PRX-07034, a Potent and Selective 5-HT6 Receptor Antagonist, Reduces Food Intake and Body Weight in Dietary-induced Obese Rats

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Introduction

5-HT6 receptor antagonists represent a novel target for the treatment of obesity. PRX-07034, a novel, potent and selective 5-HT6 receptor antagonist (IC50=10 nM; ID50=10 nM in UTP-assay), has demonstrated significant preclinical efficacy in reducing food intake and body weight along with a good preclinical safety profile. In male rats, PRX-07034 reduces food intake and body weight following subchronic dosing. Observational analysis of feeding, conditioned taste aversion and sodium appetite tests indicate that the effects on food intake and weight are specific and not due to induction of malaise or anorexic effects (Gannon et al, IUPHAR 2006). PRX-07034 lacks 5-HT2 antagonistic activity with x30-fold selectivity for 5-HT6 over other 5-HT receptor subtypes, except for 5-HT1A and 5-HT1B (K1=420 nM and 260 nM, respectively), and has 100-fold selectivity over 52 other GPCRs, ion channels and transporters, except D3 (K1=71 nM). PRX-07034 is in Phase I clinical trials and is being developed for the treatment of obesity.

Methods

DIO Study: Female Wistar rats (n=10/group) were placed on a high fat diet for 3 months and allowed to freely feed resulting in dietary-induced obese (DIO) rats. Following a one-week baseline and a week of low oral doses of PRX-07034 with no observable effects, animals were given 3 or 10 mg/kg PRX-07034 ip, bid for 3 weeks. Animals were maintained on a reverse phase light/dark cycle and dosed at 0 hr (onset of night) and 6 hrs. Body weights and food/water intake were made daily and food intake was measured at 2hr and 8hr post-dose the first day of ip dosing. An apparent chemical peptidase due to chronic ip dosing was observed in 10 mg/kg treated animals, although no behavioral abnormalities were present in animals at necropsy. Significant reductions in fat pad weight (g) were observed in DIO rats treated with PRX-07034 (30 mg/kg ip bid) or vehicle for 3 weeks. Additionally, positive controls, olanzapine (7.5 mg/kg ip, q2d) and ramiprilat (0.6 mg/kg ip, q2d) were included in the study. Food intake, water intake (data on file), body weight, fat pad weight, and plasma metabolic markers (glucose, insulin and leptin) were assessed.

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- PRX-07034 reduced body weight and food intake in DIO rats.
- Similar results were found in male rats on a high fat diet (HFD) treated with PRX-07034 (100 mg/kg po bid) for 4 weeks.

Conclusions

- In two animal models of obesity, PRX-07034 produced a gradual and maintained weight loss along with significant reductions in plasma levels of glucose, insulin and leptin.
- The weight loss was specific to fat content with no marked effects on protein or water content.
- Results suggest that PRX-07034 may provide a novel, effective and safe approach to the treatment of obesity.
- Human clinical trials (Phase I) are ongoing.