Activation of insulin/IGF-I signaling could increase hypothalamic lipid anabolism in non-diabetic IRS2-deficient mice

P1-D2-69

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The authors have nothing to disclose

Background

Insulin/insulin like-growth factor-I (IGF-I) signaling plays a critical role in central glucose bioavailability and lipid metabolism. An increase in glucose disposal can generate reducing agents through the pentose-phosphate pathway necessary for the synthesis of free fatty acids (FFA) and recent evidences suggest that nicotinamide adenine dinucleotide (NAD^+) depletion leads to abnormal lipid metabolism. Disturbances in lipid synthesis are related to the appearance of insulin resistance and diabetes. The insulin receptor substrate (IRS) 2-deficient mice ($IRS2^{-/-}$) is an excellent model to study the development of diabetes as a high proportion of them present an abrupt increase in glycemia, showing similarities with type 1 diabetes. However, the molecular mechanisms involved in the onset of diabetes in $IRS2^{-/-}$mice remain to be elucidated.

Hypothesis and objective

We hypothesized that alterations in insulin/IGF-I signaling could be related to the incidence of diabetes in $IRS2^{-/-}$mice. Thus, we analyzed the changes in hypothalamic signaling and its relationship with fatty acid metabolism in this model.

Animals and methods

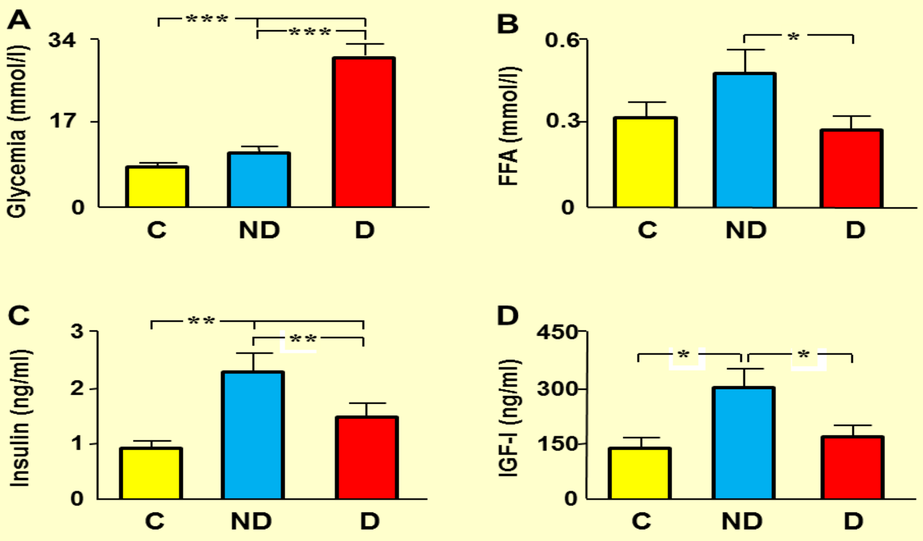
Animals

Eighteen male mice:
- Controls (C, wild type mice)
- Non-diabetic $IRS2^{-/-}$ (ND, glycemia < 11.10 mmol/l)
- Diabetic $IRS2^{-/-}$ (D, glycemia > 27.75 mmol/l)

Methods
- Serum insulin and IGF-I: ELISA
- Serum glucose and free fatty acids: colorimetric methods
- Hypothalamic insulin/IGF-I signaling: multiplexed bead immunoassay and immunoprecipitation/Western blot
- Enzymes: Western blot in hypothalamic extracts
- Metabolomic studies: nuclear magnetic resonance in hypothalamic extracts

