Rimonabant

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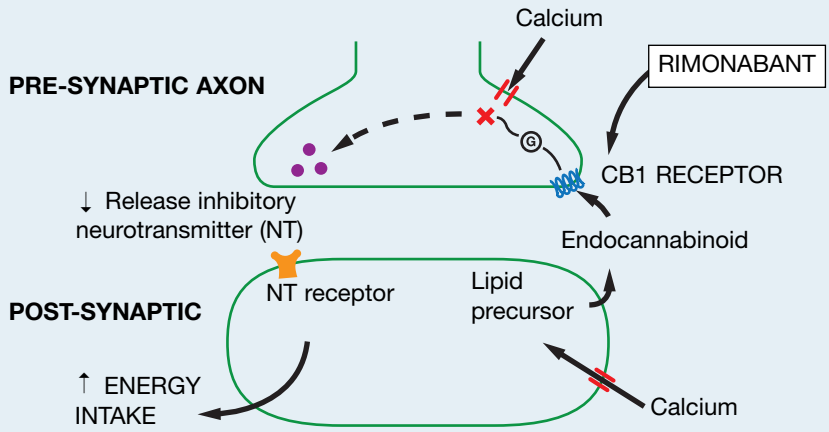
Introduction

The endocannabinoid system has been identified as a potential target for medications to encourage weight loss. Rimonabant, the first endocannabinoid antagonist to be developed, was licensed for individuals with a BMI >30kg/m^2 or BMI >27kg/m^2 plus additional risk factors for cardiovascular disease. Studies have indicated a greater weight reduction with the use of rimonabant compared with placebo. However, concerns about psychological side effects including anxiety, depression and sleep disturbance resulted in a review by the European Medicines Evaluation Agency. The marketing of rimonabant was suspended in member states in November 2008 followed by the company voluntarily withdrawing its marketing authorisation.

Figure 1. The pharmacological action of rimonabant in the brain



NOTES. Endocannabinoids are formed in a calcium dependent way from lipid precursors. They bind the G protein linked CB1 receptor which results in blocking of calcium channels and reduced intracellular calcium needed for the release of inhibitory neurotransmitters. This results in the increased activity of stimulatory neuronal activity and increased energy intake. Rimonabant antagonises at the CB1 receptor. The end result is an increase in release of inhibitory neurotransmitters, reduced stimulatory neuronal activity and satiety.

Pharmacology

Figure 1 outlines the pharmacological action of rimonabant. There are two G protein coupled cannabinoid (CB) receptors. CB1 receptors are located primarily within the brain but are also found peripherally in the liver, adipose tissue and skeletal muscle. CB2 receptors are found mostly within immune cells. Endocannabinoids (endogenous cannabinoid ligands) are derived within nerve endings where ingested polyunsaturated fatty acids are metabolised by membrane phospholipids. Activation of CB1 cannabinoid receptors sends a signal in a retrograde fashion to the hypothalamus where they regulate both orexigenic (appetite stimulating) and anorectic (appetite suppressing) mediators. When fasting, activation of this pathway will create a feeling of hunger resulting in energy intake. By blocking this pathway rimonabant causes satiety. Peripherally, rimonabant reduces lipid synthesis through blockage of cannabinoid receptors in the liver and by increasing levels of adiponectin, a hormone which down-regulates enzymes involved in lipogenesis. Additionally, the endocannabinoids are involved in both serotonergic and noradrenergic pathways within the midbrain which may explain the side effects of anxiety and depression.

Trials of safety and efficacy

A meta-analysis of the Rimonabant In Obesity (RIO) programme included safety and efficacy data from four large randomised controlled trials (RIO-Europe, RIO-Lipids, RIO-North America and RIO-Diabetes).[1] Studies ran for between 12 and 24 months. All participants were given a low calorie diet and were randomised to placebo, rimonabant 5mg/day or rimonabant 20mg/day. All studies reported a greater weight reduction compared with placebo (mean 4.7kg; p<0.0001) and those on rimonabant were five times more likely to achieve a weight loss of at least 10% (p<0.0001). The Hospital Anxiety and Depression score recorded every three months showed no significant difference between the depression score (standardised mean difference 0.08 [95% confidence interval, CI, -0.05–0.21]) in those individuals taking rimonabant compared with placebo but there was an increase in the anxiety score (0.18 [95% CI 0.07–0.28]). Individuals on rimonabant, and particularly the 20mg/day dose, reported more side effects (odds ratio 1.35 [95% CI 1.13–1.60]) including irritability, stress, insomnia, panic attacks and nightmares. Patients on rimonabant were also more likely to suffer serious adverse events than those on placebo (148 [5.9%] *vs* 67 [4.2%] respectively), and were 2.5 times more likely to withdraw from the study due to depressive illness

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(74 [3.0%] *vs* 22 [1.4%]; p=0.01; odds ratio =2.5 [1.2–5.1]). From the whole database (227 studies) two deaths from suicide have been reported in patients on rimonabant (one on 5mg/day and one on 20mg/day).

