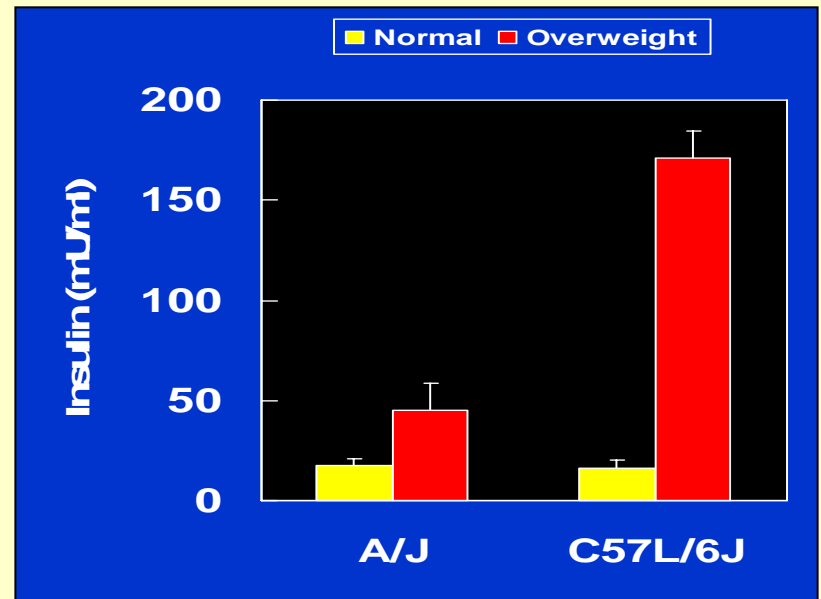


Modification of Hyperinsulinemia in the Treatment of Obesity: “South Beach” Pharmacotherapy

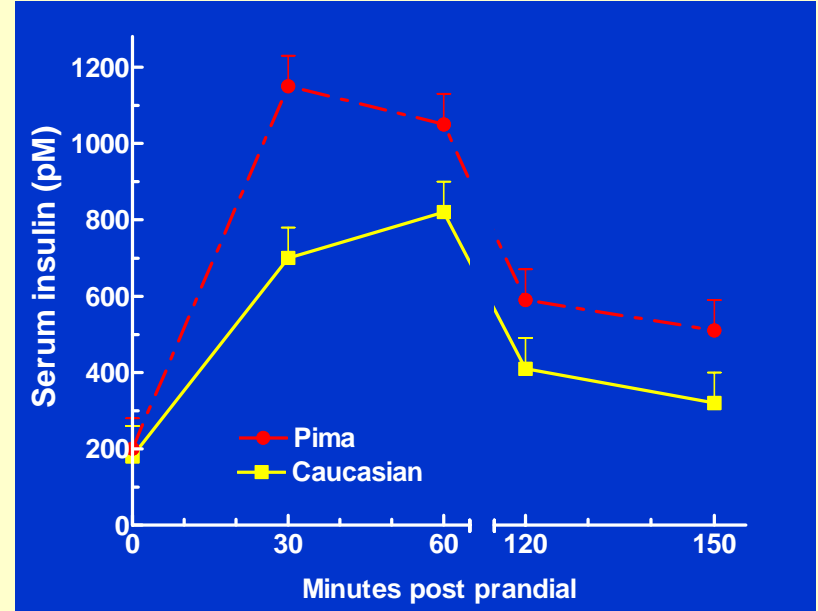
Richard S. Surwit

Duke University Medical Center

Hyperinsulinemia is Linked to Obesity in Animals



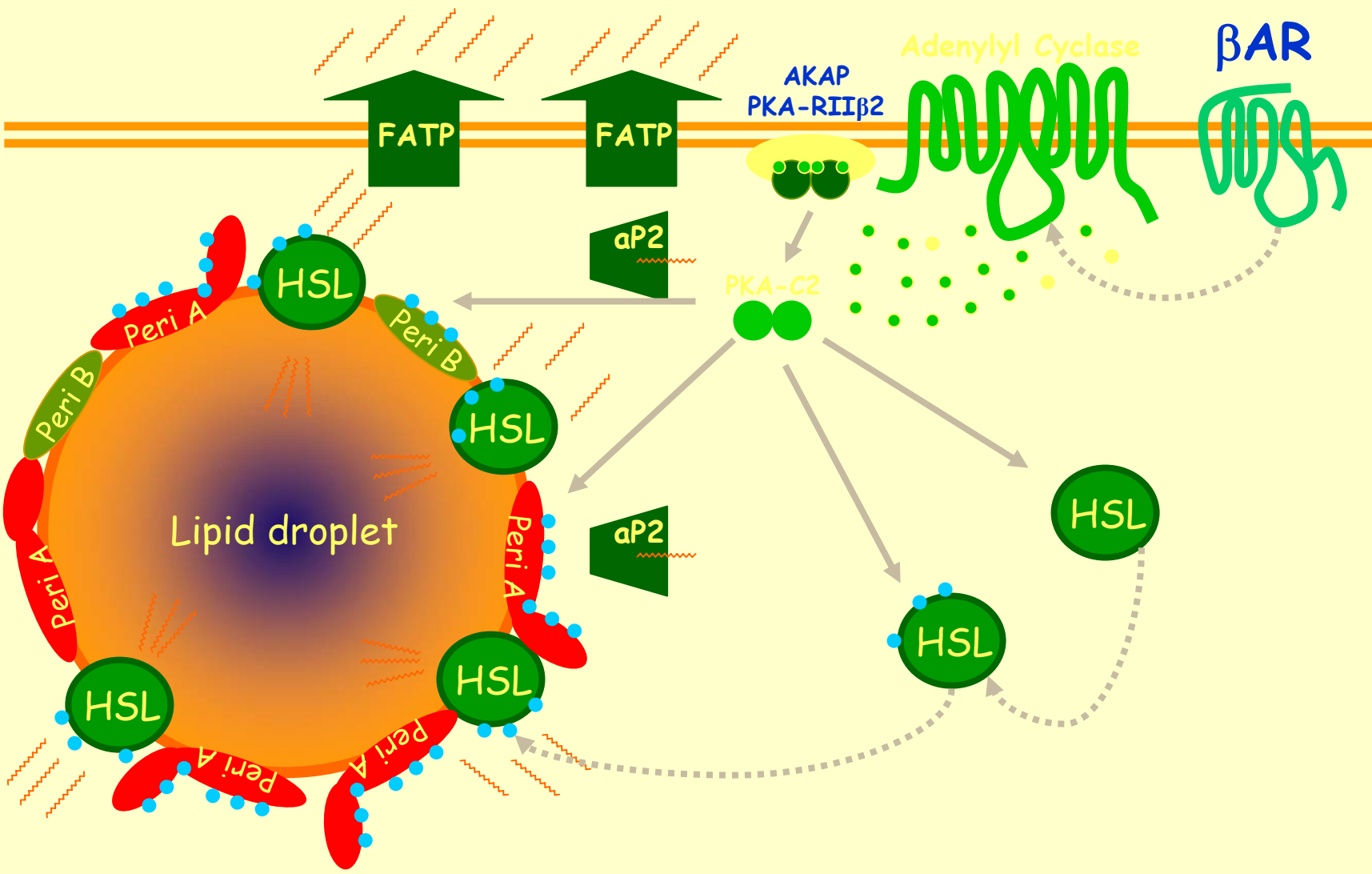
Hyperinsulinemia is Linked to Obesity in Humans



