ENKEPHALINS: More Than Just Pain Killers

These small brain proteins also help mammals learn faster

BY JOAN AREHART-TREICHEL

In 1973, word spread among pain and drug addiction researchers that there are nerve receptors for morphine in the central nervous system. A question then loomed large in their midst: Might the brain make some pain-relieving and/or addictive chemical that also interacts with the receptors? Indeed, such a substance, or rather two closely related substances, were identified in 1975 by John Hughes and Hans Kosterlitz of the University of Edinburgh. They named the related small proteins "enkephalins," from the Greek word for "brain."

Being primarily interested in pain and drug addiction, Hughes and Kosterlitz have gotten rather possessive about their *wunderkinder.* More specifically, they recently dismissed, in the BRITISH JOURNAL OF PSYCHIATRY, any other possible role for the enkephalins than pain relief. But there are other investigators around who have been exploring the behavioral effects of various small brain proteins—notably Abba J. Kastin of the Veterans Administration Hospital and Tulane University School of Medicine in New Orleans and his colleagues.

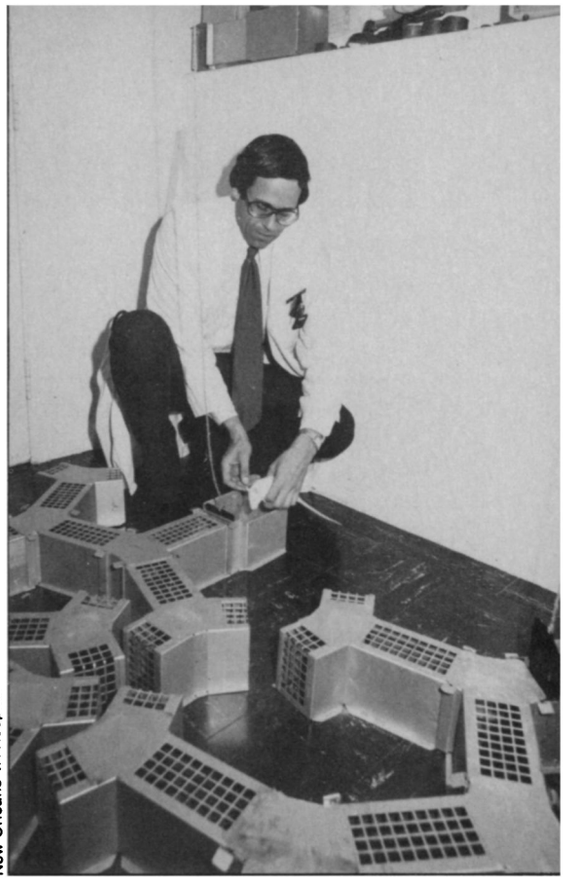
As soon as the enkephalins entered the scientific limelight, Kastin and coworker David H. Coy decided that the chemicals should be examined for their behavioral effects. And as they report in a recently published issue of PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR (5:691), one of the enkephalins at least exerts significant behavioral effects in addition to its pain-relieving activity—it can improve learning abilities.

Kastin and his colleagues injected one of the two natural enkephalins—Met-enkephalin—into the abdominal cavities of 18 hungry rats. Nineteen other hungry rats were injected with a saline solution. All of the animals were then tested over a three-day period for their ability to run a complex, 12-choice maze for a reward of food. The maze was located in an isolated, sound-attenuated room at the VA Hospital connected to a separate room in which the rats were housed and injected. Constant, indirect illumination and background white noise were present in both rooms. The animals receiving the enkephalin negotiated the maze significantly faster and made significantly fewer errors than the control animals that had received only saline.

Because all the animals had been hungry during the test, it was possible, of course, that the main action of enkephalin during the test was to increase appetite rather than to increase learning ability. This possibility, however, was ruled out by the researchers' findings that rats injected with enkephalin ate no more than control rats. Similarly, the feasibility that the enkephalin increased the ability of the rats to follow olfactory cues rather than improve their learning seemed to be eliminated by a direct test of the ability of a few of the enkephalin-injected rats to find buried aromatic food. A general augmentation of activity also was unlikely to express the faster running times of the enkephalin-injected rodents because those injected made fewer errors in the maze and in preliminary studies were no more active than control rats on several measures of activity. This lack of change in activity and lack of fecal excretion in the rats receiving enkephalin also reduced the likelihood that altered arousal led to enhanced learning results.

Other evidence that peripherally injected Met-enkephalin can influence learning, or at least the brain, came from an experiment Kastin and his co-workers just published in BRAIN RESEARCH BULLETIN (1:583). By radioactively labeling Met-enkephalin and then injecting it into the carotid artery of rats, they showed that the protein was indeed able to cross the rats' blood brain barrier—those tiny blood vessels in the brain that try to keep foreign chemicals out of the brain and often succeed in doing so. Because Hughes and Kosterlitz had shown that only when enkephalin was injected directly into the brain can it kill pain, they had concluded that enkephalin injected into the body could not have any physiological activity.

