

Effects of Treatment of C57BL/6J Mice Fed High vs. Low Fat Diets with Metformin or Rosiglitazone on Adiposity, Food Intake, Hyperglycemia and Insulin Resistance

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Abstract

The purpose of this study was to investigate the efficacy of treatment of mice with diet induced insulin resistance and obesity with metformin or rosiglitazone. Male C57BL/6J mice (n=10) were maintained for 9 wk on high fat (D-12451, 45 kcal% fat as lard; D-12330, 58kcal% hydrogenated coconut oil/HCO) or low fat (D-12450B, 10 kcal% lard; D-12328, 11 kcal% HCO) diets (Research Diets Inc, New Brunswick NJ). Mice were treated daily for 8d by oral gavage with rosiglitazone (10 mg/kg), metformin (400 mg/kg) or vehicle (0.2% hydroxypropylmethylcellulose in water). Blood glucose, plasma insulin and leptin were determined after 3d treatment, and after 7d the hypoglycemic effect of insulin (0.5 U/kg, ip) was measured. Mice fed D12451 were insulin resistant, indicated by elevated 3 hr fasting blood glucose and impaired insulin tolerance, with no significant improvement in drug-treated mice. Mice fed D12330 also had elevated blood glucose and plasma insulin, and decreased insulin tolerance. In contrast to D12451, fasting blood glucose was normalized by metformin and decreased to lesser extent by rosiglitazone in mice fed D12330. Metformin and to a lesser extent rosiglitazone significantly potentiated the hypoglycemic response to exogenous insulin in mice on low fat (D-12450B and D-12328) or D12330 high fat diet, but neither agent affected basal blood glucose in mice fed low fat diets. Both high fat diets D12451 and D12330 were associated with increased epididymal fat mass at sacrifice vs low fat diet groups. Mice treated with rosiglitazone but not metformin for 8d had further increased epididymal fat mass vs. vehicle treatment, significant in all dietary groups. In summary, C57BL/6J mice treated with metformin or rosiglitazone had improved responsiveness to exogenous insulin, except those fed the lard-based D12451 diet were very insulin resistant, had little improvement with 8d treatment with metformin, and did not respond to rosiglitazone. Metformin appeared to be a better insulin sensitizer than rosiglitazone in this model of high fat diet induced insulin resistance and obesity.



Introduction

- Treatment with some antidiabetic compounds may not produce desirable changes in body weight. Thiazolidinedione insulin sensitizers in particular will increase body weight in mice, rats and man.
- We have evaluated several commercially available high fat diets in C57BL/6J mice, and the effects of treatment with either rosiglitazone (Avandia) or metformin (Glucophage).

Methods

- C57BL/6J male mice obtained at 5 weeks age.
- Randomly assigned to 5 dietary groups

Diet ID	Source	% kcal fat	fat form	fat type	n/group
D12451	RDI	45	lard	animal	150
D12450B	RDI	10	lard	animal	50
D12330	RDI	58	hydrogenated coconut oil	vegetable	50
D12328	RDI	10	HCO control	vegetable	50

- After 10 weeks on diet, mice on each diet were assigned to groups of 10 mice/group, and were administered vehicle (hydroxypropylmethylcellulose 0.2%; 10 ml/kg, p.o.), rosiglitazone (10 mg/kg, p.o.), or metformin (400 mg/kg, p.o.) daily for 8 days.

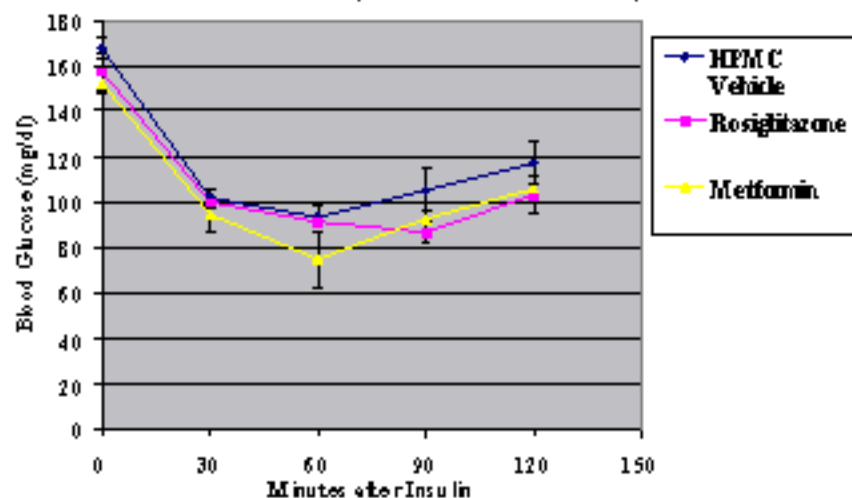
● Monitored:

- Body weight, food intake
 - Ad lib AM blood glucose, plasma insulin and leptin at 5 days treatment
 - 3 hr fasted glucose and insulin tolerance after 8 days treatment
- Another high fat diet became available after the first study had been started. Two additional groups of mice were placed on diets (D12492 and D12450B) at 5 weeks age, and events were monitored after 10 weeks on diet at the same relative times as indicated above. Additionally, fasting blood glucose, glucose tolerance and insulin tolerance were observed at 8 days drug treatment after 3 hour fast.

