CB_1 Cannabinoid Receptor Antagonists for Treatment of Obesity and Prevention of Comorbid Metabolic Disorders

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Received June 16, 2005

Introduction

The World Health Organization (WHO) recently declared[1,2] that obesity has become a global epidemic, posing a serious threat to public health[3] because of the increased risk of associated health problems. Obesity is characterized by excess of body fat, especially visceral fat, and constitutes a proinflammatory state eventually leading to serious health consequences,[4,5] including type 2 diabetes,[6−9] coronary heart disease,[10] hypertension,[9,11] certain types of cancer,[12] sleep apnea,[13] bone joint diseases,[14] nonalcoholic fatty liver disease,[15] and last but not least psychological problems.[16] In the U.S., more than 60% of the adults are overweight[17] and 19.8% of the adults are classified as obese with 7.3% having diabetes, which is an increase of 61% in obesity and 49% in type 2 diabetes in the past decade.[18] Europe as a whole is facing the same major public health problem. Especially alarming is the growing childhood obesity.[19−21]

While there are clearly genetic factors involved, the dramatic increase during just 1 decade is more likely to be due to changes in eating habits and a more sedentary life style, driven at least to a strong degree by the "abuse" of cars, computers, and television.[22] Interestingly, over the same time period public campaigns have tried to educate the populace on the importance of less fat in diets, and "designed" low-fat food entered the market but without any significant effect on "the trend".

There is growing evidence that obesity as a multifactorial, chronic disease cannot be cured by short-term dieting or exercise alone, but additional pharmacological treatments should finally lead to higher success rates.

Marijuana, the female plant of the *Cannabis sativa* genus, contains several psychoactive, hallucinogenic chemicals with euphoric and sedative effects, termed cannabinoids. The male plant, also known as hemp, contains virtually no psychoactive ingredients but is utilized commercially. Marijuana, with its active ingredients, has been used in several forms (mostly smoked) as a recreational and medicinal agent for millennia by various cultures and nations.[23−25] The structure of the main active ingredient Δ^9-tetrahydrocannabinol (Δ^9-THC, **1**; Figure 1) was elucidated by Mechoulam in 1964, but for quite some time the actions of this and related active terpenophenols were thought to be unspecific and to be mediated via perturbation of membranes.

It was only during the past decade that the therapeutic potential of the endocannabinoid system became more fully explored,[26] and dedicated research revealed pivotal information on the endocannabinoid system, its receptor subtypes[27,28] (CB_1 and CB_2), and their (endogenous) agonists of which the mixed $CB_{1/2}$ endogenous agonists anandamide (AN, **2**) and 2-arachidonoylglycerol (2-AG, **3**) and the CB_1 selective noladin ether (NE, **4**) are the best characterized thus far (Figure 2).[29]

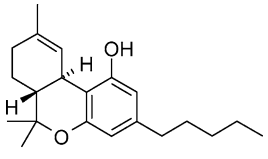

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Figure 1. Structural formula of **1**.

The CB_1 cannabinoid receptor belongs to G-protein-coupled receptor (GPCR) type of receptors and is coupled to inhibitory G proteins G(i/o). Signaling is mostly through inhibition of certain adenylyl cyclase isozymes, resulting in decreased cAMP production, decreased Ca^{2+} conductance, increased K^+ conductance, and increased mitogen-activated protein kinase activity.[26,30] The major physiological effect of cannabinoids (in the central nervous system (CNS) and neuronal tissues) is the modulation of neurotransmitter release via activation of presynaptic CB_1 receptors located on distinct types of axon terminals throughout the brain.[31] It is hypothesized that endocannabinoids, triggered by a postsynaptical depolarization and the subsequent increase of intracellular Ca^{2+}, are synthesized ("on demand") and released as retrograde messenger molecules. These stimulate presynaptic CB_1 receptors, which modulate the release of several neurotransmitters including excitatory amino acids (glutamate), inhibitory amino acids (GABA, glycine),[32] and monoamines (dopamine, serotonine, noradrenaline, acetylcholine).[33] The endocannabinoid system differs largely from other neurotransmitter systems in terms of the release mechanism. Instead of "forward looking" vesicular storage, there is a synthesis "on demand".

Compounds **2** and **3** are potentially derived from a common phospholipid precursor, likely to be *sn*-1,2-di-arachidonoylphosphatidylcholine (AAPC).[34,35]

Once released, endocannabinoids are transported into the neuronal cells by a specific uptake system and rapidly degraded by two well-characterized enzymes: fatty acid amide hydrolase (FAAH, responsible for the cleavage of **2**) and monoacylglycerol lipase (e.g., for the degradation of **3**).[35,36]

CB_1 receptors are mainly expressed in several brain areas including the limbic system (amygdala, hippocampus), hypothalamus, cerebral cortex, cerebellum, and basal ganglia. In the cerebellum and basal ganglia cannabinoids modulate locomotor activity. In the limbic system cannabinoids influence learning, memory, emotion, and motivation, and through activation of CB_1 receptors in the limbic system−hypothalamus axis cannabinoids have an important role in the control of appetite. Moreover, CB_1 receptors can be found to a lower extent in peripheral tissues including urinary bladder, testis, prostate, GI tract, heart, lung, adrenal gland, parotid gland, bone marrow, uterus, ovary, and adipose tissue.[37−40]

