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REVIEW

Prejunctional and peripheral effects of the cannabinoid CB_1 receptor inverse agonist rimonabant (SR 141716)

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Abstract Rimonabant is an inverse agonist specific for cannabinoid receptors and selective for their cannabinoid-1 (CB_1) subtype. Although CB_1 receptors are more abundant in the central nervous system, rimonabant has many effects in the periphery, most of which are related to prejunctional modulation of transmitter release from autonomic nerves. However, CB_1 receptors are also expressed in, e.g., adipocytes and endothelial cells. Rimonabant inhibits numerous cardiovascular cannabinoid effects, including the decrease of blood pressure by central and peripheral (cardiac and vascular) sites of action, with the latter often being endothelium dependent. Rimonabant may also antagonize cannabinoid effects in myocardial infarction and in hypotension associated with septic shock or liver cirrhosis. In the gastrointestinal tract, rimonabant counteracts the cannabinoid-induced inhibition of secretion and motility. Although not affecting most cannabinoid effects in the airways, rimonabant counteracts inhibition of smooth-muscle contraction by cannabinoids in urogenital tissues and may interfere with embryo attachment and outgrowth of blastocysts. It inhibits cannabinoid-induced decreases of intraocular pressure. Rimonabant can inhibit proliferation of, maturation of, and energy storage by adipocytes. Among the many cannabinoid effects on hormone secretion, only some are rimonabant sensitive. The effects of rimonabant on the immune system are not fully clear, and it may inhibit or stimulate proliferation in several types of cancer. We conclude that direct effects of rimonabant on adipocytes may contribute to its clinical role in treating obesity. Other peripheral effects, many of which occur prejunctionally, may also contribute to its overall clinical profile and lead to additional indications as well adverse events.

Keywords Rimonabant · Prejunctional · Adipocyte · Endothelium

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Introduction

Cannabinoids such as Δ^9-tetrahydrocannabinol have long been known as active ingredients of hashish and marijuana prepared from the plant *Cannabis sativa* and as such have been considered drugs of addiction. Meanwhile, it has become clear that they can act on G-protein-coupled receptors, and two subtypes of these receptors have been cloned and designated cannabinoid-1 and -2 (CB_1 and CB_2). A formal definition of these receptor subtypes has been proposed by the International Union of Pharmacology (Howlett et al. 2002). Endogenous agonists at cannabinoid receptors (referred to as endocannabinoids) including anandamide (Devane et al. 1992) or 2-arachidonoylglycerol (Stella et al. 1997) have been reported.

The term cannabinoids is used in two different meanings in the literature: chemical and functional. Traditionally, this term has been used to designate chemically related compounds isolated from the *Cannabis* plant (Razdan

1986). Some of these compounds act on cannabinoid receptors, whereas others, including cannabidiol, did not exhibit relevant affinity for these receptors in most studies, although a recent report has challenged that view (Thomas et al. 2007). Nowadays, the term cannabinoids is most frequently used to designate compounds activating cannabinoid receptors. Although some of these ligands also are cannabinoids in a chemical sense (e.g., Δ^9-tetrahydrocannabinol) or are derived from them (e.g., CP-55,940), others have an extremely different chemical structure, including aminoalkylindoles such as WIN 55,212–2 or derivatives of arachidonic acid such as the endocannabinoids. In this article, cannabinoids is always used in the second, functional meaning.

Apart from the role of exogenous cannabinoids in addiction, endocannabinoids have been implicated to play an important role in various physiological and pathophysiological control mechanisms related, e.g., to energy metabolism, pain and inflammation, and various psychiatric and neurologic conditions. Moreover, endocannabinoids can also play a role outside the central nervous system, e.g., in the cardiovascular system, airways, gastrointestinal tract, eye, reproductive function, and cancer (Kogan and Mechoulam 2008; Mendizabal and Adler-Graschinsky 2007; Pacher et al. 2006; Wierzbicki 2006). Whereas it was originally proposed that expression of CB_1 receptors is restricted to the nervous system and, to a lesser extent, the immune system (Galiegue et al. 1995), their presence can also be shown in some peripheral tissues other than prejunctional nerve endings (Shire et al. 1995).

Recently, the CB_1 cannabinoid receptor antagonist rimonabant (formerly known as SR 141716A) (Fig. 1) has become available for treating obesity in some countries (Carai et al. 2005; Gelfand and Cannon 2006; Henness et al. 2006; Wierzbicki 2006). It is also under investigation for treating drug addiction (Beardsley and Thomas 2005), and
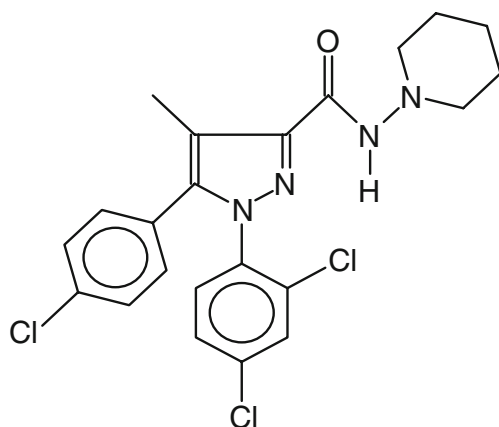
additional possible uses have been proposed (Bifulco et al. 2007). The experimental effects of rimonabant on food intake, addiction, and other effects in the central nervous system have recently been reviewed (Boyd and Fremming 2005; Fowler 2005; Shire et al. 1999). In this manuscript we systematically review rimonabant effects outside the central nervous system. As many of the peripheral rimonabant effects are related to a prejunctional inhibition of transmitter release, prejunctional rimonabant effects, including those occurring in the central nervous system, and their molecular and cellular basis are also reviewed.

Direct effects on cannabinoid and other receptors

Rimonabant is a highly specific and selective drug, i.e., it possesses a high selectivity for CB_1 receptors over dozens of other receptors (Rinaldi-Carmona et al. 1994) and an at least 100-fold selectivity for CB_1 over CB_2 receptors (Gatley et al. 1996; Hurst et al. 2002; Rinaldi-Carmona et al. 1994; Shire et al. 1996, 1999). This profile is not only important with respect to the therapeutic use of this drug but also for basic research, as the effects of cannabinoids such as anandamide or Δ^9-tetrahydrocannabinol may not always occur via cannabinoid receptors and may also involve, e.g., vanilloid receptors (Nieri et al. 2003), the so-called endothelial cannabinoid receptor (Wagner et al. 1999), metabolism to prostanoids (Grainger and Boachie-Ansah 2001; Pratt et al. 1998), or other, poorly defined, targets (Carrier et al. 2006; Kenny et al. 2002; White et al. 2001). However, rimonabant acts at noncannabinoid targets only at very high concentrations (White and Hiley 1998). In binding studies, rimonabant has an affinity for the CB_1 receptor in the low nanomolar range. In functional experiments, rimonabant is not a neutral antagonist but, rather, has been found to be an inverse agonist at the CB_1 receptor (Landsman et al. 1997; MacLennan et al. 1998; Meschler et al. 2000; Thomas et al. 2007).

Systematic modification of the amino acid sequence of the CB_1 receptor has allowed a better understanding of which parts of the receptor are critical for the binding of rimonabant. Early studies demonstrated that the second extracellular loop of the receptor, which is important in the binding of some cannabinoid agonists, does not affect the binding of rimonabant (Shire et al. 1996). A similar situation was reported for the first extracellular loop of the receptor (Murphy and Kendall 2003). Later studies showed that the fourth and fifth transmembrane domain of the receptor are relevant for conferring selectivity of rimonabant for the CB_1 over the CB_2 receptor (Shire et al. 1999). The amino acid Lys192 appears important in the inverse agonist properties of rimonabant (Hurst et al. 2002). Other authors have speculated that rimonabant inhibits the ability of transmembrane

Fig. 1 Structure of rimonabant [5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-N-(piperidin-1-yl)-1H-pyrazole-3-carboxamide]

helix 6 to move during formation of the functionally active receptor state (Fay et al. 2005).

In an attempt to further understand the structural requirements in the rimonabant molecule that are relevant for selectivity and affinity of binding to the CB_1 receptor and for the degree of (inverse) efficacy, numerous analogues have been synthesized (Dyck et al. 2004; Francisco et al. 2002; Jagerovic et al. 2006; Katoch-Rouse et al. 2003; Lange et al. 2005; Shim et al. 2002; Thomas et al. 1998; Wiley et al. 2001). Some of these analogues have even higher affinity for the CB_1 receptor than does rimonabant (Thomas et al. 1998), but whether this results in clinically superior compounds remains unknown.

A tritiated form of rimonabant has been synthesized and is commercially available as a radioligand (Hirst et al. 1996). This has proven useful in studies characterizing CB_1-receptor ligands (Brizzi et al. 2005; Muccioli et al. 2005) or the presence of CB_1 receptors in various tissues and cells (Hirst et al. 1996; Jung et al. 1997). This radioligand has also been used to investigate possible differences in receptor interaction between agonists and antagonists at the CB_1 receptor (Petitet et al. 1996).

