Enkephalins, Opiate Receptors, and General Anesthesia

Specific opiate receptors were identified in the period 1971–1973. These receptors combine in a stereospecific manner with all the known active opiates and opiate antagonists. This combination can be demonstrated physically with radioactive opiate ligands. Opiate receptors are found only in the nervous systems of vertebrates. Naloxone is a specific opiate antagonist, which blocks and reverses the effects of morphine, meperidine, methadone, fentanyl, and other opiate agonists. Thus, naloxone is highly effective in the treatment of opiate overdosage, and it is the agent of choice for such treatment. Evidently, the agonists, in combining with the receptors, promote a conformational change, which results in biochemical alterations in the neurons bearing the receptors. This change is thought to be an inhibition of adenylate cyclase activity. Naloxone occupies the receptors but stabilizes them in their inactive conformation.

The specificity of these receptors suggested that their real function was to combine with an endogenous ligand, since it seemed improbable that they would have developed, through evolution, to interact with products of the opium poppy. A deliberate search for endogenous ligands resulted, in 1975, in the discovery of endorphins, peptides with opiate-like pharmacologic action. Two pentapeptides in brain, called enkephalins, were found to have the structure tyrosine-glycine-glycine-phenylalanine-methionine (methionine-enkephalin) and tyrosine-glycine-glycine-phenylalanine-leucine (leucine-enkephalin). These pentapeptides are present throughout the brain and spinal cord at various densities in different regions.

A prominent association is between enkephalins and the pain pathways. The clearest example is in the spinal cord. Short enkephalin-containing interneurons are present in the substantia gelatinosa, at the terminals of the afferent carrier conveying pain information from the periphery. These primary afferent neurons, with cell bodies in the dorsal root ganglion, contain substance P. They impinge on the dorsal horn cells, which project rostrally in the spinothalamic pathway. Enkephalin inhibits the release of substance P from the terminals of the afferent neurons. A pathway extending downward from the brainstem activates the enkephalinergic neurons, and thus can suppress pain at the first relay. Enkephalinergic neurons are found also in the caudate, globus pallidus, amygdaloid nuclei, hypothalamus, and many other parts of the brain. Clearly, the enkephalin-containing neurons constitute a new neurotransmitter system with diverse functions, most of which are still not understood.

Just as naloxone blocks the opiate receptors when true opiates are the agonists, so does it block the opiate-like actions of enkephalin. For example, enkephalins, modified to prevent their rapid degradation by enzymes, produce analgesia when injected into the cerebral ventricles, and this action is blocked by naloxone. Other behavioral effects mediated by enkephalins (e.g., catalepsy in rats, mania and hallucinatory behavior in cats) are also blocked by naloxone. Enkephalins (like morphine) stimulate release of growth hormone and prolactin from the pituitary, by an action in the hypothalamus, and they also prevent the release of luteinizing hormone; both these effects are blocked by naloxone.

Opioid peptides of the other class have a much greater molecular weight. They were first found in the pituitary, and it was later realized that they are contained within the known pituitary hormone β-lipotropin. Interestingly, these larger endorphins contain within them the entire sequence of methionine-
enkephalin. The pituitary endorphins are closely related to ACTH; indeed, they are synthesized together with ACTH in a single precursor peptide of molecular weight 31,000. Pituitary endorphins are released into the blood by various kinds of stress. Their function remains obscure; it is not even clear what target tissue they act upon. Curiously, pituitary endorphins are also found in certain neurons in the brain.

A surprising development was the finding that acupuncture analgesia is blocked by naloxone, in man as well as in animals. This implies that acupuncture triggers the release of an endorphin at the opiate receptors in the pain pathways.

The interaction of the endorphins with the opiate receptors is not an exception to the specificity of the receptors. Although, on paper, peptides and opiates look very different, the truth is that their molecular shapes and distributions of charges are very similar. On the other hand, hundreds of compounds belonging to other drug groups have been tested, without finding any that combine with the opiate receptors. If the effects of a general anesthetic agent such as nitrous oxide are blocked by naloxone, it is very improbable that such an agent combines directly with opiate receptors. One would have to think, instead, that the agent in some manner promotes the release of an endorphin.

The earlier reports of Berkowitz et al. 5 and Finck et al. 4 indicated that in an analgesia test using a noxious stimulus, rats treated with nitrous oxide (also enflurane or cyclopropane) showed a partial antagonism of analgesia by naloxone. In the papers by Harper et al., 7 Smith et al., 8 and Bennett 8 in the present issue, in rats and mice, respectively, the experiments were replicated, using various measures of anesthesia, including determinations of the MAC, as well as nonnoxious stimuli. Adequately large doses of naloxone were administered, but no modification of the anesthetic state resulted.

It may be that general anesthetic agents release enkephalin (or other endorphins) at opiate receptor sites in the pain pathways, and it is even possible that the analgesic component of general anesthesia is due to this enkephalin release. There is no reason to think, however, that the other phenomena characteristic of general anesthesia are due to release of endogenous opioid peptides.

**References**