Anxiety, Fear and Resilience:

How to optimize the cortisol awakening response to survive and thrive

Carrie Jones ND, MPH
Medical Director, Precision Analytical Inc.

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Disclosures:

Carrie Jones, ND, MPH is the Medical Director for Precision Analytical Inc.

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Part 1: The What, Why and Where

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Comprehensive Testing Options

• DUTCH Complete (dried urine only)

DUTCH Complete

- 4-5 dried urine collections
- Progesterone metabolites
- Androgens and androgen metabolites
- Estrone, Estradiol and Estriol
- Estrogen metabolites (Phase 1 and 2 metabolism)
- Metabolized cortisol
- Free cortisol and free cortisone levels
- Overnight cortisol sample
- Free cortisol and free cortisone patterns
- MMA, KYN, XAN, Pyroglutamate
- Neurotransmitter metabolites: HVA, VMA
- 8-OHdG (DNA Damage)

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Comprehensive Testing Options

• DUTCH Plus (dried urine + saliva)

- 4 dried urine samples + 5-6 salivary samples
- Progesterone metabolites
- Androgens and androgen metabolites
- Estrone, Estradiol and Estriol
- Estrogen metabolites (Phase 1 and 2 metabolism)
- Metabolized cortisol
- Free cortisol and free cortisone levels
- Free cortisol and free cortisone patterns – focusing on the **cortisol awaking response (CAR)**
- Overnight insomnia sample
- MMA, KYN, XAN, Pyroglutamate
- Neurotransmitter metabolites: HVA, VMA
- 8-OHdG (DNA Damage)

DUTCH Plus

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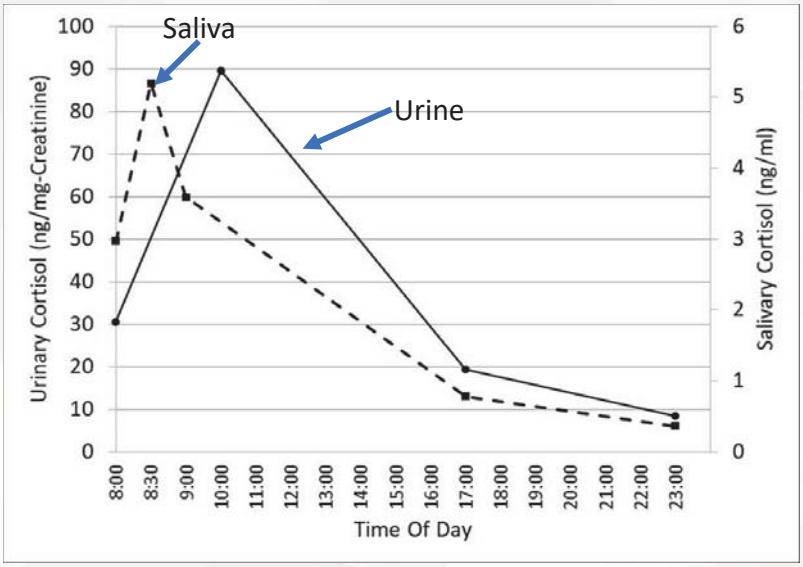
Data to be published comparing dried urine to salivary cortisol results



There is a statistical equivalence between the rise and fall in saliva and the rise in urine for free cortisol throughout the day

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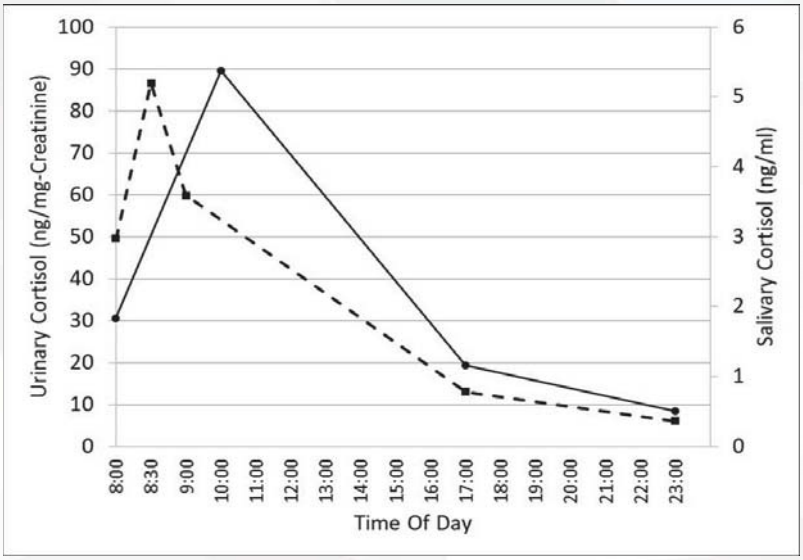
Data to be published comparing dried urine to salivary cortisol results



Remember urine shows a slightly shifted view:

- **The waking cortisol =** the cortisol made through the night
- **2 hours after waking =** the cortisol made from waking until 2 hours later

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Objectives

- Understanding the cortisol awakening response and how it gives more insight to HPA-axis dysfunction compared to most traditional or functional testing
- Review the HPA-axis process which elicits the CAR response
- How a dysfunctional CAR and relates to symptoms including anxiety, fatigue, inflammation, and autoimmunity
- Treatment options for under or over-performing CAR responses
- Review how other neurotransmitters play into anxiety and resiliency
- Discuss examples with treatment

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Does This Feel Familiar?

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Let's Cover Some Basics…

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The Central Fight, Flight, Freeze Response

Step 1: Initiation of the Response:

- Sensory nerve cells anywhere in the body pass the perception of a threat/stress from the environment (internal or external) to the **hypothalamus in the brain**

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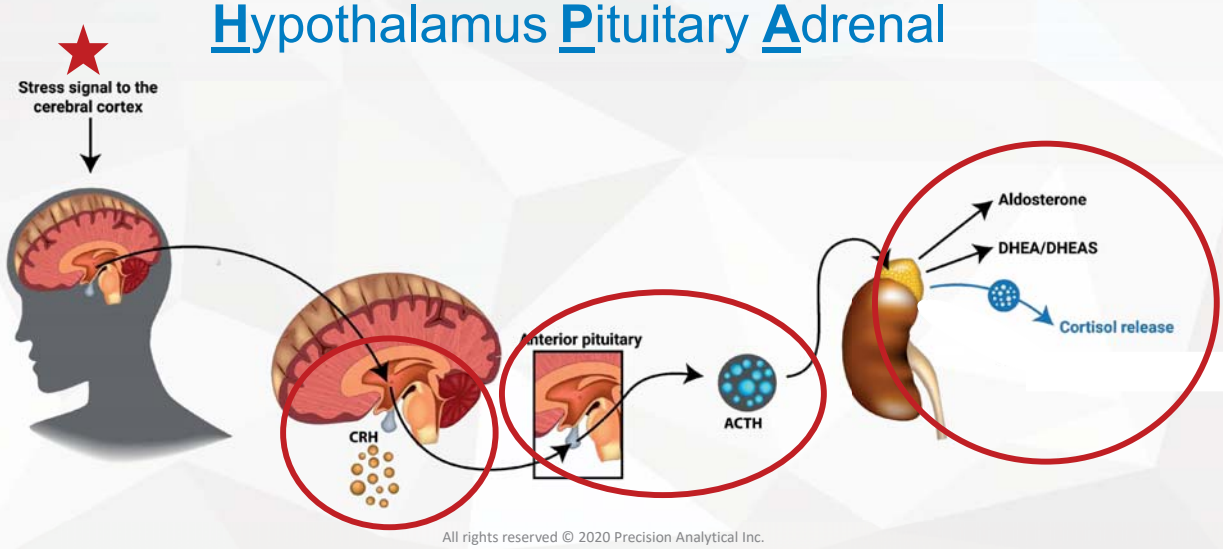
What is the HPA Axis?

Hypothalamus Pituitary Adrenal



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The Central Fight, Flight, Freeze Response

- **Simultaneously (and much faster):**

• The hypothalamus transmits a signal down the spinal cord.

