THE EFFECT OF INHIBITING FATTY ACID OXIDATION ON GLUCOSE TOLERANCE IN SAND RATS

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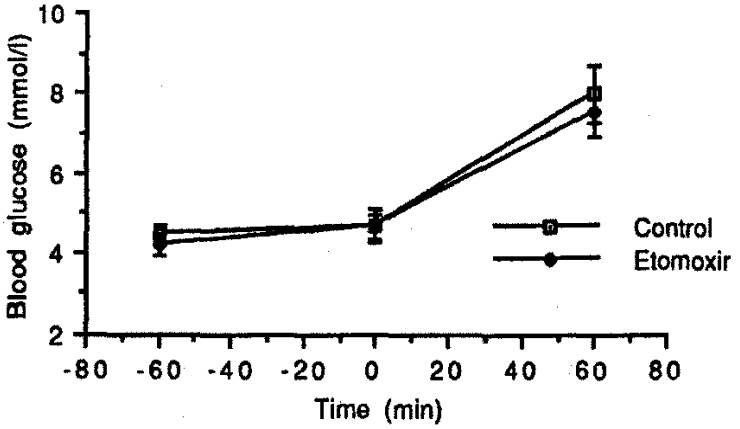
Long term feeding of high fat diets have been shown to cause insulin resistance in both normal and diabetic rats (Chisolm and O'Dea 1987). Although defects in hepatic glucose production (HGP) and metabolic clearance rate (MCR) have been demonstrated (Kruszynska et al. 1988), the underlying mechanism responsible is still poorly understood. If fatty acid oxidation is responsible for these defects then its inhibition should improve glucose tolerance. To further investigate this question we obtained a fatty acid oxidation inhibitor, Etomoxir (Byk Gulden, Konstanz). Etomoxir specifically inhibits carnitine palmitoyl transferase, thereby inhibiting long chain fatty acid oxidation.

We showed in a recent study using mildly diabetic streptozotocin rats fed a high fat diet, that a three week Etomoxir treatment improved glucose tolerance by reducing fasting HGP rather than affecting MCR (Collier et. 1989). In a previous study, Etomoxir (50mg/kg) acutely reduced fasting plasma glucose levels in diabetic rats (streptozotocin), (Reaven et al. 1988). It was postulated that a reduction in hepatic glucose production was responsible for this effect. Despite these studies it was still unclear what effect fatty acid oxidation inhibition would have in a less severe model of insulin resistance.

The current study examined the acute effects of Etomoxir (single dose) on glucose tolerance in Sand Rats (Psammomys Obesus). Eight Sand Rats were studied on two separate occasions. On one occasion an oral glucose tolerance test (O.G.T.T.) was performed (0.75 mg/kg body wt.), and on the other occasion an O.G.T.T. was performed preceded by a single oral dose of etomoxir (50mg/kg body wt.). Blood samples were taken 60 minutes before, at 0 and 60 minutes following the glucose load for glucose, TG and total cholesterol determinations.



Etomoxir tended to reduce glucose levels at one hour but the reduction was not significant (7.99±.072 vs 7.55±0.59 mmol/l) Over the two hour period, fatty acid oxidation inhibition did not affect TG (0.57±0.06 vs 0.51±0.07 mmol/l) or total cholesterol concentrations (3.51±0.38 vs 3.89±0.32 mmol/l).

These results suggest that the inhibition of fatty acid oxidation has no significant effect in animals without insulin resistance. A longitudinal study examining the effects of Etomoxir in this rat model as it develops insulin resistance may provide interesting results concerning the role of fatty acid oxidation in the development of impaired glucose tolerance.

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