Hyperinsulinemia is Thought to Inhibit Weight-Loss by Interfering with Lipolysis

- Lipolysis is stimulated by β adrenergic receptors

Adrenergic Stimulation of Lipolysis



Diazoxide

- Diazoxide is a KATP channel agonist that inhibits the flow of calcium ions into the beta cell, thus preventing secretion of insulin in response to glucose

Animal Studies

- Obesity-prone C57BL/6J mice were raised on:
 - a high fat diet (58% calories from fat)
 - a high fat diet with diazoxide (0.32%)
 - a high fat diet with a selective β -3 AR agonist (CL316, 243, .001%)
 - a high fat diet with both compounds
 - a low fat diet (11% calories from fat)

Figure 4A

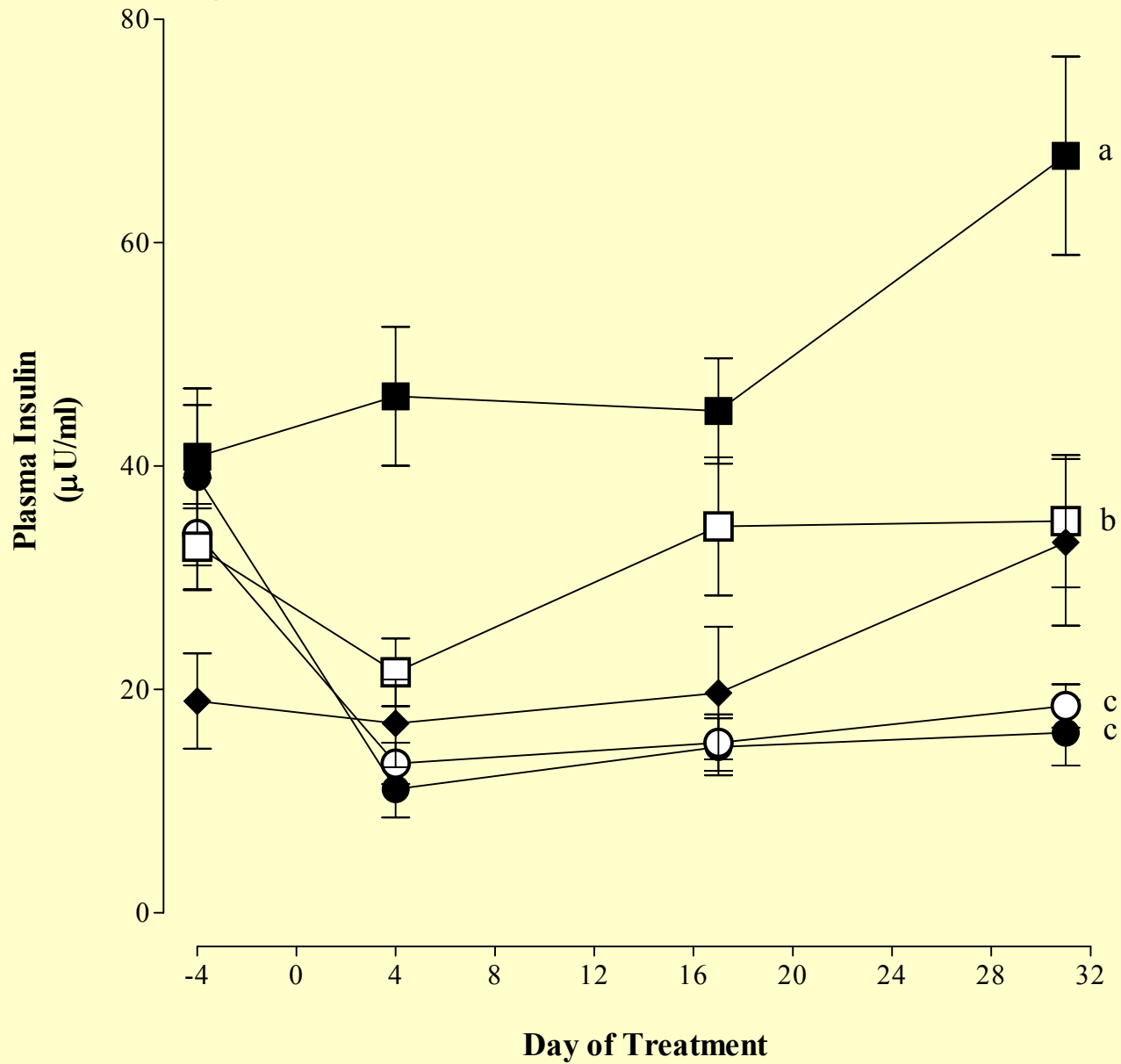


Figure 3

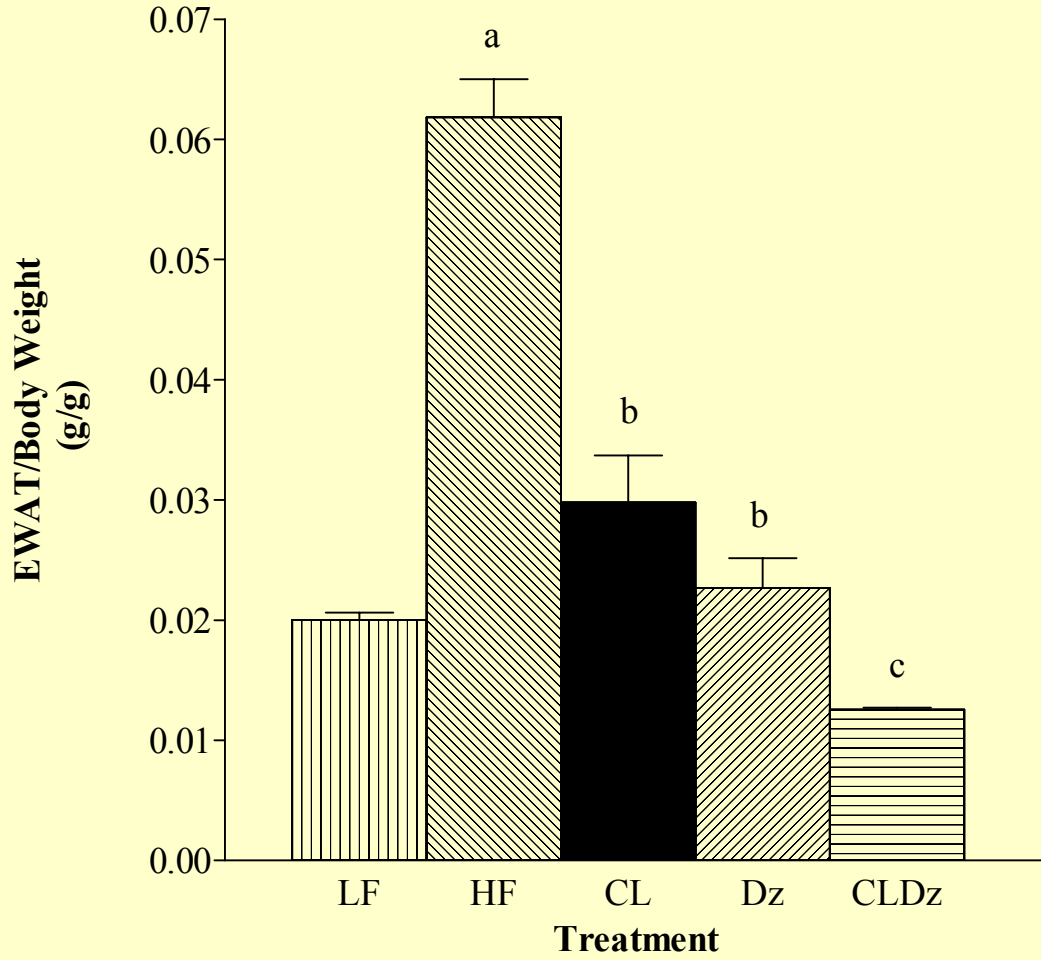


Figure 5

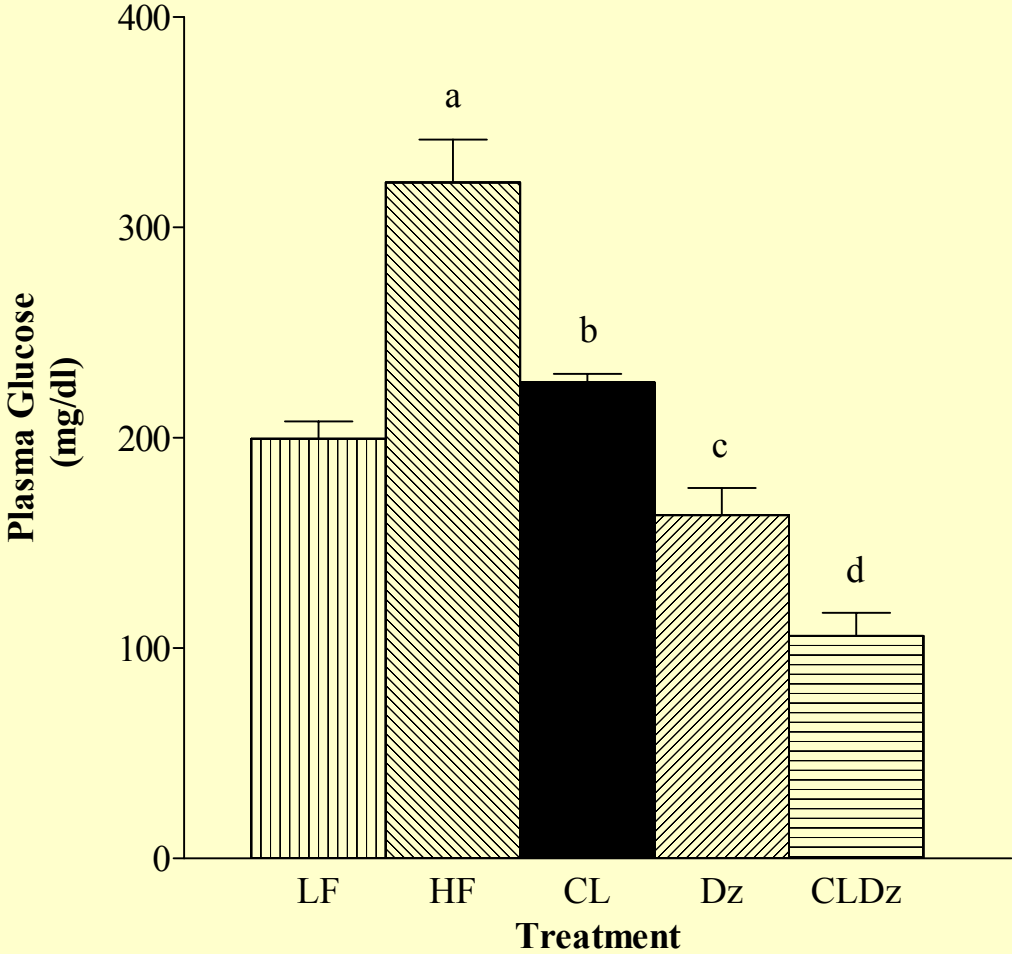


Figure 1

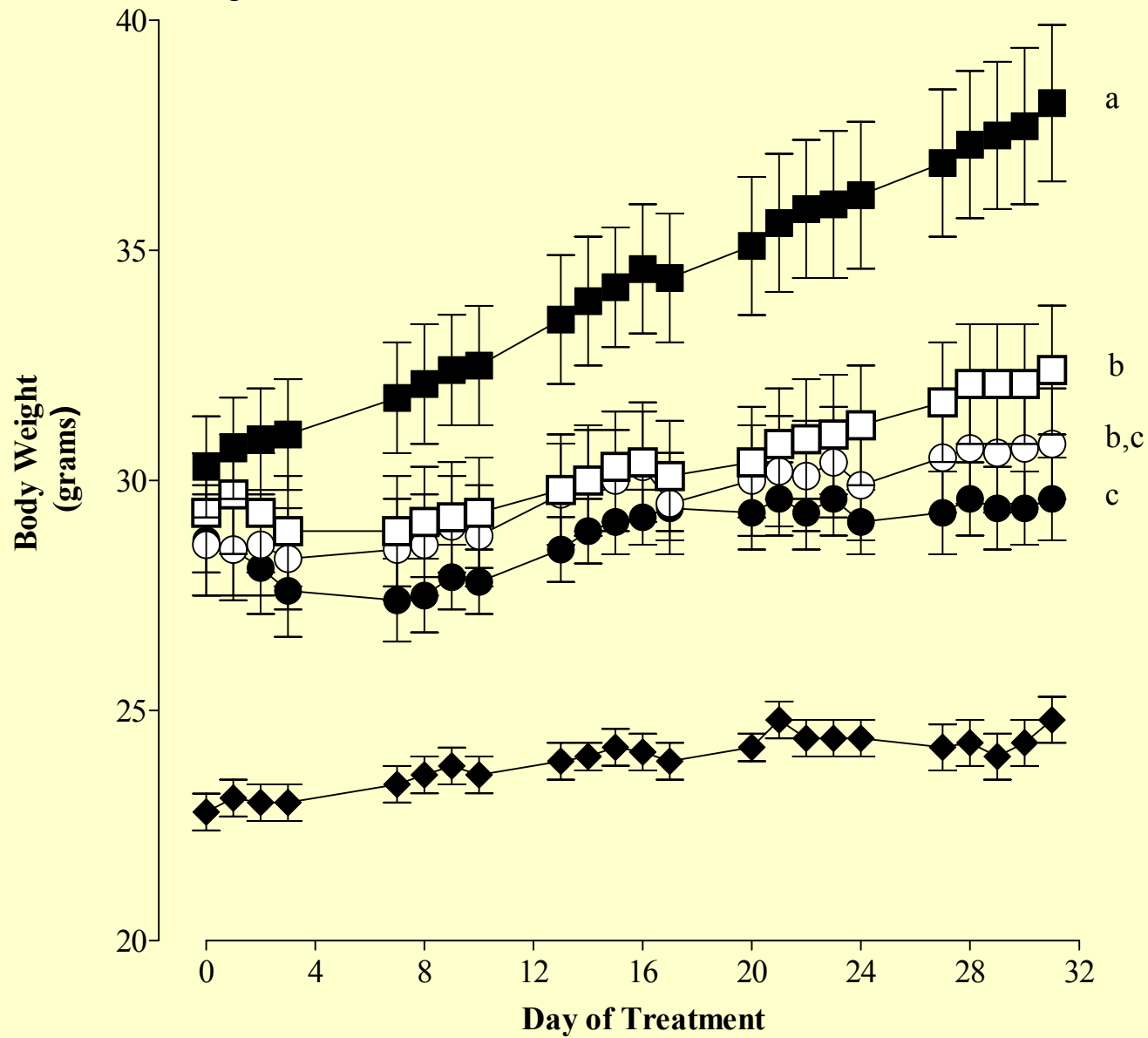
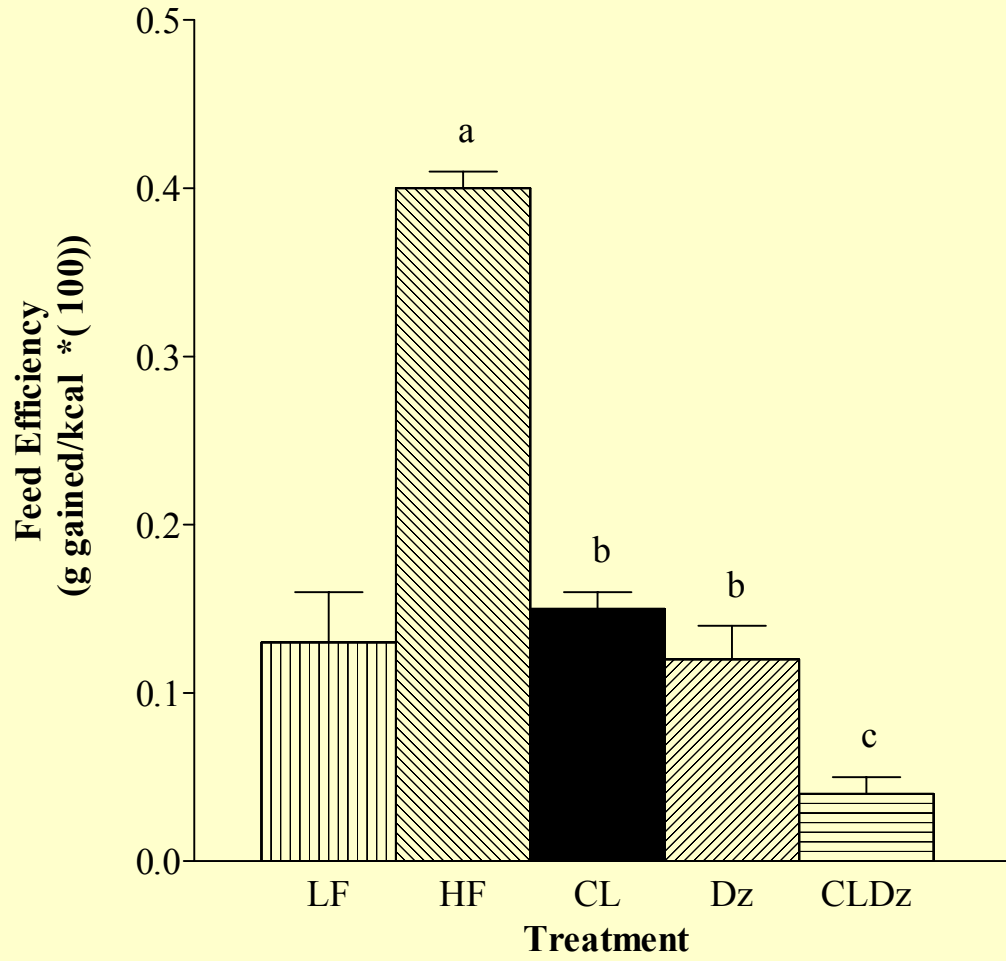