• Both the chemical messenger and nerve impulse travel to the same destination = the adrenal medulla

- ***Norepinephrine and Epinephrine*** dumped immediately

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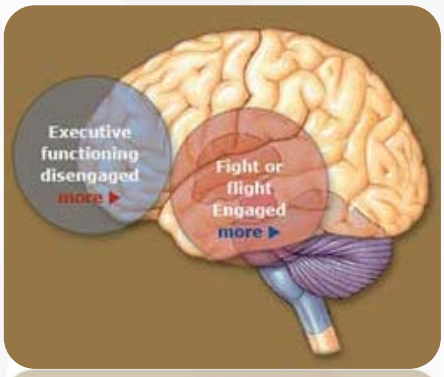
The Central Fight, Flight, Freeze Response

The Problem: When stress occurs, the HPA axis RUNS to the to the adrenals instead of going to the neocortex for logical processing



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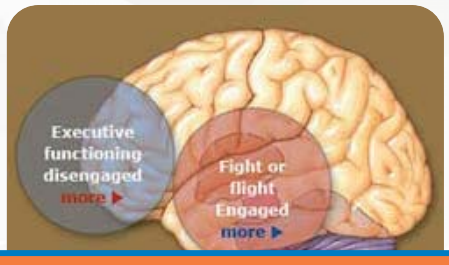

This can result in "freak out" and illogical processing

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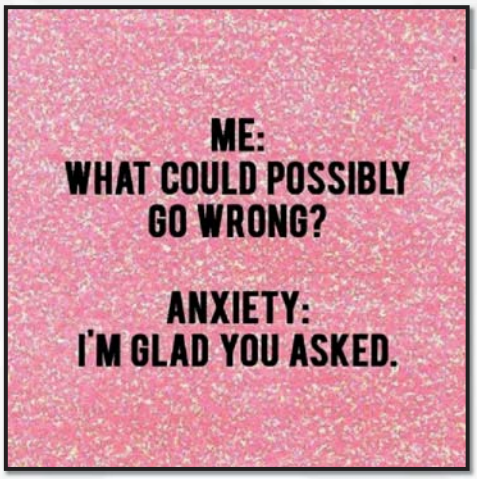
What Other Neurotransmitters are Involved?



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Neurotransmitters: Glutamate

- Considered your main **excitatory** neurotransmitter
- Very important for executive function (stimulated brain activity), cognitive function and behavior
- About 85% of glutamate is converted to glutamine and reused
- Too much due problems with the glutamate/glutamine cycle results in excitotoxicity resulting in destroyed neurons

Purves A. Fitzpatrick D. et al. 2001. Neuroscience 2nd Edition. Sinauer Associates. Sunderland, MA.

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Neurotransmitters: GABA

- Considered your primary **inhibitory** neurotransmitter
- Important for relaxation, anxiety reduction and sleep in appropriate levels

- **Clinical Pearl:** Originally thought not to cross the blood brain barrier but some recent research is questioning that or is suspecting that exogenous GABA stimulates the enteric nervous system that then stimulates the CNS to make GABA

Boonstra E, de Kleijn R, Colzato LS, Alkemade A, Forstmann BU, Nieuwenhuis S. Neurotransmitters as food supplements: the effects of GABA on brain and behavior Front. Psychol.. 2015; 6.
Purves A. Fitzpatrick D. et al. 2001. Neuroscience 2nd Edition. Sinauer Associates. Sunderland, MA.

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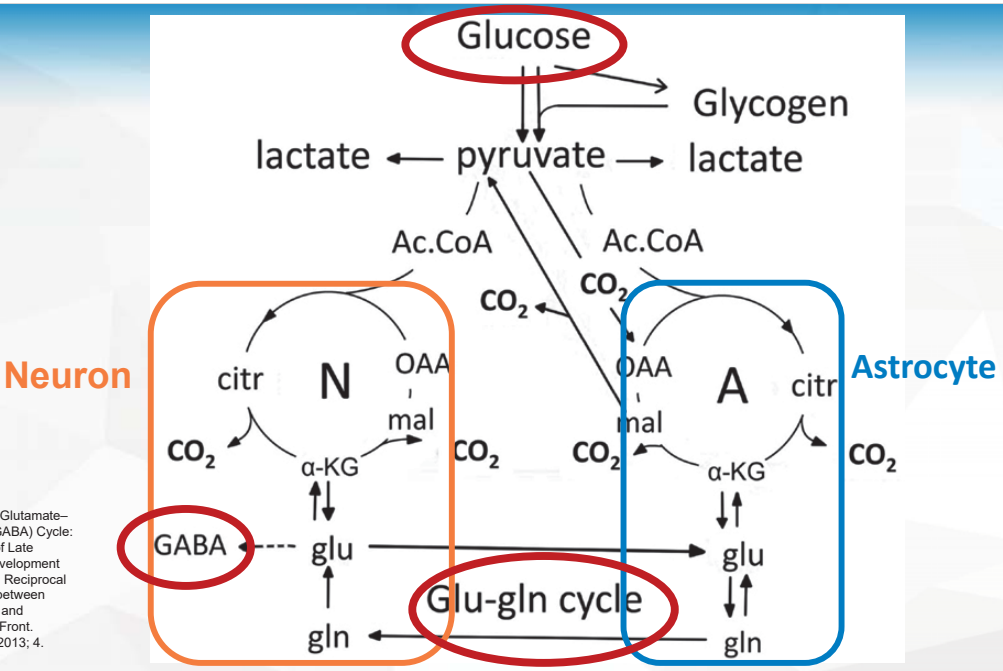

Hertz L. The Glutamate–Glutamine (GABA) Cycle: Importance of Late Postnatal Development and Potential Reciprocal Interactions between Biosynthesis and Degradation Front. Endocrinol.. 2013; 4.

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How is GABA Made/Recycled?

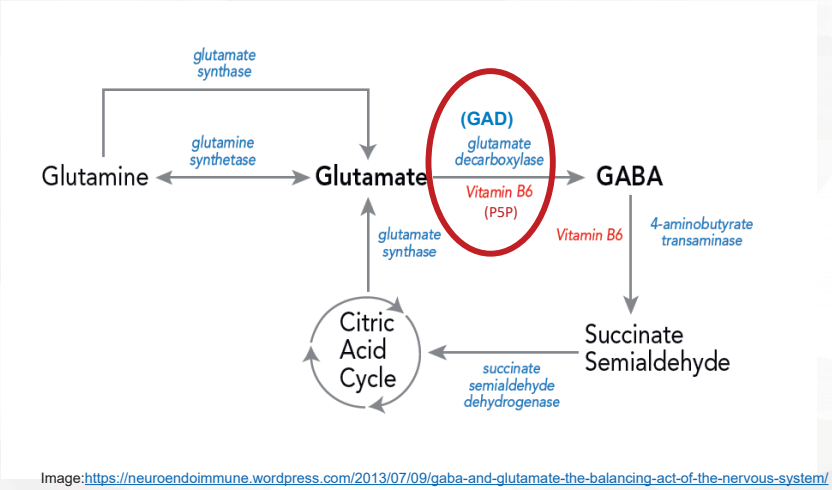

Image:https://neuroendoimmune.wordpress.com/2013/07/09/gaba-and-glutamate-the-balancing-act-of-the-nervous-system/

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Why is it important to understand all these hormones?

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Why is it important to understand all these hormones?

Anxiety, vigilance, stress and fear are running high right now possibly leading to long term sequelae

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Learning from the past:

- People quarantined during SARS in Toronto experienced higher psychological distress such as depression and PTSD afterwards
- After natural disasters, depression, anxiety, PTSD and substance abuse increases
- The 2008 stock market crash resulted in a spike in suicide among men in America and Europe
- Job loss/loss of insurance is associated with worsening mental health, increased stress, insomnia, worse well being and health decline
- Ebola understandably resulted in similar if not worse outcomes
- Australia just dealt with devastating fires

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Right now, the world is struggling with illness, separation, social isolation, financial insecurity, bereavement and death that will lead to a fall out with chronic conditions

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Citations: Learning from the past

- Chang S, Stuckler D, Yip P, Gunnell D. Impact of 2008 global economic crisis on suicide: time trend study in 54 countries BMJ. 2013; 347(sep17 1):f5239-f5239.
- Galea S. Mental Health in a Time of Pandemic. Retrieved on 3/30/2020 from https://www.psychologytoday.com/us/blog/talking-about-health/202003/mental-health-in-time-pandemic
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- Shultz JM, Baingana F, Neria Y. The 2014 Ebola Outbreak and Mental Health JAMA. 2015; 313(6):567- 568.

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How Do Sequelae Occur? First, They Impact the Amygdala

- While many areas of the brain are involved with **anxiety or fear related information processing,** the amygdala plays a huge role in **emotion-based memory processing**
  - Examples: fear, anxiety related emotions, post traumatic stress disorder (PTSD)

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How Do Sequelae Occur? First, They Impact the Amygdala

- While many areas of the brain are involved with **anxiety or fear related information processing,** the amygdala plays a huge role in **emotion-based memory processing**
  - Examples: fear, anxiety related emotions, post traumatic stress disorder (PTSD)
- Emotional intelligence
- Social interaction including personal space
- Modulation of aggression
- Alcoholism/binge drinking.

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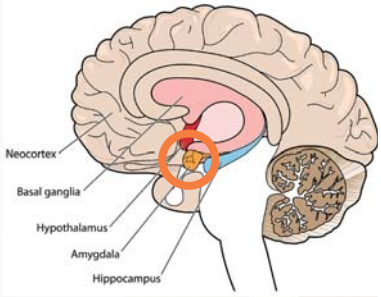
The Amygdala

- Located in the temporal lobes at the end of the hippocampus
- Has major influence on the HPA and gut/brain axis



Babaev O, Piletti Chatain C, Krueger-Burg D. Inhibition in the amygdala anxiety circuitry. Experimental & molecular medicine. 2018; 50(4):18. [pubmed]

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We feel fear to heighten our awareness and protect ourselves.

