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HISTORY OF THE DEVELOPMENT AND CLINICAL USE OF CB1 RECEPTOR INVERSE AGONISTS/ANTAGONISTS

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Introduction

In 1964, the structure of delta-9-tetrahydrocannabinol, the main psychoactive ingredient in marijuana, was identified [1]. The breakthrough was given impetus by the discovery of cannabinoid receptors and their endogenous ligands, the endocannabinoids. The endocannabinoid system (ECS) is a physiological system with an important regulatory role in numerous biological functions, both centrally and peripherally. In certain conditions it can become overactivated and induce a variety of metabolic disorders, i.e., obesity, type 2 diabetes, etc. The system has two receptor types, designated CB1 and CB2, as well as endogenous ligands and systems for their transport, synthesis, and degradation.

Key Points

- CB1 receptors may be involved in the motivational aspects of eating.
- Rimonabant can reduce the appetitive and rewarding properties of food and drink in animal models.
- An activation of peripheral metabolic processes contributes to the weight-reducing effect of rimonabant.
- Preclinical studies have shown the potential of rimonabant in the specific treatment of dyslipidemia, glycemia, and atherosclerosis and in reducing the risk of major cardiovascular events.
- Rimonabant in the RIO studies achieved clinically significant improvements in body weight, HbA1c levels in type 2 diabetics, and in lipid parameters.
- Subsequent clinical studies have demonstrated that rimonabant improves glycemic control in type 2 diabetes across a range of patient populations while improving weight loss and lipid parameters, thereby addressing multiple cardiometabolic risk factors commonly observed in type 2 diabetes.
- CB1 receptor antagonism with rimonabant represents a novel approach to the treatment of abdominal obesity and other cardiovascular and cardiometabolic risk factors.

Discovery

In the late 80s and early 90s, scientists at Sanofi wondered if antagonists of "cannabis" could promote an inhibition of appetite and thus be a potential treatment of obesity. At around the same time, the human central cannabinoid receptor (the CB1 receptor) was cloned [2]. This was followed three years later by the characterization of a second cannabinoid receptor (CB2). A high throughput screening was then performed on the cannabinoid receptors. These studies led, after optimization, to the selection of SR141716 (rimonabant). Rimonabant was found to be highly selective for the central CB1 receptor (at nM levels), exhibiting only very weak activity (at mM levels) for the cloned peripheral CB2 re-

ceptor [3]. The compound was then examined in an *in vivo* environment and, at low doses administered by the oral or intraperitoneal routes, it antagonized in a dose-dependent way the behavioural responses elicited by the cannabinoid receptor agonist WIN 55212-2 in rodents. In addition, other tests established the good bioavailability of the compound and its long duration of action.

Preclinical Profile

Numerous preclinical studies have shown that rimonabant selectively reduces the intake of palatable food or drink [4], and it is also able to diminish the intake of a high-fat diet preferred by the obese Zucker rats, without modifying the intake of a high-carbohydrate diet. Rimonabant has been studied in different models of obesity in rodents. The anti-obesity effect of rimonabant has also been studied in a model of obesity (DIO) induced by a high-fat diet in mice. In this model, rimonabant administered at a dose of 10mg/kg/day during 6 weeks produced a marked reduction in eating, which was transitory during the first weeks of treatment. Afterwards this effect tended to disappear. However, rimonabant produced a marked loss in body weight that was maintained up to the end of the 6-week treatment [5]. The initial loss in body weight was probably due to the reduction in food intake observed at the beginning of treatment. However, the fact that this effect persisted even when the mice increased their food intake to normal levels suggested a metabolic effect involving the peripheral tissues.

It has been demonstrated that the CB1 receptors are also expressed in the adipose tissue of rodents and humans and also in the cultured mouse 3T3 F442A adipose cells. This expression is increased in the adipose tissue of obese Zucker rats compared to nonobese rats [6]. Rimonabant at a dose of 10 mg/kg/day for 10 days in Zucker rats stimulated the expression of adiponectin mRNA in the adipose tissue of the obese animals. This effect was mediated by the blockade of the CB1 receptors, as rimonabant did not modify the expression in the adipose tissue of CB1 knockout mice. These results demonstrate that rimonabant, in blocking the adipocyte CB1 receptors, regulates the expression of this adiponectin protein. The increase in the levels of adiponectin could therefore be partially responsible for the peripheral metabolic effects of rimonabant. A follow-up study in Zucker rats demonstrated that rimonabant had a definite hepatoprotective effect with a reduced hepatomegaly associated with reduced elevated plasma levels of enzyme markers of hepatic damage as well as reduced local hepatic tumor necrosis factor-α levels indicative of steatohepatitis [7].

Further long-term studies in obese Zucker rats that developed chronic renal failure showed that rimonabant preserved renal function and increased survival [8]. When rimonabant was administered to Zucker diabetic rats, it prevented the development of hypoglycemia and improved β-cell function, while maintaining a normal profile of insulin secretion with a much lower impact on body weight compared to rosiglitazone treatment [9].

In addition, rimonabant positively modulates the lipid profile, reduces circulating neutrophils and monocytes, attenuates platelet activation as well as the release of proatherosclerotic chemokines, reducing cardiovascular risk in the process [10].

Clinical Studies

The preclinical studies confirmed the potential of rimonabant as a CB1 receptor antagonist as well as its potential therapeutic application in the treatment of obesity. Initial phase II clinical studies confirmed the potential of the compound in reducing body weight in obese patients. In 4 large randomized phase III clinical studies in obese or overweight patients (RIO program in over 6,600 patients) [11-14], rimonabant has shown the ability to reduce body weight and waist circumference, increase HDL cholesterol levels, reduce triglyceride and HbA1c levels and other cardiometabolic risk factors, and is thus considered a novel treatment in conjunction with diet and exercise for obese and overweight patients with cardiometabolic diseases such as type 2 diabetes or dyslipidemia.

