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REPORT

Enhancing Cognitive Function with Pregnenolone

By Julius G. Goepf, MD



As a result of normal aging, key hormone levels decline, resulting in a detrimental impact on memory and cognitive function. Scientists believe that the hormone pregnenolone has vast potential for maintaining healthy cognitive function and may be “the most potent memory enhancer yet reported.”¹

Pregnenolone is the first hormone in the pathway that generates a host of key neurohormones in the brain that are known to affect nerve cell growth and to modulate various moods. Pregnenolone therefore has a dominant effect in a wide range of nervous system functions. This is

borne out in research that has demonstrated pregnenolone’s ability to reduce the risk of dementia and improve memory, while also alleviating anxiety and fighting depression.

Increasing cognitive function is a key goal for any aging baby boomer. As natural levels of pregnenolone fall, ensuring optimal levels may represent a crucial cornerstone to every adult’s cognitive wellness program.

The formation of memory is still one of the most fascinating functions of the brain. Scientists are learning more each day about how molecules and memories interact.² An essential molecule in this interaction is pregnenolone, a key hormone that is the starting point for the production of many other important hormones in the body. There is strong evidence that pregnenolone levels diminish with advancing age and that restoring these levels may help alleviate deteriorating brain function. Before we review how pregnenolone boosts memory, let’s start with a look at the physiology of this essential hormone.

PREGNENOLONE BASICS

The conversion of cholesterol to pregnenolone constitutes the first of many steps in the synthesis of some of the body’s key hormones, including dehydroepiandrosterone (DHEA), testosterone, progesterone, estrogen, and cortisol. Nicknamed “the mother hormone,” pregnenolone is a vital building block, being the very first (and arguably the most versatile) hormone in a cascade of molecular events.³ Like newly cut lumber, which can be processed into everything from building materials to facial tissue, pregnenolone’s final products fill myriad essential roles in the body, from stimulating memory via excitatory pathways to easing anxiety through inhibitory mechanisms.^{4,5}



Pregnenolone was originally thought to be produced only in the adrenal glands and gonads (ovaries and testes). Somewhat surprisingly, the central nervous system (brain and spinal cord) also synthesizes this hormone.⁶ The discovery that certain steroids are produced and act in the central nervous system has led to the term “neurosteroids.”⁷ Another term, “neuroactive steroids” is often used for hormones that may be manufactured elsewhere in the body but have potent actions in the nervous system.^{8,9}

Neurosteroids and neuroactive steroids can have powerful effects on how individual nerve cells function. In fact, we’re now learning that these complex little molecules can act in ways similar to the more familiar neurotransmitters—the chemical messengers between nerve cells.¹⁰

Absence or reduced concentrations of neurosteroids during development and in adults may be associated with neurodevelopmental, psychiatric, or behavioral disorders.

Furthermore, normalizing levels of neurosteroids in the brain may promote neurogenesis (production of new nerve cells), neuronal survival, myelination (insulation to protect the nerve fibers), increased memory, and reduced neurotoxicity.¹¹ These discoveries have, in fact, led to the development of a whole new field of research, sometimes called “synaptocrinology,” which refers to the



actions of hormones at nerve junctions (synapses).¹²

Pregnenolone is therefore unique among the neurosteroids and neuroactive steroids, exerting exquisite control over a wide range of nervous system functions.¹³ As the body's ultimate neurosteroid raw material then, it's hard to overstate the importance of adequate (and reliable) pregnenolone supplies. To get a really good feel for just how vital a role pregnenolone plays in the nervous system, let's take a quick tour of the mysteries of memory and emotion.