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The Amygdala and ACEs

Vulnerable to stressors early in life?

Results in increased sensitivity to stress as an adult

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Childhood Trauma and Cortisol

"Compelling evidence suggests that childhood trauma is a major risk factor for the development of mood and anxiety disorders as well as certain medical diseases, including heart disease and disorders such as chronic fatigue and pain syndromes."

Heim C. Childhood Trauma and Adult Stress Responsiveness. 2009. Retrieved on September 11, 2019 from http://www.child-encyclopedia.com/brain/according-experts/childhood-trauma-and-adult-stress-responsiveness

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Childhood Trauma Has Been Associated With:

- Overexposure of cortisol negatively affects the prefrontal cortex leading to ***reduced HPA control***
- Decreased sensitivity to cortisol's feedback loop in some people but ***increased sensitivity to the feedback in others***
- Enhanced immune activation due to HPA dysfunction
  - This can lead to increased cortisol ***activating the feedback loop over time***
- Hippocampal atrophy resulting in a ***lower CAR***
- Heightened vigilance, fear and anxiety dt the ***amygdala response***

1. Heim C. Childhood Trauma and Adult Stress Responsiveness. 2009. Retrieved on September 11, 2019 from http://www.child-encyclopedia.com/brain/according-experts/childhood-trauma-and-adult-stress-responsiveness
2. Suzuki A, Poon L, Papadopoulus AS, Kumari V and Cleare AJ. Long term effects of childhood trauma on cortisol stress reactivity in adulthood and relationship to the occurrence of depression. Psychoneuroendocrinology. 2014 Dec;50:289-99. doi: 10.1016/j.psyneuen.2014.09.007. Epub 2014 Sep 17

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Pay attention to our kids in 2020
They will be the future patients struggling in our office

1. Heim C. Childhood Trauma and Adult Stress Responsiveness. 2009. Retrieved on September 11, 2019 from http://www.child-encyclopedia.com/brain/according-experts/childhood-trauma-and-adult-stress-responsiveness
2. Suzuki A, Poon L, Papadopoulus AS, Kumari V and Cleare AJ. Long term effects of childhood trauma on cortisol stress reactivity in adulthood and relationship to the occurrence of depression. Psychoneuroendocrinology. 2014 Dec;50:289-99. doi: 10.1016/j.psyneuen.2014.09.007. Epub 2014 Sep 17

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Over time, the constant stream of these hormones causes the amygdala to fire off fear-based emotions rapidly

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Over time, the constant stream of these hormones causes the amygdala to fire off fear-based emotions rapidly

This results in more anxiety, PTSD, fear, hypervigilance or aggression than the situation likely calls for and it's lasting.

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Over time, the constant stream of these hormones causes the amygdala to fire off fear-based emotions rapidly

Fear-based emotions becomes the default response

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Second, this can also lead to an increase in everyday cortisol production and in the cortisol awakening response

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Second, this can also lead to an increase in everyday cortisol production and in the cortisol awakening response

However, over time the negative feedback loop could result in lower cortisol production

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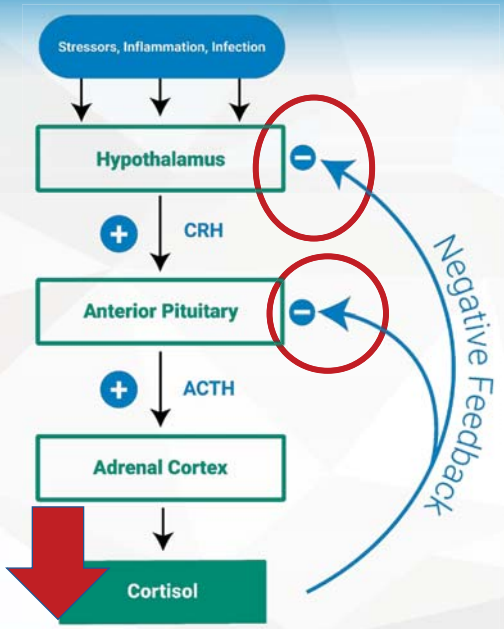
Cortisol Feedback Loop Over Time



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Patients Start Asking:

"Why Can't I Handle Stress Like I Used To?"

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The Concept of Resiliency

Do you have the flexibility (or adaptability) to survive your environment?

Taff CC, Vitousek MN. Endocrine Flexibility: Optimizing Phenotypes in a Dynamic World? Trends in Ecology & Evolution. 2016; 31(6):476-488.

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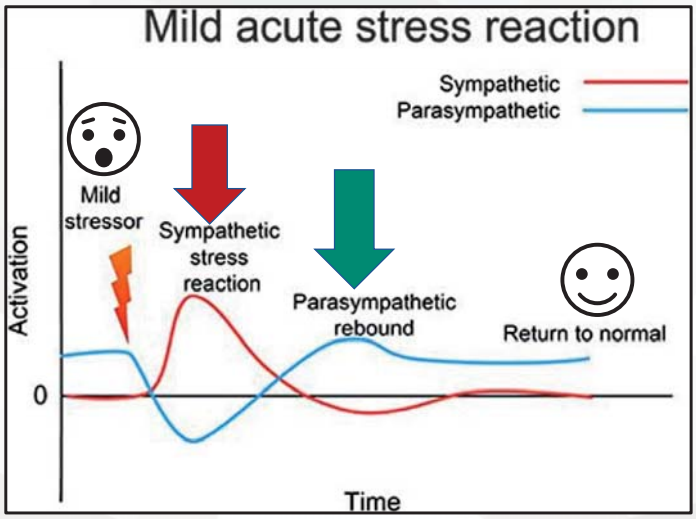
Acute Stress ➔ Chronic Stress



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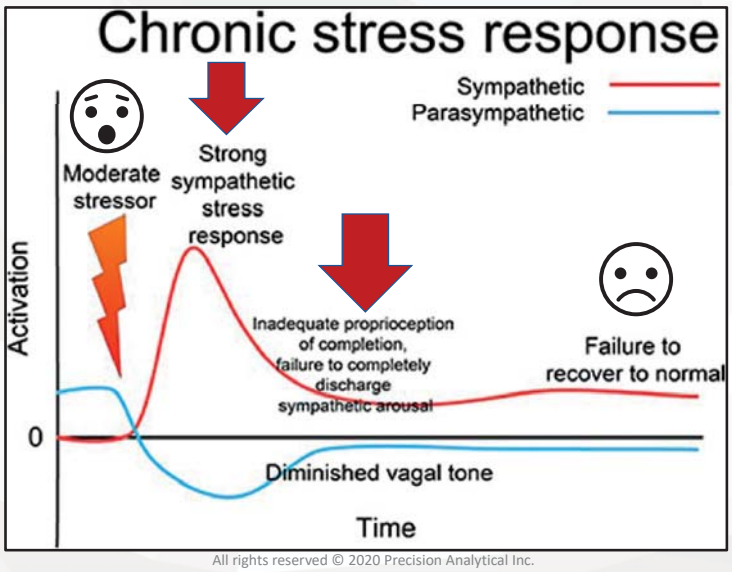

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Why is this Important?

The less flexible the whole-body system is,
or the slower the system is to adapt,
<u>the less able to survive and thrive</u>
in an environment

- Smith RL, Soeters MR, Wüst RCI, Houtkooper RH. Metabolic Flexibility as an Adaptation to Energy Resources and Requirements in Health and Disease. Endocrine reviews. 2018; 39(4):489-517. [pubmed]
- Taff CC, Vitousek MN. Endocrine Flexibility: Optimizing Phenotypes in a Dynamic World? Trends in Ecology & Evolution. 2016; 31(6):476-488.

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Dysfunction Due to an Elevated Response:

Elevated cortisol
Elevated catecholamines
Elevated glutamate
Decreased GABA

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Elevated Response Co-morbidities

- **Mood disorders –** melancholic depression, anxiety, panic attacks, hypervigilance, aggression
- **Stress disorders** - feeling 'stressed out,' overwhelmed, insomnia
- **Cardiovascular dysfunction** – high blood pressure, CAD
- **Metabolic dysfunction** – diabetes, insulin resistance, met.synd.

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Elevated Response Co-morbidities

- **Brain dysfunction** – memory, hippocampal cell death, 'brain on fire'
- **Reproductive dysfunction** – ovulatory issues, infertility
- **Gastrointestinal dysfunction** – dysbiosis, intestinal permeability, IBS

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Dysfunction Due to a Low Response:

Low cortisol
Low catecholamines
Low glutamate
Low GABA

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Low Response Co-morbidities

- **Mood disorders –** atypical depression, PTSD, SAD, anxiety (GABA)
- **Stress disorders** -burnout, less resiliency, insomnia (GABA)
- **Immune dysfunction** - infection, inflammation, and autoimmune
- **Metabolic dysfunction** – hypoglycemia, dysglycemia dt low response
- **Brain dysfunction** – memory and recall, brain fog
- **Reproductive dysfunction** – possibly from perceived 'burnout'
- **Cancer outcomes –** early mortality in breast/prostate cancer

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Improving a dysfunctional stress response can reduce these co-morbidities

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"In the darkness, any amount of light we can shine will be brighter than it ever would be otherwise."