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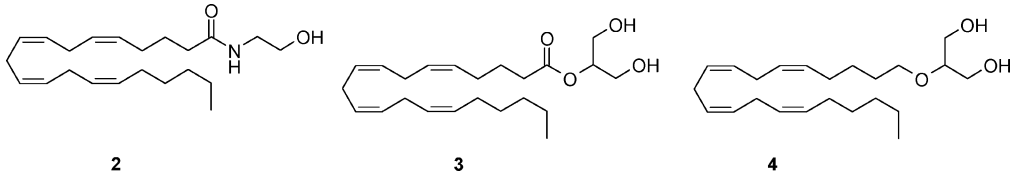
10.1021/jm058238r CCC: $33.50
Published on Web 06/17/2006



2 3 4

Figure 2. Endogenous cannabinoids.

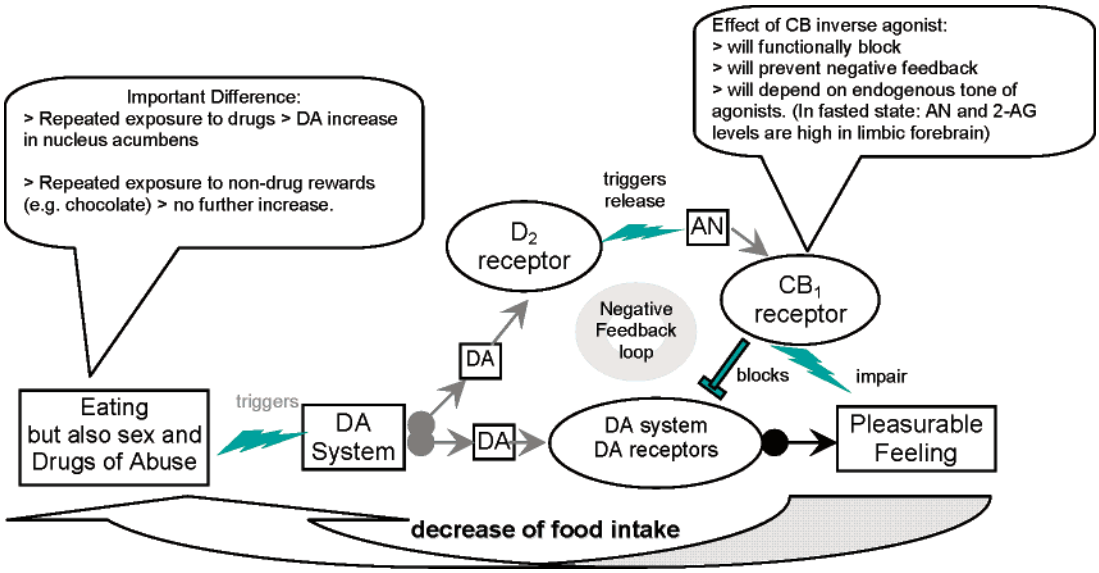


Figure 3. Sketch of speculative interactions and feedback circuits linking dopaminergic and cannabinergic systems.

CB_2 receptors are not expressed by neurons but are found on immune cells (e.g., macrophages, microglia, B-lymphocytes, natural killer cells) and in immune tissues (e.g., lymph nodes, spleen, tonsils, thymus). Although recent pharmacological data suggest the existence of additional subtypes of cannabinoid receptors,[41−43] critical evidence in the form of genes encoding such novel "CB_3" receptors is currently lacking.

Potential Mechanisms of Action and Preclinical Proof of Concept Studies

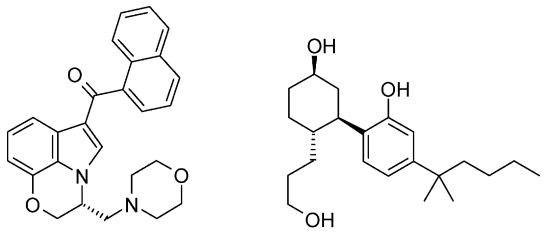
Cannabinoid receptors are more ubiquitously distributed in mammalian tissue (mostly but not exclusively in neuronal tissue) than originally thought, which is consistent with the plethora of involvements known as of today, with new findings being frequently documented in recent reviews.[26,31,44−46]

With regard to the role of the cannabinoid system in feeding and energy homeostasis, there is current experimental evidence for an interaction with several orexigenic, anorexigenic, and metabolic/anabolic pathways.

First of all it was discovered that the levels of endocannabinoids in hypothalamic feeding centers are under negative control by leptin.[47] Leptin[48] is an adipocyte hormone that can be seen as a "peripheral signal of starvation".[49] In animal models with defective leptin signaling, as for example in obese Zucker rats or either db/db or ob/ob mice, the level of endocannabinoids, predominantly **3** in the hypothalamus (but not in the cerebellum) is significantly increased.[47] In support of these observations, application of leptin (250 μg iv in Sprague Dawley (SD) rats) down-regulates hypothalamic **2** and **3** by 40−50%.[47]

The same results show up if normal animals are fasted. Also, **2** and especially levels of **3** are significantly elevated in the hypothalamus in comparison to the fed state.[50]

As already mentioned, endocannabinoids act as retrograde messengers[51] in the CNS, reduce glutamate release in dorsal and ventral striatum (especially nucleus accumbens), and thereby



5 **6** (CP 55,940)

Figure 4. Synthetic agonists widely used as pharmacological tool compounds.

modulate neurotransmission in the basal ganglia and in the mesolimbic reward system.

