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Mechanisms underlying restoration of hepatic insulin sensitivity with CB1 antagonism in the obese dog model

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Visceral fat has long been associated with the development of insulin resistance. Although the mechanism is not well understood, it has been suggested that an increase in this fat depot results in an elevation in portal vein levels of free fatty acids and/or adipokines, adversely affecting hepatic glucose production. Overactivity of the endocannabinoid system is closely related to abdominal obesity and type 2 diabetes, suggesting CB_1 receptor antagonism may exert its beneficial effects by decreasing visceral fat mass. A recent study published from our laboratory explores the role of chronic CB_1 receptor antagonism and the longitudinal changes in insulin sensitivity and fat deposition in the canine model.

Keywords: insulin resistance, visceral fat, obesity, canine, adiponectin

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Obesity has long been associated with insulin resistance and hyperinsulinemia.[1] Studies have demonstrated an increase in hyperinsulinemia and insulin resistance with weight gain that is reversed with weight loss, suggesting a cause and effect relationship.[2] Although the relationship between obesity and the development of insulin resistance has been well documented, the exact role that adipose tissue may play in the pathogenesis of this disease has not yet been elucidated. There is accumulating evidence that adipose tissue, particularly visceral (also referred to as central, omental or abdominal) adipose, may be critical in the development of insulin resistance. Visceral fat has been shown to be more lipolytically active than subcutaneous fat in the presence of catecholamines, in addition to being more resistant to the anti-lipolytic actions of insulin. As originally proposed by Vague[3] and expanded by others,[4-6] an increase in central abdominal fat tissue can lead to an elevation in the portal vein concentration of free fatty acids (FFA), leading to an increase of FFA delivered directly to the liver thereby driving glucose production upward. In addition to its lipolytic properties, visceral fat has been found to have greater gene expression of more proinflammatory adipokines than subcutaneous fat,[7] and there is also a particularly strong negative correlation between visceral adiposity and adiponectin levels.[8]

The endocannabinoid system may play a key role in the link between adiposity and insulin resistance. Overactivity of the endocannabinoid system is intimately related to abdominal adiposity and type 2 diabetes, and chronic CB_1 receptor antagonism has been shown to alleviate both obesity and insulin resistance. Recently, we reported a significant improvement in hepatic insulin resistance in dogs rendered obese and insulin resistant with a high fat, hypercaloric diet after only two weeks of treatment with a CB_1 receptor antagonist, rimonabant (RIM).[9] Hepatic insulin sensitivity was almost completely restored to pre-diet levels while visceral and subcutaneous fat depots were virtually unaltered and relatively little change in peripheral insulin sensitivity. However, there was a concomitant increase in plasma adiponectin levels which occurred with RIM that was not observed in the placebo animals, suggesting that the improvement in hepatic insulin sensitivity observed with CB_1 receptor antagonism may be mediated by adiponectin.

Although it is well known that there is a strong association between visceral

adiposity and insulin resistance, a causal relationship has yet to be determined. It has been also been considered that insulin resistance per se may cause visceral fat accumulation such that insulin resistance of subcutaneous fat would result in a reduction of fatty acid uptake by this fat depot, resulting in increased fat deposition in visceral stores. Alternatively, it had been thought that both visceral fat accumulation and insulin resistance may be related to another biological process.[10] Studies utilizing animal models with a selective reduction in visceral fat have shown that decreasing omental fat volume results in an improvement in insulin resistance, suggesting a direct relationship between this fat depot and insulin sensitivity.[11-13] However, reports in human studies have been conflicting.[14-16] In order to examine the putative relationship between visceral fat and insulin sensitivity, we employed the use of a CB_1 receptor antagonist, rimonabant. Previous studies conducted in humans[17-19] have found that RIM treatment results in favorable changes in cardiometabolic risk factors that were associated with significant reductions in waist circumference—indicating a decrease in visceral adiposity. These findings suggest that rimonabant effects on insulin resistance may be secondary to a reduction in visceral fat. However, in our study, we found a profound effect of RIM on hepatic resistance with only a minimal change in visceral fat, suggesting that the improvement in insulin sensitivity must be due to other mechanisms. Our study also revealed a highly significant increase in plasma adiponectin in the RIM treated animals that occurred in concert with the improvement in insulin sensitivity as well as a marked increase in the expression of liver adiponectin receptors (ADR1 and ADR2). Additionally, we observed increased expression of other mediators of hepatic lipid oxidation such as canitine palmitoyltransferase I and peroxisome proliferator-activated receptor-α. Together, these data indicate that RIM has a direct effect on the liver mediated by adiponectin, to increase fat oxidation. As discussed in our publication, other studies have found that activation of hepatic CB1 receptors increases hepatic gene expression of the sterol regulatory element-binding protein-1c, a lipogenic transcription factor, and its targets, acetyl-CoA carboxylase-1 and fatty acid synthase,[20] thereby contributing to diet-induced steatosis and associated hormonal and metabolic changes,[21] indicating that there may be a prevalent role of peripheral CB_1 receptors in the development of insulin resistance. A more recent study utilizing hepatic explants to examine the direct effect of CB_1 receptor antagonism on the liver demonstrated that RIM treatment increased fat oxidation,[22] confirming a direct effect of RIM on the liver. Although CB_1 receptor antagonism is well known for its central effects in mediating food intake and weight loss, increasing evidence has shown that CB_1 receptors in peripheral tissues may also play a role in directly regulating metabolic processes, giving further evidence that in our study, the improvement in insulin sensitivity was not directly related to the modest decrease in fat accumulation but due to the action of RIM on increasing adiponectin.

It has also been found that adipocyte cell size may play a determining role in determining insulin sensitivity, independent of cell number. In a separate publication[23] from our laboratory, adipocytes isolated from both visceral and subcutaneous fat depots from placebo and RIM animals were examined for qualitative changes in cell size and distribution that are undetectable by magnetic resonance imaging (MRI). We found that fat feeding altered the adipocyte size distribution in both visceral and subcutaneous fat, resulting in the appearance of very large cells (> 75 μm diameter). However, only the appearance of these hypertrophic adipocytes in visceral fat was found to be a significant predictor of hepatic insulin resistance. RIM treatment reversed the effects of high fat diet in both depots by eliminating the population of large adipocytes. Interestingly, while MRI showed volume expansion in both fat depots, we found qualitative differences at the cellular level that could not be detected by MRI. This suggests that in addition to absolute volume of adipose tissue playing a major role in the development of hepatic insulin resistance, size and distribution of adipocytes in the fat compartment are also important.

In summary, our study found an almost complete restoration of hepatic insulin sensitivity when the CB_1 receptor antagonist rimonabant was administered to animals rendered obese by a high fat hypercaloric diet. This improvement occurred in the absence of a significant change in absolute visceral fat volume, indicating that there may be a direct effect of RIM on the liver mediated by adiponectin. RIM's effect on adipose cell size and distribution in the visceral adipose tissue may also be a significant contributor in ameliorating hepatic insulin resistance. It would be of great interest to selectively examine the direct effects of RIM on peripheral tissues such as the liver and adipose in the insulin resistant dog model. Future studies comparing the effects of a peripheral vs. central CB_1 antagonist will be necessary to better distinguish whether the metabolic benefits of chronic endocannabinoid blockade are due primarily to diminished central regulation or decreased peripheral action.

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