By: Elad Nehorai

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Citations:

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Part 2: The How

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How are People Being Managed Traditionally?

- Therapy
- Anxiolytics
- Anti-depressants
- Sleep medications
- Anti-hypertensives + other heart meds
- Blood sugar/insulin medication
- Etc.

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How is Stress Typically Assessed?

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Traditional Endocrinology

Traditional Endocrinology Disease Model

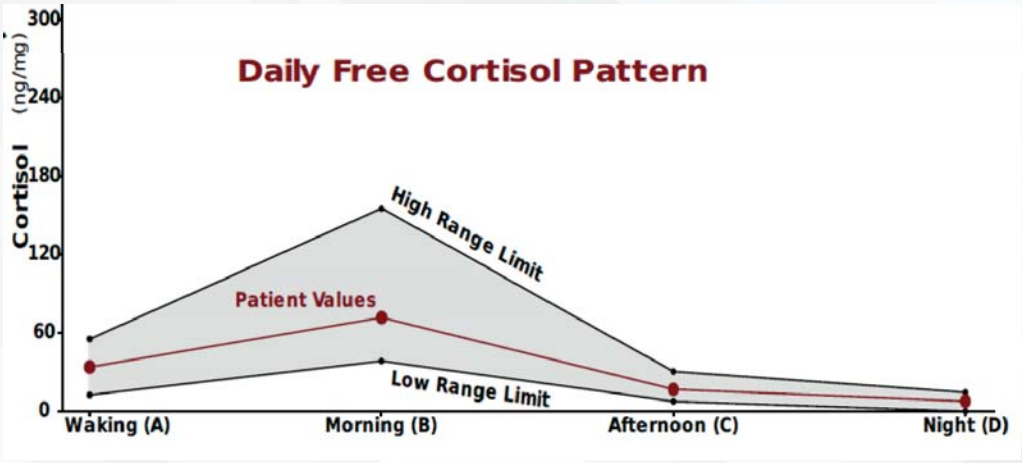
HYPOCORTISOL DISEASE STATE	"NORMAL" CORTISOL PRODUCTION	HYPERCORTISOL DISEASE STATE
ADDISON'S		CUSHNG'S

Functional Endocrinology

Traditional Endocrinology Disease Model

Functional Endocrinology Model

Assessing Stress: The Traditional 4-Point Collection



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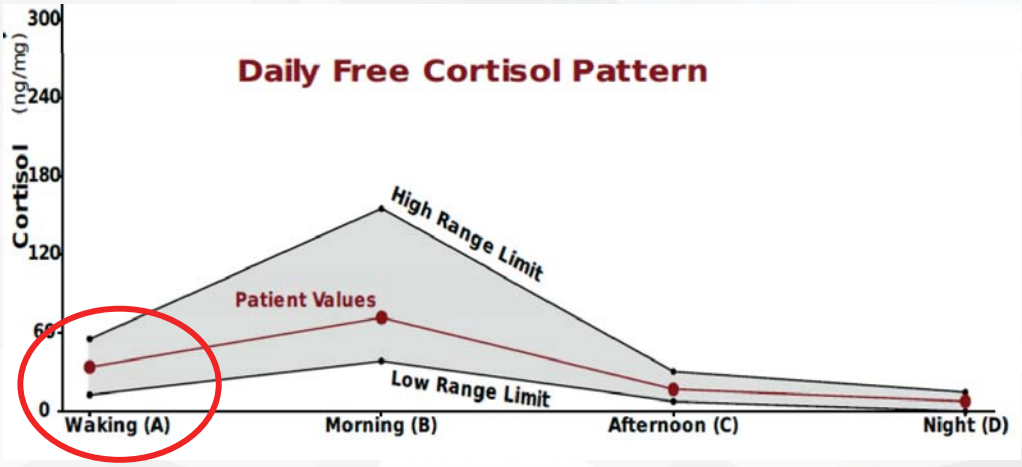

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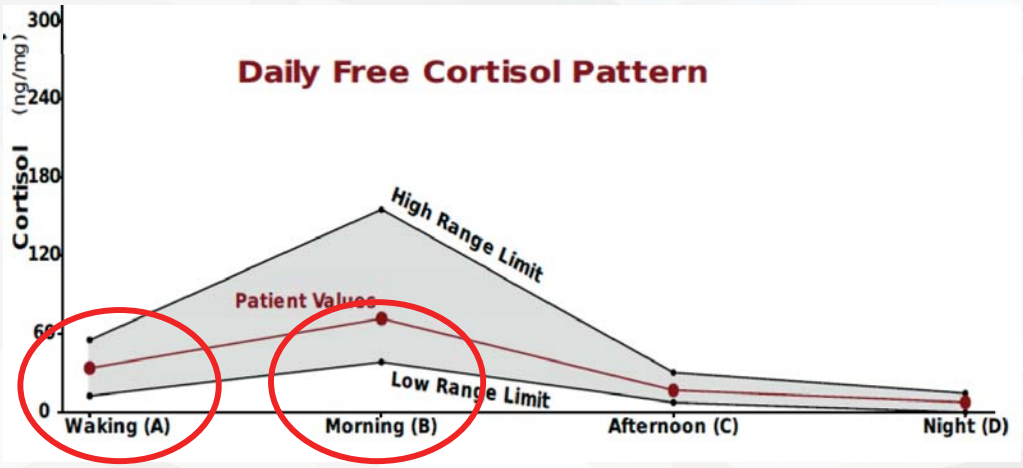

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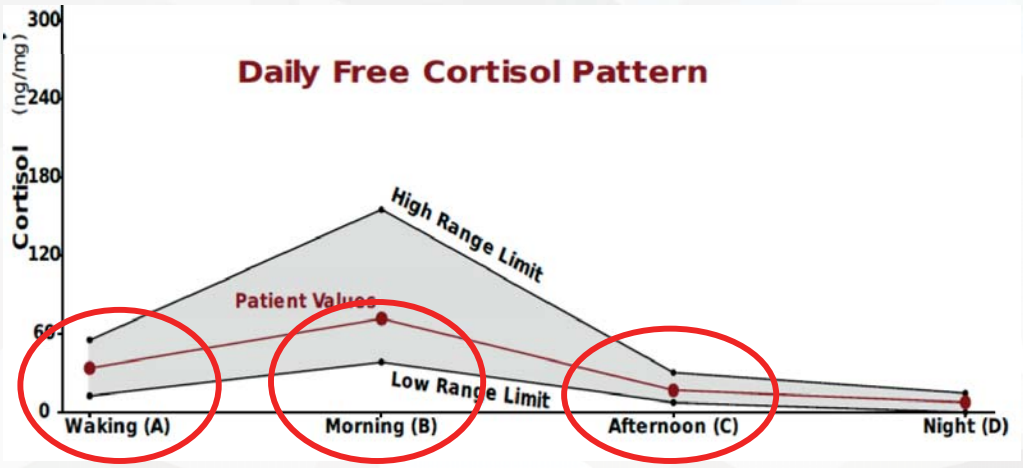

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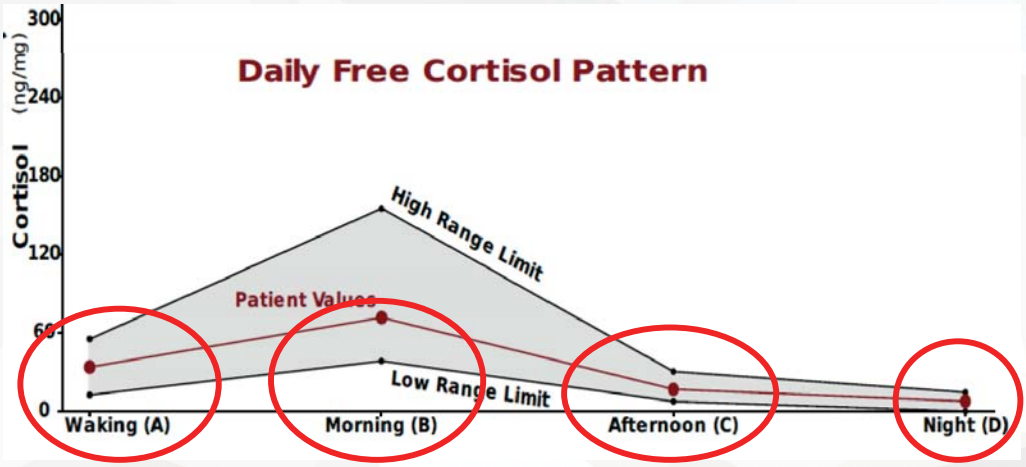

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Is This Enough Information Now?

