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MINIREVIEW

Rimonabant: Just an Antiobesity Drug? Current Evidence on Its Pleiotropic Effects

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ABSTRACT

The advent of the highly selective cannabinoid receptor (CB1) antagonist, rimonabant (SR141716; Acomplia) can revolutionize the ability of the clinicians to manage obesity. Large-scale clinical trials have demonstrated that rimonabant therapy can reduce obesity. Although, the precise mechanisms of action of rimonabant have to be further dissected, it is emerging, from both preclinical and clinical research, that not only is rimonabant an antiobesity drug, but also its pleiotropic functions affect a broad range of diseases, from obesity-related comorbidities to drug dependence and cancer. Here we review recent data from the literature and discuss the full pharmacological potential of this drug.

Studies on the effect of marijuana psychoactive principle Δ^9-tetrahydrocannabinol (THC) have evolved into the discovery and description of the endocannabinoid system. So far, this system is composed of two receptors (the widely expressed CB1 and the more restricted CB2), five endogenous lipid-like ligands [including the well known endocannabinoids anandamide (AEA) and 2-arachidonoyl glycerol], and the enzymes involved in their biosynthesis and degradation (for review, see Mechoulam et al., 1998; De Petrocellis et al., 2004; Di Marzo et al., 2004). Starting from the discovery of the endocannabinoid system, a number of studies have pointed out that altered endocannabinoid signaling and CB1 receptor expression are involved in several pathophysiological situations, ranging from neurological and psychiatric diseases to eating, cardiovascular, and reproductive disorders. More recently, it has been described that CB1 receptor stimulation by the endocannabinoid AEA can negatively modulate cancer cell proliferation in vitro (Bifulco et al., 2001, 2004) as well as tumor growth and metastatic spreading in vivo (Portella et al., 2003; Bifulco et al., 2006, 2007). CB1 or CB2 antagonistic or inverse agonistic compounds have been used to investigate the endocannabinoid network and its integration with other signaling transduction pathways (for review, see Lange and Kruse, 2005). The first highly selective CB1 receptor antagonist, rimonabant (SR141716; Acomplia) was discovered by Sanofi-Aventis (Bridgewater, NJ) (Rinaldi-Carmona et al., 1994). It showed a number of biological effects in vitro and in vivo in several pathological situations. An update on the pleiotropic effects of rimonabant does not exist, whereas the knowledge concerning endocannabinoid system has been expanded considerably; therefore, we critically analyze the current literature on the pharmacological potential of rimonabant. We aim to describe both

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ABBREVIATIONS: THC, Δ^9-tetrahydrocannabinol; AEA, anandamide (*N*-arachidonoylethanolamine); SR141716, *N*-(piperidino-1-yl)-5-(4-chlorophenyl)-1-(2,4dichlorophenyl)-4-methyl-pyrazole-3-carboxamide; CP 55,940, (1*R*,3*R*,4*R*)-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-4-(3-hydroxypropyl)cyclohexan-1-ol; WIN 55,212-2, (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo-[1,2,3-*d*,*e*]-1,4-benzoxazin-6-yl]-1-naphthalenyl-methanone; MAPK, mitogen-activated protein kinase; HDL, high-density lipoprotein; RIO, rimonabant in obesity; DA, dopamine; msP, Marchigian Sardinian alcohol preferring rats; SR144528, *N*-((1*S*)-endo-1,3,3-trimethyl bicyclo heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide); LPS, lipopolysaccharide; TNF, tumor necrosis factor; MK-0364, *N*-[(1*S*,2*S*)-3-(4-chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5(trifluoromethyl)pyridin-2-yl]oxy}propanamide; SR147778, [5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-*N*-(1-piperidinyl)-1*H*-pyrazole-3-carboxamide].

the clinical efficacy and the biological activity of rimonabant examining as much as possible the molecular aspects at the basis of rimonabant-induced effects. First, we discuss the efficacy and safety of rimonabant in reducing body weight and cardiometabolic risk factors. Second, we review the increasing literature on the other potential therapeutic properties of the CB1 receptor blocker rimonabant on behavior and in disorders related to the central nervous system. Third, we examine recent results about the antiproliferative effects of rimonabant. Finally, we discuss current data on rimonabant action as a modulator of reproductive system functions.

In Vitro and in Vivo Pharmacology of Rimonabant

The discovery of endocannabinoid system prompted the development of CB1- and CB2-selective antagonists, the first of which was the CB1-selective rimonabant (SR141716) (Fig. 1). Binding studies have demonstrated that rimonabant is a potent (pK_i = 8.4) and selective ligand for CB1 receptors, showing a high affinity (K_i = 5.6 nM) for the CB1, and low affinity (K_i > 1000 nM) for the CB2 receptor (Rinaldi-Carmona et al., 1994). Moreover, it displays a weak affinity to $Galanin_2$, MC_5, $opioid_\kappa$, and pA_2 receptors (Compton et al., 1996; Shire et al., 1996).

Functional studies confirmed its potent (pA_2 7.98–8.85) and selective CB1 receptor antagonistic activity. This compound readily displaced [^{3}H]CP 55,940 from specific binding sites (K_i = 1.98 nM) and has been shown to prevent cannabinoids from producing several of their typical effects, both in vitro and in vivo. Rimonabant potency as an antagonist has been shown by comparing its ability to attenuate WIN 55,212-2-induced inhibition of electrically evoked contractions of the mouse isolated vas deferens (K_d = 2.4 nM) with that of WIN 56,098, bromopravadoline, and iodopravadoline. It was also an effective antagonist in vivo by suppressing the hypothermia elicited by WIN 55,212-2 and psychomotor effects in mice and rats (Perio et al., 1996) (Table 1).

Saturation binding experiments with membranes prepared from rat cerebellum have shown that radiolabeled rimonabant undergoes specific, rapid, saturable, high-affinity binding to a single class of sites. This specific binding is little affected by micromolar concentrations of a variety of noncannabinoid receptor ligands. However, it is readily attenuated by the cannabinoids CP 55,940, WIN 55,212-2, Δ^9-THC, 11-hydroxy-Δ^9-THC, and AEA. Interactions with rimonabant are competitive in nature for CP 55,940, WIN 55,212-2, and Δ^9-THC, but noncompetitive for AEA, because the latter compound decreases both the affinity constant and the B_{max} of radiolabeled rimonabant (Rinaldi-Carmona et al., 1994; Petitet et al., 1996). Shire et al. (1996) have carried out experiments to identify the domain(s) of the cannabinoid CB1 receptor responsible for the recognition and binding of rimonabant. Their approach was to transfect COS-3 cells with mutated CB1 receptors or with a range of different chimeric CBl/CB2 receptors. The results obtained suggest that the fourth and fifth transmembrane domains of the CB1 receptor are essential for high-affinity binding of rimonabant, whereas the extracellular loop between these two domains is unimportant.

