Adrenal and HPA axis: Cortisol and how it affects the body

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Cortisol And The Stress Response

- Cortisol
  - Produced in the zona fasciculata in the adrenal cortex of the adrenal glands
  - It is a glucocorticoid (steroid hormone that utilizes sugar and fats to mediate an anti-inflammatory response; can influence immune response)
  - Cortisol is released in response to stress. It is also released in the presence of low blood sugar (which is a stressor).
    - Cortisol blocks insulin to keep glucose in the blood stream
    - Cortisol induces gluconeogenesis (break down of glucose from fat cells/liver)
    - Cortisol reduces protein uptake (diverts it to gluconeogenesis to keep glucose in circulation)
    - Cortisol suppresses the immune system to deal with the stress
    - Cortisol increases blood pressure (vasoconstriction)
    - Cortisol improves focus (mental and physical), improves eyesight

Cortisol And The Stress Response

Cortisol's short-term purpose:

TO KEEP YOU SAFE

To *enable* you to *run from* your saber-tooth tiger

- Your saber-tooth tiger may look like:
  - Work stress
  - Relationship stress
  - Exercise
  - Blood sugar dysregulation
  - Etc…

Cortisol And The Stress Response

- Short Term Effect of Cortisol Release:
  - Anti-inflammatory
  - Ability to have energy to fight, deal with stress
  - Increased focus
  - Increased blood pressure (vasoconstriction)
  - Increased HR and blood flow to muscles
  - Decreased digestive effort
  - Decreased sex hormone response
  - Decreased immune response

Cortisol And The Stress Response

When cortisol is released for too long, we are now over-compensating and creating a negative response in the body

Cortisol And The Stress Response

- Long Term Effect of Cortisol Release:
  - Insulin dysregulation
  - Blood sugar irregularities/dysglycemia - **diabetes**
  - **Weight gain**, specifically around the middle
  - Immune suppression, immune dysregulation
  - Chronic Fatigue
  - Gastrointestinal Issues – parasympathetic nervous system suppression such as constipation, diarrhea, heartburn, digestive complaints
  - Cardiovascular Concerns – blood vessel constriction, over compensation of the cardiovascular system (**high blood pressure**)
  - Sex Hormone Imbalances, **infertility, irregular periods, heavy periods, low libido/sex drive**

Cortisol And The Stress Response

- HIGH Cortisol
  - Cushings – a pathology of consistently high levels of cortisol, usually from a tumor that encourages improper and constant signaling to release cortisol

- LOW cortisol
  - Addison's – when the body does not have enough cortisol (or aldosterone). This can be a life-threatening disease and needs appropriate treatment

Cortisol And The Stress Response

- The stress response is a delicate process
- When there is consistent stimulation of the stress response, it can render the body unable to efficiently respond to stress, and lead to further dysregulation in the body.
- Stabilization of the stress response by supporting healthy stress management can encourage better balance throughout the whole body

Stress Response – Sympathetic Vs Parasympathetic Nervous System Response

- Sympathetic Nervous System
  - Run, Fight, Flight, Freeze
  - Action
- Parasympathetic Nervous System
  - Rest
  - Digest
  - Calm

Stress Response – Sympathetic Vs Parasympathetic Nervous System Response

- When the body is in Sympathetic drive for too long, and does not have the capacity to balance with Parasympathetic rest, we become

"Sympathetic Dominant"

- This means:
  - Our threshold to turn on that stress response is more easily reached
  - We are not able to create enough down time to allow for appropriate rest and recovery to respond to stress appropriately