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No! We must add in the CAR. This is Specifically Being Used as One Marker to Determine Resilience and Flexibility

"It has repeatedly been suggested that the CAR could be a result of the anticipated demands of the upcoming day (stress anticipation) and *could support coping with daily life stress.*"

Powell DJ, Schlotz W. Daily life stress and the cortisol awakening response: testing the anticipation hypothesis. PloS one. 2012; 7(12):e52067. [pubmed]

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How Does the CAR Work?

As awakening gets closer, the brain signals to the adrenals to release cortisol…but there is a blunting effect until the eyes open.

When the eyes open and **light** enters → the blunting releases = the body starts to switch from conscious to alert

Cortisol rises sharply = at least a 50% increase in about 30min causing the body to be in **full alertness** to start the day

Cortisol should then gradually decline throughout the day

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Can You Make The Switch?

Rapid Consciousness
(you open your eyes)

→ **20-30min** →

Full Alertness
(ready to go)

Clow A, Hucklebridge F, Stalder T, Evans P and Thorn L. The cortisol awakening response: More than a measure of HPA axis function. Neuroscience and Biohavioral Review. 2010;35:97-103.
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Can You Make The Switch?

Rapid Consciousness
(you open your eyes)

→ **20-30min** →

Full Alertness
(ready to go)

The real question is:
Do you feel alert & ready to go in the morning?
Or are you too alert? Anxious?

Clow A, Hucklebridge F, Stalder T, Evans P and Thorn L. The cortisol awakening response: More than a measure of HPA axis function. Neuroscience and Biohavioral Review. 2010;35:97-103.
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How is the Cortisol Awakening Response Measured?

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dutchplus
COMPLETE WITH CORTISOL AWAKENING RESPONSE

5 **Saliva** collections for the Cortisol Awakening Response:

1. The first collection: immediately on waking
2. The 2nd collection: 30 min after waking
3. The 3rd collection: 60 min after waking (30min after collection #2)
4. The 4th collection: around dinner
5. The 5th collection: at bedtime

Optional 6th collection: insomnia sample

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dutchplus
COMPLETE WITH CORTISOL AWAKENING RESPONSE

5 **Saliva** collections for the Cortisol Awakening Response:

The dinner and bedtime sample are STILL important to the overall circadian rhythm
These should be evaluated in conjunction with the CAR

Optional 6th collection: insomnia sample

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Salivette Swabs vs. Saliva Tubes

- Easy collection
  - Pop the salivette into your mouth
- A truer CAR result due to rapid collection = <5 min
- No spitting/passive drool
- Convenient for those with dry mouth
- Salivette's are used in nearly all of the published CAR studies
- Salivette's are used in nearly all of the published CAR studies

- Collection requires spitting/drooling into a tube
- Could result in a less accurate CAR depending on how long the collection takes for each tube
- Advised to rinse your mouth with water prior to collection – concern for dilution?

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Salivette Swabs vs. Saliva Tubes

DUTCH makes it easy with swabs

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Salivette Swabs vs. Saliva Tubes

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If you take 15 minutes to drool into a saliva tube at each time, you've missed the point of the CAR

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The DUTCH Plus Advantage

- Salivette swabs
- Reporting metabolites
- Reporting cortisone
- Reporting organic acids
  - Including VMA

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The DUTCH Plus Advantage

dutchplus

Accession # 00280397
Male Sample Report
123 A Street
Sometown, CA 90266

PRECISION ANALYTICAL INC

Organic Acid Tests (OATs)

Ordering Physician:
Precision Analytical

DOB: 1967-08-09
Age: 50
Gender: Male

Collection Times:
2017-08-09 06:01AM (S)
2017-08-09 06:31AM (S)
2017-08-09 07:01AM (S)
2017-08-09 05:01PM (S)
2017-08-09 10:01PM (S)
2017-08-09 06:01AM (U)
2017-08-09 08:01AM (U)
2017-08-09 05:01PM (U)
2017-08-09 10:01PM (U)

Category	Test	Result	Units	Normal Range
Nutritional Organic Acids				
Vitamin B12 Marker (may be deficient if high) - (Urine)				
	Methylmalonate (MMA)	Within range 1.2	ug/mg	0 - 3
Vitamin B6 Markers (may be deficient if high) - (Urine)				
	Xanthurenate	Above range 6.8	ug/mg	0 - 2.1
	Kynurenate	Above range 30.1	ug/mg	0 - 9.3
Glutathione Marker (may be deficient if low or high) - (Urine)				
	Pyroglutamate	Below range 23.2	ug/mg	43 - 85
Neurotransmitter Metabolites				
Dopamine Metabolite - (Urine)				
	Homovanillate (HVA)	Low end of range 5.6	ug/mg	4.8 - 19
Norepinephrine/Epinephrine Metabolite - (Urine)				
	Vanilmandelate (VMA)	Above range 8.8	ug/mg	2.8 - 8
Melatonin (*measured as 6-OH-Melatonin-Sulfate) - (Urine)				
	Melatonin* (Waking)	Within range 42.4	ng/mg	10 - 85
Oxidative Stress / DNA Damage, measured as 8-Hydroxy-2-deoxyguanosine (8-OHdG) - (Urine)				
	8-OHdG (Waking)	Within range 4.0	ng/mg	0 - 8.8

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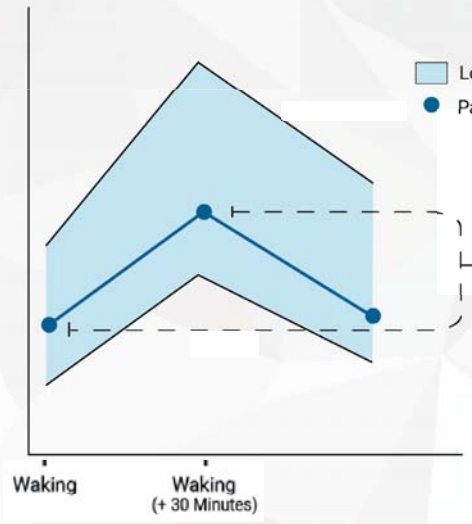
Cortisol Awakening Response



CAR	2.5 ng/mL	100%
Expected CAR	1.5 - 4 ng/mL	50 - 160%

Important to know:

1. **What is the CAR percent rise/change?**
2. **What are the actual numbers?**
3. **Are they in the reference range?**

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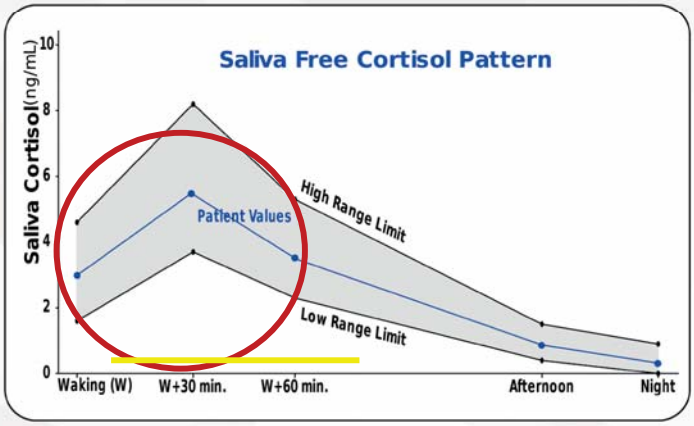
What Does the Whole Curve Look Like?



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CAR Patterns

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First, assume Cushing's and Addison's have been ruled out

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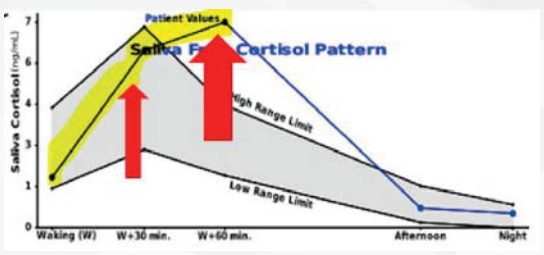
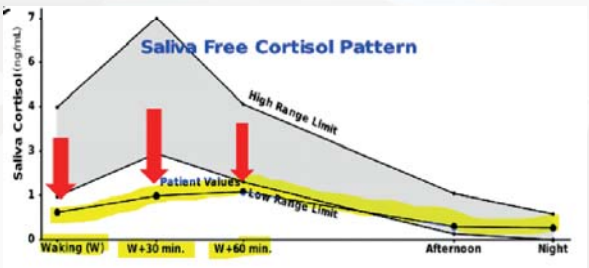
CAR Examples



Elevated CAR



Low CAR

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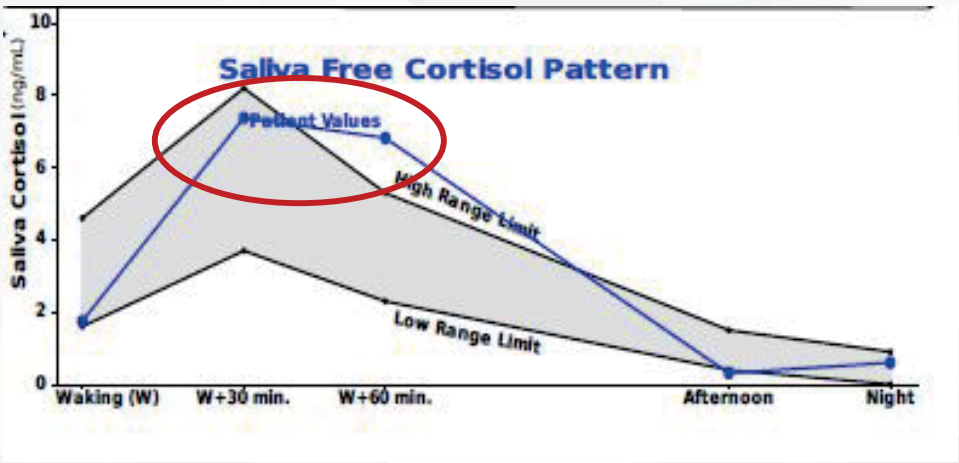
Let's Look at an Elevated CAR



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Elevated Cortisol Awakening Response: Why?

