Meet your TAs!

Rachel
- reisenba@ucsd.edu
- OH: Mondays 12-1pm by Audrey’s in Geisel

Gillian Belk
- gbek@ucsd.edu

Alex
- abj009@gmail.com
- Office: CSB226
- OH: Weds 10am-11
Medium as your dissemination

Why learn if you can’t teach it?

- Deepens understanding
- Stay engaged with the course
- Team-building
Account information

- Come up with a group name (Should be your Medium account name)
- Make a new gmail account which you can link to your new medium account.
- Share both the Email and Medium account information with your groups when you make them.

Create your Google Account
Use this exercise to solve any Product Design Challenge
1 - Longcut to writing a blog-post
2 - Read your other blog posts
3 - Write an illustrated story for use on mobile (*probably won’t be using this*)
4 - Find past years’ with the tag “Cogs163”
The Story

- Will be published under your group name.
- Please make the writing both informative, but fun.
  - Write to your audience
- Will be one blog entry per week per group on that week’s topic

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From Big Brains to Big Booties

Hannah here once again with Team Squints. It’s almost the last week of COGS 163, a 10 week journey through the brain-body connection. I think I speak for most my classmates when I say that this class has been intriguing and perspective changing.

The new outlook on the gut and endocrine system connection to the brain opens doors into what creates our everyday experiences, whether we are
Tags and other things

- After writing, please tag the story with relevant topics
- As well as **COGS163** (no space)
- Your group account will be emailed confirmation of publishing.
- CC your TAs so we can read them easier.
Grading / final notes

- This will count towards the blog portion of your grade.

- Updates to your group blog entries are due every Sunday by 11:59 p.m.

- Email us your group name otherwise we cannot find you! Won’t get credit!

- Work within your groups to divide up responsibilities. Everyone should be writing an equal amount of the posts.
How to Read a Paper

Applied to “Autonomic regulation of islet hormone secretion-Implications for health and disease” (Ahren 2000)

By Gillian and Rachel
Two Ways to Read a Paper

Way Number 1 - Overview Based

- Read Title
- Read Abstract
- Read Introduction
- Read Discussion/Conclusion
- Read Section Titles (If Applicable)
- Look at Key Figures
- Read Results

Why This Way?

- Good to understand a quick overview on the topic and the research

Way Number 2 - Figure Based

- Read Title
- Look at Key Figures
- Read Results
- Read Discussion/Conclusion
- Read Abstract
- Read Introduction

Why this Way?

- Don’t get the author’s opinion
- Can form your own opinion on the subject matter and research
Grad Perspective

Each ‘good’ paper tells a story - especially primary literature

Once you are more familiar with the field(s), and comfortable looking up unfamiliar things (proteins, brain regions, genes, etc) you should try to read these like a story from start to finish.

Benefits to this are following the experimenter’s logic: What motivated the research, what they did and how their methods evolved, and how the results may have reinforced/changed their ideas.

- Abstract - Always read first, gives overview.
- Introduction - The author gives working definitions to these concepts and explains what literature motivated the work.
  - For example: Brain regions can be identified a number of ways, which did this author use?
- Methods - The actual detailed story!
  - Results are usually found on the last few sentences of each experiment. Reinforced by the figures.
- Conclusions - what were the authors’ interpretations? Where could this research go? Ties back with introduction usually.

This method gives a whole picture of the research.

But this methods requires you to be comfortable with topics you are not an expert with.
Review

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

B. Ahren
Department of Medicine, Lund University, Malmo, Sweden

Abstract

The pancreatic islets are richly innervated by parasympathetic, sympathetic and sensory nerves. Several different neurotransmitters are stored within the terminals of these nerves, both the classical neurotransmitters, acetylcholine and noradrenaline, and several neuropeptides. The neuropeptides, vasoactive intestinal polypeptide, pituitary adenylate cyclase activating polypeptide and gastrin releasing peptide are constituent in mediating the cephalic phase of insulin secretion, in synchronising the islets to function as a unit allowing oscillations of islet hormone secretion, and in optimising islet hormone secretion during metabolic stress, e.g. hypoglycaemia and neuroglycopenia. The autonomic nerves could also be involved in the islet adaptation to insulin resistance with possible implication for the development of glucose intolerance and Type II (non-insulin-dependent) diabetes mellitus. It is concluded that islet innervation, through the
After years of intensive research, we finally have a clear picture of insulin action.
**Definition Check**