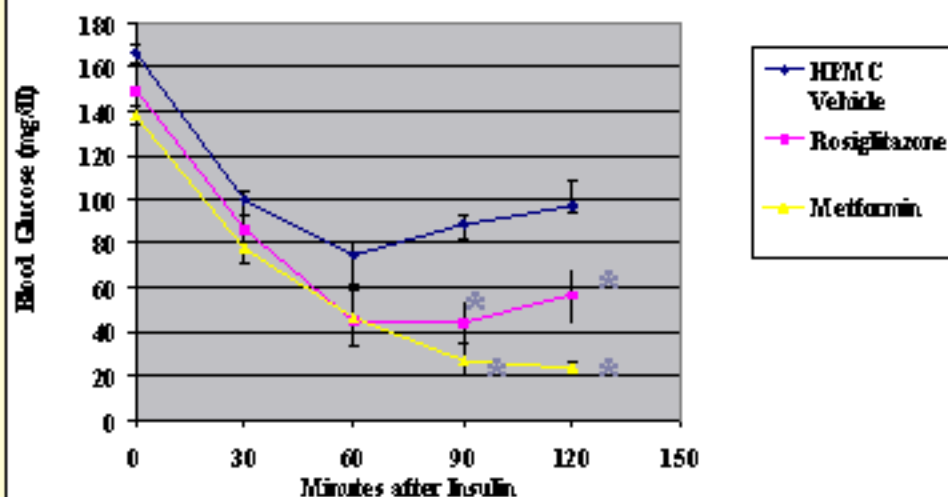
Diet ID	Source	% kcal fat	fat form	fat type	n/group
D12492	RDI	60	lard	animal	90

Insulin Tolerance (0.5 U/kg) after 8 Days Drug Treatment in C57BL/6J Mice on High or Low Fat Diet for 10 Weeks

D12451 (45kcal% Lard)

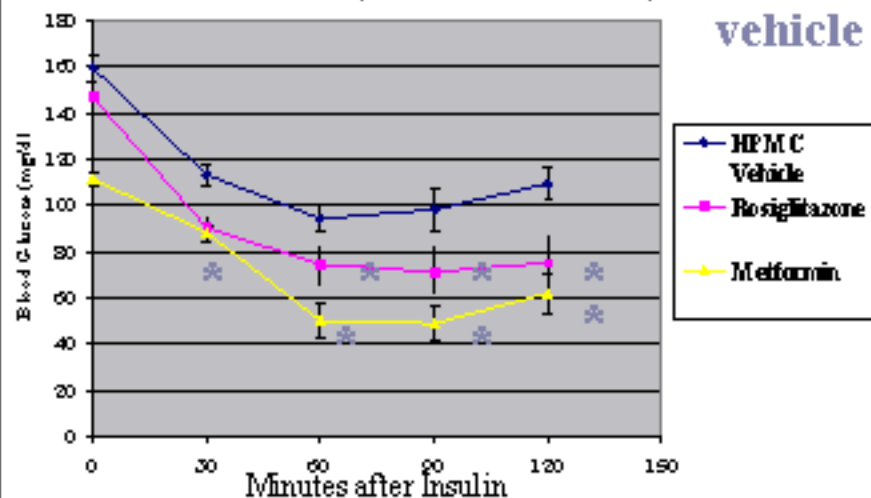


D12450B (10kcal% Lard)

