COMPARISON OF THE EFFECTS OF RIMONABANT, SIBUTRAMINE AND ORLISTAT ON ACUTE FOOD INTAKE AND IN A MODEL OF DIETARY-INDUCED OBESITY IN THE MOUSE

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Figure 1. Effect of acute oral sibutramine, rimonabant and orlistat on mash intake in mice

Table 1. Effect of weight-loss evoked by chronic sibutramine, rimonabant and orlistat treatment on plasma indices of obesity-related risk factors

**REFERENCES**

1. Dickinson et al. (2001) Physiol Behav. 74(4-5) 425-433

**SUMMARY AND CONCLUSIONS**

- Sibutramine and rimonabant, but not the lipase inhibitor, orlistat, reduce mouse food intake after acute administration.
- Chronic administration of sibutramine, rimonabant and orlistat significantly reduced the body weight of obese mice towards lean control values. In addition, plasma leptin, cholesterol, NEFAs and glycerol were reduced after drug administration.

Body composition analysis revealed that all drug treatments significantly reduced percentage fat. 95% of the weight loss observed in each of the drug treatment groups was attributable to a change in carcass fat.

In conclusion, sibutramine, rimonabant and orlistat reduce body weight in a mouse model of obesity and these effects are attributable to reduced body fat.

**METHODS**

Male C57BL/6J mice (Charles River UK) weighed 20 – 25g on arrival. In the acute food intake studies, individually housed animals were habituated for two weeks to a daily 4 hour presentation of wet mash in a dish on the cage floor. On test days, rimonabant (1, 3, 10, 30 mg/kg po), sibutramine (1, 3, 10, 30 mg/kg po) or orlistat (10, 20, 40, 80 mg/kg po) were administered 60 minutes prior to wet mash presentation. Consumption was measured at 1, 2, and 4 hours. Compounds were tested in the same mice with weekly intervals between successive drug treatments.

In the DIO mouse studies, group housed animals (n=8) were allowed ad libitum access to either a high fat diet (D12451: fat = 45% total kcal, Research Diets, New Jersey) or a standard diet (D12450B: fat = 10% total kcal) for a 16 week period. After a 7 day run-in period when all animals were given vehicle po, mice were randomized to 28 days with one of the following: vehicle (qd), rimonabant (20 mg/kg qd), sibutramine (20 mg/kg qd for week 1 and then 5 mg/kg qd), vehicle (bid) or orlistat (40 mg/kg bid).

At the study conclusion, plasma levels of various obesity-related parameters were measured. Body composition was determined by chemical analysis to assess whether drug-induced weight loss was due to changes in body fat. Briefly, carcass water was determined by freeze-drying the carcass to constant weight. The carcass was then ground using a Buchi B400 homogeniser. All remaining analysis was on the freeze-dried samples. Carcass fat, protein and ash were determined as previously described.

**RESULTS**

In the acute feeding studies, both rimonabant and sibutramine dose-dependently inhibited wet mash intake over the 4 hour period. Consistent with its pharmacological mechanism, orlistat did not affect food consumption when given acutely. Fig 1 illustrates the effects of these treatments on food intake in the first hour of the test. When administered chronically to the DIO mice, rimonabant (15.7%), sibutramine (7.5%) and orlistat (12.8%) all produced a significant reduction in body weight, compared with baseline values (Fig 2). At the study conclusion, DIO animals exhibited elevated plasma glucose, leptin, cholesterol, glycerol and non-esterified fatty acids (NEFAs) compared to lean controls. Although the magnitude of effect depended on drug treatment, the test compounds tended to reduce levels of these parameters towards those of lean controls (see Table 1).

Body composition analysis revealed that all drug treatments significantly reduced percentage body fat (see Fig. 3). 95% of the weight difference of the experimental groups from vehicle is attributable to a change in carcass fat.