

“Anxiety Peptide” Found in Brain

A peptide that occurs naturally in brain appears to act through the benzodiazepine receptor to bring about an increase in anxiety

A peptide has been discovered in human and rat brains that binds to the same receptor through which benzodiazepine drugs such as Valium and Librium exert their effects. Somewhat surprisingly, this peptide, which may be the first of a previously unknown class of neuroactive agents, appears to increase anxiety rather than decreasing it as the drugs do. Identification of the peptide may provide a better understanding of the molecular mechanisms underlying such emotional states as anxiety and fear and perhaps lead to improved tranquilizing drugs.

The discoverers of the peptide, Alessandro Guidotti, Erminio Costa, and their colleagues at the National Institute of Mental Health, obtained their first clues to its existence in the late 1970's when they showed that brain extracts decrease the binding of diazepam (Valium) to its receptor, presumably because

pound but was formed during the extraction procedures used for its isolation, it proved interesting because it turned out to evoke anxiety. “It told us,” Guidotti explains, “that if there is a [benzodiazepine receptor] ligand in brain, it could have an opposite effect to Valium.”

To assess the physiological and biochemical properties of the brain peptide that bound to the benzodiazepine receptor, the NIMH workers first had to purify it, an achievement that took nearly 5 years. The purified material has a molecular weight of 11,000 and contains 105 amino acids. The investigators have so far determined the sequence of amino acids from residue 59 to 105 and find that it does not resemble any other known mammalian peptide. They are now attempting to clone the gene for the peptide. This will permit the determination of the complete amino acid sequence.

evoking anxiety, which under some circumstances can be an entirely appropriate response. In addition, Costa points out, “Identification of the anxiety peptide confirms that the same receptor can have multiple transmitters acting on it.”

The DBI peptide is distributed in brain in a manner consistent with these proposals. “We find an uneven distribution in brain,” Guidotti explains. “It is high in areas important for control of emotion. It is particularly high in the neurons of brain areas rich in GABA receptors.” The investigators have also identified the peptide in human brains, although they have not yet determined its distribution there. Whether there are other agents in brain that can act through the benzodiazepine receptor to reduce anxiety is currently unknown.

Despite the activity of the DBI peptide in the various assays, it may not be interacting directly with the benzodiazepine receptor. It is large compared to most of the known neuroactive peptides. Perhaps more likely is the possibility that it serves instead as a source of one or more smaller peptides that do bind to the receptor. There are many examples—the endogenous opiate family provides one—in which a large precursor is split into smaller active fragments.

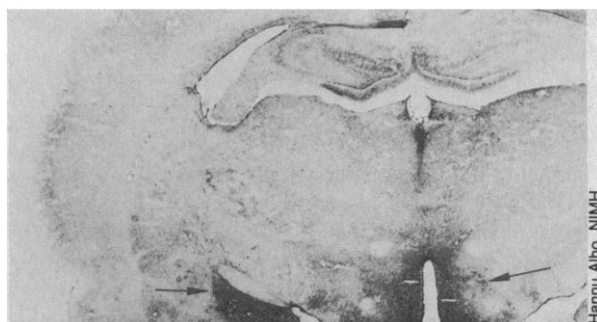
The DBI peptide has appropriate sites at which it might be cut by the protein-splitting enzymes found in brain. Moreover, when the NIMH workers digested it with an appropriate enzyme they found that one of the fragments thus formed was even more active than the parent compound. They have now determined the sequence of the 18 amino acids in the peptide,* and have shown that a totally synthetic version works, too. Finally, the investigators have evidence that there are two copies of the active fragment in the DBI peptide. Multiple copies of neuroactive peptides are frequently found in the precursor molecules.

Still in progress are experiments to determine whether the free peptide is present in brain—an obvious requirement if it is indeed the natural ligand of the benzodiazepine receptor. Nevertheless, with the molecule in hand and its structure known, a rapid test of its proposed role should be possible.

—JEAN L. MARX

*P. Ferrero, A. Guidotti, B. Conti-Tronconi, E. Costa, *Neuropharmacology* 23, 1359 (1984).

The “anxiety peptide” (dark stain) is located in brain areas, such as the hypothalamus (right arrow) and medial amygdaloid nucleus (left arrow), that are important for emotion.



the extracts contain a material that also binds to the receptor. The inhibitory material appeared to be a peptide because its action was abolished by enzymes that degrade proteins.

Merely identifying a material that binds to a receptor is not sufficient to establish that it has a natural function in the organism, however. As Guidotti notes, “It is a long way from here to a physiologically significant ligand [binder] for the benzodiazepine receptor.” In fact, over the years a number of substances that bound to the benzodiazepine receptor were identified. None of these ultimately proved to be physiologically significant, although one of them provided a valuable clue to the workings of the receptor.

The compound in question is β -carboline, which was identified by Claes Braestrup of A/S Ferrosan in Soeborg, Denmark. Although β -carboline is apparently not a naturally occurring com-

Early on investigators showed that the benzodiazepine receptor does not operate by itself but is a part of the receptor for γ -aminobutyric acid (GABA), a major inhibitory neurotransmitter in brain that acts to diminish the activity of its target neurons. Anxiety-reducing benzodiazepines such as Valium potentiate GABA's effects and produce an even greater inhibition of the neuronal activity. In contrast, β -carboline opposes GABA's effects, with the result that the neurons become more active.

By all measures so far, the new brain peptide, which the NIMH workers call the DBI (for diazepam-binding inhibitor) peptide, behaves like β -carboline, both in its electrophysiological action on the receptor itself and in animal models that are used to determine the ability of drugs to suppress or induce anxiety. Guidotti, Costa, and their colleagues propose that the peptide may act naturally to counteract GABA's inhibitory effects, thus