STIMULATION AND MEMORY

Despite the apparent complexity of brain cells, or neurons, we can simplify matters considerably by thinking about their activities as either being stimulated or suppressed. Not surprisingly, most memory formation occurs as the result of stimulation of nerve cells. Stimulation generally results in the production of nerve branches known as dendrites, which connect to additional neurons, making the entire "switchboard" larger and more complex. These structures are formed by activating special "switches" in the brain. While there are a variety of such excitatory switches, the category called NMDA (N-methyl-D-aspartate) channels (or receptors) comprises the most important group. These channels must be activated for learning and memory to occur.¹⁴

Now, here's where it gets interesting! The typical excitatory brain chemical that activates those memory-enhancing NMDA receptors is the amino acid glutamate, which is present throughout the brain.¹⁵ And while glutamate is critical for normal learning, too much excitation by glutamate over time can damage neurons—in fact, overstimulation, or excitotoxicity, by glutamate is thought to be one of the underlying factors in neurodegenerative disorders such as Alzheimer's disease.^{16,17} What makes pregnenolone so important in this context is that it seems to trigger the NMDA channels^{18,19} through a mechanism that is independent of glutamate,²⁰ which in turn may account for the observed neuroprotective effects of pregnenolone on brain cells.²¹ The bottom line of all this intricate science is that pregnenolone may play a pivotal role both in laying down memories in the first place, and then preventing their loss by directly protecting the nerve networks that store them! These complementary and versatile actions of pregnenolone are sending shock waves of interest through the scientific community because of the enormous implications for treating all sorts of age-related disorders of memory.^{5,22,23}

MAINTAINING HEALTHY PREGNENOLONE LEVELS

Strong evidence from animal studies suggests that neurosteroid levels, including pregnenolone, diminish with advancing age.²⁴ As pregnenolone is the parent compound of other vital neurosteroids such as dehydroepiandrosterone (DHEA),²⁵ declining levels of pregnenolone could leave brain cells increasingly vulnerable to damage, such as overstimulation by neurotransmitters like glutamate.^{25,26} In fact, scientists have proposed that levels of neurosteroids such as pregnenolone could serve as biological "markers" of cognitive aging in laboratory animals, allowing us to examine the age-related impact of each neurosteroid on learning and memory.^{26,27} Some human studies have also shown a correlation between neurosteroid levels, especially DHEA, and cognitive function, although more research is still needed because of the implications for conditions such as age-related cognitive decline.²⁴



BOOSTING COGNITION AND MEMORY

A decline in cognition as seen in Alzheimer's disease is associated with decreased neurosteroid levels. Alzheimer's disease is characterized by a build-up of harmful amyloid-beta plaques in the brain that block communication between nerve cells and disrupt the activities that brain cells need to survive.

Evidence suggests that neuro-steroids such as pregnenolone may offer important neuroprotection in Alzheimer's disease. When researchers introduced the destructive amyloid-beta protein into animal brains, the level of progesterone (a neurohormone synthesized from its direct precursor, pregnenolone) fell off dramatically.^{28,29} Likewise, in humans, Alzheimer's disease patients have lower levels of pregnenolone, allopregnanolone (a pregnenolone metabolite) and DHEA-sulfate (DHEAS) in all the main memory-related areas of their brains, compared with control patients.³⁰⁻³² Furthermore, the brains of patients with the highest neurosteroid levels display the lowest collections of the destructive amyloid-beta proteins.³⁰

It therefore seems reasonable to speculate that as natural levels of pregnenolone and other neuro-steroids fall with aging and the onset of neurodegenerative diseases, supplementing with these vital compounds should have a neuroprotective effect. This is exactly what researchers have found. French scientists have paved the way in this field with their study of the effects of pregnenolone on cognitive aging. In fact, the results have been startling, with pregnenolone sulfate (the form found in brain tissue) completely reversing memory deficits in older, memory-impaired rats. ³³

Even more remarkably, from a treatment standpoint, researchers have also shown that pregnenolone increases brain levels of acetylcholine, a key neurotransmitter required for optimal brain function, which becomes deficient in patients with Alzheimer's disease.³⁴ Acetylcholine is not only vital for thought and memory, it is also involved in controlling sleep cycles, especially the

phase of sleep that is associated with memory (called paradoxical sleep or the slow eye movement [REM] phase). Scientists have used this knowledge to study the effects of pregnenolone on sleep cycles and discovered that it dramatically increases memory-enhancing sleep.

