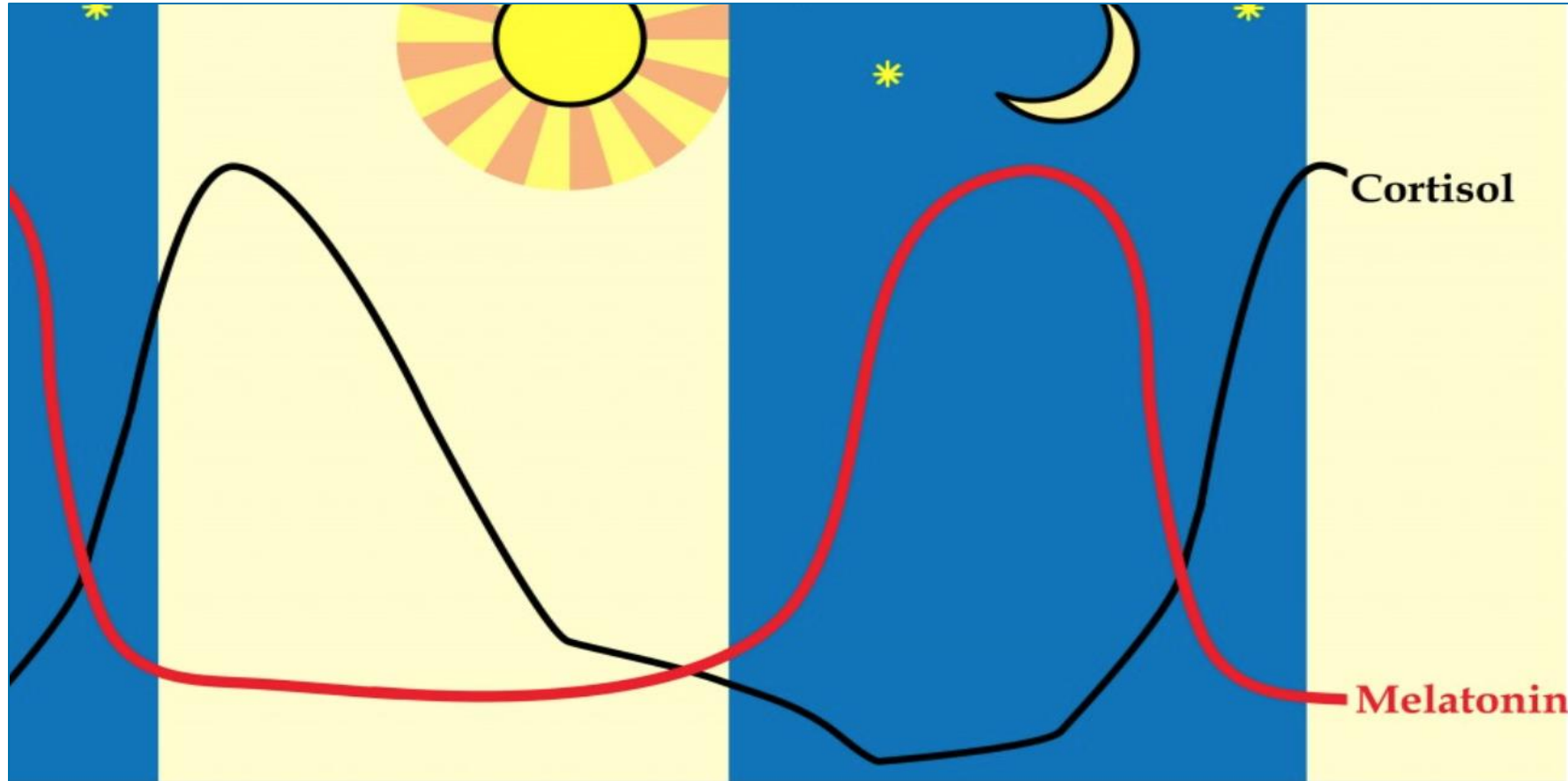


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# Inverse Relationship



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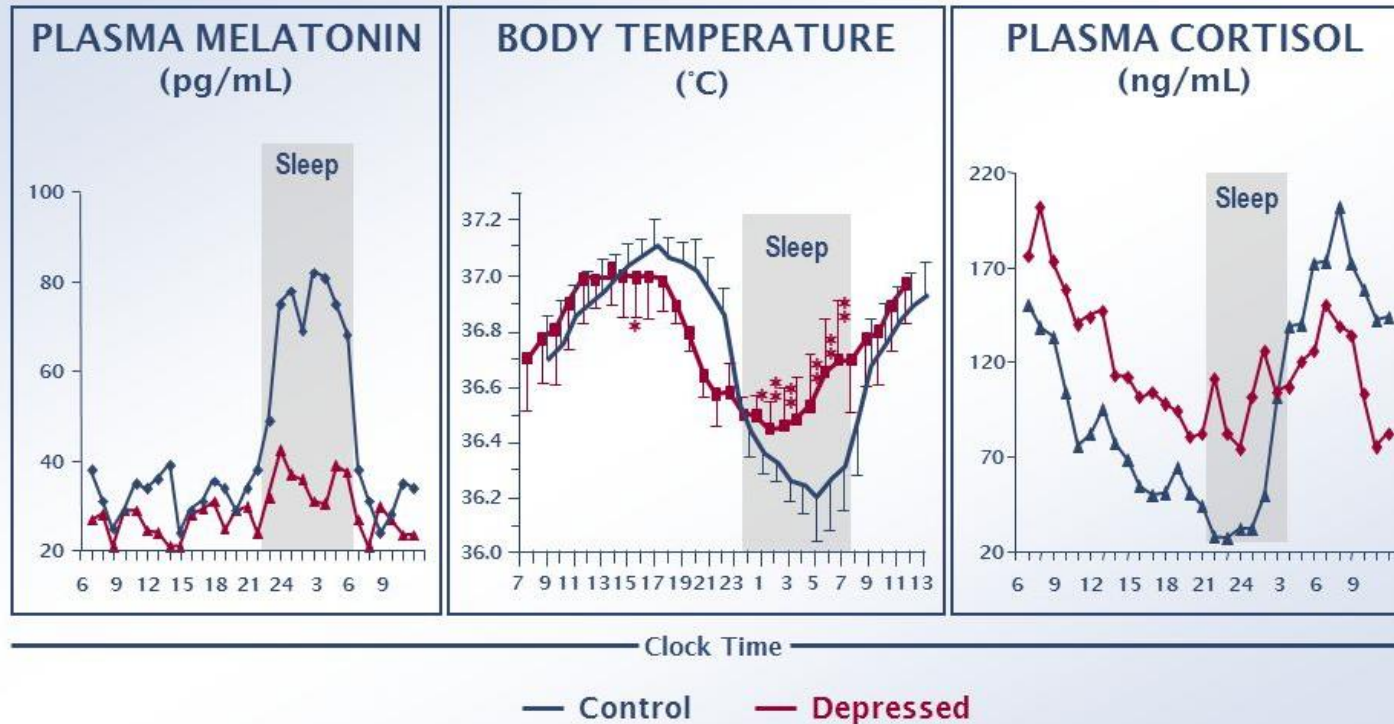
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# Circadian rhythms are flattened and disrupted in depressed patients



