HPG Axis

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"Too much of one thing can end up creating stress; this is something that no one needs in their life. But living a life in balance can provide harmony and peace."
--- Catherine Pulsifer

Definition of the HPG Axis:

The hypothalamic–pituitary–gonadal axis (HPG axis) refers to the hypothalamus, pituitary gland, and gonadal glands as if these individual endocrine glands were a single entity. Because these glands often act in concert, physiologists and endocrinologists find it convenient and descriptive to speak of them as a single system.

The HPG axis plays a critical part in the development and regulation of a number of the body's systems, such as the reproductive and immune systems. Fluctuations in this axis cause changes in the hormones produced by each gland and have various local and systemic effects on the body (Wikipedia).

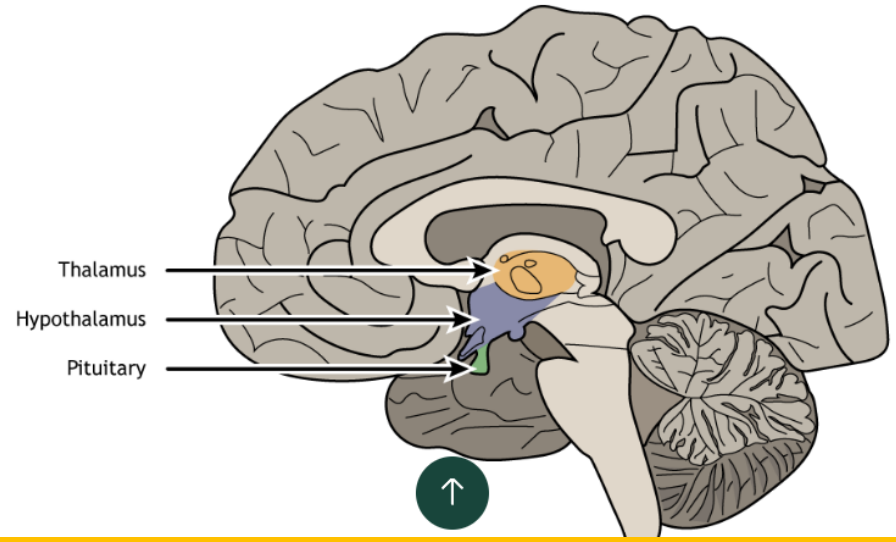
The Hypothalamus

This and the following three slides are adapted from Open Books – Click the link below to access the full article:

https://openbooks.lib.msu.edu/neuroscience/chapter/hpg-axis/

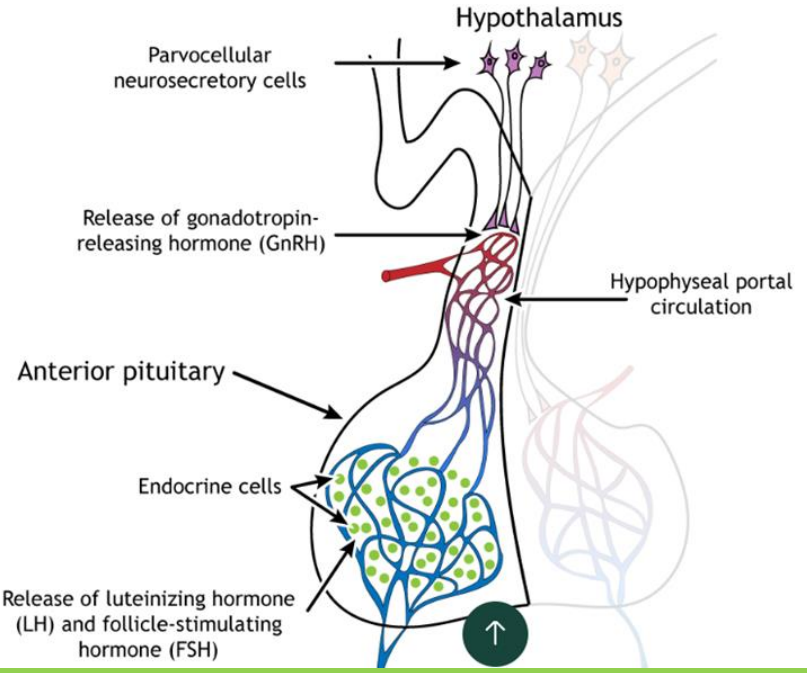
Hypothalamus

As a refresher, the hypothalamus, which is located inferior to the thalamus, integrates information from many regions of the central nervous system and maintains homeostasis in the body. They hypothalamic regulation of gonadal hormones and sex behavior is managed via hormone release by the pituitary gland.

