FREE FATTY ACIDS (FFA), A LINK BETWEEN OBESITY AND INSULIN RESISTANCE

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TABLE OF CONTENTS
1. Abstract
2. Introduction
4. FFA and Peripheral Insulin Resistance
   4.1. Effect of FFA on Basal Glucose Uptake
   4.2. Effect of FFA on Insulin Stimulated Glucose Uptake
   4.3. Cellular Location of FFA Induced Defects
   4.4. Mechanisms
5. FFA and Hepatic Insulin Resistance
6. Significance
7. Acknowledgement
8. References

1. ABSTRACT

Evidence, gained from human studies, is reviewed showing that elevation of plasma FFA levels produce peripheral and probably also hepatic insulin resistance in obese healthy and diabetic subjects. First, plasma FFA levels are elevated in most obese subjects. Second, physiological elevations of plasma FFA inhibit acutely as well as chronically insulin stimulated glucose uptake in a dose dependent fashion. Responsible for this inhibition is a FFA induced defect in insulin stimulated glucose transport and/or phosphorylation which develops after 3-4 hours of raising plasma FFA and a second defect, consisting of inhibition of glycogen synthase, the rate limiting enzyme of glycogen synthesis, which develops after 4-6 hours. FFA induced inhibition of fatty acid oxidation (Randle effect) does not affect insulin stimulated glucose uptake or glycogen synthesis and thus does not cause insulin resistance. Elevated plasma FFA levels also modestly increase insulin suppressed endogenous glucose production (EGP) although this effect has not been found by all investigators. The reasons why it has been difficult to demonstrate unequivocal effects of FFA on EGP include 1) the fact that FFA promote insulin secretion which counteracts its effect on EGP (FFA increase, while insulin decreases EGP); 2) the recognition that FFA induced increase in gluconeogenesis may be compensated by intrahepatic downregulation of EGP (i.e., by a decrease in glycogenolysis).

The FFA induced insulin resistance is physiologically important during starvation by preserving carbohydrate for oxidation in the central nervous system and during pregnancy, where the well recognized accelerated starvation pattern provides carbohydrate for the growing fetus. In obesity, however, there is no need to spare carbohydrate and the FFA induced insulin resistance may result in type 2 diabetes and other cardiovascular risk factors.

2. INTRODUCTION

Obesity is associated with insulin resistance and hyperinsulinemia, two important cardiovascular risk factors (1,2). The fact that hyperinsulinemia and insulin resistance increase with weight gain and decrease with weight loss (3-6) suggests that this is a cause and effect relationship. What remains uncertain is how obesity produces insulin resistance and hyperinsulinemia. It has recently become clear, however, that FFA play a pivotal role in this process. Plasma levels of FFA are elevated in obesity (7,8) primarily because a greater than normal amount of FFA is released from the expanded adipose tissue mass even though the rate of lipolysis from individual fat cells appears to be normal (9,10). The following is a review of the evidence, gained from studies in human subjects, which shows that elevations of plasma FFA produce peripheral and probably also hepatic insulin resistance in healthy subjects and in patients with Type II diabetes.

3. INSULIN RESISTANCE. DEFINITION

For the purposes of this review, peripheral insulin resistance is defined as inhibition of normal insulin stimulation of whole body glucose uptake. Hepatic insulin resistance is defined as inhibition of normal insulin suppression of hepatic glucose production.
Link between obesity and insulin resistance

Figure 1: Effect of plasma FFA on insulin-stimulated glucose uptake. Euglycemic-hyperinsulinemic (~ 420 pmol/l) clamping was performed in healthy volunteers for 6 h. High levels of plasma FFA were produced by the infusion of triglycerides (4.3 µmol/min) plus heparin (0.4 U A kg⁻¹ min⁻¹) (Δ, n = 4); intermediate plasma FFA levels, by infusion of triglycerides without heparin (○, n = 4); and low FFA levels, by infusion of saline alone ( *, n = 6). Data shown are mean ± SE. The inhibition of insulin-stimulated glucose uptake became statistically significant ~ 3.5 h after the start of the lipid infusion. *p < 0.05; **p < 0.01, comparing high with low FFA. Adapted from Boden et al. (14*).

Insulin stimulation of total body glucose uptake and insulin suppression of hepatic glucose production were determined with the hyperinsulinemic clamp technique (11).

4. FFA AND PERIPHERAL INSULIN RESISTANCE

4.1. Effect of FFA on Basal Glucose Uptake

When plasma FFA concentrations were increased acutely by IV infusion of a triglyceride emulsion (Liposyn II, 10% safflower and 10% soybean oil) and heparin (which enhances lipoprotein lipase activity), FFA levels rose 2-3 fold (to between 1.0 and 1.5 mM) but basal rates of glucose uptake did not change (12).