The mesolimbic, dopaminergic reward system is involved in the pleasure produced by natural rewards such as food and sex, and it is the neural substrate of drug addiction and addiction-related phenomena such as craving and dysphoria induced by drug withdrawal. The mesolimbic reward system consists of the ventral tegmental area, which is linked to the nucleus accumbens by a dopaminergic fiber tract.

Cannabinoids can activate these dopaminergic neurons, projecting from the ventral tegmental area to the nucleus accumbens.[52] However, it is thought that the effects on dopamine (DA) release are not direct but rather an indirect modulation of dopamine transmission through trans-synaptic mechanisms involving GABA-ergic and glutamatergic synapses, as well as by converging signal transduction cascades downstream of the cannabinoid and DA receptors. The dopamine and endocannabinoid systems seem to exert a mutual control on each other. There is experimental evidence that doses of the cannabinoid agonist **5** (WIN 55,212-2, Figure 4) produce ongoing fluctuations in extracellular DA in the nucleus accumbens. Cannabinergic signaling may therefore induce a release of DA, which can act via dopamine D1-like receptors[53] as a negative feedback mechanism to counteract the effects of activation of

the cannabinoid CB_1 receptor. The CB_1 receptor antagonist [*N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methylpyrazole-3-carboxamide]rimonabant (**7**) reversed and prevented all agonist-induced effects but did not show effects on dopamine release on its own.[52]

On the other hand, DA signaling via dopamine D2-like receptors may lead to up-regulation of cannabinergic signaling, which is likely to represent a negative feedback on DA signaling.[54]

Experimental evidence for these very complex and not yet fully understood interactions were obtained by serendipity during a SPECT study, when increased synaptic dopaminergic activity was observed and could be traced back to cannabis use by the subject under clinical examination.[55]

Interestingly, an independent study published in Lancet[56] revealed that the dopamine D_2 receptor density in obese subjects was decreased in proportion to their BMI. In conclusion it was hypothesized that the reward circuits were not optimally triggered by "normal" food intake and DA deficiency in obese people may lead to overeating/"pathological" eating in order to stimulate the reward system (Figure 3).

As mentioned, dopaminergic neurotransmission has been highly implicated in the reinforcing properties of many substances of abuse, including marijuana. It is, however, important to note that a crucial difference between drug and nondrug rewards seems to exist in that the increase in dopamine release induced by nondrug rewards (e.g., chocolate) was not observed following repeated exposure in contrast to still increasing DA release following repeated exposure to drugs of abuse.[57,58]

The interaction of the endogenous cannabinoid system with other central circuits involved in feeding and satiety, such as corticotropin-releasing hormone (CRH), cocaine-amphetamine-regulated transcript (CART), melanin-concentrating hormone (MCH), and preproorexin, was recently described by Cota et al.[37] Moreover they also presented evidence that CB_1 receptors are expressed in epididymal mouse adipocytes.

Several recent studies support the hypothesis that the positive effect on adiposity of the CB_1 receptor antagonist **7** is most likely mediated to some extent via metabolic mechanisms that are independent of changes in food intake.[37,38,59,60] The observation that lipogenesis in primary adipocyte cultures can be enhanced via a CB_1 receptor specific activation points to a role of cannabinergic signaling in peripheral lipogenic mechanisms and may be linked to the discovery of an interaction with adiponectin levels.[61] Adiponectin (also referred to as AdipoQ, Acrp 30, apM1, or GBP28) is a plasma protein that is exclusively expressed and secreted by adipose tissue. It has been shown to induce free fatty acid oxidation, to decrease hyperglycemia and hyperinsulinemia and to lead to body weight reduction. Compound **7** induced an overexpression of adiponectin mRNA and protein in cultured mouse adipocytes (3T3 F442A) and also stimulated respective mRNA expression in adipose tissue of obese Zucker (fa/fa) rats. Meanwhile, it is well established that PPARγ agonists elevate serum adiponectin levels.[62,63] However, since **7** had an effect on adiponectin mRNA expression in adipose tissue of wild-type mice, but not in adipose tissue of CB_1-receptor knockout mice,[61] a CB_1-receptor mediating effect is likely to contribute. Further investigations are currently ongoing to substantiate the various working hypotheses.

