The endocannabinoid system: Its intervention and subsequent effects on cardiometabolic risk

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Type 2 diabetes poses a challenge in terms of targeting multiple risk factors in those with the condition, together with the necessity for serial risk factor measurements and adherence to an increasingly complicated cocktail of drugs. One promising new approach to risk factor management in type 2 diabetes is to target the endocannabinoid system. This system comprises cannabinoid receptors, the endocannabinoids themselves and the enzymes catalysing their biosynthesis and degradation (Di Marzo and Matias, 2005). In this article the author discusses the endocannabinoid system in the context of a recently licensed drug that inhibits a specific cannabinoid receptor.

The two major endocannabinoids are anandamide and 2-arachidonylglycerol, both of which are derivatives of arachidonic acid (Di Marzo and Matias, 2005). They are not confined to the central nervous system and act in many tissues (such as the liver, muscles and gastrointestinal tissue) to maintain the cells' physiological homeostasis (Di Marzo and Matias, 2005). In the central nervous system the endocannabinoids play a major role in the regulation of appetite by blocking cannabinoid-1 (CB1) receptors in the hypothalamus and nucleus accumbens, which increases the feeling of satiety.

Rimonabant is the first drug to act upon this system and is currently licensed in the UK for use as an adjunct to diet and exercise for the treatment of obesity in people with a BMI ≥30 kg/m^2 or overweight people (with a BMI ≥27 kg/m^2) who have associated cardiovascular risk factors (such as type 2 diabetes or dyslipidaemia). However, it must be noted that only part of the reduction of body weight and overall fat mass affected by CB1 antagonists is due to anorectic action. CB1 antagonists also counteract the peripheral effect of endocannabinoids on lipogenesis and fat accumulation (Di Marzo and Matias, 2005). Inhibition of the CB1 receptor in adipocytes causes an increase in adiponectin levels (an adipokine negatively correlated with increased BMI and visceral fat), which therefore reduces the expression of enzymes involved in lipogenesis. Stimulation of CB1 receptors in the liver increases fatty acid biosynthesis, and this may be another important area where receptor blockade can reduce fat accumulation. (*Figure 1* illustrates the many systems that the endocannabinoid system acts upon.)

According to Di Marzo and Matias (2005) the

Article points

1. Endocannabinoids play a major role in the regulation of food intake.
2. The RIO-Diabetes study consisted of over 1000 overweight or obese patients with type 2 diabetes and an HbA_{1c} level of 6.5–10 % already on treatment randomised to either placebo or rimonabant and followed for a year.
3. Rimonabant produced statistically significant reductions in waist circumference, HbA_{1c} and triglycerides, with statistically significant improvement in high-density lipoprotein-cholesterol levels.

Key words

- The endocannabinoid system
- Weight loss
- HbA_{1c} reduction

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net effects of the central and peripheral actions of blocking the CB1 receptor with rimonabant are:

- reduced food intake and weight loss
- reduced fat mass relative to skeletal muscle mass
- improved cardiometabolic risk factor profile: reduced waist circumference, reduced triglycerides, raised HDL cholesterol and reduced HbA_{1c} levels.

Questions to consider regarding this system include the following.

- How does this novel action of blocking the CB1 receptor translate into clinical practice?
- Will there be a meaningful reduction of weight and improvement in cardiometabolic risk factors in patients with type 2 diabetes?

The Rimonabant In Obesity (RIO)-Diabetes study (Scheen et al, 2006a) was designed to address these questions (*Table 1* illustrates changes in some of the risk factors that the study authors analysed).

The RIO-Diabetes study

The study population included 1047 overweight or obese people who had type 2 diabetes (BMI 27–40 kg/m^2), an HbA_{1c} level of 6.5–10% and were already receiving metformin or sulphonylurea monotherapy. The individuals were given a hypocaloric diet, advice on increasing physical exercise and randomly assigned placebo or rimonabant 5 mg or 20 mg daily. The primary endpoint was weight change from baseline after one year of treatment.