Together with previous findings that pregnenolone increases nerve cell growth (neurogenesis),^{11,35} researchers have concluded that pregnenolone can improve cognitive function in older animals by increasing acetylcholine levels, which stimulate new nerve cell growth in the brain areas most closely associated with memory and learning.

PREGNENOLONE AND ACTIVE LEARNING

As well as protecting against memory loss and even recovering some failing memory, pregnenolone and other neurosteroids are showing promising results in acquiring memory and learning in the first place. Research has shown that neurosteroids improve memory performance in healthy animals and help restore memory in animals given experimental anesthesia-inducing drugs.³⁶

Scientists from the VA Medical Center in St. Louis explored pregnenolone's benefits in memory retention using a conditioning task in animals that involved learning to avoid a mild electric shock to the foot.^{37,38} To their surprise, they discovered that pregnenolone displayed beneficial effects in improving memory retention at almost incredibly low doses.¹ They also found the response to pregnenolone was much faster than expected had the supplement been working like a typical neurosteroid, leading to the conclusion that something much more dramatic was going on.

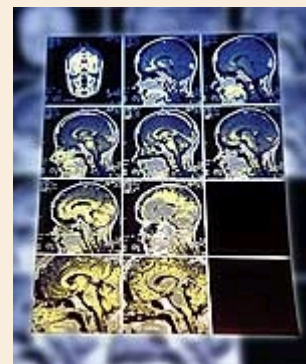
A team of French researchers found the first key to pregnenolone's swift action.³⁹

They studied the effect of pregnenolone sulfate in mice after the administration of a drug called scopolamine, which prevents the formation of memories by blocking receptors for the neurotransmitter acetylcholine in the brain. They discovered the learning deficit induced by scopolamine could be prevented by pregnenolone within a very short time. Such a rapid effect of pregnenolone on memory processes led the team to conclude that it may be acting directly at receptor sites that are known to be active in memory formation. In other words, the researchers had confirmed that pregnenolone has both neurosteroid-like and neurotransmitter-like activities—a boon for the treatment of memory impairment.

A second group of French researchers may have unlocked another door to the role of pregnenolone in learning. They found that pregnenolone dramatically stimulated the construction of ultramicroscopic structures called microtubules in brain cells.⁴⁰ Microtubules are essentially tiny intracellular “muscles” that nerve cells use to rapidly rearrange their structures, making the myriad new connections that form the “structure” of memory. In fact, pregnenolone's dramatic effect on “bulking up” nerve cells' internal muscles brought interest in the hormone to a fever pitch in France, where, in 2004, a new private company was started to develop pregnenolone derivatives as pharmaceutical drugs for memory enhancement and the treatment of Alzheimer's disease.

PREGNENOLONE: WHAT YOU NEED TO KNOW

- Pregnenolone is the “parent hormone” of the entire neurosteroid family, giving rise to important “neurohormones” that affect learning, memory, mood, sleep, and much more.
- Pregnenolone and its family members both stimulate and suppress brain cell activity in a fashion that maintains tight control over brain function.
- Pregnenolone and other neuroactive steroids can protect brain cells against the long-term damage that can lead to Alzheimer's disease and other forms of dementia.
- Hormone levels naturally decline with advancing age. People with lower pregnenolone levels are more likely to suffer from memory deficits, mood disorders, and even some mental illnesses.
- Pregnenolone supplementation improves brain function, often correcting impairments in memory and learning.
- Pregnenolone and its derivatives may even help mitigate the effects of addictive substances such as alcohol, nicotine, and narcotics.