Cellular effects

Inhibition of cyclic adenosine monophosphate (cAMP) formation, mediated by G_i proteins, is a prototypical signaling response of CB_1 receptors (Glass and Northup 1999). Accordingly, rimonabant inhibits cannabinoid-induced reductions of cAMP accumulation in cells transfected with CB_1 receptors (Calandra et al. 1999; Rinaldi-Carmona et al. 1994; Stamer et al. 2001) but not in those transfected with CB_2 receptors (Rinaldi-Carmona et al. 1994). The cannabinoid-induced inhibition of cAMP accumulation in astrocytes was also not affected by rimonabant, indicating that these cells possibly preferentially express CB_2 receptors (Sagan et al. 1999). Rimonabant also antagonizes the cannabinoid-induced inhibition of cAMP formation in various brain regions of the rat (Cadogan et al. 1997; Jung et al. 1997; Maneuf and Brotchie 1997; Mato et al. 2002; Rinaldi-Carmona et al. 1994), mouse (Sagan et al. 1999), guinea pig (Schlicker et al. 1997), and human (Mato et al. 2002) or in neuronal cells derived thereof. Antagonism of inhibition of cAMP formation has also been observed in peripheral tissues such as the rat vas deferens (Pertwee et al. 1996c) or the trabecular meshwork and ciliary process of the human eye (Stamer et al. 2001). Whereas some studies report that rimonabant does not affect intracellular cAMP levels in the absence of exogenous cannabinoids (Rinaldi-Carmona et al. 1994; Schlicker et al. 1997), others have found cAMP elevations upon in vitro or in vivo treatment with rimonabant (Mato et al. 2002; Rubino et al. 2000). Interestingly, rimonabant treatment was also found

to activate protein kinase A (Rubino et al. 2000; Tzvara et al. 2000). Whether this represents antagonism of effects of endocannabinoids and/or the inverse agonist properties of rimonabant has not been well established (see below). Moreover, rimonabant-precipitated cannabinoid withdrawal is accompanied by an increased adenylyl cyclase activity in the mouse brain (Tzvara et al. 2000).

Besides inhibition of cAMP formation, which has been shown to underlie some functional CB_1 effects (Kim and Thayer 2001), three other main signaling mechanisms coupled to $G_{i/o}$ proteins have been shown. Thus, cannabinoids inhibit calcium ion (Ca^{2+}) influx via voltage-dependent Ca^{2+} channels in rat superior cervial ganglion neurones expressing CB_1 receptors (Pan et al. 1998) and via N- and P/Q-type voltage-dependent Ca^{2+} channels in cultured rat hippocampal neurones (Twitchell et al. 1997). Rimonabant antagonized this effect in both studies, and when given alone, even increases voltage-dependent Ca^{2+} influx in the former model. Moreover, cannabinoids activate potassium ion (K^+) efflux via voltage-gated inwardly rectifying K^+ channels in a *Xenopus* oocyte expression system. This effect is antagonized by rimonabant, which, by itself, decreases K^+ efflux (McAllister et al. 1999). Finally, cannabinoids activate mitogen-activated protein kinases in Chinese hamster ovary cells expressing the human CB_1 receptor. This effect is again antagonized by rimonabant (Bouaboula et al. 1995).

In addition, cannabinoid-induced effects are coupled to a variety of other transduction mechanisms. For example, rimonabant was found to inhibit cannabinoid-induced elevations of intracellular Ca^{2+} concentrations in CB_1-receptor-transfected human embryonic kidney (HEK) 293 cells (Lauckner et al. 2005), cultured hippocampal neurones (Lauckner et al. 2005), or NG108–15 neuroblastoma cells (Sugiura et al. 1996). Interestingly, such Ca^{2+} elevations may involve G_q rather than G_i proteins and also a phospholipase C (Lauckner et al. 2005). Rimonabant can also antagonize the cannabinoid-induced inhibition of Ca^{2+} uptake into rat brain synaptosomes or NG108–15 cells, possibly also independent of G_i proteins (Rubovitch et al. 2002; Yoshihara et al. 2006). Rimonabant also inhibited the cannabinoid-induced activation of protein kinase B in prostate cancer cells (Sanchez et al. 2003a) and extracellular signal-regulated kinase in 3T3 F442A murine preadipocytes (Gary-Bobo et al. 2006), rat arteries (Su and Vo 2007), and human endothelial cells (Liu et al. 2000). Whereas rimonabant antagonized cannabinoid effects on the delayed rectifier K^+ current (I_K) in rat hippocampal neurones (Hampson et al. 2000), cannabinoid effects on shaker-related voltage-gated K^+ channels (Poling et al. 1996), on TASK-1 standing-outward K^+ currents (Maingret et al. 2001) or on delayed rectifier K^+ channels in smooth muscle of the rat aorta (Van den Bossche and Vanheel 2000) showed only partial, if any, rimonabant sensitivity.

Effects on transmitter release

Based upon the expression of cannabinoid receptors in various types of central (Shire et al. 1999) and peripheral neurones (Storr et al. 2004), numerous studies have investigated the effects of cannabinoids and rimonabant on transmitter release. Most of these studies were done on the central nervous system and focused on the release of noradrenaline, serotonin, dopamine, acetylcholine, gamma aminobutyric acid (GABA), and glutamate (described in this section). A series of studies was dedicated to noradrenaline and acetylcholine release from sympathetically and parasympathetically innervated tissues, respectively (see subsequent sections).

The release of noradrenaline is inhibited by cannabinoids in the human hippocampus (Schlicker et al. 1997) and in the hippocampus and other brain regions of the guinea pig (Kathmann et al. 1999; Schlicker et al. 1997). The inhibitory effect was antagonized by rimonabant, suggesting that a CB_1 receptor is involved. As the cannabinoid-induced effect and antagonism by rimonabant were retained in the guinea pig hippocampus under conditions not allowing propagation of impulse flow, one can assume that the CB_1 receptors are located prejunctionally on the noradrenergic neurones themselves.

An example how a CB_1 receptor is identified in detail is given in Fig. 2. Noradrenaline release in the guinea pig
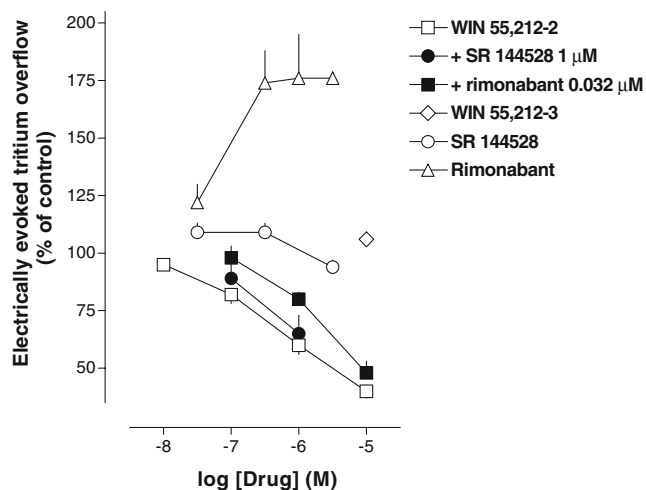
Fig. 2 Effect of various cannabinoid receptor ligands on electrically evoked tritium overflow from the guinea pig hippocampal slices preincubated with ³H-noradrenaline. Tritium overflow corresponds to quasi-physiological noradrenaline release. Noradrenaline release was inhibited by the cannabinoid receptor agonist WIN 55,212–2 but not by a high concentration of its inactive enantiomer WIN 55,212–3. The concentration-response curve of WIN 55,212–2 was shifted to the right by a low concentration of the CB_1 receptor inverse agonist rimonabant but was hardly affected even by a high concentration of the CB_2 receptor inverse agonist SR 144528. When given alone, rimonabant facilitated noradrenaline release, whereas SR 144528 had no effect. From Schlicker et al. (1997) and Szabo and Schlicker (2005)
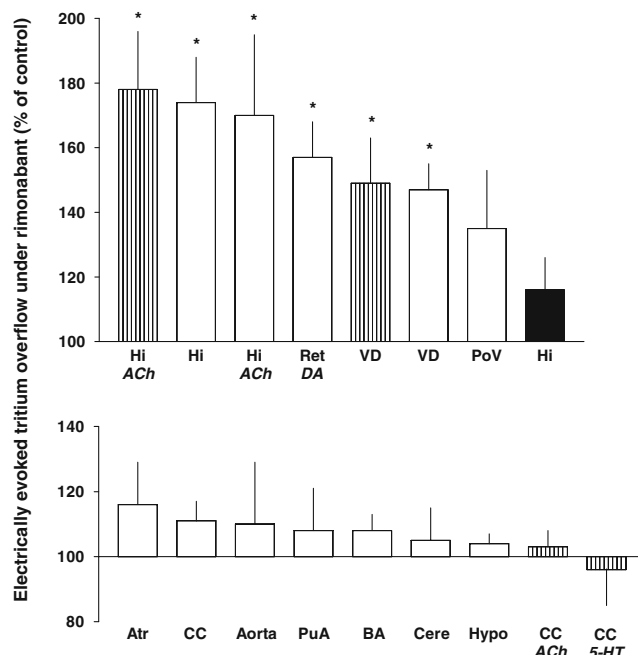
Fig. 3 Effect of rimonabant 0.32 μM on the electrically evoked tritium overflow in a variety of superfused tissues from guinea pig (*open columns*), mouse (*hatched columns*), and humans (*black column*). Experiments were carried out on the aorta, atrium (*Atr*), basilar artery (*BA*), cerebellum (*Cere*), cerebral cortex (*CC*), hippocampus (*Hi*), hypothalamus (*Hypo*), portal vein (*PoV*), pulmonary artery (*PuA*), retina (*Ret*), and vas deferens (*VD*). Tissues were labeled with ³H-noradrenaline (if not stated otherwise), ³H-choline (*ACh*), ³H-dopamine (*DA*), or [³H]serotonin (*5-HT*). Tritium overflow corresponds to the release of noradrenaline, acetylcholine, dopamine, and serotonin. Note that rimonabant (1) facilitated noradrenaline release in the guinea pig but not in the human hippocampus, (2) facilitated noradrenaline or acetylcholine release in the hippocampus of the guinea pig and mouse but failed to do so in the cerebral cortex of the respective species, and (3) had a facilitating effect in the vas deferens but was without effect in cardiovascular tissues. *$P < 0.05$, compared with the corresponding control (not shown). From Kathmann et al. (2001a), Kurz et al. (2008), Nakazi et al. (2000), Schlicker et al. (1996, 1997, 2003), Schultheiss et al. (2005) and unpublished data

hippocampus is concentration-dependently inhibited by the cannabinoid receptor agonist WIN 55,212–2, whereas even an extremely high concentration of its inactive enantiomer (the compound WIN 55,212–3) is without effect. The concentration-response curve of WIN 55,212–2 is shifted to the right by rimonabant, yielding an apparent pA_2 value of 8.2, which is close to that described for CB_1 receptors in the literature (8.0–8.2) (Rinaldi-Carmona et al. 1994). On the other hand, the apparent pA_2 value of 5.9 of the selective CB_2 receptor inverse agonist SR 144528 was lower by more than three orders of magnitude than its pK_i value at CB_2 receptors (9.2) (Rinaldi-Carmona et al. 1998). Figures 2 and 3 show that in the absence of exogenous cannabinoids, rimonabant enhanced noradrenaline release in the guinea pig hippocampus but failed to do so in the human hippocampus or in other

brain regions of the guinea pig (Kathmann et al. 1999; Schlicker et al. 1997). A facilitating effect of rimonabant was also found in the rat medial prefrontal cortex and nucleus accumbens (Tzavara et al. 2003).

