Autonomic regulation of islet hormone secretion-
Implications for health and disease

Billy & Bree
Paper 1:

Autonomic regulation of islet hormone secretion: Implications for health and disease

By Team BBB (Bree, Billy, and Boyle)
Nervous system divisions:

- Central Nervous System
- Peripheral Nervous System
  - Autonomic Nervous system
    - Parasympathetic nervous system
    - Sympathetic nervous system
  - Enteric nervous system
Anatomy of the ANS

**Somatic motor system**
- CNS
- Somatic motor neuron
- Skeletal muscle

**Autonomic motor system**
- CNS
- Autonomic ganglion
- Preganglionic fiber, *acetylcholine* as the NT
- Postganglionic fiber
  - SNS: noradrenaline, ATP, acetylcholine (sweat glands and blood vessel) and NPY
  - PSN: *acetylcholine*, peptides
- Smooth muscle
- Gland cells
- Cardiac muscle

Slide from Lu Chen
Autonomic Nervous System Control of insulin release:

**Parasympathetic**

- Lateral hypothalamus

**Sympathetic**

- Ventromedial hypothalamus

The Autonomic NS connects extensively with the pancreatic islet cells

- Autonomic NS: part of the nervous system that controls unconscious behaviors (like breathing, digestion, heart rate, etc)
  - Broken into parasympathetic (P= PJs, rest and digest) and sympathetic (S= scared, fight or flight mode).
- Pancreatic islet cells: cells in the pancreas that secrete hormones
- Nerves from the ANS richly innervate the pancreatic islets, suggesting nervous system control of pancreatic actions (namely, insulin secretion)
parasympathetic
VIP
PNCP
gastrin RP

insulin secretion

sympathetic
galanin NPY

AXS→islet interaction allows
1) oscillation/coordination
2) response to metabolic stress
3) cephalic insulin secretion
4) insulin resistance?
Parasympathetic Nerves- anatomy

What do they look like?
Pre-ganglionic nerves originate in dorsal motor tract of VAGUS →

travel to pancreas where they connect to the post-ganglionic nerves →

synapse onto islets

How do we know this?
Stain with cholinesterase: marks choline acetyltransferase (which indicates acetylcholine is nearby, suggesting a cholinergic synapse. PS is almost exclusively cholinergic).
Light/ Electron microscopy to see your staining
Parasympathetic nerves- effects

Preganglionic → Vagus → Ach → nicotinic receptor on post ganglionic cell → muscarinic receptor on B cells of pancreas

- hexamethonium
- adrenalectomy + pharmacological (to exclude nic → adrenaline mech)

- immuno
- CdNa
- Ach blockers, antagonists
- atropine / Antagonists
Muscarinic Receptors

• Receptors for acetylcholine: 5 subtypes (m1-m5)
• m3 seems to be the most important
  • Antagonist for this receptor inhibits cholinergically induced insulin release
  • Is more present in rat islets (cDNA + immunostaining)
PACAP, VIP, GRP (non-cholinergic mechanisms)

- All released upon stimulation of the vagus
- Stimulates both insulin and glucagon release, in vivo and in vitro
  - GPCR receptors (cascade pathways)
- Glucose $\rightarrow$ VIP/PACAP $\rightarrow$ GPCR $\rightarrow$ adenylate cyclase $\rightarrow$ CAMP (Ca, Na, exocytosis) $\rightarrow$ insulin

- GRP coordinates Ca oscillations in the cytosol
  - Acts via DAG and PKC pathway
Other Nerves

- Nitric oxide nerves
  - If you inhibit NO synthase, inhibit insulin
- CCK nerves stimulate insulin
Cephalic Phase of insulin action

• Autonomic and endocrine responses can be mediated by sensory mechanism (as opposed to being triggered by absorbed nutrients)

• 3 pathways:
  1) afferent from the 5 senses
  2) central integratory mechanism (ventromedial hypothalamus → dorsal motor nucleus of vagus)
  3) efferent pathway back to brain

• Sham feeding produces insulin release in rats
  • hypnosis, fake food, food tease, fake sweeteners
  • If you introduce glucose but bypass the oral cavity, you see glucose intolerance
Synchronizing islet function

• Islet B cells secrete insulin in a pulsatile manner
• Blocking pancreatic ganglia destroys the oscillation-disturbed patterns seen in diabetes
• Pulsatile treatment with insulin is more effective to suppress hepatic glucose production than continuous insulin injection in Type 1 diabetes
Insulin Secretion from Beta Cells

1.) Close K+ channels -> depolarization -> Activation of Calcium channels -> Calcium influx -> insulin containing vesicle exocytosis

2.) Activate adenylate cyclase -> increase cAMP -> activation of PKA -> insulin containing vesicle exocytosis

3.) Activate PLC -> PIP2 to IP3 and DAG -> IP3 increases calcium and DAG activates PKC -> both cause insulin secretion via exocytosis

4.) Activate PLA2 -> converts phospholipids to arachidonic acid -> AAs cause insulin release via exocytosis
Sympathetic

Fight or Flight Mode
Sympathetic nerve input on Islet Cells:

