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SCIENCE WRITERS: Release date for this story has been set to coincide with publication of the research report in *Proceedings of the National Academy of Sciences.* A press conference has been scheduled with Dr. Avram Goldstein Thursday, December 20 at 2 p.m. at the Addiction Research Foundation, 701 Welch Road, Palo Alto, Building B, 3rd floor. Please notify the News Bureau if you plan to attend. Texts of the scientific paper and photos are available on request.

ADVANCE FOR RELEASE IN AM PAPERS, FRIDAY, DECEMBER 21, 1979

PALO ALTO—

Scientists at the Addiction Research Foundation have discovered a new brain chemical, 200 times more potent than morphine, and 50 times more powerful than a previously identified chemical, beta-endorphin.

The substance is called dynorphin, from the Greek word for power (dynamis) and the word endorphin, meaning natural morphine. Dynorphin is a member of a family of brain peptides or small proteins scientists believe play a role in relieving pain and regulating behavior.

The discovery of the substance is significant because it is a step forward in understanding brain chemistry, and in particular, how Mother Nature regulates pain.

In addition, the high potency of dynorphin indicates that it binds with high specificity to its receptor, a special molecule that fits it like a lock fits a key.

Drugs or chemicals must interact with receptors in cell membranes in order to exert their effects.

It is not yet known where dynorphin acts in the brain, or what function it serves. But it may lead scientists to the discovery of a receptor, or lock, for some highly specific function, such as pain relief, and thus enable them to construct more selective and more powerful drugs which fulfill the function.

A report on the research was published Thursday, December 20 in the current issue of the *Proceedings of the National Academy of Sciences.* It was authored by Avram Goldstein, Shinro Tachibana, and Louise I. Lowney of the Addiction Research Foundation, and by Michael Hunkapiller and Leroy Hood, of the California Institute of Technology.

The Addiction Research Foundation is a nonprofit institution attempting to develop basic information and improve methods of treatment for addictive diseases.

Dr. Goldstein, director of the Addiction Research Foundation, is also professor of pharmacology at Stanford. Dr. Tachibana is a visiting scientist on leave from Eisai Ltd., a Japanese pharmaceutical firm. Mrs. Lowney is a senior research assistant at the Addiction Research Foundation.

Dr. Hood is a professor of biology at Caltech and Dr. Hunkapiller is his associate. The Caltech team have developed improved techniques for sequencing peptides and proteins in tiny amounts, thus identifying individual amino acid residues that make up the peptide chain.

The work was made possible by grants from the National Institute on Drug Abuse and the National Institutes of Health, Department of HEW.

The dynorphin story actually began in 1971, with the discovery of specialized receptors for opiates, like morphine, in nerve cells by Goldstein and his colleagues. The existence of these receptors suggested that the body may produce chemicals to fit them.

This theory was borne out four years later, when the Addiction Research Foundation group discovered morphine-like peptides in animal pituitary glands. Other substances, the enkephalins, were found in brain by researchers in Scotland and Sweden.

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These "peptides" are produced in a variety of animals, from earthworms to humans. They are located in various parts of the nervous system, in the pituitary gland at the base of the brain, in the intestine, and in other tissues. Their location in the pituitary, the master gland in the hormone system, suggests that they may regulate hormone secretion or act as hormones themselves.

Immunological methods for detecting the substances were used to "map out" their distribution in the brain. They were found in highest concentrations in those areas associated with pain pathways, and the regulation of emotional activities.

One of these peptides, beta-endorphin, has been tested in humans for its ability to relieve pain, to treat drug addiction, and to reduce symptoms of severe mental illness, but the results are far from conclusive.

At the time of the endorphin discovery, the group at Addiction Research Foundation also found another peptide, which clearly was not related to beta-endorphin. It had a lower molecular weight, was more basic, and had a more persistent effect, as measured by its ability to inhibit electrically-stimulated twitching in isolated guinea pig intestinal muscle.

This muscle is used to test activity of morphine-like compounds because it contains a receptor of the same type that seems to mediate, or unlock, analgesia.

However, the researchers could isolate only small quantities of the substance, too small for the usual tests needed to determine its structure. Conventional sequencing requires milligrams of peptide, much more than had been obtained. So Goldstein turned to the Caltech group.

By increasing the sensitivity of the technique and damping out "background noise," Dr. Hood and his associates have been able to sequence much smaller quantities of peptides and proteins. The procedure employs a step-by-step removal and analysis of the amino acid residues.

The Caltech researchers were able to identify the first 13 residues of dynorphin, using only two micrograms of material. "Theirs is a tremendously improved technique for sequencing tiny amounts of material," Goldstein said. "It is a tour de force".

The first five residues of the identified fragment contained leucine enkephalin, one of the substances discovered in 1975. However, dynorphin is about 700 times more potent than the enkephalin. The researchers believed that the increase in potency was due to the extra residues they had identified.

