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Insulin Resistance in Cats: Not All Tissues Are Equal

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"Resistance to insulin-mediated glucose uptake is characteristic of individuals with impaired glucose tolerance or non-insulin-dependent diabetes, and it also occurs commonly in patients with high blood pressure. The physiological response to a decrease in insulin-mediated glucose uptake is an increase in insulin secretion, and as long as a state of compensatory hyperinsulinemia can be maintained, frank decompensation of glucose tolerance can be prevented. …" — Gerald Reaven

Glossary of Abbreviations
EGP: Endogenous Glucose Production
LPL: Lipoprotein Lipase
PKC: Protein Kinase C
PPARα: Peroxisome Proliferator-Activated Receptor α
TCA: Tricarboxylic Acid
TNR: Tumor Necrosis Factor
T2DM: Type 2 Diabetes Mellitus
VLDL: Very Low-Density Lipoproteins

Introduction

Gerald Reaven[1] was one of the first to examine the many facets of insulin resistance in people and associate high blood pressure and central obesity with hyperinsulinemia and glucose intolerance. He called this "syndrome X." It has also been called metabolic syndrome, insulin resistance syndrome and even Reaven's syndrome in his honor. Type 2 diabetes mellitus (T2DM) would be the consequence of the "frank decompensation of glucose tolerance."

Insulin resistance is one of the risk factors for the metabolic syndrome that also encompasses:

- Abdominal obesity (excessive fat tissue in and around the abdomen)
- Atherogenic dyslipidemia
- Elevated blood pressure
- Glucose intolerance
- Prothrombotic state
- Proinflammatory state

Hallmarks of type 2 diabetes are insulin resistance of liver, muscle and adipose tissue, in addition to abnormalities in insulin secretion and splanchnic glucose uptake, all leading to hyperglycemia.

Insulin Resistance in Cats

A. Glucose Metabolism

Many consider the cat a model for type 2 diabetes. A large percentage of diabetic cats are obese or have a history of having been obese, and similar to obesity in humans, feline obesity carries a high risk of developing diabetes. However, most obese cats have normal fasting and postprandial blood-glucose concentrations, although they show hyperinsulinemia. In obese humans and other populations at high risk of developing type 2 diabetes mellitus, the progression from normal to impaired glucose tolerance is associated with a marked increase in both fasting and glucose-stimulated plasma insulin levels[2,3] and a decrease in tissue sensitivity to insulin.[2,4]

When using the gold standard method,[5] the euglycemic hyperinsulinemic clamp, to assess insulin sensitivity in cats, increasing body size was found to significantly decrease glucose effectiveness S_G. S_G represents the component of fractional glucose clearance that is independent of deviations of insulin concentrations from basal. Insulin sensitivity S_I represents the steady state increase in fractional glucose clearance per unit increase from basal of insulin concentration. No other covariate, e.g., gender or diet, was found to significantly affect glucose kinetics parameters. In a recent longitudinal study of weight increase, we also found a direct negative correlation between glucose effectiveness and increasing body mass with a low-dose intravenous glucose tolerance test.(unpublished)

Both studies predicted that endogenous glucose production (EGP) was reduced for the observed average increase of insulin concentration. A reduction of EGP was indeed seen in a study where a triple tracer method was applied to study metabolic pathways in glucose production.[6] In that study, 13C-labeled glucose was used

to measure glucose turnover by conventional indicator dilution; deuterium was used to measure the fractional contribution of glycogen, glycerol and the tricarboxylic acid (TCA) cycle to EGP; and 13C-labeled propionate was used as a gluconeogenic tracer to measure fluxes through pathways associated with the TCA cycle. Our finding that EGP in the fasted state was lower in obese cats than lean cats and that insulin was higher, whereas there was no difference in glucose concentrations, suggests that the liver of obese cats responds appropriately to the increase in insulin. We also recently examined EGP in the postprandial state (six hours post-feeding) and found that it was still lower in obese compared to lean age-matched cats.(unpublished) The lower EGP in obese cats appears to be a compensatory mechanism to assure normal fasting and postprandial glucose concentration in cats with peripheral insulin resistance.

