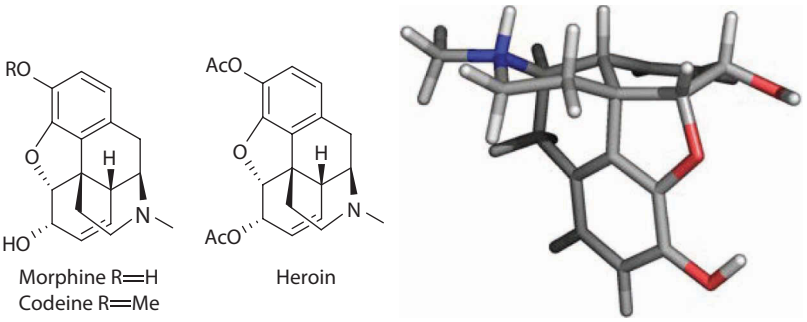

FIGURE 19.1 Chemical structures of morphine, codeine, and heroin. 3D structure of morphine.

19.1.1 Opioid Receptor Subtypes and Effector Mechanism

The idea that morphine and other opioids caused analgesia by interacting with a specific receptor arose around the 1950s. The observation 40 years earlier that the *N*-allyl analog of codeine antagonized the respiratory action of morphine was actually evidence of such a proposal. However, it was first fully realized when similar *N*-allyl analog of morphine (nalorphine) was shown to antagonize the analgesic effects of morphine.

Today, it is known that all of the opioid receptors are G-protein-coupled receptors (GPCRs) belonging to family A (Figure 19.2) that mediates its effects through G_i/G_o proteins (see Chapter 12). So far, four different opioid receptor subtypes have been cloned, sharing more than 60% sequence homology. These are termed μ, κ, and δ receptors (corresponding to MOR, KOR, and DOR, respectively) and an "orphan" receptor termed ORL_1 which was the first orphan GPCR to be cloned.

The different effects (Table 19.1) mediated by each receptor type (μ-euphoria versus κ-dysphoria; μ-supraspinal analgesia versus ORL_1-supraspinal antagonism of opioid analgesia) in the intact animal are the result of different anatomical localization and not due to different cellular responses. Each receptor type has been further subdivided into μ_1/μ_2, κ_1/κ_2, and δ_1/δ_2 receptors based on pharmacological and radioligand studies. However, the origin of this subdivision is not genetically based, and it is not known whether it arises from post-translational modification, cellular localization, or interactions with other proteins; however, it was recently shown that heterodimerization of the receptors could be important for some of these pharmacological differences.

Morphine has the ability to both excite and inhibit single neurons. Opioid inhibition of neuronal excitability occurs largely by the ability of opioid receptors to activate various potassium channels. Another well-established mechanism of action is the inhibition of neurotransmitter release. The observation in 1917 that morphine inhibited the peristaltic reflex in the guinea pig ileum (giving rise to constipation, one of the side effects of morphine) was 40 years later shown to result from inhibition of acetylcholine release. Also, glutamate, GABA, and glycine release throughout the central nervous system (CNS) can be inhibited by opioid receptor activation. In general, the CNS effects of opioids are inhibitory, but certain CNS effects (such as euphoria) result from excitatory effects.

19.1.2 Endogenous Opioid Receptor Ligands

It was proposed in the early 1970s that the physiological role of opioid receptors was not to be a target for opium alkaloids, but that endogenous agonists might exist as mediators of the opioid system. At that time, there were no hints of what kind of compounds to look for. After 2 years of collecting extracts from pig brain and applying them in a functional bioassay, Kosterlitz and coworkers in 1975 identified two closely related endogenous pentapeptide opioids (Table 19.2).