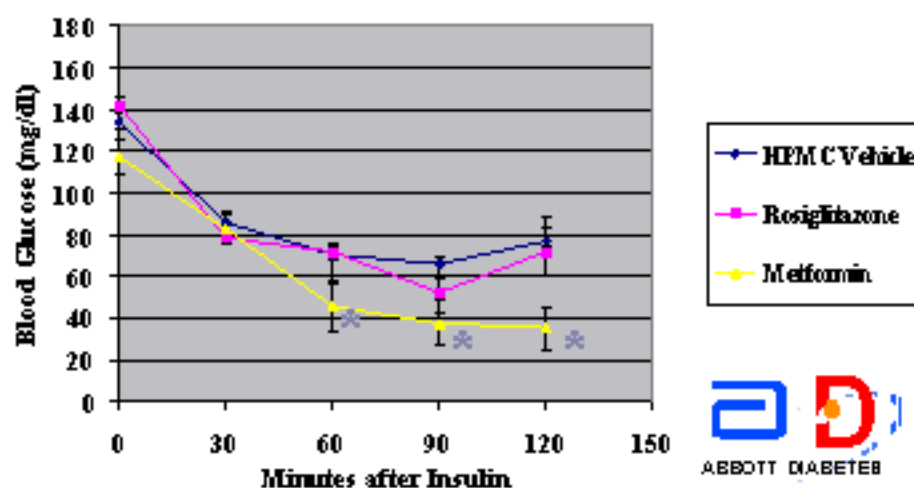


D12330 (58kcal% HCO)