To test their hypothesis, they synthesized the 13 residue peptide. It proved to be just as potent as the whole natural dynorphin molecule in the biological assay with guinea pig muscle. Less than one billionth of an ounce could completely stop the movements of the small bit of muscle tissue. In addition, naloxone, a drug which selectively blocks the action of morphine-like substances, also blocked dynorhin.

"Now we must answer these questions," Goldstein said. "What does dynorphin do? Where is it found in the brain? Under what conditions is it released? Is an abnormality of dynorphin function implicated in any disease conditions in humans?"

To "map out" the distribution of dynorphin in the brain, Goldstein and his colleagues are developing a radioimmunoassay, using antibodies made against the dynorphin molecule.

This technique also will enable the scientists to test human plasma and cerebrospinal fluid for the substance.

The most exciting aspect of dynorphin, Goldstein said, is that it indicates a level of specificity in these morphine-like peptides not previously recognized.

Ideally, Goldstein said, scientists would like to find a drug that is a strong pain killer, but has no effect on consciousness, and is not addicting.

Dynorpin may lead scientists to a specific receptor, or lock. If dynorphin is found to be a potent analgesic, and if the receptor can be identified, "it could be a big step forward in developing drugs to relieve pain without side effects," he said.

Goldstein also pointed out other areas in which the morphine-like peptides may be involved, such as mood disturbances, blood pressure collapse in shock, temperature regulation, and regulation of the sex hormones. "Dynorphin might turn out to be most selective in one of these functions rather than in pain relief," he said. "Only time and more research will give us the answers."

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QUESTIONS AND ANSWERS

gleaned from an interview with Dr. Goldstein by the Stanford University Medical Center News Bureau

Q) *What are the possible roles of dynorphin?*

A) Dynorphin is extremely potent in inhibiting electrically stimulated twitching in isolated guinea pig intestinal muscle, indicating that it binds specifically to receptors involved in analgesia. However, it is not as potent when tested in the mouse vas deferens, which contains a different type of receptor.

When dynorphin was injected into the brains of rats, catalepsy, a loss of voluntary motion observed with morphine, occurred. This indicates that dynorphin also causes changes in behavior.

Q) *How does dynorphin relate to other endorphins?*

A) Dynorphin is structurally unrelated to beta-endorphin but it does have some similar effects.

It contains leucine enkephalin, and may be a precursor molecule to that substance. It is possible that enzymatic breakdown may be Nature's way of "turning off" the action of dynorphin into less active enkephalin. To determine this, we will be trying to see if dynorphin is present in the same nerve cells as the enkephalin.

Q) *Have all the endorphins been discovered?*

A) By no means. There probably is a wide variety of these natural morphine-like compounds, which interact with a variety of opiate receptors. This complex means of interaction is evident in other systems, such as the neurotransmitters, chemical messengers which carry electrical impulses from one nerve cell to another.

Q) *How does this discovery relate to addiction research?*

A) It's too early to tell. One of the theories about addiction to opiate narcotics is that there is interference with the natural morphine-like peptides. The brain may get used to the heroin or morphine, and therefore stop producing endorphins. No such dramatic disturbance has been found, so far, for enkephalins or beta-endorphin. We will certainly want to see what happens to natural dynorphin in animals and humans during narcotic addiction.

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Q) *What impact do you think this discovery will have on understanding pain, and human disease like schizophrenia, in which a role of endorphins has been suggested?*

A) Again, we can only speculate. In pain relief by acupuncture, for example, some endorphin seems to be released, but so far it is not known which one is involved. Possibly it will prove to be dynorphin. Likewise, in schizophrenia, there are suggestive indications that there may be excessive production and release of some endorphin. However, my laboratory recently published an analysis of beta-endorphin in blood of nearly one hundred schizophrenic patients. There were no exceptional elevations in the levels. Again, maybe beta-endorphin is not the peptide that is disturbed in schizophrenia. We will be making similar measurements of dynorphin levels, to see if this new peptide may be implicated.

Q) *Is basic research in neurobiology, of the kind you are doing, really a worthwhile investment for society?*

A) I can't answer that in an objective way, of course, but there are some things worth pointing out. New discovery only comes from basic research. The greatest advances that affect people's health result from new understanding, which leads to new methods of preventing or curing illness--methods that couldn't have been developed before the new information existed. Neuropeptides obviously have a profound influence on human behavior and mental health. Every abnormality of brain function and behavior must reflect some underlying change in brain chemistry. No scientist can predict which discovery of a new brain chemical will open the door to understanding and cure of a particular mental illness, or provide new relief of pain.

Basic research really is the goose that lays the golden eggs. Just as every modern industry invests a significant part of its income in R and D, so must society invest a significant part of its gross national product in basic biomedical research, in order to guarantee—sooner or later—returns in the form of better health for the people. Our own work has been supported generously by the National Institute on Drug Abuse, a government agency. It is important to maintain adequate federal support for all biomedical research and training.

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