THE ROLE OF RIMONABANT, A CB1 RECEPTOR ANTAGONIST, IN THE TREATMENT OF OBESITY AND ASSOCIATED CARDIOMETABOLIC RISK FACTORS

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Rimonabant (SR141716) is a cannabinoid CB1 receptor antagonist showing high selectivity for the central CB1 receptor compared to the peripheral cannabinoid receptor CB2 in rat tissues and in CHO cells expressing human CB1 and CB2 receptors. It is now generally accepted that the endocannabinoid systems are involved with brain reward function. Results show that the endocannabinoids in the hypothalamus may tonically activate CB1 receptors to maintain food intake, and may increase the incentive value of food. Further evidence shows that the CB1 receptors may be involved in the motivational aspects of eating through activation of the meso-limbic system. All this evidence taken together would seem to indicate that specific CB1 antagonists like rimonabant should have some effect in body weight control and this has been confirmed in numerous pharmacological studies in different species.
Initial clinical studies with rimonabant showed that it did reduce hunger, caloric intake and body weight in obese patients. In addition, as the compound showed a very good safety profile, it was developed and advanced into long-term clinical studies for the treatment of obesity and related risk factors. In 4 large randomized Phase III Clinical trials in obese or overweight patients (RIO programme), 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 dyslipidaemia. In a follow-up clinical study, SERENADE, rimonabant was shown not only to be effective in reducing body weight but more particularly in reducing HbA1c levels in patients with type 2 diabetes who were not currently treated with any anti-diabetic medication. Global cardiometabolic risk represents the overall risk of developing type 2 diabetes and/or cardiovascular disease and is due to a cluster of modifiable risk factors including low HDL-cholesterol levels, hypertension and hyperglycaemia and emerging risk factors closely related to abdominal obesity, such as insulin resistance, high triglyceride levels, and inflammatory markers such as adiponectin. The dual role of the compound against these risk factors, essentially cardiometabolic, associated with obesity, is likely to make rimonabant a cornerstone therapy in the future management of patients with these risks.