Allopregnanolone is a metabolite of progesterone. In fact when progesterone is taken orally much of the progesterone is metabolized to allopregnanolone by the liver. So while oral progesterone is not a good way to get progesterone into the body, it is a great way to get allopregnanolone in the body. Allopregnanolone is a potent positive modulator of the GABA-A receptor and produces sedative and anxiolytic effects. The following is a great summary of the assumed mechanism of action of allopregnanolone...

PMS, Postpartum Depression, Sedative Withdrawal Believed to Have Common Brain-Receptor Link
By Richard Karel

There may be a fundamental biochemical commonality in the psychological and physical symptoms associated with premenstrual syndrome (PMS), postpartum lability and sudden withdrawal from sedatives such as benzodiazepines and alcohol.

In the article (“GABA Receptor Alpha-4 Subunit Suppression Prevents Withdrawal Properties of an Endogenous Steroid”), Sheryl S. Smith, Ph.D., an associate professor in the department of neurobiology and anatomy at Allegheny University of the Health Sciences in Philadelphia, Pa., and colleagues show how all of the above are related to increased production of the alpha-4 subunit, one of five molecules that make up the brain receptor for gamma-aminobutyric acid (GABA).

GABA is the brain's primary inhibitory neurotransmitter, functioning as an internally produced tranquilizer. But when too much alpha-4 is produced, the receptor’s capacity to use GABA is blunted, and a variety of unpleasant results occur, including increased anxiety, an increased tendency toward seizures, and other symptoms of PMS, postpartum lability, and sedative withdrawal. The first link is progesterone, a hormone that exists in high concentrations during pregnancy and prior to the onset of menstruation.

Progesterone, in both men and women, breaks down into allopregnanolone, which enhances the sedative effects of GABA, although precisely how is unknown. But immediately after pregnancy, and right before the onset of menstruation, progesterone levels plunge, leading to a corresponding drop in the metabolite allopregnanolone. Without allopregnanolone to come to the GABA receptor’s defense, the alpha-4 molecule gains the upper hand, hindering GABA’s efficacy and leading to all the unpleasant symptoms associated with PMS, postpartum mood swings, and acute sedative withdrawal.

Although the research is most relevant to women, changes in the alpha-4 subunit may occur under stress, leading to “anxiety states” in both men and women. Although the research identified allopregnanolone as the agent effecting alpha-4 subunit production, the next step will be to determine how allopregnanolone exerts its effects. This neuroactive-steroid connection may prove to be involved in sedative-hypnotic actions, aging, stress, and alcohol abuse. The steroids derived from progesterone may help explain the symptoms of pregnancy and menstruation, and perhaps one of psychiatry’s oldest conundrums: why men and women have such a striking difference in the incidence of anxiety and mood disorders.

In their study, Smith and colleagues experimentally induced progesterone withdrawal, which, as expected, triggered a sharp drop in allopregnanolone. Normally, allopregnanolone acts as an endogenous sedative by enhancing the effects of GABA. The authors found that when levels of progesterone and its metabolite allopregnanolone fell, there was a corresponding increase in the production of the alpha-4 molecule. This radically weakened GABA’s anxiolytic effects.

Following this sequence of events to its implicit conclusion, the scientists then blocked production of the alpha-4 molecule and found that, as would be expected, the progesterone withdrawal syndrome was also blocked.

Since benzodiazepines potentiate GABA, the authors decided to test the hypothesis that there is cross-tolerance to progesterone, allopregnanolone, and benzodiazepines. They found that 24 hours after
progesterone withdrawal, the GABA-potentiating effect of lorazepam fell drastically, in some cases disappearing completely. They confirmed that this was a result of the withdrawal of the progesterone metabolite allopregnanolone by using another drug to block the initial formation of allopregnanolone during progesterone exposure. When they did this, the insensitivity to lorazepam following progesterone withdrawal did not occur. Further tests found that the decreased sensitivity to lorazepam correlated with increased seizure activity. In humans, it has been reported that women who suffer from PMS are insensitive to benzodiazepines. In addition, some women suffer from catamenial epilepsy, a form of seizure activity altered by the menstrual cycle that occurs toward the end of menses when progesterone drops. Withdrawal from ethanol, another GABA-modulating drug, is also characterized by seizure susceptibility, the authors note. All of these observations point to the potential clinical relevance of the research.

“Our results indicate that fluctuations in endogenous progesterone levels may result in plasticity of the GABA-alpha receptor through the GABA-modulating allopregnanolone,” the authors conclude. “Fluctuations in levels of these neuroactive steroids are associated with the menstrual and pregnancy cycles, and are induced by stress in males. Manipulation of the GABA-alpha receptor alpha-4 subunit levels may prevent cross-tolerance with sedative drugs and reduce generalized excitability and increased seizure susceptibility associated with periods of endogenous progesterone withdrawal.”

Bibliography


