

Does Intra-portal Glucose Infusion Cause Hypoglycemia in Humans?

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Background

- Intra-portal infusion of glucose at rates approximating endogenous glucose production (EGP) causes hypoglycemia in mice.
- This paradoxical response occurs in wild type but not GLUT-2 null mice implying activation of a GLUT-2 dependent portal glucosensor.

Hypothesis

Intra-duodenal (and therefore selective delivery into the portal vein) infusion of glucose at rates approximating endogenous glucose production causes hypoglycemia in humans.

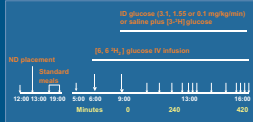
Experimental Design

- 13 healthy non-diabetic subjects were studied after an overnight fast.
- Subjects were studied on two occasions in random order. Subjects were infused intraduodenally (ID) with [$^3\text{-}^3\text{H}$] glucose and unlabeled glucose at rates of either 3.1 mg/kg/min (n=5), 1.55 mg/kg/min (n=9), 0.1 mg/kg/min (n=5) or 0 (i.e. saline; n=4).
- [6,6- $^2\text{D}_2$] glucose was infused intravenously to permit measurement of EGP, glucose disappearance and the rate of appearance of the ID infused glucose.
- Since results did not differ, the data from the 0.1 and 0 mg/kg/min studies were combined for purposes of analysis.

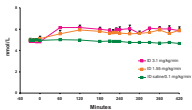
Volunteer Characteristics

Subjects	N=9	N=9	N=5
Age (yrs)	25 ± 3	25 ± 3	24 ± 4
Gender	5M/4F	4M/5F	2M/3F
BMI (kg/m ²)	24 ± 3	24 ± 4	24 ± 2
LBM (kgs)	51 ± 10	51 ± 13	49 ± 10
Body Fat (%)	22 ± 8	24 ± 11	24 ± 6

Study Design

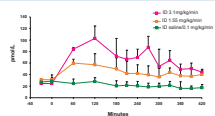


Plasma Glucose



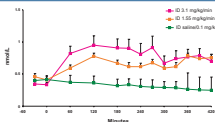
- Fasting plasma glucose concentrations did not differ (ANOVA; p=0.5) on the three study days.
- Plasma glucose concentrations fell (p<0.01) from (4.97 ± 0.08 to 4.68 ± 0.08 mmol/L) on the ID saline/0.1 mg/kg/min study day.
- In contrast, plasma glucose increased (p<0.01) on both the 1.55 mg/kg/min (5.0 ± 0.15 to 5.79 ± 0.26 mmol/L) and 3.1 mg/kg/min (4.83 ± 0.04 to 5.96 ± 0.17 mmol/L) study days.
- Glucose concentrations did not differ during the final hour of the 1.55 and 3.1 mg/kg/min study days.

Insulin



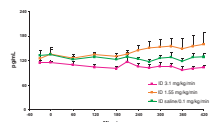
- Fasting plasma insulin concentrations did not differ (ANOVA; p=0.821) on the study days.
- Insulin concentrations fell slightly (p=0.06) from 28.1 ± 6.9 to 16.6 ± 5.37 pmol/L on the ID saline/0.1 mg/kg/min study day.
- In contrast, insulin increased (p<0.001) on both the 1.55 mg/kg/min (31 ± 7 to 39 ± 9.8 pmol/L) and 3.1 mg/kg/min (24.7 ± 3.2 to 47.5 ± 5 pmol/L) study days.
- Insulin concentrations were slightly but not significantly higher (p=0.4) during the final hour of the 3.1 than 1.55 mg/kg/min study days.
- *Plasma insulin concentrations of one individual in the 1.55 mg/kg/min group was 3 SDs greater than the other subjects in the group and therefore were excluded from analysis.