Cortisol And The Stress Response

Too much cortisol signaling and release,

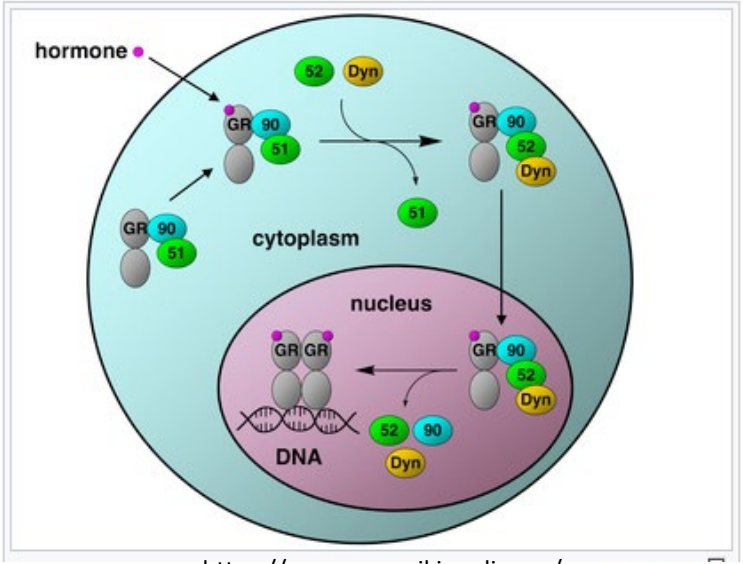
along with too much sympathetic stimulation can lead to feeling burned out, or having the inability to appropriately respond to stress

Cortisol And The Stress Response: How It Works

- The glucocorticoid must be transported into the cell
- Once inside the cell it binds to a Glucocorticoid Receptor (GR)
- Once bound, the GR carries cortisol with help of a “chaperone” called HSP90
- HSP90 is the carrier to pull cortisol via the GR from the cytoplasm of the cell to the mitochondria of the cell
- Once inside the mitochondria, HSP90 allows cortisol to unbind from the GR and act on the cell for the cortisol response

The Stress Response: How It Works

- GR
  - The GR can bind to multiple steroid hormones including estradiol, androgens like Testosterone, Aldosterone, and progesterone; here the focus is on Cortisol