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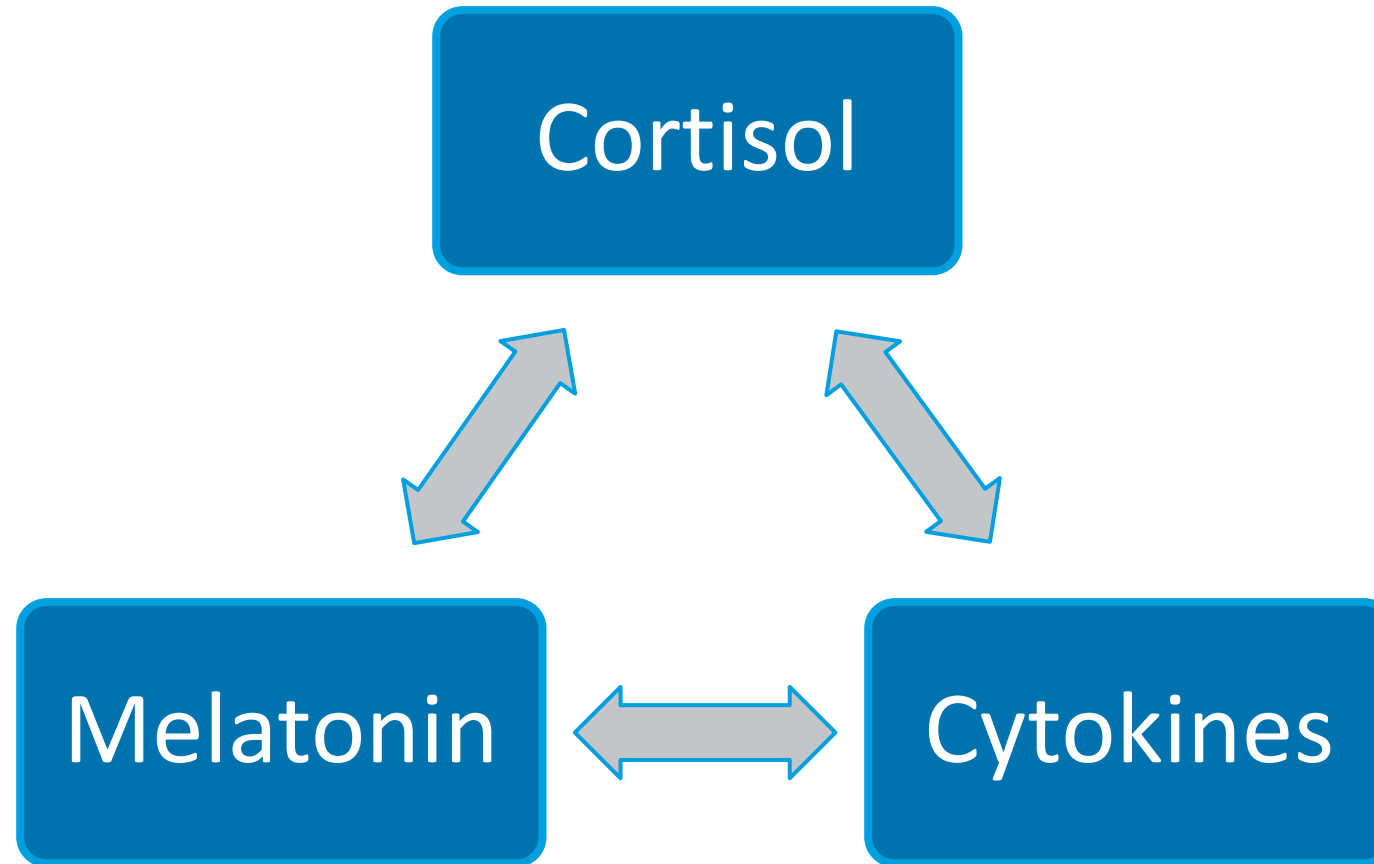


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# Cortisol and Melatonin



*Wilking M et al, 2013, Circadian Rhythm connections to stress. 19(2), 192-208*  
*W-P Chong, European Journal of Oncology Nursing 29 (2017) 79-84*



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# Cortisol and Sleep

- Depression, anxiety, stress-related disorders and chronic insomnia all share a common theme:
  - Elevated cortisol
  - Altered norepinephrine levels
  - HPA axis dysfunction
- This elevation in cortisol (independent of stress or depressive symptoms) is considered the **primary cause of the sleep disturbance** and is a marker for increased CRH activity and norepinephrine levels the following day.

*Arborelius L, et al.. J Endocrinol. 1999;160:1-12., / El Mansari et al, CNS Neurosci Ther. 2010 Apr 8.  
Gold PW, et al. N Engl J Med. 1988;319(7):413-420. / Rodenbeck A, et al. Neurosci Lett. 2002;324:159-163*



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an **absolute** cure for  
RESTLESS LEGS SYNDROME



# STUDIES SHOWING HOW INSOMNIA INCREASES INFLAMMATION LEVELS

*“When you have insomnia, you're never really asleep, and you're never really awake.” - Chuck Palahniuk*



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# Sleep loss >>>> Inflammation

- Studies in healthy participants show that when sleep is reduced from 8 to 4 hours per night, a subclinical shift in basal inflammatory cytokine production (IL6, IL17, TNFa) occurs within 2 days, and reaches clinical levels within 7 days.
- Experimental sleep loss in healthy participants show increased levels of CRP, ESR, IL6, IL17, IL1B, TNFa, PG's when deprived of 1 hour of sleep (7 vs 8) for one month.

*Clin Endocrinol Metab 2010 24(5) 775-784*

- Further studies revealed that for each hour reduction of sleep there was an 8% increase in TNFa, 8% increase in CRP, 7% increase in IL6 in habitual sleep deprived patients (6.5 to 7 hrs vs 8 hrs)

*Sleep 2001 32(2):200-4*



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# Inflammation and Sleep

Biomechanics behind poor sleep and adverse health:

- Proinflammatory responses \*\*\*
- Sympathetic Nervous System
- Renin-Angiotensin-Aldosterone System
  - Bundle of nerves in the brain that regulates wake-sleep transitions
  - Alters electrical voltage of brain waves and speed of neural firing.
  - Damage to this system results in sleep problems, narcolepsy and degenerative brain function.
- Endothelial renal functioning
  - Increased vasoconstriction and endothelial inflammation are associated with decreased delta waves sleep and decreased sleep latency.

*Biol Psychiatry 2016 80:40-52*

*Neuropsychopharmacology 2017 42:129-55*

*J Sleep Res 2014 23(1):84-93*

*Sleep Health 2016 2:75-81*



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# Inflammation and Sleep

- Elevated levels of CRP, IL6 and fibrinogen have been linked to poor sleep in otherwise healthy “robust” women.
- The level of inflammation dictates the degree between sleep deprivation and adverse clinical outcomes.
- Even 1 night of sleep disruption can impact the immune system- as seen in on call physicians.

*Eur J Intern Med 2013 24:664-70*



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# Inflammation and Sleep

- 1 week of sleep inconsistency in adolescents was associated with increased CRP levels above normal.

*Psychosom Med. 2016 78-677-85*

- Decrease in N-REM sleep and slowed transition between stages of sleep.
- Decrease delta wave sleep, up to 60%.