In summary many preclinical, in vitro, and in vivo experiments have been performed showing that CB_1 receptor antagonists can influence energy homeostasis by central and peripheral mechanisms and may represent a very promising target to treat diseases that are characterized by impaired energy balance. Already the first published studies with **7** in both rodents[64] and primates[65] showed clear differentiation, i.e., marked effects on sweet food intake versus marginal effects on regular chow intake or water drinking. Many other preclinical "proof of concept" studies have been performed in the meantime with several CB agonists and antagonists to further uncover the amount and mode of contribution of cannabinergic system modulators to energy homeostasis. Almost all of those studies were recently excellently tabulated and reviewed.[46] Common to all these studies, whether performed in rats or in mice, is the observation of a transient reduction of food intake and a marked but sustained reduction in body weight and adiposity, e.g., as shown in a recent DIO-mouse study.[59] During a 5-week oral treatment, compound **7** applied at 10 mg/kg induced a transient reduction of 48% in the first week and an overall reduction of body weight by 20% and of adiposity by even 50%.[59] In addition, insulin resistance was improved and leptin levels were lowered.

Last but not least, the lean phenotype of CB_1 receptor knockout mice,[37,66] their enhanced leptin sensitivity and resistance to diet-induced obesity,[38] and their reduced responsiveness to addictive triggers[67−70] confirm the role of the cannabinoid system with regard to energy homeostasis and reward mechanisms. Whether primarily central or primarily peripheral[71] modes of action dominate is an ongoing matter of debate.

CB_1 Receptor Antagonists/Inverse Agonists

CB_1 receptor antagonists are currently under clinical investigation for the treatment of obesity and metabolic disorders, as well as for smoking cessation and alcohol abuse.[45,72−75]

Several types of CB_1 receptor antagonists are meanwhile known, and have been disclosed in numerous patents and recently discussed in several excellent and exhaustive reviews.[45,46,72] It is noteworthy that most of the published CB_1 receptor antagonists might be better termed "inverse agonists" than neutral antagonists.[108] However, this distinction is seldom made probably because the inverse agonism on the constitutively active receptor is rarely investigated.[108]

Compound **7** was the first potent and selective CB_1 receptor antagonist/inverse agonist discovered[76] and characterized (CB_1 $K_i = 2$ nM; CB_2 $K_i > 1000$ nM)[77] by Sanofi-Synthelabo (now Sanofi Aventis). A back-up compound **8** (SR147778) also in clinical development (phase IIb) was described recently[78] and a further compound (structure not yet disclosed) was said to be in phase I as well.

Compound **7** opened the structural class of the 1,5-diarylpyrazoles (Figure 5) to which the majority of the CB_1 receptor antagonists belong, for example, as the 4-cyano analogue **9** (CP-272,871) from Pfizer and Sanofi's back-up candidate **8**. Structure−activity relationships (SARs), mainly based on receptor binding and functional antagonism, of **7** and some structural analogues have been discussed for this class[79,80] and revealed that highest affinities were reached with a para-substituted phenyl ring at the 5-position of the pyrazole ring and either a 2-chloro or 2,4-dichlorophenyl substitution pattern at the 1-position. Replacement of the (C4) methyl group in **7** by more lipophilic substituents, e.g., a bromine atom, resulted in higher CB_1 receptor affinity. Last but not least, a monocyclic five- or six-membered (heterocyclic) ring substitution at the 3-carboxamide group like the 1-piperidinyl group shows up favorably, but linear *N*-alkylcarboxamides (**10**) (e.g., from Research Triangle Institute) show affinity too.[80]

Many of the antagonist structures known to date can be seen as smart bioisosters in a wider or even the widest sense or the

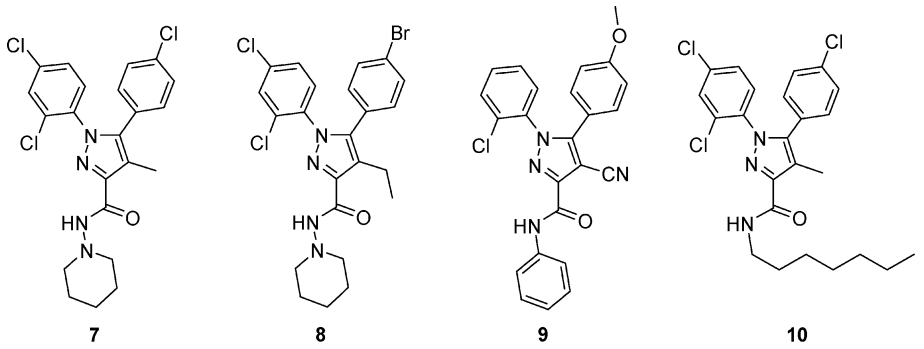


Figure 5. Structures of some selected 1,5-diarylpyrazoles.