This suggests, therefore, that insulin resistance in obese cats is not universal to all tissues and that a loss of hepatic autoregulation is an important step in the pathogenesis of feline diabetes. It is unclear what molecular mechanisms fail when hepatic glucose regulation becomes dysfunctional, although several key molecules have been identified that are involved in the regulation of glucose production in other species (for example: FOXO1/HNF-4alpha).[7,8]

In type 2 diabetics, hepatic resistance to the action of insulin must be present in the fasting and postabsorptive state to explain the excessive output of glucose by the liver causing fasting and postprandial hyperglycemia. Because hyperglycemia by itself is a potent inhibitor of EGP, the liver also must be glucose-resistant in diabetics with respect to the inhibitory effect of hyperglycemia to suppress hepatic glucose output, and this has been well-documented.[9-11] There is evidence from humans and animal models of type 2 diabetes implicating increased activity of PEPCK, a rate-limiting step in gluconeogenesis and G-6-Pase, which regulates glucose efflux from cells, in the accelerated rate of hepatic glucose production;[12,13] however, this dogma has recently been challenged by investigators who found that increased transcriptional expression of PEPCK1 and G6Pc does not account for increased gluconeogenesis and fasting hyperglycemia in patients with T2DM.[14]

B. Lipid Metabolism

Lipids play an important role in the insulin resistance syndrome. The lipid profile of obese cats is similar to obese people in many, but not all, aspects. Obese cats show an increase in plasma triglycerides and non-esterified fatty acids, suggesting resistance of adipocytes to the effect of insulin. When we examined lipoprotein lipase (LPL) activity and expression, the enzyme that causes the hydrolysis of triglycerides primarily of chylomicrons and very low-density lipoproteins (VLDL), we found that LPL was low in adipose tissue and higher in muscle tissue in obese cats. LPL mRNA levels also were higher in muscle from obese cats, and a significantly higher muscle/fat ratio was seen in obese compared to lean cats.[15] In humans and cats, the low adipose tissue LPL activity correlated inversely with tumor necrosis factor (TNF), which is thought to be a major regulator of adiposity through suppression of adipocyte LPL and induction of apoptosis.[16]

The differential tissue expression of LPL expectedly favors a partitioning of fatty acids away from adipose tissue toward muscle tissue. Indeed, when we examined muscle fat using magnetic resonance imaging, we found an increase in intracellular and extracellular fat deposition in muscle in obese cats. Increased lipid deposition in muscle has been associated with insulin resistance in cats and many other species.[15,17,18] The increased partitioning of fatty acids into muscle tissue is thought to cause insulin resistance because uptake of free fatty acids negatively influences glucose transport.[19] An increase in muscular fatty acid uptake increases intracellular fatty acyl-CoA and diacylglycerol concentrations, which activate protein kinase C (PKC). The result is a decrease in insulin signaling and insulin-stimulated glucose transport activity. We have shown that decreased GLUT4 expression is an early change in developing obesity in cats and is evident before overt glucose intolerance is present.[20]

The increased amount of non-esterified fatty acids being shuttled to the liver in obesity is one of the factors involved in increased production and secretion of VLDL.[21] Despite the high VLDL concentrations, long-term obese cats have no change in baseline LDL concentrations, indicating that VLDL is metabolized rapidly and LDL clearance is increased to maintain normal levels. Similar to obese patients with insulin resistance, obese cats have high triglycerides largely due to this increase in triglycerides in the VLDL fractions, which in long-term obese cats was on average 500% higher, whereas it was approximately 180% higher in newly obese cats compared to lean cats. Overproduction of VLDL has been associated with decreased expression of peroxisome proliferator-activated receptor α (PPARα), which is involved in the upregulation of genes involved in fatty acid oxidation.[22] PPARα has been found to be low in obese cats.[23]

The overproduction of VLDL in cats is associated with an increase in the VLDL particle number. The particles were large and medium size, which, in people, has been associated with cardiovascular disease.[24] Large VLDL particles are linked with small LDL and HDL particles.[25] Increased levels of small, dense LDL have been shown to be strongly associated with coronary artery disease risk in people. In obese cats, an almost threefold increase

in very small and medium small LDL particles was found. Small HDL particles also have been associated with cardiovascular disease in people and were found in significantly higher numbers in obese cats.

In recent years, postprandial lipemia has received great attention in people as an early marker for cardiovascular disease. Postprandial lipid measurements unmask abnormalities earlier than lipid measurements in the fasting state, and it is currently thought that postprandial lipemia creates metabolic perturbations, which predict cardiovascular disease.[26] The postprandial phase is regarded as a major determinant of oxidative stress.[27] During this phase, VLDL and LDL are enriched with peroxidation-prone triglycerides. Postprandial remnant-like particles have been shown to increase cellular oxidant content and impair endothelial function.[28] Insulin-resistant subjects have a much greater postprandial lipemia than healthy subjects exposing them to greater risk of lipid peroxidation.[29] We will present data on postprandial lipid measurements in cats and on oxidative stress markers.

While obese cats show dyslipidemia and many show changes in glucose clearance and insulin resistance, a selective accumulation of fat in the abdomen with increasing obesity is not a feature of developing obesity in cats, the dyslipidemia of obese cats is not atherogenic and does not lead to hypertension, and fasting glucose intolerance is not common, even in long-term obese cats.

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