That the enkephalins have not been shown to have an analgesic action if injected peripherally, however, suggests that the behavioral effects of Met-enkephalin may be different from its pain-relieving effects in the brain. Kastin and company have now shown that this is indeed the case. They injected an analog (a closely related chemical) of enkephalin into the abdominal cavities of five rats. The analog seemed to make the rats negotiate a maze faster than did the 19 rats mentioned earlier that had received saline. Yet this analog, known as [D-Phe4]-Met-enkephalin, has virtually no opiate activity. This finding strongly suggests that Met-enkephalin influences learning in a manner separate from its pain-killing activity. Still other evidence that the pain-relieving and learning influences of Met-enkephalin are different came when the investigators injected morphine or saline into the abdomens of rats. Morphine not only did *not* improve the rats' negotiation of the maze; it slowed them down and made them make more errors compared to the rats that had received saline.



New Orleans VA Hospital

Kastin puts a rat in the maze used to show learning effects of Met-enkephalin.

How might Met-enkephalin exert its behavioral effects then? Whereas both the enkephalins and morphine are known to exert pain relief via specific opiate nerve receptors in the brain, Kastin speculates that Met-enkephalin may enhance learning by acting on other nerves in the brain. Results that he and his co-workers recently reported in LIFE SCIENCES (19:1283), in fact, suggest that Met-enkephalin injected into the body influences nerves in the brain that use dopamine as their nerve-transmitting chemical.

Although Met-enkephalin's ability to enhance learning may sound suspicious at first encounter, such an ability is really not surprising if one is familiar with the origin of the enkephalins. Specifically, Kastin and his colleagues have shown

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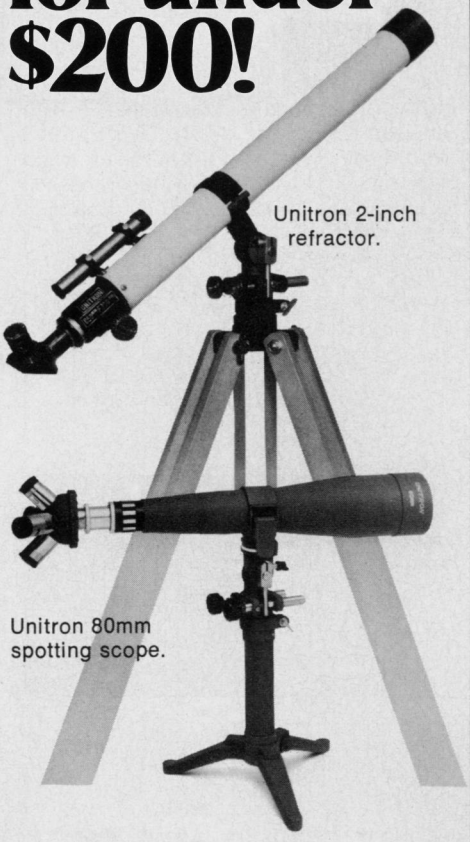

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. . . Enkephalins

that a short amino acid sequence in the pituitary hormone MSH (melanocyte-stimulating hormone) also enhances learning by making rats negotiate a maze faster than normal. This small protein derives from a large brain protein from which the enkephalins also originate. It is called beta-lipotropin (SN: 7/2/77, p. 6). Still other beta-lipotropin-derived proteins—the endorphins—have likewise been found to exert a variety of behavioral effects in rats, both by Roger Guillemin's group at the Salk Institute in La Jolla and by Kastin and Curt A. Sandman, a psychologist at Ohio State University. One endorphin can transform angry rats into docile ones. Another makes rats anxious. A third makes rats groom. And so on. In brief, in view of the enkephalins' origin and the startling diversity of behavioral effects exerted by their chemical cousins, it is hardly amazing that one of the enkephalins at least can influence learning.

Might Met-enkephalin help people learn better? Kastin feels that it may, but as he points out, the enkephalins, like morphine, have addictive properties. Thus he would be reluctant trying it in clinical trials. Anyway, MSH exerts similarly positive effects on learning and is not addictive, and Kastin and Sandman are already achieving positive results among both healthy and mentally retarded subjects by using MSH to enhance attention and learning (SN: 9/25/76, p. 207). With Lyle H. Miller of Temple University in Philadelphia, they will also soon undertake studies to see whether MSH can improve the attention span and learning abilities of older people and whether a more potent analog of MSH might be even more effective than MSH in helping the mentally retarded.

Nonetheless, the use of Met-enkephalin as a human behavioral drug has not been altogether ruled out. And even if it is never used clinically to enhance learning, its behavioral effects represent another exciting discovery about the brain's small proteins. □

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long-range cruise missiles. Not surprisingly, the Russian press and official spokesmen have roundly condemned both new weapons.

Even within the U.S. government there seems to be disagreement over the likely impact of the weapons. The Pentagon argues that both weapons will not only add new capability and versatility to the U.S. arsenal but also force the Soviet Union to divert large amounts of funds from offensive to defensive projects. To counter the cruise missile would require years of R&D in radar and missile technology, and to shield tanks against neutron radiation would also require a massive effort. Disarmament specialists contend that introducing such new weapons now will only make the Russians less conciliatory in the forthcoming SALT talks.

Whatever the outcome of this debate, another fundamental change in potential warfare has clearly resulted from technological progress. The cruise missile is a logical, perhaps inevitable, product of large-scale integration of electronic circuitry. Although technical details remain classified, the mininuke is probably an equally logical extension of the basic research that may someday solve the world's energy problems through controlled fusion. During the 30 years that have passed since the first military use of atomic energy, scientists have been proclaiming how much they want to have a voice in how their discoveries are put to use. Now another technological weapons revolution is shaping up, challenging that resolution more perhaps than at any other time since Hiroshima. □

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