of diarrhea. Morphine and codeine are mostly used as analgesics. Fentanyl is a very potent analgesic used in anesthesia. Meperidine is used for acute pain. Methadone is applied to control withdrawal of heroin from addicts. Antagonists are used for reversal of some of the effects induced by agonists. Thus, naloxone has been used to reverse coma and respiratory depression of opioid overdose (methadone and heroin). It is also indicated as an adjunct agent to increase blood pressure under septic shock. Naltrexone has been approved as adjunctive therapy in the treatment of alcohol dependence and the treatment of narcotic addiction to opioids. However, there are also potential indications including obesity, obsessive compulsive disorder, and schizophrenia.

19.2 CANNABINOID RECEPTORS

The plant *Cannabis sativa* has for millennia been used for recreational and medicinal purposes, as it can be seen from old Chinese, Assyrian, and Roman literature. However, it was first in 1964 that the active principle causing the psychoactive effects was isolated and found to be Δ^9-tetrahydrocannabinol (THC) (Figure 19.8). Originally, it was thought that THC due to its lipophilicity somehow acted through fluidizing the cellular membranes, but in the early 1990s it was discovered that THC activates two receptors, cannabinoid receptor-1 (CB_1-receptor) and cannabinoid receptor-2 (CB_2-receptor). Cannabinoid effect in rodents is characterized by the so-called tetraed test. In this test, measurement of spontaneous activity, thermal pain sensation, catalepsy, and rectal temperature are made, and compounds with cannabinoid activity should produce hypomotility, analgesia, catalepsy, and hypothermia. Shortly after the discovery of the receptors, two endogenous compounds were identified that could activate these receptors, i.e., anandamide (arachidonoylethanolamide) and 2-arachidonoylglycerol (2-AG) (Figure 19.8), and they are called endocannabinoids. Both endocannabinoids are of lipid nature and thus not very water soluble. They associate with albumin in the extracellular space and endocannabinoids can function in an autocrine and paracrine fashion where they are formed "on demand" and then degraded, i.e., they are not stored in vesicles like neurotransmitters or peptide hormones. Tissue levels of anandamide and 2-AG are usually in the pmol/g and nmol/g tissue, respectively, but it is not clear whether these levels represent the ligand concentration available to the receptors. However, it is generally considered that

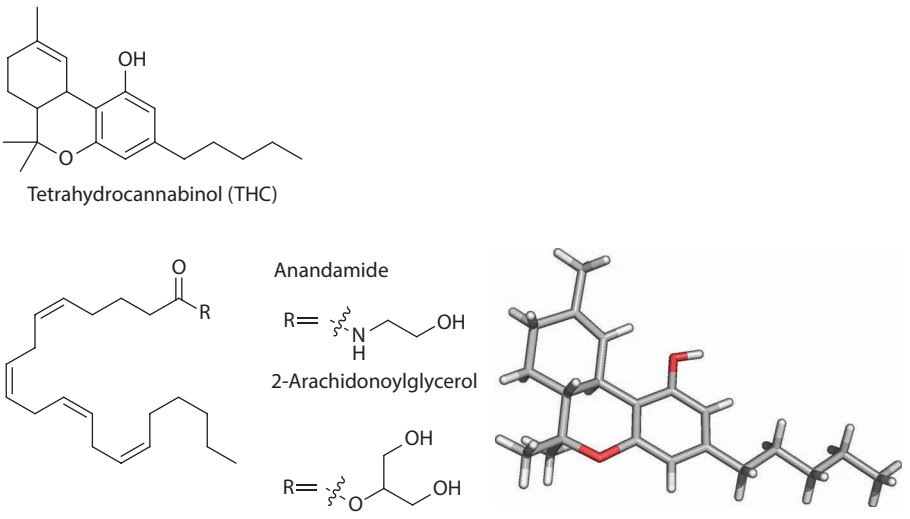

FIGURE 19.8 Plant cannabinoid (THC) and the two endocannabinoids, anandamide and 2-arachidonoyl glycerol. R = arachidonoyl.