

Oral delivery of mouse [D-Leu-4]-OB3, a synthetic peptide amide with leptin-like activity, in male C57BL/6J wild type and *ob/ob* mice: effects on energy balance, glycemic control, and serum osteocalcin levels.

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ABSTRACT

We have recently shown that intranasal administration of mouse [D-Leu-4]-OB3 reconstituted in Intravail® to male Swiss Webster mice resulted in significantly higher bioavailability than commonly used injections methods of delivery. The absorption profile associated with intranasal delivery of mouse [D-Leu-4]-OB3 showed an early peak representing absorption across the nasal mucosa, and a later peak suggesting a gastrointestinal site of uptake.

Aim and Methods: In the present study, we examined the effects of orally administered (by gavage) mouse [D-Leu-4]-OB3 on energy balance, glycemic control, and serum osteocalcin levels in male C57BL/6J wild type and *ob/ob* mice allowed food and water *ad libitum*, or calorie restricted by 40% of normal intake.

Results: In wild type mice fed *ad libitum*, oral delivery of mouse [D-Leu-4]-OB3 reduced body weight gain, food intake, and serum glucose, by 4.4%, 6.8% and 28.2%, respectively. Serum osteocalcin levels and water intake were essentially the same in control and treated wild type mice. In *ob/ob* mice fed *ad libitum*, mouse [D-Leu-4]-OB3 reduced body weight gain, food intake, water intake, and serum glucose by 11.6%, 16.5%, 22.4% and 24.4%, respectively. Serum osteocalcin in *ob/ob* mice treated with mouse [D-Leu-4]-OB3 was elevated by 161.0% over controls. Calorie restriction alone caused significant weight loss in both wild type (9.0%) and *ob/ob* (4.8%) mice, and mouse [D-Leu-4]-OB3 did not further enhance this weight loss. As expected, serum glucose levels in wild type and *ob/ob* mice were significantly reduced by calorie restriction alone. Mouse [D-Leu-4]-OB3 further reduced serum glucose in wild type mice, and normalized levels in *ob/ob* mice. Calorie restriction alone reduced serum osteocalcin levels by 44.2% in wild type mice, and by 19.1% in *ob/ob* mice. Mouse [D-Leu-4]-OB3 prevented this decrease in groups of mice.

Conclusions: The results of this study suggest that oral delivery of mouse [D-Leu-4]-OB3 in Intravail® is possible, and may have potential not only as an alternative therapy in the treatment of human obesity and some of its associated metabolic dysfunctions, but also may help to prevent and/or reverse at least some of the bone loss which accompanies osteoporosis, anorexia nervosa, and other wasting diseases.

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