

LE Magazine June 2004

## REPORT

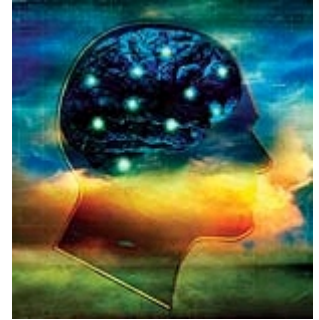
### Recharge With Pregnenolone

This little-known hormone fights fatigue, boosts memory, and more.

By Dave Tuttle

*One of the most frustrating aspects of aging is memory loss. Whether as benign as forgetting where you left the car keys or as debilitating as Alzheimer's disease, this reduction in mental function challenges us and makes us long for the mental vigor of our youth.*

*Traditionally, scientists have thought that little could be done about deteriorating brain function. New research has shown, however, that this kind of mental decline is not inevitable. Scientists have found that a naturally occurring hormone called pregnenolone not only improves memory and concentration, but also fights fatigue, relieves arthritis, speeds injury recovery, and enhances mood.*



### An Essential Hormone

Testosterone, estrogen, cortisol, DHEA, and pregnenolone are members of a family of natural hormones that are essential for human survival. All of these hormones contain four carbon-ring structures attached to each other, and appear very similar.<sup>1</sup> Small differences in structure, however, produce dramatic changes in function. Testosterone, the “male” hormone, is only slightly different chemically from estrogen, the “female” hormone. Yet this minor dissimilarity causes men to grow facial hair and women to develop breasts.

Another thing these hormones have in common is that they are made from cholesterol. While often vilified, cholesterol is an indispensable raw material that the body uses for several essential biological reactions. It is required for the production of vitamin D, the absorption of calcium, and the production of bile. Cholesterol also is needed to make myelin, the fatty coating that surrounds the nerves in the brain and spinal cord.

Each of the body's cells contains mitochondria. Primarily involved with energy production, these organelles also contain an enzyme that breaks off a few side chains from the cholesterol molecule to turn it into pregnenolone. This enzyme is more active in some tissues and organs than in others, and as a result some parts of the body produce more pregnenolone than others. The primary sources of this hormone are the adrenal glands, liver, and gonads (testicles and ovaries). Scientists have discovered that pregnenolone also can be manufactured in the brain from cholesterol instead of being transported through the blood-brain barrier from other parts of the body. This supports recent findings showing that pregnenolone is involved in a variety of brain-related functions such as memory, concentration, and mood.



Pregnenolone also can be converted into the other hormones, which is why it is sometimes referred to as the mother of those hormones. Hormones released by the pituitary gland regulate these conversions. The body can change pregnenolone into DHEA or progesterone, depending on its needs at a given moment. In turn, both of these hormones can be chemically manipulated to produce androstenedione, the direct precursor to the sex hormones, which include testosterone and other androgens as well as estradiol and the other estrogens. The progesterone molecule also can be altered to make cortisol (the so-called “stress hormone”) and aldosterone (involved in blood pressure regulation). None of this would be possible if the body did not contain pregnenolone.

Clearly, pregnenolone is an essential hormone in people of all ages. The average young adult produces about 14 mg per day. As with other hormones, however, pregnenolone production declines with age. At age 75, the body produces about 60% less pregnenolone than it did at age 35.<sup>2</sup> As the body's supply of pregnenolone diminishes, so does the availability of its other related hormones. This has led scientists to consider pregnenolone supplementation as a way to turn back the clock on aging and counter the consequences of this dramatic drop in hormone levels.



### Less Fatigue, More Endurance

Because pregnenolone concentrations in the brain are much higher than those found in blood plasma,<sup>3</sup> it is not surprising that this hormone has a number of mental benefits. Several classic studies have found that oral administration of pregnenolone reduces fatigue while providing more endurance.<sup>4</sup> In one experiment, five college students trained at a constant pace on a machine that produced exhaustion. At different times, they were given oral pregnenolone, an oral adrenal cortical hormone, or injected progesterone. Only the pregnenolone had a significant influence on their scores during a three-hour run.