**INSULIN**

- A Protein hormone responsible for taking blood glucose (aka the sugar in your blood) **FROM** the blood **TO** your cells
- Like a taxi shuttling insulin to your cells
- Happens **AFTER** you eat (or when you think of eating)

**GLUCAGON**

- A Protein hormone responsible for dumping glucose **FROM** the liver **TO** your blood
- Happens between meals
Definition Check Part 2

- Insulin and Glucagon work together in a **feedback loop**
- Both are never 100% on or off
- Work together to create an optimal blood sugar levels at all times

![Diagram showing the role of insulin and glucagon in maintaining blood sugar levels](image)
The First Pass

- **READ THE TITLE:** Autonomic regulation of islet hormone secretion ± Implications for health and disease

- **AUTONOMIC:** Referring to the AUTOMATIC nervous system:
  - Sympathetic Nervous System: **FIGHT OR FLIGHT**
  - Parasympathetic Nervous System: **REST AND DIGEST**

- What’s an islet anyway?
  - Referring to the pancreatic ISLETS OF LANGERHANS
  - Made up of mostly beta cells (**insulin & amyllyn**) and alpha cells (**glucagon**)
The First Pass: Read the Abstract

Abstract

The pancreatic islets are richly innervated by parasympathetic, sympathetic and sensory nerves. Several different neurotransmitters are stored within the terminals of these nerves, both the classical neurotransmitters, acetylcholine and noradrenaline, and several neuropeptides. The neuropeptides, vasoactive intestinal polypeptide, pituitary adenylate cyclase activating polypeptide and gastrin releasing peptide are constituents of the parasympathetic nerves, whereas the neuropeptides galanin and neuropeptide Y are localised to sympathetic nerve terminals. Furthermore, the neuropeptide calcitonin gene-related peptide is localised to sensory nerves and cholecystokinin is also an islet neuropeptide, although the nature of the cholecystokinin nerves is not established. Stimulation of the autonomic nerves and treatment with neurotransmitters affect islet hormone secretion. Thus, insulin secretion is stimulated by parasympathetic nerves or their neurotransmitters and inhibited by sympathetic nerves or their neurotransmitters. The islet autonomic nerves seem to be of physiological importance in mediating the cephalic phase of insulin secretion, in synchronising the islets to function as a unit allowing oscillations of islet hormone secretion, and in optimising islet hormone secretion during metabolic stress, e.g. hypoglycaemia and neuroglycopenia. The autonomic nerves could also be involved in the islet adaptation to insulin resistance with possible implication for the development of glucose intolerance and Type II (non-insulin-dependent) diabetes mellitus. It is concluded that islet innervation, through the contribution of all branches of the autonomic nerves and several different neurotransmitters is of importance both for the physiology and pathophysiology of the islets. [Diabetologia (2000) 43: 393–410]

Keywords Islets, parasympathetic, sympathetic, acetylcholine, vasoactive intestinal polypeptide, pituitary adenylate cyclase activating polypeptide, gastrin releasing peptide, noradrenaline, galanin, neuropeptide Y, calcitonin gene-related polypeptide, cholecystokinin, insulin secretion, glucagon secretion, cephalic phase, oscillation, hypoglycaemia, impaired glucose tolerance, diabetes.
Abstract Summary

- The Sympathetic Nervous System (SNS) and Parasympathetic Nervous System (PNS) innervate the pancreas

**The PNS uses:**
- Acetylcholine (Ach) **Neurotransmitter**
- Vasoactive Intestinal Polypeptide (VIP)
- Pituitary Adenylate Cyclase Activating Polypeptide (PACAP)
- Gastrin Releasing Peptide (GRP)

**The SNS uses:**
- Noradrenaline/Norepinephrine **Neurotransmitter**
- Adrenaline/Epinephrine **Hormones**
- Galanin **Hormone**
- Neuropeptide Y

- The PNS stimulates insulin release (REST AND DIGEST)
- The SNS inhibits these effects
- Both may influence hormone secretion during metabolic stress
- They may be involved in insulin resistance and Type-II Diabetes Mellitus
Review - Your Nervous System Comes in Two Parts

Part 1 - Central Nervous System

- Your Brain and Spinal Cord
  - That’s about it

Part 2 - Peripheral Nervous System

- Sensory Nervous System
  - Sensory Nerves

- Motor Nervous System
  - Motor Nerves

- Autonomic Nervous System
  - Visceral (involuntary) motor neurons

- Somatic Nervous System
  - Somatic (voluntary) motor neurons

- Sympathetic Nervous System
  - Fight or Flight
  - Expending Energy

- Parasympathetic Nervous System
  - Rest and Digest
  - Conserving Energy
How Your Autonomic Nervous System Works
How Organs talk to one another!!!
The First Pass: Read the Conclusions

