

Poster #241

Trodusquimine (MSI-1436) Enhances Glucose Tolerance in a Murine Model of Insulin Resistance

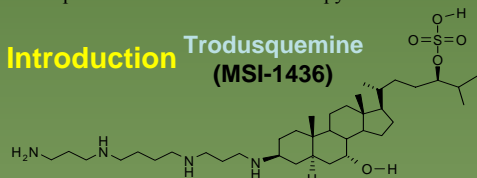
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Abstract

Trodusquimine (MSI-1436) is an allosteric inhibitor of protein tyrosine phosphatase 1B (PTP1B) which has been shown to elicit weight loss and improve glucose tolerance in a diet-induced model of obesity and genetically obese models. Trodusquimine has been shown to improve fasting and postprandial blood glucose levels. To further characterize this glucose tolerance enhancement, AKR/J mice were treated with rapamycin (2 mg/kg daily, IP) to induce a glucose intolerant state. The mice were treated with either MSI-1436 (5 mg/kg, q3dx3, IP) or vehicle and OGTTs were performed 24 days after last treatment. MSI-1436 corrected the rapamycin-induced glucose dyshomeostasis. Trodusquimine shows potent improvement in glucose tolerance and supports development as an anti-diabetic therapy.

Introduction Trodusquimine (MSI-1436)



- Trodusquimine is a small molecule that causes weight loss in wild type, genetically obese, and diet-induced, obese animal models.
- Phase I clinical trials for obesity were initiated in May of 2007.
- Trodusquimine is a selective PTP1B inhibitor (>150 fold specificity over the highly homologous enzyme, TCPTP). PTP1B is a negative regulator of insulin signaling.

Objective

To characterize the anti-diabetic properties of trodusquimine. To assess the effect of trodusquimine treatment on glucose tolerance and insulin sensitivity.

Acknowledgement

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Figure 1: Study Design, AKR/J Mice

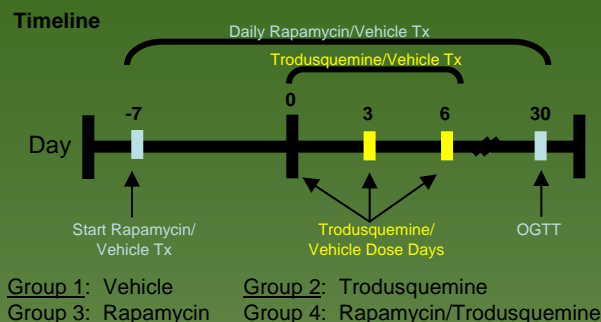
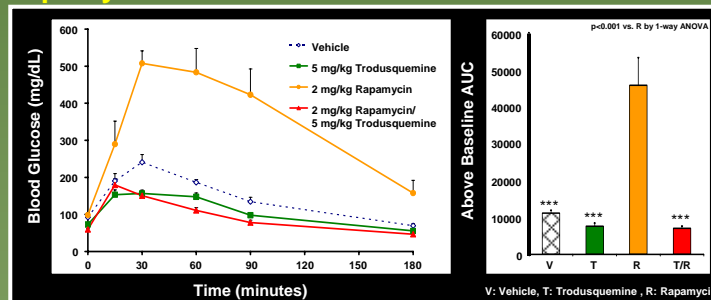
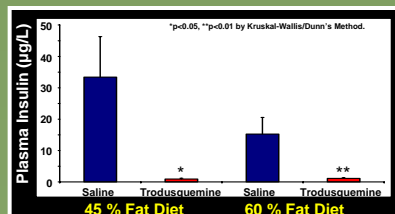


Figure 2: Trodusquimine Alleviates Rapamycin-Induced Glucose Intolerance



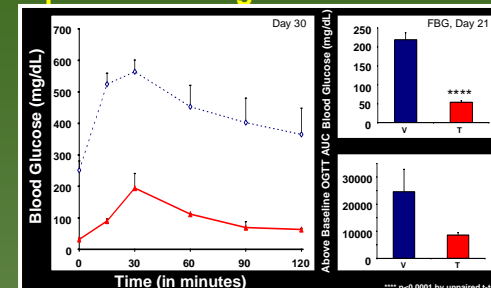
AKR/J mice were treated daily with rapamycin (2 mg/kg; daily from Day -7 to Day 30), trodusquimine (5 mg/kg; Days 0, 3, and 6), or both. After an overnight fast, an oral glucose tolerance was performed (Day 30) by measuring blood glucose levels at 0, 15, 30, 60, 90, and 180 minutes following a p.o. bolus of 1.5 g/kg glucose. Mice treated with trodusquimine and rapamycin (red) demonstrated improved glucose tolerance as compared to mice treated with rapamycin alone (orange). Data shown is Mean + SEM, n=3-4 per group.

Figure 3: Trodusquimine Treatment Lowers Plasma Insulin Levels



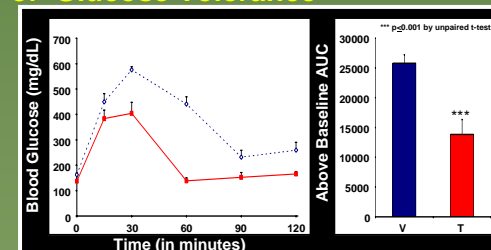
Male AKR/J mice were fed ad libitum on a 45% fat kcal or 60% fat kcal diet and postprandial plasma insulin levels were measured after 4 weekly treatments of trodusquimine (10 mg/kg bolus, 5 mg/kg for subsequent doses). Plasma insulin levels were markedly reduced in trodusquimine-treated mice on both diets. Data shown is Mean + SEM, n=5-8 per group. Portions of this figure were previously presented at ADA 2007.

Figure 4: Trodusquimine Improves Fasting Blood Glucose



Female *ob/ob* mice were treated with 5 mg/kg (i.p.) trodusquimine on Days 0, 3, 6, and 9. On Day 21, overnight fasting blood glucose levels were measured (upper right panel). On Day 30 and following an overnight fast, an oral glucose tolerance test revealed improved glucose tolerance as compared to vehicle control. Data shown is Mean + SEM, n=2-4 mice/group.

Figure 5: Extended Improvement of Glucose Tolerance



Female *ob/ob* mice were treated with trodusquimine (5 mg/kg on Days 0, 7, and 14, followed by weekly doses of 1 mg/kg from Days 35-98, and 5 mg/kg on Days 105, 112, and 119) or saline. An OGTT (Day 122) confirmed that improved glucose tolerance is maintained over time. Data shown is Mean + SEM, n=5-7 mice/group.

Conclusions

- Trodusquimine improves insulin sensitivity in mice.
- Trodusquimine lowers plasma insulin levels.
- Trodusquimine treatment improves fasting blood glucose and glucose tolerance in hyperglycemic animal models and these effects are maintained over time.

References

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