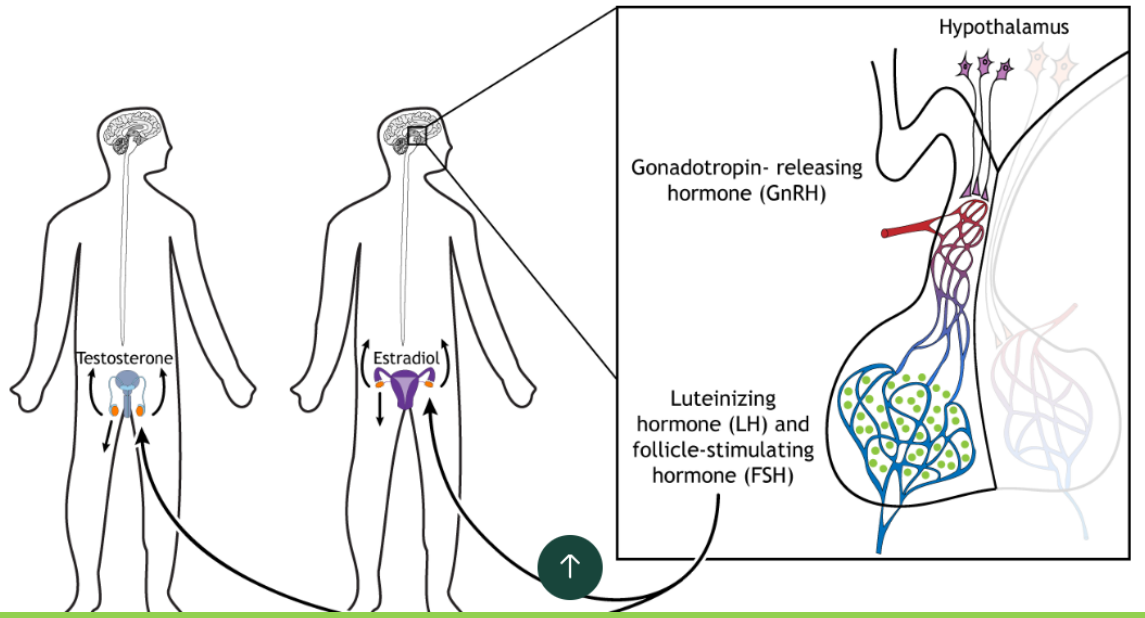


Hormone Release in the HPG

Gonadal hormone release relies on anterior pituitary function. In the hypothalamus, the parvocellular neurosecretory cells release a hormone called gonadotropin-releasing hormone (GnRH) into the hypophyseal portal circulation. When GnRH reaches the anterior pituitary, it causes the endocrine cells of the pituitary to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH) into the general circulation.