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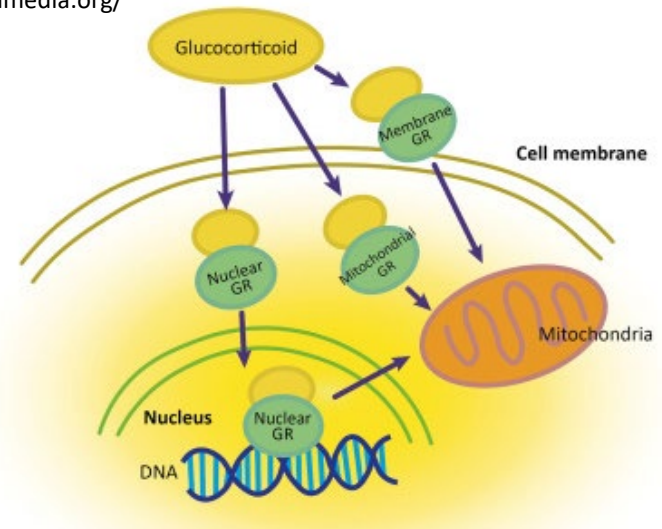
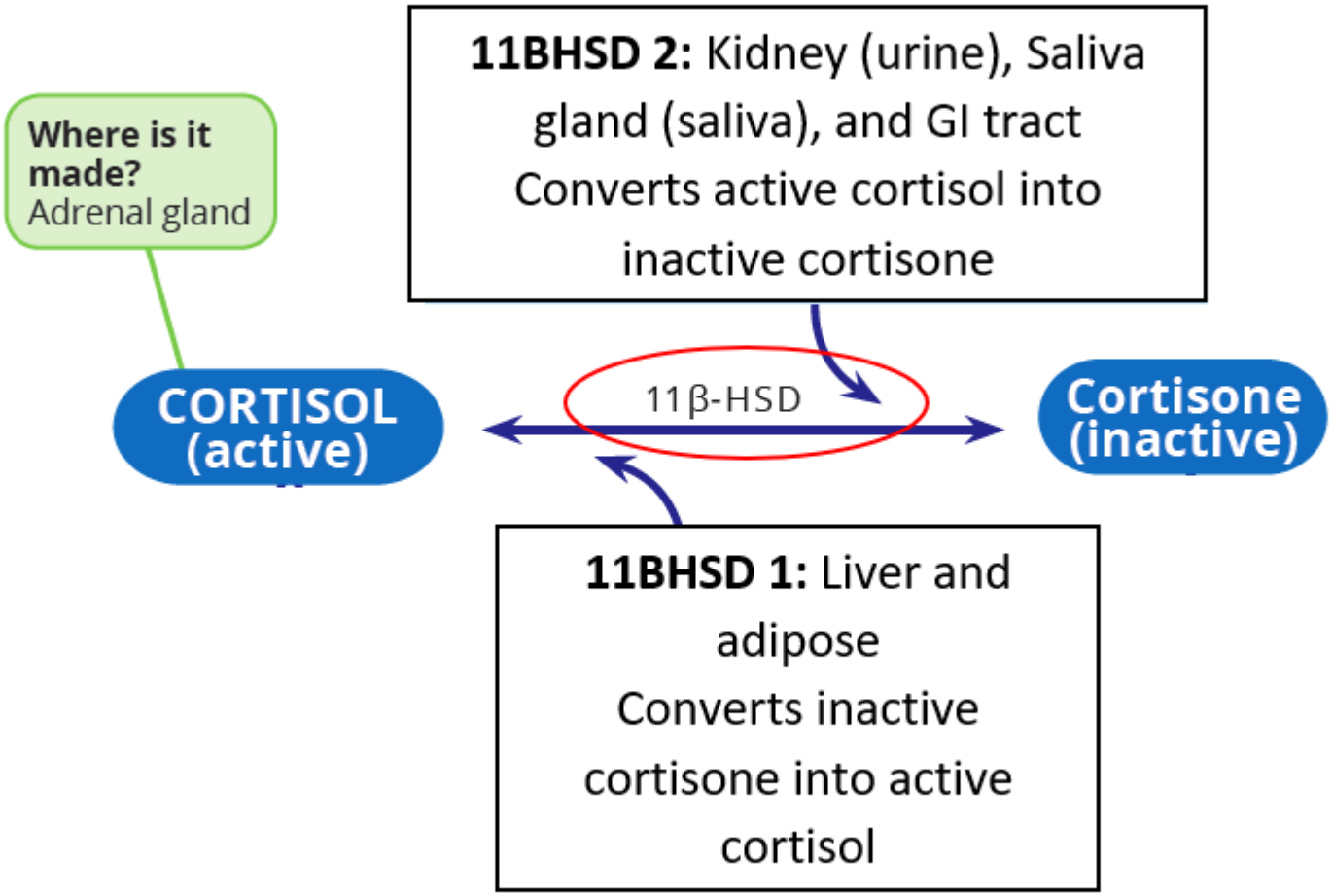
- HSP 90
  - Heat Shock Protein 90
  - Protects cells from “heat shock” but also from a multitude of stressors
  - Also known as “stress proteins”



