19.2.4 Other Cannabinoid Receptors?

Since 2-AG and especially anandamide have a number of pharmacological effects that cannot be fully explained by activation of the known cannabinoid receptors, it has been suggested that there may exist more cannabinoid-like receptors. GPR55 has been suggested to be such a new cannabinoid receptor since it can be activated by both THC, 2-AG, anandamide, and the cannabinoid receptor agonist CP 55,940 (Figure 19.12). Another cannabinoid receptor agonist, WIN 55,212-2, can, however, not activate GPR55, and recently, the endogenous agonist for GPR 55 has been found to be lysophosphatidylinositol. A number of agonists (e.g., CP 55,940, WIN 55,212-2, and O-1812) and antagonists (e.g., Rimonabant, AM251, and LY 320135) (Figure 19.12) have been developed. Especially, anandamide can activate a number of other receptors, e.g., vanilloid receptor, and ion channels as mentioned earlier, and this may add to the confusion of the existence of additional cannabinoid receptors. 2-AG can at an apparently allosteric site activate GABA-A receptor.

19.2.5 Therapeutic Use and Potential

THC in capsules (Marinol/Dronabinol, Solway Pharmaceutical) is used for the treatment of nausea and vomiting that are common side effects of chemotherapy, and for the stimulation of appetite in AIDS patients. A synthetic THC-analog (Nabilone/Cesamet, Valeant Pharmaceuticals) (Figure 19.12) is also on the market for the same treatments. In Canada, THC in the form of an extract of cannabis sativa called Sativex (GW Pharmaceuticals) is provided as a mouthspray for multiple sclerosis patients, who can use it to alleviate neuropathic pain and spasticity. Sativex also contains other cannabinoids including cannabidiol that may add to its function. Medicinal cannabis, i.e., marihuana or hashish prescribed by a doctor for increased well-being and alleviation of pain, spasticity, or loss of appetite by patients having AIDS, cancer, and multiple sclerosis, has been approved in several countries, and there is a strong lobby for approval in certain U.S. states.

Sanofi-Aventis brought a CB_1-antagonist (SR141716A, Rimonabant, trade name Acomplia, Figure 19.12) on the European marked in 2006 for the treatment of obesity (body mass index above 30). Large clinical trials had shown that Rimonabant induced a weight loss of approximately 10% of initial body weight within 1 year. Discontinuation of Rimonabant treatment resulted in regain of lost weight. It was suspended by Sanofi in 2008 due to risk of depression and suicide. Many drug companies stopped their development of comparable CB_1 agonists for weight loss. A CB_1-receptor antagonist that does not cross the blood–brain barrier may possibly also have beneficial effects on energy metabolism.

Emerging evidence points to a possible participation of the endocannabinoid system in the regulation of the relapsing phenomenon of drug abuse in animal models. CB_1-receptor seems to be important in drug- as well as cue-induced reinstatement of drug-seeking behavior. Stimulation may elicit relapse not only to cannabinoid seeking but also to cocaine, heroin, alcohol, and methamphetamine, and this effect is significantly attenuated in animal experiments by pretreatment with CB_1-receptor antagonists. CB_2 agonists have shown positive results in preclinical studies on various forms of pain and atopic dermatitis.

Potential clinical application involves drugs that can increase or decrease endocannabinoid levels (i.e., FAAH-inhibitors and monoacylglycerol-lipase [MAGL] inhibitors or diacylglycerol-lipase inhibitors, respectively) or serve as agonists/antagonists for the two cannabinoid receptors (Table 19.3). Thus, the potential is large but so is the risk of side effects since the endocannabinoid system appears to be so ubiquitous.

19.2.6 FAAH Inhibitors and Anandamide Uptake Inhibitors

As discussed earlier, it is not clear whether an anandamide transporter exists and several compounds believed to be uptake inhibitors have turned out to be inhibitors of FAAH. As an example of an experimental FAAH-inhibitor, URB 597 is shown (Figure 19.11).