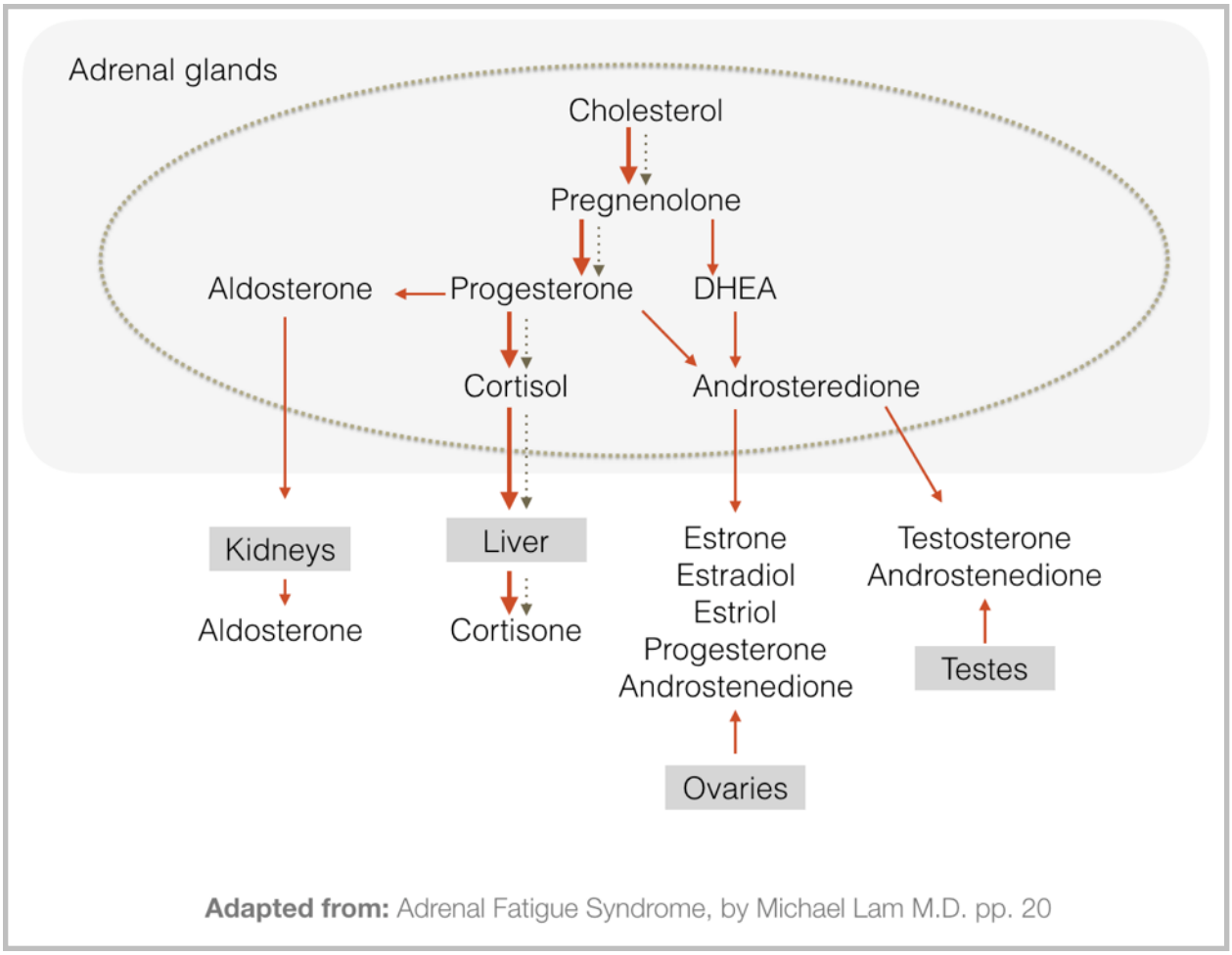
HPA-D: HPA Basic Physiology - Part 2

The hypothalamus is the major control tower of all hormone production in the body and the governor of the stress response. Two hypothalamic nuclei with the biggest influence on the stress response system are the paraventricular nucleus, PVN, and the superchiasmatic nucleus, or SCN. The PVN releases corticotropin-releasing hormone and argenine vasopressin. The superchiasmatic nucleus, or SCN, is the main controller of the circadian clock. The circadian clock regulates a wide range of genes that implement things like insulin sensitivity, immune function, antioxidant activity, and pain sensitivity, just to name a few. The SCN controls circadian secretion of cortisol in two ways: by activating the HPA axis release of corticotropin-releasing hormone and by regulating the sensitivity of the adrenals to ACTH. The SCN is affected by light exposure and the 24-hour light–dark cycle. However, the saving grace is that the superchiasmatic nucleus is one of the few tissues in the entire body that doesn't have glucocorticoid receptors and isn't affected by cortisol. If it did have those receptors and the HPA axis was disrupted, then it couldn't be retrained by light exposure. This connection between light, the