C-peptide



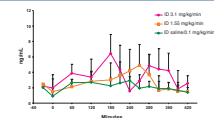
- Fasting plasma C-peptide concentrations did not differ (ANOVA; p=0.26) on the study days.
- C-peptide concentrations fell (p<0.001) from 0.4 ± 0.04 to 0.3 ± 0.05 mmol/L on the ID saline/0.1 mg/kg/min study day.
- In contrast, C-peptide increased (p<0.01) during the ID 3.1 mg/kg/min (0.33 ± 0.04 to 0.74 ± 0.11 mmol/L).
- C-peptide also increased (p<0.06) in all nine subjects during the ID 1.55 mg/kg/min infusion however, the magnitude of the increase was more variable (0.43 ± 0.05 to 0.75 ± 0.21 mmol/L).
- C-peptide concentrations did not differ (p=0.5) during the final hour of the 1.55 and 3.1 mg/kg/min study days.

Glucagon



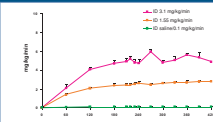
- Fasting plasma glucagon concentrations did not differ (ANOVA; p=0.185) on the three study days.
- Glucagon concentrations tended to fall on the 3.1 mg/kg/min study day, and remain unchanged on the ID saline/0.1 mg/kg/min study day but the differences were not significant.

Growth Hormone



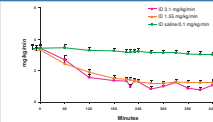
Growth hormone concentrations did not differ on the three study days either before or during the ID infusions.

Rate of Appearance of ID Glucose



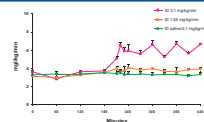
- The systemic rate of appearance of ID infused glucose increased during the first three hours of the 1.55 and 3.1 mg/kg/min infusions reaching a plateau thereafter.
- The appearance of ID glucose was greater (ANOVA; p<0.0001) during the final hour of the 3.1 than 1.55 mg/kg/min ID infusion (2.73 ± 0.15 vs. 5.25 ± 0.27).
- ID infused tracer appearance averaged 105 ± 14%, 108 ± 3%, and 113 ± 18% during the ID 0.1 mg/kg/min, 1.55 and 3.1 mg/kg/min infusions indicating negligible splanchnic extraction.

Endogenous Glucose Production



- Fasting endogenous glucose production (EGP) did not differ (ANOVA; p=0.5) on the study days.
- EGP fell (p<0.01) from 3.38 ± 0.21 to 3.05 ± 0.05 the ID saline/0.1 mg/kg/min study day.
- ID infusion of glucose at 3.1 and 1.55 mg/kg/min resulted in greater (p<0.001) suppression of EGP than did ID saline/0.1 mg/kg/min.
- EGP did not differ (p=0.1) during the final hour of the ID 1.55 and 3.1 mg/kg/min infusions.

Glucose Disappearance



- Fasting glucose disappearance did not differ (ANOVA; p=0.76) on the study days.
- Glucose disappearance fell slightly (p=0.4) from 3.29 ± 0.4 to 3.24 ± 0.22 the ID saline/0.1 mg/kg/min study day.
- ID infusion of glucose at 3.1 and 1.55 mg/kg/min resulted in a greater (ANOVA; p<0.001) increase in glucose disappearance than did ID saline/0.1 mg/kg/min to 6.3 ± 0.13 and 3.76 ± 0.2 mg/kg/min respectively.
- Glucose disappearance during the final hour of the 3.1 mg/kg/min infusion was greater (p<0.001) than that present during the final hour of the ID 1.55 mg/kg/min infusion.

Summary

Intra-duodenal glucose infusion at rates of 1.55 and 3.1 mg/kg/min resulted in

- An increase in plasma glucose concentrations
- Comparable suppression of endogenous glucose production and appearance of ID infused glucose
- Greater rates of glucose disappearance and slightly higher insulin concentrations during the 3.1 than 1.55 mg/kg/min

Conclusion

In summary, intra-duodenal glucose infusion at rates bracketing normal EGP does not cause hypoglycemia in non-diabetic humans.