With respect to the effect of cannabinoids on noradrenaline release, marked species differences occurred, as cannabinoids were devoid of an effect in the hippocampus of the rat and mouse (Gifford et al. 1997; Schlicker et al. 1997). In an in vivo model, peripherally administered cannabinoids even increased the activity of noradrenergic neurones, i.e., enhanced the firing rate of noradrenergic neurones of the locus coeruleus in a rimonabant-sensitive manner (Mendiguren and Pineda 2006), whereas locally administered cannabinoids were without an effect. The explanation for this phenomenon may be that the cannabinoid receptors involved are located on an inhibitory neurone projecting to the locus coeruleus. Cannabinoids also affect noradrenaline release from sympathetic neurones, and the corresponding studies are described in sections related to the respective peripheral tissues.

The effects of cannabinoids and rimonabant on serotonin release have been rarely studied. A cannabinoid-related inhibition of serotonin release was found in the hippocampus of the mouse in vitro. This effect was counteracted by rimonabant, which, however, did not affect serotonin release by itself (Nakazi et al. 2000) (Fig. 3). On the other hand, rimonabant facilitated serotonin release in the medial prefrontal cortex and nucleus accumbens of the rat in vivo (Tzavara et al. 2003).

Based upon the role of the dopaminergic system in addiction, several studies have investigated cannabinoid effects on dopaminergic neurotransmission. Studies on the role of cannabinoids on dopamine release in the central nervous system have been less consistent than those on other transmitters, as, depending on the experimental system, a facilitating or inhibitory effect of cannabinoids on dopamine release (or a related parameter) was found. In the mesolimbic dopamine system, which is the molecular substrate for addiction, cannabinoids were reported to increase the firing rate of dopaminergic neurones (Cheer et al. 2000, 2003; Diana et al. 1998; French 1997; Pistis et al. 2001) or to increase dopamine release in vivo (Cheer et al. 2004). Rimonabant, which inhibits such effects of exogenous agonists, apparently does not alter dopamine release (Cheer et al. 2004) or the firing rate of dopaminergic neurones in the absence of exogenous cannabinoids (Cheer et al. 2000, 2003; Diana et al. 1998; French 1997; Pistis et al. 2001). The cannabinoid-induced increase in dopamine release and firing rate of dopaminergic neurones may be related to activation of inhibitory cannabinoid receptors located on tonically active inhibitory (GABAergic) interneurones synapsing with the dopaminergic neurones in the ventral tegmental area. The phenomenon that addictive drugs that activate prejunctional inhibitory receptors nonetheless facilitate dopamine release is also true for μ opioid receptor agonists such as morphine; the latter compounds again act via "inhibition of the inhibitor" (GABAergic interneurones).

The situation is even somewhat more complicated with respect to another dopaminergic tract, namely, the nigrostriatal system. Whereas in vitro studies in the rat striatum showed rimonabant-sensitive inhibitory effects of exogenous cannabinoids (Cadogan et al. 1997; Kathmann et al. 1999), in vivo studies in the same tissue reported stimulatory effects (Malone and Taylor 1999). The cannabinoid receptors in the latter model may be located on GABAergic interneurones synapsing with the dopaminergic perikarya. In addition, one has to assume that the increase in firing rate may offset the prejunctional inhibition of dopamine release occurring at the level of the dopaminergic axon terminals. Interestingly, dopamine D_2 receptor agonists enhance the release of endocannabinoids in the rat striatum, indicating the possible presence of a feedback loop (Giuffrida et al. 1999). An influence of cannabinoids on dopamine release (or the firing of dopaminergic neurones) has also been found in another two dopamine systems. Thus, cannabinoids increased the firing rate of the rat mesocortical system in a manner sensitive to rimonabant, which was ineffective in the absence of an exogenous agonist (Diana et al. 1998). Again, the prejunctional receptors may be located on a GABAergic interneurone. Moreover, cannabinoids inhibited dopamine release from guinea pig retinal cells in a manner sensitive to rimonabant. The latter very markedly facilitated dopamine release when given alone (Schlicker et al. 1996) (Fig. 3).

Many studies have been done related to acetylcholine release both in the peripheral nervous system (see below in sections related to the various tissues) and in the brain. In general, cannabinoids inhibit acetylcholine release, and rimonabant antagonizes this effect, suggesting that acetylcholine release is under the control of a prejunctional inhibitory CB_1 receptor. The inhibitory effects of cannabinoids on acetylcholine release are absent in CB_1-receptor knockout mice (Degroot et al. 2006; Kathmann et al. 2001b; Schlicker et al. 2003), corroborating the findings with rimonabant that demonstrate mediation via a CB_1 receptor. However, it should be mentioned that cannabinoids did not inhibit acetylcholine release in some studies in the rat nucleus accumbens (Gifford and Ashby 1996; Tzavara et al. 2003) or striatum (Gifford et al. 1997), and in some in vivo settings, they even enhanced release in rats. The latter effect was similarly sensitive to rimonabant as the inhibition of acetylcholine release (Acquas et al. 2000, 2001). Again, the explanation may be that the cannabinoid receptors are not located directly on the cholinergic neurone but on an inhibitory interneurone projecting to the cholinergic neurone.

Interestingly, rimonabant does not only antagonize the effects of exogenous cannabinoids on acetylcholine release, but in some cases, although not consistently, influences acetylcholine release in a manner opposite to that of the exogenous agonist (Fig. 3). Generally, this phenomenon may reflect antagonism of endogenously present cannabinoids or may be related to the inverse agonist properties of rimonabant. In other words, this may point to the fact that the receptors are constitutively active (Fig. 4). Evidence for the former possibility (Fig. 4A,B) was presented for the CB_1 receptor, leading to the inhibition of acetylcholine release in human cerebral cortex slices (Steffens et al. 2003). In this preparation, AM 404, an endocannabinoid uptake inhibitor, inhibited acetylcholine release, most probably due to the fact that the amount of endocannabinoids in the synaptic cleft was further increased because the mechanism for removal of the endocannabinoids (the sink) was blocked. Moreover, O-1184, a partial CB_1-receptor agonist without inverse agonist properties, facilitated acetylcholine release, most probably due to the fact that the latter drug behaved as an antagonist toward the endocannabinoids accumulating in the biophase of the receptor. Evidence for the second possibility (Fig. 4C,D) comes from the study by Gifford et al. (2000) in which acetylcholine release was studied in rat hippocampal synaptosomes, i.e., in isolated nerve endings in which endogenously formed cannabinoids (if present) are efficiently removed by the superfusion stream and therefore cannot accumulate in the receptor biophase. Unfortunately, experiments of that type have been carried out only in a few models, and therefore, a decision as to whether the first, the second, or both mechanism(s) is (are) involved cannot be reached.

CB_1 receptors have been found on axon terminals of neurones containing the inhibitory transmitter GABA, e.g., in the hippocampus (Katona et al. 1999; Tsou et al. 1999). Cannabinoids have consistently been found to inhibit GABA release, and rimonabant was consistently reported to antagonize this effect. Such findings were obtained in vitro and in vivo in several brain areas including cerebral cortex, hippocampus, and cerebellum both in mice (Engler et al. 2006) and rats (Chan and Yung 1998; Ferraro et al. 2001a; Hajos et al. 2000; Kofalvi et al. 2005; Paton et al. 1998; Pistis et al. 2002; Szabo et al. 2002; Wilson and Nicoll 2001).