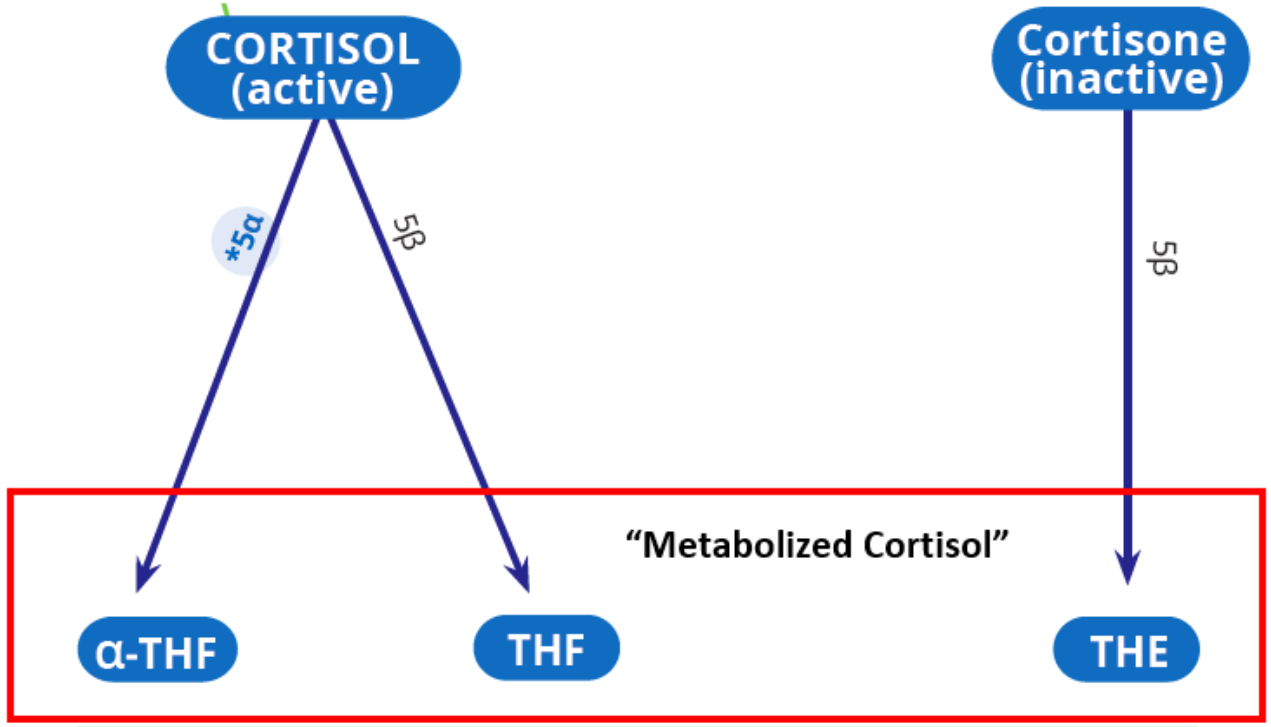
Choi, G. E., & Han, H. J. (2021). Glucocorticoid impairs mitochondrial quality control in neurons. *Neurobiology of Disease*, *152*, 105301. https://doi.org/10.1016/j.nbd.2021.105301

Cortisol Metabolism



- Free cortisol is active and moves into cells easily
- Free cortisone is made *from free cortisol* and is inactive
- Free cortisone is made to protect cells from too much active cortisol while also maintaining a supply of cortisol that can be reactivated
- Notice that cortisone is made in the kidneys **(urine)** and saliva gland (makes **saliva)**- **BOTH FLUIDS USED TO MEASURE FREE CORTISOL**