NPY: Neuropeptide Y
NA: Noradrenalin

Effects of Galanin on Beta Cells

Galanin causes opening of K+ Channels

This results in a hyperpolarization of the beta cells, which inactivates the voltage sensitive channels that only open upon depolarization.
Effects of NPY on Beta Cells

NPY inhibits AC

As a result, there is less cAMP and PKA activation, which causes less insulin secretion.
Effects of NA on Beta Cells

When bound to $\alpha_2$ - NA causes decrease insulin secretion by the same mechanism as galanin

**BUT**

When bound to $\beta_2$ - NA causes ACTIVATION of AC -> increases insulin secretion

The net effect is dependent on the ratio of the receptors.
NA on Other Islet Cells

- Increases Glucagon secretion from alpha cells
- Increases PP secretion from F cells
- Increases somatostatin from delta cells
Overall Effect of Sympathetic Innervation of Islet cells

- Decrease insulin (NPY, NA, Galanin)
- Increase glucagon (NA)
- Increase in Blood Glucose

Why?

INCREASE FUEL AVAILABILITY IN EXCITED STATE
Other & sensory nerve input:

- CGRP
- SP

Other nerve

- CCK
- NO

CCK: cholecystokinin
NO: nitric oxide
SP: Substance P
CGRP: Calcitonin gene-related polypeptide

Effects of Sensory Nerve Innervation on Beta Cells

- CCRP inhibits insulin release and stimulates glucagon secretion
- SP has been observed to increase and decrease insulin release
SAT-650: Substance P Promotes Proliferation of Adult Pancreatic Ductal Cells but Not Differentiation into Beta-Cells

Nan Zhang¹, Di Gao¹, Qian Shen¹ and Lei Sha¹

¹China Medical University School of Pharmacy, Shenyang, China
Role Of Islet Autonomic Nerves in Maintenance of Homeostasis

• This is part of the “so what”
  – By this point, we should be wondering why we care about autonomic innervation of islet cells
  • (the answer is because they are important for many homeostatic parameters)
Glucose Tolerance Test:

- **Blood glucose level**
  - 300 mg/100ml
  - 250 mg/100ml
  - 200 mg/100ml
  - 150 mg/100ml
  - 100 mg/100ml
  - 50 mg/100ml

- **Diabetic Reaction**
- **Insulin Level**
- **50% Normal Reaction**

Time:
- 1 hour
- 2 hours
- 3 hours
- 4 hours
- 5 hours

Glycopenic Stress (hypoglycemia)

• Islet nerves are activated under hypoglycemic conditions
  – Sympathetic -> inhibits insulin secretion and increases glucagon
• This suggests that the islet nerves mediate compensatory mechanisms during metabolic stress.
Exercise Stress

• Researchers found that the sympathetic nerves to the islet cells are also activated during exercise—This increase glucagon secretion and decrease insulin secretion
  • This allows for more hepatic glucose production
Kidney tubules cannot reabsorb the excess filtered glucose.

The extra glucose spills over in urine (glycosuria).

The excess glucose causes osmotic diuresis (polyuria). Polyuria reduces plasma water, leading to excessive thirst (polydipsia).

Ketonuria
Polyuria
Glycosuria

Polydipsia
Hypovolaemic stress

- Low blood volume
- Sympathetic nerves are activated
  - Increases blood glucose by decreasing insulin and increasing glucagon
    - Leads to an increased plasma osmotic pressure, which pulls water from the cell into the blood
Type 2 Diabetes and Hyperinsulinemia

• Insulin resistance -> increased insulin secretion from beta cells
  – Why?
Insulin Resistance

Increased Blood Glucose

Increased glucose mediated insulin secretion
Adipocyte-Derived DNA Triggers Inflammation

DNA released from dying fat cells stimulates inflammation within murine fat tissue.

By Anna Azvolinsky | March 25, 2016

Dying fat cells in obese mice release cell-free DNA, recruiting immune cells that can drive chronic inflammation and insulin resistance within adipose tissue, according to a study published today (March 25) in Science Advances. The observed accumulation of macrophages in murine fat tissue depended on the expression of Toll-like receptor 9 (TLR9). Obese mice missing TLR9 had fewer macrophages and were more insulin sensitive compared to their TLR9-expressing counterparts. The new work may partly explain how obesity can drive chronic inflammation.

"Many mechanisms are involved in obesity-related adipose tissue inflammation and insulin resistance," study coauthor Dajju Fukuda of University of Tsukahama, Japan, wrote in an email to The Scientist. "We think that our result is one of [these mechanisms]."

"This is a very important piece to help explain the inflammatory basis of metabolic disease," Gokhan Hotamisligil, a professor of genetics and metabolism at the Harvard T.H. Chan School of Public Health told The Scientist. "This paper offers a possibility of explaining how inflammation within fat tissue starts. Conceptually, this builds on ideas that have been brewing in the field for two decades," added Hotamisligil, who was not involved in the study.

"This is very novel because, I think, few would have thought to home in on DNA released from dead adipocytes as a signal to attract immune cells," said Andrew Greenberg, director of the Obesity and Metabolism Laboratory at Tufts University in Boston who was also not involved in the work.
Researchers show that there is upregulated cholinergic (parasympathetic/acetylcholine) activation of islet cells, which leads to increase insulin secretion