The effects of cannabinoids and rimonabant on the release of the excitatory transmitter glutamate have been examined in mice (Freiman and Szabo 2005; Hoffman et al. 2005; Kofalvi et al. 2003, 2005) and rats (Brown et al. 2003; Gerdeman and Lovinger 2001; Hoffman et al. 2003; Huang et al. 2001; Levenes et al. 1998). Whereas one study found a cannabinoid-induced enhancement of glutamate release in the rat prefrontal cortex in vitro and in vivo (Ferraro et al. 2001b) and another one reported a cannabinoid-induced elevation of glutamate levels in primary cultures of rat cerebral cortex neurones (Tomasini et al. 2002), the vast majority of studies reported inhibition of glutamate release by cannabinoids (Brown et al. 2003; Freiman and Szabo 2005; Gerdeman and Lovinger 2001; Hoffman et al. 2005; Huang et al. 2001; Kofalvi et al. 2003, 2005; Levenes et al. 1998; Slanina and Schweitzer 2005). Both the stimulatory and the inhibitory cannabinoid effects on glutamate release were rimonabant sensitive, indicating that CB_1 receptors are involved in both instances. The reason for the differential influence of cannabinoids on

Fig. 4 Two explanations for the facilitating effect of rimonabant on transmitter release. The first explanation says that endocannabinoids (blue symbols) are accumulating in the biophase of the cannabinoid CB_1 receptors, thereby reducing transmitter release (A). Addition of rimonabant (red symbols) attenuates the extent of inhibition due to its competitive antagonism (B). The second explanation says that the receptors are constitutively active, i.e., they occur in the active state (R*) coupled to $G_{i/o}$ proteins, eventually reducing transmitter release (C). Addition of the inverse agonist rimonabant isomerizes the receptor to the state not coupled to $G_{i/o}$ proteins (R, broken circles). Therefore, the constitutive inhibition is lost, and facilitation is observed (D)
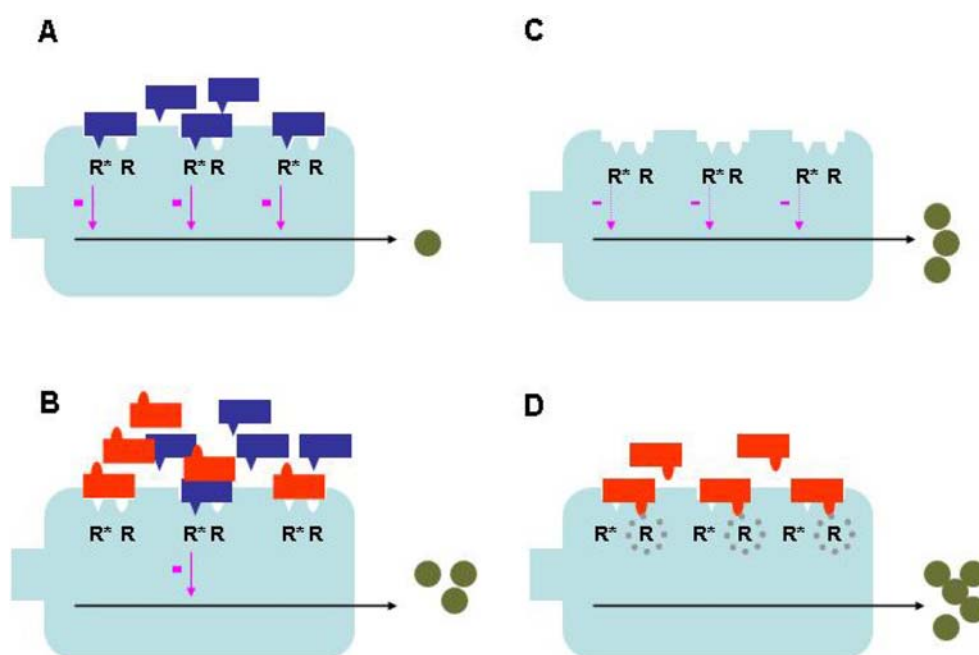
glutamate release might be that the CB_1 receptor leading to the facilitation of glutamate release is not located on the glutamatergic neurone itself but rather on an interpolated inhibitory interneurone. In the study by Slanina and Schweitzer (2005) in which cannabinoids had an inhibitory effect on glutamate release, rimonabant facilitated glutamate release in the absence of exogenously added cannabinoids, suggesting that the CB_1 receptor in this model is subject to an endogenous tone. Finally, there is evidence from studies with CB_1-receptor knockout mice that the CB_1 receptor may not be the sole receptor involved in cannabinoid-induced inhibition of glutamate release (Kofalvi et al. 2003, 2005). Thus, WIN 55,212–2 inhibited glutamate release also in CB_1-receptor-deficient mice (Kofalvi et al. 2003, 2005), and the effect of WIN 55,212–2 was counteracted by rimonabant (Hajos et al. 2001).

Although a rimonabant-sensitive effect of cannabinoids on GABA and glutamate release has been found in many studies [for a more complete review, see Szabo and Schlicker (2005)], rimonabant had an effect of its own in very few studies only. For example, in the paper by Slanina and Schweitzer (2005) in which cannabinoids had an inhibitory effect on glutamate release, rimonabant facilitated glutamate release in the absence of exogenously added cannabinoids, suggesting that the CB_1 receptor in this model is subject to an endogenous tone. The reason why rimonabant had no effect of its own in most studies might be that an endogenous tone is rarely associated with CB_1 receptors affecting GABA and glutamate release. Another (and perhaps more plausible) explanation might be that the vast majority of studies dedicated to GABA and glutamate was carried out with the patch-clamp technique, i.e., with single cells, and that a slight endogenous tone might be overlooked under this experimental scenario.

There is increasing evidence that the CB_1 receptors leading to the inhibition of GABA or glutamate release are implicated in a local feedback loop, referred to as depolarization-induced suppression of inhibition and excitation (DSI and DSE, respectively). This phenomenon [for a more complete review, see Vaughan and Christie (2005)] means that depolarization of the postsynaptic membrane leads to the formation and subsequent release of endocannabinoids that, after having passed the synaptic cleft, activate the inhibitory prejunctional CB_1 receptors of the preceding GABAergic or glutamatergic neurone. This phenomenon of backward signaling appears to be unique to the latter neurones. It has so far not been shown for other transmitters either in the central or peripheral nervous system.

Taken together the overall data suggest that cannabinoids, acting on CB_1 receptors, inhibit transmitter release in the central nervous system. Interestingly, this applies similarly to excitatory transmitters such as glutamate and inhibitory transmitters such as GABA. The rationale for inhibiting two physiologically opposing transmitter systems remains to be elucidated. One has to consider, however, that the distribution of CB_1 receptors differs markedly. For example, cholinergic neurones in the mouse hippocampus are endowed with CB_1 receptors subject to an endogenous tone. Such an endogenous tone is, however, missing at the CB_1 receptors on the cholinergic neurones in the cerebral cortex. Finally, striatal cholinergic neurones are not endowed with prejunctional CB_1 receptors at all (Schlicker et al. 2003). Cannabinoids, as with other drugs leading to addiction, markedly increase the firing rate of dopaminergic neurones projecting from the ventral tegmental area to the nucleus accumbens. This phenomenon (probably related to activation of CB_1 receptors on a GABAergic interneurone) may represent the cellular substrate of the addictive effects of cannabinoids.

Cardiovascular effects

The cardiovascular system is one of the peripheral tissues expressing CB_1 receptors on cell types other than prejunctional nerve endings. Whereas one study reported the presence of CB_1-receptor messenger ribonucleic acid (mRNA) on vascular smooth muscle cells (Sugiura et al. 1998), other investigators largely failed to confirm this (Domenicali et al. 2005). A recent report on human coronary vascular smooth muscle also has detected CB_1-receptor mRNA but only at low levels (Rajesh et al. 2008), possibly explaining why this has not been consistently seen in earlier studies. On the other hand, the expression of CB_1 receptors has repeatedly been shown at the mRNA and protein level in endothelial cells from various vascular beds of rats (Domenicali et al. 2005; Lepicier et al. 2007) and humans (Liu et al. 2000; Rajesh et al. 2007; Sugiura et al. 1998), although the evidence is not unequivocal (McCollum et al. 2007). Messenger RNA and immunoreactivity for CB_1 receptors has also been reported from murine cardiomyocytes (Mukhopadhyay et al. 2007; Pacher et al. 2005). Thus, in the cardiovascular system, cannabinoids and rimonabant may act not only by central and prejunctional peripheral mechanisms but also by direct endothelial effects and, perhaps, at the levels of vascular smooth-muscle cells and cardiomyocytes.

Numerous studies have investigated the effects of cannabinoids and rimonabant on cardiovascular function. Upon systemic administration, they can affect blood pressure regulation under both normal and pathophysiological conditions. Some studies suggest that cannabinoids can cause brief pressor responses followed by longer-lasting depressor responses, of which only the latter appear to be

rimonabant sensitive (Malinowska et al. 2001a; Varga et al. 1995). With few exceptions (Wang et al. 2005), the vast majority of studies in rats (Batkai et al. 2004b; Garcia et al. 2001; Niederhoffer et al. 2003; Varga et al. 1995), mice (Jarai et al. 2000), rabbits (Niederhoffer and Szabo 1999), and guinea pigs (Calignano et al. 1997a) reported exogenous cannabinoids to reduce blood pressure in a rimonabant-sensitive manner. A cannabinoid-induced, rimonabant-sensitive lowering of heart rate has been reported in mice (Jarai et al. 2000), and an anandamide-induced rimonabant-sensitive lowering of cardiac contractility has been shown in mice (Pacher et al. 2004) and, based upon elevations of endogenous anandamide levels, proposed in doxorubicin-induced cardiotoxicity (Mukhopadhyay et al. 2007). A similar effect, which was sensitive to the CB_1 antagonist AM251, has been reported in rats with liver cirrhosis (Batkai et al. 2007).

Blood pressure alterations could, in principle, result from effects on the brain, heart, vasculature, or—at least in chronic studies—the kidney. Whereas reports on acute rimonabant effects on renal function surprisingly are lacking to the best of our knowledge, despite the presence of CB_1 receptors in the kidney (Engeli et al. 2005), one recent study reported that a 12-months treatment of obese Zucker rats with rimonabant (3 and 10 mg/kg per day) does not alter renal blood flow but attenuates proteinuria and lowers plasma creatinine while improving glomerular filtration rate (Janiak et al. 2007). Nonrenal effects on blood pressure have been addressed in several studies. The possibility of centrally mediated cardiovascular cannabinoid effects is emphasized by studies showing blood pressure increases upon intra-cisternal injection to rats (Pfitzer et al. 2004) or rabbits (Niederhoffer and Szabo 2000), or blood pressure reduction upon intrathecal injection to rats (del Carmen Garcia et al. 2003). Whereas all of these effects were rimonabant sensitive, it remains to be determined whether the conflicting observations relate to the site of administration or other factors.