- Anxiety/panic attacks/fear/hypervigilance on waking/close after waking
- Anticipatory stress for the day
- Waking up in acute pain or inflamed or infection
- Stressful event happens first thing…but is this their normal?
- They drank caffeine or took stimulants first thing (<30min of waking)
- Depression (not SAD) – not a high CAR cause but due to a high CAR
- Ovulation (some research says at ovulation = higher CAR than the rest of the month)

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Elevated Response:

Consider doing any "elevated response" suggestions *within 30min of waking* for maximum impact

And always address their sleep

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How To Address an Elevated Response

- Seek therapy if needed
- Seek social connection – call/video a friend/family
- Meditation, breathing work, journaling, yoga, Heartmath™, RESPeRATE™, emotional freedom technique (EFT)
- Grounding exercises
- Shaking exercises
- Vagal nerve exercises
- Increase oxytocin
- Reduce cell phone/EMF exposure – avoid the phone immediately on waking

Church D, Stapleton P, Mollon P, et al. Guidelines for the Treatment of PTSD Using Clinical EFT (Emotional Freedom Techniques). Healthcare (Basel, Switzerland). 2018; 6(4):. [pubmed]
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What are Grounding Exercises?

- Walking barefoot in grass or on the sand
- Washing hands in cold water, holding an ice cube
- Take a walk
- Put on fun music and feel the rhythm, dance
- Repeating centering statements
  (My name is____, today is____, I live in____, my favorite color is___)
- Count backwards by 7 from 100 (100…93…86…79…)

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What are Shaking Exercises?

- **Be like Taylor Swift and literally "Shake it off"**
- Imagine how an animal shakes after a stress or fright
- Shake out your hands for 30sec -1minute
- Shake out your arms for 30sec - 1minute
- Shake out each leg for 30sec - 1minute
- Stand up and twist back and forth while shaking out the arms
- Bounce on the balls of your feet while shaking out your body

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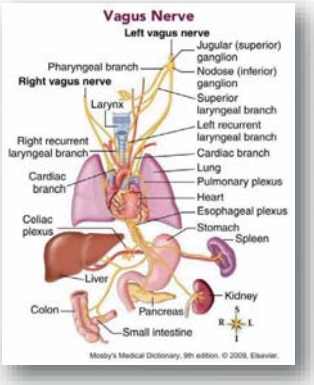
What Stimulates the Vagus Nerve?

- End a shower in cold water
- Dip face in cold water
- Singing, laughing, chanting, humming LOUDLY
- Gargle
- Meditation
- Address the gut
- Yoga
- Rhythmic breathing
- Lay on the right side



Breit S, et al. Vagus Nerve as Modulator of the Brain–Gut Axis in Psychiatric and Inflammatory Disorders. Front. Psychiatry. 2018;9(44):https://doi.org/10.3389/fpsyt.2018.00044

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What Increases Oxytocin?

- Physical touch
  - Hugging, kissing, cuddling those you love (including pets)
- Words of encouragement and appreciation
- Genuine laughing – not just LOL
- Meditation and prayer
- “Eat, drink and be merry” with your friends and family (1.5 meters apart or on video!)
- Breastfeeding

Uvnas-Moberg K and Petersson M. [Oxytocin, a mediator of anti-stress, well-being, social interaction, growth and healing]. Z Psychosom Med Psychother. 2005;51(1):57-80.

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Elevated Response: General

- A **quality multi-vitamin** is a good start but consider extra…
- **B vitamins**
  - Especially vitamin B5 (500mg) and B6 (P5P specifically: 10-50mg, watch neuropathy)
- **Vitamin C** – 100mg-1000mg/day
  - Remember dividing it up into smaller doses greatly increases absorption
  - Acts as an antioxidant in the adrenal gland
  - Humans don’t make their own vitamin C
- **Magnesium** – 250-500mg or Epsom salt baths
  - Needed for many things but also to make GABA with B6, ↑BDNF, inhibit NMDA receptors
- **Essential fatty acids** – 1000-4000mg/day

Neil Boyle. The Effects of Magnesium Supplementation on Subjective Anxiety and Stress—A Systematic Review Nutrients. 2017; 9(5):429.

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Elevated Response:
Calming Support

- **GABA support**
  - GABA – 250-1000mg/day
    - Primary inhibitory neurotransmitter in the brain, not thought to cross the BBB, acts via ENS
  - Pregnenolone – 10-100mg/day
    - Pregnenolone → ALLO = supports GABA-A receptors
- **Amino Acids:**
  - L-theanine – 200-600mg/day (drink organic matcha)
    - Relaxed alertness, often used for anxiety too (inhibits glutamate receptors, ↑BDNF)
  - 5-HTP – 50mg-300mg/day
    - Serotonin supportive but be careful if on antidepressant meds
  - Tryptophan – 500-1000mg/day
    - Serotonin supportive but be careful if on antidepressant meds
  - (L-taurine) – 250 – 3000mg/day
    - Calming to CNS as helps K, Na, Mg, Ca in/out of cells

Pinna G, Uzunova V, Matsumoto K, et al. Brain allopregnanolone regulates the potency of the GABAA receptor agonist muscimol. Neuropharm. 2000;30(3):440-448.
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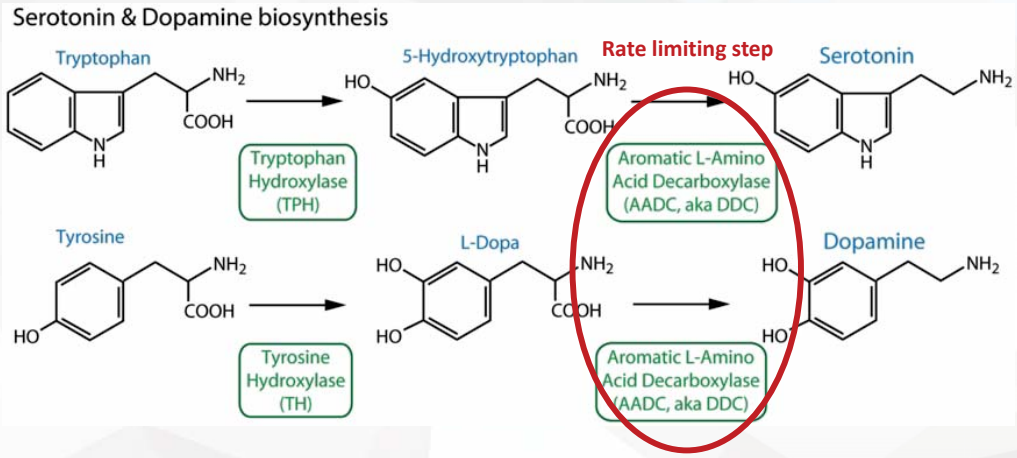
Careful – Don't Deplete Dopamine



http://home.sandiego.edu/~cloer/bio382/382seqanalysis1.html

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Elevated Response
General Cortisol Calming Herbs

- **Magnolia officinalis** – 250-500mg (night)
  - Want the Honokiol to be >90%, ↑BDNF
- **Ziziphus vulgaris (Jujube)** – 100-500mg/(night)
  - Specifically for those who can't sleep through the night
- **Skullcap (Scutellaria baicalensis)** – 250-500mg/(night)
  - Stronger nervine, anxiolytic

These specifically work to inhibit 11b-HSD1

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Elevated Response
General Cortisol Calming Herbs

- **Chamomile** – commonly used as a tea
  - Pretty commonly known
- **Milky oat seed (Avena sativa)** – 250-1000mg/day
  - Nervine, often used topically for skin conditions
- **Passionflower (Passiflora incarnata)** – 250-500mg/day
  - Nervine, often compared to benzos in anxiolytic effect w/o side effects
- **Maca Lepidium – 1000-2000mg/day**
  - Alkaloids affect hypothalamus and pituitary (reduces ACTH and thus cortisol)
- **Hemp-derived CBD –** big topic requiring a separate lecture

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Elevated Response: Adaptogens