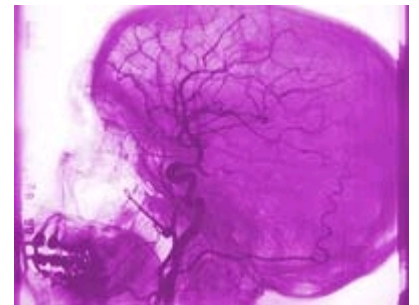
A study of aviators found that pregnenolone improved their functioning and perception of their work. Fourteen subjects took 50 mg of pregnenolone daily and performed tests with an automatic scoring device that operated like the joystick for a video game. Researchers found that the improvements the aviators experienced during the two weeks of administration had a cumulative effect that continued for several days afterward.

In another experiment, 25-75 mg of pregnenolone were given daily to 8 leather cutters, 12 lathe operators, and 77 optical workers. While there was little benefit compared to placebo when the workers were not “under pressure,” productivity rose when the level of work-related stress was higher. Once again, the effect outlasted the length of the study. The subjects also felt that they tired less easily and were better able to cope with the demands of their jobs. No side effects were reported in any of these studies.

### Potent Memory Enhancer

When older people are asked about the negative consequences of aging, memory loss is usually at the top of their list. The inability to recall a lifetime’s most memorable moments (or even where you left an important document) is frustrating at best and debilitating at worst. Several factors are responsible for this decline in memory.<sup>5</sup> As we age, the functioning of the brain’s neurotransmission system deteriorates. This leads to negative changes in the release of a key neurotransmitter known as acetylcholine, ranging from a minor decline to severe alterations (as in the case of Alzheimer’s disease). The creation of brain cells also is diminished, at least in the hippocampus. Scientists have found that pregnenolone effectively combats both these factors.

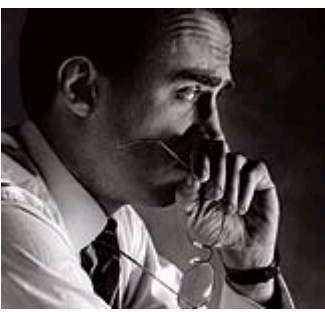
Pregnenolone and its sulfated form, pregnenolone sulfate, are able to work their magic on memory and mental function in surprisingly small doses. This is because they work simultaneously on two receptor complexes. Pregnenolone sulfate is able to reduce the activity of a receptor complex known as GABA<sub>A</sub>. GABA is a neurotransmitter that literally cools the brain, protecting the nerve cells from burning out from all their activity.<sup>6</sup> Too much GABA, however, can depress brain function, making the brain sluggish. By altering the extent of GABA-induced changes in membrane permeability, pregnenolone is able to reduce the increase in GABA transmission that occurs normally in older individuals.<sup>7</sup> This counteracts the aging brain’s decline in mental sharpness.



Pregnenolone also works the other side of the equation by increasing the activity of the NMDA (N-methyl-D-aspartate) subtype of glutamate receptors. Glutamate is a major excitatory neurotransmitter whose enhanced action recharges the brain and makes it more capable of handling the day’s activities. These dual changes induce increased acetylcholine release in the parts of the brain most involved with cognitive processes.<sup>8</sup>

Pregnenolone also promotes greater growth of brain cells. A recent study revealed that pregnenolone sulfate counteracted the usual age-related decline in neurogenesis in the hippocampuses of rats.<sup>5</sup> The researchers found a 55% increase in cell proliferation in the dentate gyrus, where newborn cells differentiate into neurons. This effect continued for several weeks after a single infusion, suggesting that long-lasting benefits could be achieved from ongoing supplementation. Of course, the more brain cells you have, the more memories you are likely to retain.

Various animal studies have demonstrated pregnenolone’s effectiveness in enhancing learning and memory. A French study of young and aged rats found the older rats had significantly lower levels of pregnenolone sulfate.<sup>9</sup> This was associated with poor performance in two mazes that measured various aspects of spatial memory. Seven hours after the older rats were injected with pregnenolone sulfate, they performed significantly better in both mazes. There were also dramatic relative increases in the amounts of the hormone in the plasma and hippocampuses of the older rats, indicating that at least some of the pregnenolone sulfate was able to cross the blood-brain barrier. The researchers noted that the seven-hour time delay in improvement was such that a mechanism involving any of pregnenolone’s metabolites could have been responsible for the memory enhancements.