In some experiments, rimonabant has been found to produce effects that are opposite in direction from those produced by cannabinoid receptor agonists. In particular, it can increase locomotor activity in mice (Compton et al., 1996), improve social short-term memory in rats and mice (Terranova et al., 1996), augment forskolin-induced stimulation of cyclic AMP production in cells transfected with CB1 (Felder et al., 1995), increase the amplitude of electrically evoked contractions of various isolated tissue preparations (Pertwee et al., 1996), and enhance electrically evoked release of acetylcholine from both rat hippocampal slices and the myenteric longitudinal muscle of guinea pig small intestine (Gifford and Ashby, 1996).

Increasing evidence suggests that rimonabant behaves also as an inverse agonist in some membrane preparations. Indeed, Bouaboula et al. (1997) found that Chinese hamster ovary cells, transfected with the CB1 receptor, displayed high constitutive activity of both MAPK and adenylate cyclase and this increase was inhibited by rimonabant. They also observed that guanosine 5′-*O*-(3-[^{35}S]thio)triphosphate enhanced the binding of rimonabant, a feature usually described for inverse agonists. The issue on inverse agonistic properties of rimonabant has been reviewed thoroughly by Pertwee (2005).

The pharmacokinetic/pharmacodynamic profile of rimonabant, as expected by both preclinical and clinical studies showed that rimonabant is distributed widely in brown fat, it could reduce total energy intake and body weight gain in obese rats, and the most effective dose in reducing body weight in obese human subjects was 20 mg/day (Table 1).

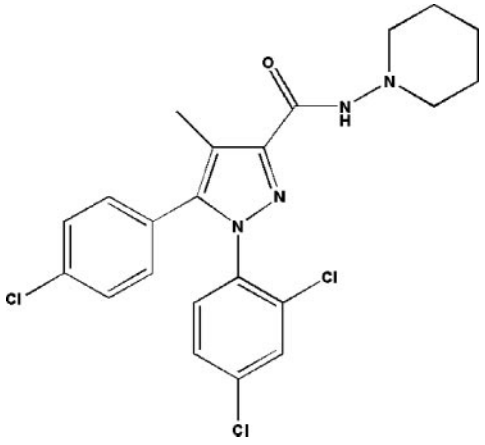

Fig. 1. Chemical structure of rimonabant.

Effect of Rimonabant on Weight Loss and Cardiovascular Risk Factors

The assessment of the clinical efficacy of rimonabant as an antiobesity drug was carried out in multinational, randomized and placebo-controlled trials on patients who were overweight (body mass index higher than 27 kg/m^2) or obese (body mass index ≥30 kg/m^2) (Van Gaal et al., 2005; Pi-Sunyer et al., 2006). A cumulative weight loss and a significant change of waist circumference from the baseline were observed in patients receiving 20 mg/day of rimonabant. It is noteworthy that rimonabant also caused an increase of high-density lipoprotein (HDL) cholesterol levels and a reduction of triglycerides, fasting insulin, and insulin resistance derived from homeostasis model assessment, which was calcu-

lated by multiplying fasting insulin by fasting glucose and dividing by 22.5 (Pi-Sunyer et al., 2006).

After 1 year of rimonabant treatment (20 mg/day), the levels of HDL cholesterol, triglycerides, and the other above-mentioned parameters were twice those attributable to the concurrent weight loss alone as assessed by analysis of covariance (Pi-Sunyer et al., 2006). In addition, in patients who completed the study in the second year and received 20 mg of rimonabant, levels of triglycerides and fasting insulin declined rapidly from baseline, suggesting a direct pharmacological effect of rimonabant on glucose and lipid metabolism outside the weight loss achieved (Pi-Sunyer et al., 2006).

In another recent trial aimed to assess the effects of rimonabant in overweight patients with dyslipidemia (Déspres et al., 2005), a significant weight loss was reached in the majority of patients completing the 12 month study and receiving 20 mg/day of rimonabant. During the treatment, the levels of triglycerides significantly decreased, whereas HDL cholesterol increased compared with both placebo group and that treated with 5 mg/day rimonabant. Furthermore, the prevalence of metabolic syndrome, a collection of factors (abdominal adiposity, hypertriglyceridemia, low HDL cholesterol, hypertension, and fasting hyperglycemia) increasing the risk of type 2 diabetes and cardiovascular disease (Nesto, 2005), was reduced in the same subset of patients (Pi-Sunyer et al., 2006). Indeed, the population of patients matching the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATPIII) criteria for the metabolic syndrome (54% of the total) fell to the half of baseline after they received 20 mg of rimonabant (Déspres et al., 2005).

The overall observations strongly suggest that rimonabant could modulate positively risk factors for a number of obesity related comorbidities through weight loss-dependent and -independent pathways. In the sense of testing the clinical efficacy of the drug in new therapeutic strategies, we point out that future research should be focused on its potential pharmacological action in primary clinical outcome of the metabolic syndrome (e.g., cardiovascular disease, coronary hearth disease, cerebrovascular disease, and peripheral artery disease, which have been associated with the high prevalence of the metabolic syndrome) (Nesto, 2005). It is noteworthy that the treatment with 20 mg of rimonabant for 1 year increases significantly the levels of plasma adiponectin compared with the placebo group (Déspres et al., 2005). This finding is not unexpected because an enhanced adiponectin serum level has been associated with weight reduction (Yang et al., 2001). Indeed, serum adiponectin levels are inversely correlated to obesity, metabolic syndrome, and type 2 diabetes (Gable et al., 2006); therefore, the observation that rimonabant improves the levels of either adiponectin or fasting insulin and induces favorable changes in insulin resistance derived from homeostasis model assessment, strongly suggests a possible pharmacological application of rimonabant in diabetes. Recently, it has been demonstrated that 20 mg/day of rimonabant can improve a number of cardiovascular

TABLE 1
Pharmacodynamics and pharmacokinetics of rimonabant
Data at http://www.emea.eu.int.