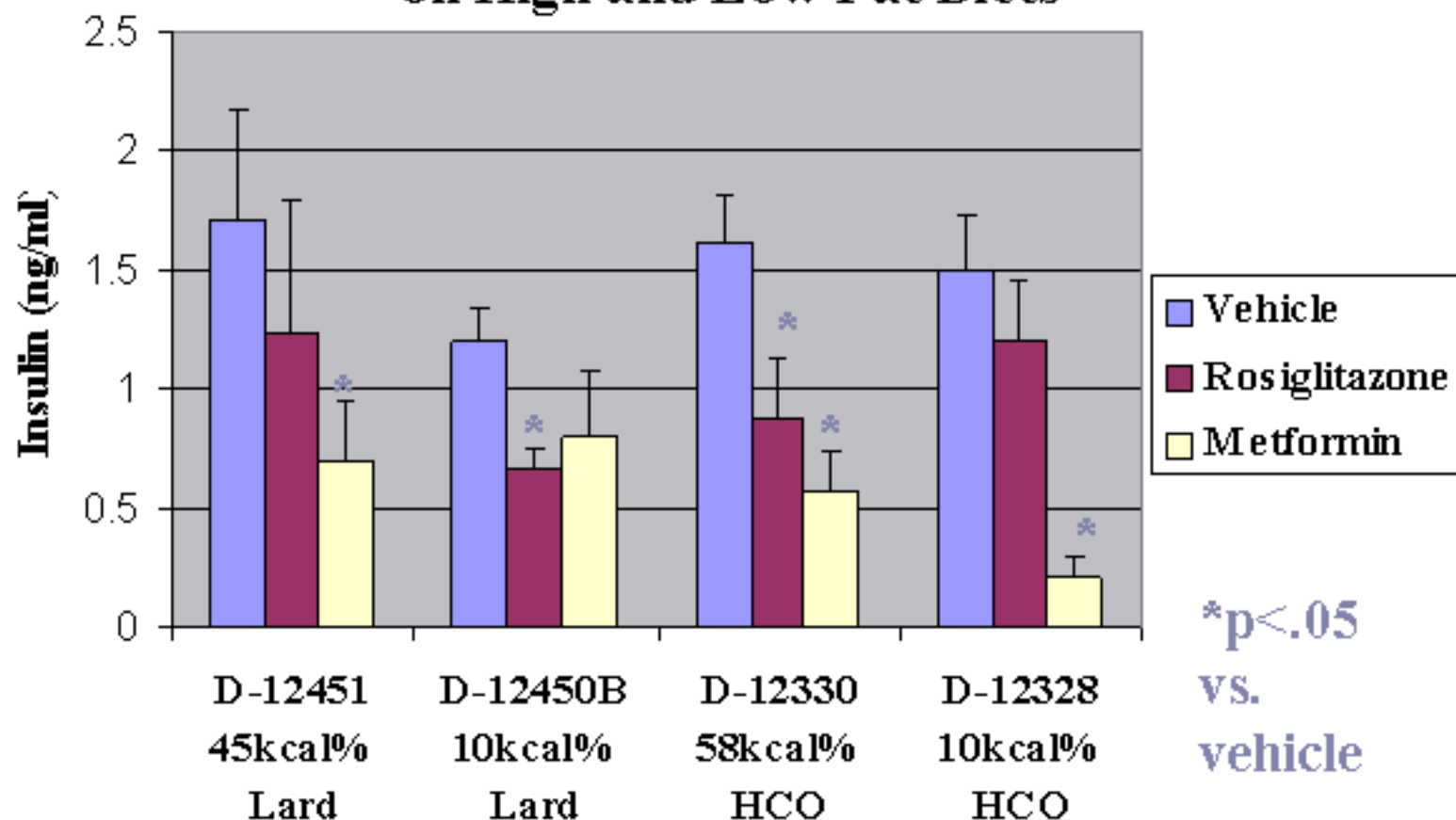
***p<.05 vs. vehicle**



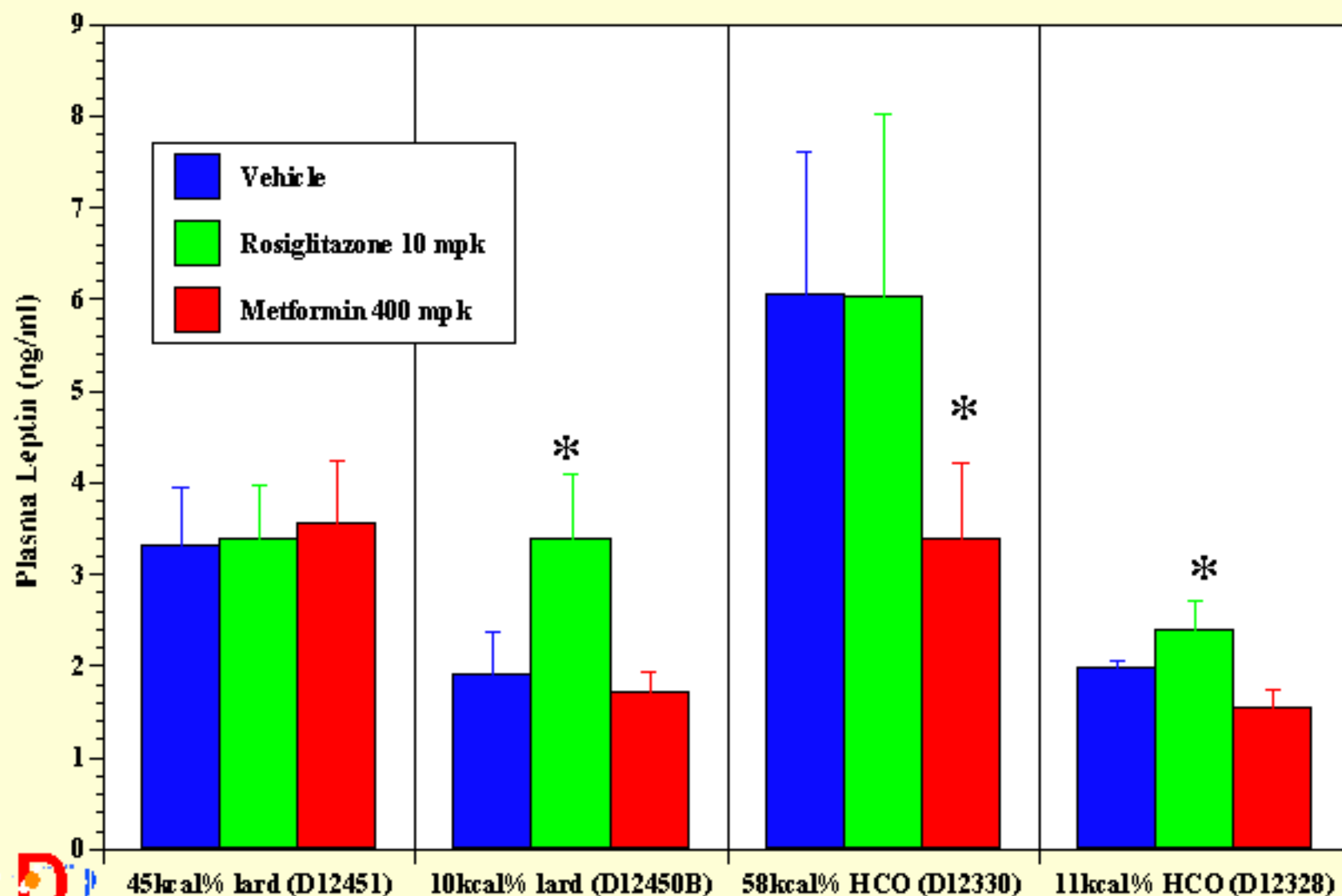
D12328 (10kcal% HCO)



