Neurotransmitters and Hormones in the Brain

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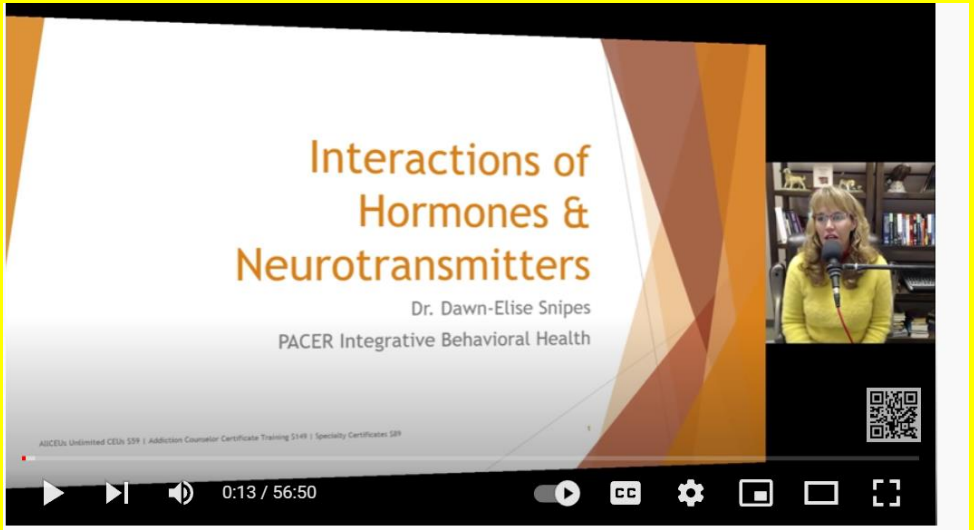
"Biology gives you a brain. Life turns it into a mind."
—Jeffrey Eugenides

Several of the following slides are adaptations of Dr. Dawn-Elise Snipes superlative lecture, *Interactions of Hormones & Neurotransmitters*.

Please click the link below to listen:
https://youtu.be/TjE8uDOI4_M



Serotonin –

Serotonin carries messages between nerve cells in the brain and throughout your body. Serotonin plays a key role in such body functions as mood, sleep, digestion, nausea, wound healing, bone health, blood clotting and sexual desire.

Serotonin is a neurotransmitter, and some also consider it a hormone.

- Serotonin is a neurotransmitter with seven families (5-HT1-5-HT7) and approximately 15 receptor subtypes.
  - Mood
  - Energy and glutamate release
  - Respiration
  - Blood pressure
  - Appetite
  - Pain perception
  - Bone density
  - Memory
  - Learning and cognition
  - Motivation and dopamine release
  - Acetylcholine, dopamine and norepinephrine release in the frontal cortex
  - GI motility

Serotonin

- Serotonin is among the many neurotransmitters that participate in the regulation of cortisol, prolactin and growth hormone secretion
  - Low dopamine → low prolactin
  - Prolactin regulates behavior, the immune system, metabolism, reproductive systems
  - Prolactin decreases estrogen and testosterone
  - Prolactin is high during times of stress

Serotonin Interactions

Purple indicates an increase and orange a decrease.

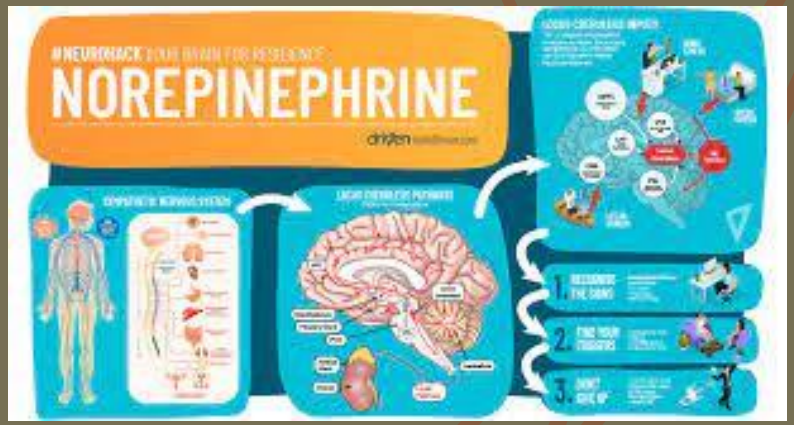
- SNAGGED-E
  - Serotonin
  - Norepinephrine*
  - Acetylcholine
  - Glutamate
  - GABA
  - Endorphins
  - Dopamine
    - In PFC Low DA and high 5HT → Aggression
    - In emotion processing areas
  - Endocannabinoids work with 5HT to modulate the HPA-Axis
- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid hormones increase 5HT responsiveness
  - Testosterone
  - DHEA
  - Oxytocin
  - Progesterone
  - Estrogen

Norepinephrine

Norepinephrine, also called noradrenaline, is both a neurotransmitter and a hormone. As a neurotransmitter, it's a chemical messenger that helps transmit nerve signals across nerve endings to another nerve cell, muscle cell or gland cell. As a hormone, it's released by your adrenal glands, which are hat-shaped glands that sit on top of each kidney.

