

# Pharmacology of AMR-MCH-18, an antagonist of the MCH<sub>1</sub> receptor for the treatment of obesity

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## INTRODUCTION

Obesity is a growing concern for public health in industrialized nations across the globe. In the United States alone, over 60% of the population is overweight and over 30% of these people are obese.<sup>1</sup> Obesity is associated with a variety of comorbidities such as diabetes, dyslipidemia, coronary heart disease, stroke and certain cancers.<sup>2</sup> Current pharmaceutical treatments suffer from weak efficacy and significant side effects that limit their use. Therefore, a major need exists for safer, more effective weight loss agents.

Melanin concentrating hormone (MCH) is a cyclic, 19 amino acid neuropeptide expressed in the zona incerta and lateral hypothalamus that regulates food intake and body weight.<sup>3</sup> Antagonism of the MCH<sub>1</sub> receptor has been shown to be a promising new approach for the treatment of obesity.<sup>4</sup>

AMR-MCH-18 is representative of a novel structural class of selective, high affinity MCH<sub>1</sub> receptor antagonists identified by AMRI. The in vitro and in vivo properties of AMR-MCH-18 are presented.

## METHODS and RESULTS

The affinity of AMR-MCH-18 for the MCH<sub>1</sub> receptor (Fig. 1) was determined using a binding assay with [<sup>3</sup>H]AMR-MCH-1 and cloned human MCH<sub>1</sub> receptors.<sup>5</sup> A panel of more than 80 GPCRs, ion channels and cytochrome P450s was used to demonstrate the selectivity of AMR-MCH-18 for the MCH<sub>1</sub> receptor. Selectivity against the hERG potassium channel was established using a mini-patch clamp assay.

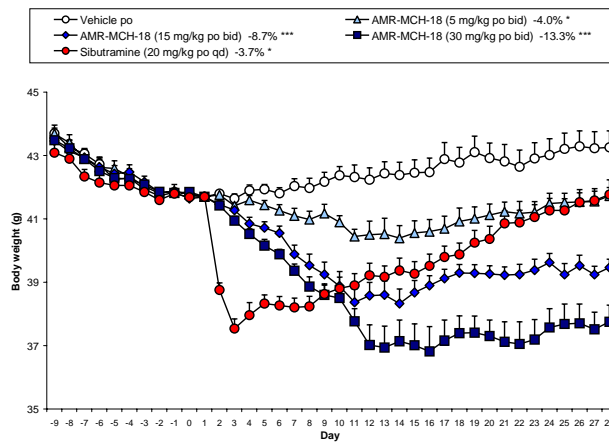
The in vivo efficacy of AMR-MCH-18 was demonstrated in a chronic, 28-day feeding study with male dietary-induced obese (DIO) C57BL/6J mice (Fig. 2). The mice were group housed and given free access to a high fat diet (D12451 45% of Kcal derived from fat; Research Diets, New Jersey, USA) and tap water for 14 weeks to induce obesity. At the end of the 14 week period, the animals were singly housed for an additional two week period and placed on reverse phase lighting (lights off for 8 h from 09:30 – 17:30 h). After a 14-day baseline run in period with bi-daily oral vehicle dosing, animals were treated with AMR-MCH-18 twice daily (at 08:45 h and 14:45 h) by oral gavage at doses of 5 mg/kg, 15 mg/kg and 30 mg/kg. Changes in body weight and food intake were compared to positive control sibutramine. Unlike sibutramine, which showed rapid onset of weight loss followed by significant weight gain, AMR-MCH-18 was characterized by gradual weight loss that was maintained throughout the course of the four week study. Measurement of food intake showed a sustained reduction in the groups treated with AMR-MCH-18 (15 mg/kg and 30 mg/kg) (Fig. 3). In contrast, sibutramine reduced food intake in the first week, and then increased food consumption in weeks two through four. An oral glucose tolerance test on days 29 and 30 showed improvements in insulin sensitivity and glucose tolerance (Fig. 4). Following termination, analysis of body composition (water, fat, protein and ash content) demonstrated that the weight loss caused by AMR-MCH-18 was associated with selective reduction in fat mass (Fig. 5). Analysis of terminal plasma samples revealed significant improvement in plasma leptin levels concomitant with fat loss (Fig. 6). Also following the DIO mouse study, coronal sections of the brain containing the caudate putamen were removed and used to determine the ex vivo MCH<sub>1</sub> receptor occupancy (Fig. 7).

## 1. In Vitro Profile of AMR-MCH-18

Assay	AMR-MCH-18
MCH <sub>1</sub> Binding <sup>1</sup> (K <sub>i</sub> , nM)	4.3 ± 0.9
CYP Isoform Inhibition <sup>2</sup> (IC <sub>50</sub> , μM)	>10
t <sub>1/2</sub> (HLM) <sup>3</sup> (min)	151
t <sub>1/2</sub> (MLM) <sup>4</sup> (min)	197
Receptor Selectivity Panel <sup>5</sup>	80 receptors evaluated Dopamine Transporter, K <sub>i</sub> = 0.59 μM 5-HT Transporter K <sub>i</sub> = 0.65 μM
hERG <sup>6</sup> (IC <sub>50</sub> , μM)	31 ± 8

<sup>1</sup>Human receptor; <sup>2</sup>CYP isoforms tested, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4; <sup>3</sup>HLM = Human Liver Microsomes; <sup>4</sup>MLM = Mouse Liver Microsomes; <sup>5</sup>Panel of 80 receptors, including GPCRs, ion channels tested at 1 μM; <sup>6</sup>Mini patch clamp.