- **Ashwagandha (Withania somnifera)** – 250-1000mg/day
  - Can be a thyroid stimulant, be wary with Graves, has calming/anxiolytic properties, ↑BDNF?
- **Siberian ginseng (Eleutherococcus)** 250-500mg
  - Good general tonic, good for people who still have vitality but are a little depleted, ↑BDNF?
- **Rhodiola rosea** – 100-500mg/day
  - Can be more stimulating than people think (dose dependent), can cause insomnia, can be drying (good for night sweats), neuroprotective, increase SIRT1, increases Hsp70, ↑BDNF?
- **Holy basil (Tulsi/Ocimum sanctum)** – 250-1500mg/day
  - Nervine, anxiolytic

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Elevated Response: Adaptogens

- **Cordyceps sinensis (fruiting body)** – 100-500mg/day
  - Stamina, improved physical health, contains beta-glucans (immune support)
- **Schisandra berries (chinensis) –** 500-2000mg/day (eat the berries)
  - Nervine but helps you feel focused/alert, improve cognitive health, liver protective, TCM uses it for liver heat (anger), increase Hsp70, increases glutathione
- **Bacopa monnieri** – 200-600mg/day
  - Reduces brain inflammation, improve cognition, hyperactivity, attention, ↑BDNF

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Citations: General Calming Herbs

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- Horigome H, Homma M, Hiran T, Oka T, Niitsuma T, and Hayashi T. Magnolol from Magnolia officinalis inhibits 11beta-hydroxysteroid dehydrogenase without increases of corticosterone and thymocyte apoptosis in mice. Planta Med. 2001;67(1):33-7.
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Citations: Adaptogens

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- Mishra LC, Singh BB and Dagenais S. Scientific basis for the therapeutic use of Withania somnifera (ashwagandha): a review. Altern Med Rev. 2000:5(4):334-346.
- Nemetchek MD, Stierle AA, Stierle DB and Lurie DI. The Ayurvedic plant Bacopa monnieri inhibits inflammatory pathways in the brain. J Ethnopharmacol. 2017;2:197-92-100.
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- Sowndhararajan K, Deepa P, Kim M, Park SJ and Kim S. An overview of neuroprotective and cognitive enhancement properties of lignans from Schisandra chinensis. Biomed Pharmacother. 2018;97:958-968.
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BDNF (Brain Derived Neurotrophic Factor)

- Important for neuronal survival and development
- Protects against glutamate toxicity
- Big player in synaptic plasticity and neurotransmitter release
- Heavily concentrated in hippocampus (learning, long term memory)
- Also made by platelets, T-cells, monocytes/macrophages
- Downregulation linked with:
  - Depression (esp. depression associated with hypercortisolism)
  - Alzheimer's and other neurodegenerative disorders
  - PTSD
  - Epilepsy

- Sangiovanni E, Brivio P, Dell'Agli M, Calabrese F. Botanicals as Modulators of Neuroplasticity: Focus on BDNF. Neural Plast. 2017;2017:5965371.
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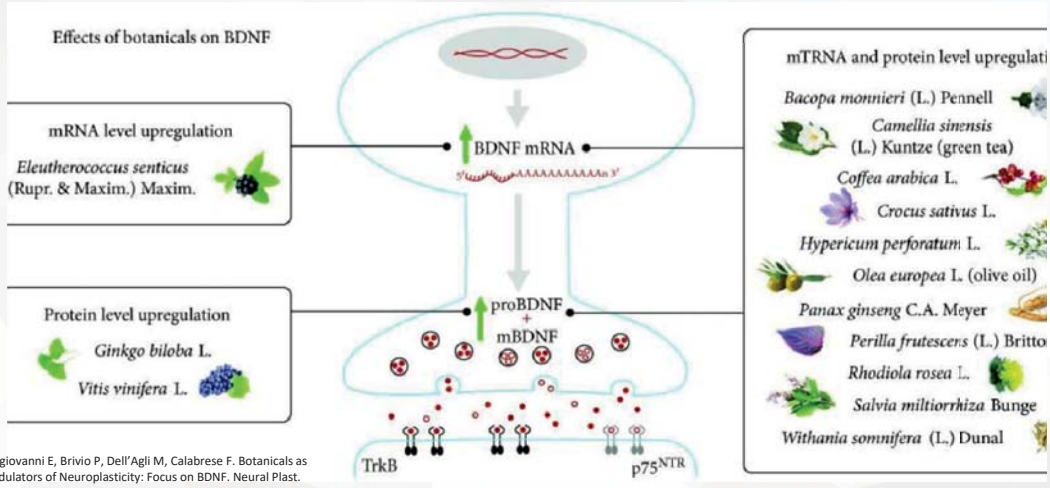
BDNF (Brain Derived Neurotrophic Factor)

Glucocorticoids downregulate BDNF



Sangiovanni E, Brivio P, Dell'Agli M, Calabrese F. Botanicals as Modulators of Neuroplasticity: Focus on BDNF. Neural Plast. 2017;2017:5965371.

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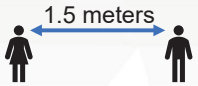
What Else Increases BDNF?

(not an exhaustive list)

- Exercise – especially strength training and HIIT
- Deep sleep
- Intermittent fasting/caloric restriction
- Regular enjoyable socializing (social isolation ↓BDNF)
- Zinc
- Magnesium threonate
- Omega 3 fatty acids
- DHEA
- Niacin
- Magnolia



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Citations: BDNF

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- Zielinski MR, Kim Y, Karpova SA, et al. Chronic sleep restriction elevates brain interleukin-1 beta and tumor necrosis factor-alpha and attenuates brain-derived neurotrophic factor expression. Neurosci Lett. 2014;19:27-31.

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Improve Sleep Function:

- Avoid blue/white light 1-2 hours before bed
  - Wear blue light blocking glasses
- Avoid alcohol and sugar before bed
- Avoid caffeine intake in the afternoon and evening
- Be aware of stimulatory exercise in the evening
- Work on winding down 1-2 hours before bed
  - Take a bath, read a real book, relax with your family, journal, meditate
- Sleep in a cool room temperature
- Consider a sleep study evaluation for apnea or disordered breathing
- Evaluate other factors affecting sleep: animals, partner, children, noises, mold in the bedroom

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Let's Look at a Low CAR

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Low Cortisol Awakening Response: Why?

- Excessive amounts of psychological burnout
- Sleep deprivation!! Sleep apnea/disordered breathing
- Traumatic brain injury or a any damage to hypothalamus or pituitary
- Hippocampal damage **(*the hippocampus controls the CAR)**
- Chronic pain – HPA down regulation
- PTSD
- SAD – Seasonal Affective Disorder
- Poor HPA communication
- Fluorescent lights
- Suppressive medications

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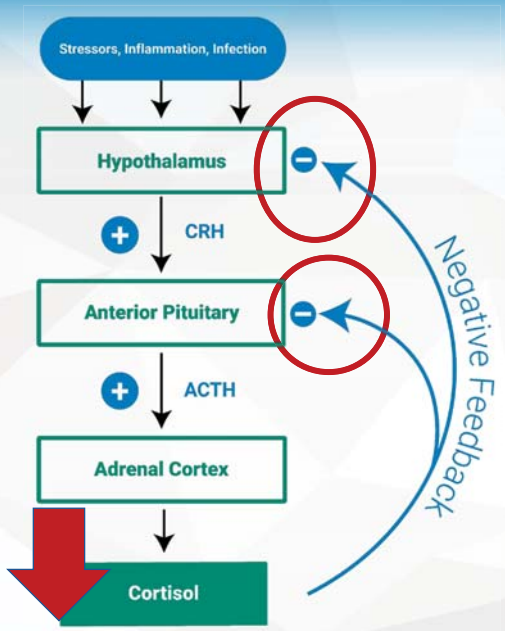
Remember the Cortisol Feedback Loop



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Over time, high cortisol can result in low cortisol

Always keep this feedback loop in mind with chronic conditions and the current global situation at-hand

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Suppressive Medications to Ask About:

*it's amazing what patients don't tell you

- Steroid medications
  - Inhalers, nasal sprays, oral pills, topical creams
- Opioid medications
- Accutane (Roaccutane, Isotretinoin)
- Aspirin (some say 300-600mg ↓ ACTH)

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Low Response

Consider doing any "low cortisol" suggestions
***within 30min of waking* for maximum impact**
And always address their sleep

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Low Response: Lifestyle

- Seek therapy if needed
- Seek social connection – call/video a friend/family
- Shaking, grounding, vagal, oxytocin, EFT support all applies here
- Start with the brain
- "HPA retraining" *(Dr. Jones phrase – not a medical term)*
- Use adaptogens, nutrients, and brain support
- Consider light therapy immediately on waking for the CAR
  - Sun/full spectrum lights
- Light movement/exercise on waking

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If It All Starts with the Brain…

- Follow a strict circadian rhythm
- Get the gut healthy and work on the vagus nerve
- Improve blood flow and oxygen in the brain

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Increase Blood/Oxygen to the Brain

- Exercise – cardio, weights and inversion poses
- Stop smoking
- Normalize your blood sugar
- Neurofeedback, bio-tuning, cranial-sacral work, energy medicine
- Acupuncture/chiropractic/massage/lymphatic stimulation = upper back, shoulders, neck

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Increase Blood/Oxygen to the Brain

- HBOT – hyperbaric oxygen therapy
  - Post-TBI – increases oxygen levels in blood and tissues to improve brain repair
- Test for iron overload (hemochromatosis)
  - Iron deposits can affect brain function
- Reduce EMF/Cell phone to the head
  - In rats, 6 hours/day x 2 months = increased vacuolation in the brain (cellular vacuum and delivery). Cell phones also increase brain temperature.