	Preclinical Studies	Clinical Studies
Primary and secondary pharmacodynamics	Potent and selective CB1 antagonistic activity in vitro (pA_2, 7.98–8.85) Reversion of WIN55212-2-induced hypothermia and psychomotor effects in mice and rats (either i.p. or p.o.; ID_{50} from 0.2 to 1.7 mg/kg) Long-lasting and selective inhibition in sucrose drinking (75%) in models for obesity (1 and 3 mg/kg, p.o.) Reduced intake of the preferred high-fat diet (37%), total energy intake in obese rats (by 30%) and body weight gain (93%) (3 mg/kg/day; for 12 days, p.o.). Reduction of known risk factors associated with obesity, serum leptin (81%), insulin (78%), glucose (67%) (10 mg/kg/day) Reduction of nicotine self-administration at 0.3 mg/kg and cue-induced nicotine seeking at 1 mg/kg in the self-administration paradigm and at 3 mg/kg in the conditioned place preference test in several animal models (see text). Increase of the number of shocks (0.3 mg/kg) in the punished drinking test (3 mg/kg) and percentage of time spent into open arms at 10 mg/kg in the elevated plus maze test. Decrease of immobility time from 3 mg/kg, p.o. in the forced swimming test.	Obesity: reduction of hunger, daily caloric intake and mean body weight (7-day repeated doses of 20 mg) Antagonism of cannabis effects: inhibition of cannabis-induced effects [e.g., heart rate increase (90-mg single dose, 40-mg repeated doses)].
Pharmacokinetics:		
Adsorption	Oral bioavailability low to moderate (12% male rats, 46% female rats, 18% male macaques) Extensive first pass metabolism peak concentration after 1–3 h steady state pharmacokinetic: 1 week once-daily dosing.	Rapidly absorbed upon oral administration. Decreased absorption with increased dose; C_{max} reached 2 h after 20-mg dose; low solubility and high permeability Steady state: 13 days in normal-weight volunteers, 39 days in obese patients
Distribution	Volume of distribution > total body water (11.5 l/kg rats, 24.4 l/kg macaques) Tissues with greatest uptake: liver, adrenals, brown fat, kidneys, lymph nodes; High binding (up to 100%) to plasma proteins.	Never administered i.v. Extensive distribution Very high binding to plasma proteins, mainly albumin (mean-99.9%)
Metabolism	Amidohydrolysis, oxidative metabolism on the piperidine moiety, glucuronidation of the acid, hydroxy phase 1 metabolism.	Metabolized by CYP3A4 and hepatic amidohydrolase Metabolites inactive against human cloned CB1 receptors
Excretion	Long terminal half-life in rats (7.3 h) and macaques (20 h) and medium clearance (~1 l/h/kg) Excretion via bile in the feces (>70%), small amount in urine. Excreted in milk (rats).	Mean terminal half-life: 10 days, in normal-weight volunteers, 16 days, in obese patients. Clearance, 5 l/h. After a 20 mg/kg dose: 32% excretion as unchanged in feces; 3% in urine and 61% in feces over 312 h. Biliary excretion of metabolites

and metabolic risk factors in patients who are overweight or obese and have type 2 diabetes (Scheen et al., 2006).

To date, safety evaluation and recording of adverse events from all RIO studies have reported nausea, diarrhea, and upper respiratory tract infections in the first month of treatment. Serious adverse effects, such as psychiatric (depressed mood disorders), nervous system, and gastrointestinal disorders occur more frequently in patients treated with 20 mg/day compared with the patients in the placebo group during the first year (Déspres et al., 2005; Van Gaal et al., 2005; Pi-Sunyer et al., 2006). Further studies are required to assess the long-term effects of rimonabant, beneficial or adverse, beyond 2 years.

Although rimonabant has been shown to be a powerful agent for the treatment of obesity, as assessed by the mentioned clinical trials, its biological mechanism of action remains unclear. Key questions still have to be tackled: Is the weight loss induced by the CB1 receptor blocker rimonabant a consequence of an action to central level or is it the result of a control at peripheral energy metabolism? What signal transducing events are involved in weight loss?

In nongenetic-induced obese mice, body weight loss seems to consist of an early phase that depends on regulation of food intake and a second phase that is independent of food intake regulation in which weight loss is maintained probably through a sustained reduction of adiposity. Therefore, it is conceivable that rimonabant interferes with both the regulation of the expression and release of hypothalamic neuropeptides involved in the control of appetite and with peripheral metabolism. In agreement with this hypothesis, the treatment with rimonabant of mice lacking the cocaine-amphetamine-regulated transcript, an anorexigenic peptide, does not affect feeding behavior (Ravinet Trillou et al., 2003), whereas this compound inhibits starvation-induced hyperphagia in neuropeptide Y-deficient mice and reduced body weight in leptin knockout mice (Di Marzo et al., 2001). The reduction of body weight by rimonabant is likely to involve the modulation of more than one orexigenic pathway controlling food intake at central level. In this sense, recent data showing a functional colocalization of CB1 receptor and orexin 1 receptor, have demonstrated that the treatment with rimonabant of Chinese hamster ovary cells expressing both receptors, completely prevented orexin response, thus providing further insights that the weight loss achieved in vivo could be partly ascribed to the blockade of CB1/orexin 1 receptor cross-talk (Hilairet et al., 2003). On the other hand, the finding that the CB1 receptor-mediated lipogenetic activity in primary murine adipocytes can be blocked by rimonabant (Cota et al., 2003) intriguingly supports the idea that this compound may also function at peripheral level by decreasing lipoprotein lipase activity. In line with this hypothesis, in obese Zucker (fa/fa) rats, rimonabant stimulates Acrp30 mRNA, an adipocytokine exclusively expressed by adipocytes and regulating fatty acid oxidation. This stimulation has been also found to occur within 30 min of rimonabant treatment of cultured mouse 3T3 F442A preadipocyte cells (Bensaid et al., 2003). The Acrp30 mRNA inhibition was accompanied by a reduced adipocyte proliferation and an enhanced cell maturation (Gary-Bobo et al., 2006). The effect is mediated by the inhibition of MAPK phosphorylation. It is noteworthy that rimonabant, working as an inverse agonist, is able to switch off MAPK activation from the insulin receptor-tyrosine kinase and insulin-like growth factor receptors (Bouaboula et al., 1997). Moreover, endocannabinoid tonic activation of CB1 receptor in liver induces mRNA expression of the lipogenic transcription factor sterol regulatory element binding protein-1c, its target enzymes acetyl coenzyme-A carboxylase, and fatty acid synthase, also increasing the rate of fatty acid synthesis (Osei-Hyiaman et al., 2005). Blockage of CB1 receptor stimulation by rimonabant significantly reduces de novo fatty acid synthesis in mice, thus providing the evidence for the involvement of fatty acid biosynthetic pathway in the sustained reduction of body weight. The reported outcomes explain how rimonabant induces its effects at central and peripheral levels, even though it would be of interest to study whether other G-protein and/or orexigenic pathways could be responsible for the rimonabant-induced antiobesity effects and whether there are mechanisms of action independent from the interaction with the CB1 receptor.

