The Regulation of Liver Glucose Production and Uptake

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An Organ Systems Approach to Experimental Targeting of the Metabolic Syndrome

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DAILY GLUCOSE PROFILE

“Ordinary Daily Life”

OGTT

**Tracer Method**

- $3^{-3}\text{H}$ Glucose infusion
- Data analysis with two compartment model

**A-V Difference Method**

- Blood glucose difference across organ
- Blood flow across organ
\[ ([\text{Portal}] \times BF_p) + ([\text{Arterial}] \times BF_A) \Rightarrow ([\text{Hepatic}] \times BF_{\text{Total}}) \]
Glucose Production =

Glycogenolysis + Gluconeogenesis – Lactate Production – Glucose Oxidation
DISTRIBUTION OF LIVER BLOOD FLOW

Hepatic Vein

Liver

Hepatic artery (20%)

Portal vein (80%)

Intestine

Artery
Pancreatic Clamp

ARterial Plasma Glucose (mg/dl)

ARterial Plasma Insulin (µU/ml)

Glucose Production (mg/kg/min)
EFFECT OF A SELECTIVE INCREASE IN INSULIN

PLASMA INSULIN (μU/ml)

PLASMA GLUCAGON (pg/ml)

TIME (Min)
EFFECT OF A SELECTIVE INCREASE IN INSULIN

Pancreatic Clamp +/− Insulin

- ARTERIAL PLASMA GLUCOSE (mg/dl)
- NET HEPATIC GLUCOSE OUTPUT (mg/kg/min)
- NET GLY (mg/kg/min)
- GNG FLUX (mg/kg/min)

TIME (Min)
EFFECT OF SELECTIVE INSULIN DEFICIENCY

Pancreatic Clamp
Saline

Pancreatic Clamp
↓ Insulin

PLASMA INSULIN (µU/ml)

PLASMA GLUCAGON (pg/ml)

TIME (Min)

0 20 40

0

0 50 100

0

0 50 100

-40 0 60 120 180

-40 0 60 120 180

Portal
Art

Portal
Arterial
EFFECT OF SELECTIVE INSULIN DEFICIENCY

Pancreatic Clamp

+/- Insulin

ARTERIAL PLASMA GLUCOSE (mg/dl)

-40 0 60 120 180
0 100 200 300

NET HEPATIC GLUCOSE OUTPUT (mg/kg/min)

-40 0 60 120 180
-5 0 5 10

TIME (Min)

Control

Pancreatic Clamp

+/- Insulin

NET GLY (mg/kg/min)

-40 0 60 120 180
0 2 4 6

GNG FLUX (mg/kg/min)

-40 0 60 120 180
0 2 4 6

TIME (Min)
** (Redrawn from Holther-Nielsen et al.: Metabolism 45: 82-91, 1996) +
EFFECT OF A SELECTIVE INCREASE IN GLUCAGON
EFFECT OF A SELECTIVE INCREASE IN GLUCAGON

![Graphs showing changes in arterial plasma glucose, net hepatic glucose output, and glycolysis flux with and without glucagon.](image_url)
EFFECT OF SELECTIVE GLUCAGON DEFICIENCY

Pancreatic Clamp

Saline

PLASMA INSULIN (µU/ml)

0 10 20 30

-40 0 60 120 180

PLASMA GLUCAGON (pg/ml)

0 40 80 120

-40 0 60 120 180

Pancreatic Clamp

Glucagon

Portal

Arterial

EFFECT OF SELECTIVE GLUCAGON DEFICIENCY

Pancreatic Clamp

Saline

PLASMA INSULIN (µU/ml)

0 10 20 30

-40 0 60 120 180

PLASMA GLUCAGON (pg/ml)

0 40 80 120

-40 0 60 120 180

Pancreatic Clamp

Glucagon

Portal

Arterial

EFFECT OF SELECTIVE GLUCAGON DEFICIENCY

Pancreatic Clamp

Saline

PLASMA INSULIN (µU/ml)

0 10 20 30

-40 0 60 120 180

PLASMA GLUCAGON (pg/ml)

0 40 80 120

-40 0 60 120 180

Pancreatic Clamp

Glucagon

Portal

Arterial

EFFECT OF SELECTIVE GLUCAGON DEFICIENCY

Pancreatic Clamp

Saline

PLASMA INSULIN (µU/ml)