As a neurotransmitter, norepinephrine is made from dopamine. Norepinephrine is made from nerve cells in the brainstem area of your brain and in an area near your spinal cord.

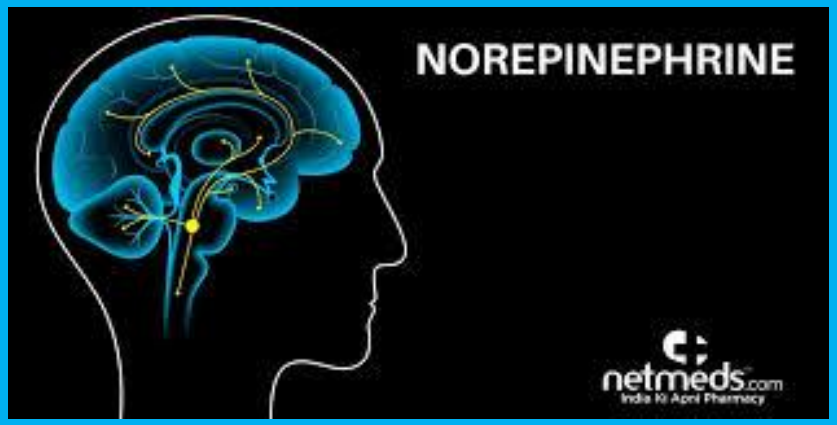
Norepinephrine is part of your sympathetic nervous system, which is part of your body's emergency response system to danger — the "fight-or-flight" response. Medically, the flight-or-flight response is known as the acute stress response.



- Produced from Phenylalanine->Tyrosine->L-dopa->Dopamine->Epinephrine->Norepinephrine
- Regulates
  - Circadian rhythms
  - Attention and focus
  - Heart rate and blood pressure regulation
  - Regulates release of glucose and fatty acids into the blood
  - Mood (too much can cause panic)
- Modulates immune response. Suppress neuroinflammation when released in the brain.
  - Up to 70% of norepinephrine projecting cells are lost in Alzheimer's Disease

Functions of Norepinephrine

- SNAGGED-E
  - Serotonin
  - ~~Norepinephrine~~
  - Acetylcholine (but AC reduces serotonin....)
  - Glutamate
  - GABA
  - Endorphins
  - Dopamine
  - Endocannabinoids
- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid
  - Testosterone
  - DHEA
  - Oxytocin
  - Progesterone which may account for depression with oral contraceptives
  - Estrogen



Norepinephrine Interactions

Purple = decrease Orange = increase

Acetylcholine

Acetylcholine has numerous functions in the body. It can be found in all motor neurons, where it stimulates muscles to contract. From the movements of the stomach and heart to the blink of an eye, all of the body's movements involve the actions of this important neurotransmitter.

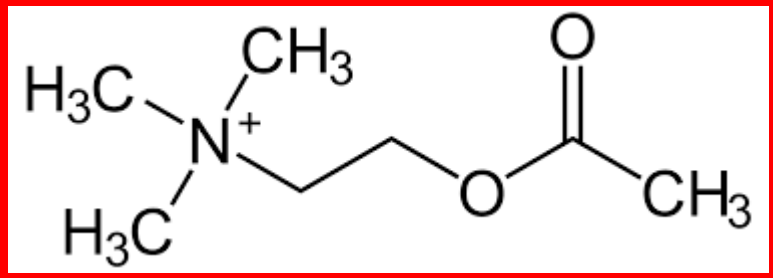
It is also found in many brain neurons and plays an important role in mental processes, such as memory and cognition.

Some cells of the body have what are known as cholinergic synapses. These synapses convert an electrical signal into acetylcholine, which then interacts with acetylcholine receptors on the other side of the synapse to trigger another electrical signal.

