The Pituitary's Powerful Protein

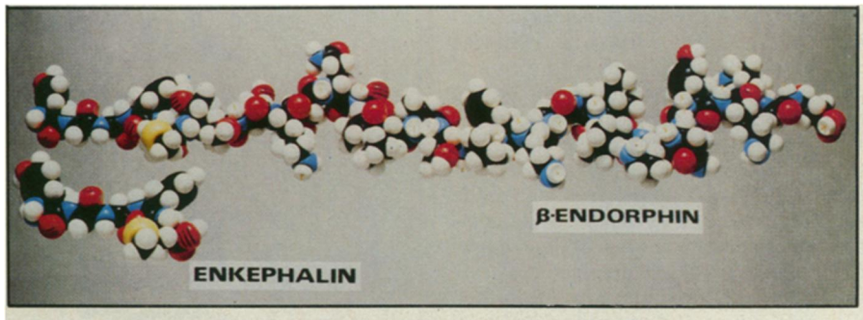
Segments of a large pituitary gland protein, which affect the brain in all sorts of ways, promise to be some of the most exciting drug finds of the 20th century

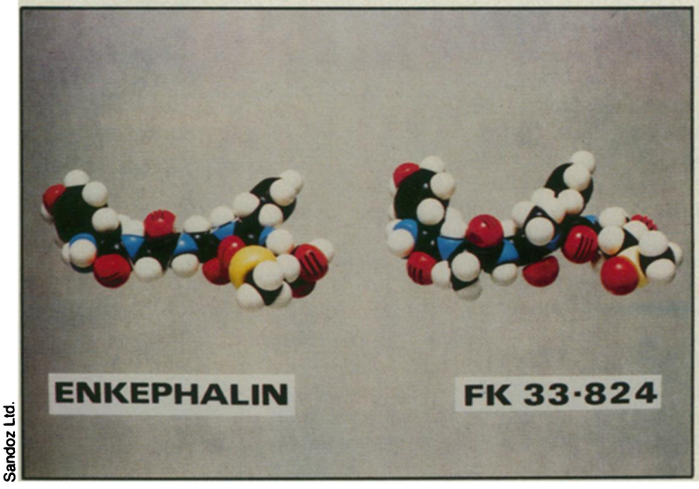
BY JOAN AREHART-TREICHEL

Visualize in the pituitary gland, which hangs just below the brain, a protein hormone being enzymatically snipped into smaller pieces, those pieces being extracted, synthesized and injected back into humans or animals, and each segment producing one or more dramatic psychological effects, such as pleasure, improved concentration or relief from the symptoms of mental retardation or schizophrenia.

Sound like something out of science fiction? Absolutely! Particularly since the pituitary gland, until recently, was thought to make only proteins that serve as master hormones in the body, not chemicals that affect the brain and central nervous system. And particularly since no one molecule, whether natural or manmade, has ever been known to produce segments with so many different and largely beneficial pharmacological effects. Yet the protein described above *does* exist, and the scenario outlined is really unfolding today in laboratories around the world. What's more, segments of the protein promise to be some of the most exciting drug finds of the 20th century.

The potent pituitary protein we're talking about is called beta-lipotropin. C. H. Li of the University of California in San Francisco discovered it in 1964 and found that it plays a hormonal role in the body — it helps mobilize fats. Discoveries by Li and other researchers during the past four years, however, have revealed that beta-lipotropin has another role as well — it is the raw material of a set of pharmacologically active molecules. Enzymes in the pituitary apparently have the ability to chop beta-lipotropin into smaller segments, and these segments exert fascinating psychological-behavioral effects, at least if extracted from the pituitary and reinjected into humans or animals. The segments of beta-lipotropin that have been isolated from the pituitary so far include: chains of amino acids 41 through 58 (which has been named beta-MSH), of amino acids 61 through 91 (beta-endorphin), of amino acids 61 through 76 (alpha-endorphin), of amino acids 61 through 77 (gamma-endorphin) and of amino acids 61 through 65 (methionine enkephalin). Let's take a look at what is now known about the psychopharmacological actions of each....