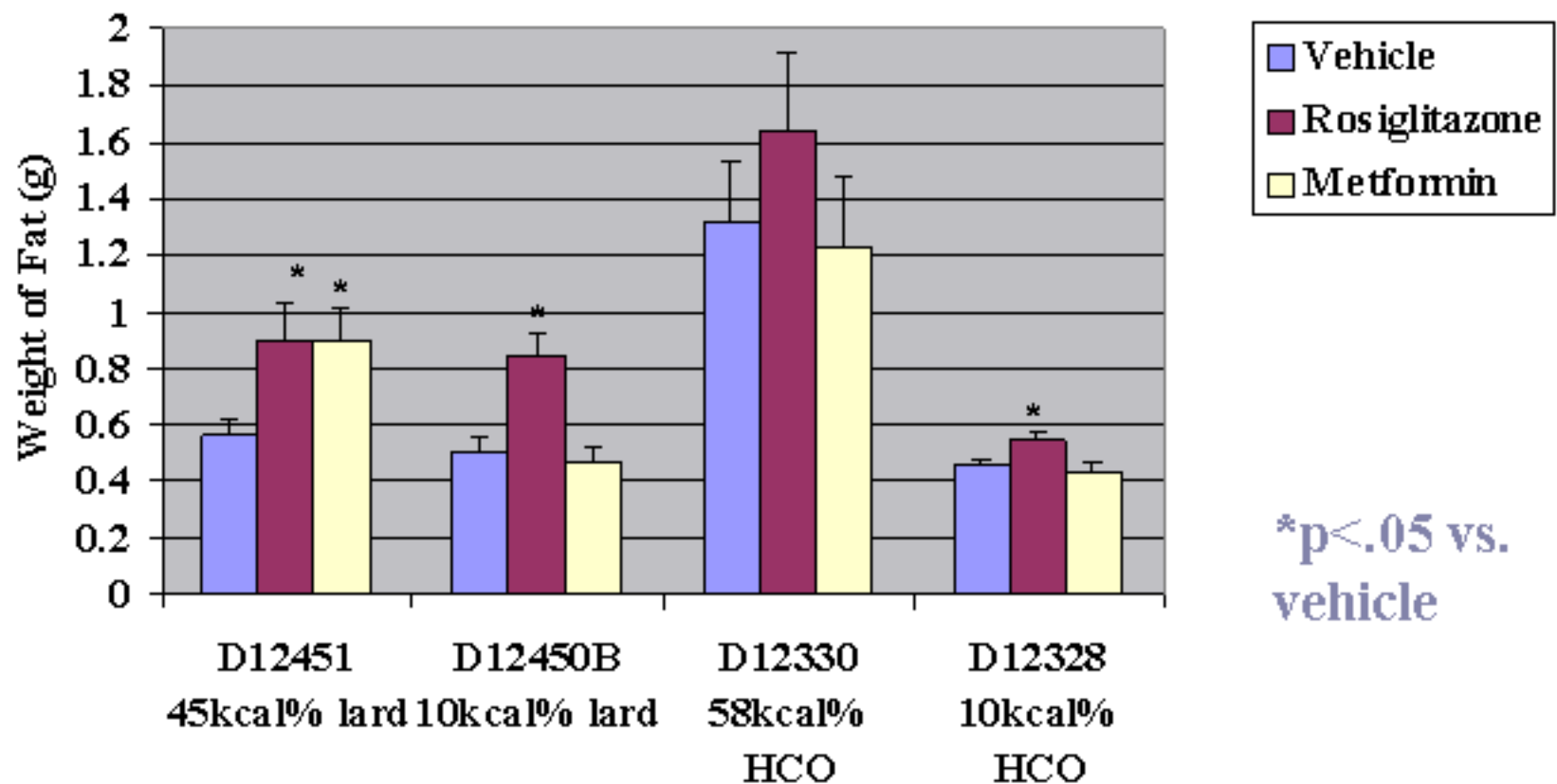
Effects of Rosiglitazone and Metformin Treatment on Plasma Insulin in C57BL/6J Mice on High and Low Fat Diets