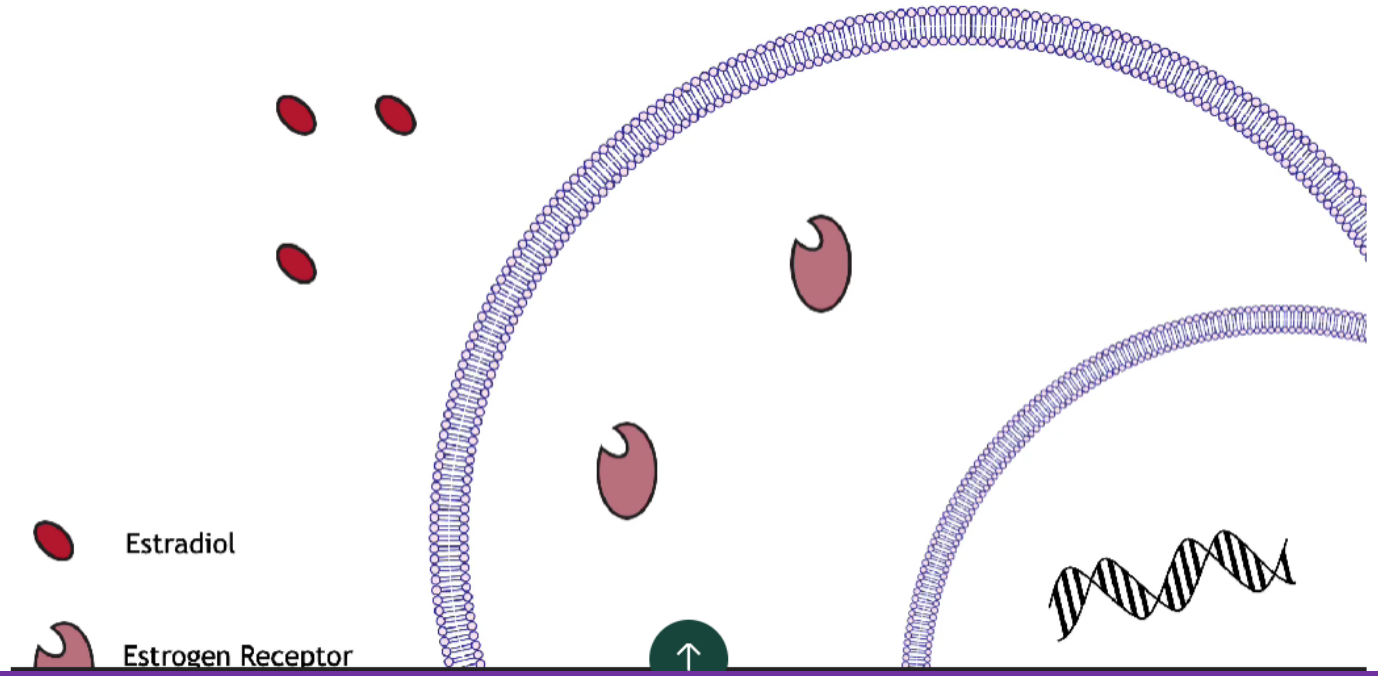


The LH and FSH travel through the circulatory system and can act on the gonads, either the testes in males or ovaries in females. In response to the pituitary hormones, the testes release testosterone, an androgen, and the ovaries release estradiol, an estrogen, into the blood stream. After puberty, the LH and FSH are also critical for the maturation of sperm and egg cells.



Hormone Release in the HPG

Once the gonadal hormones enter the circulation, they are able to act on cells that express either androgen receptors or estrogen receptors. Like cortisol, testosterone and estradiol are steroid hormones and can cross the phospholipid bilayer. Inside the cell, the hormones bind to receptors which then dimerize and move to the nucleus The receptors can bind to DNA at special promotor regions and act as transcription factors, turning on specific genes.