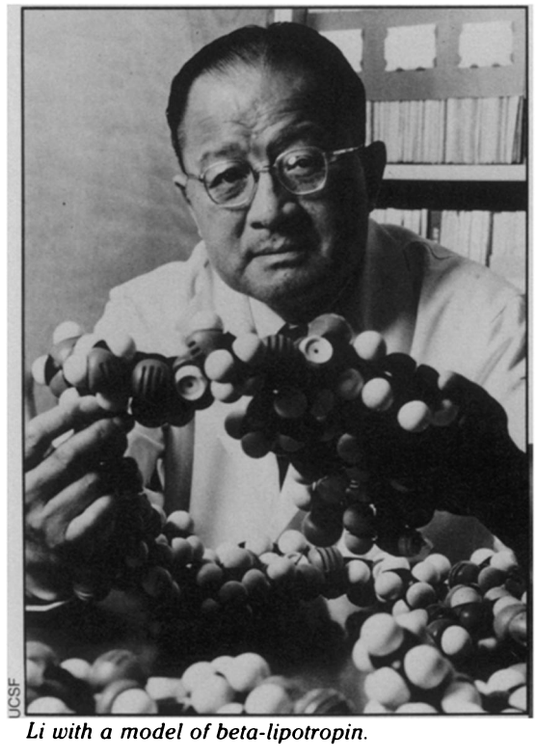


Sandoz Ltd.

A chemical model of methionine enkephalin (above) compared with a model of the larger molecule that contains it, beta-endorphin. Enkephalin (below) compared with a model of an analog of it that is being tested in clinical trials.

While beta-MSH per se has not been explored very much psychopharmacologically, part of it — amino acids 47 through 53 — has. This seven-amino-acid peptide is also called MSH/ACTH 4-10 because it is identical to a seven-amino-acid sequence in two pituitary gland hormones — 7 through 13 in MSH (melanocyte-stimulating hormone) and 4 through 10 in ACTH (adrenocorticotropic hormone). MSH/ACTH 4-10 has been found to help mentally healthy subjects remember and concentrate better, mentally retarded subjects to comprehend and work better and senile subjects to remember better — feats that drugs now available cannot claim. These findings come from Abba J. Kastin of the Veterans Administration Medical Center in New Orleans and Tulane University School of Medicine, Curt A. Sandman of Ohio State University and Lyle Miller of Boston University School of Medicine.

A decade ago, Kastin, Miller and Sandman found that MSH/ACTH 4-10 changed the behavior of rats in ways totally unrelated to ACTH's and MSH's usual hormonal effects in the body. Might the minuscule peptide have some potent behavioral effect on people? Kastin, Sandman and Miller ran a preliminary trial in healthy human subjects, then a carefully controlled experiment. Some subjects got an injection of the peptide, while others received a saline, or salt, injection. An opened book containing geometric forms was placed in front of them. The book was then closed, and they were asked to draw the figures they had seen. The persons



UCSF

Li with a model of beta-lipotropin.

who had received the peptide remembered the figures better than did those who had been given the placebo, indicating that the peptide improved visual retention.

The peptide can also reduce anxiety and help people concentrate better, the researchers subsequently found. This time subjects — medical students — were shown a group of dots. The students who had received the protein distinguished, better than those who had received salt injections, that the dots were arranged in pairs. They were also less distracted than the control subjects were. One of the students who had received the peptide exclaimed, "Wow! I sure didn't get saline. I feel like I could study now and it would really stick."

Then Kastin, Sandman and Miller injected 20 retarded patients with either MSH/ACTH 4-10 or a salt solution and gave them the task of selecting particular shapes or colors from a variety of figures they were shown. The patients who received the protein comprehended the task more rapidly than did the patients given a placebo (SN: 9/25/76, p. 202). And, most recently, Kastin, Sandman and Miller have found that an oral analog of MSH/ACTH 4-10 increased the workshop performance of mentally retarded subjects and injections of MSH/ACTH 4-10 significantly improved the visual memories of elderly senile men. One man's memory, in fact, improved 100 percent.

Beta-endorphin's psychopharmacological effects were first explored in 1975 when Li and other workers found that the protein produced a powerful analgesic activity in mice (up to 50 times that of morphine) and in 1976 when Nobel laureate Roger Guillemin and colleagues at the Salk Institute in LaJolla, Calif., and David Segal of the University of California at San Diego found that beta-endorphin put rats in a "waxy" state — one in which their limbs remained in any posture in which they were placed. This state is strikingly similar to that produced in rats by major tranquilizers currently used to treat human mental illness. So, upon learning of the results of Guillemin and his team, Nathan S. Kline, a psychiatrist at the Rockland Research Institute in Orangeburg, N.Y., and Heinz Lehmann, a psychiatrist at McGill University in Montreal, speculated: "Might beta-endorphin possibly help psychiatric patients for whom other drugs had failed?" (Kline and Lehmann were appropriate scientists to ask such a question since they had pioneered in the use of antipsychotic drugs during the 1950s.) The researchers made arrangements with Li to synthesize some beta-endorphin so they could try it on some psychiatric patients.