superchiasmatic nucleus, and circadian disruption is the mechanism that explains why exposure to artificial light at night and bright light in the morning can have such a profound impact on our health via the production of ACTH and cortisol, and why counseling patients on regulating their exposure to light must always be part of an HPA axis treatment.

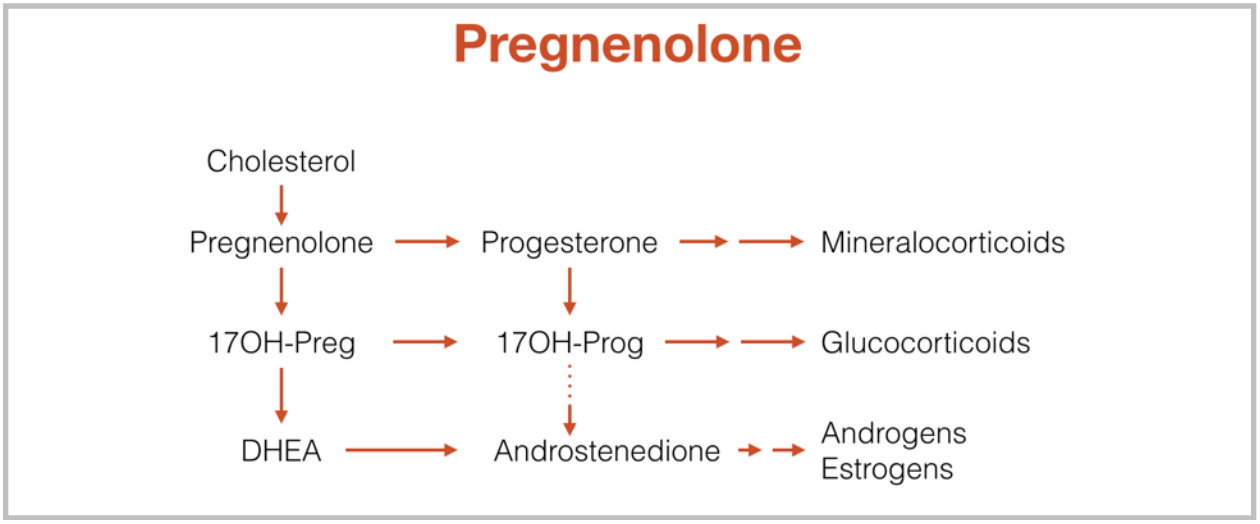
As a side note, it was recently discovered that CRH is also produced outside of the hypothalamus in other areas of the brain, but also in other tissues like the gut and the skin. This led researchers to speculate that the gut and the skin have their own mini-HPA axis, and it goes a long way toward explaining the gut–brain–skin connection that I've written and spoken so often about. So you will often see, as a clinician, patients with this triad of conditions. You'll see someone come in, for example, and they've got acne or psoriasis or eczema; they've got IBS, bloating, digestive type of symptoms; and they've got brain fog or mood issues, or anxiety or something like that. You'll see that triad of symptoms very regularly, and whenever you see that group, you should immediately be thinking of the HPA axis because of the relationship between CRH and all of these other tissues.



