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Comparative pharmacology of AMR-MCH-1 and AMR-MCH-2, MCH₁ receptor antagonists for the treatment of obesity

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Melanin-concentrating hormone (MCH) is a cyclic, 19 amino acid neuropeptide. In mammals, MCH is highly expressed in the zona incerta and lateral hypothalamus and regulates food intake and energy homeostasis through interaction with the MCH₁ receptor (Collins, et al., 2003; Skofitsch et al., 1985). Antagonists of the MCH₁ receptor have been shown to be a promising new approach for the treatment of obesity (Collins, et al., 2003; McBriar, 2006).

AMR-MCH-1 (4-(benzyloxy)-1-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-indazol-5-yl)pyridin-2(1H)-one) is representative of a novel structural class of selective, high affinity MCH₁ receptor antagonists identified by AMRI (Sargent, et al. 2008). AMR-MCH-1 was found to bind to the human MCH₁ receptor with a $K_i$ value of 2.6 nM and determined to be a functional antagonist at the MCH₁ receptor with an $IC_{50}$ value of 14 nM in an aequorin-based Ca²⁺ mobilization assay. AMR-MCH-1 demonstrated significant and sustained reductions in food intake and body weight in a chronic, 28-day feeding study in male dietary-induced obese (DIO) C57BL/6J mice (diet D12451). At twice daily oral doses of 30 mg/kg and 60 mg/kg, AMR-MCH-1 produced weight losses of 11.1% and 13.9%, respectively, compared with 5.8% for positive control sibutramine (20 mg/kg po qd). AMR-MCH-1 also caused sustained reduction in weekly food intake (by 24% and 22% in week 1; 11% and 12% in week 2; and 12% and 7% in week 3 for 30 mg/kg and 60 mg/kg, respectively; non-significant reductions were observed in week 4). Fat pad analysis indicated that the weight loss caused by AMR-MCH-1 was associated with reductions in fat mass of 27.5% and 44.6% compared to vehicle for the 30 mg/kg bid and 60 mg/kg bid dose groups, respectively. The brain levels of AMR-MCH-1 at the 6 hour time point following the final dose were found to be 1,377 ng/g and 3,226 ng/g for the 30 and 60 mg/kg bid dose groups, respectively. Improved brain penetration was achieved through a modified structural class, represented by AMR-MCH-2 (2-(4-chlorophenyl)-5-(1-(2-(pyrrolidin-1-yl)ethyl)-1H-indazol-5-yl)furo[3,2-c]pyridin-4(5H)-one). AMR-MCH-2 maintained high affinity for the MCH₁ receptor, with a $K_i$ value of 5.2 nM and a functional $IC_{50}$ antagonist value of 23 nM. AMR-MCH-2 demonstrated improved efficacy versus AMR-MCH-1 in 5-day feeding studies in DIO mice with once a day oral dosing (qd). At 30 mg/kg qd, AMR-MCH-2 showed 4.5% weight loss compared to the 2.8% weight loss provided by AMR-MCH-1 at twice the dose (60 mg/kg qd). The improved efficacy was correlated with increased brain exposure. At 6 hours following a single 10 mg/kg oral dose of AMR-MCH-2, DIO mice were found to have brain concentrations of 2,253 ng/g with a brain to plasma ratio of 16. These data indicate that AMR-MCH-1 is a high affinity MCH₁ receptor antagonist that causes sustained weight loss in obese mice and that structural modification to AMR-MCH-2 yields improved brain penetration and improved efficacy.