*Best Pract Res Clin Endocrinol Metag. 2010;24(5):775-784*

*Nature Review Neurosci., 2009;10:199-210*



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# Inflammatory Ailments

- Asthma
- Allergies
- Gastritis
- Irritable Bowel Syndrome
- Ulcerative Colitis and Crohn's disease
- Arthritis
- Diabetes
- Cancer
- Cardiovascular disease
- Bacterial/Viral infections.



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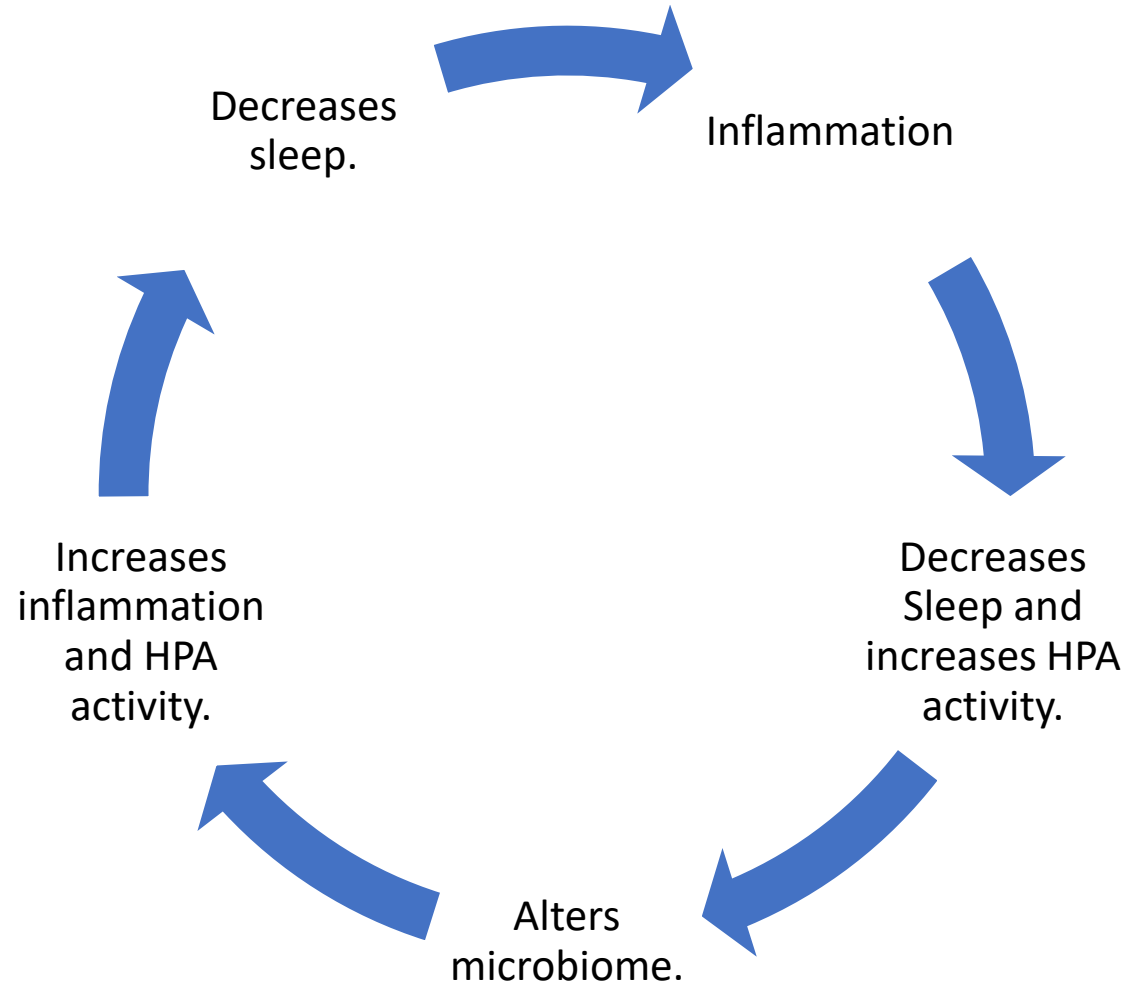


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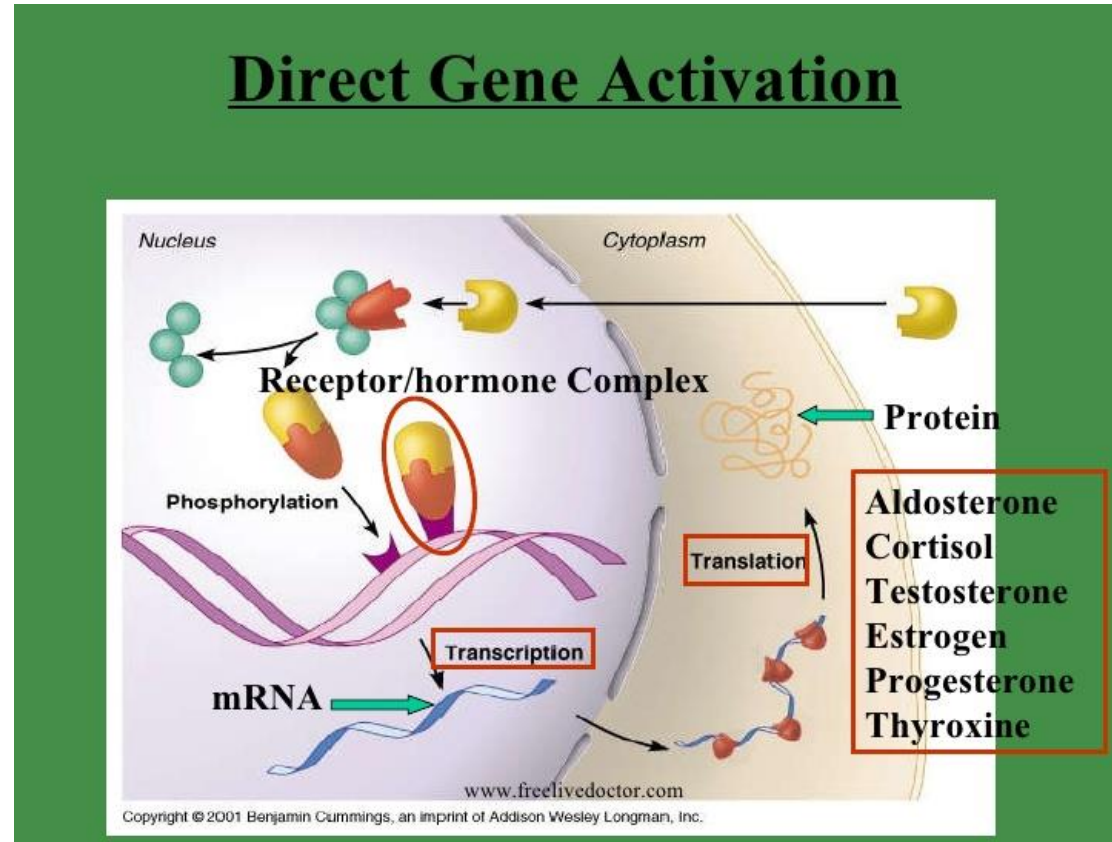
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# Hormone-Gene Interaction



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## FKBP5 rs3800373

### FK Binding Protein 5

- **Associated with altered HPA activity**

A allele: variant

C allele: normal

1. Increased FKBP5 production.
2. Increased blocking of glucocorticoids on hypothalamus.
3. Increased loss of negative feedback in the HPA axis.
4. Prolonged stress response.
5. Increased insomnia or sleep disturbances.
6. Increased cytokine production.

