Steroids May Influence Changes in Mood

Some steroids depress nerve cell activity in the brain and others enhance it, possibly contributing to the mood changes associated with steroid fluctuations in disease or stress

A person with too much of the hormone cortisol in the bloodstream may be depressed, and have Cushing's disease, anorexia nervosa, or clinical depression. But why? Perhaps one reason is that a metabolite of cortisol may act like a barbiturate and depress nerve cell function in the brain.

It has been known for some time that barbiturates are effective as sedatives and anesthetics because of their ability to inhibit or depress nerve cell activity. New information indicates that a metabolite of a steroid hormone in rats, 3α, 5α-tetrahydrodeoxycorticosterone (THDOC), appears to act like a barbiturate. If humans produce a similar metabolite, perhaps it also inhibits nerve cell activity in the brain and spinal cord and makes the person feel depressed.

Maria Majewska, Rochelle Schwartz, and Steve Paul of the National Institute of Mental Health (NIMH) and Neil Harrison and Jeffery Barker of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) find that the deoxycorticosterone metabolite, THDOC, acts very much like the barbiturate, pentobarbital. They measure the effects of the compounds on rat brain and spinal cord neurons grown in laboratory culture dishes and in membrane vesicles prepared from rat brain. Their new results appeared in the 23 May issue of *Science*.

Now, the NIMH and NINCDS researchers have evidence that some steroid metabolites inhibit or depress nerve cell function and that other steroids appear to excite nerve cells. An intriguing aspect of these effects is that both the inhibitory and excitatory steroids appear to interact with the same receptor molecules in nerve cell membranes, but in opposite ways.

Courtesy of *The New Yorker*, January 16, 1978

The inhibitory steroid metabolites, such as THDOC, both mimic and enhance the effects of a normally occurring inhibitory neurotransmitter, GABA (gamma-aminobutyric acid). This effect is like that of pentobarbital, and if large numbers of neurons are affected, the result is depression of central nervous system activity.

In contrast, excitatory steroids block GABA's normal inhibitory effects. And when nerve cells are less inhibited, they become more excitable. Thus, both inhibitory and excitatory steroids appear to act at a specific kind of receptor, the $GABA_A$ receptor.

"There seems to be quite an intricate interaction among steroids in regulating GABA-mediated signals," says Majewska. Some people produce more of the inhibitory steroids and others produce more of the excitatory ones. So depending on what category of steroid is produced most, the effects on an individual's mood and behavior can be opposite—either depressive or excitatory.

Cortisol, corticosterone, and the THDOC metabolite are steroid hormones produced by the adrenal glands. Normally, the hypothalamus releases corticotropin-releasing hormone (CRH), which signals the pituitary gland to release adrenocorticotropic hormone (ACTH). ACTH then triggers the outer portion of each adrenal gland to release its steroid hormones.

But in Cushing's disease, depressive illness, and stress, the adrenals release greater than usual amounts of steroid hormones into the bloodstream. This may result in higher circulating levels of the barbiturate-like metabolite that depresses nerve cell function. Thus, recent data from different laboratories are pointing in the same direction. Majewska's findings can be correlated with results from two papers in a recent issue of the *New England Journal of Medicine*.

Philip Gold at NIMH and George Chrousos, of the National Institute of Child Health and Human Development, and their colleagues have just reported that high cortisol levels are common in patients with Cushing's disease, anorexia nervosa, and depression. In 22 May issue of the *New England Journal*, Gold and his co-workers describe methods by which they distinguish the cause of high blood cortisol levels in Cushing's disease and depressed patients. They also report that elevated cortisol in anorexia and depression may reflect a failure in the appropriate signals to the hypothalamus, a gland in the brain that initiates the chain of command in cortisol production.

The concept that steroid hormones have direct effects on nerve cell membranes counters the traditional notion of their mechanism of action. There is a great deal of evidence that steroid hormones act on many different kinds of body tissues, including nerve cells, by going through cell membranes, binding to receptors in the cytoplasm, and ultimately affecting gene expression in the nucleus.

The new evidence suggests that, in addition to this well-documented mode of action, steroids also interact with surface membrane receptors to change the excitability of nerve cells rapidly and directly.

Perhaps the new evidence, that normally occurring steroid hormones and their metabolites directly affect nerve cell excitability, has implications for patients with abnormal levels of circulating steroids.

The Majewska group's data show that

THDOC and a metabolite of the sex steroid, progesterone, act like barbiturates. Surprisingly, the two steroid metabolites are even more potent than pentobarbital in enhancing the inhibitory effects of GABA.

"This is speculation," says Barker, "but if cortisol can be converted to an active metabolite, and if the metabolite crosses the blood-brain barrier and enters the cerebrospinal fluid and the brain, then the metabolite might be expected to amplify the inhibitory effects of GABA. If these events take place, they might help to explain why the central nervous system is depressed when there are abnormally high levels of cortisol in the blood."

Majewska points out that when steroid levels are high in the bloodstream, they will also be high in the cerebrospinal fluid (CSF) that bathes the brain. "The brain is like a sponge for steroids," she says. Steroids are very soluble in cell membranes and would be expected to cross the blood-brain barrier and enter the CSF.