Rimonabant-Induced Effects on Drug Dependence

CB1 receptors are expressed at high levels in brain regions thought to play a key role in relapse-like behavior and conditioning processes. In these regions, CB1 receptors modulate the release of a variety of neurotransmitters (De Vries and Schoffelmeer, 2005) implicated in drug seeking behavior, smoking cessation, and alcohol addiction, suggesting that rimonabant could offer a novel approach for the treatment of behavior-related disorders (for review, see Beardsley and Thomas 2005; De Vries and Schoffelmeer, 2005).

Smoking Cessation. Pharmacological studies aimed to investigate the effect of rimonabant on motivational effects of nicotine in rats, demonstrated that a single administration of rimonabant (0.3 and 1.0 mg/kg) on two consecutive days reduced nicotine infusions and the presses of active lever from the first day of treatment (Cohen et al., 2002). Given the findings that rimonabant reduced responding for nicotine-associated cues, even after several months of nicotine abstinence, and antagonizes dopamine release caused by nicotine addiction, it is reasonable that the CB1 receptor antagonist can reduce both nicotine-seeking behavior and nicotine-reinforcing effects, probably by preventing nicotine-induced dopamine (DA) release in limbic dopaminergic areas during self-administration (Cohen et al., 2002, 2005). The action of rimonabant on both reducing nicotine craving and weight gain may be, at least in part, the result of a common mechanism involving a dopamine receptor-mediated process (Duarte et al., 2004). In this respect, studies of rimonabant treatment on conditioned response for nicotine- and sucrose-associated cues in a long-term extinction-reinstatement animal model demonstrated a strongly decrease cue-induced reinstatement of nicotine- and sucrose-seeking behavior (De Vries et al., 2005). The blockade of CB1 receptors attenuated reinstating responding for stimuli associated with nicotine infusion and sucrose delivery in a similar fashion. Preclinical studies seem to support this evidence: 1) rimonabant reduces nicotine self-administration, DA turnover in nucleus accumbens, and reinstatement of nicotine-seeking behavior (Fagerstrom and Balfour, 2006); 2) The STudies with Rimonabant And Tobacco Use (STRATUS-US), studying 787 smokers at 11 clinical trial sites in the United States, showed that 36% of patients treated with 20 mg/day rimonabant quit smoking,

whereas only 20.6% of patients treated with placebo and 20.2% of patients treated with 5 mg/day of rimonabant were successful (Anthenelli and Despres, 2004). Previous findings suggest that rimonabant may represent a novel drug for the treatment of tobacco dependence and may be effective not only as an aid for smoking cessation but also in the maintenance of abstinence.

Ethanol Dependence. A large body of research lines suggests functional interactions between the cannabinoid receptor CB1 and ethanol dependence; CB1 receptor is also involved in the mechanism mediating alcohol relapse (Maldonado et al., 2006). Rimonabant treatment induces a decrease in voluntary ethanol intake in alcohol-preferring rats (Colombo et al., 1998) and decreases ethanol consumption in mice (Arnone et al., 1997). Cippitelli and coworkers (2005) analyzed the effects of cannabinoid receptor blockade by rimonabant on alcohol self-administration and cue-induced relapse in Wistar and genetically selected Marchigian Sardinian alcohol preferring rats (msP) rats, in which the acquisition of ethanol self-administration was quicker than in wild-type strains. Rimonabant was found to reduce either ethanol self-administration or cue-induced relapse to ethanol self-administration and was more efficacious in the msP rats than in Wistar rats. It is noteworthy that strong differences in CB1 receptor mRNA levels between ethanol-naive msP and Wistar rats have been found, suggesting that the effects of rimonabant could be ascribable to the genetically determined different levels of CB1 receptor in brain regions responsible for ethanol dependence. This assumption is also supported by the finding that CB1−/− mice and rimonabant-treated mice consume significantly less alcohol than the corresponding untreated wild-type mice (Wang et al., 2003). However, a reduction of the reinforcing properties of ethanol in the self-administration paradigm has also been observed in animal models of ethanol seeking elicited by environmental stimuli (Economidou et al., 2006). Therefore, considering the rimonabant-mediated reduction of reward-related responding to ethanol, it could be of relevant interest to test this compound in preclinical studies, aimed at proving its pharmacotherapeutic properties in the treatment of ethanol dependence.

Psychostimulants and Opioid Seeking. Although rimonabant administration does not interfere with cocaine self-administration in monkeys (Tanda et al., 1997) and relapse induced by exposure to stress in rats, it reduced relapse to cocaine-seeking behavior produced by re-exposure to cocaine-associated cues (De Vries et al., 2001). Likewise, rimonabant blocked the relapse of methamphetamine-seeking behavior in rats also preventing the reinstatement of methamphetamine-seeking behavior, when administered before the cue phase of the test session (Anggadiredja et al., 2004).

Concerning opioids, several studies have revealed solid evidence for the existence of a functional interaction between cannabinoid and opioid system, suggesting that CB1 receptor may play an important role in the mechanism underlying relapse to heroin seeking (Tanda et al., 1997; Navarro et al., 2001). For the most part, in opiate self-administration and opiate-induced place preference in rats and mice, using heroin and morphine, acute administration of rimonabant (3.0 mg/kg) reduced heroin self-administration in Wistar rats and blocked heroin and morphine self-administration in mice. Because rimonabant does not interact directly with opioid receptors, it could interact with dopaminergic system in the nucleus accumbens, attenuating extracellular dopamine release (Navarro et al., 2001). Furthermore, rimonabant attenuated (by about 50%) the reinstatement of heroin-seeking behavior caused by both a priming injection of heroin and a re-exposure to heroin-paired stimuli. In addiction, rimonabant dose-dependently reduced responding for heroin in fixed and progressive ratio schedules of reinforcement (De Vries et al., 2003; Spano et al., 2004). These observations indicate that the selective CB1 receptor antagonist rimonabant might be used to attenuate both the reinforcing/motivational properties of heroin and the reinstatement of heroin seeking after prolonged withdrawal (Fattore et al., 2005).