*Wilker s, Translational Psychiatry. 2014;4:403*

*Binder E, Psychoneuroendocrinology. 2009 Dec; 34(1): 186-195*



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**NR3C21 rs5522**

## **Nuclear Receptor Subfamily 3 Group C**

- **Associated with altered HPA activity**

**C allele: variant**

**T allele: normal**

1. Fewer mineralocorticoid receptors on the HPA axis.
2. Less binding of cortisol onto HPA axis.
3. Increased loss of negative feedback in the HPA axis.
4. Increased ACTH.
5. Increased depression, panic attacks, impulsivity, ADD and ADHD.
6. Altered sleep patterns – waking between 2:00am-4:00am.
7. Increased cytokine production.

*Psychoneuroendocrinology, 2015 Feb;52:92-110*

*J of clin Endocrinology and Metabolism, 2006 Dec;91(12): 5083-5089*



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## CRCH1 rs242939

# Cortico-releasing hormone receptor

- Associated with altered HPA activity

C allele: variant

T allele: normal

1. Increased number of CRH receptors
2. Increased binding and stimulation of the HPA axis
3. Increased response to anti-depressants (both bowel and brain)
4. Increased depression and panic attacks
5. Increased obesity.
6. Increased bloating and gas and irregular bowel movements.
7. Increased cytokine production.

*Nat Neurosci. 2003 Oct;6 (10):1100-7  
Depress Anxiety, 2009;26 (11):984-92*



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## COMT rs4680

### Catechol O-Methyltransferase

- Involved in the metabolism and clearance of dopamine, norepinephrine and estrogens

#### Met or G allele:variant Val or A allele:normal

1. Increased levels of norepinephrine, dopamine and estrogen
2. Increased anxiety
3. Reduced stress tolerance
4. Tendency to worry
5. Improved alertness in some mental tasks

*Hamidovic et al, 2010*



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## IL-6 rs1800795 Interleukin 6

- An inflammatory cytokine that serves as a messenger with nearby cells

G allele: variant

C allele: normal

1. Increased IL-6 levels.
2. Increased inflammation and reduced glutathione.
3. Insomnia and sleep disturbances.
4. Crosses BBB and can break it down.
5. Increased obesity (high levels in adipose tissue)
6. Decreased microflora

*Bashashati M, et al, Cytokine 2017 Nov;99:132-138*



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## TNF $\alpha$ 1800629

### Tumor Necrosis Factor alpha

- Proinflammatory cytokine with close linkage to the transcriptional activity of HLA class I and II

A allele: variant

G allele: normal

1. Increased TNF- $\alpha$
2. Increased auto-immune conditions, especially gluten sensitivity
3. Increased IL-6 and reduced glutathione.
4. Crosses BBB.
5. Increased HPA activity and sleep disturbances.
6. Decreased microflora

*Greco L, et al, Am J Hum Gen 1998 62, 669-675*

*Saif K, et al, Sci Rep 2016;6:32677*



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## CRY1 rs8192440

### Cryptochrome 1

- **CRY1 Cryptochrome 1 produces proteins that block the activity of the CLOCK gene which regulates natural circadian pattern.**

G allele: variant

A allele: normal

1. Increased Cryptochrome 1 protein production.
2. Increased negative feedback within the sleep loop.
3. Altered ability to transition from one stage of sleep to the next
4. Especially from waking into stage 1, or REM into stage 1
5. Delays the onset of sleep from 2 to 2.5 hours compared to non carriers
6. Increased weight gain, cholesterol.

*Cell Press Gene mutation helps explain night owl behavior." vol 169, issue 2 pg 203-205, April 2017.*



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## Clock rs1801260

- **Regulates Circadian Rhythms.**

G allele: variant

A allele: normal

1. Increased positive feedback in the sleep loop.
2. Increased stimulation at night – night owl.
3. Difficulties falling and staying asleep.
4. Difficult time adjusting to time changes.
5. Increased obesity.
6. Increased anxiety and depression.
7. Increased inflammation

*M Garaulet, Int J Obes (London) 2010 Mar., 34(3) 516-523*



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## FUT2 rs602622

### Alpha 1,2-Fucosyltransferase

- Regulates B<sub>12</sub> absorption through the gut, as well as gut microbial strains and adhesion to the intestinal mucosa

A allele: variant

G allele: normal

1. Lower intestinal microbial diversity and Bifidobacterium levels
2. Altered bowel patterns
3. Maximal B<sub>12</sub> absorption
4. Increased bloating and gas

*Tong M, et al, ISME J 2014;8(11):2193-206  
Wacklin P et al, PLoS One 2011;6(5):e20113*



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# Protocol

- 1.Reduce cortisol, adrenaline, and noradrenaline production
- 2.Reestablish negative feedback in HPA axis
- 3.Reduce inflammation
- 2.Regulate circadian rhythms
- 3.Regulate melatonin production
- 4.Increase sedating and calming properties (GABA)



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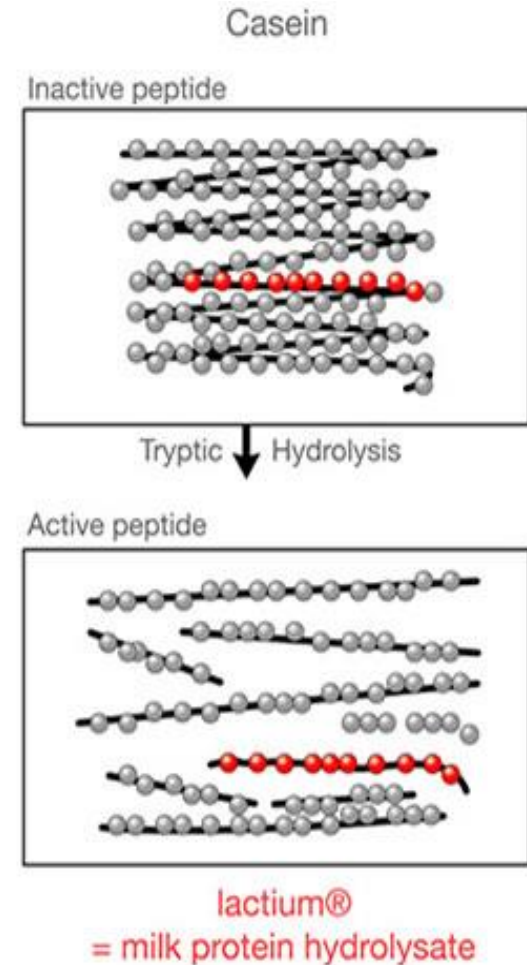
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# Lactium

- Bioactive tryptic decapeptide that binds to the GABA (A-1) receptor (calming) and not PBR receptor (sedating)<sup>‡</sup>
- Promotes the sensitivity of the hypothalamus to cortisol (Supports feedback loop)<sup>†</sup>
- Moderates cortisol and CRH during acute and chronic stress<sup>†</sup>



Medina, J. H., Peña, Mol. Neurobiol. 6, 377–386 1992  
Papadopoulos, V. Endocr. Rev. 14, 222–240 1993  
Laurent Miclo\* Emmanuel Perrin. The FASEB Journal June 2001



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# L-Theanine

- Increases alpha wave activity
- Decreases beta wave activity
- Partial agonist for N-methyl-D-aspartate (NMDA) receptor
- Boosts GABA
- Reduces sensations of anxiety.