0 10 20 30

-40 0 60 120 180

PLASMA GLUCAGON (pg/ml)

0 40 80 120

-40 0 60 120 180

Pancreatic Clamp

Glucagon

Portal

Arterial

EFFECT OF SELECTIVE GLUCAGON DEFICIENCY

Pancreatic Clamp

Saline

PLASMA INSULIN (µU/ml)

0 10 20 30

-40 0 60 120 180

PLASMA GLUCAGON (pg/ml)

0 40 80 120

-40 0 60 120 180

Pancreatic Clamp

Glucagon

Portal

Arterial
EFFECT OF SELECTIVE GLUCAGON DEFICIENCY

**ARTERIAL PLASMA GLUCOSE (mg/dl)**

**NET HEPATIC GLUCOSE OUTPUT (mg/kg/min)**

**GNG FLUX (mg/kg/min)**

**Pancreatic Clamp +/− Glucagon**

**Time (Min)**

**Control**

**Glucagon**

**NET GLY (mg/kg/min)**

**Pancreatic Clamp +/− Glucagon**

**Time (Min)**
GLUCAGON VS GLUCOSE PRODUCTION
( INSULIN BASAL AND FIXED )

GLUCOSE PRODUCTION
( mg/kg/min )

HEPATIC SINUSOIDAL GLUCAGON
( pg/ml )
CATECHOLAMINES AND STRESS

**Arterial Plasma Epinephrine (pg/ml)**

- Overnight: 0
- Fast: 500
- Moderate Exercise: 1000
- Infection: 1500
- Ketoacidosis: 3000
- Hypoglycemia (40 mg/dl):

**Arterial Plasma Noradrenaline (pg/ml)**

- Overnight: 0
- Fast: 200
- Moderate Exercise: 400
- Infection: 600
- Ketoacidosis: 800
- Hypoglycemia (40 mg/dl):
EFFECT OF A SELECTIVE INCREASE IN EPINEPHRINE

Pancreatic Clamp

Saline

PLASMA EPI (pg/ml)

PLASMA NOREPI (pg/ml)

Time (Min)

Pancreatic Clamp

Epinephrine

Arterial

Portal

Time (Min)
EFFECT OF A SELECTIVE INCREASE IN EPINEPHRINE

ARterial plasma glucose (mg/dl)

Net hepatic glucose output (mg/kg/min)

Pancreatic Clamp +/- Epinephrine

NET GLY (mg/kg/min)

GNG flux (mg/kg/min)

Control

Epinephrine

TIME (Min)

-40 0 60 120 180

-40 0 60 120 180
EFFECT OF A SELECTIVE INCREASE IN SINUSOIDAL NOREPINEPHRINE

Pancreatic Clamp
Saline

Pancreatic Clamp
Norepinephrine

PLASMA EPI (pg/ml)

PLASMA NOREPI (pg/ml)

TIME (Min)

Arterial
Portal

Arterial
Portal
EFFECT OF A SELECTIVE INCREASE IN SINUSOIDAL NOREPINEPHRINE

ARTERIAL PLASMA GLUCOSE (mg/dl)

Pancreatic Clamp

+/− Portal Norepi

NET HEPATIC GLUCOSE OUTPUT (mg/kg/min)

Pancreatic Clamp

+/− Portal Norepi

GNG FLUX (mg/kg/min)

Control

TIME (Min)
DISPOSITION OF AN ORAL GLUCOSE LOAD

GLUCOSE

Muscle + Fat

Liver

CNS

RBC
INSULIN AND GLUCOSE AS STIMULATORS OF HEPATIC GLUCOSE UPTAKE

Peripheral Glucose Infusion

BLOOD GLUCOSE (mg/dl)

ARTERIAL PLASMA INSULIN (μU/ml)

NET HEPATIC GLUCOSE BALANCE (mg/kg/min)

TIME (Min)

OUTPUT

INPUT
OGTT IN THE CONSCIOUS DOG

BLOOD GLUCOSE (mg/dl)

ARTERIAL PLASMA INSULIN (μU/ml)

NET HEPATIC GLUCOSE BALANCE (mg/kg/min)