Key Takeaways

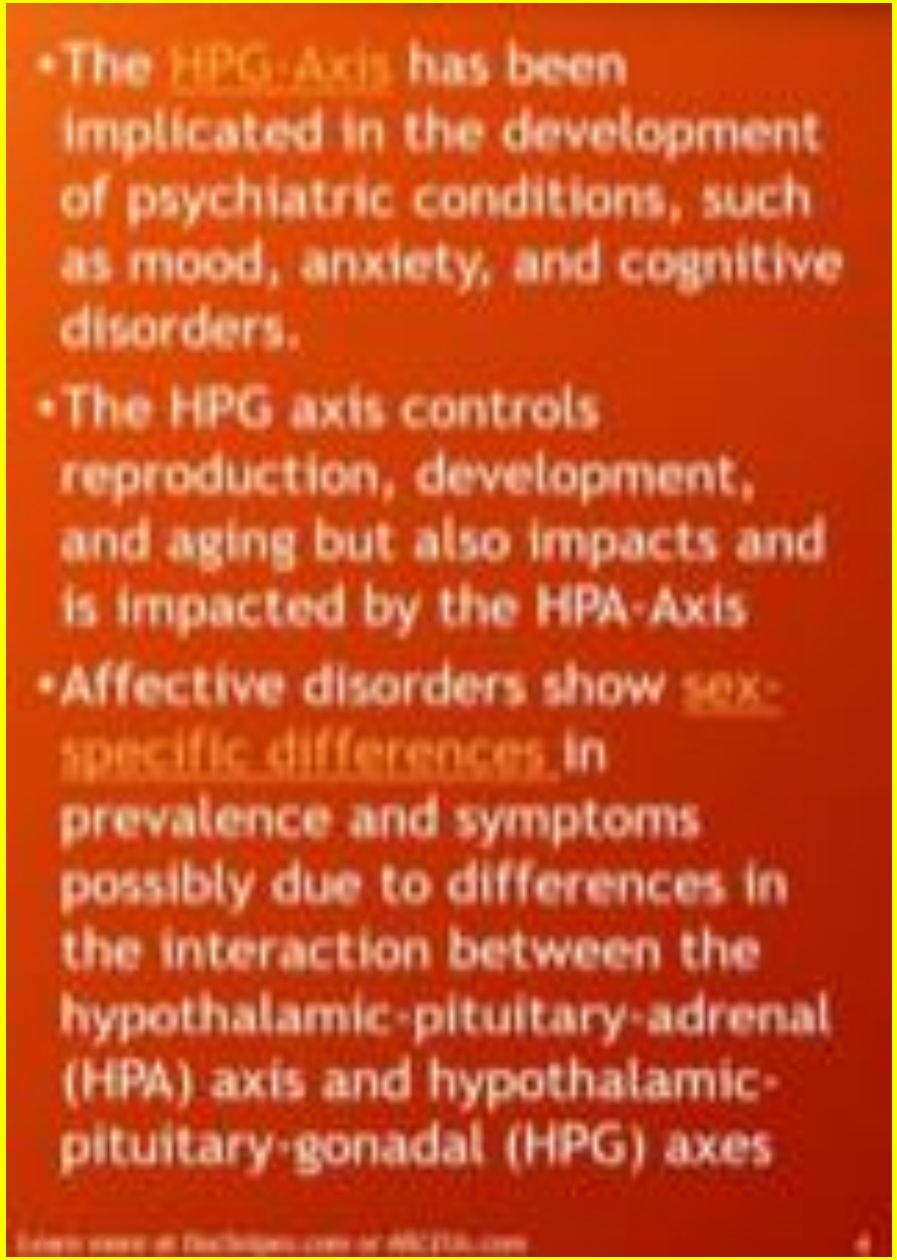
- The hypothalamus directly controls release of gonadal hormones by controlling hormone release from the anterior pituitary
- The hypothalamus releases gonadotropin-releasing hormone (GnRH)
- The anterior pituitary releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH)
- The ovaries release estradiol
- The testes release testosterone
- Gonadal hormones bind to receptors and alter DNA transcription

In summary

The following several 22slides are adaptations of Dr. Dawn-Elise Snipes excellent presentation on the HPG Axis.

Click the link below for the full lecture:
https://www.youtube.com/watch?v=3VQ6J048akQ&ab_channel=DocSnipes

HPG and Mental Health



HPG and Mental Health

- Alterations in the HPG axis during important reproductive health events, such as pregnancy and menopause, and aging alter the sensitivity of neurotransmitter systems in both sexes
  - *In women, Perimenopause is characterized predominantly by estrogen deficiency, whereas, the postpartum period is more complex, characterized by deficiencies in sex hormones as well as hypothalamus-pituitary-adrenal (HPA) axis hormones*

- Alterations in the HPG axis during important reproductive health events, such as pregnancy…
  - *In men, during the postpartum period testosterone levels drop (reducing aggression and arousal and increasing sympathetic responses to the baby)*
  - *Cortisol, vasopressin and prolactin also increase which can contribute to depressed mood*

Stress, the HPA, and the HPG Axes

- The HPA axis is a critical endocrine system that orchestrates the stress response.
- When under chronic stress, the HPA-Axis "recalibrates"
  - People with mood disorders often exhibit either hyper or hypo-cortisolemia.
- Gonadal steroids, particularly oxytocin and testosterone, can act in a synergistic manner to decrease HPA axis gain and anxiety-related behaviors