RELIEVING ANXIETY

Every silver lining has its cloud, however, and the brain's intricate system for generating memory is no exception. Discoveries of

memory enhancement by stimulating brain cells have led to the realization that overstimulating these pathways can also cause anxiety.⁴ In addition, many anti-anxiety drugs in common use today have an unpleasant side effect—they also impair memory and learning.⁴² Generally speaking, substances that enhance memory have the risk of producing anxiety, whereas those that allay anxiety pose the risk of impairing memory. Let's see where pregnenolone fits into this seeming paradox.

There's remarkably good news here. Again it's related to the speed with which pregnenolone acts on nerve cells, and on its role as the "parent" hormone that quickly gives rise to other hormones to counteract any potentially negative effect of overstimulating neuronal pathways. By providing a stockpile of raw material, so to speak, ample pregnenolone levels allow brain cells to manufacture just the right chemical (excitatory or anti-anxiety) at just the moment when each is needed.^{4,6}



Here's how it works: just as pregnenolone itself acts at excitatory receptors in the brain to stimulate nerve cell activity and enhance learning, other neurohormones produced from pregnenolone (such as allopregnanolone) act on inhibitory brain receptors, called gamma amino-butyric acid (A) (GABA(A)) receptors, which suppress brain cell activity to produce a calming, anti-anxiety, and even sleep-inducing effect.⁴³

Research from a decade ago brought this point home dramatically.⁴⁴ Scientists treated mice with anti-anxiety drugs called benzodiazepines (similar to Valium®) until the animals developed tolerance to the drugs (that is, the drugs no longer were effective). When the drugs were abruptly stopped, the mice developed marked withdrawal symptoms and anxiety, which were reduced markedly when pregnenolone sulfate was given at the same time as the anti-anxiety drugs. Pregnenolone also completely abolished the animals' drug tolerance, a finding that has tremendous implications for

human use, because of its potential to help patients discontinue long-term benzodiazepines.

As neurosteroids are known to affect anxiety in humans as well,⁴⁵ researchers from the University of California in San Francisco performed two studies of pregnenolone and anti-anxiety medications.⁴⁶ First, they provided 17 healthy volunteers with either pregnenolone (15 mg by mouth for two weeks followed by 30 mg by mouth for two more weeks) or placebo for four weeks. Pregnenolone was well tolerated in this initial study. In the second study, the volunteers were given the anti-anxiety drug diazepam (Valium®) 0.2 mg as a single dose immediately after the first study. Individuals who had received pregnenolone in the first study showed significantly less sedation and a reduction in memory impairment after taking diazepam compared with those who had taken placebo in the first study. Furthermore, the anxiety-relieving effect of diazepam was unaffected. The researchers concluded, powerfully, that pregnenolone taken as a supplement while on an anti-anxiety medication could reduce many adverse effects of the medication, such as sedation and memory impairment.

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COMBATING MENTAL HEALTH DISORDERS

There is increasing evidence that lower levels of pregnenolone are associated with a variety of mental health conditions beyond anxiety, including depression, phobias, and even schizophrenia.^{9,47-49} In fact, one study published just this year revealed that schizophrenic patients with the lowest levels of pregnenolone were also most likely to have high levels of anxiety.⁵⁰

OVERCOMING CHEMICAL DEPENDENCY

Many of the addictive substances humans consume can have potent negative effects on learning and memory—effects that are exacerbated by aging. Both alcohol and nicotine impair learning and leave long-term marks on memory as well. However, a number of studies have shown that pregnenolone sulfate overcomes the memory impairment caused by addictive substances such as alcohol and nicotine.^{51,52}



These impressive findings have been echoed by another study looking into the effects of neurosteroids in nicotine and morphine dependence—two problems that are faced by millions of older adults.⁵³ Again, pregnenolone and other neurosteroids were shown to counteract the anxiety-like behavior that is associated with nicotine or morphine withdrawal. In fact, this study together with the recent discovery that pregnenolone and other neurosteroids have potent effects on the so-called sigma receptors, which have long been associated with addictive behaviors,³⁶ have generated tremendous excitement in the scientific community with the prospect that neurosteroids such as pregnenolone may offer powerful relief to sufferers of these tragic conditions.²²