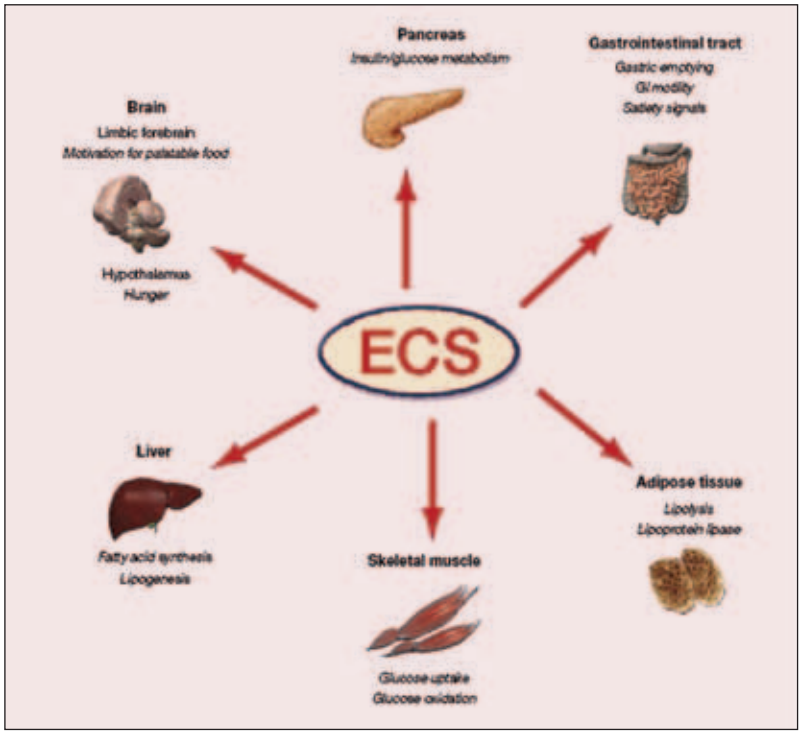

Figure 1. The effect of the endocannabinoid system (ECS) on body tissues. (Cota et al, 2003; Liu et al, 2005; Matias et al, 2006; Osei-Hyiaman, 2005; Pagotto and Pasquali, 2005).

Safety and tolerability

The licensed dosage for rimonabant is 20 mg. Rimonabant was generally well tolerated but the incidence of adverse events – mainly depressed mood disorders, nausea and dizziness – was slightly greater in the 20 mg rimonabant group. Hospital Anxiety and Depression (HAD) scores were, however, much the same across the three treatment groups and the trend towards slight increases in HAD scores with rimonabant 20 mg/day was considered marginal. No serious adverse events were linked to psychiatric disorders. Those with severe psychiatric illness or those taking antidepressants were excluded from the trial and remain a group within which the safety of rimonabant has yet to be determined.

Impact on clinical practice

Weight gain is a continual challenge for healthcare professionals managing people with type 2 diabetes as some of the treatments themselves can cause weight gain (UKPDS Group, 1998). The action of rimonabant on reducing weight, waist circumference and HbA_{1c} levels, together with a positive effect on dyslipidaemia, confirms the findings from other studies with rimonabant in people without diabetes (Despres et al, 2005, Pi-Sunyer et al, 2006). Particularly important are the changes in food behaviour: a decreased desire for high-fat foods and sugary snacks was observed (assessed using a visual analogue scale within the RIO trial protocol).

In the UK Prospective Diabetes Study (UKPDS), a 0.9% reduction in levels of HbA_{1c} resulted in a 25% reduction in the risk of microvascular complications and a 16% reduction in combined fatal and non-fatal myocardial infarction (UKPDS Group, 1998). From a general practice viewpoint, a net reduction of 0.7% in HbA_{1c} could be beneficial in achieving Quality and Outcomes Framework targets. Significantly more of the study participants in

Page points

1. Any reduction in HbA_{1c} is associated with reduced risk of vascular complications associated with diabetes.
2. Rimonabant is currently indicated for the treatment of obese or overweight patients.
3. The role of the endocannabinoid system, particularly in lipid metabolism, needs further research.