Figure 2



Adrenergic Stimulation of Lipolysis

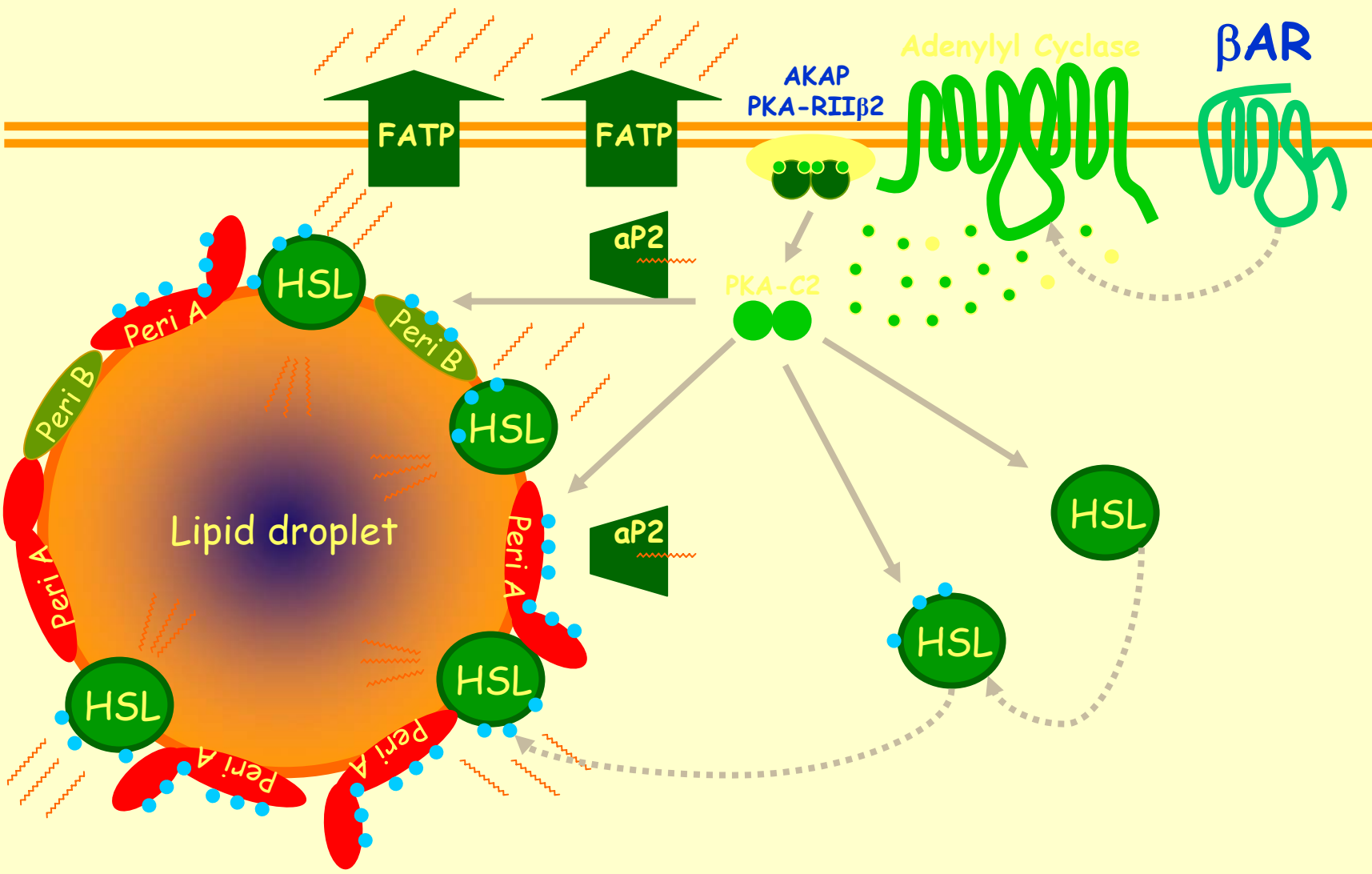
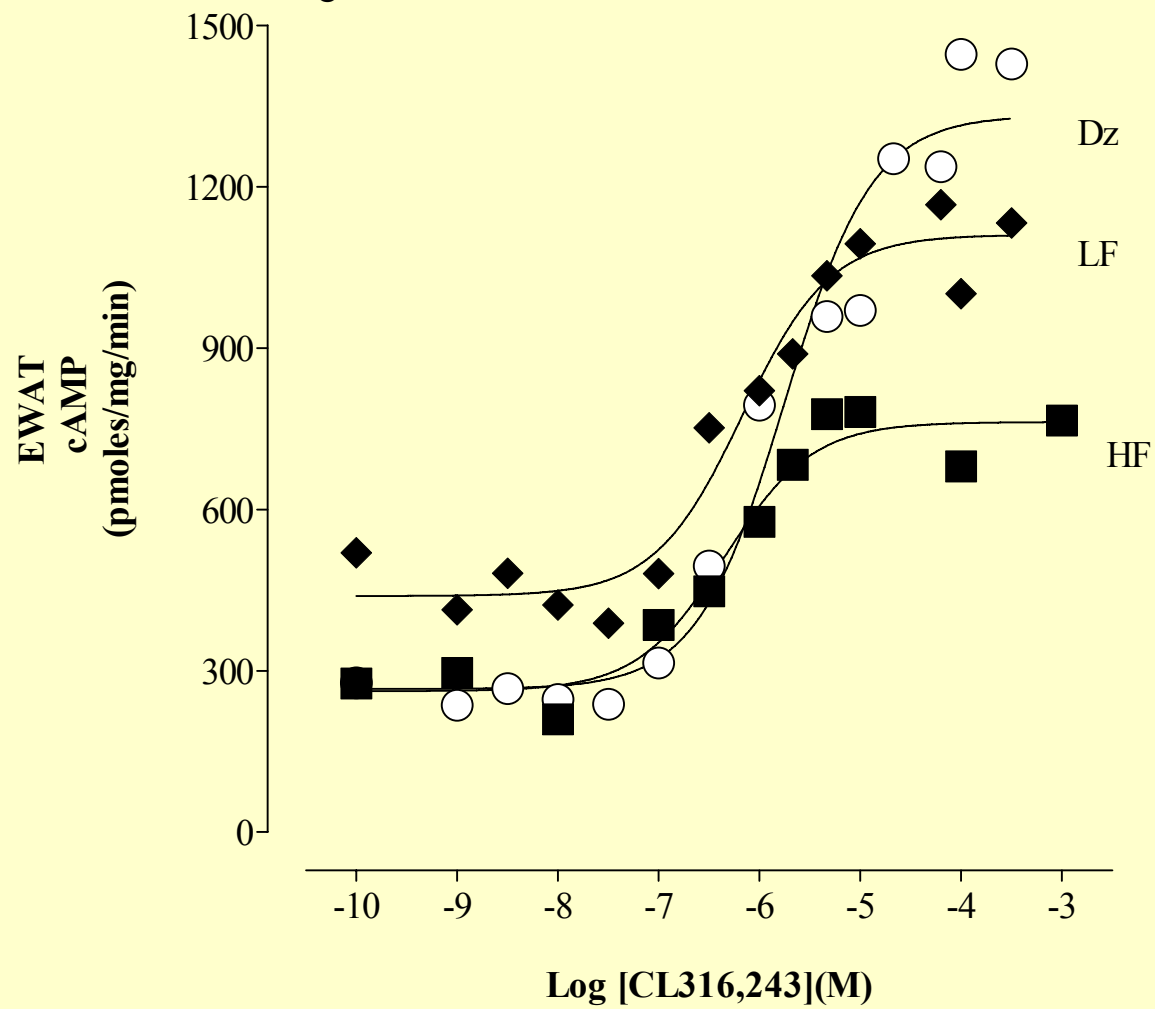