*Nutrients* 2019; 11(10):2362

*J or Functional Foods* 2011; 3(3):171-178



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# Passiflora Incarnata (Passionflower)

- Contains apigenin (flavonoid) that increases GABA<sub>A</sub>1 and PBR receptor binding in the hippocampus and hypothalamus
- Studies show that when alanine is extracted out of passion flower, the sedating and calming effect of the plant is lost, and no increase in GABA was seen in mouse brain samples or serum human levels
- Contains the highest levels of alanine (amino acid) and chrysin (flavonoid) which increase GABA production



Medina JH, et al. *Biochem Pharmacol.* 1990 Nov 15;40(10):2227-31/  
Carratu B, *J Food sci* 2008 June;73(5):C323-8



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# Need for GABA with Sleep

- Researchers obtained cerebrospinal fluid from 32 patients suffering from insomnia
- They added the cerebrospinal fluid to cells genetically engineered to produce GABA receptors and monitored electrical activity as a sign of receptor binding to determine the concentration of GABA in each sample
- Insomniacs' cerebrospinal fluids caused no spike in electrical activity in the GABA receptor cells
- They then added GABA to the mixture, which significantly triggered electrical activity in the cells.
- The researchers concluded that insomniacs have significantly lower GABA levels than normal sleepers

*Rye D, et al 21 Nov 2012:Vol. 4, Issue 161, pp. 161ra151*



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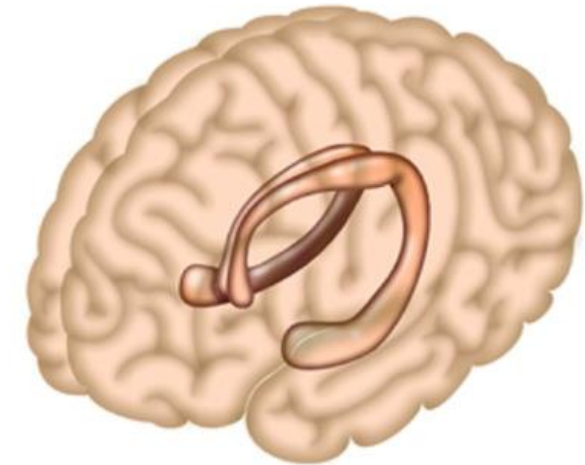


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# Melatonin

- Sleep deprivation and the build up of too much adenosine blocks hippocampal consolidation of short-term memory, and impairs long term potentiation and neural plasticity
- Melatonin has a neuro-protective effect against chronic sleep deprivation; it is a strong anti-oxidant for the whole body, but specifically for the hippocampus
- Reducing/regulating cortisol helps prevent adenosine build up



*Jared M et al, J NeuroSci 2016, Feb 24;36(8):2355-2363*



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UNDA



Garden of Life



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# 5-HTP 5-Hydroxytryptamine

- Precursor to serotonin and melatonin (MAOA, TPH2, 5-HTTLPR).
- Used for sleep tremors, arousal, nightmares and sleepwalking.
- Induces hypothermia needed for sleep.
- Increases N-REM sleep.
- Ability to override IL-6 induced insomnia.

*Curr Treat Options Neurol 2018; 5:20(7):26*

*Sleep 2008 1; 31(1):21-33*



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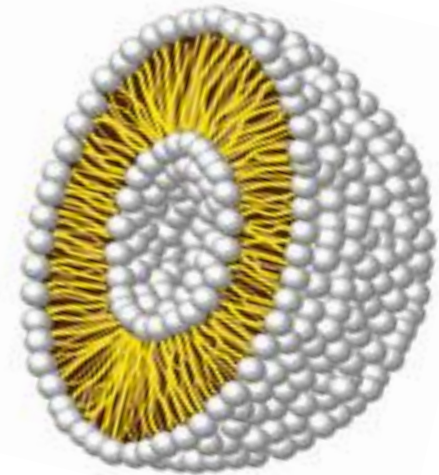
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# Liposomal Glutathione

- Reduces IL-6 and TNF-a.
- Neutralizes ROS.
- Conjugates and removes xenobiotics.
- Studies show that insomniacs are significantly lower in glutathione peroxidase compared to normal sleepers.
- Animal studies show that sleep deprivation significantly lowers intra-cellular GSH.
- Liposomal form protects against gastric degradation and enhances absorption.



*Antioxidants 2020; 9(7):62*

*Prog Neuropsychopharmacol Biol Psychiatry 2012; 1;37(2):247-51.*



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# N-Acetyl Cysteine

- Decreases IL-6, IL-1B and TNF-a.
- Increases GSH.
- Reduces ROS via supporting SOD.
- Readily crosses the BBB and increases glymphatic activity and increases BDNF.
- Reduces severity of sleep apnea.

*Indian J Chest Dis Allied Sci 2011; 53(3):153-62*

*Curr Neurovasc Res 2016; 13(2):107-14*



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# Case Study 1



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# Case Study 1 – Mary

- 46-year-old female, going through perimenopause who had a difficult time falling asleep and would wake at 3:33 am with difficulties falling back asleep.
- Despite feeling tired the next day, she was more anxious and restless.
- She had a history of anxiety but did not have any stressors in her life at the present time.
- She thought it was due to menopause (despite no real flashes or sweats) and tried HRT (pharmaceutical and natural) with no effects.
- She used Imovane 3 or 4 nights a week, but still woke fatigued the next morning.
- Shortly after her joints started aching. When she took Advil, her sleep improved that night slightly, but only for that night.



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# Mary's Genotyping

- **CRY1 – A/G**: blocks Clock genes, unable to transition to deep sleep.
- **Clock -A/A**: normal circadian rhythm control.
- **FKBP5 – A/A**: increased FKBP5 protein and loss of negative feedback.
- **NR3C2 – T/C**: decreased GC receptors and decreased feedback.
- **CRCH1– C/C**: increased CRH receptors and activity.
- **IL6 – C/G**: increased IL-6 and inflammation.
- **TNF-a – G/A**: increased TNF-a and inflammation.



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# Treatment Recommendations

- Sereniten Plus – 2 BID empty stomach for 8 weeks and then reduce to 1 BID.
- Liposomal Glutathione- 2 caps BID for 8 weeks and then 1 cap per day.
- NAC- 1 cap BID empty stomach for 8 weeks and then 1 per day.
- Best Rest– 2 caps at 8:30 pm until 10 days of consistent sleep, then reducing to 1 PRN and changing to 3 mg of melatonin.
- Anti-inflammatory genetic diet ([www.feedyourgenes.ca](http://www.feedyourgenes.ca))



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# Mary's Outcome

- 4 days later she was falling asleep easily, and one week later she fell back to sleep very quickly when she woke in the middle of the night.
- 2 weeks into the program she was sleeping deeply and “without fear” of falling or staying asleep. Her joint and muscle pain had reduced by “65 to 70%”.
- Her restless and anxious feelings which began to subside by day 4 were almost completely gone by the 3<sup>rd</sup> week.
- 1 month later she was sleeping more soundly than she had in a long time despite not realizing she wasn't sleeping well, felt balanced with little to no joint or muscle tenderness.



