Novel Mechanisms Regulating Glucose Transport in the Lung of Influenza-Infected and Non-Infected Diabetic Mice

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Introduction

• The prevalence and morbidity due to diabetes has consistently increased over the years, in addition to the mortality caused by respiratory infections such as influenza (Fig 1A).
• Hyperglycemia has recently been identified as an independent risk factor for pulmonary infections.
• The mechanisms governing glucose transport in the lung, especially in hyperglycemic patients, is not well understood.
• Glucose is thought to diffuse passively from the blood to the airway surface liquid, and glucose transporters (GLUTs) may be required to actively transport glucose into the cell from the airway (Fig 1B).

Hypothesis

Diabetes will alter the regulation of glucose transport in the lung, which will be rescued by metabolic therapy.

Methodology

Type 1 Diabetic
1. Control C57BL/6 mice
2. Type 1 Diabetic mice (streptozotocin-induced, T1Dx, 8 weeks)
3. Diabetic mice treated with insulin (subcutaneous pump, 8 weeks)

Type 2 Diabetic
1. Control C57BL/6 mice
2. Control mice treated with metformin (200 mg/kg/day)
3. Type 2 diabetic (T2Dx), high-fat diet fed, 60% kcal from fat (Fig 3)
4. T2Dx mice treated with metformin

Insulin Treatment Rescues Hyperglycemia in Type 1 Diabetic Mice

Fig 4: Mean ± SE of [glucose] and body weight, n=8-10/group. A) Mice injected with streptozotocin (STZ) became markedly hyperglycemic, while insulin-treated mice maintained normoglycemia. B) Body weight was not different between groups. *p<0.05 vs control, #p<0.05 vs baseline via 2-way RM ANOVA. T1Dx: Type 1 diabetic mice.

Metformin Treatment Rescues Alterations of GLUT Protein Expression in the Lung of Influenza-infected and Non-infected Type 1 Diabetic Mice

Fig 6: Mean ± SE of [glucose] and body weight, n=8-10/group. A) Mice fed a high-fat diet became markedly hyperglycemic, while metformin-treated mice maintained normoglycemia. B) High-fat diet mice, regardless of treatment, had significantly greater body weight than either control group. *p<0.05 vs control, #p<0.05 vs baseline via 2-way RM ANOVA. T1Dx: Type 1 diabetic mice.

Conclusion

• Both insulin and metformin treatment rescued alterations of GLUT-4, GLUT-10, and GLUT-12 protein expression in upper lung of type 1 and type 2 diabetic mice, respectively.
• In both T1Dx and T2Dx groups, the non-diabetic mice demonstrated an upregulation of GLUT trafficking to the cell surface when infected with the flu compared to the non-infected mice.
• These novel findings suggest that 1) the regulation of glucose transport is altered in the upper lung during hyperglycemia, potentially worsening the response to influenza infection, and 2) in vivo insulin or long-term metformin treatment rescues GLUT protein alterations in the diabetic lung.
• Insights gained from this study could lead to the identification of novel metabolic therapeutic targets for diabetic patients affected by concurrent respiratory infections.

Fig 7: Top panels: representative western blots. Bottom panels: Mean ± SE total protein expression of A) GLUT4 B) GLUT2, C) GLUT12 (n=3-5/group) in adult rodent upper lung. *p<0.05 vs Control, †p<0.05 vs Control + Flu. 2-tailed t-test. GLUT: Glucose transporter; T1Dx: Type 1 diabetic animal; Met: Metformin; Flu: Influenza. Method: Western blotting.

Fig 8: Top panels: representative western blots. Bottom panels: Mean ± SE total protein expression of A) GLUT4 B) GLUT2, C) GLUT12 (n=3-5/group) in adult rodent upper lung. *p<0.05 vs Control. †p<0.05 vs Control + Flu. 2-tailed t-test. GLUT: Glucose transporter; T2Dx: Type 2 diabetic animal; Met: Metformin; Flu: Influenza. Method: Western blotting.

Fig 9: Schematic diagram of alterations in pulmonary glucose transport and utilization during diabetes and how these alterations may cause increased viral replication...

References


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