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Ms S Busbridge
East Kent Research Ethics Committee
c/o South East Coast Strategic Health
Authority
Preston Hall
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Dear Ms Busbridge

RE: 07/Q1803/1 "The effect of rimonabant on energy expenditure, fat metabolism and body composition"

I enclose the final research report for this study. I apologise for the delay in providing this.

Yours sincerely

Professor Margot Umpleby
Head of Diabetes and Endocrinology

Final Report

07/Q1803/1 The effect of rimonabant on energy expenditure, fatty acid metabolism, triacylglycerol metabolism and body fat distribution

Aims: Although the CB1 antagonist rimonabant has been shown to reduce food intake in diet induced obese mice, the effect was transient, yet a decrease in body weight was prolonged suggesting an effect on energy expenditure (1). The aim of this study was to determine if, when energy intake is maintained at pre-treatment levels in obese subjects, rimonabant still induces weight loss due to effects on energy expenditure. Clinical trials with rimonabant have shown treatment decreased plasma triglycerides, adiponectin and improved insulin sensitivity (2). However the studies did not include a control group with matched weight loss, so these effects may have been a consequence of weight loss rather than a direct effect of rimonabant. The current study investigated whether in a dietary intervention group, matched for weight loss in the rimonabant treated group, changes insulin sensitivity, triglyceride and fatty metabolism were different from the rimonabant treated group. In addition measurements of muscle and adipose tissue gene expression, whole body fat distribution, intrahepatocellular lipid and intramyocellular lipid were made. Mid-way through the study the European Medicines Agency withdrew marketing authorisation for rimonabant, Sanofi-Aventis subsequently withdrew rimonabant from the market and the study was terminated prematurely.

Results: Studies were completed in 14 obese (BMI, 33.0±1.9 kg/m2; body weight, 86.6±6.7kg) (mean±SD) post-menopausal women (57.8±4.7y) randomised into two groups with seven in each group. Depression, measured with the Becks depression score did not change during treatment in the rimonabant group. The study showed that when post-menopausal obese women were treated with rimonabant for 12 weeks with daily energy intake maintained throughout this period, they lost 2.6±0.5 kg (mean±SEM) in weight with a 3.7±1.4 cm reduction in waist circumference. In the age and BMI matched group who followed a dietary intervention to achieve the same weight loss (3.1±1.0 kg) there was a similar reduction in waist circumference (3.5±2.5 cm). In the diet group there was a decrease in resting energy expenditure (REE) from 1453±76 to 1386±76 kcals/day ($p=0.055$) as would be predicted with weight loss but this was not found in the rimonabant group (1434±59 to 1436±50 kcals/day) suggesting rimonabant influences energy expenditure. Activity energy expenditure (AEE) measured with an Actiheart monitor over a 5 day period before and after treatment decreased by 57kcal/d in the diet group, although this did achieve statistical significance. There was no change in AEE in the rimonabant group.

In the diet group the reduction in energy intake was due to a decrease in fat intake, mainly saturated and monounsaturated fatty acids, and carbohydrate intake. There was a similar decrease in total fat mass in both groups, although this did not achieve statistical significance. Intrahepatocellular lipid and intramyocellular lipid did not change significantly in either group. Insulin sensitivity measured as glucose infusion rate increased in both groups after the intervention but was not different between groups. There was a significant decrease in adiponectin in the diet group but no change in the rimonabant group. Leptin decreased significantly in both groups ($p<0.01$).

Plasma triglyceride (TG) decreased in the diet group ($p<0.02$) but showed no change in the rimonabant group. In the diet group very low density lipoprotein 1 (VLDL1) TG tended to decrease ($p=0.07$) as did VLDL1 absolute secretion rate ($p=0.06$). In the rimonabant group although there was no change in VLDL1 TG, VLDL1 absolute secretion rate tended to increase ($p=0.06$) and the change between the 2 groups in VLDL1 TG and absolute secretion rate was significant ($p=0.02$, $p=0.007$ respectively). VLDL1 fractional catabolic rate, VLDL2 TG concentration, fractional catabolic rate and absolute secretion rate did not change in either group.

Palmitate production rate (a measure of lipolysis) and palmitate metabolic clearance rate increased following treatment with rimonabant ($p<0.05$, $p<0.05$ respectively) with no change in the concentrations of plasma FFA, palmitate, glycerol or β hydroxybutyrate. There was no change in these measurements in the diet group.