Cortisol Metabolism

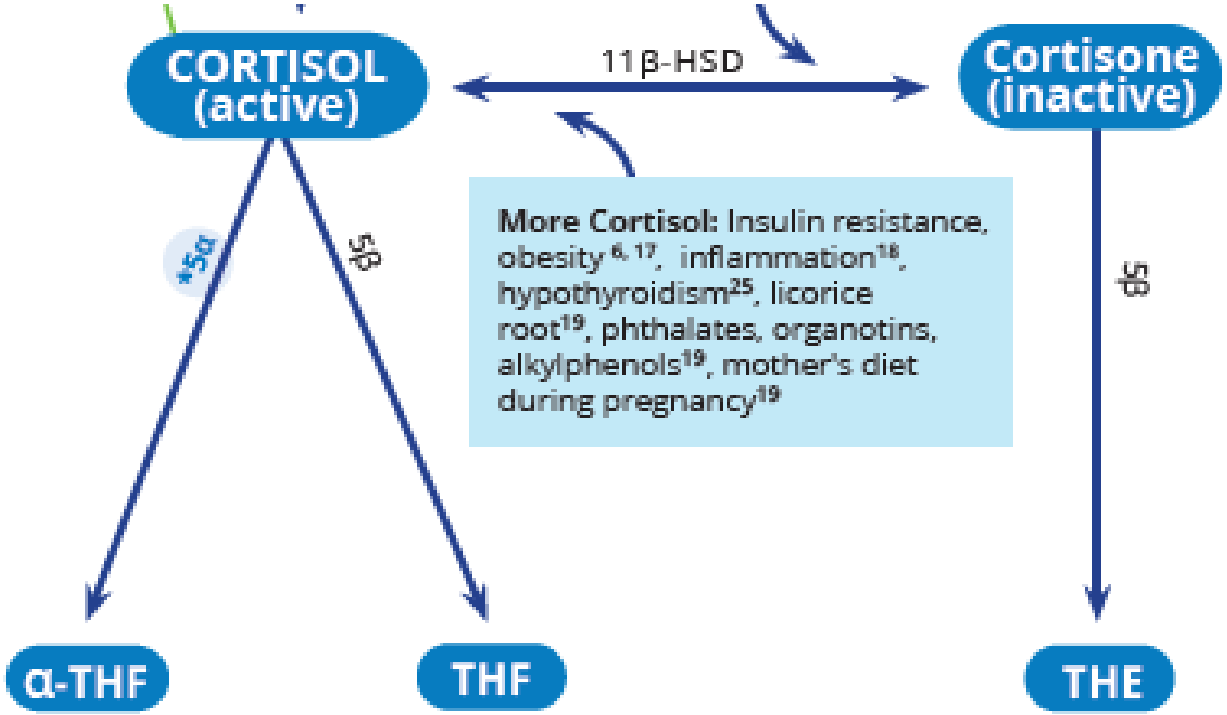


Cortisol Metabolism/Clearance

Cortisol is metabolized by 5α/5β-reductase (and 3α-HSD) to α/β-THF & THE for excretion. This process is particularly increased in obesity, high insulin and hyperthyroid. It may be slowed in cases of hypothyroidism, anorexia or poor liver function.

- Cortisol and cortisone are metabolized by 5a and 5b reductases
- Metabolized comes from free cortisol and cortisone

The Stress Response: How It Works



Deactivation happens in the kidney, saliva gland, and GI tract

Reactivation can occur in fat cells and the liver

~5% of cortisol is free
THF = Cortisol Metabolites
THE = Cortisone Metabolites
11b-HSD 1
    Activates to cortisol
11b-HSD 2
    Deactivates to cortisone