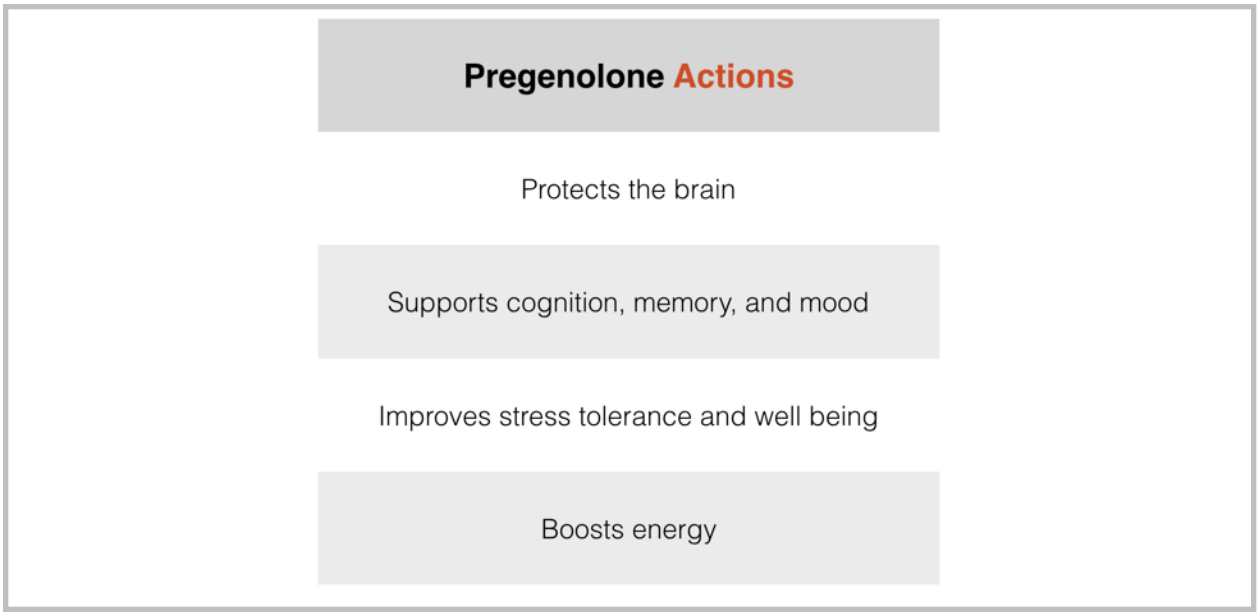
The adrenal glands produce steroid hormones as part of the stress response. A steroid is a chemical with a four-carbon ring structure attached to each other. Cortisol, DHEA, testosterone, progesterone, and estrogen are all steroid hormones with molecular structures similar to each other. The adrenals also produce DHEA and pregnenolone, which are known as pro-hormones. They function as hormones themselves, but they also act as precursors to downstream hormones like cortisol and testosterone, as you can see here on the diagram on the slide. In general, the upstream pro-hormones like pregnenolone and DHEA are gentler in their effect, whereas the downstream hormones like cortisol and testosterone are more potent. So if you need to kind of brush up on hormone physiology, we're going to talk more about it later, but you could pause the video and take a look at this slide.

Adrenal medulla	Adrenal cortex
Epinephrine	Glucocorticoids
	Mineralcorticoids
	Androgens