A rimonabant-sensitive decrease of the neurogenic vasopressor response following peripheral administration of cannabinoids has been reported from pithed animals (Malinowska et al. 1997; Niederhoffer and Szabo 1999), suggesting that cannabinoid-induced blood pressure lowering can occur independent of the central nervous system. Rimonabant-sensitive blood pressure lowering in pithed animals was typically accompanied by a reduced noradrenaline spillover into the general circulation (Niederhoffer et al. 2003; Niederhoffer and Szabo 1999), indicating a possible prejunctional site of action. Further evidence for the prejunctional location comes from experiments in pithed rats and rabbits, where the cannabinoid agonist WIN 55212–2, although lowering blood pressure in animals with electrical stimulation of sympathetic nerves,

i.e. upon release of endogenous noradrenaline, did not affect blood pressure upon administration of exogenous noradrenaline (Malinowska et al. 1997; Niederhoffer and Szabo 1999; Pfitzer et al. 2005). The situation is further complicated by the fact that cannabinoids also inhibit neurogenic vasodilatation in a rimonabant-sensitive manner (Duncan et al. 2004; Ralevic and Kendall 2001).

Findings that rimonabant-sensitive cannabinoid-induced blood pressure lowering was accompanied by reduced cardiac function (Batkai et al. 2004b; Malinowska et al. 2001b; Niederhoffer et al. 2003) and/or decreased peripheral resistance (Batkai et al. 2004b; Garcia et al. 2001) may suggest that some of the cannabinoid-induced cardiovascular effects may occur at the cardiac and/or vascular level, a possibility that has been directly investigated in numerous studies.

In line with in vivo observations of reduced cardiac contractility upon cannabinoid administration, it was reported that cannabinoids can also exert rimonabant-sensitive negative inotropic effects in the Langendorff-perfused rat heart (Krylatov et al. 2005). Studies in rat models of heart failure (Mukhopadhyay et al. 2007) or liver cirrhosis (Batkai et al. 2007) in which endogenous anandamide concentrations increase and cardiac contractility is improved by rimonabant or other CB_1 antagonists further support a role of this receptor in regulating inotropic functions. The vast majority of studies with isolated cardiovascular tissues were performed with blood vessels. With very few exceptions (O'Sullivan et al. 2005), exogenous cannabinoids have routinely been reported to cause dilatation of isolated blood vessels in a variety of species (Table 1). All responses listed in Table 1 were rimonabant sensitive, including the rarely reported vaso-constriction (O'Sullivan et al. 2005), whereas in a few preparations, cannabinoid-induced vasodilatation was insensitive to rimonabant (Grainger and Boachie-Ansah 2001; Plane et al. 1997; Pratt et al. 1998; White et al. 2001). Conflicting findings have been reported regarding a potential role of the endothelium in vasodilatation. Whereas some studies found cannabinoid-induced vasodilatation to be endothelium independent, others reported it to be at least partly endothelium dependent (Table 1). Rimonabant was typically found to inhibit both the endothelium-dependent and -independent vasodilatation (Table 1). A role of endocannabinoids in the endothelium is further supported by findings that they stimulate Ca^{2+} influx in cerebromicrovascular endothelial cells in a rimonabant-sensitive manner (Golech et al. 2004). Moreover, rimonabant inhibits cannabinoid-induced activation of extracellular signal-regulated kinase (Su and Vo 2007) and nitrous oxide (NO) formation in blood vessels (Poblete et al. 2005), and NO synthase inhibitors can attenuate cannabinoid-induced vasodilatation (Ho and Hiley 2003). However, rimonabant-

Table 1 Effects of cannabinoids and rimonabant on blood vessels

Vessel	Species	Cannabinoid-induced effect	Dependent on endothelium	Antagonism by rimonabant	Comment	References
Aorta	Rabbit	–	Yes	1 μM	CB_1 receptor not involved	Mukhopadhyay et al. (2002)
Coronary artery	Rat	–	Yes	2 μM	CB_1 receptor possible but not likely	Fulton and Quilley (1998)
		–	?	3 mg/kg	In vivo study (coronary blood flow studied); CB_1 receptor possible	Wagner et al. (2001b)
Cerebral blood flow	Rat	–	?	3 mg/kg	CB_1 receptor possible	Wagner et al. (2001b)
Mesenteric artery	Rabbit	–	Yes	10 μM	Cannabinoids act directly on gap junctions	Chaytor et al. (1999)
		*	Yes	30 μM	CB_1 receptor possible	Fleming et al. (1999)
		–	No	1–3 μM	CB_1 receptor unlikely	Kagota et al. (2001)
	Rat	–	Yes	3 μM	CB_1 receptor possible but not likely	Ishioka and Bukoski (1999)
			Yes	0.5–5 μM	Endothelial cannabinoid receptor; rimonabant increases perfusion pressure in rats pretreated with lipopolysaccharide	Wagner et al. (1999)
			Yes	1–3 μM	Endothelial cannabinoid receptor	Ho and Hiley (2003)
			Yes	3 μM	Endothelial cannabinoid receptor?	Hoi and Hiley (2006)
			No	1 μM	CB_1 receptor unlikely	White and Hiley (1997a)
			No	3 μM	CB_1 receptor possible but not likely	Domenicali et al. (2005)
		+	Yes	0.1 μM	CB_1 receptor possible	O'Sullivan et al. (2005)
	Mouse	–	Yes	1 μM	Endothelial cannabinoid receptor	Jarai et al. (1999)
Hepatic artery	Rat	–	No	3 μM	CB_1 receptor possible	Zygmunt et al. (1997)
Iuxtamedullary afferent arterioles	Rat	–	?	1 μM	CB_1 receptor possible	Deutsch et al. (1997)

+ Constriction, – dilatation, * inhibition of acetylcholine- or bradykinin-induced vasodilatation, ? not tested

sensitive cannabinoid-induced vasodilatation has also been observed in the presence of NO synthase inhibition (Zygmunt et al. 1997). Taken together, these findings demonstrate that cannabinoids and rimonabant can affect vascular function not only by prejunctional inhibition of neurotransmitter release but also via direct effects on the endothelium. This raises the intriguing possibility that the endothelium may be one of the peripheral tissues under the direct control of endocannabinoids.

The type of receptor or mechanism involved in the effects of the endocannabinoids on the endothelium is, however, not well understood. Table 1 shows that in almost all models, high concentrations of rimonabant (≥1 μM)

were necessary for antagonism, i.e., concentrations much higher than those used in true CB_1-receptor models, including that shown in Fig. 2 in which a concentration of 0.032 μM was effective. A poor rimonabant sensitivity was also found for the cannabinoid-induced Ca^{2+} elevations in endothelium-derived cell lines, possibly involved in the endothelial effects of the cannabinoids (Mombouli et al. 1999). Although in some of the models listed in Table 1 a true CB_1 receptor may be involved, other mechanisms appear to be more plausible for part of the other cannabinoid-related effects. In some vascular preparations, including the rat mesenteric artery, a special endothelial anandamide receptor may be involved (Ho and Hiley 2003;

Hoi and Hiley 2006; Jarai et al. 1999; Wagner et al. 1999). This receptor, although not affected by the standard cannabinoid receptor agonist WIN 55,212–2, is activated by anandamide and abnormal cannabidiol, a synthetic derivative of the naturally occurring cannabidiol. The latter drug acts as an antagonist at this receptor, which has, however, so far not been cloned. In another model, the mesenteric artery of the rabbit, anandamide and its stable analogue methanandamide cause relaxation by a special mechanism involving the gap junctions (Chaytor et al. 1999). Rimonabant possesses a low potency as an antagonist both for the endothelial anandamide receptor and for the gap-junction-related vasodilatory mechanism.

Whereas all of the above studies on vascular tone used administration of exogenous cannabinoids, several other studies tested vascular rimonabant effects in the absence of exogenously added cannabinoids. Some of these studies, particularly when using high rimonabant concentrations, reported effects that apparently are unrelated to CB_1 receptors, as they were also observed in CB_1 knockout mice (Bukoski et al. 2002) or failed to be mimicked by other CB_1-receptor antagonists (Stanford et al. 2001). Such nonspecific effects may occur, e.g., by direct effects on Ca^{2+} channels (White and Hiley 1998). On the other hand, rimonabant may also affect vascular tone in the absence of exogenous cannabinoids by mechanisms involving CB_1 receptors. For example, Ca^{2+}-induced vasodilatation in rat isolated mesenteric vessels can be inhibited by rimonabant and enhanced by an inhibitor of anandamide metabolism (Ishioka and Bukoski 1999). Similarly, rimonabant was also shown to inhibit the endothelium-dependent vasodilatation induced by K^+-channel openers in rat mesenteric arteries (White and Hiley 1997b). On the other hand, rimonabant did not affect K^+-channel opener-induced vasodilatation in rat coronary vessels (Fulton and Quilley 1998). Taken together, these data indicate the possibility that some agents may generate the formation and release of endocannabinoids, which then act on CB_1 receptors, possibly on the endothelium, to cause vasodilatation. Indeed, it has been speculated that endocannabinoids such as anandamide or 2-arachidonoylglycerol may be the elusive endothelium-derived hyperpolarizing factor (Randall et al. 1996; Randall and Kendall 1997). However, further studies are necessary to confirm this hypothesis [which has been questioned, e.g., by Kagota et al. (2001)] and to exclude that artefacts of high rimonabant concentrations have led to erroneous conclusions.