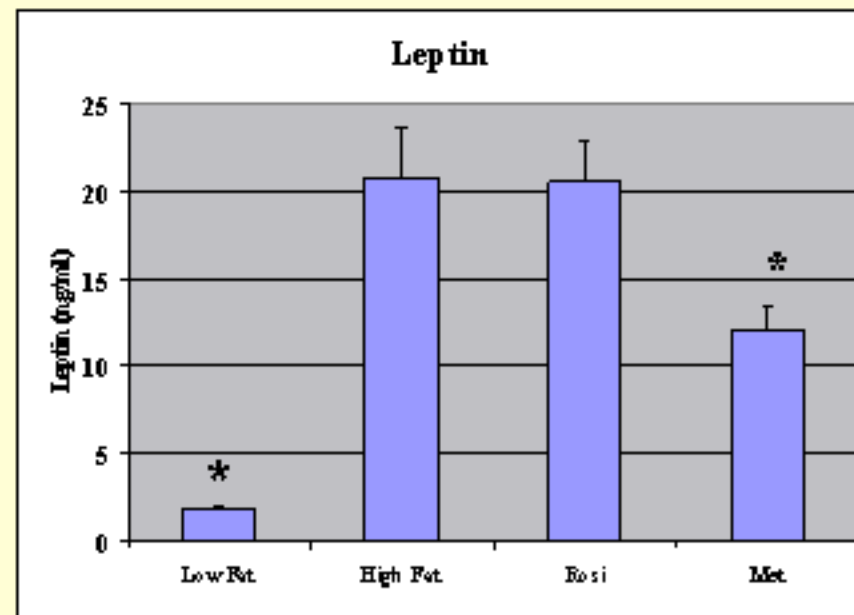
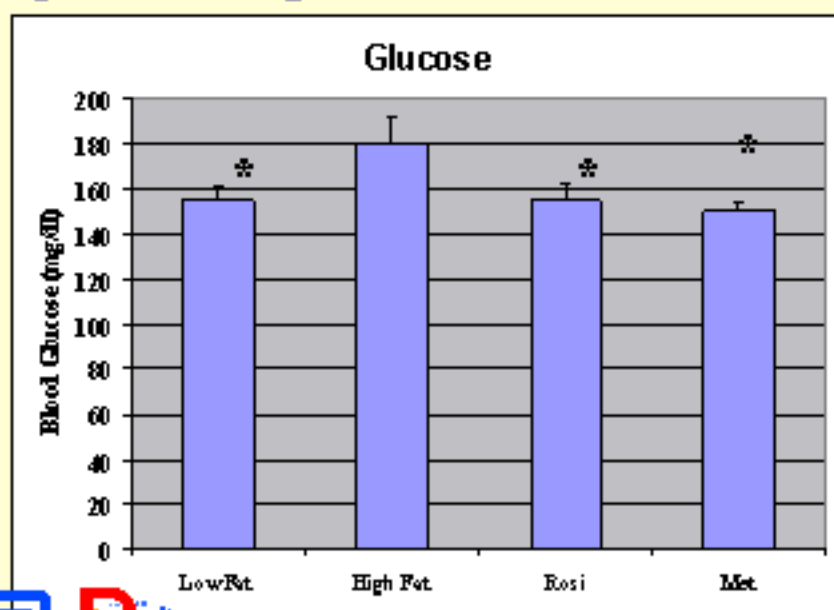
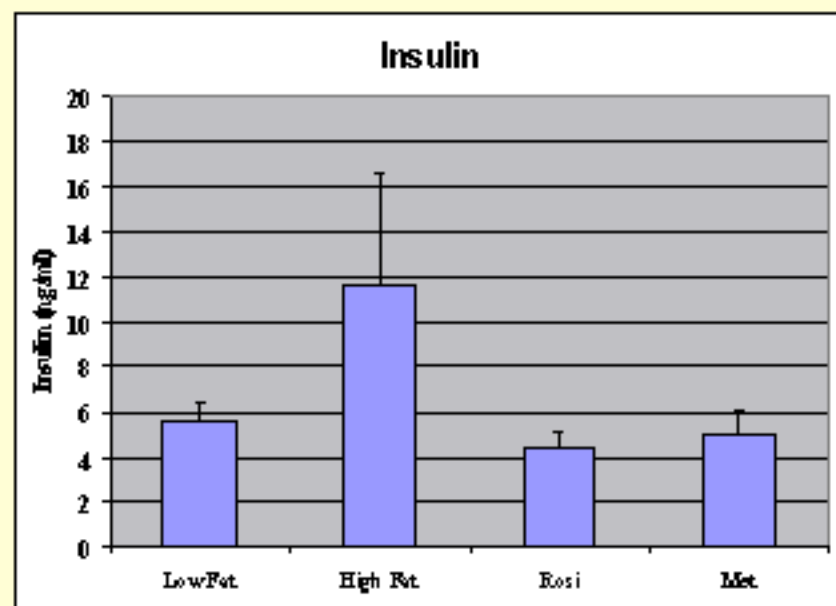
Effects of Rosiglitazone and Metformin Treatment on Plasma Leptin in C57BL/6J Mice on High and Low Fat Diets