Other scientists have explored pregnenolone's benefits for conditioned learning tasks. These involve passive or active avoidance exercises that measure memory of a negative experience, as well as reinforcement experiments in which animals learn to operate a lever to gain access to a stimulus such as water or food. In one experiment, 3- and 16-month-old mice performed a passive-avoidance task that involved learning to not step down a device.<sup>10</sup> Before receiving pregnenolone sulfate injections, the older mice showed a substantial deficit in memory retention. After a pretraining injection of pregnenolone sulfate, however, the retention performance of the older mice after a 24-hour delay improved in a dose-dependent fashion.

Subsequent comparison of the results showed a positive correlation between the rats' learning performance and concentrations of pregnenolone sulfate in their hippocampuses. Interestingly, no such correlation was found between levels of the hormone and changes in other brain areas such as the cortex or amygdala, suggesting that the hippocampus is primarily where pregnenolone plays its role in memory enhancement.

Several other studies have confirmed these results. One performed at the Universite de Lille in France infused pregnenolone sulfate into rat brains.<sup>11</sup> The scientists found that the infusion not only improved recognition memory of a familiar environment, but also boosted acetylcholine release by more than 50%. This underscores the link between pregnenolone and the vital neurotransmitter acetylcholine.

Another French study examined the relationship between pregnenolone and cognitive performance.<sup>12</sup> Rats with memory impairment exhibited low pregnenolone sulfate concentrations compared to animals with normal memory performance. An intracerebral infusion of pregnenolone sulfate reversed these memory deficits. The researchers also found that the injections dramatically increased neurogenesis (the creation of new brain cells). These findings indicate the extent to which pregnenolone sulfate can influence cognitive processes, particularly in older subjects.

## REPORT

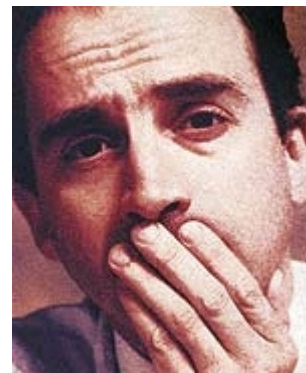
### Recharge With Pregnenolone

This little-known hormone fights fatigue, boosts memory, and more.

By Dave Tuttle

#### Counteracting Depression

Another likely benefit of pregnenolone is a reduction in depression and related disorders. Historically, the relatively high incidence of depression in older adults has been attributed to the loss of loved ones or the negative psychological effects of debilitating disease. Although these factors can certainly influence a person's mood, in recent years scientists have found that depression is usually associated with levels of serotonin and other neurotransmitters. For example, the antidepressant Prozac® increases serotonin levels in the brain by inhibiting the reuptake of this neurotransmitter. The inhibition of GABA release is also thought to enhance mood by preventing the brain from becoming too sluggish and lethargic. Pregnenolone's ability to control GABA levels strongly suggests that this hormone may be a valuable addition to the arsenal of antidepressant medications, especially considering its lack of side effects.



While human studies of pregnenolone supplementation have not been completed, compelling evidence suggests that pregnenolone plays a role in depression. In a study of 27 patients with depression and 10 healthy volunteers, the depressed subjects had lower levels of pregnenolone in their cerebrospinal fluid than the healthy individuals.<sup>13</sup> Cerebrospinal fluid circulates in the spinal column and brain, indicating that the brains of the depressed patients were exposed to less pregnenolone than those of the healthy subjects. In another study that matched 12 healthy controls with 12 men who had generalized social phobia and were not taking medication, concentrations of pregnenolone sulfate were significantly lower in the plasma of the patients with social phobia, again implying that pregnenolone plays a role in mood states.<sup>14</sup>