Specific evidence for use in diabetes

The RIO-Diabetes study randomised 692 patients with type 2 diabetes on metformin or sulphonylurea with inadequate glucose control (HbA_{1c} of between 6.5% and 10%) with one-year follow up.[2] All patients were given a low calorie diet and advice about physical exercise. The mean change in weight loss, the primary endpoint, was higher in the rimonabant group compared with placebo (change from baseline -1.4kg placebo group, -2.3kg rimonabant 5mg/day, -5.3kg rimonabant 20mg/day; p-value <0.0001 20mg *vs* placebo). HbA_{1c} followed a similar pattern (0.1% placebo group, -0.1% rimonabant 5mg/day, -0.6% rimonabant 20mg; p-value <0.0001 20mg *vs* placebo). The change in HbA_{1c} from baseline was not affected by the type of oral hypoglycaemic. Statistical analysis found that the change in HbA_{1c} was twice that which would be expected by the effect of weight loss alone, suggesting an independent mechanism on glucose haemostasis. Other secondary endpoints including increased HDL cholesterol and lower triglycerides were seen for patients on rimonabant. Adverse events were reported more commonly in those on rimonabant, including nausea, dizziness, diarrhoea, fatigue and anxiety. Discontinuation due to adverse events was greater in those on rimonabant, particularly those on the higher dose (5% placebo group, 8% rimonabant 5mg/day, 15% rimonabant 20mg/day). A slight increase in the Hospital Anxiety and Depression score was noted in the rimonabant group (change from baseline -0.2 with placebo *vs* 0.3 with rimonabant 20mg/day) but no serious adverse events due to psychiatric conditions were reported. A greater improvement in self-esteem was reported in the 20mg/day rimonabant group (p-value 0.004) which is most likely due to weight loss.

The SERENADE study assessed the efficacy of rimonabant as a single agent to control blood glucose levels in type 2 diabetes.[3] A total of 281 patients with type 2 diabetes for between two months and three years and not on medication were given dietary advice and randomised to placebo or 20mg/day rimonabant. Patients with a history of depression were not excluded. Reduction in HbA_{1c}, the primary endpoint, was greater in the treatment group than in the placebo group (-0.8% *vs* -0.3% respectively; p=0.0002). This effect was more pronounced in those with a baseline HbA_{1c} of >8.5% (-1.9% *vs* -0.7%). In addition, at the end of the study more patients in the treatment group had achieved an HbA_{1c} level of <7% (51% *vs* 35%). Twenty-nine of the patients treated with rimonabant who were not overweight had a mean decrease in HbA_{1c} of -0.78% despite a minimal weight loss of 0.53kg. Weight loss was greater in the rimonabant group in keeping with the RIO studies (-6.7kg rimonabant 20mg/day *vs* -2.8kg placebo at six months). Rimonabant treatment was associated with a reduction in non-HDL cholesterol and triglycerides as well as an increase in HDL cholesterol. Total cholesterol and LDL cholesterol levels were unaltered. More patients in the rimonabant group dropped out compared with placebo (27 *vs* 15 respectively). Using a psychiatric questionnaire, patients on rimonabant had a higher rate of anxiety (eight [5.8%] *vs* five [3.6%]) and depressed mood (eight [5.8%] *vs* one [0.7%]), but depression was reported more in the placebo group (2.9% *vs* 1.4%). One patient in the rimonabant group expressed suicidal ideation.

Discussion

Treatment with rimonabant causes a significantly greater reduction in weight compared with placebo with additional beneficial effects on secondary endpoints like HbA_{1c} and lipid profile. However, more patients reported adverse events on rimonabant and the drop out rate was higher. Despite most studies excluding patients with depression there was still an increase in the prevalence of anxiety and depression in the rimonabant treated groups although only a few participants reported serious psychological side effects or suicide attempts. This safety concern was enough to result in the withdrawal of rimonabant from the market. The history of rimonabant demonstrates the importance of post-marketing surveillance in picking up safety concerns for drugs which might not be immediately apparent during the development process. The endocannabinoid system remains a potential target for the development of drugs to treat obesity, but developing any such drug will be difficult because of the need to demonstrate absolute safety.

Key points

- The endocannabinoid system is a target for the development of drugs used to treat obesity
- The first endocannabinoid receptor antagonist, rimonabant, showed good clinical efficacy for weight loss and some secondary endpoints particularly relevant to patients with diabetes, such as improved HbA_{1c} and lipid profiles
- Post-marketing surveillance of drugs that have come to the market is an important part of the drug development process as safety concerns may only come to light with more widespread use
- Rimonabant was withdrawn from use because of concerns about an increase in anxiety and depression in those treated

Conflict of interest statement

Dr Fisher has served on advisory panels for sanofi-aventis and has received lecture fees.

References

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