According to Gold, "There may be other ways in which GABA and adrenal steroid hormones interact." For instance, GABA may inhibit cortisol production by blocking CRH release from the hypothalamus. And in addition to their direct actions on surface membrane receptors for GABA, the steroid hormones may enhance the inhibitory effects of GABA indirectly, by acting through intramembrane enzymes.

Gold thinks one problem in depressed patients is an abnormally high level of CRH produced by the hypothalamus, a condition that may result from too little GABA inhibition of CRH production.

"The clinical observation of the effects of glucocorticoids on mood are very complex," says Gold. "These steroids may produce euphoria in short-term low doses and depression in long-term high doses."

Majewska proposes that many of the mood changes associated with stress, the menstrual cycle, and pregnancy may be related to the effects that steroids and their metabolites have on nerve cells in the brain. And with depression, Cushing's disease or anorexia nervosa, when blood steroid levels increase, mood changes such as anxiety and depression may be even more pronounced. ■ **DEBORAH M. BARNES**

ADDITIONAL READING

M. D. Majewska *et al.*, "Steroid hormone metabolites are barbiturate-like modulators of the GABA receptor," *Science* **232**, 1004 (1986).

P. W. Gold *et al.*, "Responses to corticotropin-releasing hormone in the hypercortisolism of depression and Cushing's disease," *N. Eng. J. Med.* **314**, 1329 (1986).

P. W. Gold *et al.*, "Abnormal hypothalamic-pituitary-adrenal function in anorexia nervosa: Pathophysiologic mechanisms in underweight and weight-corrected patients," *ibid.*, p. 1335.

Briefing:

The Ocean's Deserts Are Blooming

Oceanographers are increasingly confident that they have been underestimating the biological productivity of almost half of the world's ocean. On a recent research cruise to the central North Pacific, supposedly one of the least productive regions of the world's ocean, they found two to three times as much organic matter being created through photosynthesis as had been reported in the past. Although part of the problem may have been with the traditional carbon-14 method of productivity measurement, oceanographers strongly suspect that they have not sampled the ocean often enough to catch the pulses of high productivity that may account for much of the total production in such waters.

The North Pacific cruise last August and September was part of a project on the study of plankton rate processes in oligotrophic (least productive) oceans. On the cruise, independent groups measured productivity using three different techniques, all of which depended on measuring changes in a few hundred milliliters of water collected in bottles. One technique is the traditional carbon-14 method in which photosynthesis incorporates carbon-14–labeled carbonate in new organic matter. A second technique involves the labeling of the water with oxygen-18, which shows up in the oxygen produced by photosynthesis. The third technique is a conventional titration of the resulting oxygen that is precisely controlled by a computer.

The results of the three methods agreed well with each other, according to project coordinator Richard Eppley of Scripps Institution of Oceanography, and recorded primary productivity at the rate of 550 milligrams of carbon per square meter per day, which is two to three times the value previously reported for the study area about 640 kilometers north of Hawaii. In fact, the rates are similar to those found on the project's 1982 cruise much nearer Hawaii. In that case, the relatively high productivity had been attributed to the proximity of the islands.

Eppley says that the group cannot explain the higher productivity, but the ultraclean approach applied to all three methods may have played a role. George Knauer of the University of Southern Mississippi had recommended that water sampling and handling equipment be as clean as possible to avoid poisoning the phytoplankton, especially with toxic trace metals. Time limitations prevented a complete comparison of traditional and ultraclean conditions, but the project workers agree that they now have more confidence in the data when ultraclean methods are used. They also agree that results might be even more reliable if bottles could be avoided entirely. Despite the care they took, microscopic inspection revealed phytoplankton dying during the incubation of the water samples, presumably because a bottle is not as hospitable as the ocean.

An alternative to small bottles has been huge, ocean-scale volumes of seawater bottled up by natural ocean processes. In the latest such experiment, William Jenkins and Joel Goldman of the Woods Hole Oceanographic Institution used published data from 18 years of observations near Bermuda in the Sargasso Sea. They measured productivity by following the photosynthetically produced oxygen temporarily trapped during the summer within the warm, stable upper 100 meters. They found a rate of 50 grams of carbon per square meter per year, a rate so high that the amount of nitrate nutrient in the water could not possibly fuel it.

Jenkins and Goldman suggest that the needed nitrate mixes upward from deeper waters only now and then, possibly during stirring by storms, to create a localized pulse of high productivity. This hypothesis would make it less likely that oceanographers' relatively skimpy sampling would produce representative results. Nutrient supply from below would also tend to create two layers of differing productivity, Jenkins and Goldman point out. The upper layer would be the traditional low-nutrient, biological desert where perhaps 90% of what little organic matter is produced would be destroyed and its nutrients recycled to fuel further production.

In the lower layer, just above the source of nutrients, nutrient supply would be higher and thus production could be higher, but recycling would be less efficient, allowing perhaps 50% of the organic matter produced to escape by falling into deep water. Knauer and his colleagues in the Vertical Transport and Exchange (VERTEX) research program have found evidence of such a two-layer structure in the oligotrophic North Pacific. Trevor Platt and William Harrison of the Bedford Institute of Oceanography have argued recently that, overall, recycling under the conditions proposed for a two-layer system would be less efficient than previously assumed. That could help explain the difference between bottle methods and large-scale methods, a comparison of which requires some estimate of recycling efficiency. ■ **RICHARD A. KERR**