#### Help for Spinal Cord Injuries

Because pregnenolone is naturally found in the cerebrospinal fluid, researchers have sought to determine whether it can help accident victims with spinal cord injuries. Pregnenolone was found to promote recovery when used in combination with other drugs.<sup>15</sup>

Researchers gave pregnenolone, indomethacin (an anti-inflammatory substance), and bacterial lipopolysaccharide (a stimulator of cytokine secretion) to rats both individually and in combination for 21 days. While the use of indomethacin and lipopolysaccharide eased the histopathological damage to some extent, there was little recovery of motor function. Adding pregnenolone to the mix produced a striking reduction in histopathological damage, and the tissue was spared from secondary injury (a common occurrence with spinalcord victims when the components of the inflammatory response become destructive). This three-way combination worked so well that 11 of the 16 animals were able to stand and walk after 21 days, four of them almost normally. The survival rate improved as well, possibly due to the protection that pregnenolone offered against the toxic

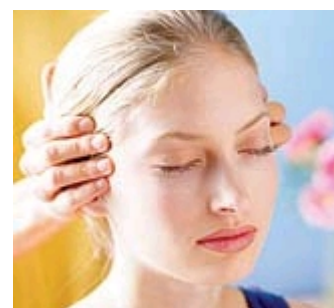
effects of the other two drugs. Pregnenolone also increased the vascularization of the spared tissue and made the cellular matrix denser, while reducing the extent to which cavities formed on the injured tissue.

The researchers concluded that pregnenolone facilitated recovery by giving rise to the greatest number of other hormones, which are known to assist with coordinative processes within and between the neural, metabolic, and immune systems. Because of its dual action in inhibiting GABA release and boosting glutamate levels, pregnenolone can "exert remarkable synergistic amplification of excitatory transmission,"<sup>15</sup> triggering the cascade of reactions needed for cell recovery.

Pregnenolone holds great promise in helping accident and trauma victims recover from their injuries. While the extent of benefit still must be quantified, it seems clear that the cascade of reactions produced by pregnenolone may be valuable in addressing a variety of medical conditions.

## Benefits for Rheumatoid Arthritis

Pregnenolone has been shown to relieve the symptoms of rheumatoid arthritis. As noted earlier, this hormone alters the permeability of cell membranes, lessening swelling and associated pain with a resulting increase in strength. Pregnenolone also may play a role in reducing the formation of COX-2, which would counteract the availability of various inflammatory compounds.



A number of studies have confirmed that pregnenolone has dramatic anti-arthritic effects, though the daily oral dosage required—approximately 500 mg—is significantly more than the dose needed to realize mental improvements.<sup>4</sup> Pregnenolone is most helpful in the initial stages of arthritis before the pathological process has progressed too far. Moreover, a comparative study of cortisone and pregnenolone found that improvements lasted longer after the study ended when pregnenolone was administered. Because cortisone has several negative side effects, concurrent use with pregnenolone should permit a reduction in the cortisone dosage, helping to reduce the suffering of persons with rheumatoid arthritis. More research is needed, however, to determine the ideal combination dosage. Unfortunately, pregnenolone is not beneficial for osteoarthritis, a condition in which little inflammation exists.

## Summary

Physicians have recommended hormone-replacement therapy to older individuals for many years. Usually, however, the hormones replaced are the end-product hormones: testosterone or estrogen. Recent research suggests that there may be another way. By providing your body with the mother of hormones—pregnenolone—you can let your body decide through its various feedback mechanisms which hormones it needs. If more DHEA is required, the supplemental pregnenolone will be converted to this hormone, and if estrogen or testosterone is in short supply, the pregnenolone molecule will be altered to produce the optimal amount. If your physiological requirement is a combination of hormones, this, too, can be achieved.

By its very nature, pregnenolone works with your body to achieve optimal health and longevity. Pregnenolone's many functions underscore its role as one of the most important hormones in the human body. Pregnenolone reduces fatigue and increases endurance. It also provides the brain with the hormonal and neurotransmitter support it needs to retard memory loss, thus helping to improve concentration and focus. Moreover, it helps those with arthritis, depression, and traumatic injuries.