SAFETY CONSIDERATIONS

The possibility that thousands of older adults may suffer from low pregnenolone levels is of concern. However, there is plenty of evidence favoring careful supplementation to prevent or mitigate memory loss and a host of other mental and emotional health issues. Because cancers of the breast, uterus, ovaries, and prostate may grow faster in the presence of sex hormones derived from pregnenolone,⁵⁴⁻⁵⁹ it's important to collaborate with your health care provider if you have any such conditions, to be sure that supplementation is right for you.

NEUROSTEROID LEVELS MAY HELP EARLY DIAGNOSIS OF ALZHEIMER'S

The levels of neurosteroids in the brains of patients with Alzheimer's disease may be so profoundly low that testing for them has been suggested as a means of making an early diagnosis and distinguishing the condition from other forms of dementia.³² Researchers in the Czech Republic tested blood samples from 40 men and women with Alzheimer's disease and 24 with vascular dementia (related to impaired blood flow to the brain).⁴¹ They analyzed the samples for a host of neurohormones as well as amino acids known to be associated with vascular disease. When they ran the results through a standard mathematical model called regression analysis, the researchers were able to correctly detect 89% of the patients with Alzheimer's disease from among the entire group.

If these findings hold up to further scrutiny, they suggest that by using this simple blood testing screen of neurosteroids and amino acids, physicians might be able to identify cases of Alzheimer's disease early enough to treat in order to slow down the disease.

CONCLUSION

Our knowledge of pregnenolone and its “family members,” the neurohormones, is at an exciting early stage. What we know is that these powerful molecules exert rapid and profound effects on vital brain structures, intimately affecting how we think, learn, and remember. It’s fair to say that studies of pregnenolone and other neurosteroids are changing the way we think about steroids and the actions of hormones in general. Animal studies and early human trials show promising results of supplementation with this exceptionally versatile natural substance. Furthermore, dozens of new trials that are now in progress will surely shed even more light in the future on how pregnenolone can help protect and promote healthy brain function.



If you have any questions on the scientific content of this article, please call a Life Extension Health Advisor at 1-800-226-2370.

