Brain Peptides and Psychopharmacology

Proteins isolated from the brain and used as drugs can improve and apparently even transfer mental states and behavior

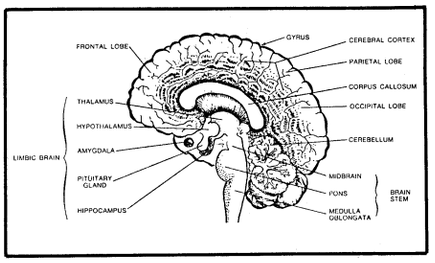
BY JOAN AREHART-TREICHEL

The past 15 years have brought marked advances in peptide chemistry. Scientists, in turn, have capitalized on these advances to isolate tiny proteins (peptides) from the brain, to use them as drugs and to show that they can improve and apparently even transfer various mental states and behavior—learning, attention, memory, motivation, anxiety, depression, pain.

Although much remains to be learned about these potent molecules—how they compare chemically, where they are made in the brain and where they act—researchers are confident that some of them or their analogs can be used to help persons with psychophysiological or behavioral problems, notably the mentally retarded, senile, and depressed, plus schizophrenics, hyperactive youngsters and chronic pain patients, in ways that are currently not available with other drugs.

The psychopharmacologically active peptides of the longest-term action and probably the greatest clinical interest are hormones made by two closely related structures in the brain—the hypothalamus and the pituitary. The hypothalamus is a cluster of cells that oozes minuscule amounts of peptide hormones. These peptides act on the pituitary gland. The pituitary then releases other peptide hormones that act on hormones throughout the body. Both the hypothalamic and pituitary hormones used to be thought to work exclusively as hormones. Then evidence started building that they have other effects as well—that they influence mental states and behavior.

Much of the pioneering work in animals showing the extrahormonal effects of these peptides was conducted by David de Wied, director of the Rudolf Magnus Institute of Pharmacology in Utrecht, Holland, and his colleagues. In 1958, for instance, he and Arthur Mirsky and Robert Miller of the University of Pittsburgh injected the pituitary hormone ACTH into rats and found some positive effects on memory. In 1965, de Wied took another pituitary hormone—MSH—and injected it into rats without pituitaries; it restored normal behavior. Then, with the help of Saul Lande, a biochemist at Yale University, he came up with more hormonal material that favorably influenced learning and memory in rats. It was closely related to another pituitary hormone, vasopressin (SN: 5/20/72, p. 355).



The various areas of the brain. Peptides arise in certain of these areas and exert actions in others.

Still other pioneering animal studies were conducted by Abba J. Kastin, an endocrinologist at the Veterans Administration Hospital and Tulane Medical Center in New Orleans, Lyle H. Miller, a psychologist at Temple University School of Medicine in Philadelphia, and Curt A. Sandman, a psychologist at Ohio State University. Meanwhile, they started obtaining similar results in humans, results which have multiplied during the past several years.

The MSH hormone can improve visual retention in human subjects, the investigators reported in 1971 (SN: 1/29/72, p. 78). Since that study was only of a small group of people they subsequently published the results of a comparable but more carefully controlled study in 1974. Some subjects got an injection of MSH, others of salt. None knew whether they were getting the real thing or a placebo. An opened book containing geometric forms was placed in front of the subjects. The book was closed and the subjects were then asked to draw the figures they had seen. Those who had received the MSH remembered the figures better than did the subjects who got a placebo, again suggesting that MSH could improve visual retention.

It also seems to enhance attention in humans. Subjects were given a very mild shock in the wrist. The researchers recorded the electrical responses of the subjects' brains to shock. The subjects were urged to be prepared for another shock. Again the electrical responses of their brains were recorded. The brains of the subjects who had received MSH gave a much larger brain response than did the subjects who had not gotten MSH, suggesting that the peptide enhances attention.

The researchers subsequently discovered that MSH may also reduce anxiety. This time they studied 40 subjects—ten received MSH, 10 ACTH, and 20 a saline injection. Both MSH and ACTH improved the subjects' visual retention and made them less anxious, whereas the saline group did not experience improved visual retention or diminished anxiety. Still another behavioral bonus may be achieved with MSH. It seems to help people concentrate better. Subjects were exposed to a group of dots. Those who had received MSH distinguished earlier than control subjects that the dots came in pairs; they were also less distracted than the controls while performing this task.

One of the most significant clinical findings Kastin and company have come up with to date is that a fragment of ACTH and MSH can enhance attention and improve memory in the mentally retarded. Sandman reported these results at a conference on neuropeptide and behavior held at Temple University School of Medicine in June. Ten retarded patients were put in sound-attenuated chambers in comfortable chairs and injected with either a peptide or saline. The subjects had to figure out certain tasks that the experimenters were doing. Those given a peptide paid better attention and learned quicker than did the patients given a placebo: They were quicker to perceive when visual stimuli were switched.