On the other hand, it is possible that endocannabinoids and CB_1 receptors play a role in pathophysiological settings. This has been investigated in a variety of models. For example, exogenous cannabinoids were found to reduce mean arterial pressure to a greater extent in rats fed a high-sodium diet compared with those with normal

sodium, and such blood pressure lowering was rimonabant sensitive (Wang et al. 2005). The roles of cannabinoids and rimonabant have also been explored with regard to cardiac arrhythmia and myocardial infarction. Whereas anandamide was found to reduce adrenaline-induced arrhythmia in rats, this was not sensitive to rimonabant (Ugdyzhekova et al. 2000, 2001). Exogenously added endocannabinoids such as anandamide were also reported to reduce ischemia/reperfusion damage in the isolated rat heart. Whether other endocannabinoids such as 2-arachidonoylglycerol or synthetic cannabinoids mimic this effect has not been fully resolved, but the majority of studies suggests so (Lepicier et al. 2003, 2007; Underdown et al. 2005; Wagner et al. 2001a, 2006). The beneficial effects of ischemic preconditioning (Bouchard et al. 2003) or of exogenous cannabinoids (Joyeux et al. 2002; Lagneux and Lamontagne 2001; Lepicier et al. 2003, 2007; Underdown et al. 2005) were consistently blocked by CB_2 antagonists such as SR 144528. In contrast, rimonabant either had no effect (Joyeux et al. 2002; Lagneux and Lamontagne 2001), blocked the protection by some but not other cannabinoids (Bouchard et al. 2003; Lepicier et al. 2003), or, in a few studies, was similarly effective as a CB_2 antagonist (Bouchard et al. 2003; Underdown et al. 2005). Accordingly, it has been proposed that protection against ischemia/reperfusion injury is largely mediated by CB_2 receptors (Pacher and Hasko 2008). Apart from acute heart failure in the context of myocardial ischemia, a shock syndrome can also occur after massive hemorrhage or due to sepsis, the latter being mimicked by administration of the bacterial endotoxin/lipopolysaccharide (LPS). LPS was found to stimulate formation of anandamide by macrophages (Wagner et al. 1997). In addition, administration of rimonabant was shown to increase mean arterial pressure, pulse pressure, respiratory rate, and, most importantly, survival in rat models of hemorrhagic shock (Cainazzo et al. 2002; Varga et al. 1998; Wagner et al. 1997). Similarly, rimonabant reversed the adverse effects of LPS on blood pressure, cardiac contractility, and systemic vascular resistance (Batkai et al. 2004a). Interestingly, the latter effect was not mimicked by another CB_1 inverse agonist, AM251, indicating a possible specific benefit with rimonabant. Rimonabant was also found to inhibit the LPS-induced blood pressure lowering effect in pithed rats (Godlewski et al. 2004). Finally, rimonabant was found to increase arterial pressure and peripheral resistance in rats with liver cirrhosis but not in control rats (Batkai et al. 2001; Ros et al. 2002). Rimonabant also exhibited beneficial effects in a rat model of doxorubicin-induced cardiomyopathy (Mukhopadhyay et al. 2007). Taken together, these animal findings raise the possibility that rimonabant may be beneficial for the cardiovascular system of patients with liver cirrhosis or septic shock (Mendizabal and Adler-Graschinsky 2007).

On the other hand, myocardial infarction in patients undergoing rimonabant treatment could be more damaging than in those not receiving rimonabant, but no clinical data are available in this regard.

Gastrointestinal effects

The expression of CB_1 receptors in the gastrointestinal tract has been demonstrated at the protein level by immunological (Casu et al. 2003) as well as radioligand binding techniques (Ross et al. 1998). Accordingly, cannabinoid agonists can modulate various functional responses in the gastrointestinal tract (Table 2). In general, cannabinoids dampen secretion and motility. In detail, cannabinoids reduce the electrically induced twitch response and secretion in the ileum and electrically induced peristalsis in the colon in vitro, The effect on the electrically induced ileal contraction was also shown in human tissue. In vivo, cannabinoids reduce esophageal sphincter relaxation, pentagastrin- or vagally induced acid secretion in the stomach, gastric emptying, intraluminal fluid accumulation in the small intestine, gastrointestinal transit, and defecation (Table 2). Interestingly, although cannabinoids inhibit the intestinal motility evoked by nerve stimulation, they do not affect that evoked by the muscarinic receptor agonist carbachol (Croci et al. 1998). These data indicate that cannabinoids act by inhibiting transmitter release rather than by directly affecting intestinal smooth-muscle function. Accordingly, direct evidence for prejunctional inhibition of transmitter release has been obtained in release (Pertwee et al. 1996b) and electrophysiological studies (Storr et al. 2004). Rimonabant has consistently been found to counteract the cannabinoid-induced effects, indicating

Table 2 Effects of rimonabant on functional parameters in the gastrointestinal tract

Functional parameter	Species	Effect of cannabinoids	Antagonism by rimonabant	Effect of rimonabant by itself	References
Transient lower esophageal sphincter relaxations	Dog	–	Yes	+	Lehmann et al. (2002)
Gastric contraction	Mouse	–	Yes	0	Mule et al. (2007)
Pentagastrin- or vagally induced acid secretion in the stomach	Rat	–	Yes	0	Coruzzi et al. (1999, 2006)
Ouabain-induced acid secretion in the stomach	Rat	ND	ND	+	Borrelli (2007)
Gastric emptying	Rat	–	Yes	0	Izzo et al. (1999b), Landi et al. (2002)
Stress-induced gastric ulcer	Rat	–	Yes	0	Germano et al. (2001)
Intraluminal fluid accumulation in small intestine	Rat	–	Yes	+	Izzo et al. (1999a)
Electrically induced twitch response and acetylcholine release in ileum	Human	–	Yes	0 or +	Croci et al. (1998), Guagnini et al. (2006)
	Guinea pig	–	Yes	+	Coutts and Pertwee (1997), Guagnini et al. (2006), Pertwee et al. (1996b)
Electrically induced ileal secretion	Rat	–	Yes	0	Tyler et al. (2000)
Electrically induced peristalsis in distal colon	Mouse	–	Yes	+	Mancinelli et al. (2001)
Excitatory junction potential in colon	Mouse	–	Yes	+	Storr et al. (2004)
Fast inhibitory junction potential in colon	Mouse	–	Yes	0	Storr et al. (2004)
Gastrointestinal transit	Rat	–	Yes	0 or +	Izzo et al. (1999c), Landi et al. (2002)
	Mouse	–	Yes	+	Calignano et al. (1997b), Carai et al. (2004, 2006), Casu et al. (2003), Izzo et al. (1999a, 2000, 2001a, b)
Defecation	Mouse	–	Yes	0	Izzo et al. (1999a)

– Inhibition, + facilitation, 0 no effect, *ND* not determined

that they occur via CB_1 receptors. In some instances, rimonabant alone elicited effects in the opposite direction to those obtained with cannabinoids (Table 2), which may reflect antagonism of the effects of tonically formed endogenous cannabinoids and/or the inverse agonist properties of rimonabant. The rimonabant-induced enhancement of intestinal motility develops tolerance within several days of treatment (Carai et al. 2004), which is in line with the observation that CB_1-receptor knockout mice do not exhibit major alterations of gastrointestinal transit time (Carai et al. 2006). Studies in dogs indicate that a cannabinoid agonist can inhibit transient lower esophageal sphincter relaxations and that such inhibition is antagonized by rimonabant but not by a CB_2 antagonist. Moreover, in the absence of exogenous cannabinoids, rimonabant enhanced transient lower esophageal sphincter relaxations (Lehmann et al. 2002). As the cannabinoid agonist did not affect responses of gastric vagal mechanoreceptors to distension within the same study, these responses may occur centrally rather than locally in the esophagus. Rimonabant was also found to inhibit the formation of indomethacin-induced intestinal ulcers in rats. This beneficial effect may be related to an influence on immune cells rather than neurones, as in the same study, the production of tumor necrosis factor (TNF) was inhibited as well (Croci et al. 2003). However, there appear to be other pathogenetic factors, as ulcer formation (but not production of TNF) was also antagonized by the CB_2-receptor inverse agonist SR 144528 (Croci et al. 2003). On the other hand, in a mouse model of colitis, rimonabant aggravated symptoms, as did genetic ablation of CB_1 receptors, whereas a cannabinoid agonist as well as the lack of the enzyme degrading the endocannabinoid anandamide had a beneficial effect (Massa et al. 2004). These findings raise the possibility that drugs such as rimonabant may have potential in treating some disorders of the gastrointestinal tract but may also adversely affect others, such as esophageal reflux disease.

Urogenital effects

Cannabinoid receptors have been described in various urogenital tissues, including the urinary bladder, vas deferens, and uterus. CB_1 receptors have been identified by immunohistochemistry in the rat prostate where they apparently exist on glandular rather than smooth-muscle cells (Tokanovic et al. 2007). Nevertheless, rimonabant reversed WIN 55,212–2 inhibition of field stimulation-induced prostatic contraction, an effect mimicked by cyclooxygenase inhibition (Tokanovic et al. 2007). The authors interpreted these findings to suggest that epithelial CB_1 receptors in the prostate stimulate cyclooxygenase and that the prostanoids formed (e.g., prostaglandin E_2) in turn inhibit smooth-muscle contraction. However, a prejunctional CB_1 receptor must also be considered under these experimental conditions. Further studies related to cannabinoid and rimonabant effects on the prostate are discussed in the section on "Cancer".