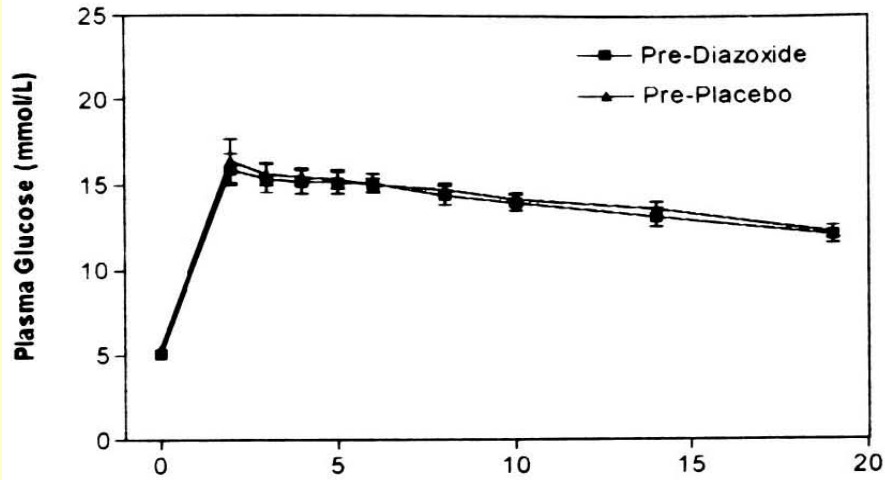
Figure 7



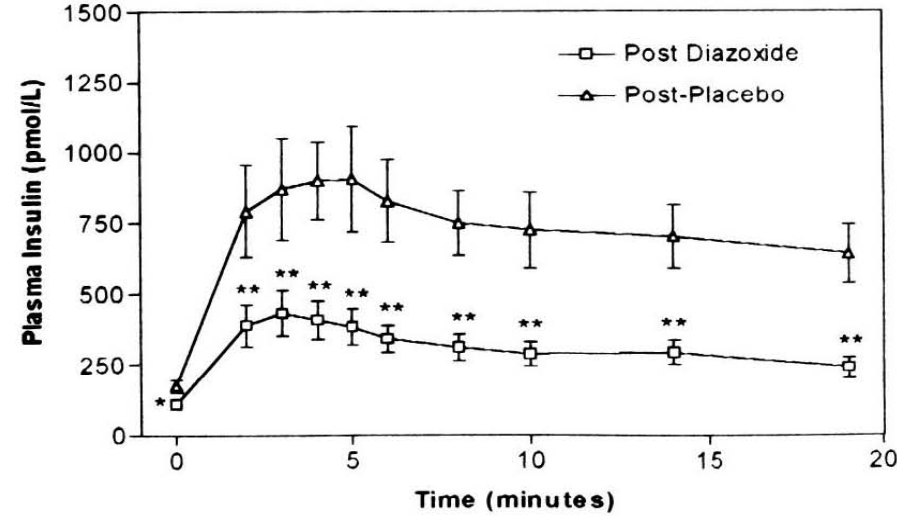
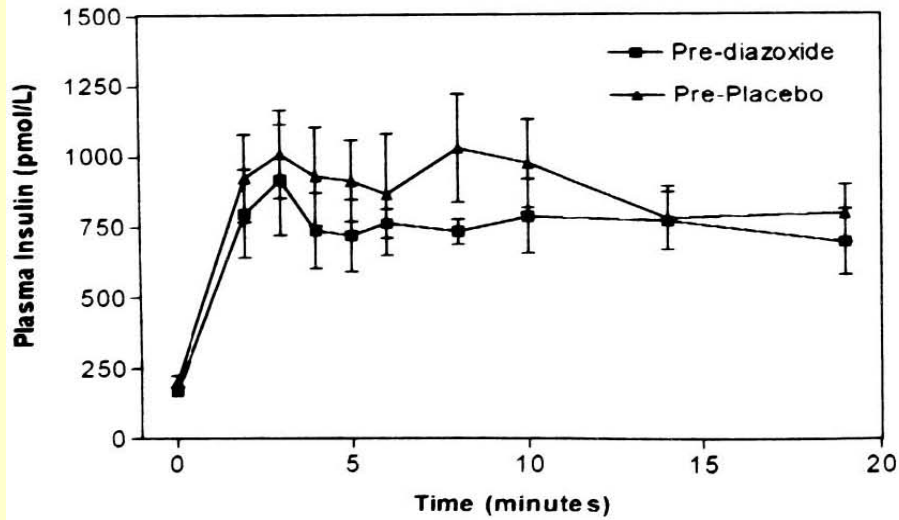
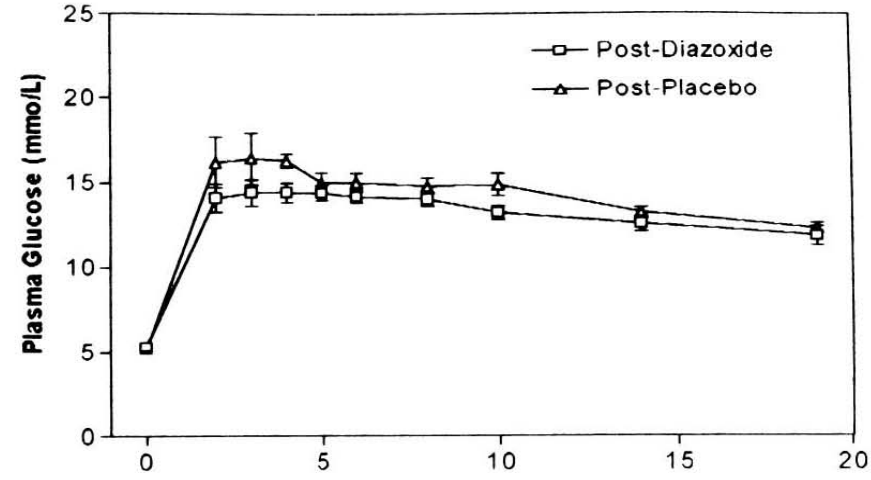
Human Studies