- Muscle control
- Arousal
- Attention
- Memory
- Motivation

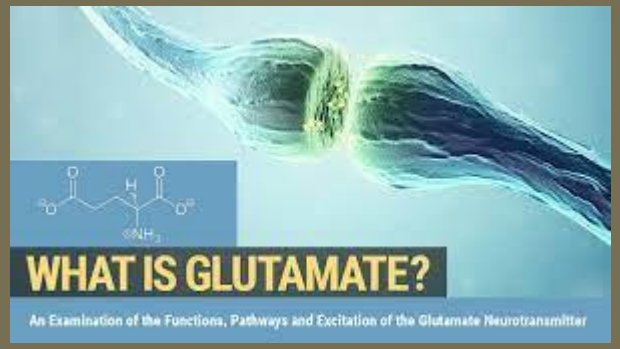
Acetylcholine

- SNAGGED-E
  - Serotonin
  - Norepinephrine
  - ~~Acetylcholine~~
  - Glutamate in the absence of glutamate or when there is glutamate resistance, ACh becomes primary excitatory NT
  - GABA
  - Endorphins
  - Dopamine
  - Endocannabinoids
- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid
  - Testosterone
  - DHEA
  - Oxytocin
  - Progesterone
  - Estrogen



Acetylcholine interactions

Purple = decrease Orange = increase



Glutamate

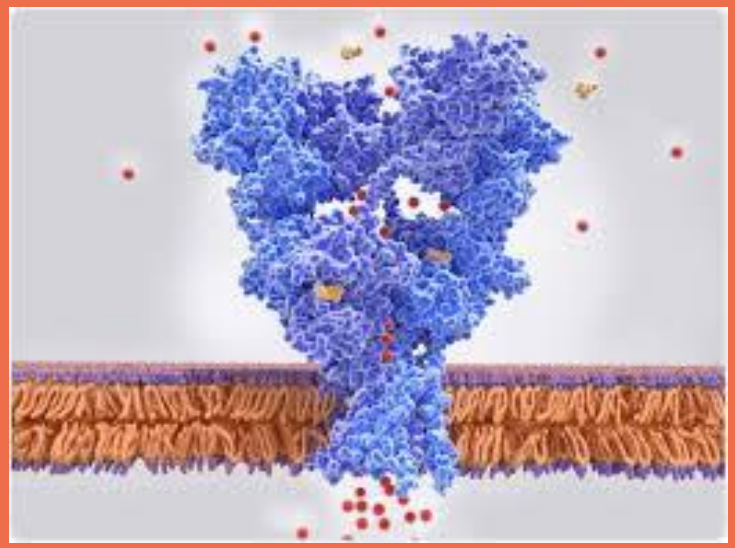
- Main excitatory neurotransmitter but can excite cells to their death "excitotoxicity"
- Testosterone was shown to significantly increase the toxicity of glutamate concentration, whereas estradiol significantly attenuated the toxicity

Glutamate is the most abundant free amino acid in the brain and is at the crossroad between multiple metabolic pathways. Considering this, it was a surprise to discover that glutamate has excitatory effects on nerve cells, and that it can excite cells to their death in a process now referred to as "excitotoxicity". This effect is due to glutamate receptors present on the surface of brain cells.

Powerful uptake systems (glutamate transporters) prevent excessive activation of these receptors by continuously removing glutamate from the extracellular fluid in the brain. Further, the blood–brain barrier shields the brain from glutamate in the blood. The highest concentrations of glutamate are found in synaptic vesicles in nerve terminals from where it can be released by exocytosis.

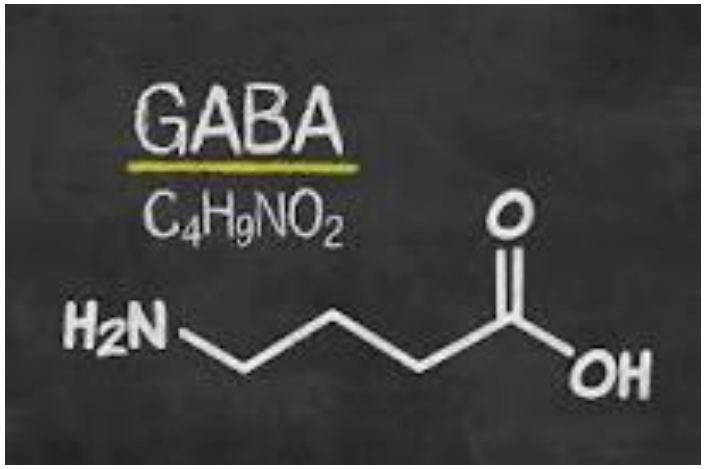
In fact, glutamate is the major excitatory neurotransmitter in the mammalian central nervous system. It took, however, a long time to realize that. The present review provides a brief historical description, gives a short overview of glutamate as a transmitter in the healthy brain, and comments on the so-called glutamate–glutamine cycle. The glutamate transporters responsible for the glutamate removal are described in some detail.