In the summer of 1977, Kline and Lehmann injected the beta-endorphin provided by Li into one healthy control and 14 psychiatric patients who had not been helped by available drugs. The group included four schizophrenics, two depressives, two anxiety victims, an obsessive-compulsive, three personality-disordered patients, a mentally defective patient and an autistic patient. The results — reported last December at the annual meeting of the American College of Neuropsychopharmacology and updated at an American Psychiatric Association meeting (SN: 11/11/78, p. 326) — were even more striking than Kline and Lehmann had hoped. Beta-endorphin countered depression and anxiety within five to 10 minutes after injection and for up to four to six hours following. Even more impressive, the protein also lessened or vanquished schizophrenic hallucinations and helped subjects regain their healthy personalities, which, with several booster injections of beta-endorphin, have continued more than 10 months.

As soon as Kline and Lehmann can obtain enough synthetic beta-endorphin (it's incredibly expensive — $3,000 an injection), they intend to undertake a larger, more scientifically rigorous study, using carefully matched control subjects, to further document and investigate beta-endorphin's therapeutic value for psychiatric patients. Meanwhile, other researchers are exploring beta-endorphin's ability to relieve terminal cancer pain and to ease the anguish of opiate withdrawal.

The psychopharmacological effects of alpha-endorphin and gamma-endorphin have not been explored to the degree that those of MSH/ACTH 4-10 and beta-endorphin have. However, Guillemin and company did find, in 1976, that alpha-endorphin produced an analgesic and tranquilizing effect on rats, and that gamma-endorphin induced violence, irritability and sensitivity to pain in rats. Then, earlier this year, David de Wied of the University of Utrecht, the Netherlands, and his colleagues reported that an analog (a similar but not identical synthetic copy) of gamma-endorphin helped a handful of

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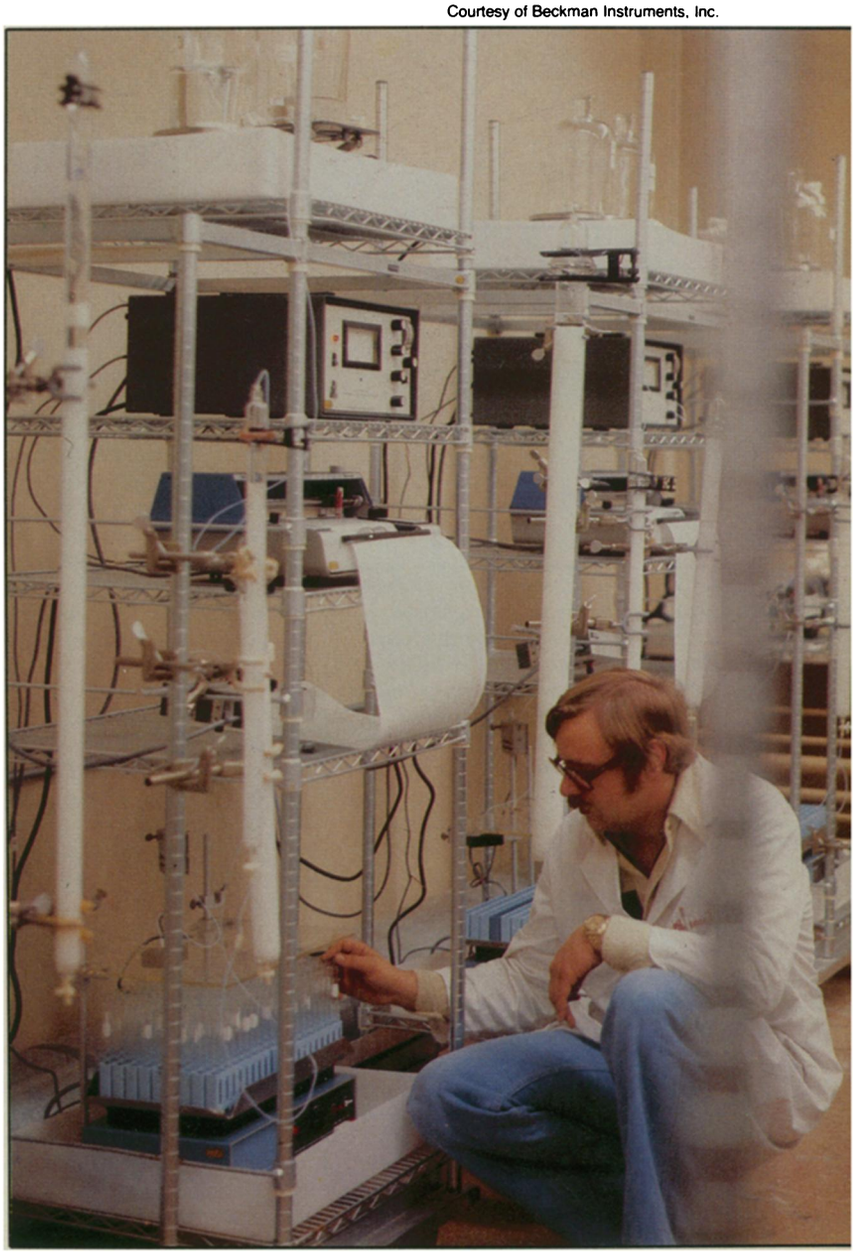
Courtesy of Beckman Instruments, Inc.



