## Hormone mimics get harder to pigeonhole

When the idea that some pesticides and other contaminants might act like hormones first gained widespread attention 4 years ago, researchers tended to describe these agents as environmental estrogens. Almost invariably, the substances appeared to imitate the body's primary female sex hormone.

Now, a study in the just-published March Environmental Health Perspectives suggests that many pollutants designated as estrogens may also mimic to some extent androgens, the male sex hormones.

Pollutants have usually been defined as estrogens or androgens on the basis of their ability to bind to one of two types of specialized, gene-activating proteins called steroid receptors. A new study by Benjamin J. Danzo of the Vanderbilt University School of Medicine in Nashville, Tenn., finds that some environmental contaminants can bind to both estrogen and androgen receptors

Ironically, even androgen mimics that are devoid of estrogen activity might feminize a male animal if they bound to an androgen receptor—and thus shut out natural androgens—yet failed to turn it on (SN: 1/22/94, p. 56).

Many of the 11 pollutants that Danzo tested also attached to other binding proteins. Unlike steroid receptors, which allow hormones to turn on genes in the nucleus of a cell, these binding proteins trigger hormone action at the surface of cells, Danzo explains.

## Node emerges on brain's emotional network

Scientific teams armed with high-tech imaging devices are enmeshed in a search for interconnected brain structures that coordinate emotion and influence the emergence of mood disorders. One part of this network lies near the front of the brain, adjacent to the bundle of nerve fibers that connects the cerebral hemispheres, a new study finds.

This region, situated within a neural locale called the prefrontal cortex, exhibits signs of sluggish activity during bouts of major depression and evidence of heightened activity during periods of manic euphoria and restlessness, contend psychiatrist Wayne C. Drevets of the University of Pittsburgh Medical Center and his coworkers in the April 24 NATURE.

Moreover, the left hemisphere volume of this prefrontal site drops sharply in people suffering from major depression or manic depression, compared to folks free of past and current mental disorders, the group reports.

Prefrontal tissue loss of this magnitude reflects either disturbances in brain development or the ravages of repeated, extreme mood shifts, the researchers theorize. In either case, the resulting communication breakdown between this prefrontal location and other brain structures involved in emotion—such as the amygdala—distorts emotional responses and social decisions, they argue.

For example, a cerebral scenario of this type may contribute to the intense guilt and anxiety over one's actions often seen in people with major depression.

"This new finding is consistent with an evolving body of data that is defining an elaborate brain network involved in mood regulation," remarks psychiatrist Helen S. Mayberg of the University of Texas Health Science Center at San Antonio.

Mayberg and her colleagues have found that neural activity in the same

general prefrontal segment noted in Drevets' study varies according to whether or not depressed individuals benefit from antidepressant drugs (SN: 3/8/97, p. 141).

Drevets and his colleagues studied positron emission tomography (PET) images and found a prefrontal area with reduced blood flow in the brains of 11 people with manic depression, compared to 39 individuals who had no history of severe psychiatric disorders. A higher-resolution PET camera then enabled the scientists to locate the site of the most severe drops in prefrontal blood flow in 7 additional volunteers with manic depression, compared to 12 more controls.

High-resolution PET scans also enabled the team to identify comparable prefrontal blood flow drops in 10 people diagnosed with major depression, Drevets' team asserts. At the time of testing, all participants with a mood disorder cited moderate to high levels of depression; none had received any psychoactive drugs for at least 4 weeks.

Preliminary PET data from four people in the manic phase of manic depression indicate that neural activity in the critical prefrontal region exceeds that observed in controls.

Another brain-viewing technique, magnetic resonance imaging, revealed marked volume reductions in the prefrontal area's left side for all the depressed volunteers, whether diagnosed with major depression or manic depression.

These findings delineate with unprecedented precision one component of a brain system that organizes emotional responses to complex personal and social situations, writes neuroscientist Antonio R. Damasio of the University of Iowa College of Medicine in Iowa City in an accompanying comment.

— B. Bower

The new findings "certainly have changed my perception of the risks that these [pollutants] pose," the reproductive endocrinologist says. If hormone mimics can simultaneously work through more than one receptor or binding protein, the effects of exposures below those previously expected to be discernible may combine or piggyback to cause harm, he says.

In his new study, Danzo placed natural estrogens or androgens into test tubes containing estrogen receptors, androgen receptors, or one of two binding proteins—androgen-binding protein from rat prostates and sex-hormone-binding globulin from humans. He then dumped a large quantity of some hormone-mimicking pollutant into each mix. The pollutants included nonylphenol, a building block of many plastics, and several pesticides that commonly taint food or the environment.

By comparing how much natural hormone bound to the receptors or binding proteins—with and without the pollutant—he was able to measure the binding of the pseudohormone.

While there were no surprises among the compounds that bound to the estrogen receptor, Danzo says he was amazed to see how many pollutants bound to the androgen receptor: DDT and three of its breakdown products, two ingredients of lindane (gamma- and delta-HCH), dieldrin, atrazine, and pentachlorophenol. In earlier studies, other scientists had described many of these substances—dieldrin, atrazine, and some of the DDT breakdown products—as estrogens

Most of the test compounds also linked to at least one binding protein.

"If [Danzo] is right about the androgen receptor stuff here, it would be striking" and potentially "a major cause for concern," says endocrinologist Nira Ben-Jonathan of the University of Cincinnati Medical School. However, Ben-Jonathan adds that she's reserving judgment until Danzo verifies the identities of the receptors and binding proteins that he used.

Toxicologist Devra Lee Davis of World Resources Institute in Washington, D.C., is impressed by Danzo's preliminary findings. "Scientifically, this important study presents an almost dizzying array of possibilities about the potential for synergistic effects of many different [environmental hormones]" and why "even low concentrations of these things could be of great concern."

If there were to be an effect on humans, Davis says, "it would most likely occur in rapidly dividing cells," such as those in the fetus, young children, or the tissue that produces sperm. "It may even have an influence on the sex of children or the ability of couples to have children," she speculates.

— J. Raloff

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