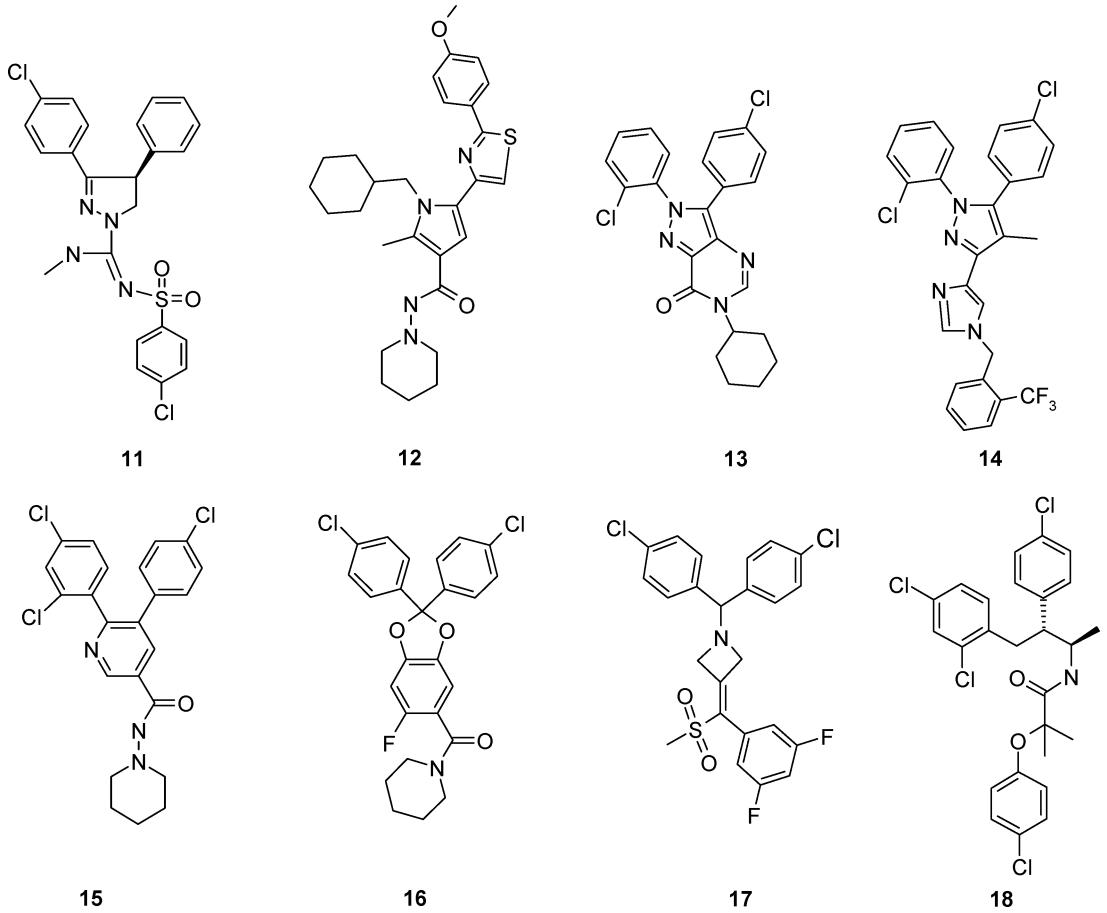


Figure 6. Noncomprehensive collection of examples of CB_1 antagonists from various structural classes.

results of scaffold attempts based on the "classic" 1,5-diarylpyrazoles by replacing the five-membered pyrazole core by other four-, five-, or six-membered, bicyclic-, tricyclic-, or tetracyclic cores and acyclic spacers. Some examples of these structural classes are depicted in Figure 6.

Besides some peer-reviewed original publications from Solvay about 3,4-diaryl-4,5-dihydropyrazoles (covering **11** (SLV 319), 4,5-diarylimidazoles, 2,3-diaryl-1,2,4-triazoles, and thiazoles, most structural information is currently retrieved from patent literature. **11** is a CB_1 selective (about 1000-fold versus CB_2) antagonist/ inverse agonist that showed potent in vivo activity after oral administration.[81]

Pyrroles such as **12** were described in Hoffmann-La Roche patent applications. The rigidified pyrazole **13**, where scientists from Pfizer linked the 3-carboxamide back to the 4-position of the pyrazole, is one of many examples of a bicyclic moiety. Compound **14** is an example where the nitrogen of the heterocyclic ring serves as a hydrogen bond acceptor, mimicking C═O or S═O moieties in other antagonists. Just one of several examples of replacing the central five-membered heterocyclic ring with a six-membered ring core is shown by compound **15**, with a central pyridine ring. Six-membered ring cores are described in patents from Astra Zeneca, Merck & Co., Sanofi-Aventis, and Virginia Commonwealth UnivOrganix. Another more complex example is shown with compound **16**, with a benzodioxole core as disclosed by Hoffmann-La Roche. Several diarylmethylazetidines such as **17** have been disclosed by Aventis (now Sanofi-Aventis), but related ones were also disclosed by researchers from Vernalis. Finally, CB_1 receptor antagonists with acyclic spacers, such as **18**, are described in several patents from Merck & Co.