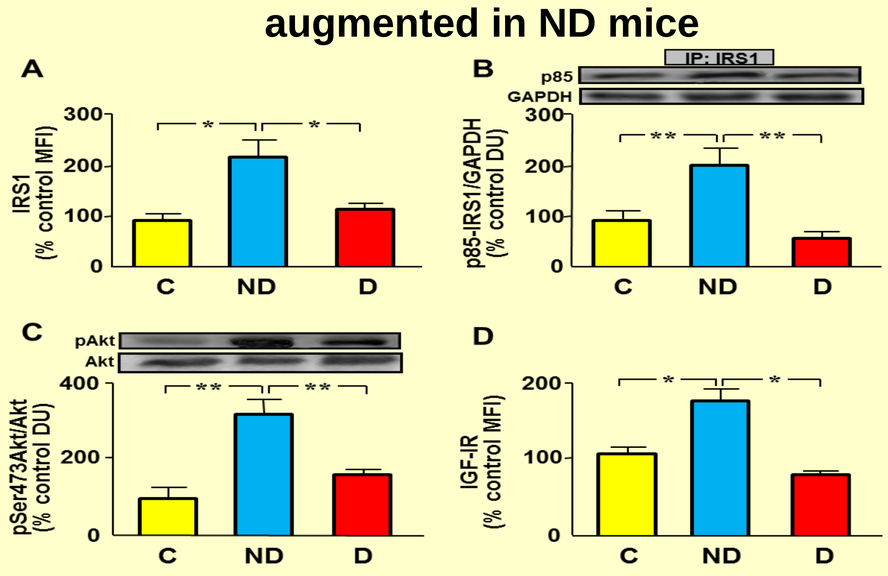
Results

1 Serum metabolite and hormone levels are modified in $IRS2^{-/-}$ mice



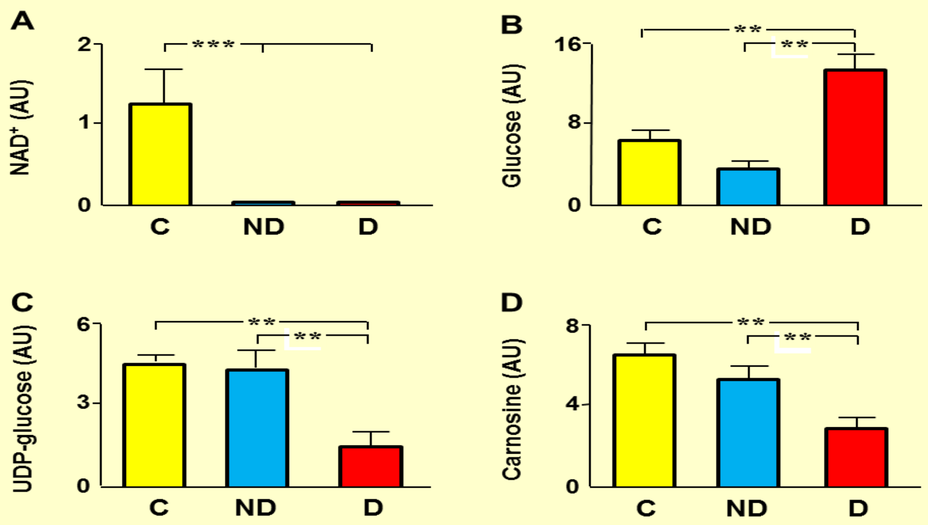
A. *Glycemia in controls (C), non-diabetic IRS2 deficient (ND) and diabetic IRS2 deficient mice (D).* ***B****. Serum free fatty acid concentrations (FFA) in the same groups.* ***C.*** *Serum insulin levels in the same groups.* ***D****. Serum insulin-like growth factor-I (IGF-I) in the same groups. *p<0.05, **p<0.01, ***p<0.001.*

2 Activation of hypothalamic insulin/IGF-I signaling is augmented in ND mice



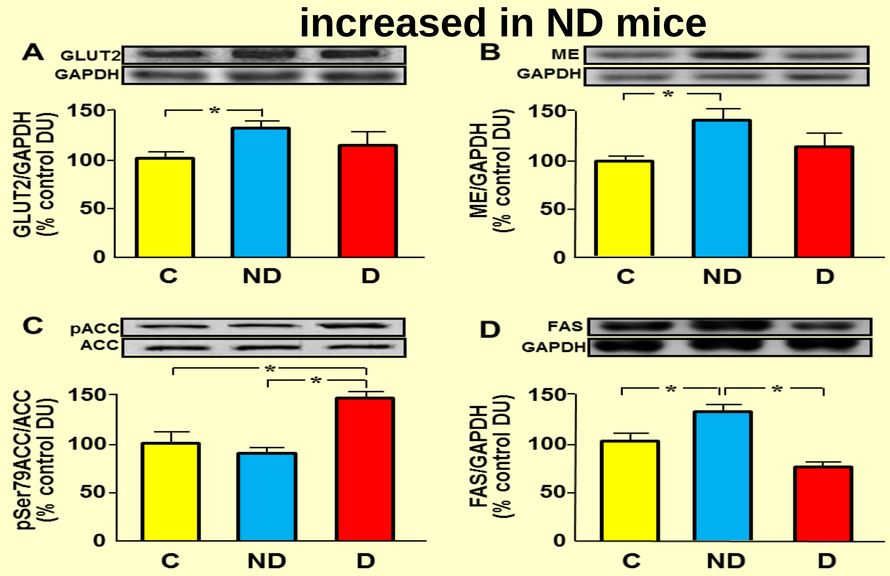
A. *Relative levels of insulin receptor substrate 1 (IRS1) in controls (C), non-diabetic IRS2 deficient (ND) and diabetic IRS2 deficient mice (D).* ***B.*** *Relative levels of the regulatory subunit of PI3K (p85) associated to IRS1 in the same groups.* ***C.*** *Relative protein levels of Akt phosphorylated on serine 473 (pSer473-Akt) in the same groups.* ***D.*** *Relative protein levels of insulin-like growth factor-I receptor (IGF-IR) in the same groups. *p<0.05 **p<0.01. DU, densitometry units; MFI, median fluorescent intensity.*

3 Metabolite profiling in the hypothalamus of ND mice is related to deregulation of lipid homeostasis



A. *Levels of hypothalamic nicotinamide adenine dinucleotide (NAD^+) in controls (C), non-diabetic IRS2 deficient (ND) and diabetic IRS2 deficient mice (D).* ***B****. Levels of glucose in the same groups.* ***C.*** *Levels of uridine diphosphate (UDP)-glucose in the same groups.* ***D****. Levels of carnosine in the same groups. **p<0.01, ***p<0.001. AU, arbitrary units.*

4 Reduction capacity and fatty acid anabolism are increased in ND mice



A. *Relative levels of glucose transporter 2 (GLUT2) in controls (C), non-diabetic IRS2 deficient (ND) and diabetic IRS2 deficient mice (D).* ***B.*** *Relative protein levels of malic enzyme (ME) in the same groups.* ***C****. Relative protein levels of acetyl CoA carboxylase phosphorylated on Ser79 (pSer79/ACC) in the same groups.* ***D.*** *Relative protein levels of fatty acid synthase (FAS) in the same groups. *p<0.05. DU, densitometry units.*

Conclusion

Increased hypothalamic insulin/IGF-I signaling might be a triggering factor for the occurrence of diabetes in $IRS2^{-/-}$mice.