THE PARASYMPATHETIC SIGNALLING PATHWAY

Dorsal Motor Nucleus of the Vagus

Intrapancreatic Ganglia

Postganglionic Nerve

ISLET OF LANGERHANS

VAGUS NERVE

INSULIN

β

β

β
Inhibiting/Stimulating Insulin Release

Dorsal Motor Nucleus → Vagus Nerve → Postganglionic Nerve Nicotinic Receptors

Stimulation

Hexamethonium

Agonist

Islet Muscarinic (m3) Receptors

Exogenous Ach

Atropine

Agonist

Insulin Release
Pancreatic Polypeptide (PP)

Glucagon
- Increases Blood Glucose
- Glycogen Breakdown

Also...

Vagus Nerve

Postganglionic Nerve

Nicotinic Receptors

Ach

Islet Muscarinic (m3) Receptors

Ach

Somatostatin

Inhibits Insulin and Glucagon

Reduces Stomach Acid Secretion

Pancreatic Polypeptide (PP)

Pancratic Self-Regulation

Gastric Juice Secretion
Read the Introduction- In this case, the bulk of the paper

General Concept

- Who, what, and how does the brain talk to the pancreas and the islets of Langerhans
- Who?
  - Receptors
- What?
  - Through signals called neurotransmitters
- How?
  - Through Neurons!
Background - Receptors

- What? They are molecules that recognize only certain signals
  - Receptors only recognize a unique molecule or sets of similar molecules
- Where? On the Cell membrane OR inside your cell
  - Cell membranes are the bouncers that dictate what goes in and out of your cells
- They create a signal transduction or a cascade effect inside the cell
  - In this case, insulin release
m3 Ach Receptors in Beta Cells

Calcium

PLA$_2$ + Ach → Gq → PLC → PIP$_2$ → DAG → IP$_3$ → Calcium → INSULIN RELEASE
Figure 2 Other Receptors
Other Types of Receptors in Beta Cells

- VIP$_2$ Receptor
  - Binds Vasoactive Intestinal Peptide (VIP) and Pituitary Adenylate Cyclase Activating Peptide (PACAP)
- PAC$_1$ Receptor
  - PACAP specific
- Both of these are G$_s$-Protein Coupled Receptors
- Both stimulate insulin and glucagon release
Figure 2
GRP Receptors
Other Types of Receptors in Beta Cells

- **GRP Receptors**
  - Bind Gastrin Releasing Peptide
  - Also a Gq-coupled receptor like the m3AchR (activates PLC and PLD)
  - Stimulate both insulin and glucagon release
Figure 2
Sympathetic Signaling
THE SYMPATHETIC SIGNALLING PATHWAY

Hypothalamus

Celiac/Paravertebral Ganglia

Spinal Cord (Levels C8-L3)

SPLANCHNIC NERVE

Postganglionic Nerve

ISLET OF LANGERHANS

β

INSULIN

β

β
Regulating Insulin Release

Sympathetic Ganglion → Postganglionic Nerve Adrenoceptors → Beta Cell $\beta_2$ adrenoceptors → Insulin Release

- Atropine (blocks Acetylcholine receptors)
- Hexamethonium (blocks Acetylcholine release)
- NE (Norepinephrine)
- Phentolamine (alpha antagonist)
- Clonidine (alpha agonist)
- Beta Cell $\alpha_2$ adrenoceptors
- Alpha Cell $\beta_2$ and $\alpha_2$ adrenoceptors

Glucagon Release
And...

**Pancreatic Polypeptide (PP)**
- Glycogen Breakdown
- Increases Blood Glucose
- Pancreatic Self-Regulation
- Gastric Juice Secretion

**Glucagon**
- Inhibits Insulin and Glucagon

**Somatostatin**
- Reduces Stomach Acid Secretion
Other Things to Know about the SNS

- $\beta_2$ adrenceptors are Gs-protein coupled receptors (activate adenylate cyclase)
- $\alpha_2$ adrenceptors are Gi-protein coupled receptors (block adenylate cyclase)

Non-adrenergic mechanisms

- The SNS also inhibits insulin release using galanin and neuropeptide Y
- Galanin and NPY inhibit insulin secretion in some animals, but this is VERY species-dependent
- Really depends on the receptors present at the time and in each animal
- The NPY receptor Y1 seems to be a Gi-protein coupled receptor
Figure 2
Non-Adrenergic Mechanisms
Sensory Nerves