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Citations: Brain

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It All Starts with the Brain: Supplements

- **Bacopa monnieri** – 200-600mg/day
  - Reduces brain inflammation, improve cognition, ↓hyperactivity, ↑attention,↑BDNF
- **Cordyceps sinensis (fruiting body)** – 100-500mg/day
  - Increased learning and memory, eNOS, GABA and glutamate in the brain
- **Omega 3 fatty acids** – 1000-3000mg/day
- **Rosemary** – use as a spice, inhale the essential oil, drink the tea
  - Diterpine "has cognitive enhancing powers," antioxidant, increases Nrf-2 (phase 2 detoxification), protects against LPS damage, anti-inflammatory (inhibits TNF-a and IL-6), increases acetylcholine, will suppress iron absorption from the gut

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It All Starts with the Brain: Supplements

- **Ginkgo biloba** – 150-1500mg/day
  - Shown to affect recall, recognition, reaction time, attention, concentration through antioxidant effect, improved blood flow and neuroprotection, ↑ BDNF
- **Pyrroloquinoline quinone (PQQ)** – 10-40mg (often paired with Co-Q10)
  - Increase nerve growth factor, protects NMDA receptors, antioxidant to peroxynitrite (improving mitochondrial health), reduces C-reactive protein and IL-6.
- **Maca Lepidium** – 1000-2000mg/day
  - Alkaloids affect hypothalamus and pituitary (reduces ACTH and thus cortisol but some say its adapatogenic), antidepressant effect

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Citations: Brain Supplements

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Low Response: General

- A **quality multi-vitamin** is a good start but consider extra…
- **B vitamins**
  - Especially vitamin B5 (500mg) and B6 (P5P specifically: 10-50mg, watch neuropathy)
- **Vitamin C** – 100mg-1000mg/day
  - Remember dividing it up into smaller doses greatly increases absorption
  - Acts as an antioxidant in the adrenal gland
  - Humans don't make their own vitamin C
- **Magnesium** – 250-500mg or Epsom salt baths
  - Needed for many things but also to make GABA with B6, ↑BDNF, inhibits NMDA receptors
- **Essential fatty acids** – 1000-4000mg/day

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Low Response: Mitochondria

- **Co-Q10** – 10-150mg
- **L-Carnitine** – 500-2000mg/day
- **a-Lipoic Acid** – 200-600mg/day
- **Glutathione/NAC**
- **B vitamins**
- **NADH** – 25-50mg/day
- **Essential fatty acids** – 1000-3000mg/day
- **Curcumin** – 150-500mg/day
- **PQQ** – 10-40mg/day
- **Intermittent fasting + cold exposure (ie. shower)**

These are examples of your co-factors, transporters, anti-oxidants needed for mitochondria

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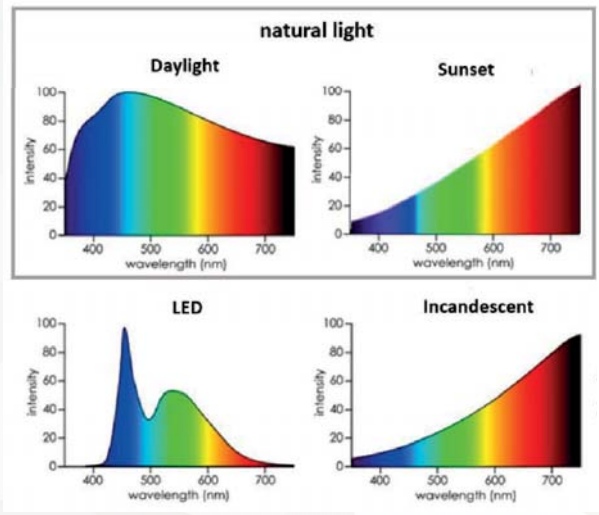
Natural Daylight vs Fluorescent



https://www.sunlightinside.com/light-and-health/natural-light-versus-artificial-light/

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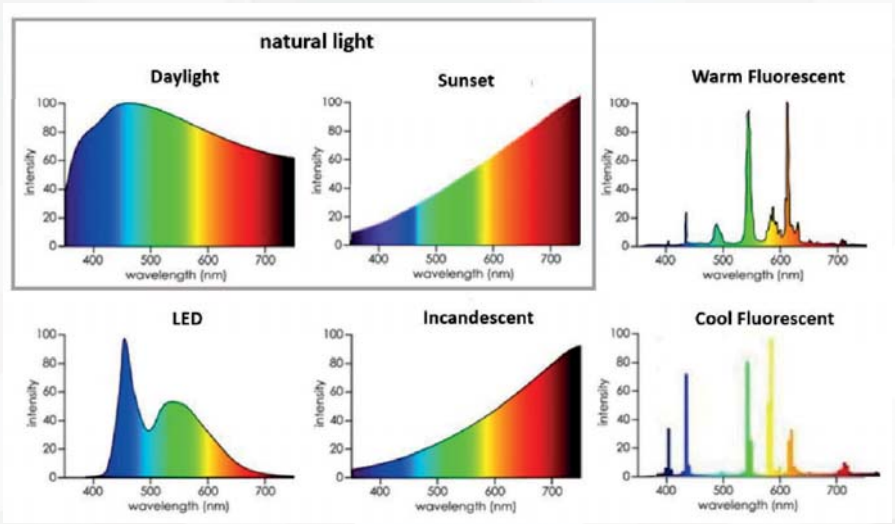
Natural Daylight vs Fluorescent



https://www.sunlightinside.com/light-and-health/natural-light-versus-artificial-light/

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Low Response: Adaptogens

- **Ashwagandha (Withania somnifera)** – 250-1000mg/day
  - Can be a thyroid stimulant, be wary with Graves, has calming/anxiolytic properties, ↑BDNF?
- **Siberian ginseng (Eleutherococcus)** 250-500mg
  - Good general tonic, good for people who still have vitality but are a little depleted, ↑BDNF?
- **Rhodiola rosea** – 100-500mg/day
  - Can be more stimulating than people think (dose dependent), can cause insomnia, can be drying (good for night sweats), neuroprotective and increases SIRT1, increases Hsp70, ↑BDNF?

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Low Response: Adaptogens

- **Cordyceps sinensis (fruiting body)** – 100-500mg/day
  - Stamina, improved physical health, contains beta-glucans (immune support)
- **Schisandra berries (chinensis) –** 500-2000mg/day (or eat the berries)
  - Nervine but helps you feel focused/alert, improve cognitive health, liver protective, TCM uses it for liver heat (anger), increases Hsp70, increases glutathione
- **Bacopa monnieri** – 200-600mg/day
  - Reduces brain inflammation, improve cognition, hyperactivity, attention, ↑BDNF

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Low Response: Adaptogens

- **Panax ginseng (Asian ginseng – red and white forms)** – 100-500mg/day
  - Good tonic for the completely exhausted, could decrease glucose, increases acetylcholine, anti-inflammatory, can be heating and stimulating, ↑BDNF
- **Licorice (Glycyrrhiza glabra)** – 50-600mg/day
  - Inhibits 11b-HSD2 to increase cortisol
  - Watch for hypertension and hypokalemia

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Citations:

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Low Response: Glandulars

Adrenal glandular extracts may be considered, however there is limited clinical research available regarding their clinical impact

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Low Response: Glandulars

Adrenal glandular extracts may be considered, however there is limited clinical research available regarding their clinical impact

I tend to prescribe adrenal glandulars in cases of low cortisol with really low vitality. I prescribe them in the morning for 3-4 months then re-test. Watch for side effects such as anxiety and insomnia.

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Remember, Practitioner Heal Thyself

Me trying to excel in my career, maintain a social life, drink enough water, exercise, text everyone back, stay sane, survive, socially isolate and be happy

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Summary:

- Fear and anxiety response heavily impacts resilience, stress, blood sugar, inflammation, autoimmune, mood and more
- CAR collection requires 3 saliva samples in first 60 minutes upon waking
- Treatment considerations are not difficult, but timing is everything
- Remember grounding, shaking, vagal, oxytocin exercises daily to support the HPA axis
- Remember sun/full spectrum light exposure daily in the morning for circadian rhythm
- Get off phones, computer, tablet at night. Wear blue light blocking glasses.
- Proper sleep will probably "fix" >50% of CAR issues

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Summary:

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…and that concludes our talk

Thank you for listening.
Looking forward to our upcoming
Q & A webinar!

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