Many more examples and more detailed descriptions can be found in some excellent recent patent literature reviews.[45,46,72,82,83]

Several 3D models of the CB_1 receptor have been published in the meantime.[84−89] They were mainly based on the bovine rhodopsin structure, starting either from the inactive form

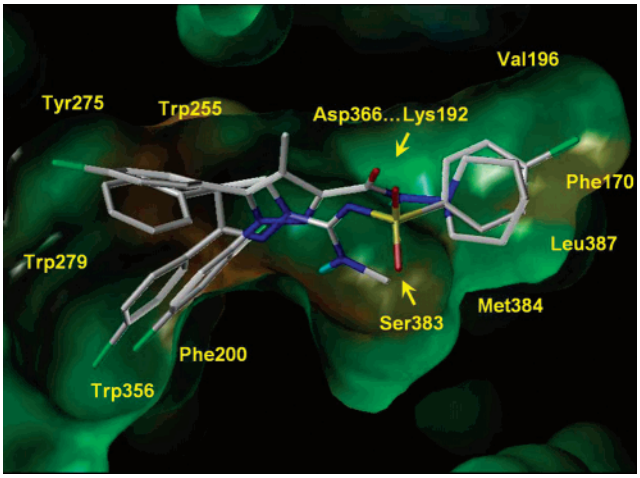


Figure 7. Illustration of potential interaction sites of **7** and **11** with a homology model[81] of the CB1 receptor.

(following the hypothesis that antagonists are thought to bind to and stabilize the active or inactive receptor) or from considering the "inverse agonist" character of most of the currently known CB_1 receptor "antagonists", by studying the interaction with the model of an active receptor.[87,90] It is currently hypothesized that hydrogen bonding of the C3 substituent of **7** with lysine 192 is responsible for its higher affinity for the inactive receptor state,[91] which may explain its inverse agonism. Inverse agonism is often explained within a dynamic two-state model. In this model a constitutively active "on " state is interchangeable with a constitutively inactive "off" state of the receptor (not spontaneously coupled to effector mechanisms). In terms of this model inverse agonists increase the proportion of receptors in the "off" relative to the "on" state.[108] Neutral antagonists, however, should not modify the number of receptors in each state.

Recent modeling studies also involving **11** further strengthened the validity of the model by showing that despite a considerably different chemotype, most likely the same binding epitope and key interactions as for **7** are involved (Figure 7). The model was also able to explain the stereoselectivity of **11** versus its distomer.[81]

Clinical Studies

Currently, there are four CB1 receptor antagonists in clinical studies for treatment of obesity and prevention of comorbid metabolic disorders: compound **7** and its backup compound from Sanofi-Aventis, compound **11** pursued jointly by Solvay and BMS, and a compound (structure not yet disclosed) investigated by Pfizer.

According to public databases, Sanofi pursued a phase II meta-trial in November 1998 to compare the relative efficacy of four investigational candidates, compound **7**, eplivanserin, reminertant, and osanetant, for safety and efficacy in schizophrenia. However, **7** did not appear to demonstrate efficacy, and Sanofi-Synthelabo discontinued the development for this indication but initiated clinical trials directed toward obesity and smoking cessation.

The clinical development of **7** is far advanced, and its marketing authorization approval by regulatory authorities was expected at the end of 2005 or early in 2006.

The phase III program on **7** includes seven clinical trials that are part of two clinical development programs. The RIO (*r*imonabant *i*n *o*besity) program has enrolled over 6600 overweight or obese patients worldwide in four clinical trials designed to explore the role of **7** in obesity management: weight loss and weight maintenance, prevention of weight regain after prior weight loss, and improvement of obesity-related risk factors such as diabetes and dyslipidemia. RIO—North America and RIO—Europe are 2-year studies. RIO—Lipids and RIO—Diabetes are 1-year studies.

The STRATUS (*st*udies with *r*imonabant *a*nd *t*obacco *u*se) program has enrolled over 6500 patients in three phase III trials worldwide. The studies are designed to explore the role of **7** in smoking cessation and long-term abstinence and prevention of weight gain upon smoking cessation. STRATUS—U.S. and STRATUS—EU are 10-week studies with a 42-week follow-up off treatment. STRATUS—Worldwide is a 1-year study with a 1-year follow-up off treatment.

Results of both the RIO—Lipids and STRATUS—U.S. trials were presented in March 2004 for the first time to the scientific community at the American College of Cardiology annual meeting in New Orleans, LA. The 1-year data of the second clinical trial in obese patients (RIO—Europe) were presented by Luc Van Gaal in August 2004 at the European Society of Cardiology Congress in Munich, Germany, and meanwhile a peer-reviewed paper has been published in the Lancet[92] summarizing the clinical phase III data of the RIO—Europe study.

Briefly, the RIO—Europe study was designed as a multicenter, randomized, double-blind, placebo-controlled parallel group study. A total of 1507 patients with body-mass index of 30 kg/m^2 or greater or body-mass index greater than 27 kg/m^2 with treated or untreated dyslipidaemia, hypertension, or both were randomized to receive double-blind treatment with placebo, 5 mg of **7**, or 20 mg of **7** once daily in addition to a mild hypocaloric diet (600 kcal/day deficit). The primary efficacy endpoint was weight change from baseline after 1 year of treatment in the intention-to-treat population.

Weight loss at 1 year was significantly greater in patients treated with 5 mg of compound **7** (mean of −3.4 kg [SD = 5.7], $p = 0.002$ vs placebo) and 20 mg (−6.6 kg [SD = 7.2], $p < 0.001$ vs placebo) compared with placebo (−1.8 kg [SD = 6.4]). Significantly more patients treated with 20 mg of **7** than with placebo achieved weight loss of 5% or greater ($p < 0.001$) and 10% or greater ($p < 0.001$). The 20 mg dose of **7** produced significantly greater improvements than placebo in waist circumference, HDL-cholesterol, triglycerides, insulin resistance, and prevalence of the metabolic syndrome. The effects of **7** at 5 mg were of less clinical significance.