- The sensory neuropeptides are calcitonin gene-related peptide (CGRP) and substance P (SP)
- The role of these are not understood
  - Glucose homeostasis? Regulation of hormone secretion? Who knows?
- CGRP **inhibits insulin** secretion and **stimulates glucagon** secretion
- CGRP is related to islet-amyloid polypeptide (IAPP)
  - Amyloid fibrils in diabetes :
- SP has been seen to both stimulate and inhibit insulin secretion
- **Capsaicin** causes CGRP levels to drop
Other Nerves

- Inhibition of Nitric Oxide (NO) synthase inhibits insulin release
- Cholecystokinin (CCK) stimulates insulin release
  - Binds to CCK-A receptors (Gq)
- There is also a direct nerve connection from the duodenum to the pancreas
  - This is an “entero-pancreatic neural mechanism”

https://joystreamhealth.wordpress.com/2012/01/08/watercure-relieves-diseases/
Figure 2
CCK Receptors
Figure 1
Figure 2

All the parts together
The Experiment - Cephalic Phase

[Diagram showing a dog thinking about pizza, leading to an increase in insulin]

INSULIN
Cephalic Phase

- Proven by “sham feeding”
  - Food that’s sweet without glucose in it
  - Food with sugar that can’t be metabolized
- Proven with hypnosis
  - You’re getting very sleepy....imagine your favorite pizza ➔ Increased insulin
- Sight, smell, and expectation of food
  - Waiting for your food at a restaurant? Your blood glucose is plummeting.
- It’s caused by the parasympathetic NS

(sorry not sorry)
The Experiment

- Saline (control) showed increased insulin → cephalic response
- Trimetophane (ganglionic antagonist) severely reduced it
- Atropine (muscarinic antagonist) also reduced it
- CONCLUSIONS:
  - cephalic phase exists
  - It’s both cholinergic and noncholinergic (indicated by the atropine data)
Figure 3

Breakfast

Insulin (pmol/l x 15 min)

S
T
A

* * *

Insulin (pmol/l)

Glucose (mmol/l)

Time (minutes)
Synchronization of Islet Function

- Beta cells secrete insulin in a pulsatile manner and are regulated in a pulsatile manner
- Beta cells are synchronized to the islet as a whole
- Islets are synchronized to the pancreas as a whole
- The pancreas oscillation is important for the liver to be able to absorb insulin
- The pancreatic ganglia govern this
  - Nicotinic blockers and tetrodotoxin abolish the oscillation of insulin
- A transplanted islet secretes independently until it is innervated
- Both Type-2 Diabetes and impaired glucose tolerance have disturbed oscillatory patterns
Homeostatic Mechanisms

- Glycopenic Stress
  - Too much glucagon, too little insulin → too little glucose in blood (hypoglycemia)
  - Often seen in Type-1 Diabetes

- Normally compensated by:
  - Glucose release by liver
  - Inhibition of peripheral glucose uptake
  - Adrenaline and cortisol release
  - Pancreatic Peptide and Norepinephrine release
  - Galanin and VIP release

\[ \text{Stress} \quad \rightarrow \quad \text{Sympathetic NS Activity} \]
Homeostatic Mechanisms

- Exercise Stress
  - Too much glycogen broken down and used → hypoglycemia
  - Liver needs to make new glucose for fuel
- Normally compensated by:
  - Increased glucagon
  - Decreased insulin
  - Increased norepinephrine and galanin
  - Increased epinephrine

EXERCISE → SYMPATHETIC NS ACTIVITY

“Refusing to go to the gym is not the same thing as resistance training.”
Homeostatic Mechanisms

- Hypovolemic Stress
  - Too little blood volume ➔ hypovolemia
  - Need to increase concentration of blood to increase volume

- Normally compensated by:
  - Increased glucagon
  - Decreased insulin
  - Increased norepinephrine and galanin
  - Increased epinephrine

BLOOD VOLUME ➔ SYMPATHTETIC NS ACTIVITY
Insulin Resistance

- People who are resistant to insulin secrete more insulin
- Increased cholinergic innervation can contribute as well
- Hyperinsulinemia is reduced by atropine (m3AchR blocker)
- Carbachol returned insulin secretion and glucose intolerance to normal in insulin resistant high-fat fed mice
- Hyperinsulinemia evolves before the onset of obesity
Food for Thought

- Atherosclerosis
- Hypertension
- Chronic Inflammation
- Insulin Resistance
- Type II Diabetes
- Obesity
- Cancer
- Low HDL

Billy and Bree’s Slides