4.2. Effect of FFA on Insulin Stimulated Glucose Uptake

In healthy subjects, acute elevation of plasma FFA by IV lipid/heparin infusion inhibited total body glucose uptake dose dependently after a lag period of 3-4 hours “figure 1”. Inhibition of CHO oxidation occurred ~ 2 h earlier than the inhibition of glucose uptake. The latter was reversed ~ 3 hours after discontinuation of lipid/heparin infusions (13) “figure 2”.

Other studies showed that the lipid induced inhibition of insulin stimulated glucose uptake was linear (14,15) “figure 3” and occurred similarly in healthy subjects and in patients with Type II diabetes (14-20). The long delay of 3-4 hours between the start of the insulin and lipid infusions and the development of significant insulin resistance was the most likely reason why the inhibitory effect of FFA on glucose uptake was not found in many previous studies (21-25).

The linear relationship between plasma FFA levels and insulin stimulated glucose uptake in healthy controls and patients with Type II diabetes suggested that for every 100 µM increase in plasma FFA, peripheral insulin sensitivity decreased by ~ 8% “figure 3”. It needs to be emphasized, however, that the total range of insulin stimulated glucose uptake was approximately 2 fold higher in healthy controls than in patients with Type II diabetes (15) “figure 4”. Thus, FFA could account for maximally 50% of peripheral insulin resistance in patients with Type II diabetes. Several potential problems could affect the interpretation of these results. First, the infused triglyceride emulsion (Liposyn II) contained a considerable amount of glycerol (2.5 grams/100 ml). We have shown, however, that this amount of glycerol did not affect glucose uptake (15).

Second, the data showing that elevation of plasma FFA decreased peripheral glucose uptake in response to insulin were all produced in acute experiments. Their relevance relative to the long term effects of elevated plasma FFA, for instance during obesity could, therefore, be questioned. It was, however, shown that lowering of plasma FFA below basal values caused an increase in insulin stimulated glucose uptake (13) “figure 1”. This indicated that basal FFA levels exerted long term inhibitory effects on peripheral glucose uptake.

4.3 Cellular Location of FFA Induced Defects

To determine the cellular location of the fat induced inhibition of insulin stimulated glucose uptake, glucose fluxes through all major pathways of intracellular glucose utilization were determined non-invasively. Rates of glucose uptake and glycolysis were estimated with 3-H-glucose and glycogen synthesis was obtained by subtracting glycolysis from glucose uptake. The validity of these methods has been validated (26). CHO oxidation was determined by indirect calorimetry and non-oxidative glycolysis (lactate and alanine formation) by subtracting CHO oxidation from glycolysis. Using these methods, it was found that lipid/heparin infusion inhibited rates of glucose uptake, glycogen synthesis and glycolysis about equally (15). In normal controls, for instance, plasma FFA concentrations of ~ 600 µM inhibited insulin stimulated glucose uptake, glycogen synthesis and glycolysis all by ~ 50% while in patients with Type II diabetes, a higher plasma FFA concentration of ~ 1200 µM resulted in a ~ 90% inhibition “figure 5”. These results suggested a FFA induced defect at the level of transport and/or phosphorylation (the methods used could not differentiate between these two possibilities). A primary defect at the level of glycogen synthesis or glycolysis, on the other hand, would have produced disproportionate reductions in the flux rates through these pathways.
Figure 2. Plasma FFA levels, and rates of CHO oxidation (COX) and glucose disappearance ($G_{\text{Rd}}$) in healthy men during lipid/heparin infusion (solid circles) and during lipid/heparin infusion from 0-120 min followed by saline infusion from 120-360 min (open circles) * $p < 0.05$, **$p < 0.01$, ***$p < 0.005$ comparing the 2 groups. Adapted from Boden et al. (13*).