- SNAGGED-E
  - Serotonin
  - Norepinephrine
  - Acetylcholine
  - Glutamate
  - GABA
  - Endorphins
  - Dopamine
  - Endocannabinoids strive to keep glutamate activation within tolerable limits
- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid reduces glutamate levels by stimulating reuptake
  - Testosterone: Protects neurons against glutamate-induced toxicity and oxidative stress
  - DHEA: As a steroid affords some level of neuroprotection
  - Oxytocin receptors are on dopamine and glutamate neurons
  - Progesterone
  - Estrogen regulates glutamate and neurotoxic effects



Glutamate Interactions

Purple = increase Orange = decrease

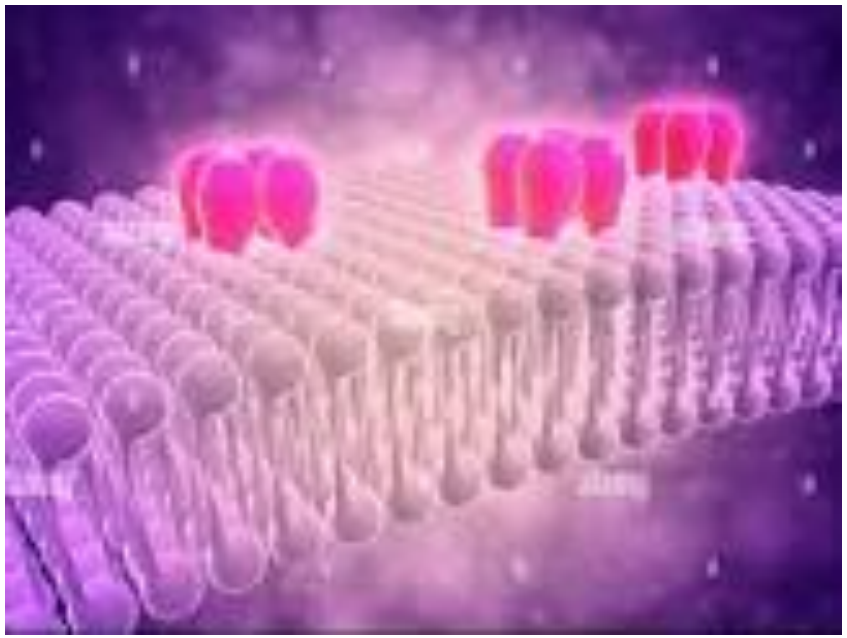


- GABA is the main inhibitory neurotransmitter in adults
- Created from glutamate
- GABA is considered the major excitatory neurotransmitter in many regions of the brain before the brain matures
- Assists in neurogeneration
- Assists in reducing anxiety and fear
- Produced at relatively high levels in the insulin-producing B-cells of the pancreas
- Suppresses inflammation
- Regulates muscle contraction

Gamma-aminobutyric acid (GABA) is a neurotransmitter, a chemical messenger in your brain. It slows down your brain by blocking specific signals in your central nervous system (your brain and spinal cord).

GABA is known for producing a calming effect. It's thought to play a major role in controlling nerve cell hyperactivity associated with anxiety, stress and fear.
Scientists also call GABA a non-protein amino acid neurotransmitter.

- SNAGGED-E
  - Serotonin
  - Norepinephrine
    - $GABA_A$ receptors increase the release of NE
    - $GABA_B$ receptors decrease NE
    - NE modulates synthesis of GABA
  - Acetylcholine
  - Glutamate
  - GABA
  - Endorphins
  - Dopamine
  - Endocannabinoids
- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid
  - Testosterone
  - DHEA
  - Oxytocin
  - Progesterone
  - Estrogen