References

1. Flood JF, Morley JE, Roberts E. Pregnenolone sulfate enhances post-training memory processes when injected in very low doses into limbic system structures: the amygdala is by far the most sensitive. *Proc Natl Acad Sci USA*. 1995 Nov 7;92(23):10806-10.
2. Nikitin VP. A new mechanism of synapse-specific neuronal plasticity. *Neurosci Behav Physiol*. 2007 Jul;37(6):559-70.
3. Wojtal K, Trojnar MK, Czuczwar SJ. Endogenous neuroprotective factors: neurosteroids. *Pharmacol Rep*. 2006 May;58(3):335-40.
4. Gibbs TT, Russek SJ, Farb DH. Sulfated steroids as endogenous neuromodulators. *Pharmacol Biochem Behav*. 2006 Aug;84(4):555-67.
5. Maurice T, Phan VL, Urani A, et al. Neuroactive neurosteroids as endogenous effectors for the sigma1 (sigma1) receptor: pharmacological evidence and therapeutic opportunities. *Jpn J Pharmacol*. 1999 Oct;81(2):125-55.
6. Paul SM, Purdy RH. Neuroactive steroids. *FASEB J*. 1992 Mar;6(6):2311-22.
7. Baulieu EE. Neurosteroids: a new function in the brain. *Biol Cell*. 1991;71(1-2):3-10.
8. Baulieu EE. Neurosteroids: of the nervous system, by the nervous system, for the nervous system. *Recent Prog Horm Res*. 1997;5:21-32.
9. Dubrovsky BO. Steroids, neuroactive steroids and neurosteroids in psychopathology. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005 Feb;29(2):169-92.
10. Wu FS, Gibbs TT, Farb DH. Pregnenolone sulfate: a positive allosteric modulator at the N-methyl-D-aspartate receptor. *Mol Pharmacol*. 1991 Sep;40(3):333-6.
11. Mellon SH. Neurosteroid regulation of central nervous system development. *Pharmacol Ther*. 2007 Jun 16.
12. Mukai H, Takata N, Ishii HT, et al. Hippocampal synthesis of estrogens and androgens which are paracrine modulators of synaptic plasticity: synaptocrinology. *Neuroscience*. 2006;138(3):757-64.
13. Mellon SH, Griffin LD, Compagnone NA. Biosynthesis and action of neurosteroids. *Brain Res Brain Res Rev*. 2001 Nov;37(1-3):3-12.
14. Verkhratsky A, Kirchhoff F. NMDA Receptors in glia. *Neuroscientist*. 2007 Feb;13(1):28-37.
15. Castner SA, Williams GV. Tuning the engine of cognition: a focus on NMDA/D1 receptor interactions in prefrontal cortex. *Brain Cogn*. 2007 Mar;63(2):94-122.
16. Cosman KM, Boyle LL, Porsteinsson AP. Memantine in the treatment of mild-to-moderate Alzheimer’s disease. *Expert Opin Pharmacother*. 2007 Feb;8(2):203-14.
17. Wenk GL. Neuropathologic changes in Alzheimer’s disease: potential targets for treatment. *J Clin Psychiatry*. 2006;67 Suppl 33-7.