The most common adverse events occurring with **7** were nausea (placebo, 4.3%; compound **7** at 5 mg, 5.1%; compound **7** at 20 mg, 12.9%), diarrhoea (placebo, 3.0%; compound **7** at 5 mg, 6.0%; compound **7** at 20 mg, 7.2%), dizziness (placebo, 4.9%; compound **7** at 5 mg, 7.0%; compound **7** at 20 mg, 8.7%), and arthralgia (placebo, 6.9%; compound **7** at 5 mg, 9.6%; compound **7** at 20 mg, 7.8%). These events, however, were for the most part mild to moderate in intensity and considered to be transient, based on the occurrence mainly during the first months of the study.

Frequencies of serious adverse events (classified by organ systems) were similiar in all groups except for psychiatric disorders (placebo, 0.3%; compound **7** at 5 mg, 0.3%; compound **7** at 20 mg, 1.5%).

After 1 year there were no significant changes in the HAD scale subscores for depression (placebo, 2.7 [SD = 2.9]; compound **7** at 5 mg, 2.7 [SD = 2.7]; and compound **7** at 20 mg, 3.4 [SD = 3.4]) or anxiety (4.4 [SD = 4.0], 4.5 [SD = 3.7], and 5.6 [SD = 4.1]). Similar proportions of patients with postbaseline depression subscores of 11 or greater were noted

in the placebo (23, 8.5%), compound **7** at 5 mg (40, 7.5%), and compound **7** at 20 mg groups (41, 7.9%). No specific changes in laboratory parameters for hematology, kidney, or liver functions were reported, and no effect on blood pressure was noted. Mean heart rate remained unchanged from baseline with compound **7** at 20 mg, and QTcF decreased by 5.7 ms (SD = 16.3) in the placebo group and 3.6 ms (SD = 16.9) in the compound **7** at 20 mg group.

While the RIO—Europe trial was taken as an example, data from the RIO—Lipids trial and the RIO—North America trial (presented by Dr. Xavier Pi-Sunyer at the American Heart Association Scientific Sessions, November 2004 in New Orleans, LA) match up quite well and support the overall robust picture thus far. In addition, the most recent study (RIO—Diabetes), presented by Dr. André Scheen at the American Diabetes Association annual meeting in San Diego, CA, in June 2005 showed that **7** improved glycemic control and reduced body weight, waist size, and other lipid parameters in a group of overweight type 2 diabetic patients.

With regard to other CB1 receptor antagonists in clinical development, no details have been made public so far. Status information can be retrieved from company home pages and database providers. In summary, (1) Sanofi-Aventis reported to have compound **8** as a back-up compound in phase II and another compound (structure not yet disclosed) in phase I; (2) Solvay Pharmaceuticals and Bristol-Myers Squibb entered into a joint development and future commercialization agreement and developed compound **11** as a novel antiobesity compound; (3) Pfizer announced the development of a CB_1 antagonist (structure not yet disclosed) for the potential treatment of obesity.

Outlook, Additional Opportunities, and Potential Pitfalls

In the meantime, while obesity is clearly classified as a disease (listed in the International Classification of Diseases (ICD-9-CM) and grows with epidemic proportions, many still consider it as just an "unhealthy condition". Some reasons for this perception among patients and physicians are quite clear; the obese subject does not necessarily feel sick. He or she may just be "short of breath", in an overall poor physical condition, and socially stigmatized. Furthermore, the "point of hard-to-return" or even "no return" on the pathway to severe cardiovascular disorders, type 2 diabetes, and other comorbidities may still be somewhat far away. With this in mind, clinical efficacy, tolerability, and safety deserve an even greater attention than in the case of some other diseases.

In the search for efficacy, there is probably a gap between clinically meaningful weight loss over time (as seen by physicians) and the expectations of the patients. Weight loss of 5—15% over a 1-year period (!) is regarded as clinically meaningful, going concomitantly with improvements in insulin sensitivity and lipid profiles, and causes a significant delay or even prevention of the onset of comorbid conditions such as hypertension and type 2 diabetes.[93−95] However, key for clinicians (and patients) is not just the initial weight reduction but also subsequent weight maintenance. These clinical assessments of a "healthy weight loss" are reflected in numerous guidelines of national health organizations.[96−98] Key for most patients is to lose much weight (>20%) in a very short period and to maintain it without behavioral modifications,[99−101] expectations that cannot be matched with current therapies (besides surgery) and might be hardly achievable with safe therapies at all.

Compound **7** as the clinically most advanced CB_1 receptor antagonist seems to yield weight loss effects that are slightly superior to approved medicines (Sibutramine, Orlistat) but roughly in the same ballpark. However, no clinical head to head studies have been conducted so far between CB_1 receptor antagonists and other available therapeutics, and therefore, efficacy can only be estimated by looking at weight loss data from the recent RIO studies and body weight changes previously reported in clinical trials with other antiobesity drugs.