Although pregnenolone has long been overlooked because it is “upstream” on the hormone pathway, its many benefits to human health suggest that this vital hormone has just begun to receive the attention it so richly deserves.

---

## References

---

1. Sahelian R. *Pregnenolone: A Practical Guide*. Marina del Rey, CA: Longevity Research Institute; 1996.
2. Havlíková H, Hill M, Hampl R, Stárka L. Sex- and age-related changes in epitestosterone in relation to pregnenolone sulfate and testosterone in normal subjects. *J Clin Endocrinol Metab*. 2002 May;87(5):2225-31.
3. Lanthier A, Patwardhan VV. Sex steroids and 5-en-3b-hydrosteroids in specific regions of the human brain and cranial nerves. *J Steroid Biochem*. 1986 Sep;25(3):445-9.
4. Roberts E. Pregnenolone from Selye to Alzheimer and a model of the pregnenolone sulfate binding site on the GABA<sub>A</sub> receptor. *Biochem Pharmacol*. 1995 Jan 6;49(1):1-16.
5. Mayo W, George O, Darbra S, et al. Individual differences in cognitive aging: implication of pregnenolone sulfate. *Prog Neurobio*. 2003 Sep;71(1):43-8.
6. Regelson W, Colman C. *The Superhormone Promise: Nature's Antidote to Aging*. New York, NY: Simon & Schuster; 1996.
7. Roberts E, Sherman MA. GABA—the quintessential neurotransmitter: electroneutrality, fidelity, specificity, and a model for the ligand binding site of GABA<sub>A</sub> receptors. *Neurochem Res*. 1993 Apr;18(4):365-76.
8. Darnaudéry M, Koehl M, Pallarés M, Le Moal MJ, Mayo W. The neurosteroid pregnenolone sulfate increases cortical acetylcholine release: A microdialysis study of freely moving rats. *J Neurochem*. 1998 Nov;71(5):2018-22.
9. Vallée M, Mayo W, Darnaudéry M, et al. Neurosteroids: deficient cognitive performance in aged rats depends on low pregnenolone sulfate levels in the hippocampus. *Proc Natl Acad Sci USA*. 1997 Dec 23;94(26):14865-70.
10. Vallée M, Mayo W, Le Moal M. Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and

memory in cognitive aging. Brain Res Rev. 2001 Nov;37(1-3):301-12.

11. Darnaudery M, Pallares M, Piazza PV, Le Moal M, Mayo W. The neurosteroid preg- nenolone sulfate infused into the medial sep- tum nucleus increases hippocampal acetyl- choline and spatial memory in rats. Brain Res. 2002 Oct 4;951(2):237-42.

12. Mayo W, Le Moal M, Abrous DN. Pregnenolone sulfate and aging of cognitive functions: Behavioral, neurochemical, and morphological investigations. Horm Behav. 2001 Sep;40(2):215-7.

13. George M, Guidotti A, Rubinow D, Pan B, Mikalaukas K, Post R. CSF neuroactive steroids in affective disorders: pregnenolone, progesterone and DBI. Biolog Psychiatry. 1994 May 15;35(10):775-80.

14. Heydari B, Le Melleo JM. Low preg- nenolone sulfate plasma concentrations in patients with generalized social phobia. Psychol Med. 2002 Jul;32(5):929-33.

15. Guth L, Zhang Z, Roberts E. Key role for pregnenolone in combination therapy that promotes recovery after spinal cord injury. Proc Natl Acad Sci USA. 1994 Dec 6;91(25):12308-12.

All Contents Copyright © 1995-2009 Life Extension Foundation All rights reserved.

**LifeExtension®**

These statements have not been evaluated by the FDA. These products are not intended to diagnose, treat, cure or prevent any disease. The information provided on this site is for informational purposes only and is not intended as a substitute for advice from your physician or other health care professional or any information contained on or in any product label or packaging. You should not use the information on this site for diagnosis or treatment of any health problem or for prescription of any medication or other treatment. You should consult with a healthcare professional before starting any diet, exercise or supplementation program, before taking any medication, or if you have or suspect you might have a health problem. You should not stop taking any medication without first consulting your physician.