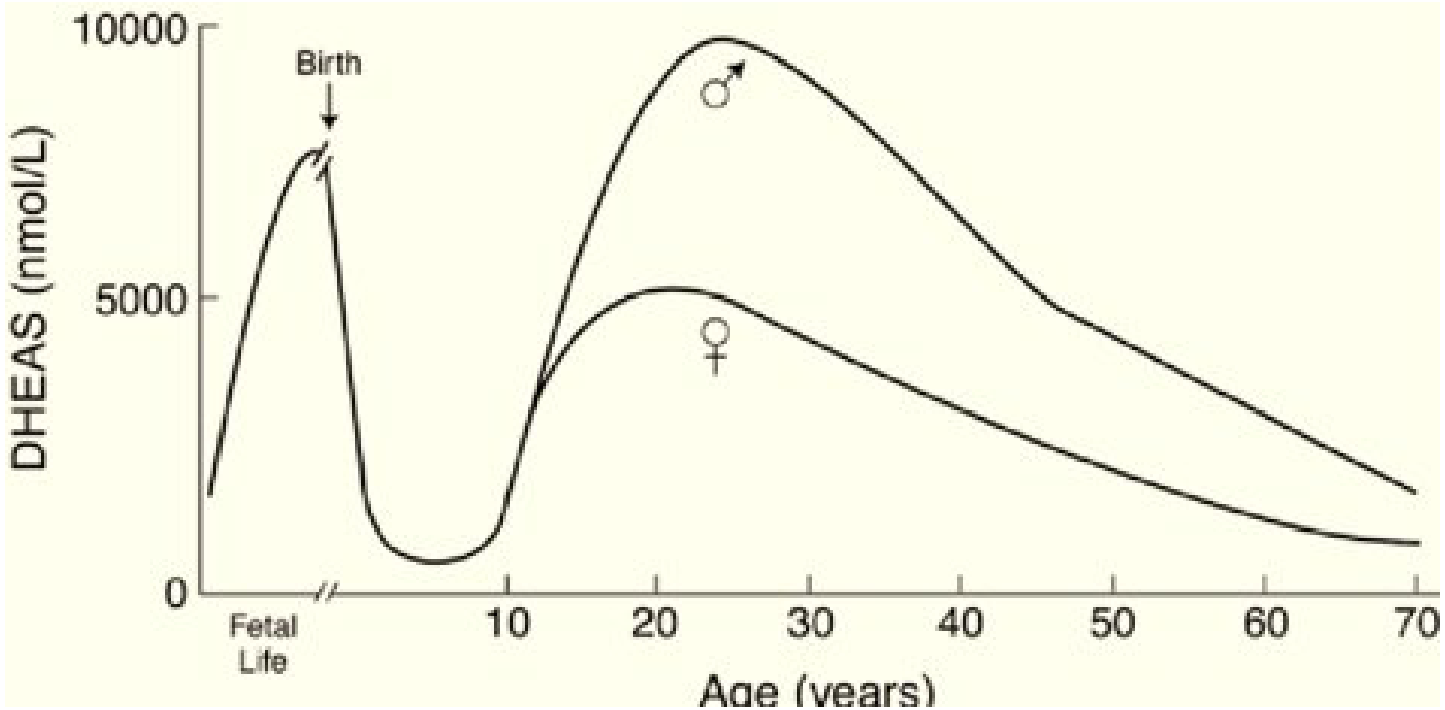
DHEA And The Stress Response

- DHEA – Dehydroepiandrosterone; produced in the adrenal glands (adrenal cortex), gonads, and the brain
- DHEA is also released with the ACTH signal from the brain (same as cortisol)
- With chronic stress, DHEA will be affected along with cortisol
- DHEA balances cortisol in acute stress and in general
  - This means that DHEA can offset the negative effects of cortisol
  - In many cases, it may be important to review the ratio of cortisol to DHEA to understand the negative effect of cortisol (ie, if DHEA is higher than cortisol, this may be more protective, or vice versa, if DHEA is lower than cortisol this may be a risk factor for long term effects of high cortisol such as metabolic syndrome, high blood pressure, etc)

Seely J, et al. Endocrinology. 2005; 146: 3605-3613.