the 20 mg treatment group achieved an HbA_{1c} of <7% (mean baseline HbA_{1c} for this group was 7.5%). The improvements in dyslipidaemia seen with rimonabant in this study complement the cardiovascular risk reduction consequent to reducing abdominal obesity and HbA_{1c}. In the UKPDS a low level of HDL cholesterol was found to be the second most important risk factor for developing coronary artery disease in patients with type 2 diabetes, after LDL cholesterol levels (Turner et al, 1998). Reduced HDL cholesterol and raised triglyceride levels are constituents of metabolic syndrome. The IDF definition of metabolic syndrome details abdominal obesity as a prerequisite risk factor for the syndrome and emphasises the importance of targeting abdominal obesity, which is independently associated with each of the other metabolic syndrome components (International Diabetes Federation, 2005). Participants treated with rimonabant in this study had improvements in all of the components of metabolic syndrome (see *Table 1* for data); however, although there was a significant reduction in supine systolic blood pressure with 20 mg rimonabant daily, there was no significant reduction in supine diastolic blood pressure.

Conclusions

Will RIO-Diabetes alter clinical practice? It may do. Certainly, addressing abdominal obesity must now become a key focus and few will deny that dyslipidaemia in diabetes is also a major target for intervention. Rimonabant is a new therapeutic agent and data from RIO-Diabetes have shown it to have the ability to target cardiometabolic risk factors in people with type 2 diabetes. Although RIO-Diabetes was only a year-long study, we can expect longer-term data to be published in the future. It is encouraging that rimonabant can change eating behaviour by reducing appetite and decreasing the desire for high-fat foods: an essential process in sustaining weight loss.

Rimonabant is currently indicated for the treatment of obese or overweight people with associated risk factors such as type 2 diabetes and dyslipidaemia (Joint Formulary Committee, 2006). RIO-Diabetes has confirmed its benefits for people with type 2 diabetes. It is in targeting cardiometabolic risk that the role of the endocannabinoid system, particularly in lipid metabolism, needs further research to allow us to harness the full potential of intervening in its processes. ■

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Table 1. Changes in weight and other risk factors in the RIO-Diabetes (data are mean [SD] or n (%). Adapted from Scheen et al, 2006a.

	Placebo	20 mg/day rimonabant	*P* value
Weight			
Number of people with data at last visit	345	336	
Change from baseline (kg)	-1.4 (3.6)	-5.3 (5.2)	<0.0001
≥5 % weight loss	50 (14.5 %)	166 (49.4 %)	<0.0001
>10 % weight loss	7 (2.0 %)	55 (16.4 %)	<0.0001
Waist circumference			
Number of people with data at last visit	344	336	
Change from baseline (cm)	-1.9 (5.5)	-5.2 (6.1)	<0.0001
HbA_{1c}			
Number of people with data at last visit	317	315	
Change from baseline (%; mean 7.3 %)	0.1 (1.0)	-0.6 (0.8)	<0.0001
*Change in people with HbA_{1c} ≥8.0 % (%)	-0.3	-1.1	≤0.001
People who achieved target of <6.5 %	66 (21 %)	135 (43 %)	<0.0001
People who achieved target of <7 %	151 (48 %)	214 (68 %)	<0.0001
Fasting insulin			
Number of people with data at last visit	314	311	
Change from baseline (μIU/ml)	0.4 (14.8)	-0.7 (9.9)	0.25
HDL cholesterol			
Number of people with data at last visit	314	318	
Change from baseline (mmol/l)	7.1 % (13.5)	15.4 % (17.4)	<0.0001
Triglycerides			
Number of people with data at last visit	314	317	
Change from baseline (mmol/l)	7.3 % (43.0)	-9.1 % (44.3)	<0.0001
Supine systolic blood pressure			
Number of people with data at last visit	345	336	
Change from baseline (mmHg)	1.6 (13.2)	-0.8 (12.8)	0.02
Supine diastolic blood pressure			
Number of people with data at last visit	345	336	
Change from baseline (mmHg)	-0.7 (8.4)	-1.9 (8.2)	0.06
High-sensitivity C-reactive protein			
Number of people with data at last visit	308	313	
Change from baseline (mg/l)	-0.0 (10.0)	-1.4 (5.2)	0.02
Leptin			
Number of people with data at last visit	290	294	
Change from baseline (ng/ml)	3.1 (7.5)	-0.3 (6.0)	<0.0001

**Taken from sub-set analysis of patients having HbA_{1c} of ≥ 8.0 % (from Scheen et al, 2006b).*