GABA Interactions

Purple = increase Orange = decrease

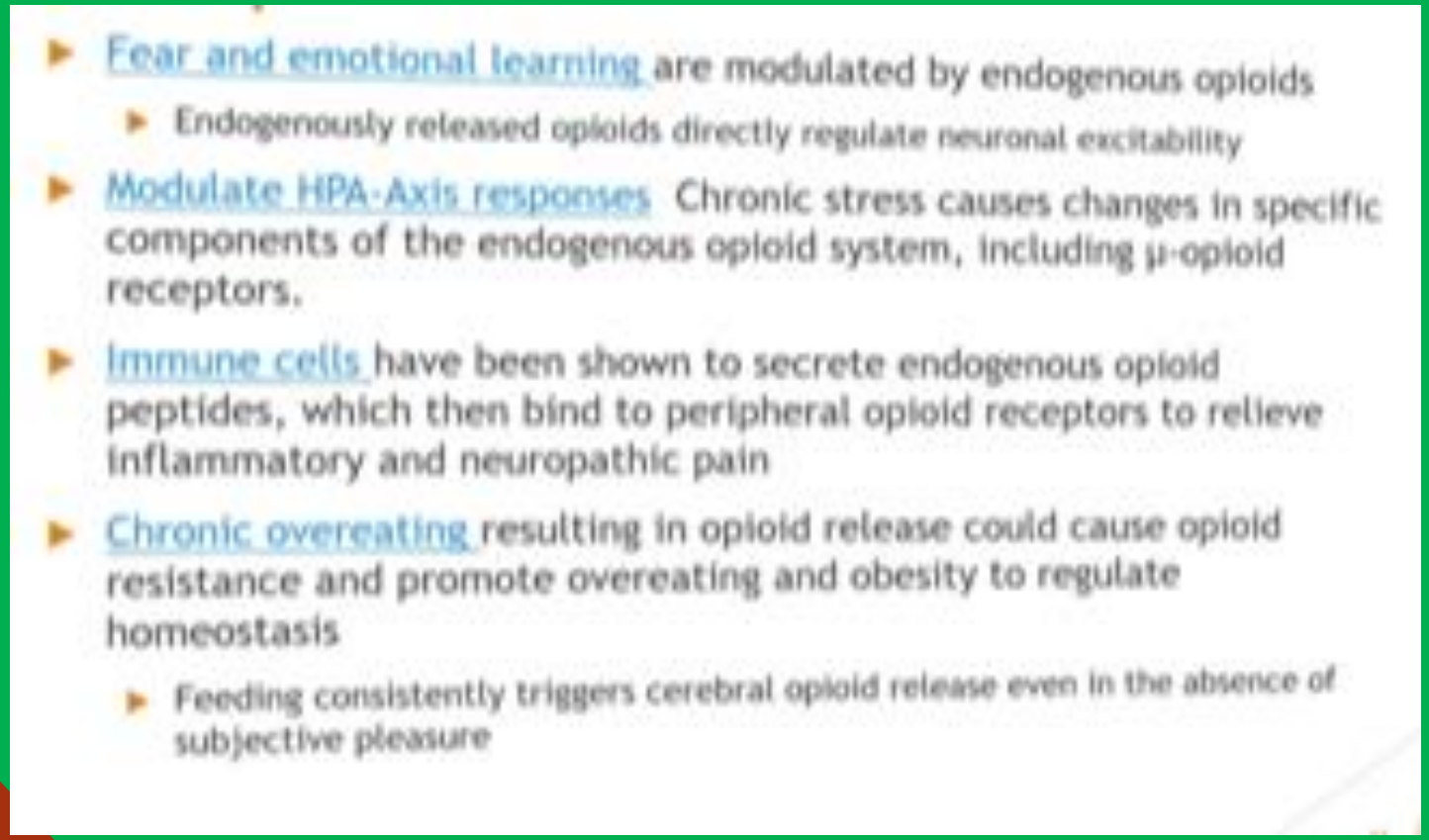
Endorphins

Endorphins, also known as endogenous opioids, are groups of protein chains called peptides. They're mostly controlled and released by the hypothalamus and pituitary gland.

They are a type of neurotransmitter — and in some cases, they are thought to be hormones, too — that act on opiate receptors to alleviate pain and promote feelings of pleasure.

Interestingly, the term endorphin comes from the words "endogenous," meaning from the body, and "morphine, an opiate pain reliever.