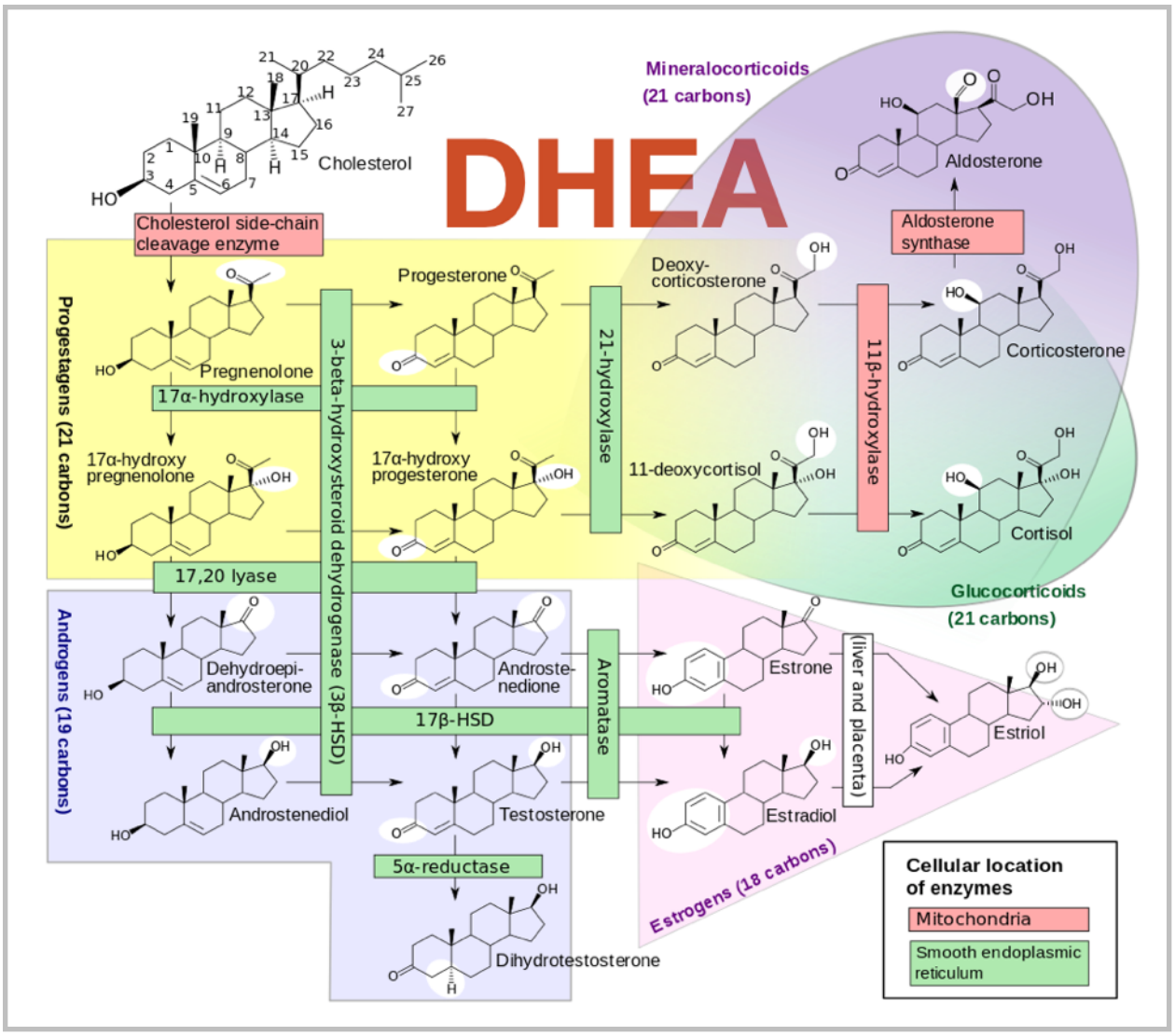
The adrenal glands have two compartments, the adrenal medulla, which secretes epinephrine and is responsible for the fight-or-flight response, and then the adrenal cortex, which comprises 80 percent, the majority of the adrenal gland, and it produces glucocorticoids like cortisol, mineralocorticoids like aldosterone, and androgens like DHEA. The adrenal cortex also produces some sex hormones, but in limited amounts, although in women who have entered menopause, it shares the primary burden of sex hormone production. So let's talk about the adrenal steroid hormones in a little bit more detail.



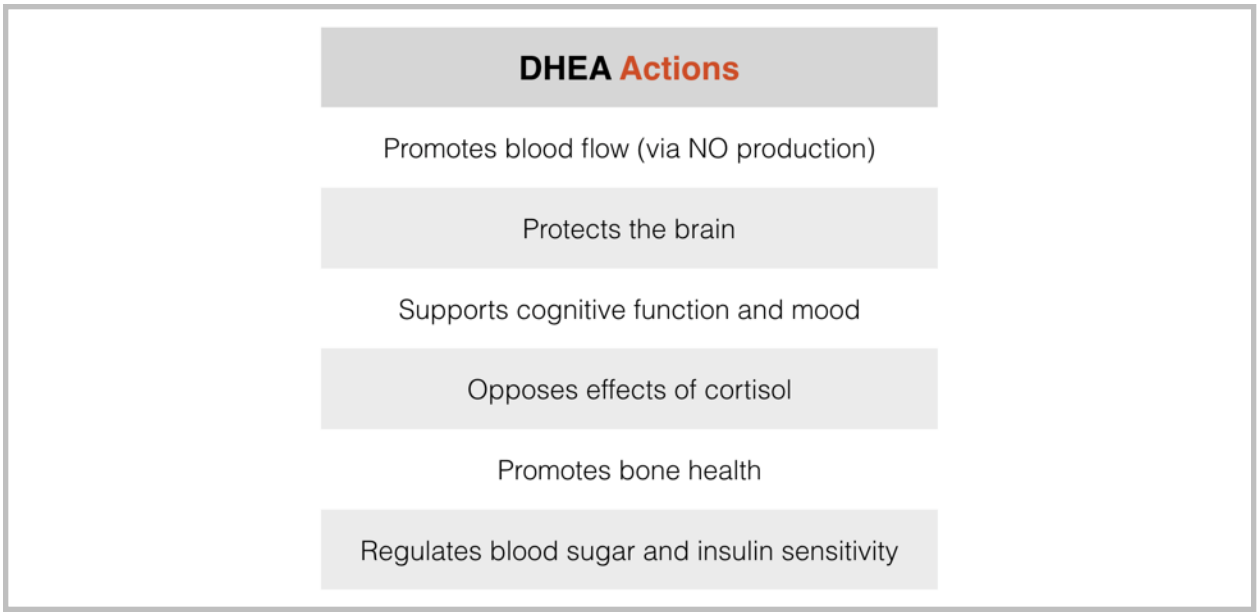
Pregnenolone is a pro-hormone made from cholesterol. It is produced both in the adrenals and the central nervous system, the brain and the spinal cord. It's a precursor of the progesterones, mineralocorticoids, glucocorticoids, androgens, and estrogens, as well as the neuroactive steroids. Pregnenolone is biologically active in its own right, though, and it acts primarily as a neurosteroid, according to the most recent research. A neurosteroid is something synthesized in the brain or by an adrenal gland that can then reach the brain through the bloodstream and then have effects on brain functions.