Rimonabant-Induced Effects on Neurodegenerative Disorders

Until endocannabinoid system was discovered, the role of CB1 receptor in the physiology and pathology of nervous system has received particular attention because of its selective and relatively high expression within the central nervous system. The CB1 receptor is localized mostly in the brain (Herkenham et al., 1990) and spinal cord (Herkenham et al., 1991a) and is expressed in the output nuclei of basal ganglia, in the substantia nigra pars reticulata and globus pallidus. Intermediate receptor levels have also been found in the cortex, hippocampus, thalamic nuclei, hypothalamus, and cerebellum (Herkenham et al., 1990, 1991a,b; Jansen et al., 1992; Thomas et al., 1992). The endogenous ligands of CB1 receptor are synthesized upon demand by neurons in response to depolarization (Freund et al., 2003); once released from postsynaptic neurons, they can function as retrograde synaptic messengers. They travel backward across synapses, activate CB1 on presynaptic axons, and inhibit neurotransmitter release (Szabo et al., 1998; Wilson and Nicoll, 2002). Because of these properties, the endocannabinoid system could offer new pharmacological targets to alleviate motor symptoms and supply neuroprotection in neurological disorders such as Parkinson's and Alzheimer's disease, Huntington's chorea, and multiple sclerosis. Despite the projectile findings on this issue, recently well reviewed (Fernandez Ruiz and Gonzales, 2005; Robson, 2005; Valverde et al., 2005; Walker and Hohmann, 2005; Pertwee, 2006), inconclusive results were reported on early study carried out with rimonabant. Rimonabant increased the frequency and duration of seizures in a rat model of viral encephalopathy (Borna disease virus rats) (Solbrig et al., 2005), whereas the hyperkinetic state (vertical activity) induced by L-DOPA was decreased by the subcutaneous injection of rimonabant in the reserpine-treated rat model of Parkinson's disease. On the other hand, discrepant results have been obtained about the effects of this compound on quinpirole-induced hyperactivity. Rimonabant administered alone has no evident effects on motor activity (Giuffrida et al., 1999; Segovia et al., 2003); when injected 1 h before quinpirole, however, it potentiates motor stimulation, thus suggesting a complex interaction between CB1 receptor, its agonists and dopamine receptors (Segovia et al., 2003). Moreover, rimonabant reverses the neuroprotective effect of CB1 agonists in primary neuronal cultures from spinal cords in vitro (Abood et al., 2001) and in animal models of both genetic and pharmacologically induced

Huntington's disease in vivo (Lastres-Becker et al., 2003; Centonze et al., 2005), also causing epileptic activity during development (Bernard et al., 2005). It is surprising that rimonabant was ineffective in producing hyperalgesia in rats and by itself is able to exert antinociceptive effect, probably by blocking the action of CB1 receptor stimulation on presynaptic GABA release (Naderi et al., 2005).

Rimonabant Antiproliferative Effects

Because hyperplasia of adipose tissue is a crucial event for the development of obesity, the antiproliferative effect of rimonabant has been investigated on mouse preadipocytes. A reduced proliferation and an induced late maturation of adipocytes, without lipid droplet accumulation, mediated by an inhibition of basal and serum-induced p42/44 MAPK pathway was observed (Gary-Bobo et al., 2006). The MAPK pathway, strongly activated by a high-fat diet in white adipose tissue and required for the development of obesity (Bost et al., 2005), is inhibited by rimonabant through pertussin toxin-sensitive tyrosine kinase receptors, such as those for insulin or insulin-like growth factor 1, therefore displaying a negative intrinsic activity ascribable to inverse agonism (Bouaboula et al., 1997; Landsman et al., 1997).

The endocannabinoid system is implicated in the pathogenesis of chronic liver diseases associated with hepatic fibrosis (Mallat and Lotersztajn, 2006). CB1 receptors in particular are highly up-regulated in human cirrhotic specimens and in liver fibrogenic cells. Recent findings have emphasized the idea that CB1 receptor antagonism by rimonabant administration in mice counteracts the wound-healing response to acute liver injuries by decreasing the accumulation of hepatic myofibroblasts and the levels of the profibrogenic cytokine transforming growth factor β1. The antiproliferative effect depends on CB1 receptor signaling, as revealed by the absence of antiproliferative effects in $Cnr1^{-/-}$ hepatic myofibroblasts. As previously observed in several cell systems, the molecular pathways mediating CB1 antagonism effects involve decreased phosphorylation of extracellular signal-regulated kinase MAPK and Akt, both in $Cnr1^{-/-}$ cells and in wild-type cells treated with rimonabant (Teixeira-Clerc et al., 2006).

Together, these findings provide evidence for an antifibrotic effect of rimonabant and suggest that rimonabant might represent a therapeutic tool for the treatment of some pathological liver conditions in humans.

Rimonabant Antitumor Effects

The studies conducted from the late 1990s on the endocannabinoid system have provided strong evidence for a key role of the endocannabinoids in the control of cancer cell growth, invasion, and metastasis processes in a way dependent on CB receptor activation (for review, see Bifulco and Di Marzo, 2002; Bifulco et al., 2006, 2007).

The selective CB1 receptor antagonist rimonabant attenuates the antitumor effects of anandamide-related compounds or other cannabinoid agonists in thyroid, breast, and prostate cancers (Bifulco et al., 2001; Portella et al., 2003; Sarfaraz et al., 2005; Grimaldi et al., 2006); the effects are dependent on CB1 receptor activation. In other tumor types, such as glioma, rimonabant failed to revert the antiproliferative action of cannabinoid agonists, whereas the selective CB2 antagonist SR144528 (Sanchez et al., 2001) or a combination of the CB1/CB2 antagonists can partially prevent this effect (Jacobsson et al., 2001). However, a 48-h preincubation with these antagonists seems to enhance the AEA-mediated cell death of glioma cells, suggesting a more complex mechanism of action (Maccarrone et al., 2000a).

Considering the antitumor properties of the cannabinoid receptor agonists, it could be expected that cannabinoid receptor antagonists, such as rimonabant, if used alone, would enhance proliferation of normal and malignant cells, leading to cancer. Some data excluded this possibility, reporting rather that not only agonists to cannabinoid receptors but also antagonists, used alone, are able to inhibit cancer growth (Bifulco et al., 2004) or induce apoptosis in cancer cells (Derocq et al., 1998; Powles et al., 2005).

Our group provided the first observation of a potential antitumor action in rimonabant in rat thyroid cancer cells (KiMol) in vitro and in thyroid tumor xenografts induced by KiMol injection in athymic mice. In this model, rimonabant was able to partially prevent the antitumor effect of the inhibitors of endocannabinoid degradation and of the anandamide metabolically stable analog (2-methylarachidonyl-2′-fluoro-ethylamide). However, rimonabant, when used alone, in the same model and at the same dose shown previously to counteract the 2-methylarachidonyl-2′-fluoro-ethylamide effect (0.7 mg/kg intratumoral, twice a week for two weeks), did not enhance tumor growth, exerting a small but significant antitumor effect on thyroid tumors, both in vitro and in vivo (Bifulco et al., 2004).

It is noteworthy that micromolar concentrations of rimonabant decreased viability of primary mantle lymphoma cells isolated from tumor biopsies of two patients after treatment with micromolar concentrations of rimonabant (Flygare et al., 2005). Moreover, rimonabant showed an additive negative effect as well on the viability of the mantle cell lymphoma cell line Rec-1 when combined with equipotent doses of AEA. Bifulco et al. (2004) and Flygare et al. (2005) supported the evidence of the antitumor action of rimonabant, but they did not investigate or provide a molecular mechanism of action. They proposed that the observed effects could be ascribed to: 1) a tonic antiproliferative action mediated by the local endocannabinoids through mechanisms independent from CB1 receptor, particularly when CB1 receptors are blocked by the antagonist rimonabant; and 2) the inverse agonist properties of rimonabant on the receptor. These possibilities could explain the paradox whereby both CB1 agonists and antagonists display antitumor activity.