18. Hige T, Fujiyoshi Y, Takahashi T. Neurosteroid pregnenolone sulfate enhances glutamatergic synaptic transmission by facilitating presynaptic calcium currents at the calyx of Held of immature rats. *Eur J Neurosci.* 2006 Oct;24(7):1955-66.
19. Sliwinski A, Monnet FP, Schumacher M, Morin-Surun MP. Pregnenolone sulfate enhances long-term potentiation in CA1 in rat hippocampus slices through the modulation of N-methyl-D-aspartate receptors. *J Neurosci Res.* 2004 Dec 1;78(5):691-701.
20. Sabeti J, Nelson TE, Purdy RH, Gruol DL. Steroid pregnenolone sulfate enhances NMDA-receptor-independent long-term potentiation at hippocampal CA1 synapses: role for L-type calcium channels and sigma-receptors. *Hippocampus.* 2007;17(5):349-69.
21. Maurice T, Gregoire C, Espallergues J. Neuro(active)steroids actions at the neuromodulatory sigma1 (sigma1) receptor: biochemical and physiological evidences, consequences in neuroprotection. *Pharmacol Biochem Behav.* 2006 Aug;84(4):581-97.
22. Maurice T, Urani A, Phan VL, Romieu P. The interaction between neuroactive steroids and the sigma1 receptor function: behavioral consequences and therapeutic opportunities. *Brain Res Brain Res Rev.* 2001 Nov;37(1-3):116-32.
23. Vajda FJ. Neuroprotection and neurodegenerative disease. *J Clin Neurosci.* 2002 Jan;9(1):4-8.
24. Vallee M, Mayo W, Le MM. Role of pregnenolone, dehydroepiandrosterone and their sulfate esters on learning and memory in cognitive aging. *Brain Res Brain Res Rev.* 2001 Nov;37(1-3):301-12.
25. Stomati M, Monteleone P, Casarosa E, et al. Six-month oral dehydroepiandrosterone supplementation in early and late postmenopause. *Gynecol Endocrinol.* 2000 Oct;14(5):342-63.
26. Vallee M, Purdy RH, Mayo W, Koob GF, Le MM. Neuroactive steroids: new biomarkers of cognitive aging. *J Steroid Biochem Mol Biol.* 2003 Jun;85(2-5):329-35.
27. Vallee M, Mayo W, Darnaudery 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.
28. Urani A, Romieu P, Roman FJ, Maurice T. Enhanced antidepressant effect of sigma(1) (sigma(1)) receptor agonists in beta (25-35)-amyloid peptide-treated mice. *Behav Brain Res.* 2002 Aug 21;134(1-2):239-47.
29. Urani A, Romieu P, Roman FJ, et al. Enhanced antidepressant efficacy of sigma1 receptor agonists in rats after chronic intracerebroventricular infusion of beta-amyloid-(1-40) protein. *Eur J Pharmacol.* 2004 Feb 20;486(2):151-61.
30. Schumacher M, Weill-Engerer S, Liere P, et al. Steroid hormones and neurosteroids in normal and pathological aging of the nervous system. *Prog Neurobiol.* 2003 Sep;71(1):3-29.
31. Weill-Engerer S, David JP, Sazdovitch V, et al. Neurosteroid quantification in human brain regions: comparison between Alzheimer's and nondemented patients. *J Clin Endocrinol Metab.* 2002 Nov;87(11):5138-43.
32. Marx CE, Trost WT, Shampine LJ, et al. The neurosteroid allopregnanolone is reduced in prefrontal cortex in Alzheimer's disease. *Biol Psychiatry.* 2006 Dec 15;60(12):1287-94.
33. Mayo W, Le MM, Abrous DN. Pregnenolone sulfate and aging of cognitive functions: behavioral, neurochemical, and morphological investigations. *Horm Behav.* 2001 Sep;40(2):215-7.
34. Mayo W, George O, Darbra S, et al. Individual differences in cognitive aging: implication of pregnenolone sulfate. *Prog Neurobiol.* 2003 Sep;71(1):43-8.
35. Mayo W, Lemaire V, Malaterre J, et al. Pregnenolone sulfate enhances neurogenesis and PSA-NCAM in young and aged hippocampus. *Neurobiol Aging.* 2005 Jan;26(1):103-14.
36. Monnet FP, Maurice T. The sigma1 protein as a target for the non-genomic effects of neuro(active)steroids: molecular, physiological, and behavioral aspects. *J Pharmacol Sci.* 2006 Feb;100(2):93-118.
37. Roberts E, Bologna L, Flood JF, Smith GE. Effects of dehydroepiandrosterone and its sulfate on brain tissue in culture and on memory in mice. *Brain Res.* 1987 Mar 17;406(1-2):357-62.