As a neurosteroid, pregnenolone may promote neurogenesis, which is the production of new nerve cells, neuronal survival, myelination, which is the insulation that protects the nerve fibers in the CNS and the brain, increased memory, and reduced neurotoxicity. Pregnenolone and other neuroactive steroids can protect the brain cells against the long-term damage that can lead to things like Alzheimer's disease and other forms of dementia. Pregnenolone naturally declines with age, and it, along with DHEA, has been proposed as a marker for age-related cognitive decline. Studies on pregnenolone go back to the 1940s, and it's been shown to boost energy, elevate mood, improve memory and cognitive performance, and improve stress tolerance and overall well-being. However, when we're talking about supplementing with pregnenolone, which we'll discuss more later in the unit, it is a hormone of course, it can be quite potent and it can be tricky to work with, so we'll come back to that in the treatment section.



DHEA stands for dehydroepiandrosterone, and it's considered the daughter of pregnenolone. It's a precursor to testosterone, estrogen, and other corticosteroids. It's a weak androgenic hormone produced in the adrenal glands, but also in the brain and central nervous system. It's a neurosteroid just like pregnenolone is. It has many of the same effects as pregnenolone, but it's more potent. It plays a fundamental role in the maintenance of hormonal balance and vitality, which is why some have referred to it as an anti-aging hormone, and why it's been proposed along with pregnenolone as a marker for aging.



DHEA is converted into DHEA sulfate in the blood and then back to DHEA when it's taken up by the tissues. The levels of DHEA sulfate are typically much higher than DHEA, so that is often the form that is tested. Up until the year 2000, DHEA was mainly studied in its role as a precursor to androgens and estrogens, but now we understand that DHEA has direct effects itself. For example, it promotes the production of nitric oxide by activating endothelial nitric oxide synthase in the epithelium of the blood vessels, which could explain its cardiovascular benefits. Nitric oxide is a powerful regulator of blood flow. DHEA has a neuroprotective effect; it counters the potentially harmful effect of glucocorticoids like cortisol in the brain, which explains its role in regulating cognitive function and mood. DHEA promotes bone health by regulating osteoblast activity and suppressing osteoclast-mediated bone breakdown. It promotes insulin sensitivity and regulates blood sugar; it enhances immunity, whereas cortisol suppresses it; it protects against stress-induced immune dysfunction; it's an antioxidant and an anti-inflammatory agent in the skin; and that's just a short list of its functions. It has many more.

By age 80, levels of DHEA typically fall by as much as 80 to 90 percent compared to what they were during young adulthood. All of these functions explain why reduced levels of DHEA are linked with the pathophysiology underlying numerous age-associated disease states like cognitive decline, cardiovascular disease, bone loss, cancer, depression, sexual dysfunction, and various inflammatory disorders. DHEA is frequently used as a supplement and can be used effectively, but as with pregnenolone, you have to be cautious and be aware of certain things, which we'll talk about later. Note that the conversion of DHEA to androgens and estrogens varies considerably among individuals depending on age and gender, and supplementing with DHEA alone to replace androgens and estrogens is not really reliable for this reason.