**Effect of the MCH1 antagonist, GW803430, on body weight, food and water intake, glucose tolerance, fat pad weight, ex vivo binding and various plasma parameters in dietary-induced obese C57BL/6J mice**

**S.C. CHEETHAM1, K. DICKINSON1, S. GODDARD1, P. GUZZO2, M. RENA2, M. VICKERS1**

RenaSci Consultancy Ltd, Nottingham, NG1 1GF, U.K. AMRI2, NY 12203, USA.

**INTRODUCTION**

Melanin-concentrating hormone (MCH) is a nineteen amino acid cyclic neuropeptide derived from pre-pro-MCH (Naton, 1994). Two human MCH receptors have now been identified, MCH1, (SLC1-1) and MCH2 (Chambers et al., 1999; Satoh et al., 1999; Hill et al., 2001). There is a considerable body of evidence indicating a role for MCH in the control of food intake and energy balance: icv administration of MCH to rats increases food intake (Gu et al., 1996); MCH mRNA is overexpressed in ob/ob mice and fasted mice (Qi et al., 1996); MCH overexpressing mice are hypertrophic, mildly obese, hyperglycaemic and insulin resistant (Ludwig et al., 2001); MCH knockout mice are leaner than wild-type mice due to hypophagia and increased metabolic rate (Shimada et al., 1998). The MCH1 receptor appears to mediate the orexigenic effects of MCH (Chambers et al., 1999). Numerous MCH receptor antagonists for the potential treatment of obesity have appeared in recent years with at least two compounds entering clinical development (Menendez-Andino and Wos, 2001). This study has evaluated the effects of chronic administration of the MCH1 antagonist, GW803430 (Hertzog et al., 2006) on body weight, food and water intake, glucose tolerance, fat pad weight, body composition, ex vivo binding and plasma levels of various metabolic parameters in dietary induced obese (DIO) C57BL/6J mice.

**METHODS**

Male C57BL/6J mice (4-6 weeks; Harlan UK Ltd) were group housed (2 mice per cage) in polycarbonate cages with free access to high fat diet (D12415: 45% kcal derived from fat; Research Diets USA) and tap water at all times (214±4°C; 55±20% humidity; normal phase 12-light dark cycle). Animals were singly housed on a reverse phase light-dark cycle at week 14 for a 2 week period. After a 7 day baseline run-in period when all animals were given vehicle once per day orally, mice were subsequently dosed for 32 days with GW803430 (1, 3 or 10 mg/kg, po) or sibutramine (20 mg/kg, po). Food intake, water intake and body weight were recorded daily. On day 28, mice were fasted at 16:00h and on Day 29 animals underwent an oral glucose tolerance test (OGTT). Each mouse was given vehicle, GW803430 or sibutramine and 60 minutes later was administered D-glucose (2g/kg, po). A blood sample was taken immediately before the glucose load and 15, 30 and 60 minutes post-glucose from the tail vein into lithium heparin tubes (Starstedt Micravette CB300) and plasma separated by centrifugation. Plasma samples were frozen and subsequently thawed for assay of glucose and insulin. At the end of the OGTT food was returned to the animals and dosing continued until Day 32. On the Day 33 after final body weight, food and water intake readings five animals from each group were dosed and killed by rising CO2 to minimise any fluid loss 6 h after dosing. The remaining five animals were killed 24 h after the final dose on Day 32. Terminal blood samples were taken by cardiac puncture using EDTA coated tubes. Plasma was then separated by centrifugation and stored at -78°C until assayed for glucose, insulin, lepin, triglycerides (gycerol and triacylglycerol), NEFA and total cholesterol using commercially available kits and protocols. All tissues were excised and coronal sections containing the caudal cerebellum and striatum containing the MCH1 receptors was determined as described in Viggers et al., this meeting. Retroperitoneal and epididymal fat pads were removed, weighed and then returned to the carcasses which were stored at -20°C for body composition analysis. Body fat, protein, water and ash levels of the carcasses were determined using standard chemical analysis techniques (Dickinson et al., 2001).

**RESULTS**

GW803430 (1, 3 and 10 mg/kg, po) and sibutramine (20 mg/kg, po) dosed for 32 days significantly reduced the body weight of DIO mice by 12.5%, 13.2%, 16.0% and 8.5%, respectively, compared to vehicle treated controls (Fig 1). GW803430 and sibutramine produced significant effects on food intake but the pattern of effects were different. GW803430 significantly decreased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatment. In contrast, GW803430 and sibutramine had no significant effect on water intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 2 (by 16%) and 3 (by 10%). Neither compound altered this parameter during week 4 (Fig 2). GW803430 had no significant effect on water intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1 (by 30%) and increased average weekly food intake during weeks 2 (by 16%) and 3 (by 10%) during week 1). Neither compound altered this parameter during week 4 (Fig 2). GW803430 had no significant effect on water intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine significantly decreased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine had no significant effect on food intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine had no significant effect on food intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine had no significant effect on food intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine had no significant effect on food intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine had no significant effect on food intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments. In contrast, GW803430 and sibutramine had no significant effect on food intake whereas after an initial decrease GW803430 increased average weekly food intake during weeks 1, 2 and 3 (by 16%, 10% and 13%, 1 mg/kg, 19%, 12% and 8% 3 mg/kg, 27%, 10% and 12%, 10 mg/kg, respectively) compared to vehicle treatments.

**SUMMARY**

In conclusion, GW803430 significantly decreased body weight in a mouse model of obesity. These effects were predominantly due to a reduction in body fat. Improvements in insulin sensitivity, as measured in an OGTT, and changes in terminal plasma parameters, were generally commensurate with the weight loss.

**REFERENCES**


Viggers et al. This meeting. Poster number (584.27/SS8).