Figure 3. Relationship between insulin stimulated glucose uptake and plasma FFA in 7 patients with NIDDM and in 6 non-diabetic controls. Data from controls were obtained during euglycemic (~ 5 mM)-hyperinsulinemic (~ 450 pM) clamping. Data from patients with NIDDM were obtained during hyperinsulinemic (~ 11 mM)-hyperinsulinemic clamping. Adapted from Boden et al. (14,15*).
uptake (G) because insulin was infused to lower their blood glucose. Glucose uptake could not be obtained in the diabetic patients with NIDDM and 6 nondiabetic control subjects. Preclamp mmol/l) hyperinsulinemic (~ 500 pmol/l) clamping in 7 patients with NIDDM and 6 nondiabetic control subjects. Preclamp glucose uptake could not be obtained in the diabetic patients because insulin was infused to lower their blood glucose concentrations into the normal range. Insulin-stimulated glucose uptake (G) was ~ 2 times higher in nondiabetic than in diabetic individuals (30 vs. 58 µmol/kg fat free mass, p < 0.01). Triglyceride plus heparin infusion (II) decreased insulin-stimulated glucose uptake by ~50% in diabetic and nondiabetic individuals. EU, euglycemia; FFM, fat free mass. Adapted from Boden et al. (14,15*).

Figure 4. Insulin-stimulated glucose uptake at comparable low plasma FFA (< 100 µmol/l) and euglycemia in diabetic and nondiabetic subjects. Shown are insulin-stimulated glucose uptakes before (●) and after (▲) 4 h of euglycemic (~ 4.8 mmol/l) hyperinsulinemic (~ 500 pmol/l) clamping in 7 patients with NIDDM and 6 nondiabetic control subjects. Preclamp glucose uptake could not be obtained in the diabetic patients because insulin was infused to lower their blood glucose concentrations into the normal range. Insulin-stimulated glucose uptake (G) was ~ 2 times higher in nondiabetic than in diabetic individuals (30 vs. 58 µmol/kg fat free mass, p < 0.01). Triglyceride plus heparin infusion (II) decreased insulin-stimulated glucose uptake by ~50% in diabetic and nondiabetic individuals. EU, euglycemia; FFM, fat free mass. Adapted from Boden et al. (14,15*).

Figure 5. Effects of elevated plasma FFA on rates of glucose uptake (G), glycogen synthesis (GS), and glycolysis (GLS) in 7 patients with NIDDM during hyperinsulinemic (~ 900 pmol/l) isoglycemic (~ 11 mmol/l) clamping and in 6 nondiabetic control subjects during euglycemic-hyperinsulinemic clamping (~ 500 pmol/l) clamping. Total length of bars represent insulin-stimulated G, GS, or GLS, set as 100%. The darkly shaded parts of the bars represent insulin-stimulated G, GS, or GLS after 4 h of elevated plasma FFA (~ 1,200 µmol/l in NIDDM, ~ 600 µmol/l in controls). FFA inhibited insulin-stimulated G, GS, or GLS similarly in patients with NIDDM and in normal control subjects, regardless of blood insulin and FFA levels. ■, lipid; , saline. Adapted from Boden et al. (14,15*).

Figure 6. Defects of glucose utilization produced by FFA. The inhibition of carbohydrate oxidation (defect 1) was the earliest demonstrable defect. It developed during the initial 2 h of lipid infusion, but did not inhibit insulin-stimulated glucose uptake or glycolysis. The inhibition of glucose transport and/or phosphorylation (defect 2) developed after 3–4 h, while the inhibition of glycogen synthesis (defect 3) developed after 4–6 h of high plasma FFA. E.C., extracellular; I.C., intracellular.

The evidence reviewed here indicates that physiological elevations of plasma FFA increases peripheral (and probably also hepatic) insulin resistance in a dose dependent manner. This FFA induced insulin resistance serves important physiological purposes during periods of prolonged starvation and during normal pregnancy. During starvation, rising plasma FFA produce peripheral insulin resistance, which preserves precious carbohydrate resources for oxidation in the central nervous system. Pregnancy, on the other hand, has been characterized as a state of accelerated starvation (52). FFA rise because of an increase.
in maternal fat deposition during the early part of pregnancy and as result of increased plasma levels of lipolytic gestational hormones (for instance, human placental lactogen and human chorion gonadotropin) (53). The resulting insulin resistance preserves carbohydrate for the growing fetus. In obesity, however, the FFA induced insulin resistance becomes counterproductive since there is no need to spare glucose. The insulin resistance in obesity is associated with several cardiovascular risk factors including hypertension, dyslipidemia, hyperuricemia and abnormal fibrinolysis (54). Whether or not any these are cause and effect relationships is presently not clear. Moreover, whether or not the FFA mediated insulin resistance will result in deterioration of glucose tolerance depends largely on the ability of the FFA to stimulate insulin secretion. Appropriate insulin secretory responses would largely avoid the need to compensate for the FFA induced insulin resistance with additional, hyperglycemia stimulated insulin secretion. Defective insulin responses, on the other hand, would worsen hyperglycemia.

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Link between obesity and insulin resistance


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