- Gonadal hormones affect reproductive organs and also influence several other bodily functions by interacting with major neuroendocrine systems including thyroid hormones, stress hormones, and the autonomic nervous system.
- The HPA axis is affected by similar factors as the HPG axis
- Interestingly, alterations in maternal care can produce significant effects on both HPG and HPA physiology, as well as behavior in the offspring at adulthood (ACEs)

Functions of Estrogen

- Increases muscle mass
- Regulates fat distribution
- Anti-inflammatory
- Mediate formation of secondary sex characteristics
- Regulates energy expenditure
- Maintains bone density
- Improves coagulation
- Helps maintain healthy cholesterol levels
- Assists with fluid balance
- Promotes lung function
- Sexual behavior

- Increasing serotonin and serotonin receptors in the brain
- Estrogen modulates higher order cognitive processes driven by dopamine such as learning, reward processing, working memory, and impulse control

Functions of Testosterone

- Regulate sex drive (libido)
- Fat distribution
- Bone and muscle mass
- Improves insulin response
- Anti-inflammatory
- Strength
- Production of red blood cells
- Production of sperm
- Converted to estrogen (small amounts)
- Enhances cognition
- Increases dopamine, serotonin, GABA

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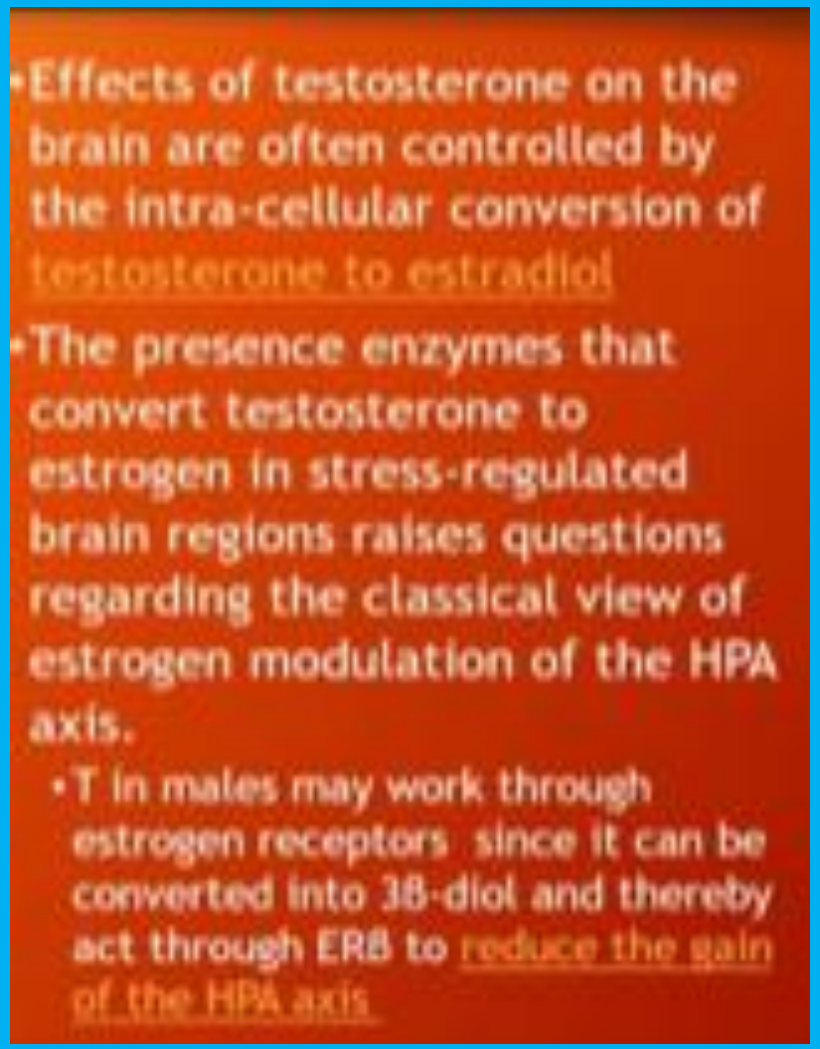
Testosterone Effects