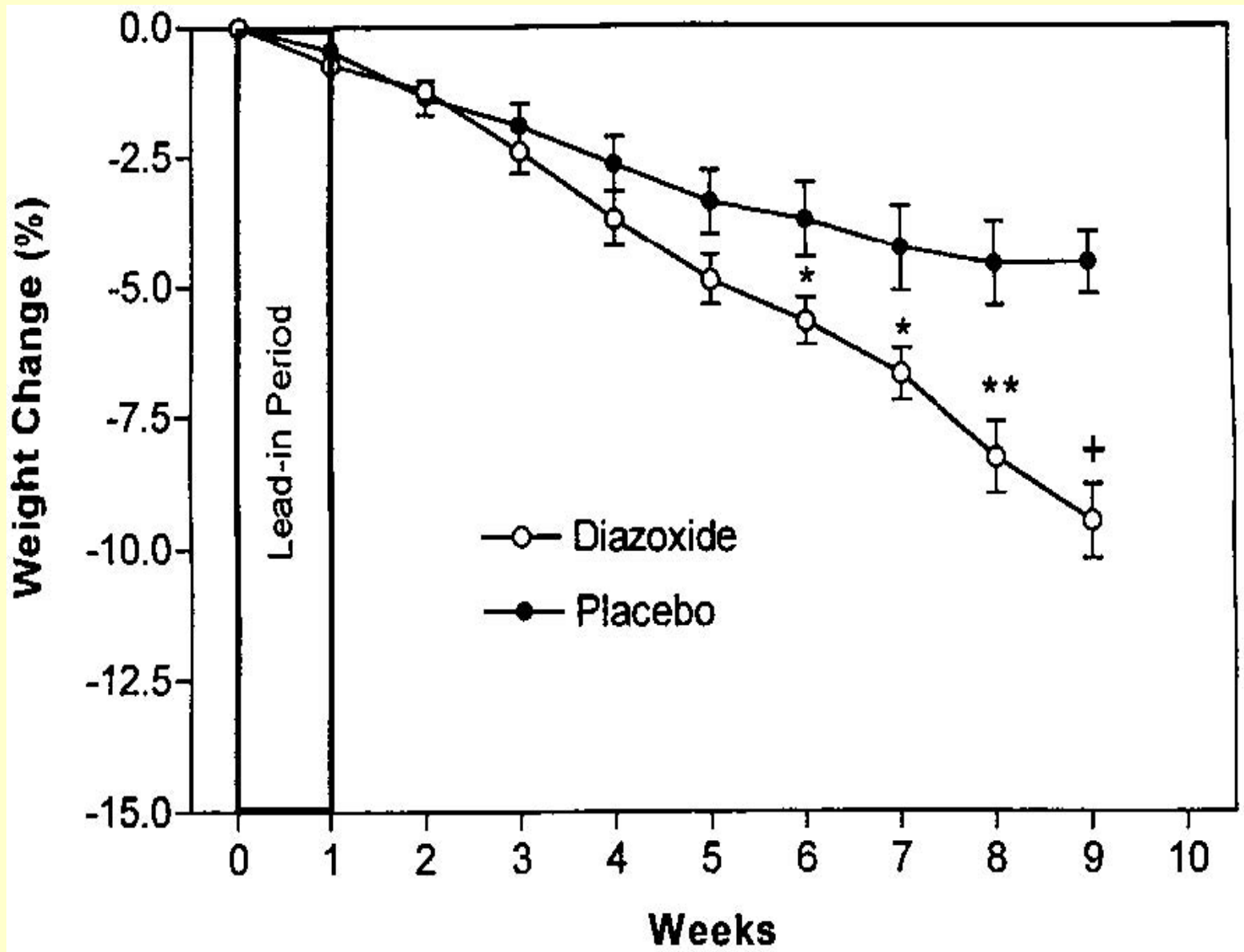
- Twenty-four hyperinsulinemic adults (BMI > 30) were placed on a 1260 Kcal diet for 8 weeks and given either:
 - .2 mg/kg of diazoxide in divided doses
 - a placebo

Pre-treatment



Post-treatment





Conclusions

- Hypersinsulinemia is associated with down regulation of β adrenergic stimulation of lipolysis
- Reduction of hyperinsulinemia by diazoxide improves β adrenergic signaling in the adipocyte
- Reduction of hypersinsulinemia results in attenuation of diet-induced obesity in mice and improved weight loss in humans.

Collaborators

- Sheila Collins
- Tonya Dixon
- Ann Petro
- Kiefer Daniel