In the isolated mouse bladder cannabinoids cause a rimonabant-sensitive inhibition of field-stimulation-induced contraction without affecting the contraction elicited by muscarinic or purinergic receptor agonists. In the absence of exogenous cannabinoids, rimonabant slightly increased bladder contraction (Pertwee and Fernando 1996). These results suggest that the cannabinoid and rimonabant effects on the murine bladder occur prejunctionally and that an endogenous tone is developing. Later studies confirmed a rimonabant-sensitive inhibition of neuronally stimulated contractions of isolated bladder in mouse and extended these findings to rats. On the other hand, no such inhibition was seen in the isolated bladder of dogs, pigs, cynomolgus monkeys, or humans, indicating that the inhibitory effect of cannabinoids on bladder contractility is species dependent (Martin et al. 2000). In line with the in vitro data from rodents, in vivo studies in rats demonstrated a cannabinoid-induced reduction of micturition thresholds, which became even more prominent under conditions of bladder inflammation or after sympathectomy. Rimonabant antagonized this effect and, in the absence of exogenous cannabinoids, increased micturition threshold, at least after sympathectomy, again suggesting an endogenous tone (Dmitrieva and Berkley 2002).

Cannabinoids inhibit cAMP accumulation (Pertwee et al. 1996c) and noradrenaline release (Schlicker et al. 2003) in mouse vas deferens in a rimonabant-sensitive manner. Accordingly, cannabinoids inhibit the field-stimulation-induced contraction of the vas deferens of mice in a rimonabant-sensitive manner (Lay et al. 2000; Pertwee et al. 1995; Rinaldi-Carmona et al. 1994). When given alone, rimonabant increased both noradrenaline release (Schlicker et al. 2003) and neurogenic contraction in this tissue (Pertwee et al. 1996a). A similar cannabinoid effect was found in the rat vas deferens, and there is an endogenous cannabinoid tone in this tissue, as well (Christopoulous et al. 2001).

Other research has been dedicated to the effects of cannabinoids and rimonabant on penile erection. In general, an increase in penile erection was found after systemic administration of rimonabant in an apomorphine-induced erection model (da Silva et al. 2003) or its injection into the paraventricular nucleus in male rats (Melis et al. 2006; Succu et al. 2006a, b). In some cases, the rimonabant-induced increase of penile erection was accompanied by an increase in glutamic acid (Succu et al. 2006a, b) and NO (Succu et al. 2006a) in the paraventricular dialysate, or the activation of neuronal NO synthase (Melis et al. 2006). The rimonabant-induced increase of penile erection was inhibited by cannabinoids (Melis et al. 2004, 2006; Succu

et al. 2006b), an N-methyl-D-aspartate (NMDA) antagonist, NO synthase inhibitors (Melis et al. 2004, 2006), and a GABA$_B$-receptor agonist (Melis et al. 2006). Thus, rimonabant has the potential to affect penile erection, but until now there has been no evidence that this involves a peripherally mediated effect.

Cannabinoids can also affect the female genital tract and embryonic development. Whereas cannabinoids can cause relaxation of the human pregnant myometrium (Dennedy et al. 2004) and contraction of the nonpregnant rat uterus (Dmitrieva and Berkley 2002), both effects were rimonabant sensitive. Whereas low concentrations of cannabinoids promote embryo attachment and outgrowth of blastocysts in a rimonabant-sensitive manner (Liu et al. 2002), higher cannabinoid concentrations can inhibit mouse embryonic development in a rimonabant-sensitive manner by preventing blastocyst development (Liu et al. 2002; Paria et al. 1998; Yang et al. 1996). Whereas this apparently biphasic cannabinoid dose-response curve makes it difficult to predict what rimonabant may do with respect to embryonic development, the use of rimonabant is not recommended in pregnant women.

Immunological effects

Cannabinoids can affect the immune system in a complex manner. They can reduce (1) expression of proinflammatory cytokines (Carrier et al. 2006; Ihenetu et al. 2003a, b; Klein et al. 1998; Ortega-Gutierrez et al. 2005; Sacerdote et al. 2005; Smith et al. 2000, 2001), (2) lymphocyte activation and proliferation (Carayon et al. 1998; Carrier et al. 2006; Derocq et al. 1995; McKallip et al. 2002; Patrini et al. 1997; Roa et al. 2004), (3) cytolytic activity (Massi et al. 2000), and (4) macrophage activation (Sacerdote et al. 2000). Moreover, cannabinoids can increase endogenous anti-inflammatory pathways, e.g., by increasing levels of corticosterone (Newton et al. 2004) or the endogenous interleukin (IL)-1 receptor antagonist (Molina-Holgado et al. 2003). Therefore, the net effect of cannabinoids is considered to be anti-inflammatory and/or immunosuppressive. Although CB$_2$-receptor mRNA occurs in much higher density in immune cells than does CB$_1$-receptor mRNA (Cabral and Staab 2005), rimonabant has been reported to at least partly inhibit some cannabinoid effects on the inflammatory and immune system. Thus, the cannabinoid-induced downregulation of inflammatory cytokines, including TNF-α, was reported to be rimonabant sensitive in mice (Klein et al. 2004; Smith et al. 2000, 2001), rats (Cabral et al. 2001; Ortega-Gutierrez et al. 2005), and humans (Ihenetu et al. 2003b). Similarly, rimonabant was beneficial in a rat model of adjuvant-induced arthritis, although this may at least partly be due to

effects on sensorial hypersensitivity (Croci and Zarini 2007). Moreover, rimonabant may at least partially reverse cannabinoid-induced reductions of natural killer cell cytolytic activity (Massi et al. 2000), reductions of NO release (Cabral et al. 2001; Molina-Holgado et al. 2002; Ponti et al. 2001; Sheng et al. 2005), and enhancements of release of endogenous IL-1 receptor antagonist (Molina-Holgado et al. 2003). Accordingly, rimonabant treatment caused greater inflammatory responses in a mouse model of colitis, thereby mimicking the phenotype of CB$_1$-receptor knock-out mice (Massa et al. 2004). Furthermore, rimonabant (as with the CB$_2$-receptor inverse agonist SR 144528) aggravated the allergic responses in a mouse model of cutaneous contact hypersensitivity (Karsak et al. 2007). On the other hand, rimonabant may also exhibit antiproliferative and immunomodulatory effects on human peripheral blood mononuclear cells (Malfitano et al. 2008). Therefore, the role of rimonabant for overall immune function remains elusive.

Metabolic and endocrine effects

Whereas the beneficial clinical effects of rimonabant in obesity were originally thought to be only mediated in the central nervous system, a peripheral effect via CB$_1$ receptors expressed in adipocytes (Bensaid et al. 2003; Blüher et al. 2006; Engeli et al. 2005; Osei-Hyiaman et al. 2005; Yan et al. 2007) may also contribute. The role of these receptors in the regulation of adipocyte function may further increase in obesity, as adipocyte expression of CB$_1$ receptors is upregulated in obese rats (Bensaid et al. 2003). Nevertheless, it remains difficult to specifically assign rimonabant in vivo effects on adipocyte function (Jbilo et al. 2005; Osei-Hyiaman et al. 2005) to a central or peripheral site of action in in vivo studies. However, studies in isolated adipocytes or cell lines derived thereof have clearly demonstrated that at least part of the effects of rimonabant on the function of these cells is exerted locally. Thus, in cultured mouse adipocytes, rimonabant was reported to increase the expression of mRNA and protein of Acrp30, an adipocyte-derived plasma protein involved in the control of free-fatty-acid oxidation, hyperglycemia, and hyperinsulinemia, an effect that was absent in CB$_1$-receptor knockout mice (Bensaid et al. 2003). Moreover, rimonabant can inhibit the proliferation of preadipocytes and induce their differentiation to mature adipocytes, possibly by causing inhibition of extracellular signal-regulated kinase (Gary-Bobo et al. 2006). Accordingly, the expression of CB$_1$ receptors in human visceral adipose tissue was inversely correlated with visceral fat mass (Blüher et al. 2006). All of these effects may contribute to the metabolic improvements reported upon rimonabant treatment in obese and/or diabetic patients, but the specific

relative roles of such peripheral compared with central effects remain to be established (Brizzi et al. 2005; Jbilo et al. 2005; Wierzbicki 2006).

Cannabinoids can affect secretion of several hormones, including those released by the pituitary and several peripheral glands. Exogenously added cannabinoids can reduce secretion of luteinizing hormone (LH) and testosterone in mice without affecting their synthesis. Whereas rimonabant alone did not affect serum LH, it blocked the cannabinoid effect (Wenger et al. 2001). The same study also found that CB_1-receptor knockout mice have markedly lowered basal serum concentrations of LH, an effect no longer susceptible to either cannabinoids or rimonabant. Similar findings were obtained for testosterone, which is released under the control of LH. It remains to be determined why CB_1-receptor knockout has different effects on the LH/testosterone system than does acute blockade of these receptors by rimonabant. In rats, exogenous cannabinoids can reduce not only the release of LH but also of other pituitary hormones such as follicle-stimulating hormone and prolactin, with inhibition of the latter being rimonabant sensitive (Fernandez-Ruiz et al. 1997). On the other hand, cannabinoids can increase the release of adrenocorticotropin from the pituitary in a rimonabant-sensitive manner, and this is reflected in corresponding alterations of plasma corticosterone concentrations (Manzanares et al. 1999).

Despite the very limited expression of CB_1 receptors in many peripheral tissues (Engeli et al. 2005), it is found, e.g., in the thyroid gland (Porcella et al. 2002). Accordingly, cannabinoids can lower serum concentrations of the thyroid hormones tri-iodothyronine and thyroxine in a rimonabant-sensitive manner (Porcella et al. 2002). CB_1 receptors are also expressed in the liver (Engeli et al. 2005), and CB_1 antagonists not only have beneficial hemodynamic effects in animal models of liver cirrhosis (Batkai et al. 2001, 2007) but may also beneficially affect the fibrotic disease process within the liver (Teixeira-Clerc et al. 2006). On the other hand, adrenals apparently lack CB_1-receptor expression, but nevertheless, cannabinoids can reduce adrenaline release in pithed rabbits or isolated rabbit adrenals upon electrical stimulation in a rimonabant-sensitive manner, indicating that this may reflect a prejunctional site of action (Niederhoffer et al. 2001). Studies in CB_1-receptor knockout mice suggest a role in the regulation of bone mass and remodeling (Tam et al. 2006), but possible effects of rimonabant or other CB_1 antagonists have not been reported in this regard.

