

Both obese and anorexic women have low levels of 'feel good' neurosteroid

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Women at opposite extremes of the weight spectrum have low levels of the neuroactive steroid allopregnanolone, according to new research published in the journal *Neuropsychopharmacology*.

Previous research has linked low levels of allopregnanolone—known to scientists as "allo"—to depression and anxiety, which are common mood disorders associated with anorexia nervosa and obesity.

Allo is a metabolite of the <u>hormone progesterone</u>, one of the two major female hormones (the other being estrogen). Allo binds to receptors for the neurotransmitter gamma-aminobutyric acid (GABA) in the brain. These receptors are also the targets of anti-anxiety drugs such as benzodiazepines. Allo works by enhancing the signal produced when GABA binds to its receptor, generally producing a positive mood and feelings of well-being.

More than 50 percent of <u>women</u> with anorexia nervosa have depression or anxiety, and 43 percent of adults who are obese have depression.

Low levels of allo have been linked to depression and anxiety in numerous previous studies, including people with depression and posttraumatic stress disorder. But the chemical—and its impact on mood—has not been measured in anorexic or obese women.

"We are beginning to see more and more evidence that low allo levels are tightly linked to depression, anxiety, <u>post-traumatic stress disorder</u>



and other mood disorders," said Graziano Pinna, associate professor of psychiatry in the University of Illinois at Chicago College of Medicine and an author on the paper. "To see that women with anorexia nervosa and obesity have low levels adds to the picture that the role of allo is under-recognized in mood disorders."

Pinna's colleagues, led by Dr. Karen Miller, professor of medicine at Harvard Medical School, recruited 12 women with anorexia nervosa and amenorrhea (stopped having their menstrual periods) whose body mass indices were less than 18.5; 12 normal-weight women with BMIs between 19 and 24; and 12 obese women with BMIs at 25 or higher. None of the women had received a diagnosis of depression or ever took antidepressants. The average age of the participants was 26 years old.

Participants completed questionnaires to assess for depression and anxiety and had blood drawn. Blood measurements of allo and other hormones were performed by Pinna's lab at the UIC. The lab had previously developed a novel, highly sensitive method technology to detect sex hormones and their metabolites. Pinna's lab is one of only three in the United States performing these measurements, which use gas chromatography and mass spectrometry to pick up extremely small levels of these chemicals in blood serum, saliva and brain tissue.

The researchers found that in women with anorexia nervosa and in obese women, blood levels of allo were 50 percent lower than they were in women with normal BMIs, and women who were clinically obese had allo levels approximately 60 percent lower than women with normal weights.

The researchers also found that levels of allo in all participants correlated with the severity of their depression and anxiety symptoms as measured by the questionnaires. Participants with lower levels of allo had greater severity of depression symptoms.



Progesterone levels were similarly low across all groups, suggesting that the decrease in allo in participants with anorexia nervosa and obesity may have been caused by improper functioning of enzymes responsible for the metabolism of <u>progesterone</u> into allo.

"Women with anorexia nervosa had low progesterone because they were amenorrheic, and the other two groups also had low progesterone levels because their blood was taken in the follicular phase when progesterone is naturally low," said Pinna. "That we found that <u>obese women</u> had lower allo levels than normal weight participants adds to growing evidence that this steroid is involved in depression and anxiety regardless of how much progesterone is available to begin with."

Pinna believes that the enzymes that convert progesterone into allo may not be working properly, causing decreases in allo that lead to <u>mood</u> <u>disorders</u>. "Drugs that increase the efficacy of these enzymes may be useful in helping to boost allo levels," he said. "But more research is needed to figure out exactly the deficit in the metabolism of progesterone into allo so that precision medicines using allo as a biomarker can be developed."

"Depression is an incredibly prevalent problem, especially in women, and also particularly at the extremes of the weight spectrum," said Miller. "The hope is that a greater understanding of mechanisms contributing to these disorders—including abnormalities in the regulation of hormones and their neuroactive metabolites—may lead to new targeted therapies in the future."

Pinna is leading preclinical studies of drugs designed to boost allo levels using several pharmacological strategies. These drugs have had promising effects in mouse models of PTSD and <u>depression</u>.

More information: Laura E Dichtel et al, Neuroactive Steroids and



Affective Symptoms in Women Across the Weight Spectrum, *Neuropsychopharmacology* (2017). DOI: 10.1038/npp.2017.269

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