

HEALTHY AGING

Pregnenolone and Memory

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The anti-inflammatory neurotransmitter-hormone that both stimulates and relaxes the brain

My great aunt Mila loves sewing almost as much as she loves animal prints. She once gave me a leopard print headband and matching purse, made of the same cloth from which she'd fashioned for herself a blouse, an apron, and dinner napkins. From a single roll of feline-inspired fabric, she'd created (much to her husband's chagrin) countless creations.

Much like that roll of fabric from which various articles were cut and created, pregnenolone is the raw material from which a myriad of other hormones are made. Its applications in the body are vast and versatile,[1],[2],[3] especially with respect to mood, memory, and cognitive function.

Of the many biochemical reactions in the body that help produce hormones like dehydroepiandrosterone (DHEA), testosterone, progesterone, estrogen, and cortisol, all share the same first step: the conversion of cholesterol to pregnenolone. This is why pregnenolone is sometimes referred to as "the mother hormone." [4] (This is also why it is important to have some cholesterol in the diet, to ensure proper hormone production.)

Pregnenolone, the anti-inflammatory neurotransmitter-hormone

Unlike most hormones, which are secreted by the various glands of the endocrine system (such as the ovaries, testes, thyroid, or adrenal glands), pregnenolone is produced by specialized cells in the brain *and* in the glands. Specifically, pregnenolone is made in the gonads (the ovaries in women; the testes in men) and in the adrenal glands. [5] Walking the line between neurotransmitter and hormone, pregnenolone is known as a neurohormone, or neurosteroid. [6]

Pregnenolone and its derivatives have also been shown to enhance learning and memory, reduce dementia risk, relieve depression, alleviate anxiety, enhance locomotor activity (the ability to move physically), and promote the growth and survival of brain cells. [7] Pregnenolone thus carries great potential with respect to both preventing and treating neurological conditions.

“ Lower levels of pregnenolone have been noted in neuroinflammatory diseases like depression, multiple sclerosis (MS), Parkinson’s disease, Alzheimer’s disease, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease), and may thus play a role in both preventing and managing these conditions.

In addition to serving as a precursor to other steroid hormones, pregnenolone also has anti-inflammatory effects and has been shown to help balance the immune system in a variety of inflammatory conditions. [8] Lower levels of pregnenolone have been noted in neuroinflammatory diseases like depression, multiple sclerosis (MS), Parkinson’s disease, Alzheimer’s disease, and amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease), [9], [10] and may thus play a role in both preventing and managing these conditions. [11]

Pregnenolone and the aging brain

Considering that pregnenolone is the precursor to other vital neurohormones [12] insufficient levels of the neurohormone can leave the brain (and body) more vulnerable to a host of ailments. [13] Pregnenolone levels unfortunately decline with age, subsequently dragging down the body’s production of other hormones and neurohormones in the process. [14] This can have detrimental effects on memory, mood, and cognitive function and can increase the risk of various neurodegenerative and neuroinflammatory diseases like Parkinson’s and Alzheimer’s diseases. [15] (More on Alzheimer’s disease below.)

In humans, a cross-sectional study of older individuals found that the higher the neurosteroid levels a person has, the better their cognitive function – especially in males. [16] Regardless of age, individuals with

suboptimal pregnenolone levels have also been found to be at increased risk of mood issues, memory deficits, neurodegenerative conditions, and even mental illness.[17]

There is evidence, thankfully, that the normalization of neurosteroid levels in the brain may stimulate neurogenesis (the creation of new brain cells), improve the longevity of brain cells and make them more resistant to toxicity, increase memory, and even support the growth of myelin (the substance that protects the nerves and expedites their signals).[18]

Brain energy without the jitters

Memory formation is largely caused by the stimulation of nerve cells, and that stimulation mainly occurs when an excitatory chemical known as glutamate binds to a channel in the brain known as the N-methyl-D-aspartate (NMDA) receptor.[19],[20]

Although glutamate plays a key role in memory and learning, too much of the neurotransmitter can be overly stimulating and eventually toxic to neurons (brain cells). This can excessively excite the brain into activated, agitated states, such as those seen in ADD/ADHD,[21] addiction[22], anxiety,[23] and sleep disturbances. [24] (This response can also be triggered by the glutamate found in the food additive monosodium glutamate, or MSG.[25]) Alterations of the NMDA receptor may even be associated with the pathophysiology of schizophrenia.[26] But what is to be done, if the same molecule that signals memory and learning can also irritate the nervous system?

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Pregnenolone offers a novel approach to supporting memory by triggering NMDA channels *without* the use of glutamate.[27],[28],[29] This means pregnenolone may stimulate the brain while also protecting it, [30] in turn supporting not only memory and learning, but also potentially staving off a host of neurodegenerative diseases.[31]

Pregnenolone for anxiety

Whereas glutamate is the primary excitatory neurotransmitter in the brain, GABA is the main inhibitory neurotransmitter; the two oppose one another. Although pregnenolone stimulates brain activity by acting

directly upon excitatory NMDA receptors, recall that it's also a precursor to *other* neurohormones. One such neurohormone derived from pregnenolone is allopregnanolone, which binds to gamma amino-butyric acid subunit A (GABA_A) receptors, thereby exerting an *inhibitory*, or calming, effect on the nervous system. [32]

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Many natural and pharmaceutical therapies marketed to those with anxiety, high stress levels, addictive cravings, and poor sleep quality work by stimulating GABA receptors.[33],[34] Some of these medicines, however, can quickly become addictive, as is the case with a class of anti-anxiety drugs known as benzodiazepines. These GABA-targeting drugs can also come with unpleasant side effects like sedation and memory impairment. Pregnenolone, however, may offer anxiety sufferers a gentler, less addictive, non-sedating alternative to benzodiazepines and may even be used in conjunction with benzodiazepines to dampen their side effects. In fact, one study found that patients suffering from anxiety experienced fewer side effects from benzodiazepines if they concurrently took a daily pregnenolone supplement.[35]

Pregnenolone for Alzheimer's disease

In addition to the effects described above, pregnenolone may also offer significant protection against Alzheimer's disease (AD).