More important than sheer weight loss are the remarkable improvement of lipid profiles and the reduction of risk factors for the metabolic syndrome, leading to an overall reduction of independent cardiovascular risk factors. It can be hypothesized that the multiple mode of action, i.e., central mechanisms via limbic, hypothalamic, and other nonhypothalamic circuits, as well as peripheral mechanisms (e.g., blockade of CB_1 receptors on adipocytes), may lead to potential superiority of CB_1 receptor antagonists as far as efficacy is concerned.

In the search for potential pitfalls, it is too premature to come to a final picture; the endocannabinoid system is still a "young" area of very active research, and a lot of new discoveries can be expected. The search for potential issues with regard to safety and tolerance and parameters to be monitored, when antagonizing physiologically relevant mechanisms such as CB_1 receptor-dependent mechanisms, requires that a close look is taken at the role of the endogenous ligands/agonists and at the role of constitutively active receptors.

The variety of organs and subdomains of organs (e.g., CNS) that express CB_1 receptors is huge. In addition, there is evidence that different endogenous ligands may play different roles in certain central as well as peripheral areas, and it is likely that while some receptors in certain areas are tonically stimulated, there may be no tonus of endocannabinoids in other areas. It is thus hard to make any risk assessment on pure theory. Obviously the endocannabinoid system modulates the release of several neurotransmitters and plays a general role in a "stress recovery system", which is usually silent but becomes transiently activated to relax, rest, forget, protect, and eat.[102,103] More specifically, it is involved in feeding and energy balance, cognition and memory processes (e.g., the eradication of aversive memories[104]), sleep, reinforcement of "substances" (incl. alcohol and chocolate) of abuse, nausea, and vomiting,[105] movement and posture, pain perception, emotion and mood regulation, female and male reproduction, and a variety of other gastrointestinal, cardiovascular, and respiratory functions. All this needs to be taken into account when looking at the reported adverse side effects.

On the basis of what has been made public thus far for **7**, the safety profile seems to exceed expectations,[92] with side effects being mild and transient. It is noteworthy to point out that apart from potential side effects that might be affiliated with the intended mechanism of action, every active compound needs to be explored independently for its specificity and selectivity in addition to the mandatory toxicological and safety evaluations. With knowledge that some structural epitopes of the TRPV1,[106] PPAR-α,[107] and possibly some other receptors seem to overlap with the CB_1 receptor, it is not unlikely that for some of the disclosed agonists/antagonists and inverse agonists, complex interaction profiles might show up.

In regard to other CB_1 receptor antagonists in the development pipeline of several companies, on the basis of preclinical data, it is not unlikely that significantly improved clinical efficacy is in reach. The overall and final conclusions must come from carefully conducted clinical studies.

Obesity is at least in part a life-style-dependent disease, which must not mean that therapies should be (dis-)qualified as life-

style drugs. The severity of the medium- to long-term consequences for each patient and the huge and increasing impact on the economy will eventually lead to safe and efficacious medical treatments as a necessary adjunct but not a substitute for behavioral modifications. The CB_1 receptor antagonists thus far show the promise of becoming a major component in future treatment regimes.

While this Miniperspective highlights the perspectives of CB_1 receptor antagonists in obesity and metabolic disorders, one must not overlook the possibility that drugs with this mechanism may enrich our portfolio for treating other diseases, such as neuroinflammatory disorders, cognitive disorders, septic shock, psychosis, gastrointestinal disorders, and for sure, since it is already clinically proven, addiction.

Biographies

Jochen Antel received his Diploma and Ph.D. in Chemistry from University of Göttingen (Germany) with Professor George M. Sheldrick. He joined Kali-Chemie Pharma in 1989, which later became Solvay Pharmaceuticals GmbH. Starting his industrial career as Head of CADD Laboratory, he became 1999 Discovery Program Manager Obesity responsible for building up research and early development activities in the area of obesity and related metabolic diseases. Currently he is leading the teams for gastrointestinal and metabolic disorders within Solvay Pharmaceuticals.

Peter C. Gregory completed his B.Sc. and Ph.D. in Physiology and Biochemistry at Southampton University with Professor Kenneth Munday. There followed postdoctoral research fellowships in Glasgow University in Professor Murray Harper's laboratory and in Leeds University in Professor Gordon Mcdowall's laboratory before he moved to the Gastrointestinal Physiology Department at the Rowett Research Institute in Aberdeen. In 1988 he joined Kali-Chemie Pharma, which later became Solvay Pharmaceuticals GmbH, to lead the prokinetic program in the Gastrointestinal Pharmacology Department. Currently he is Senior Scientist responsible for in vivo pharmacology in the areas of obesity and related metabolic disorders as well as for pancreatic enzyme supplementation.

Ulrich Nordheim received the degree Doctor of Medicine at the Albert-Ludwigs-University, Freiburg i. Br., Germany, in 2001. Following postdoctoral research at the University of Basel, Switzerland, in Professor K. G. Hofbauer's laboratory, he joined Solvay Pharmaceuticals in 2004 where he is currently Clinical Research Director for obesity and gastrointestinal disorders.

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JM058238R