**ABSTRACT**

Metaprotease Aminopeptidase 2 (MetAP2) is a broadly expressed metalloenzyme that cleaves amino-terminal methionine residues from newly synthesized proteins. Its key known substrates include thyroid hormone and glyceraldehyde-3-phosphate dehydrogenase (1). Multiple studies (2-4) have demonstrated dramatic weight loss in obese mice treated with MetAP2 inhibitors. Although it has been postulated that MetAP2 inhibitors drive weight loss by reducing adipose tissue blood vessel growth (3,3), recently published studies (4) have revealed a lack of effect on adipose tissue blood vessel density or function, despite substantial weight loss. The current study was conducted to assess the long term effects of MetAP2 inhibitor treatment in order to assess its tolerability, durability of effect, impact on plasma glucose and insulin, and hepatic fatty acid metabolism. 

**CONCLUSIONS**

This study evaluated the effects of treatment for nine months with fumagillin, a prototype MetAP2 inhibitor in high fat diet-fed male C57Bl/6 mice. Treatment reduced high-fat diet-induced hyperphagia and normalized body weight and fat pad size. Significant changes in liver functions were observed, including:

- Reduced liver weights and fat content (data not shown)
- Increased hepatic hydroxybutyrate levels
- Fasting glycemia was improved and insulin concentrations were normalized, indicating treatment improved insulin sensitivity.

MetAP2 inhibition appears to be well-tolerated and shows promise as a strategy to reverse hyperinsulinemia and other obesity-associated metabolic adaptations while driving rapid loss of excess body fat.

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**METAP2 AND ZGON-201**

- **Methionine Aminopeptidase 2** (MetAP2) is a broadly expressed metalloenzyme that cleaves amino-terminal methionine residues from newly synthesized proteins.

**ZGON-201** (fumagillin) is a well-characterized, highly selective MetAP2 inhibitor (5) suitable for use as a prototype inhibitor for clinical trials. It is a natural product isolated from Aspergillus fumigatus.