38. Flood JF, Morley JE, Roberts E. Memory-enhancing effects in male mice of pregnenolone and steroids metabolically derived from it. *Proc Natl Acad Sci USA*. 1992 Mar 1;89(5):1567-71.
39. Meziane H, Mathis C, Paul SM, Ungerer A. The neurosteroid pregnenolone sulfate reduces learning deficits induced by scopolamine and has promnestic effects in mice performing an appetitive learning task. *Psychopharmacology (Berl)*. 1996 Aug;126(4):323-30.
40. Murakami K, Fellous A, Baulieu EE, Robel P. Pregnenolone binds to microtubule-associated protein 2 and stimulates microtubule assembly. *Proc Natl Acad Sci USA*. 2000 Mar 28;97(7):3579-84.
41. Bickova M, Ripova D, Hill M, et al. Plasma levels of 7-hydroxylated dehydroepiandrosterone (DHEA) metabolites and selected amino-thiols as discriminatory tools of Alzheimer's disease and vascular dementia. *Clin Chem Lab Med*. 2004 May;42(5):518-24.
42. Savic MM, Obradovic DI, Ugresic ND, Bokonjic DR. Memory effects of benzodiazepines: memory stages and types versus binding-site subtypes. *Neural Plast*. 2005;12(4):289-98.
43. Reddy DS. Pharmacology of endogenous neuroactive steroids. *Crit Rev Neurobiol*. 2003;15(3-4):197-234.
44. Reddy DS, Kulkarni SK. Neurosteroid coadministration prevents development of tolerance and augments recovery from benzodiazepine withdrawal anxiety and hyperactivity in mice. *Methods Find Exp Clin Pharmacol*. 1997 Jul;19(6):395-405.
45. Brambilla F, Biggio G, Pisu MG, et al. Plasma concentrations of anxiolytic neurosteroids in men with normal anxiety scores: a correlation analysis. *Neuropsychobiology*. 2004;50(1):6-9.
46. Meieran SE, Reus VI, Webster R, Shafton R, Wolkowitz OM. Chronic pregnenolone effects in normal humans: attenuation of benzodiazepine-induced sedation. *Psychoneuroendocrinology*. 2004 May;29(4):486-500.
47. Baghai TC, di MF, Schule C, et al. Plasma concentrations of neuroactive steroids before and after electroconvulsive therapy in major depression. *Neuropsychopharmacology*. 2005 Jun;30(6):1181-6.
48. Dubrovsky B. Neurosteroids, neuroactive steroids, and symptoms of affective disorders. *Pharmacol Biochem Behav*. 2006 Aug;84(4):644-55.
49. Strohle A, Romeo E, di MF, et al. GABA(A) receptor-modulating neuroactive steroid composition in patients with panic disorder before and during paroxetine treatment. *Am J Psychiatry*. 2002 Jan;159(1):145-7.
50. Ritsner M, Maayan R, Gibel A, Weizman A. Differences in blood pregnenolone and dehydroepiandrosterone levels between schizophrenia patients and healthy subjects. *Eur Neuropsychopharmacol*. 2007 Apr;17(5):358-65.
51. Martin-Garcia E, Pallares M. The neurosteroid pregnenolone sulfate neutralized the learning impairment induced by intrahippocampal nicotine in alcohol-drinking rats. *Neuroscience*. 2005;136(4):1109-19.
52. Martin-Garcia E, Pallares M. Intrahippocampal nicotine and neurosteroids effects on the anxiety-like behaviour in voluntary and chronic alcohol-drinking rats. *Behav Brain Res*. 2005 Oct 14;164(1):117-27.
53. Concas A, Sogliano C, Porcu P, et al. Neurosteroids in nicotine and morphine dependence. *Psychopharmacology (Berl)*. 2006 Jun;186(3):281-92.
54. Fiet J, Dore JC, Go AL, Ojasoo T, Raynaud JP. Multivariate analysis of plasma hormones in patients with metastatic prostate cancer receiving combined LHRH-analog and antiandrogen therapy. *Prostate*. 1993;23(4):291-313.
55. Geldof AA, Dijkstra I, Newling DW, Rao BR. Inhibition of 3 beta-hydroxysteroid-dehydrogenase: an approach for prostate cancer treatment? *Anticancer Res*. 1995 Jul;15(4):1349-54.
56. Bickova M, Szamel I, Hill M, Tallova J, Starka L. Allopregnanolone, pregnenolone sulfate, and epitestosterone in breast cyst fluid. *Steroids*. 2001 Jan;66(1):55-7.
57. Angeli A, Dogliotti L, Naldoni C, et al. Steroid biochemistry and categorization of breast cyst fluid: relation to breast cancer risk. *J Steroid Biochem Mol Biol*. 1994 Jun;49(4-6):333-9.

58. Bradlow HL, Hershcopf R, Martucci C, Fishman J. 16 alpha-hydroxylation of estradiol: a possible risk marker for breast cancer. *Ann NY Acad Sci.* 1986;464:138-51.

59. Chen YH, Huang LH, Chen TM. Differential effects of progestins and estrogens on long control regions of human papillomavirus types 16 and 18. *Biochem Biophys Res Commun.* 1996 Jul 25;224(3):651-9.

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