After the RIO program, different clinical studies were initiated to assess the therapeutic potential of the compound in the treatment of type 2 diabetes and other cardiovascular risk factors. These included the SERENADE study, where the drug was found to improve glycemic control in newly diagnosed naive type 2 diabetic patients [15]. More recently, the ARPEGGIO study demonstrated an improvement in glycemic control in a difficult population of type 2 diabetic patients inadequately controlled by insulin alone, with a significant decrease in HbA1c levels being observed [16]. In the ADAGIO-Lipids study, rimonabant was active against certain biomarkers indicative of atherogenic dyslipidemia in abdominally obese patients, e.g., fatty acid index, alanine transaminase, high-sensitivity C-reactive protein, and adiponectin [17]. Further studies included the STRADIVARIUS study, where the effect of rimonabant over 18 months on the progression of atherosclerosis was measured by IVUS endpoints. Rimonabant failed to show a statistically significant effect on the primary endpoint, but did show encouraging results across 4 IVUS endpoints [18].

Current/Future Clinical Studies

In the cardiovascular area, as a follow-up to the STRADIVARIUS study, the AUDITOR study will specifically look for an effect on the inhibition of atherosclerosis progression as assessed by carotid artery intima-media thickness (CIMT) in overweight patients. In addition, the ongoing RAPSODI study will assess the efficacy and safety of long-term administration of rimonabant to delay the onset of type 2 diabetes in patients with a pre-diabetic status. Finally, the CRESCENDO study (~17,000 patients), due to be completed in 2011, will see whether rimonabant treatment can reduce cardiovascular events in abdominally obese patients with high cardiovascular risk factors.

References

1. Mechoulam R and Gaoni Y. Isolation, structure, and partial synthesis of an active constituent of hashish. J Am Chem Soc 1964; 86: 1646-7.
2. Matsuda LA, Lolait SJ, Brownstein MJ, et al. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990; 346: 561-4.
3. Rinaldi-Carmona M, Barth F, Heaulme M, et al. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 1994; 350: 240-4.
4. Arnone M, Maruani J, Chaperon F, et al. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. Psychopharmacology (Berl) 1997; 132: 104-6.

5. Ravinet Trillou C, Arnone M, DelGeorge C, et al. Anti-obesity effect of SR141716, a CB1 receptor antagonist, in diet-induced obese mice. Am J Physiol Regul Integr Comp Physiol 2003; 284: R345-R53.
6. Bensaid M, Gary-Bobo M, Esclangon A, et al. The cannabinoid CB1 receptor antagonist SR141716 increases Acrp30 mRNA expression in adipose tissue of obese fa/fa rats and in cultured adipocyte cells. Mol Pharmacol 2003; 63: 908-14.
7. Gary-Bobo M, Elachouri G, Gallas JF, et al. Rimonabant reduces obesity-associated hepatic steatosis and features of metabolic syndrome in obese Zucker fa/fa rats. Hepatology 2007; 46: 122-9.
8. Janiak P, Poirier B, Bidouard JP, et al. Blockade of cannabinoid CB1 receptors improves renal function, metabolic profile, and increased survival of obese Zucker rats. Kidney Int 2007; 72: 1345-57.
9. Chamiot-Clerc P, Duquenne C, Ludop-Maignel J, et al. Effects of rimonabant on metabolic parameters and pancreatic function in male ZDF rats: comparison with rosiglitazone. Diabetologia 2007; 50: S343 (abstract).
10. Schafer A, Pfrang J, Neumuller J, et al. The cannabinoid receptor-1 antagonist rimonabant inhibits platelet activation and reduces pro-inflammatory chemokines and leukocytes in Zucker rats. Br J Pharmacol 2008; 154: 1047-54.
11. Després JP, Golay A and Sjöström L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. N Engl J Med 2005; 353: 2121-34.
12. Pi-Sunyer FX, Aronne LJ, Heshmati HM, et al. Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. JAMA 2006; 295: 761-75.
13. Scheen AJ, Finer N, Hollander P, et al. Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomised controlled study. Lancet 2006; 368: 1660-72.
14. Van Gaal LF, Rissanen AM, Scheen AJ, et al. Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. Lancet 2005; 365: 1389-97.
15. Rosenstock J, Hollander P, Chevalier S, et al. SERENADE: the Study Evaluating Rimonabant Efficacy in Drug-naive Diabetic Patients: effects of monotherapy with rimonabant, the first selective CB1 receptor antagonist, on glycemic control, body weight, and lipid profile in drug-naive type 2 diabetes. Diabetes Care 2008; 31: 2169-76.
16. Hollander PA, Amod A and Litwak LE. Rimonabant improves glycemic control in insulin-treated type 2 diabetes: the ARPEGGIO trial. Diabetes 2008; 57: A95 (abstract).
17. Després JP, Ross R, Boka G, et al. Rimonabant reduces both intra-abdominal adiposity and liver fat and improves cardiometabolic risk factors: the ADAGIO-Lipids trial. Presented at the late breaking session of the 77th European Atherosclerosis Society meeting, Istanbul, Turkey, 2008.
18. Nissen SE, Nicholls SJ, Wolski K, et al. Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: The STRADIVARIUS randomized controlled trial. JAMA 2008; 299: 1547-60.