As compared with healthy controls, patients with AD have been observed to have lower levels of pregnenolone and the pregnenolone-derived neurohormones allopregnanolone and DHEA-sulfate (DHEAS) in the main memory-related areas of the brain.[36] The brains of individuals with the highest neurosteroid levels were found in another study to have the lowest number of amyloid-beta proteins, the type of proteins characteristic of AD.[37] In another study, furthermore, the introduction of amyloid-beta protein into the brains of animals resulted in a dramatic drop in the levels of progesterone, another important neurohormone derived from pregnenolone.[38]

A significant correlation between pregnenolone sulfate and cognitive performance has also been established in animal models: rats with memory impairments tend to have much lower concentrations of the neurohormone as compared to rats with normal memory. Furthermore, it's also been shown that

introducing pregnenolone sulfate into the brains of these animals can *reverse* memory deficits – a rather compelling finding.[39]

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The inverse relationship between Alzheimer’s disease and neurosteroid levels is clear – so clear that some researchers have suggested using neurosteroid testing as a screening tool to help catch AD sooner and differentiate it from other forms of dementia.[40]

Pregnenolone for cognitive function and memory

Rat studies have illuminated some of the mechanisms by which pregnenolone can help reverse cognitive deficits. In addition to the above-noted mechanism of stimulating NMDA receptors without the use of glutamate, pregnenolone also appears to stimulate the release of the neurotransmitter acetylcholine (ACh) in various regions of the brain.[41] This is relevant to human health, as it’s been noted that individuals with AD tend to have lower levels of ACh than those without the disease.[42]

ACh is an important neurotransmitter, supporting not only memory, but also the sleep-wake cycle. In fact, infusions of pregnenolone in rat models has been shown to dramatically increase rapid eye movement (REM) sleep (also known as “paradoxical sleep”). REM is the most restful phase of slumber, and there is no shortage of studies demonstrating the correlation between REM sleep and memory consolidation.[43]

Pregnenolone infusions in animal models have also been shown to increase neurogenesis (the growth of new nervous system cells) in the hippocampus, a part of the brain largely important for emotional regulation and memory formation.[44] In humans, supplementation with pregnenolone sulfate was likewise shown to improve cognitive function in patients with schizophrenia who were on phencyclidine, an antipsychotic drug with a known side effect of cognitive impairment.[45]

In conclusion

Considering all of this evidence, researchers have concluded that pregnenolone may not only prevent cognitive decline by stimulating the growth of new brain cells, but also enhance cognitive function by increasing ACh levels, and support the type of sleep important for memory-consolidation.[46],[47]

Taking all of this into consideration, it seems that supplementation with pregnenolone can offer our minds, moods, and memories a significant boost. Choosing forms prepared in a lipid matrix can help bypass the liver and deliver the pregnenolone directly into the circulation, while micronization may prolong its availability in the bloodstream and tissues,[48] supporting optimal bioavailability of this versatile, important neurohormone. (No leopard print required.)

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[Dr. Erica Zelfand](#)

<http://www.drzelfand.com>



Dr. Erica Zelfand is a family physician, medical writer, and teacher. She is deeply committed to a patient-centered, root-cause-oriented, nature-honoring approach to healing. After graduating from medical school with high honors, Dr. Zelfand completed a family practice residency at the National University of Natural Medicine (NUNM), followed by an additional four years of post-doctoral training in pediatrics. As an engaging presenter, Dr. Zelfand enjoys being adjunct faculty at her alma mater and appearing on numerous podcasts and health summits.

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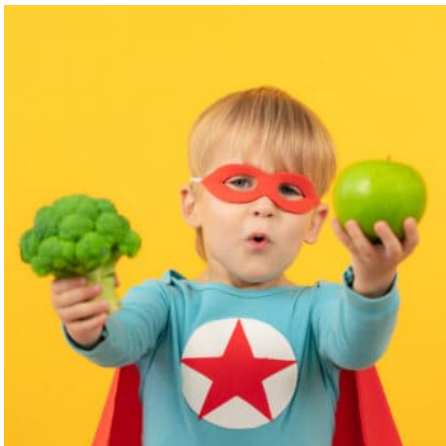
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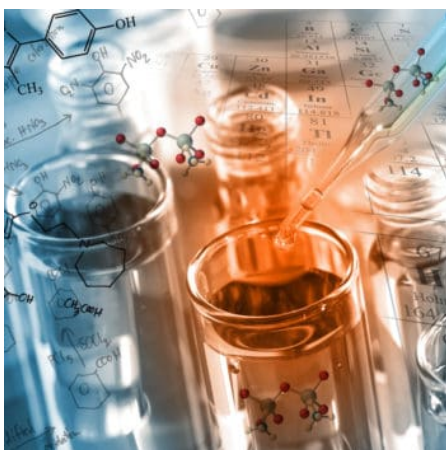
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