We have reported that rimonabant exerts antitumor effects on breast cancer in vitro and in a mouse model in vivo, providing for the first time a new mechanism of action for this drug (Sarnataro et al., 2006). Rimonabant, at nanomolar concentrations, is able to inhibit human breast cancer cell proliferation; it is more effective in highly invasive metastatic MDA-MB-231 cells than in less invasive T47D and MCF-7 cells, depending on both the presence and the different expression levels of the CB1 receptor. The antiproliferative effect is characterized by a G_1/S phase cell cycle arrest, without induction of apoptosis. The in vitro observed effect has also been confirmed in vivo: after 2 weeks of treatment, rimonabant reduces the volume of xenograft tumors induced by MDA-MB-231 injection in mice. The molecular mecha-

nism at the basis of rimonabant function implicates an inhibition of p42/44 MAPK phosphorylation and requires lipid rafts/caveolae integrity. This suggests that rimonabant's effects on cell proliferation and signaling requires the presence of CB1 receptor in lipid rafts (Sarnataro et al., 2006).

Rimonabant-Induced Effects on Fertility

During the last few years, accumulating evidence has indicated that the endocannabinoid system may play an important role in modulating reproductive system functions and fertility. Some reports have underlined the presence of both CB1 receptor subtype in human sperm (Rossato et al., 2005) and significant concentration of endocannabinoids in female and male genital tract fluids (Schuel et al., 2002). This finding suggests that the control of the endogenous tone of endocannabinoids and its interaction with the CB receptors are checkpoints in reproduction (for review, see Maccarrone and Finazzi-Agrò, 2004). However, CB1 receptor activation by AEA is responsible for a reduced sperm motility and inhibition of capacitation-induced acrosome reaction in human sperm specimens. The CB1-selective antagonist rimonabant is able to block the negative effects of AEA on motility of sperm without compromising sperm viability or motility per se (Rossato et al., 2005). Moreover, Melis and coworkers (2006) reported that rimonabant was able to induce penile erection in male rats when injected into the paraventricular nucleus of hypothalamus. This effect was associated with an increase of glutamic acid leading to the activation of neuronal and nitric-oxide synthase in oxytocinergic neurons mediating penile erection (Succu et al., 2006). However, it is possible that rimonabant-induced penile erection also implies an increase in dopaminergic neurotransmission (da Silva et al., 2003).

Few data on the effects of rimonabant on fertility are available, whereas a large body of the recent literature has been focused on the interaction and possible regulation of reproductive processes by endocannabinoid system. Endocannabinoids are involved in implantation (attachment and outgrowth of blastocysts), pregnancy (myometrial contractility) (Liu et al., 2002; Dennedy et al., 2004), and miscarriage (Maccarrone et al., 2000b). Therefore, it is possible to speculate that not only a decreasing AEA concentration in human reproductive tract secretions but also the administering of rimonabant may represent therapeutic tools in pathological situations such as recurrent abortions characterized by increased levels of AEA.

Other Effects of Rimonabant

The promising results obtained in several experimental model systems, proposing rimonabant as a potential therapeutic tool for the treatment of several pathological conditions, have recently promoted investigations to ascertain the potential benefit effects of this compound, mainly as a CB1 receptor antagonist, in other disorders affecting the central nervous system, the immune system, and the circulatory system. In this sense, the high concentration of cannabinoid CB1 receptors expressed in hippocampus suggests that the cannabinoid neurochemical system may play a role in learning and memory processes (Takahashi et al., 2005). Some evidence supports the idea that the natural and synthetic cannabinoids impair cognitive processes in humans, nonhuman primates, and rodents (Braida and Sala, 2000) and seem to inhibit hippocampal extracellular acetylcholine release (Terranova et al., 1996). Rimonabant reverses many of the biochemical physiological and behavioral effects of cannabinoid receptor agonists; e.g., it attenuates the memory impairment produced by AEA and THC (Mallet and Beninger, 1998; Mishima et al., 2001). Rimonabant, which per se does not influence memory processes at the dose of 0.5 mg/kg, completely antagonizes the impairment produced by the synthetic cannabinoid CP 55,940 (Braida and Sala, 2000).

Finally, blockade of CB1 receptor by rimonabant improves amnesia induced by the β-amyloid fragment in mice, suggesting that endogenous cannabinoids may be involved in cognitive impairment induced by these fragments. The injection of rimonabant alone does not cause any significant change in the capacity of mice to retain passive avoidance responses, and its effect may be observed only when CB1 are activated by their antagonists (Mazzola et al., 2003). From these few available data, it is not yet possible to support a potential therapeutic application of rimonabant in memory impairment or to propose a mechanism of action; therefore, further research is needed in this direction. Because CB1 receptor mRNA has been detected outside the brain in many other tissues, including immune system cells (Klein et al., 2003), recent articles on the role of endocannabinoids in the modulation of the immune system have led researchers to consider the therapeutic potential of rimonabant in the inflammation process.

Croci et al. (2003) proposed that rimonabant may interfere with immune-inflammatory pathogenic mechanisms such as that underlying indomethacin's ulcerogenic action. They observed that oral administration of rimonabant is able to dose-dependently prevent indomethacin-induced small intestinal ulcers in rats. This effect was associated with a higher inhibition of TNFα levels and myeloperoxidase activity compared with CB2 receptor antagonist SR144528. Rimonabant produced similar inhibitory effects in CB1 receptor knockout mice, suggesting that its antiulcerogenic action does not rely on CB1 antagonism. However, in the same CB1 knockout mice, rimonabant failed to counteract the increase of LPS-induced TNFα plasma levels that is CB1 receptor-dependent. This observation suggests that rimonabant could probably act with distinct mechanism of actions, modulating the inflammatory process in different ways. The inhibition of TNFα levels by rimonabant is of particular interest, because an increase in plasma levels of this cytokine has been found in patients who are obese, and it could be involved in the regulation of glucose transport and insulin sensitivity (Hube and Hauner, 1999). In supporting the rimonabant anti-inflammatory action, its systemic administration could improve rat survival and endotoxin LPS-induced hypotension (Varga et al., 1998). It is noteworthy that the inhibition of LPS-induced hypotension by rimonabant does not depend on the presence of CB1 receptor, because rimonabant induces similar effects in CB1-deficient mice (Bátkai et al., 2004). Furthermore, other findings also pointed out that rimonabant was able to raise blood pressure, perhaps by counteracting the increased expression of CB1 receptor (Bátkai et al., 2001). On the bases of the previous findings, it seems clear that the role of cannabinoid system and the complex action of rimonabant on the circulatory system and its patho-