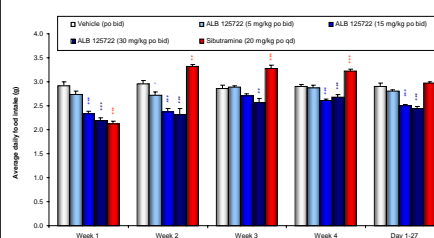
## 2. Effect of Chronic Administration of AMR-MCH-18 on Body Weight in Male C57BL/6J DIO Mice



Data are adjusted means (n = 9-10). SEMs are calculated from the residuals of the statistical model. Data analysed by ANCOVA with body weight on Day 1 as covariate. On Day 28, animals were split into two cohorts and underwent an oral glucose tolerance test. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

• AMR-MCH-18 caused weight loss of 4.0%, 8.7% and 13.3% at 5, 15 and 30 mg/kg bid, respectively.

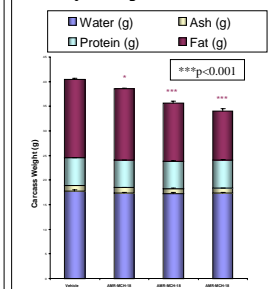
## 3. Effect of AMR-MCH-18 on Food Intake



Data are adjusted means (n = 10). SEMs are calculated from the residuals of the statistical model. Data analysed by ANCOVA with body weight on Day 1 as covariate. Multiple comparisons against the vehicle group are by Wilcoxon test (AMR-MCH-18) and multiple t-test (sibutramine). \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

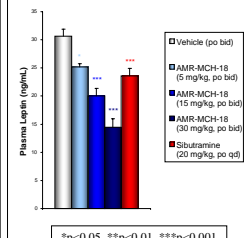
• AMR-MCH-18 caused statistically significant reductions in average daily food intake at 5 mg/kg in week 2 (8.3%), at 15 mg/kg in weeks 1, 2 and 4 (20.1%, 19.7% and 10.0%, respectively) and at 30 mg/kg in weeks 1, 2, 3 and 4 (24.6%, 21.6%, 9.8% and 7.4%, respectively).

## 5. Effect of AMR-MCH-18 on Body Composition



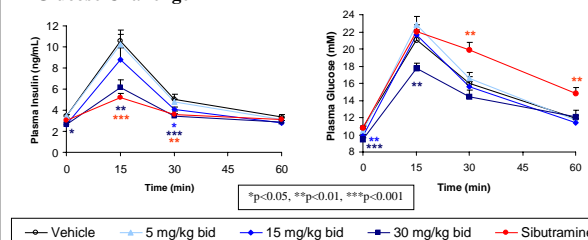
• 70%, 87% and 89% of the total weight loss caused by AMR-MCH-18 was due to reductions in fat mass for the 5, 15 and 30 mg/kg bid dose groups, respectively.

## 6. Effect of AMR-MCH-18 on Plasma Leptin



• AMR-MCH-18 (5, 15 and 30 mg/kg bid) significantly reduced circulating levels of plasma leptin (by 5.5, 10.8 and 16.2 ng/mL, corresponding to 17.9%, 35.2% and 52.8%, respectively) compared to vehicle control.

## 4. Effect of AMR-MCH-18 on Plasma Insulin and Glucose Following Glucose Challenge



• Reductions in fasted plasma insulin were observed prior to glucose challenge (2.0%, 22.9% and 25.1%\*) and at 15 minutes (3.5%, 17.0% and 41.8%\*\*), 30 minutes (4.7%, 20.1%\* and 32.6%\*\*\*), and 60 minutes (8.7%, 17.6% and 14.6%) following challenge for the 5, 15 and 30 mg/kg doses, respectively. AMR-MCH-18 (5, 15 and 30 mg/kg po bid) dose-dependently reduced fasted (baseline) plasma glucose by 3.1%, 8.9%\*\* and 12.5%\*\*\*, respectively. The 30 mg/kg po bid dose also significantly reduced plasma glucose at 15 minutes by 15.9%\*\* (\*p<0.05, \*\*p<0.01, \*\*\*p<0.001).

## CONCLUSIONS

- AMR-MCH-18 is a selective, high affinity MCH<sub>1</sub> receptor antagonist.
- AMR-MCH-18 causes gradual weight loss in obese mice.
- Weight loss is accompanied by reduction in food intake.
- Weight loss is associated with selective reduction in fat mass and accompanied by reduction in circulating plasma leptin.
- AMR-MCH-18 improves insulin sensitivity and glucose tolerance in obese mice.

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