Scientists have been studying the impact of hormones on learning and memory for many years. Take the neurosteroid pregnenolone, for example. It was the subject of experiments 20 years ago, when it was found "to play an important role in the motivational value of environmental cues, in the acquisition of knowledge, and in the long term memory of learned behavior."1-2

Pregnenolone is a steroid hormone precursor that the body normally manufactures using cholesterol as the primary raw material. It is converted into a multitude of steroids and neurosteroids.

100 Times More Potent
Although all these substances have been found to help maintain normal healthy cognitive function, pregnenolone seems to have truly extraordinary activity. In a recent study with laboratory animals,3 pregnenolone was found to be 100 times more effective for supporting memory function than other steroids or steroid-precursors.

Despite the lack of documented human experience for the cognitive role of pregnenolone, its use for treating arthritis goes back to the 1940s. Although it has fallen into disuse for this purpose with the development of more sophisticated anti-inflammatory drugs, pregnenolone's safety record and low toxicity should be sufficient to encourage its continued evaluation for cognitive function.

In rats, the levels of the sulfate form of pregnenolone in the hippocampus region of the brain have clearly related to cognitive performance; the higher the levels, the greater the performance.4

As is the case with the steroid-hormone precursor DHEA (which is a metabolite of pregnenolone), pregnenolone levels also decline with age. When people take DHEA supplements to restore more youthful levels, signs of aging improve. In animal studies, DHEA has been shown to extend maximum life span.

It's true that pregnenolone and DHEA are technically steroids, but they do not produce the strong hormonal influences of fully formed steroids, such as estrogen, testosterone, or progesterone. Consequently pregnenolone (and DHEA) promotes only minimal anabolic, androgenic and estrogenic activity.

Ground-breaking Study
In 1992, the results of a study on memory were published in the Proceeding of the National Academy of Science that made the world stand up and take notice.4 Indeed, when I read about this study a day before publication I immediately called one of the authors to obtain a copy. After reading it, I faxed a copy to John Morgenthaler, Steve Fowkes, and Durk Pearson and Sandy Shaw. Durk said he had some pregnenolone under refrigeration and couldn't wait to try it.

What was so remarkable about the study was that the researchers observed a large, clear cognitive response using an amount of pregnenolone so small that results were evident over a range of dose from 1 to 10,000 times. In other words, pregnenolone was effective at the picomolar level, an infinitesimally small amount.
In the study, rats were placed in a standard maze shaped like the letter T, and given a short time to find their way to the correct arm of the T. If, after 5 seconds, they did not reach the correct arm, they received a mild electric shock until they succeeded. Once they performed the test properly, they were given any one of a number of steroids or a placebo and then tested again in a week to see how well they remembered "foot-shock active avoidance" procedure. Although almost all steroids reduced the number of runs it took to relearn the procedure, ie, improved their shock-avoidance performance, pregnenolone was effective at doses 100 times lower than any of the other compounds.

The scientists offered no explanation of the mechanism by which the pregnenolone and the other steroids enhanced performance, but they were elated that pregnenolone, a substance with no known toxicities, was effective at such low levels.

Pregnenolone may enhance memory, in part, through its impact on N-methyl-D-aspartate (NMDA) receptors in the brain. Because specific pregnenolone receptors have not yet been demonstrated, it is thought that it may exert its effects through its role as a precursor of a many other steroids. The result is the near-optimal transcription modulation of genes required for achieving the accommodating changes of memory processes.

The following conclusions have been drawn from laboratory experiments with rodents:

- The finding that fewer than 150 molecules of pregnenolone significantly enhanced post-training memory processes when injected into a region of the brain known as the amygdala. This establishes pregnenolone as the most potent memory enhancer ever reported and the amygdala as the most sensitive brain region for memory enhancement yet tested.
- Pregnenolone blocks the inhibitory amino acids glycine and gamma-aminobutyric acid (GABA), as well as non-NMDA glutamate, thus helping regulate the balance between excitation and inhibition in the central nervous system.
- Pregnenolone acts to enhance memory after the training or learning experience.

References