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# Summary

- The natural rise in cortisol at perimenopause/menopause triggered her stress genes into full production quickly resulting in hyper-adrenal syndrome.
- The increased stress response in turn triggered her inflammatory genes and the variant side of her clock gene.
- The increased inflammation further stimulated the stress response and sleep difficulties.
- Long term treatment for sleep is about the stress and inflammation.



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# Case Study 2



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# Case Study 2 - Anna

- Anna is a 37-year-old female who is a self-proclaimed poor sleeper. She has difficulties falling asleep and it would often take up to 2 hours, however the past 2 years she had been sleeping well.
- She recently returned from a trip to India with a moderately severe case of Giardia with extreme bloating after eating anything and very loose stools. She increased binding CHO's in attempts to stop the diarrhea.
- Anna had a history of IBS, so was not too concerned by this, and delayed getting treatment.
- Her GI symptoms continued for several weeks, but then her sleep became quite disrupted, so she went to her GP who was more concerned about the bowels and put her on metronidazole.
- The diarrhea eventually settled but her bowel remained bloated, and her sleep continued to worsen, and she now felt exhausted and withdrawn.



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# Anna's Genotyping

- **CRY1 – A/G**: blocks Clock genes, unable to transition to deep sleep.
- **Clock – G/G**: abnormal circadian rhythm control.
- **FKBP5 – C/A**: increased FKBP5 protein and loss of negative feedback.
- **NR3C2 – T/T**: normal number of GC receptors, normal feedback.
- **FUT2 – G/G**: decreased microbiome proliferation.
- **IL6 – G/G**: significant increase in IL-6 and inflammation.
- **TNF-a – G/A**: increased TNF-a and inflammation.
- Serotonin genes (TPH2 and 5-HTTLPR – hetero) and CHO gene (GIPR variant).



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# Treatment Recommendations

- Sereniten Plus– 2 BID empty stomach for 2 weeks and 2 in the middle of the night if she woke, then 2 per day for 2 weeks and then 2 PRN.
- L-Glutamine – 2 scoops BID empty stomach for 1 tub, reducing to half dose for a second tub.
- Liposomal Glutathione- 1 cap BID for 8 weeks and then 1 per day.
- NAC- 1 cap BID empty stomach for 8 weeks and then 1 per day.
- SeroPlus– 1 in the am and 2 before bed.
- Rest Reset– 2 caps at 8:30 pm until 10 days of consistent sleep.
- HMF Intensive 500 – 1 sachet a day with food.
- Reduced her CHO's to twice a day only 1/3 the size of the protein for 8 weeks. Diet set out by [www.feedyourgenes.ca](http://www.feedyourgenes.ca)



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# Outcome

- Within 10 days her bloating began to subside.
- 2 weeks later she was falling asleep easily but still waking tired, but her moods were beginning to improve.
- She increased CHO's significantly on 2 occasions which flared her bowel and disrupted her sleep for 2 days each time.
- 1 month later her sleep was about 90% better and bowels normal unless she indulged in CHO's.



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# Summary

- The Giardia triggered her FUT2 and IL-6 genes which further increased inflammation in her bowel.
- This then reduced her serotonin and increased her cortisol through TPH2, 5-HTTLPR, FKBP5 which further disrupted GABA and melatonin.
- The increased CHO's aggravated her GIPR gene further increasing inflammation.
- Controlling her sleep is about regulating the inflammation in her bowel.



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# Long Term Sleep Control

## Mary

- Close to normal Sleep Genes.
- Increased Inflammatory Genes.
- Increased Stress Genes.
  
- Long term control for sleep is about controlling the inflammatory and stress genes, not the sleep genes.

## Anna

- Abnormal Sleep Genes.
- Increased Inflammatory Genes.
- Increased inflammation in bowel.
- Close to normal Stress Genes.
  
- Long term control for sleep is about controlling the inflammatory response both inside and outside of the bowel.



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# Case Study 3



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# Case Study 3 - James

- James is a 41 yr. old male who broke his wrist playing basketball.
- He has always been a self-proclaimed type A person, “work hard, played hard and thrived off of it.”
- 2 days after breaking his arm, he started feeling anxious and experiencing chest tightness and palpitations. Only had this once before when he started crossfit training.
- He thought it was because he couldn’t work out as intensely as he was before, yet he was still spinning daily.
- At his 1 week follow up he mentioned these feelings to his surgeon who then took his BP – 152/79 (his normal – 115/75).
- His wrist was healing well at one week despite increased tissue swelling.
- Soon after he started waking at 2:30 am with difficulties.
- Blood work revealed increased ESR, CRP, CK.
- GP gave him Ativan 0.5 mg prn.



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# James Genotyping

- CRY1 – A/A: normal sleep patterns.
- Clock -A/A: normal circadian rhythm control.
- FKBP5 – C/A decreased HPA feedback.
- NR3C2 – T/C: decreased GC receptors and decreased feedback.
- CRCH1– T/T: normal CRH receptors and activity.
- IL6 – G/G: significantly increased IL-6 and inflammation.
- TNF-a – G/G: significantly increased TNF-a and inflammation.



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# Treatment Recommendations

- Advil 1 extra strength tab BID for 48 hours.
- Liposomal Glutathione- 2 cap BID for 4 weeks, 1 cap BID for 4 weeks, and then 1 per day.
- NAC- 2 cap BID for 4 weeks, 1 cap BID for 4 weeks, and then 1 per day.
- Curcumasorb – 1 cap BID for 4 weeks (then reduce to 1 per day – CYPA12)
- Sereniten Plus– 2 BID empty stomach for 4 weeks and 2 in the middle of the night if he woke, then 2 per day for 2 weeks and then 2 PRN.
- Increased the length of cardiovascular exercise he did, but decreased the intensity (according to his exercise genes)



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# James's Outcome

- In the first 48 hours his heart palpitations and chest tightness began to ease.
- By the end of the first week, he felt much calmer, and his sleep was starting to improve.
- He thought everything was due to stress, so he stopped taking everything except the Sereniten Plus.
- 3 days later his palpitations began to return, woke at 4 am again.
- 6 days later he returned back to his normal treatment plan and 2 weeks later he had no “stress” symptoms, was sleeping well and his soft tissue swelling had reduced by about 50%.
- At his 8-week ortho appointment his bone was healing well, he was transitioned into a removable cast, and his soft tissue swelling was gone.



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# James Summary

- James's had kept his stress genes in their “off position” through his “active” lifestyle- play hard and work hard.
- His perfect sleep genes helped him repair, rest and rejuvenate each night from this lifestyle.
- He had never injured anything before, nor had he ever had a bad cold or flu.
- Only when he did Crossfit (wrong style of exercise) did he trigger his inflammatory genes and exercise some these symptoms.
- It was this inflammatory response from breaking his wrist that turned on his stress genes and greatly stimulated the HPA axis, as well as inhibiting melatonin production and stage 4 sleep.
- James's long term stress control is about controlling his inflammation.