Other peripheral effects

Cannabinoid receptors have been described in various other tissues such as the nonneuronal parts of the eye and the airways. Based upon the clinical observation that smoking marijuana can decrease the intraocular pressure (IOP), several studies have been done on ocular function. In vivo studies with topical cannabinoid administration in rabbits have consistently demonstrated a lowering of IOP, an effect that has been abolished by either systemic (Laine et al. 2002; Pate et al. 1998) or local administration of rimonabant (Song and Slowey 2000). The synthetic cannabinoid WIN 55,212–2 administered as eye drops lowered intraocular pressure in humans suffering from glaucoma (Porcella et al. 2001). CB_1-receptor expression in the ciliary process and trabecular meshwork tissues, as demonstrated in bovine and human eyes (Stamer et al. 2001), may be the mechanistic basis for these observations. Systemic administration of rimonabant alone increased IOP in rabbits (Pate et al. 1998), a finding in line with the presence of anandamide in the human eye (Stamer et al. 2001). Moreover, rimonabant was also reported to inhibit prostaglandin-induced contraction of human ciliary muscle (Romano and Lograno 2007). If rimonabant also increases IOP in humans, this could be associated with an increased risk for glaucoma.

Cannabinoids can affect airway function in rats (Yousif and Oriowo 1999), guinea pigs (Calignano et al. 2000; Yoshihara et al. 2004, 2005), and humans (Patel et al. 2003). Many of these effects are rimonabant insensitive and rather involve vanilloid or CB_2 receptors. Thus, inhibition of the electrically induced contraction of the guinea pig trachea is vanilloid-receptor mediated (Nieri et al. 2003), whereas the sensory nerve-related activation of the guinea pig and human vagus nerve (Patel et al. 2003) or the inhibition of electrically stimulated rat (Yousif and Oriowo 1999) and guinea pig airway contraction (Yoshihara et al. 2004, 2005) is CB_2-receptor mediated. A CB_2 receptor has also been implicated in the inhibition of capsaicin-induced bronchoconstriction in some studies (Patel et al. 2003; Yoshihara et al. 2004, 2005). By contrast, other in vitro studies using electrically induced noradrenaline release (Vizi et al. 2001) and in vivo studies using capsaicin-induced bronchoconstriction (Calignano et al. 2000) reported an inhibitory effect of cannabinoids in the guinea pig in a rimonabant-sensitive and hence CB_1-mediated manner. The latter study also reported that cannabinoids can cause bronchospasm when the constricting tone exerted by the vagus nerve was removed, and this also was blocked by rimonabant. Finally, that study found that rimonabant alone can enhance capsaicin-induced bronchospasm. Thus, cannabinoids appear to be beneficial with regard to bronchospasm in most settings, Whereas most investigators propose that these effects are not rimonabant sensitive, some controversy persists in this regard. Therefore, watching for possible adverse effects of rimonabant in subjects with obstructive airway disease appears warranted.

Cancer

A possible relationship of cannabinoids to cancer has been investigated, but a consistent pattern has not emerged. CB$_1$ receptors are expressed to a greater extent in human prostate cancer than in normal prostatic tissue (Sarfaraz et al. 2005), and such expression has also been found in prostate cancer cells lines such as PC-3 (Sanchez et al. 2003a), DU-145 (Melck et al. 2000), and LNCaP cells (Sanchez et al. 2003b). In prostate cancer cells, cannabinoids can stimulate both growth-promoting pathways such as protein kinase B, phosphatidylinositol-3-kinase pathway, and Raf-1 stimulation (Sanchez et al. 2003b; Sarfaraz et al. 2005) or nerve-growth-factor production (Velasco et al. 2001). Whereas some studies have found growth-promoting cannabinoid effects in prostate cancer (Sanchez et al. 2003b), others reported growth inhibiting and proapoptotic responses (Melck et al. 2000; Sarfaraz et al. 2005). Whereas these conflicting data do not allow definitive conclusions regarding the role of cannabinoids in prostate cancer, it is noteworthy that all of the above responses were at least partially rimonabant sensitive.

Similarly, conflicting cannabinoid effects have been reported with breast cancer. Some studies reported that cannabinoids inhibit human breast cancer cell proliferation induced by prolactin and nerve growth factor by decreasing levels of prolactin receptors and nerve growth factor Trk receptors in a rimonabant-sensitive manner (Melck et al. 1999, 2000). Moreover, rimonabant-sensitive inhibition of breast cancer cell migration by cannabinoids has been found (Grimaldi et al. 2006). In contrast, other studies showed that not cannabinoids but rimonabant inhibits breast cancer cell proliferation (Sarnataro et al. 2006). In such studies, rimonabant inhibited cell proliferation by G1/S cell-phase arrest, decreased expression of cyclin D and cyclin E, and increased levels of cyclin-dependent kinase inhibitors.

Whereas fewer studies have looked into cannabinoid and rimonabant effects in other types of cancer, rimonabant-sensitive inhibitory effects of cannabinoids on tumor cell growth were reported for thyroid (Bifulco et al. 2001, 2004) and liver cancer (Upham et al. 2003). On the other hand, rimonabant was found to have additive inhibitory effects with anandamide on mantle cell lymphoma (Flygare et al. 2005) and not to affect cannabinoid-induced growth inhibition in C6 glioma cells (Jacobsson et al. 2001; Sanchez et al. 1998, 2001). Moreover, lower levels of CB$_1$-receptor mRNA expression or immunoreactivity were correlated with longer survival in pancreatic ductal adenocarcinoma patients (Michalski et al. 2008), raising the possibility that inhibition of these receptors may be beneficial in pancreatic cancer. In conclusion, controversial data have been reported with regard to cannabinoid and rimonabant effects on tumor cell growth. If rimonabant-sensitive cannabinoid-induced inhibition of growth exists in at least some tumors, the possibility arises that chronic use of rimonabant might promote tumor growth. Whereas no clinical data have been presented to support this hypothesis, such potential adverse effects on long-term use of rimonabant should be monitored.

Conclusions

This review is dedicated to rimonabant, an inverse agonist at cannabinoid receptors. This drug is specific, i.e., acts via cannabinoid receptors (as opposed to noncannabinoid receptors), and selective, i.e., has much more affinity for CB$_1$ than for CB$_2$ receptors. Although CB$_1$ receptors are more abundant in the central nervous system, rimonabant also has many effects in the periphery. Here we have described the effects of rimonabant in the peripheral system together with its prejunctional receptor-mediated effects in the periphery and the central nervous system. With respect to the periphery, its effects on the cardiovascular system, urogenital system, airways, immune system, gastrointestinal tract, eye, reproductive system, and cancer are covered.

In the cardiovascular system, cannabinoids decrease blood pressure via a central site of action by activating prejunctional receptors on the sympathetic nerve endings, a decrease in peripheral resistance, and reduced cardiac function in a rimonabant-sensitive manner. However, cannabinoid-related and rimonabant-sensitive effects that are expected to increase blood pressure have also been reported, e.g., by administering cannabinoids to the brain, sensory nerve endings, or vessels. Conflicting findings have been reported about the effect of rimonabant on cannabinoid-induced endothelium-dependent and -independent vasodilatation. Cannabinoids may play a role in myocardial infarction and in hypotension affiliated with a series of pathophysiological conditions, including several forms of shock, as well as liver cirrhosis. Again these effects are rimonabant sensitive.

In the gastrointestinal tract, cannabinoids inhibit intestinal secretion, an effect counteracted by rimonabant. Most studies focused on intestinal motility, which is inhibited by cannabinoids in a rimonabant-sensitive manner. Another site of action of cannabinoids is the urogenital system. Cannabinoid receptors are present in the urinary bladder, vas deferens, and uterus. Most studies reported cannabinoids to inhibit contraction in a rimonabant-sensitive manner in both the bladder and vas deferens. Cannabinoid-induced contraction in the uterus is rimonabant sensitive and dependent on pregnancy. Cannabinoids also affect embryo attachment and outgrowth of blastocysts. The effects of rimonabant on the immune system are not clear.

As CB_2 receptors are expressed in immune cells to a much more marked extent than are CB_1 receptors, one would expect that rimonabant does not show a pronounced effect. However, rimonabant has been reported to at least partly inhibit some cannabinoid effects. In the endocrine system, cannabinoids affect secretion of several hormones, including LH, testosterone, follicle-stimulating hormone, prolactin, corticosterone, and adrenocorticotropin. This secretion takes place in several glands, including the pituitary, thyroid, and adrenals. Cannabinoids inhibit secretion of some, while stimulating secretion of other, hormones. Not all effects of cannabinoids on hormone secretion are rimonabant sensitive. Cannabinoid receptors have also been described in the eye and airways. Cannabinoids decrease IOP, which is counteracted by rimonabant. Cannabinoids can also affect airway function; most of the effects of cannabinoids in the airways are insensitive for rimonabant. The last topic of this review is cancer. The effects of cannabinoids have been described in various types of cancer, including breast and prostate cancer. Conflicting results have been reported about the effects on tumor growth.

These data raise the possibility that rimonabant and perhaps other CB_1-receptor inverse agonists may not only be effective in treating obesity and addictive disorders but also have potential benefits in patients with metabolic syndrome and some gastrointestinal disorders. On the other hand, these data also raise the possibility that such drugs may worsen myocardial infarction, glaucoma, asthma, and/or cancer and may cause pregnancy to fail. All of these additional potentially beneficial and harmful effects need to be addressed in clinical studies.

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