DHEA and The Stres Response

DHEA also has a significant pattern through life stages



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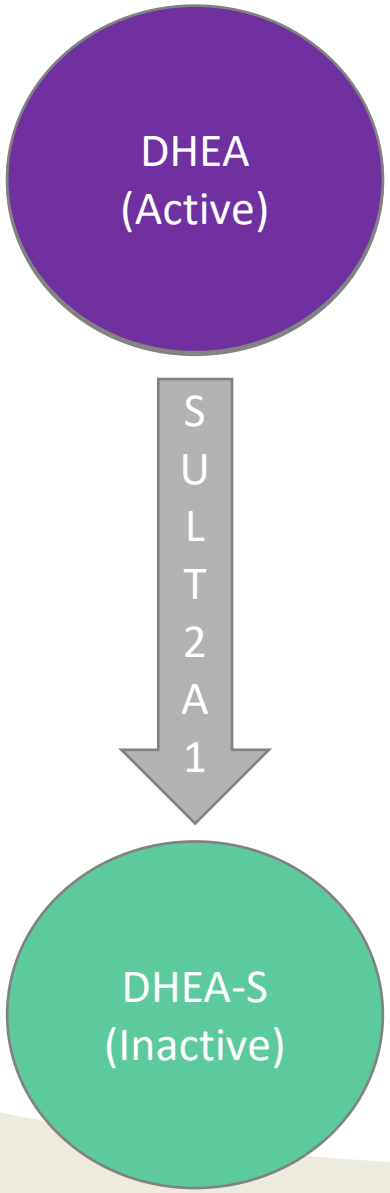
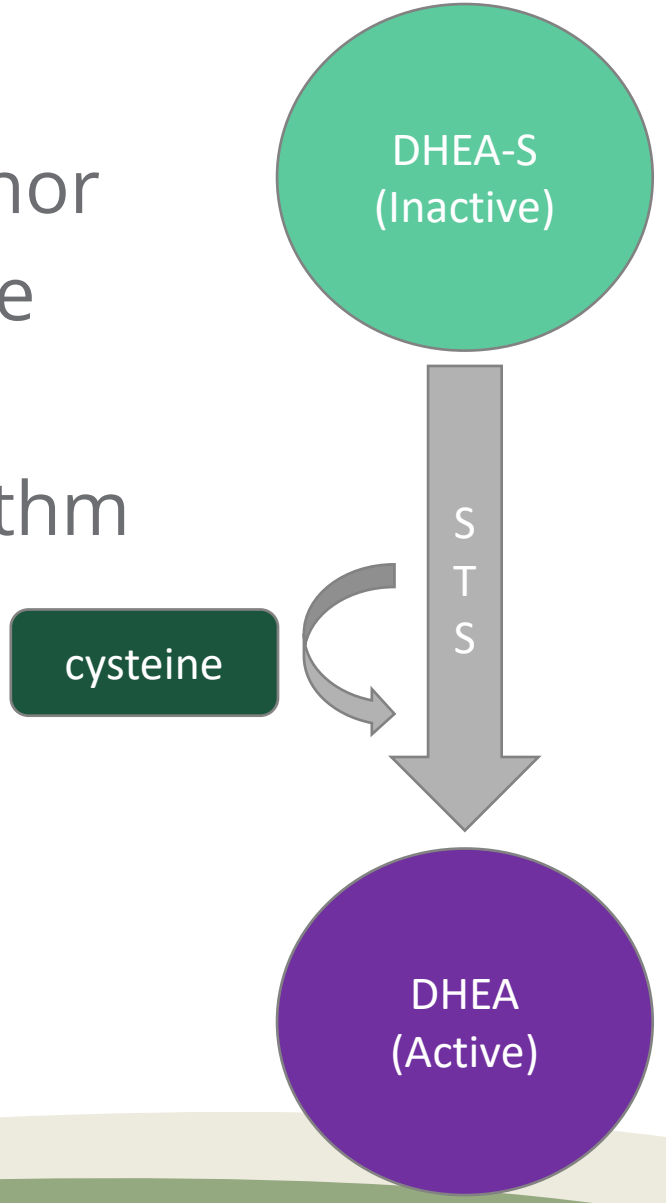
DHEA And The Stress Response

- DHEA is seen as a parent hormone – it is a major precursor to most other steroid hormones
- DHEA plays in both the sex hormone and adrenal hormone worlds
  - DHEA supplies about 75% of estrogens to pre-menopausal women, and in menopause [androgens] supply 100% of estrogens
  - DHEA-sulfate does not cross the blood brain barrier
  - DHEA-sulfate does not follow a diurnal pattern through the day, it is constant and most abundant, and is therefore a better measurement of adrenal/stress reserve
  - DHEA and DHEA-S have been found to heavily influence brain and nervous system functions – specifically mood, neurotransmitter regulation and production (more specifically with dopamine), immune function, and endothelial function
  - DHEA is still not greatly understood though there is a lot of new information and research regarding its purpose and function

Stress Response – How It Works



- DHEA to DHEA-s needs a sulfur donor
  - DHEA-s to DHEA requires cysteine
    - DHEA has a diurnal rhythm
- DHEA-s does not have a diurnal rhythm



Thank You!

If you are interested in learning more about hormones, each week we hold one-hour long mentorship sessions! Once you are a registered DUTCH provider, you can book these through our online scheduling link. Please call to get registered today.

For questions, contact:

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