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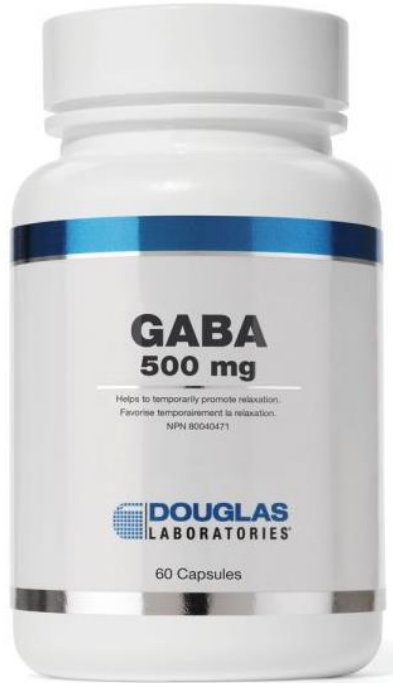
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# GABA Options



- GABA (gamma-aminobutyric acid) functions as a neurotransmitter in the brain
- It is synthesized in the brain from another amino acid, glutamate, and functions as an inhibitory neurotransmitter, temporarily promoting relaxation in the body



## Each Capsule Contains<sup>†</sup>

GABA (Gamma Aminobutyric Acid) ..... 500 mg

## EACH CAPSULE CONTAINS:

GABA (gamma-aminobutyric acid) ..... 700 mg



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# Melatonin Options

(Melatonin 3 mg- expected back in stock mid-March; the other Melatonin options- currently in stock)



PR - Prolonged-release tablet option






SR - Sustained-release capsule option



EACH SPRAY (0.15 mL) CONTAINS:  
Melatonin..... 1 mg

## Each Tablet Contains<sup>‡</sup>

Melatonin ..... 3 mg

Medicinal Ingredients (per capsule)    v 3

Melatonin  
(as MicroActive<sup>®</sup> melatonin sustained-release complex) ..... 3 mg



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# L-Theanine

each vegetable capsule contains  v 2  
L-Theanine .....200 mg

This formulation provides Suntheanine<sup>®</sup>, a clinically researched form of L-Theanine that has been utilized in scientific studies to support relaxation by decreasing cortisol levels during stress and regulating neurotransmitter activity in the brain.



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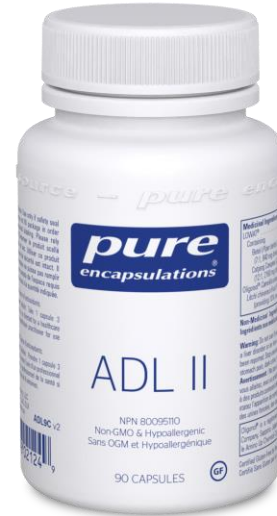


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# ADL II (formerly AdipoLean) & WheyBasics

- ADL II offers betel and catjang cowpea extracts, along with a unique combination of lychee and green tea extracts
- ADL II provides antioxidant support



- WheyBasics provides 21 grams of high-quality, cold-processed, undenatured whey protein per serving in a great-tasting, naturally flavored and sweetened formula
- Whey protein naturally contains all essential amino acids and contains immunoglobulins and lactoferrin to support antibody production



### Medicinal Ingredients (per capsule):

LOWAT® .....	300 mg
Containing	
Betel ( <i>Piper betle</i> ) Leaf Extract (7:1, 840 mg dried equivalent) .....	120 mg.
Catjang Cowpea ( <i>Dolichos biflorus</i> ) Seed Extract (12:1, 2160 mg dried equivalent) .....	180 mg.
Oligonol® <i>Camellia sinensis</i> Leaf/ Litchi <i>chinensis</i> Fruit Pericarp Extract (providing 10% monomeric procyanidins) .....	17 mg..

### Medicinal Ingredients (per scoop [approximately 26.4 g]):

Whey Protein Isolate (from <i>Bos taurus</i> milk) .....	25 g
(providing 84% whey protein)	



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# Liposomal Glutathione

- Liposomal Glutathione offers enhanced absorption liposomal glutathione for powerful antioxidant support
- Glutathione is a key component of the antioxidant system. The purified phosphatidylcholine delivery system offers natural liposomal form that protects the glutathione bonds from the degradation that can occur in digestion and has demonstrated superior antioxidant support



each softgel capsule contains **16 sg**  
 l-glutathione-phosphatidylcholine complex.....343.75 mg  
 providing:  
     l-glutathione..... 250 mg  
     phosphatidylcholine..... 93.75 mg



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# Best – Rest Formula

Best-Rest Formula supports sleep quality and a healthy sleep cycle.

- This unique blend contains valerian, and hops, which are traditionally used in Herbal Medicine as a sleep aid.
- Melatonin and GABA are also included in this formulation to support regulation of the sleep-wake cycle and promote relaxation respectively



**Medicinal Ingredients** (per capsule):

Vitamin B6 (pyridoxal 5-phosphate) .....	1.6 mg
Melatonin .....	0.5 mg
GABA (gamma-aminobutyric acid) .....	150 mg
L-Theanine .....	25 mg
Valerian ( <i>Valeriana officinalis</i> ) Root Extract .....	200 mg
(3-6:1, 600-1200 mg dried equivalent; standardized to contain 0.8% valerenic acid)	
Lemon Balm ( <i>Melissa officinalis</i> ) Leaf Extract .....	75 mg
(8:1, 600 mg dried equivalent; standardized to contain 5% rosmarinic acid )	
Hops ( <i>Humulus lupulus</i> ) Strobile Extract .....	75 mg
(10:1, 750 mg dried equivalent)	
Passionflower ( <i>Passiflora incarnata</i> ) Aerial Parts Extract .....	50 mg
(6:1, 300 mg dried equivalent; standardized to contain 3.5% vitexins)	
Chamomile ( <i>Matricaria recutita</i> ) Flower Extract .....	50 mg
(7:1, 350 mg dried equivalent)	



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# Sereniten Plus Options

(Sereniten Plus Douglas Laboratories, stock almost depleted, expected back in stock mid-March;  
Sereniten Plus Pure Encapsulations currently in stock)

- Offers support for occasional stress with a blend of Lactium®, L-theanine, and vitamin D
- Helps temporarily reduce symptoms of mild mental and physical stress



## Medicinal Ingredients (per capsule)

Lactium® Milk Protein Hydrolysate.....	175 mg
(alpha S1-casein tryptic hydrolysate)	
Suntheanine® L-Theanine.....	50 mg
Vitamin D <sub>3</sub> (cholecalciferol).....	2.5 mcg (100 IU)



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# Rest Reset (expected back in stock end of March)

Rest Reset supports multiple aspects of sleep and both mild physical and mental stress management.

- The ingredient Lactium has been shown to have multiple effect on the GABA – receptor, promoting relaxation
- Passionflower provides a calming effect
- Melatonin regulates the body’s sleep-wake cycles – supporting sleep onset, normal circadian rhythms and total sleep time



Each Capsule Contains:

Passionflower Aerial Parts Extract ( <i>Passiflora incarnata</i> )	425 mg
(4-6:1) (1,700-2,550 mg dried equivalent)	
Alpha S1-Casein Tryptic Hydrolysate (Lactium®)	175 mg
Melatonin	3 mg



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# TMC (Tri-Metabolic Control™)



- Blend of dolichos biflorus, piper betle, and acetyl-L-carnitine
- Source of antioxidants that helps protect cells against the oxidative damage caused by free radicals.

