1. INTRODUCTION

It is well known for many centuries already that opium, derived from the poppy plant, causes pain relief and euphoria. This latter is thought to be an important factor in the addictive properties of opium (Van Ree, 1979). After the discovery of morphine as the most effective analgesic and addictive component of opium, attempts were made to prepare morphine related drugs in order to separate the desired analgesic and the undesirable addictive properties. Although these attempts were not very successful, the structure activity relationship studies have revealed the concept that specific opiate receptors are present in the body. In 1973 binding studies with brain tissue indeed have suggested the existence of such receptors (Terenius, 1973). Subsequently the presence of endogenous substances that can activate these receptor systems was postulated. This suggestion accords well with findings showing that animals and humans have to a certain extent control over pain sensation. It was demonstrated in 1975 that brain tissue contains two pentapeptides, called enkephalins, that have morphine-like properties as assessed using isolated tissue preparations in vitro (Hughes et al., 1975). Since then several peptides with morphine-like action have been isolated from brain and other tissue. These substances are called endorphins (endogenous morphine). Soon after their discovery these peptides have been implicated in pain related mechanisms, in chronic pain and various psychopathological disorders such as psychosis, depression, mania and addiction.

2. ENDORPHIN SYSTEMS

The several presently known endorphins belong to three major families, arising from three distinct systems. Each system contains a big precursor molecule of about 240 amino acids. Enzymatic processing can release from this molecule peptide fragments with a certain biological function. These fragments are however also precursor molecules for smaller peptides with other biological activity. This may illustrate the neuropeptide concept, that enzymatic processing of peptide molecules can evoke specific information enclosed in the molecule (De Wied, 1977). The three endorphin systems are designated as pro-opiomelanocortin, pro-enkephalin and prodynorphin.

Pro-opiomelanocortin is located predominantly in the pituitary, but also in neuronal pathways in the brain (Watson et al., 1979). From the basal hypothalamus (nucleus arcuatus) and the brain stem (nucleus tractus solitarius) these pathways spread to several structures of the limbic system and to the brain stem. In addition pro-opiomelanocortin is present in the gut and peripheral nerves. Enzymatic processing can release from pro-opiomelanocortin the hormones β-lipotropin (β-LPH) and adrenocorticotropic (ACTH). β-LPH is further processed to the opioid peptide β-endorphin, which
is the precursor molecule for at least two opioid peptides, α- and γ-endorphin. The structure of the N-terminal part of these opioid peptides is identical to that of Met-enkephalin, but this enkephalin is not derived from these peptides.

Pro-enkephalin is located peripherally (e.g. in the adrenal medulla) and in widely distributed short neuronal pathways in the brain (Watson et al., 1979). Peptides belonging to this system have been demonstrated among others in the basal ganglia, hypothalamus, midbrain and spinal cord. Pro-enkephalin is processed to several opioid peptides, including the pentapeptides Met- and Leu-enkephalin, but also to longer sequences.

Pro-dynorphin is present in the hypothalamic-hypophyseal neuronal pathway, but also in other parts of the brain, such as the hippocampus and the spinal cord (Watson et al., 1981). The N-terminal part of the sequence of the opioid peptides derived from pro-dynorphin e.g. dynorphin and α- and β-neo-endorphin, is identical to that of Leu-enkephalin.

Several subpopulations of opioid receptors have been proposed. Some information is available that the opioid peptides belonging to a certain family can activate a specific subclass: β-endorphin may activate the μ, but also the δ receptor, enkephalins may activate the δ and to some extent the η receptor, while dynorphin may activate predominantly the κ receptor (Ward, 1982). However, the exact relationship between these subclasses of opioid receptors and the physiological roles of the different opioid peptides have so far not clearly been elucidated.

3. OPIATE EFFECTS OF ENDORPHINS

β-Endorphin is the most potent peptide in mimicking morphine-like action, at least when injected into body fluids. The other endorphins are also active, but more of these peptides is needed, presumably because of the more rapid degradation of the shorter endorphins. Injection of β-endorphin into the cerebrospinal fluid of animals leads to a variety of behavioral changes which are also observed after administration of morphine. Thus, β-endorphin induces antinociception, hypothermia, hormonal changes, excessive grooming, and at higher dose levels profound immobilization and muscular rigidity. Most if not all of these effects are blocked by the specific opiate antagonists naloxone and naltrexone. β-Endorphin also shows common actions with morphine-like drugs after repeated administration. Thus, tolerance develops to the effect of β-endorphin on pain perception following repeated treatment (Van Ree et al., 1976). Chronic administration of β-endorphin induces physical dependence, characterized by withdrawal symptoms (Wei and Loh, 1976). Low doses of β-endorphin causes self-injecting behavior, indicating inherent addiction properties (Van Ree et al., 1979). Most if not all of these effects are however elicited by injecting rather high doses as compared to the amount of β-endorphin available in the brain, and can therefore be considered as pharmacological rather than physiological actions.

4. ENDORPHINS AND PAIN

Opioid receptors and various endorphins are present at different levels of the spinal cord and in brain pathways, activated by painful stimuli and involved in pain detection, pain sensation, tolerance to pain and the response to pain. The physiological role of endorphins can be tested by using opiate antagonists like naloxone, which block the opiate action of endorphins, or specific antisera to endorphins which inactivate the physiologically available endorphins. The studies with naloxone in both animals and humans do not indicate a major role of endorphins in pain perception. In general naloxone did not affect the pain threshold of animals and humans.