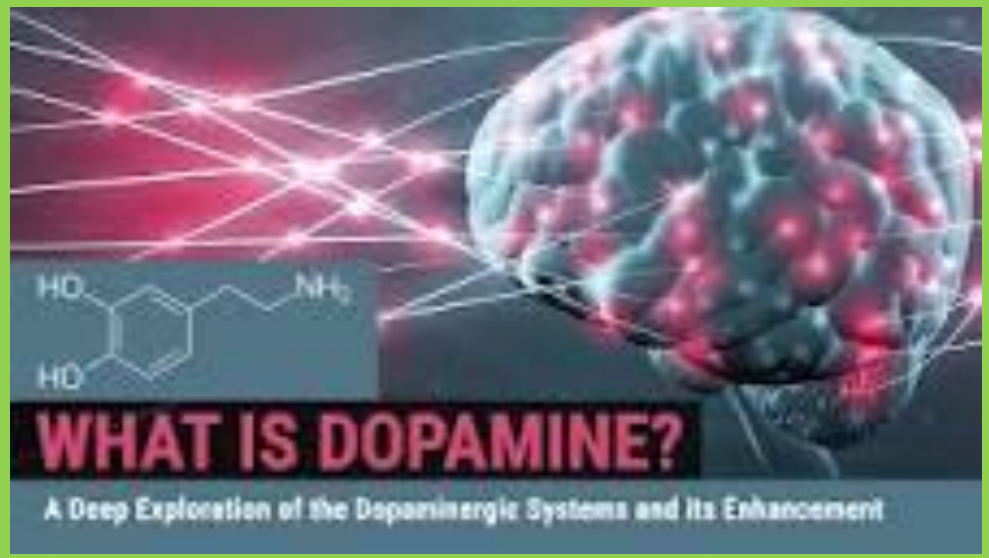
While various forms of endorphins exist, beta-endorphins are the most studied and known for their pain-relieving effects. Though they're not fully understood, they' are thought to be involved in how we perceive pain and pleasure.



Dopamine

Dopamine is a neurotransmitter made in your brain. It plays a role as a “reward center” and in many body functions, including memory, movement, motivation, mood, attention and more. High or low dopamine levels are associated with diseases including Parkinson’s disease, restless legs syndrome and attention deficit hyperactivity disorder (ADHD).

- Motivation
- Executive function
- Mood
- Movement (erectile dysfunction, restless legs, Parkinson’s disease)
- Energy and Wakefulness (people with Parkinson’s or on antipsychotics are often sleepy)
- Learning, attention & memory (prefrontal cortex)
- Regulates insulin
- Immune system
- Reduces gastrointestinal motility and protects intestinal mucosa
- Regulates the flow of information from other areas of the brain (problem solving) (Frontal lobe and thalamus)
- L-Tyrosine produces dopamine, adrenaline, thyroid hormones



Dopamine Interactions

Purple = increase Orange = decrease

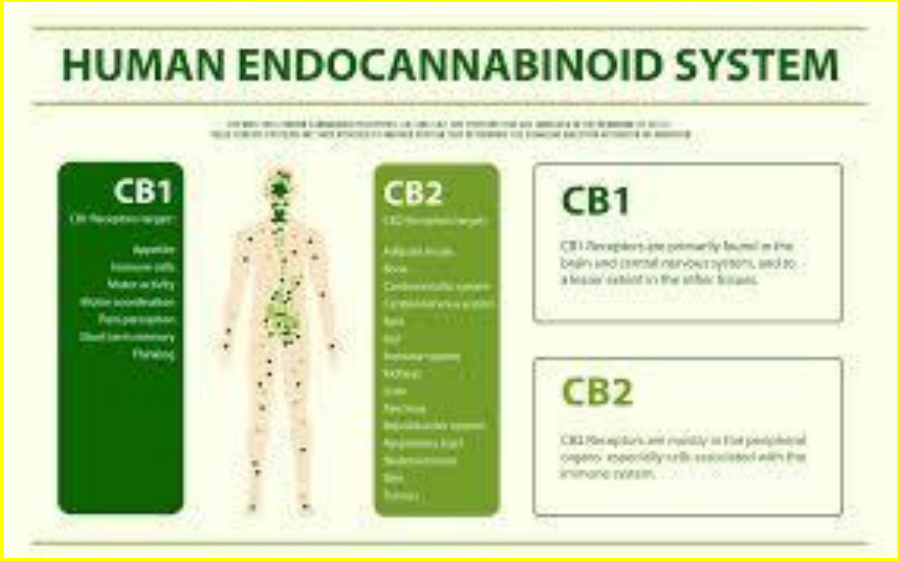
- SNAGGED-E
  - Serotonin
  - Norepinephrine
  - Acetylcholine
  - Glutamate
  - GABA
  - Endorphins
  - Dopamine
  - Endocannabinoids

- CAT T. DOPE
  - Cortisol
  - Adrenaline: Adrenaline and noradrenaline are made from dopamine
  - Thyroid hypothyroid causes dopamine receptor sensitivity
  - Testosterone
  - DHEA (low DHEA in schizophrenia)
  - Oxytocin
  - Progesterone
  - Estrogen

Endocannabinoids

The endocannabinoid system is an active and complex cell signaling network. It involves a combination of endocannabinoids, enzymes, and cannabinoid receptors that help regulate several functions in the human body.

The discovery of the ECS is relatively new. In the early, a chemist isolated the first endocannabinoid in the human brain. Since that time, researchers have been learning more about this system and the role it plays in bodily functions. ‘Endo” refers to “within,” as in within the body.