Progesterone and it's functions

- Progesterone is the precursor to cortisol and is increased in response to stress.
- Low progesterone can cause low cortisol.
- Progesterone has anxiolytic properties thought to modulate the stress response
- Under chronic stress and reduced levels of cortisol and progesterone, estrogen dominates
- Estrogen Dominance: Mood swings, increased anxiety, weight gain, hair loss, sleep disruption, memory/cognitive disruption

- Progesterone receptors are found in hypothalamus, hippocampus, cortex, and amygdala.
- Progesterone influences the CNS in both sexes through interaction with multiple neurotransmitter receptors including glutamate, GABA-A and nicotinic receptors

DHEA

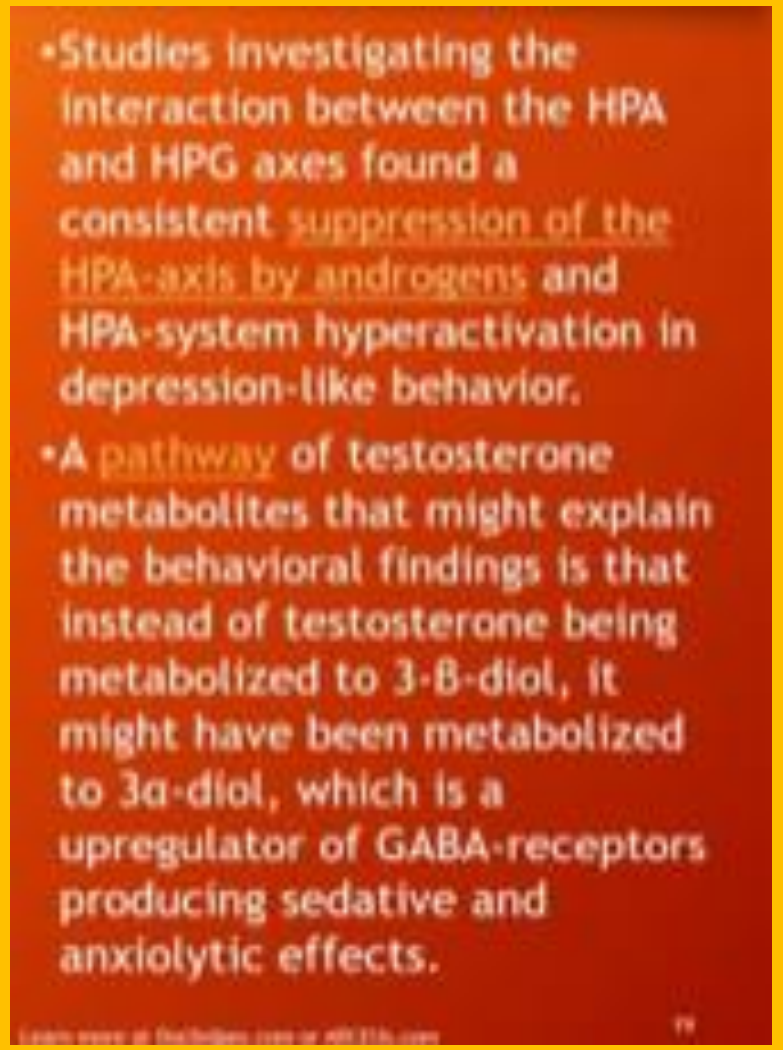
- DHEA is actually a steroid hormone produced in the adrenal glands
- It assists in the creation of the androgen and estrogen sex steroids both in the gonads and in various other tissues
- DHEA is positively related to cortisol
- DHEA elevation by itself produces stimulatory effects and can exaggerate glucocorticoid resistance
- Glucocorticoid resistance leads to increased secretion (tolerance)

Stress, the HPA-Axis and the HPG-Axis

- Excess stress cont…
  - Oxidative stress plays a central role in the development of many different disorders, including PCOS, diabetes, neurocognitive and neuropsychiatric disorders, including anxiety disorders and depression