TABLE 2
Overview of rimonabant effects

Pathological Conditions	Preclinical Studies		Clinical Studies	Effects	References
	In Vitro Models	In Vivo Models			
Obesity, metabolic syndrome, and associated cardiovascular diseases	Mouse preadipocytes			Inhibition of cell proliferation and MAPK activity; induction of adiponectin and GAPDH mRNA	Gary-Bobo et al., 2006
		Nongenetic-obese mice, C57BL/6J and CB1$^{-/-}$ mice		Body weight loss and early reduction of food intake; weight loss maintained with normal diet Reduction of de novo fatty acid synthesis in mice	Di Marzo et al., 2001; Arnone et al., 2003; Bensaid et al., 2003; Cota et al., 2003 Osei-HYiaman et al., 2005
			RIO Lipids, RIO Europe, RIO North America, RIO diabetes	Weight loss and reduced waist circumference; increased HDL levels and reduction of triglycerides, fasting insulin and insulin resistance; weight loss reduction, improvement of glucose control and metabolic parameters in type 2 diabetes	Despres et al., 2005; Van Gaal et al., 2005; Pi-Sunyer et al., 2006; Scheen et al., 2006;
Neurodegenerative disorders	Primary neurons			Blockade of neuroprotective effects of CB1 receptor agonists	Abood et al., 2001
		BDV rats, reserpine treated rats, quinpirole-treated rats, R6/2 Huntington's disease mice, malonate-treated rat, Wistar rats,		Increase of convulsive phenomena; reduction of hyperkinetic state; potentiation of hyperkinesias; blockade of neuroprotective effects of CB1 receptor agonists; inhibition of neuroprotection; epileptic activity during development; analgesic properties	Giuffrida et al., 1999; Lastres-Beker et al., 2003; Segovia et al., 2003; Bernard et al., 2005; Centonze et al., 2005; Naderi et al., 2005; Solbrig et al., 2005
Drug seeking (psychostimulants and opioids), alcohol dependence, Nicotine dependence		Wistar, Long-Evans, Lister Hooded rats; Wistar, Wistar/msP rats, Wistar rats, Sprague-Dawley rats	STRATUS-US	Cocaine, attenuation of drug and cue-induced reinstatement; heroin, suppression of drug-induced reinstatement and attenuation of cue-induced reinstatement; methamphetamine, blockage of methamphetamine and cue-induced reinstatement; alcohol, reduction of cue induced reinstatement; attenuation of cue induced reinstatement, reduction of conditioned behavior after withdrawal 36% patients quit smoking	De Vries et al., 2001, 2003, 2005; Anggadiredja et al., 2004; Anthenelli and Despres, 2004; Spano et al., 2004; Cippitelli et al., 2005; Cohen et al., 2005; Economidou et al., 2006
Cancer	Rat thyroid cancer KiMol cells; human mantle cell lymphoma (MCL); Human breast cancer cells MDA-MB-231	Thyroid cancer xenografts in athymic mice Breast cancer xenografts in athymic mice		Inhibition of thyroid tumor growth; decreased viability; additive effect with anandamide; antiproliferative effect with G_1/S phase cell cycle arrest, linked to lipid rafts/caveolae localization of CB1 receptor signaling; reduced volume of xenograft tumors in mice	Bifulco et al., 2004; Flygare et al., 2005; Sarnataro et al., 2006
Infertility	Human sperm	Sprague-Dawley rats		Antagonizing the negative effects of increased levels of anandamide on sperm motility and acrosome reaction. Enhancement of penile erection	Rossato et al., 2005 Da Silva et al., 2003; Melis et al., 2006
Liver fibrosis	Human and murine hepatic myofibroblasts	CD1, C57BL/6J, Cnr1−/− mice		Reduction of wound-healing response to acute liver injury; inhibited progression of fibrosis; growth inhibition of hepatic myofibroblasts	Teixeira-Clerc et al., 2006
Chronic inflammatory diseases: ulcer		Crl:CD BR rats C57BL/6J and CB1$^{-/-}$ mice		Prevention of indomethacin-induced ulcers in rats and mice	Croci et al., 2003

logic conditions needs further insights, to better clarify the molecular mechanisms and the signaling pathways evoked by rimonabant in determining such CB1-dependent and -independent effects.

Conclusions and Perspectives

Collected results clearly show that rimonabant can have a plethora of pharmacological effects in a number of physiopathological conditions (Table 2). Because of rimonabant's selectivity for the cannabinoid CB1 receptor, the effects are mainly ascribable to its antagonistic properties, even though some evidence for its inverse agonistic action has also been provided (Bouaboula et al., 1997; Landsman et al., 1997; Navarro et al., 2001). Rimonabant represents a promising therapeutic tool in the treatment of obesity, as evidenced by clinical trials, and weight loss is achieved probably via central and peripheral mechanisms. Rimonabant is able to centrally target food intake regulation, acting on neurotransmitter release. The blockage of the CB1 receptor could result in a reduction of dopamine release that has been found to be enhanced in corticolimbic structures as a consequence of the rewarding effect of palatable food (Spanagel and Weiss, 1999). Furthermore, rimonabant reduced obesity in leptin (ob/ob) and leptin receptor (db/db) knockout mice (Di Marzo et al., 2001) and blocked CB1/OX1 receptor cross-talk (Hilairet et al., 2003), suggesting that it could exert a negative effect on genetically obese animals with an altered leptin neuroendocrine pathway and inhibit the CB1-mediated tonic orexigenic effect caused by increased levels of endocannabinoids. The modulation of nervous system functions is also at the basis of its pharmacological action on ethanol and sucrose consumption, drug-seeking behavior, and nicotine addiction. Above all, rimonabant may operate by preventing drug-induced DA release and turnover in dopaminergic areas, leading to an attenuation of either ethanol reward-related response or to nicotine-, psychostimulant-, and opioid-related relapse. However, by blocking CB1 receptor, rimonabant can act on GABAergic neurons stimulating GABA release (Naderi, 2005). This effect results in an induction of convulsive phenomena and epileptic activity in animal models of encephalopathy and Parkinson's disease (Bernard et al., 2005; Solbrig et al., 2005). These observations, together with the finding that rimonabant prevents the benefit effects of CB1 receptor agonists in genetic and pharmacologically induced Huntington's disease (Lastres-Becker et al., 2003; Centonze et al., 2005), suggest that the drug is not suited to the treatment of neurodegenerative diseases and motor-related disorders. We should point out that rimonabant, used alone, does not induce an alteration of motor activity in normal rats; therefore, we could hypothesize that its adverse effects on nervous system functions could be limited to an already established pathological condition. On the other hand, this issue needs further evaluation to better clarify the exact role and physiopathological consequences of rimonabant-regulated GABA and DA release.