- Endocannabinoids maintain emotional, physiological and cognitive stability
  - Appetite, digestion, metabolism
  - Chronic pain Inflammation and other immune system responses
  - Mood and stress response
  - Learning and memory
  - Motor control
  - Sleep
  - Cardiovascular and reproductive system function
  - Bone remodeling and growth
  - Skin and nerve function
- CB1 receptors are mostly found in the brain and GABA, glutamate, dopamine and serotonin.
- CB2 receptors are mostly found within the immune system

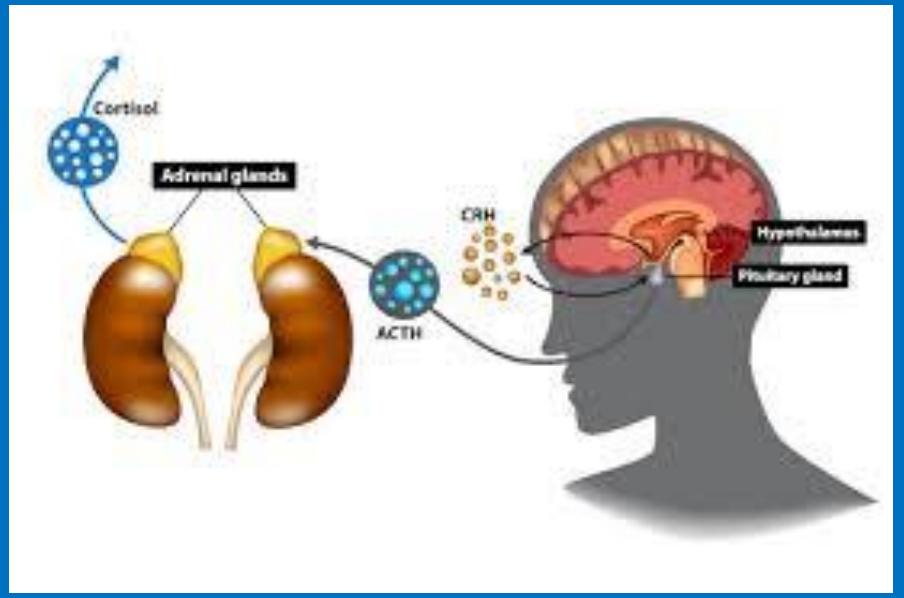
Cortisol

Cortisol is a steroid hormone that your adrenal glands, the endocrine glands on top of your kidneys, produce and release. Cortisol affects several aspects of your body and mainly helps regulate your body's response to stress.

It is a glucocorticoid hormone that your adrenal glands produce and release. Glucocorticoids are a type of steroid hormone. They suppress inflammation in all your bodily tissues and control metabolism in your muscles, fat, liver and bones. Glucocorticoids also affect sleep-wake cycles.

- SNAGGED-E
  - Serotonin
  - Norepinephrine
  - Acetylcholine
  - Glutamate
  - GABA
  - Endorphins
  - Dopamine
  - Endocannabinoids modulate HPA-Axis

- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid Chronic elevation of cortisol and Thyroid Stimulating Hormone can result in reduced availability of thyroid hormones.
  - Testosterone
  - DHEA
  - Oxytocin (love and protect)
  - Progesterone is the precursor to cortisol and is released in response to stress. Low progesterone can cause low cortisol.
  - Estrogen is suppressed in response to cortisol in a healthy HPA/HPG axis. Under chronic stress and reduced levels of cortisol and progesterone, estrogen becomes dominant.



Cortisol Interactions

Purple = increase Orange = decrease

The endocannabinoid system

Named for the plant that led to its discovery—is one of the most important physiologic systems involved in establishing and maintaining human health. Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells.

With its complex actions in our immune system, nervous system, and virtually all of the body's organs, the endocannabinoids are literally a bridge between body and mind. By understanding this system, we begin to see a mechanism that could connect brain activity and states of physical health and disease.

It plays a critical role in maintaining the homeostasis of the human body, which encompasses the brain, endocrine, and immune system, to name a few. ECS is a unique system in multiple dimensions. To begin with, it is a retrograde system functioning post- to pre-synapse, allowing it to be a "master regulator" in the body.