- Excess stress leads to
  - Hypothyroid and glucocorticoid resistance (both symptoms of HPA-Axis dysregulation) can cause disruption of the HPG-Axis
  - GC-resistant subjects had higher free floating cortisol
  - Stress-induced elevations of cortisol and reductions in the neuroprotective hormones DHEA and estrogen/testosterone cause enhanced oxidative stress

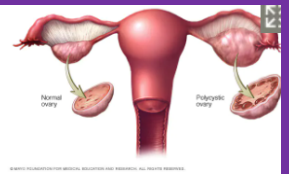
HPA and HPG Axes in Depression



Stress, the HPA and POCS

- Chronic stress in adulthood mediates HPG activity
  - In women, stress activates a sympathetic neural pathway originating in the hypothalamus which releases norepinephrine into the ovary, which produces a noncyclic anovulatory ovary that develops cysts (PCOS)
  - GC resistance was found in more than 50% of patients with PCOS (depression, facial hair, hair loss, oily skin)

Polycystic ovary syndrome (PCOS) is a hormonal disorder common among women of reproductive age. Women with PCOS may have infrequent or prolonged menstrual periods or excess male hormone (androgen) levels. The ovaries may develop numerous small collections of fluid (follicles) and fail to regularly release eggs.



Polycystic ovary syndrome

HPA and HPG Axes and Neurocognitive Function

- Additionally, gonadotropins which are regulated by the HPG axis have also been associated with cognitive decline
- People with cognitive dysfunction often have a high concentration of glucocorticoids resulting in the extensive loss of neurons
- Men and women with Alzheimer's Disease, anxiety, depression and other neurocognitive issues have lower levels of testosterone and estrogen than those without NC/MH issues

- Hormones are among the major physiological regulators for brain development, therefore any dysfunction of the endocrine system is implicated in the onset/progression neurocognitive issues
- Neurocognitive disorder development involves progressive dysregulation of the HPA and HPG axes
- HPA axis dysfunction contributes to cognitive decline through reciprocal dysregulation of the HPG Axis- reductions in neuroprotective testosterone/ estrogen

HPG-Axis and Insulin Sensitivity, cont.

- Chronic activation of the HPA-Axis contributes to alterations in the HPG Axis including reductions in testosterone/estrogen
- Insulin resistance & diabetes are highly correlated with reductions in testosterone and estrogen
- The presence of functional insulin receptors in the hippocampus and cerebral cortex is necessary for cognitive functions and regulate glutaminergic and GABAergic transmission

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HPG-Axis and Insulin Sensitivity

- Any imbalance in insulin thus leads to neuronal dysfunction resulting in memory impairment
- Insulin affects HPG axis and insulin changes in diabetes and obesity can affect the HPG-Axis
- Dysregulated insulin signaling, impaired glucose uptake and insulin resistance are some of the prime factors in the onset/progression of many neurocognitive issues

- In males, testosterone increases with acute bouts of exercise with evidence of lower testosterone in endurance athletes possibly due to the restricted energy availability negatively affecting hormone levels
- In females decreased energy availability over an extended period inhibits the HPG axis, leading to menstrual irregularities and lower bone density.