## Each Capsule Contains<sup>‡</sup>

LOWAT <sup>®</sup> .....	150 mg
Providing	
Betel pepper ( <i>Piper betle</i> ) Leaf Extract (7:1) .....	60 mg (420 mg dried equivalent)
Catjang ( <i>Dolichos biflorus</i> ) Seed Extract (12:1) .....	90 mg (1080 mg dried equivalent)
Acetylcarnitine (N-acetyl L-carnitine hydrochloride) .....	150 mg



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# Resveratrol EXTRA

Source of antioxidants for the maintenance of good health

each vegetable capsule contains  v 0

japanese knotweed ( <i>Polygonum cuspidatum</i> ) extract (root) .....200 mg (standardized to contain 50% trans resveratrol (100 mg))
red wine ( <i>Vitis vinifera</i> ) extract (fruit) .....50 mg (standardized to contain 25% total polyphenols (12.5 mg))
grape ( <i>Vitis vinifera</i> ) extract (seed) .....50 mg (standardized to contain 92% polyphenols (46 mg))
vitamin c (ascorbyl palmitate) .....4.2 mg



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# N-Acetyl-L-Cysteine Formulations

(Amino NAC - currently in stock; NAC 600 mg - expected back in stock end of April)



**EACH CAPSULE CONTAINS:**  
N-Acetyl-L-Cysteine (NAC) ..... 500 mg

each vegetable capsule contains  v 0

N-Acetyl-L-Cysteine (L-alpha-Acetamido-beta-mercaptopropionic acid) .....600 mg  
vitamin C (from 5 mg of ascorbyl palmitate) .....2.1 mg



- NAC, a precursor to glutathione, scavenges free radicals and decreases oxidative stress produced by heavy metals
- Several animal studies suggest that NAC administration may help to moderate the effects of mercury and cadmium accumulation in the kidneys and liver
- NAC also has a high affinity for lung tissue, which it supports through antioxidant action



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# HMF Intensive & HMF Intensive Shelf-stable

**Genestra HMF Probiotics** are science-based, research-driven formulations that reflect the latest advancements in the field of probiotics. They are backed by over 20 years of clinical evidence and industry leadership.

The highest standards in manufacturing, quality assurance and purity are adhered to.

Optimized freeze-drying technology preserves bacterial activity, ensures survival during storage and safeguards the guarantee of potencies through expiration.

Research-based human clinical trials associated with the specific human sourced proprietary strains in the formulations demonstrate their safety and efficacy.

A wide variety of shelf-stable options is now available; and Genestra HMF formulations are all suitable for those with dietary sensitivities.



Refrigerated Format



Shelf stable Format

## EACH CAPSULE CONTAINS:

<b>Probiotic Consortium</b> .....	25 billion CFU
<i>Lactobacillus acidophilus</i> (CUL-60 & CUL-21) .....	19 billion CFU
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> (CUL-34) & <i>Bifidobacterium bifidum</i> (CUL-20) .....	6 billion CFU

HMF Intensive provides 25 Billion CFU of clinically studied Genestra HMF probiotic strains per capsule. The formulation is vegan friendly; Gluten, Dairy, Soy and GMO free; and is offered in refrigerated and shelf-stable formats



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UNDA



\* Plummer, SF, Garaiova, I, Sarvotham, T, Cottrell, SL, Le Scouiller, S, Weaver, MA, Tang, J, Dee, P, Hunter, J. Int J Antimicrob Agents. 2005; 26(1): 69-74.

\* Madden, JA, Plummer, SF, Tang, J, Garaiova, I, Plummer, NT, Herbison, M, Hunter, JO, Shimada, T, Cheng, L, Shirakawa, T. Int Immunopharmacol. 2005; 5(6): 1091-1097.

\* Williams, EA, Stimpson, J, Wang, D, Plummer, S, Garaiova, I, Barker, ME, Corfe, BM. Aliment Pharmacol Ther. 2009; 29(1): 97-103

# HMF Intensive 500 & HMF Multi Strain 50



## EACH SACHET (5 g) CONTAINS:

<b>Probiotic Consortium</b> .....	500 billion CFU
<i>Bifidobacterium animalis</i> subsp <i>lactis</i> (CUL-34) .....	285 billion CFU
<i>Bifidobacterium bifidum</i> (CUL-20) .....	15 billion CFU
<i>Lactobacillus salivarius</i> (CUL-61) .....	100 billion CFU
<i>Lactobacillus acidophilus</i> (CUL-60) .....	50 billion CFU
<i>Lactobacillus acidophilus</i> (CUL-21) .....	50 billion CFU

HMF Intensive 500 provides 500 Billion CFU of clinically studied Genestra HMF probiotic strains per sachet. This high-potency formulation is vegan friendly, Gluten, Dairy, Soy and GMO free.

## EACH CAPSULE CONTAINS:

<b>Probiotic Consortium</b> .....	50 billion CFU
<i>Lactobacillus acidophilus</i> (CUL-60) .....	10 billion CFU
<i>Lactobacillus acidophilus</i> (CUL-21) .....	10 billion CFU
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> (CUL-34) .....	4.75 billion CFU
<i>Bifidobacterium bifidum</i> (CUL-20) .....	0.25 billion CFU
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> (HN019) .....	5 billion CFU
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> (BL-04) .....	3.75 billion CFU
<i>Lactobacillus salivarius</i> (CUL-61) .....	3 billion CFU
<i>Lactobacillus paracasei</i> (CUL-08) .....	2 billion CFU
<i>Lactobacillus casei</i> (CUL-06) .....	2 billion CFU
<i>Lactobacillus gasseri</i> (CUL-09) .....	2 billion CFU
<i>Bifidobacterium breve</i> (CUL-74) .....	2 billion CFU
<i>Lactobacillus plantarum</i> (CUL-66) .....	2 billion CFU
<i>Lactobacillus acidophilus</i> (NCFM®) .....	1.25 billion CFU
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> (CUL-62) .....	1.5 billion CFU
<i>Saccharomyces cerevisiae</i> subsp. <i>boulardii</i> (CNCM-I-1079) .....	0.5 billion CFU

HMF Multi Strain 50 provides 15 Probiotic strains totaling 50 Billion CFU per capsule. This formulation is vegan friendly, Gluten, Dairy, Soy, FOS and GMO free.



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# PureGenomics Platform



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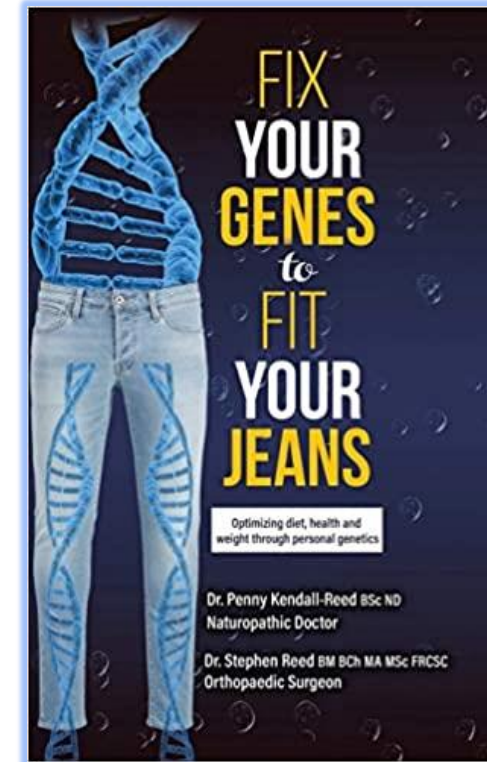


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# Thank you!



*Fix Your Genes to Fit Your Jeans* is the newest book by Dr. Penny Kendall-Reed ND and her husband, Dr. Stephen Reed MD. Now available at Amazon, Indigo Chapters and other retailers.



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