The future of beta-lipotropin segments as commercial drugs depends on large amounts of synthetic copies of the segments being available for clinical tests. Scientists at Beckman Instruments, Fullerton, Calif., one of whom is pictured here, are now making large batches of synthetic enkephalins for clinical tests and soon will be turning out large batches of synthetic beta-endorphin for this purpose as well. Until now, synthetic beta-endorphin has only been available in small research quantities and thus has been prohibitively expensive.

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schizophrenics who had not benefited from conventional drugs. One was a 19-year-old female suffering from hallucinations and delusions and engaging in magic rituals. After six days of receiving the analog, her psychotic symptoms vanished and didn't return when she stopped taking the drug. On the basis of these findings, the researchers concluded, "a controlled trial seems justified."

A number of psychopharmacological effects for methionine enkephalin (and for a related brain protein with only one amino acid difference — leucine enkephalin) have also been noted in animals. After the enkephalins were identified in 1975 by John Hughes and Hans Kosterlitz of the University of Aberdeen in Scotland, American, Swiss and British investigators reported what investigators had been hoping for — that the enkephalins are indeed the brain's own natural pain-relieving molecules (natural morphine, so to speak). In 1976, Candace B. Pert and colleagues at the National Institute of Mental Health revealed that an enkephalin analog caused profound, long-lasting pain relief when injected into rats. Last year Kastin and David Coy developed an enkephalin analog that relieved pain in rats for a period 30 times longer than the natural enkephalins could. They also found that methionine enkephaline can improve learning in rats (SN: 7/23/77, p. 59). And earlier this year, the natural enkephalins were found to have three more psychopharmacological effects on rats — the ability to induce pleasure, trigger epilepsy and reduce memory loss (SN: 4/29/78, p. 280).

That scientists have documented so many fascinating and largely beneficial psychopharmacological effects for various beta-lipotropin segments, of course, does not make these segments available at the corner drugstore. Before that happens, the protein segments must be approved as drugs by the Food and Drug Administration and marketed by a drug company. Fortunately for those eager to obtain the proteins, pharmaceutical companies are already actively exploring the marketing potential of various proteins and of their analogs.

Scientists at Sandoz Ltd. in Basle, Switzerland, for instance, synthesized a number of compounds similar to the natural enkephalins but with much greater stability. They have zeroed in on one compound — FK 33-824 — because it showed good pain-relieving activity in animals after being given orally. They are now testing this compound in human subjects to see how well it relieves pain, whether it produces addiction and tolerance like the natural enkephalins do, and whether it triggers any other psychological or behavioral effects. Researchers at Eli Lilly and Co. in Indianapolis have also designed a number of enkephalin analogs that they hope will be more stable than the natural molecules but will relieve pain just as well. They are now testing the most promising analog in mice. Investigators at Burroughs-Wellcome Co. in Research Triangle Park, N.C., are likewise pursuing the ideal analog of the pain-relieving enkephalins. So far they have shown that some of their analogs, if given orally or by injection, can get through the brain's blood-brain barrier and relieve pain.

Taking these drug company efforts into account, as well as the usual decade lag time between discovery and marketing of a new drug, it's quite possible that one or more beta-lipotropin segments, or their analogs, might become commercially available within the next 10 to 15 years. This certainly is the view of Kastin, Kline and some other scientists in this field. In fact, Kastin predicts that more psychopharmacologically active pituitary proteins may pop up as well, because the first amino acid stretch of beta-lipotropin has not yet been examined with that goal. Also, there are indications that beta-lipotropin may be part of an even larger pituitary gland chemical, one three times its size (SN: 7/2/77, p. 6; 2/18/78, p. 102). If this is indeed the case, then one can visualize segments of this protein, upon injection, producing still a new welter of psychopharmacological effects. Sound preposterous? Sure it does. But no more so than what has already happened with that marvelous molecule discovered by Li 14 years ago. □