Clinical benefits from the hypothalamic peptides were also reported at the Temple meeting. The hypothalamic peptide MIF can virtually abolish the symptoms of Parkinson's disease if given in conjunction with L-Dopa and other current standard treatments for Parkinson's, reported Kastin and André Barbeau of the Clinical Research Institute of Montreal. The hypothalamic peptide TRH may also help schizophrenics, according to Nicholas Plotnikoff of Abbott Laboratories.

Still other peptides are being culled from the brain that are perhaps more provocative. Their existence was not previously known, and they have no known physiological role other than a psycho-

pharmacological one. They sound like something out of science fiction; a number of scientists even doubt their existence. These are peptides taken from the brains of trained animals that, when injected into untrained animals, apparently transfer the learned behavior.

During the early 1960s, researchers fed the brains of flatworms trained to respond to light or to navigate a maze, to untrained flatworms. The recipients seemingly copied the donors' behavior. These experiments have not, however, been replicated to everyone's satisfaction. In 1965, Ejnar Fjerdingstad of the University of Copenhagen took a crucial experimental leap from the worm to a vertebrate—the rat. He trained rats to go to light in order to receive water, then injected the brain material from trained rats into untrained ones. The recipients did not imitate the donors' learned habit right off. But they did acquire it faster than control rats that had not been injected, implying that the injected brain material indeed boosted learning and memory.

Georges Ungar and his colleagues at Baylor College of Medicine then went further. They accumulated several pounds of brain from 4,000 rats that had been trained to fear the dark. They tested different fractions of this brain material for learning and memory transfer ability in recipient rats until they narrowed the material down to what appeared to be the actual learning-memory molecule. It, like the pituitary and hypothalamic behavior molecules, turned out to be a peptide. They dubbed it "scotophobin," after the Greek for "fear of the dark," and announced their achievement in late 1970. Due to the controversial nature of the research, NATURE delayed publishing it until 1972 and then only with a commentary and critique (SN: 8/12/72, p. 100).

Undaunted by NATURE's treatment, Ungar and his colleagues have since isolated four more peptides from the brains of trained animals that, when injected into untrained animals, appear to transfer the learned behavior. One taken from rat brains and called "ameletin" produces habituation to a sound stimulus. Two other peptides taken from goldfish brains and called "chromodiopsins" trigger blue-avoidance or green-avoidance behavior. The fourth, taken from the brains of rats and called "alpha-antendorphin," produces a tolerance to morphine.

Two brain peptides that act like morphine, in fact, have also been isolated by a team of Scottish researchers. They do not transfer learned behavior as Ungar's peptides do but rather act more like the pituitary and hypothalamic peptides in improving existing mental states. Specifically, they were taken from pig brains and when injected into untrained rats produced pain relief (SN: 6/26/76, p. 406).

The peptides go by the name of "enkephalins," and researchers are excited about them because they represent the first natural pain-relieving molecules to be found in the brain and body. They have stimulated so much interest that articles about them spew off the scientific press nearly every week now. One of the questions investigators are now asking is whether the peptides have any physiological role other than pain relief.

Crucial questions are being posed about all the psychologically active peptides discovered to date. For one: How do the peptides compare chemically? The comparable psychopharmacological activity of MSH and ACTH can be attributed to a common amino acid sequence they both share. In other words, if this sequence of six amino acids is removed from the complete hormones, it produces the same psychopharmacological effects as if it remained in the hormones. The two enkephalins' comparable activity can be attributed to amino acid sequences identical except for one amino acid. Interestingly,