The molecular aspects at the basis of rimonabant-induced effects are not fully understood but seem to be related to the inhibition of the key steps of the CB1 signaling pathway. The molecular mechanism of action involves the inhibition of MAPK signaling. This pathway is activated by high-fat diet in white adipose tissue and is required for the development of obesity (Bost et al., 2005). Rimonabant, in agreement with its inverse agonistic properties, is able to inhibit CB1 receptor and switch off MAPK activation from the insulin receptor-tyrosine kinase and insulin-like growth factor receptors (Bouaboula et al., 1997). It is possible that this mechanism could be implicated also in the modulation of cardiovascular risk factors through a weight reduction-independent pathway, but how this occurs and the other biological pathways regulated by rimonabant and involved in glucose metabolism remain to be established. MAPK inhibition usually correlates with antiproliferative effects in both normal and cancer cells (Hou et al., 2004; Stepulak et al., 2005; Yoon and Seger, 2006) and the treatment of adipocytes and hepatic myofibroblasts with rimonabant strongly reduces proliferation through this pathway. More recently, we have provided evidence for an antiproliferative effect of rimonabant in thyroid and breast cancer cells (Bifulco et al., 2004; Sarnataro et al., 2006). In the last cellular model, we found that rimonabant strongly reduces cell growth by perturbing raft/caveolae integrity and

TABLE 3
CB1 antagonists in clinical development
Data at http://www.clinicaltrials.gov

Drug	Manufacturer	Clinical Phase	Study Type
Rimonabant	Sanofi-Aventis	III	Reducing the risk of major cardiovascular events in abdominally obese patients
			Effects on abdominal obese patients with dyslipidemia
			Amount and the activity of visceral fat in abdominally obese patients with metabolic syndrome
			Effects on abdominally obese patients with impaired fasting blood glucose with or without other comorbidities
			Effect on high density lipoprotein kinetics in patients with abdominal obesity and additional cardiometabolic risk factors
		II	Reduction of voluntary ethanol drinking
CP-945,598	Pfizer	III	2-year weight loss efficacy and safety in obese subjects
			Long-term study on weight loss and safety in obese subjects
			Obesity in overweight patients with type 2 diabetes
MK-0364	Merck	II	Weight maintenance in obese subjects Weight loss in obese and overweight subjects
Ave-1625	Sanofi-Aventis	II	Effects on abdominally obese patients with atherogenic dyslipidemia
SR147778	Sanofi-Aventis	II	Efficacy and safety in obese subjects
SLV-319	Solvay Pharmaceuticals Bristol-Myers Squibb	Moved to Phase II	

excluding CB1R from lipid rafts. We found that rimonabant's inhibitory effect on extracellular signal-regulated kinase 1/2 in the highly invasive and metastatic MDA-MB-231 breast cancer cells requires lipid raft integrity, thus suggesting that the role of lipid rafts in the receptor-dependent signaling would be to make favorable the CB1R-ligand encounter and the activation of CB1-dependent signaling (Sarnataro et al., 2006). Moreover, rimonabant causes a down-regulation of both the Acrp30 protein, sterol regulatory element binding protein-1c, and fatty acid synthase enzyme. At the same time, it is able to induce an up-regulation of adiponectin and glyceraldehyde 3-phosphate dehydrogenase, markers of adipose tissue functions, finally causing a reduction of adipocyte cell proliferation, a stimulation of fatty acid oxidation (Bensaid et al., 2003) or, alternatively, an inhibition of de novo fatty acid synthesis (Osei-Hyiaman et al., 2005).

Additional targets for the pharmacological effects of rimonabant include reproduction system functions. The role of the endocannabinoid system in reproduction and fertility has been reported (Dennedy et al., 2004; Maccarrone et al., 2004) but few available data demonstrated an increase in the number of penile erections in animal models that were probably due to an activation of dopaminergic and oxitocinergic neurotransmission mediated by rimonabant (da Silva et al., 2003; Melis et al., 2006; Succu et al., 2006). Therefore, it could be of great interest to intensify this issue, taking into account that the reproductive cascade of hormones and their regulation is tightly associated with energy metabolism and thus with the leptin pathway (Chehab, 2000). Finally, rimonabant seems to exhibit some beneficial effects in indomethacin-induced intestinal ulcer in rats, the effect being associated to a significant reduction of TNFα levels and myeloperoxidase activity (Croci et al., 2003), but these data on the potential application of rimonabant in inflammatory process, such as the results on a potential role of rimonabant in the treatment of memory impairment, are still quite scanty.

In light of the public health implications of the obesity pandemic, CB1 blockade strategy aimed to treat obesity and related disorders has encouraged several pharmaceutical companies to develop new and more selective CB1 antagonists, some of which are already in clinical trials (Table 3). At the moment, available data are not exhaustive to state the advantage of rimonabant competitor compounds; indeed, reported side effects are comparable and there are no data on long-term safety and efficacy. Moreover, in the pharmacotherapy of obesity, it would be necessary to take into account clinical and genetic parameters. We recently demonstrated a strong association between a polymorphic variant of CB1 receptor and glycemia and triglyceride concentration in patients who are overweight or obese (Gazzerro et al., 2007), and polymorphic variants in the codifying or promoting regions of CB1 receptor have been also associated to mood disorders and predisposition to depression (Barrero et al., 2005). Therefore, a subselection of patients' eligibility based on polymorphic CB1 receptor variants could influence the efficacy of the treatment and the incidence of side effects. Finally, rimonabant, showing antiobesity, anti-inflammatory, and antitumor properties, could be a preferential choice in breast cancer patients treated with chemotherapy, because excess adiposity is linked to risk of postmenopausal breast cancer, and the weight gain after chemotherapy is linked with higher frequency of recurrent breast cancer (Harvie et al., 2005). Several authors proposed that local production of adipokines and inflammatory cytokines by adipocytes within the stroma surrounding breast epithelial cells may be directly linked to the growth of breast cancer (Manabe et al., 2003). Taken together, this evidence suggests that rimonabant could limit secretions by adipose tissue and improve the recurrence control in patients who have breast cancer and are obese and overweight.

In conclusion, we foress other potential applications of rimonabant in related and nonrelated obesity pathologic conditions. On the bases of the pleiotropic effects described here, it represents a promise beyond its antiobesity action. Further studies will improve our understanding of the mechanisms of several diseases and will clarify the potential clinical impact of rimonabant "pleiotropic effects."

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