Palmitate oxidation rate increased in the rimonabant group (p=0.05) and decreased in the diet group (p=0.06) with a significant difference in the change in palmitate oxidation rate between groups (p=0.008).

Discussion: This study found that treatment, of a small group of post-menopausal women, with rimonabant for 12 weeks with daily energy intake maintained at pre-treatment levels throughout, resulted in weight loss suggesting that rimonabant can increase energy expenditure in humans as has been shown previously in rodents (1). The mechanism may be related to an increase in fatty acid oxidation since palmitate oxidation was increased. This also confirms previous animal studies (1,3).

In the BMI matched group who followed a dietary intervention to achieve the same weight loss there was a decrease in resting energy expenditure which was not found in the rimonabant group. REE is approximately 60% of total energy expenditure. Non resting energy expenditure accounts for the remaining 30% of total energy expenditure (TEE). Leibel et al (4) showed that weight loss of 10% in obese subjects was associated with a decrease in total energy expenditure (TEE) of 8kcal/d/kg fat free mass. Approximately half the decrease in TEE was due to a decrease in REE and half to a decrease in non resting EE. Using these figures the weight loss in the diet group would be expected to be associated with a decrease in TEE of 120kcal/d. The mean decrease in REE of 67kcal/d is in line with the findings of Leibel et al (4). It would be expected that the remaining decrease in EE would be accounted for by a decrease in non resting energy expenditure. Non resting energy expenditure measured with an Actiheart monitor over a 5 day period decreased by 57kcal/d in the diet group. The decrease in the sum of REE and AEE is very similar to that found by Leibel et al (4).

While the maintenance of REE and AEE in the rimonabant group (approximately 100kcal/d) accounts for some of the decrease in weight, it is insufficient to account for all of it. A weight loss of 1kg (part fat and part lean body mass requires a loss of 7,000kcal (5). This equates to 200 kcal/day in the rimonabant group. The extra energy expenditure could be due to an increase in the thermic effect of feeding, which accounts for approximately 10% of TEE, but was not measured in this study and/or activity energy expenditure not measured with the Actiheart monitor. This monitor will not detect small movements such as fidgeting-like activities at low work loads (unpublished data). Levine et al has shown that these movements at very low work intensities are associated with substantial increases in energy expenditure and may contribute substantively to energy balance (6).

A decrease in VLDL secretion rate with weight loss has been described previously (7). The increase in VLDL1 secretion rate with rimonabant was unexpected. Since only 50% of the increase in palmitic acid production rate was accounted for by an increased rate of oxidation this could be explained by an increased delivery of fatty acids to the liver resulting in increased TG synthesis and export.

This study demonstrates that rimonabant can cause weight loss when energy intake is maintained and that this is in part due to an increase in fatty acid oxidation. The study highlights the need to develop endocannabinoid antagonists which specifically target the peripheral system since these could be effective at reducing weight by increasing energy expenditure rather than reduced appetite, which may have less central side effects.

References

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2. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J; RIO-North America Study Group. 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 Feb 15;295(7):761-75.
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development of diet-induced steatosis, dyslipidemia, and insulin and leptin resistance in mice. *J Clin Invest.* 2008;118:3160-9.
4. Liebel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *New Engl J Med* 1996; 332: 621-628.
5. Kahn CR, Weir GC King GL, Jacobson AM, Moses AC, Smith RJ. Joslins diabetes mellitus 14th ed. 2005 Lippincott Williams & Wilkins
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Publications/presentations

Presentations at the 3rd International Congress on Prediabetes and Metabolic Syndrome, Nice 2009

Sarac I, Backhouse K, Shojaee-Moradie F, Robertson D, Frost G, Bell J, Russell-Jones D, Umpleby AM. The effects of rimonabant on insulin sensitivity and plasma lipid levels in comparison with a hypocaloric diet

Backhouse K, Sarac I, Shojaee-Moradie F, Robertson D, Frost G, Bell J, Russell-Jones D, Umpleby AM. Rimonabant causes weight loss when daily energy intake is maintained at pre-treatment levels.

A full paper has been written and is currently being reviewed by all authors. It is expected that this will be submitted within the next month.

Information for participants

All participants were informed about the findings of the study. The information sheet is enclosed.