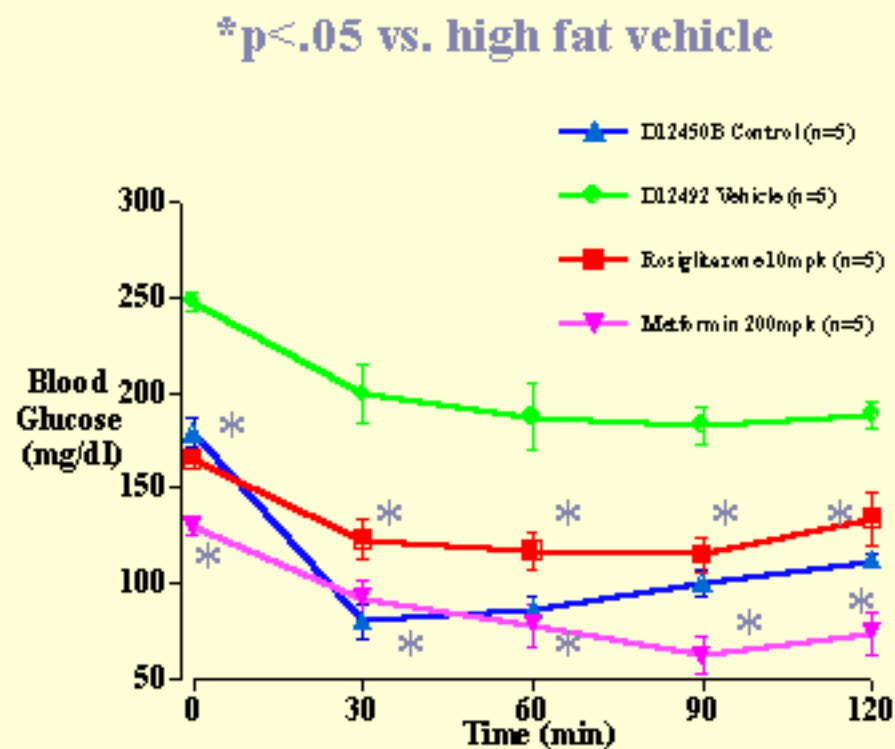
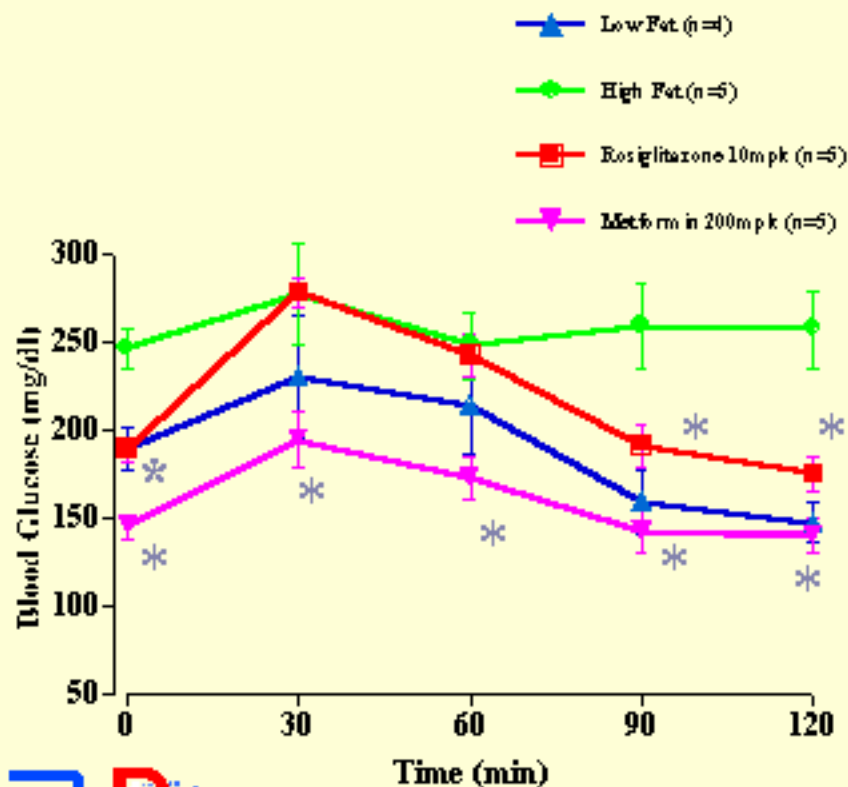
Effect on Epididymal Fat Pad Weight of Eight-Day Drug Treatment of C57BL/6J Mice after 10 Weeks of Test Diet