- SNAGGED-E
  - Serotonin
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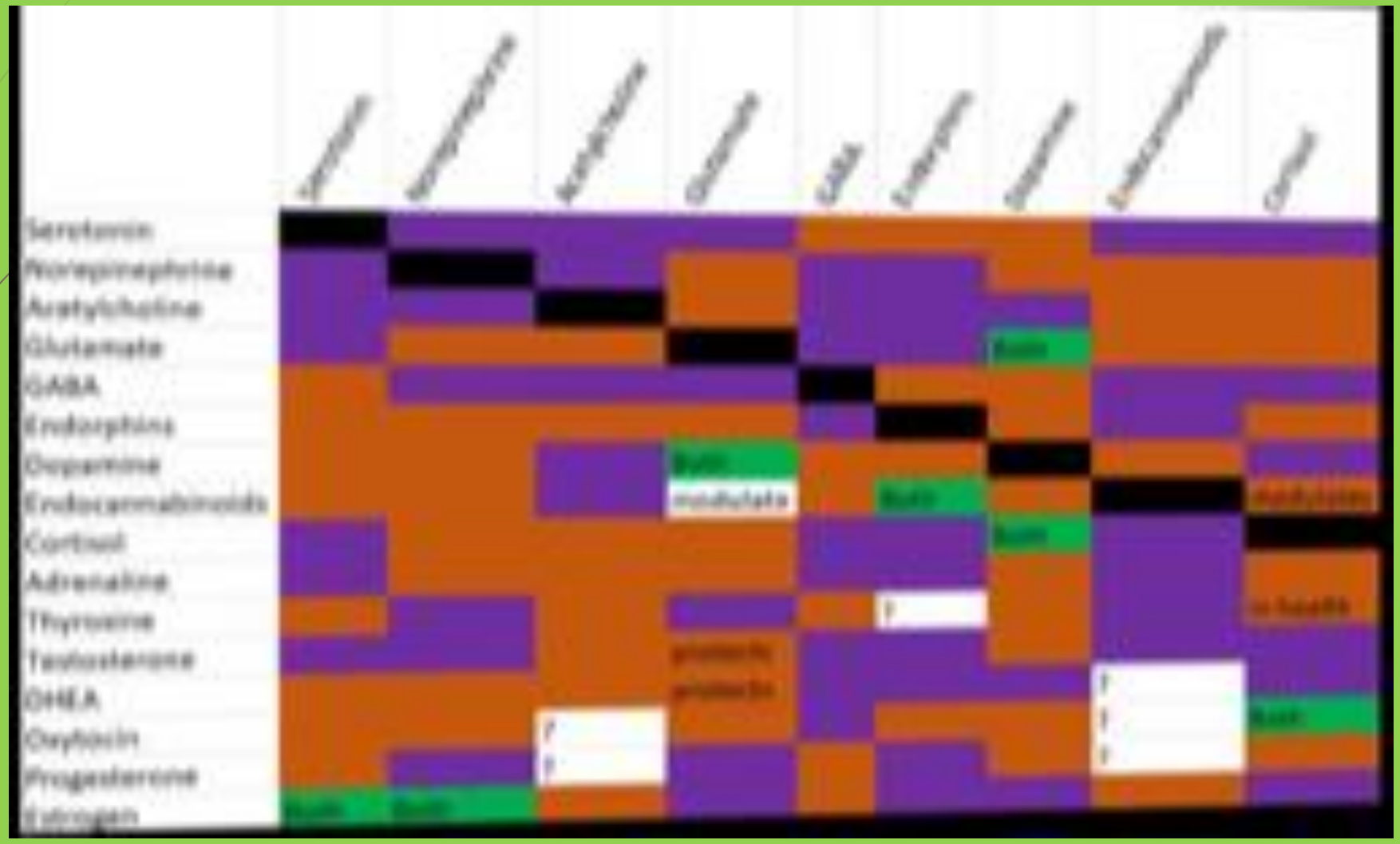
  - Dopamine
  - Endocannabinoids
- CAT T. DOPE
  - Cortisol
  - Adrenaline
  - Thyroid
  - Testosterone
  - DHEA
  - Oxytocin
  - Progesterone
  - Estrogen

Endocannabinoid Interactions

Purple = increase Orange = decrease

This chart compiled by Dr. Snipes nicely shows a summary of the interactions discussed previously

Purple = increase Orange = decrease



In summary

- Neurotransmitters and hormones exist in a very delicate balance.
- Changing one often results in a cascade of other changes
- Mood and cognitive symptoms may be caused by problems with a variety of different neurotransmitters or hormones
- Aging naturally reduces certain hormones and consequently neurotransmitters
- Differential diagnoses requires exploring the possibility of a deficit in a neurotransmitter or hormone due to
  - Insufficient raw materials to make it
  - Deficiency in other chemicals that trigger its release
  - Excess of chemicals that degrade it or trigger reuptake
  - Problems in neuronal signaling within the system.