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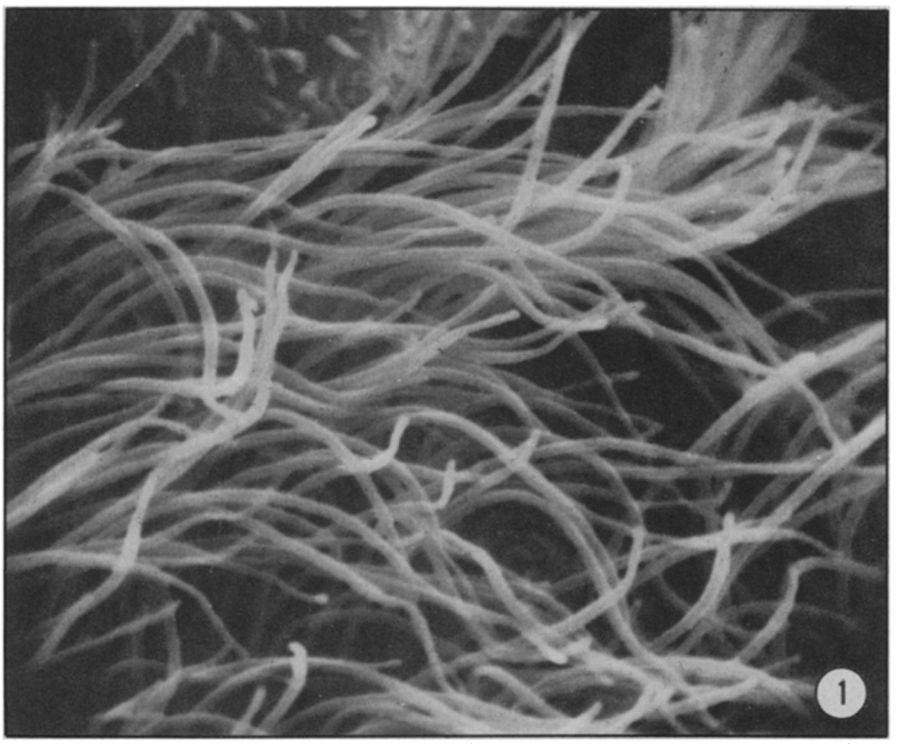
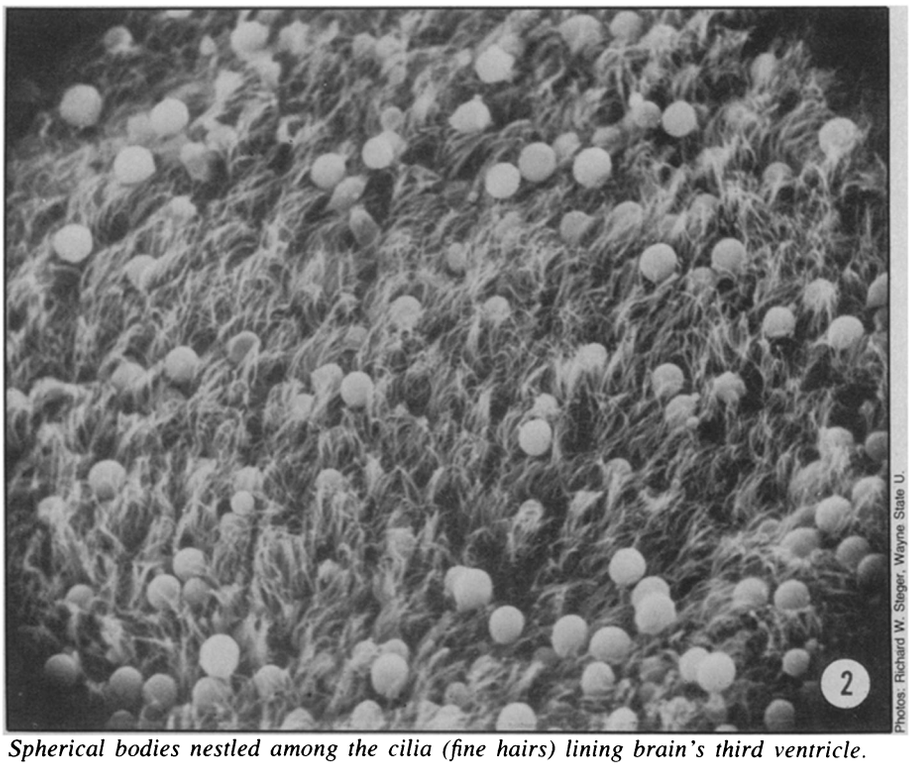


Cilia lining the brain's third ventricle, which may transport hypothalamic peptides.



Spherical bodies nestled among the cilia (fine hairs) lining brain's third ventricle.

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the enkephalins and alpha-antendorphin are almost identical in chemistry yet have almost opposite biological effects—the enkephalins relieve pain and alpha-antendorphin antagonizes it by lessening morphine's pain-relieving effects. As for the other peptides, they differ significantly in their amino acid sequences.

Another question: Where are the peptides made in the brain? The question has been fairly well answered for the hypothalamic and pituitary peptides—they are made in the hypothalamus and pituitary respectively. There is also reason to believe that the enkephalin-like materials are made in the pituitary. As for the peptides that transfer learned behavior, though, no one—not even Ungar—is sure of their origin.

Still a third matter of dispute: Where do the peptides act, either when endogenously present in the brain or when injected as drugs? Some evidence suggests that they act on the more primitive areas of the brain linked with emotions and basic drives. One study suggests that the pituitary peptides act on the thalamus, and another shows that the enkephalins act on the brainstem, just as morphine does. Likewise nettling: How do the peptides move from their origin to the target area of the brain? For instance, the thalamus and hypothalamus are connected by the third ventricle of the brain. Some hypothalamic peptides have been tentatively identified there. Are the peptides on their way to the pituitary gland to influence pituitary hormones, or are they on their way to other parts of the brain, say the thalamus, to influence mental states and behavior?

Finally: Once the peptides reach their nerve targets, how do they affect them? Scientists are far from sure, but they have some opinions. The peptides may be neurotransmitters; they may act on neurotransmitters, or they may skirt the neurotransmitters and act directly on the membranes of neurons and influence levels of the intracellular messenger cyclic AMP in the neurons.

Because neuroscientists have a great deal more to learn about the actions of neurons in the brain, not to mention the origin of various mental states and behavior and what they constitute, it will probably be years before they pinpoint the sites of actions of these peptides and determine exactly how they influence mental states and behavior. Long before then, however, there is a good chance that some of the peptides or at least their analogs will be alchemized into drugs to treat persons with various psychophysiological or behavioral problems. A number of drug companies are looking into these possibilities. And if there is anything the pioneers in this field agree on, it is that this is only the start of a new era of using brain peptides to favorably influence the mind and behavior. □