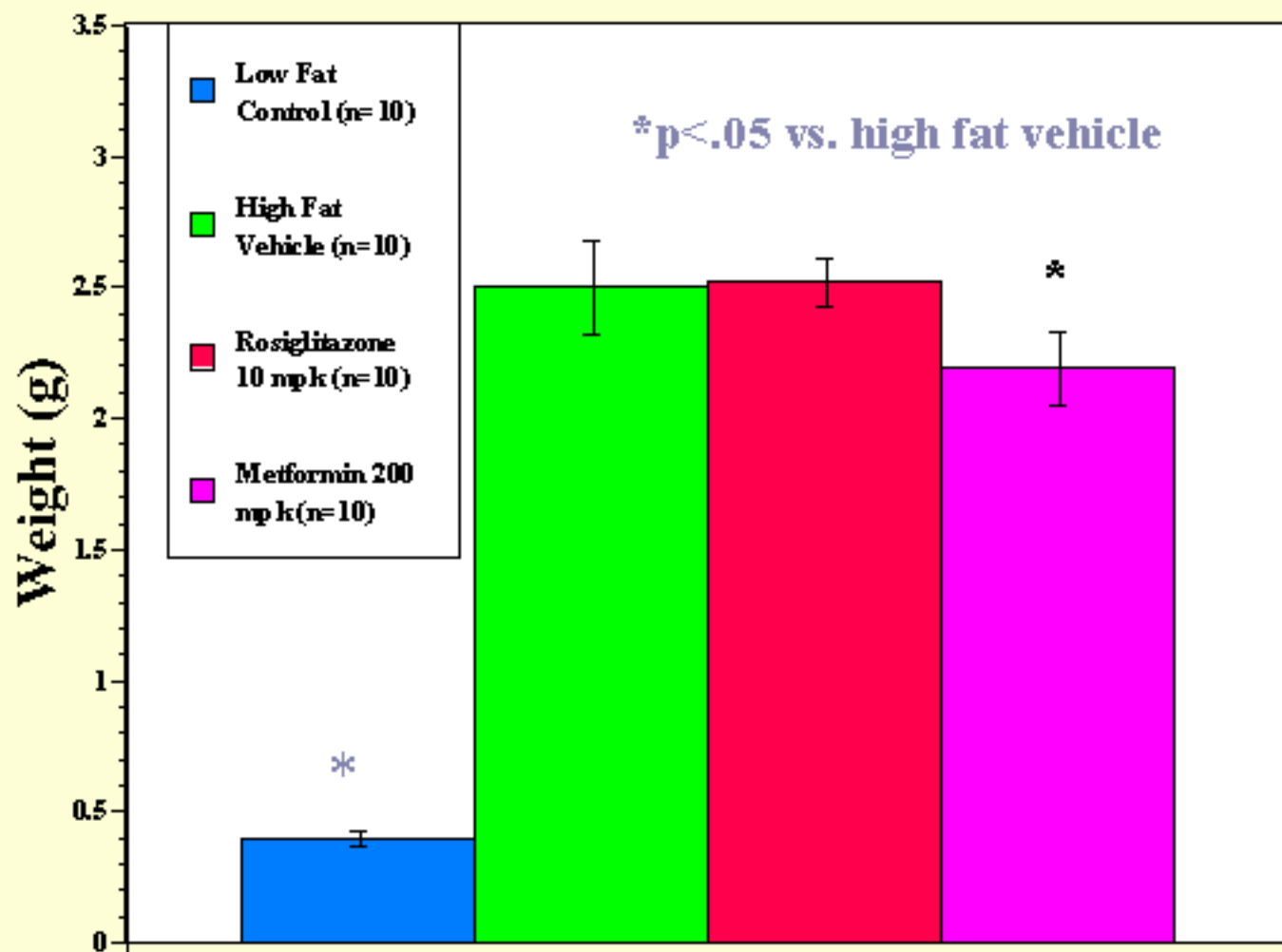
Effects of 5 Days Treatment with Rosiglitazone (10 mpk qd, po) or Metformin (400 mpk qd, po) On Blood Glucose, Plasma Insulin and Leptin in Mice Fed High Fat (60 kcal% lard, D12492) Diet for 10 Weeks
* $p < .05$ vs. high fat vehicle



Effects of Seven Day Treatment with Rosiglitazone (10 mpk qd) or Metformin (400 mpk qd) on Glucose (2 g/kg, po) and Insulin (0.25 U/kg, ip) Tolerance in C57BL/6J Mice on High Fat Diet (D12492) for 10 Weeks



Effects of Eight Days Treatment with Rosiglitazone, or Metformin on Epididymal Fat Pad Weight in C57Bl/6 Mice Fed 60 kcal% Lard (D12492) For 10 Weeks



Summary

- Treatment of mice maintained on 45 kcal% lard (D12451) with rosiglitazone did not result in a significant improvement of insulin sensitivity. Metformin treatment resulted in decreased blood glucose, and increased hypoglycemic response to insulin.
- Both agents resulted in improvement of postprandial and fasting glycemic state and response to exogenous insulin in mice on very high fat diets, 58 kcal% HCO (D12330) or 60 kcal% lard (D12492).
- Metformin improved glucose tolerance better than rosiglitazone in mice fed the 60 kcal% lard (D12492) diet. Metformin significantly decreased circulating insulin in mice on most diets, except low (D12328) and high (D12492) fat diets. It also potentiated hypoglycemic responses to exogenous insulin in mice fed low fat diets chronically. Metformin significantly decreased plasma leptin in mice on 58 kcal% HCO (D12330) or 60 kcal% lard (D12492) diets.
- Rosiglitazone consistently elevated epididymal fat mass in mice on low fat (D-12450B or D12328) or 45 kcal% lard high fat diet (D1451), but not in mice on the very high fat diets (D12330 or D12492) which had considerably larger epididymal fat pads than the other groups.