Oral Glucose

Portal

Arterial

Glucagon

Insulin

Output

Uptake

TIME (Min)
CONTROL OF GLUCOSE ENTRY INTO THE LIVER

- Glucose Load
- Portal Signal
- Insulin Level

Liver
EFFECT OF THE ROUTE OF GLUCOSE ADMINISTRATION ON GLUCOSE DISPOSITION IN THE BODY

-30 0 90 180 min

Tracers and Indocyanine Green
SRIF + Basal Portal Glucagon
Basal Portal Insulin
4 X Basal Portal Insulin

+ or

Peripheral Glucose  Portal Glucose
Portal Glucose  Peripheral Glucose
EFFECT OF THE ROUTE OF GLUCOSE ADMINISTRATION ON GLUCOSE DISPOSITION IN THE BODY

BLOOD GLUCOSE (mg/dl)

<table>
<thead>
<tr>
<th>Treatment Period</th>
<th>Artery</th>
<th>Portal</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pe</td>
<td></td>
<td></td>
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<tr>
<td>Po</td>
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</tbody>
</table>
EFFECT OF THE ROUTE OF GLUCOSE ADMINISTRATION ON GLUCOSE DISPOSITION IN THE BODY

**Graphs:**

- **Arterial Plasma Insulin (µU/ml):**
  - Control, Pe, Po

- **Arterial Plasma Glucagon (pg/ml):**
  - Control, Pe, Po

- **Hepatic Glucose Load (mg/kg/min):**
  - Control, Pe, Po

- **Net Hepatic Glucose Balance (mg/kg/min):**
  - Control, Pe, Po

Output, Uptake
HEPATIC GLUCOSE LOAD VS NET HEPATIC GLUCOSE UPTAKE

NET HEPATIC GLUCOSE UPTAKE (mg/kg/min)

HEPATIC GLUCOSE LOAD (mg/kg/min)

Portal Signal Active
Portal Signal Inactive
INSULIN VS NET HEPATIC GLUCOSE UPTAKE IN THE PRESENCE OF BASAL GLUCAGON AND A 2X BASAL HEPATIC GLUCOSE LOAD

NET HEPATIC GLUCOSE UPTAKE (mg/kg/min)

HEPATIC SINUSOIDAL INSULIN (µU/ml)

Portal Signal Active
Portal Signal Inactive
ARTERIAL-PORTAL GLUCOSE GRADIENT VS NET HEPATIC GLUCOSE UPTAKE IN THE PRESENCE OF BASAL GLUCAGON, 4X BASAL INSULIN AND 2X BASAL HEPATIC GLUCOSE LOAD

NET HEPATIC GLUCOSE UPTAKE (mg/kg/min)

ARTERIAL - PORTAL BLOOD GLUCOSE GRADIENT (mg/dl)
### Effect of Glucagon on Hepatic Glucose Uptake

<table>
<thead>
<tr>
<th>Time (Min)</th>
<th>Basal Portal Ins+GGN</th>
<th>Portal Insulin (4-Fold Basal)</th>
<th>Portal Glucose (3.8 mg/kg/min)</th>
<th>Peripheral Glucose (to double HGL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-120</td>
<td></td>
<td></td>
<td></td>
<td>Peritoneal Somatostatin</td>
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<tr>
<td>0</td>
<td></td>
<td></td>
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</tr>
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<td>90</td>
<td></td>
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<tr>
<td>330</td>
<td></td>
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</tr>
</tbody>
</table>

**Hi GGN**
- (n=6)

| Portal Glucagon (ng/kg/min) | 1.2 |

Or

**Lo GGN**
- (n=6)

| Portal Glucagon (ng/kg/min) | 0.30 | 0.25 | 0.20 |
Glucose Infusion
Hormone Manipulation

Arterial Blood Glucose (mg/dl)
- High GGN
- Low GGN

Arterial Plasma Insulin (μU/ml)

Arterial Plasma Glucagon (pg/ml)

Time (Min)
HEPATIC GLUCOSE LOAD (mg/kg/min)

TOTAL GLUCOSE INFUSION (mg/kg/min)

NET HEPATIC GLUCOSE BALANCE (mg/kg/min)

Glucose Infusion
Hormone Manipulation

Time (Min)

High GGN
Low GGN

Output
Uptake

Total Glucose Load

Hormone Manipulation

Glucose Infusion