Interventions

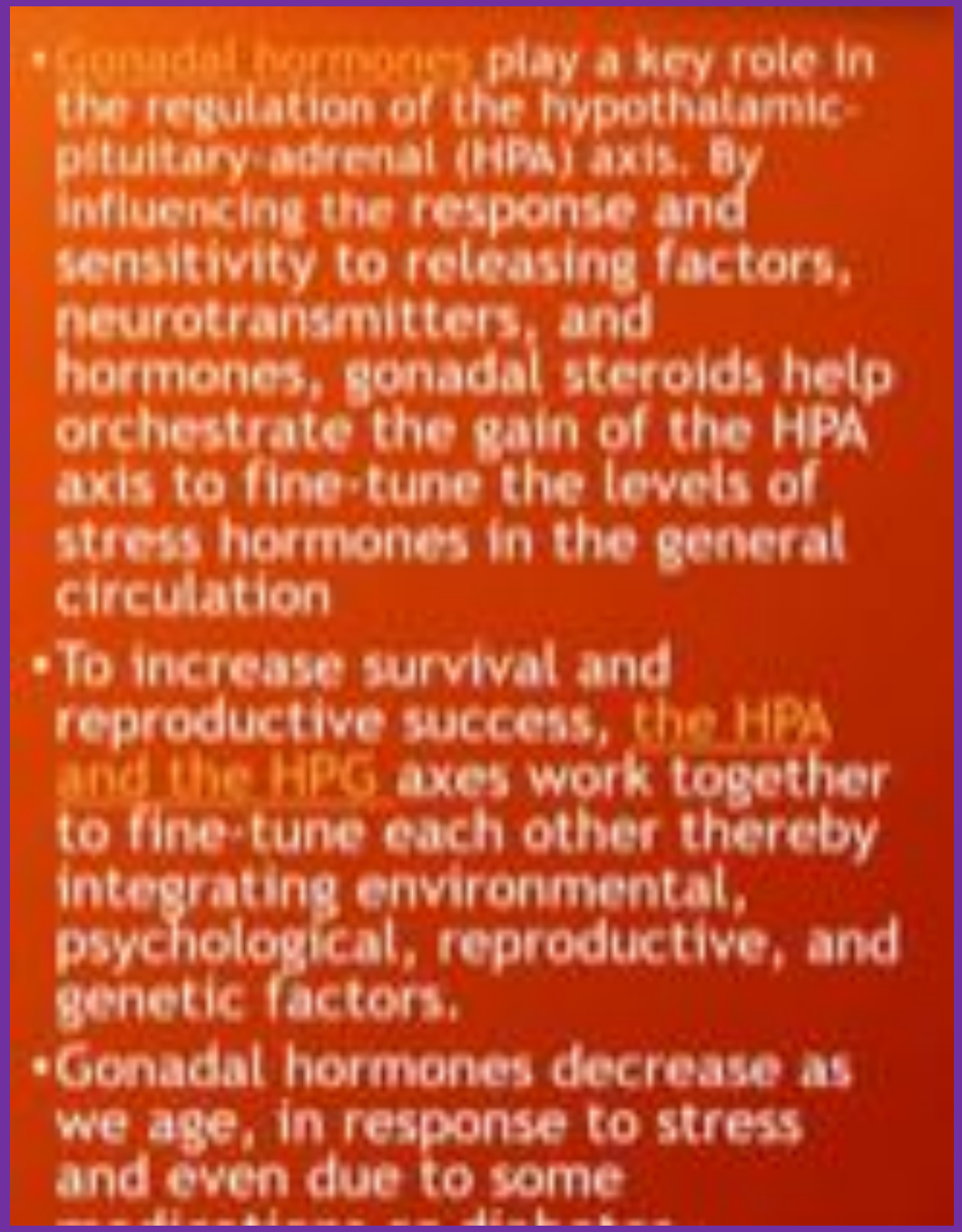
- Cognitive
  - Distress tolerance
  - Increase awareness of cognitive distortions /biases
  - Increase positive attitude and appraisals (Hardiness / Dialectics)
  - Improve problem solving
- Environmental
  - Safety (Sights, sounds, smells)
  - Aromatherapy: Bergamot, lavender, rose, rose geranium (may increase estrogen)
  - Weighted blankets or vests
  - Finances and housing

- Relational
  - Improve supportive relationships
  - Enhance interpersonal skills
  - Develop self-esteem

Interventions

- Physical
  - Sleep
  - Nutrition Improvement
  - Stimulant reduction
  - Pain
  - Hormone balance (Thyroid/gonadal)
  - Promote feelings of physical relaxation: Yoga, Tai Chi
- Affective
  - Reduce dysphoric emotions
  - Promote feelings of physical and emotional relaxation: Mindfulness, Meditation
  - Laughter

In summary


Gonadal hormones play a key role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. By influencing the response and sensitivity to releasing factors, neurotransmitters, and hormones, gonadal steroids help orchestrate the gain of the HPA axis to fine-tune the levels of stress hormones in the general circulation
To increase survival and reproductive success, the HPA and the HPG axes work together to fine-tune each other thereby integrating environmental, psychological, reproductive, and genetic factors.
Gonadal hormones decrease as we age, in response to stress and even due to some