Activation of Sterol Receptor Element Binding Protein-1c and NFkB by Atypical Protein Kinase C in Liver mediates Lipid Abnormalities and Insulin Resistance in Murine Obesity Models

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Background Information

1. Atypical protein kinase-C (aPKC), a subfamily of the protein kinase C (PKC) isoforms, has been shown to play a role in the regulation of lipid metabolism and insulin sensitivity.
2. aPKC is activated in response to insulin and participates in the regulation of glucose and lipid metabolism.
3. Ablation of aPKC in adipose tissue leads to increased lipogenesis and decreased lipolysis.

Questions Addressed

1. What accounts for differences in the severity of insulin resistance and obesity in obesity models with different alleles for the aPKC gene?
2. How does aPKC regulate the expression of genes involved in lipid metabolism and insulin sensitivity?
3. Are there differences in the effects of aPKC on lipid metabolism and insulin sensitivity between different strains of mice?

Figure 1: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding- and Insulin-Dependent Increases in Activities of Signaling Factors in Muscle (left) and Liver (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

Findings and Conclusions:

1. Like 6 hours insulin treatment (Figure 5), high fat feeding activates IKKβ in muscle (a) and liver (b) of HFF mice.
2. Expression of KI-ζ in liver improves activation of aPKC (a), PKB/Akt (b) and IRS1/PI3K (c) in muscles of HFF mice through inhibition of hepatic NFκB activity, as well as decreases in hepatic SREBP-1c (d) and FAS (e) expression.

Figure 2: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h)- and Insulin (60 min)-Dependent Increases in Triglycerides, Cholesterol and Glucose in Muscle (left) and Liver (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

Findings:

1. Levels of triglycerides, cholesterol and glucose are increased in fed HFF mice.
2. Expression of KI-ζ in liver improves activation of aPKC (a), PKB/Akt (b) and IRS1/PI3K (c) in muscles of HFF mice through inhibition of hepatic NFκB activity, as well as decreases in hepatic SREBP-1c (d) and FAS (e) expression.

Figure 3: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 4: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 5: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 6: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 7: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 8: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 9: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Figure 10: Effects of Adenovirally-Mediated Expression of Kinase-Inactive PKC-ζ (KI-ζ) on Feeding (6 h) and Insulin (60 min) Increases in Activities of Signaling Factors in Liver (left) and Muscle (right) in High Fat-Fed Mice. (Vec=Adenovirus Vector Alone.)

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Summary

1. In Het-MKO mice, knockdown of IRS-2 with shRNA leads to impaired activation of hepatic aPKC (b), but normal activation of hepatic PKB/Akt (c) in HFF mice.
2. Expression of KI-ζ in liver diminishes activation of hepatic NFκB (d) and FAS (e) expression in HFF mice.
3. Inhibition of hepatic aPKC improves insulin signaling to muscle and liver.

Conclusions

1. In Het-MKO mice, activities of SREBP-1c, IKKβ and NFκB are excessively activated in the fed state.
2. In Het-MKO mice, aPKC functions upstream of SREBP-1c, IKKβ and NFκB.
3. Inhibition of hepatic aPKC improves insulin resistance in muscle.

SREBP-1c and IKKβ activity, and therefore release of inflammatory proteins and possibly obesity itself, in murine obesity models, i.e., HFF, Het-MKO, and ob/ob.