The role of insulin receptor signaling in the brain

L. Plum, M. Schubert, J. Brüning, 2005

The Insulinators: A. Bustamante, I. Ulloa, K. Ninh, S. Mohamed
Agenda

- Intro about insulin
- Insulin Pathways: MAP-K and PIP2-PIP3
- Melanocortin System
- Central insulin action and peripheral metabolism
- Insulin receptors role in reproduction, learning and memory, ND disease and MetS
- Questions?
New finding!! Insulin has a role in the CNS

- Regulate energy homeostasis
- Reproductive endocrinology
- Neuronal survival
Insulin can pass the blood brain barrier through receptor mediated transcytosis
What are insulin’s effects on the brain?

Condition #1; Inject brain with insulin
What are insulin’s effects on the brain?

Condition #1; Inject brain with insulin

Anorexigenic effect: Limit food intake
What are insulin’s effects on the brain?

Condition #2: Inhibition of insulin
What are insulin’s effects on the brain?

Condition #2: Inhibition of insulin

Orexigenic effect: increase food intake
Hypothalamus

- The target for insulin
- Insulin receptors located here
- Motivation and reward
- Drives the desire to eat
So, why should I care?

It’s all about BALANCE
Let’s say you had a meal...

- And it is rich in **carbohydrates**
- **Increase** your **glucose** levels
- Body responds with releasing **B-cell islets** that are apart of the **pancreas** which releases **insulin**.

PRETTY SIMPLE RIGHT?
Cephalic Responses

- Normally: insulin is secreted after a meal
- But it can also be secreted to cues that predict meal onset, like
  - Food odors
  - Time of day
INSULIN SECRETION

LIVER

PANCREAS

SKELETAL MUSCLE
Insulin’s arch nemesis: Glucagon

- Prevents blood glucose levels from dropping too low
- Converts stored glycogen (in the liver) to glucose into the bloodstream, through a process known as **GLYCOGENOLYSIS**
- Also produces glucose from amino acids molecules known as **GLUCONEOGENESIS**
How does my body do this?

I know it is, but let's break it down.
STEP ONE

- Insulin binds to and activates the membrane bound Insulin receptor, which is a **DIMER**.
  - A molecule or molecular complex consisting of two identical molecules linked together.
- Beta cells contain the **tyrosine kinase domain**
  - Protein that phosphorylates tyrosine amino acids on target proteins and enzymes.
- Once insulin goes in the IR cavity closes, cause the B subunits also close cause an cross phosphorylation.
STEP TWO

- One of the phosphorylated tyrosine residue of IR, attracts a protein known as **INSULIN RECEPTOR SUBSTRATE (1)**
- IRS is then phosphorylated by insulin receptor kinase, at 4 tyrosine residue.
- Fun Fact: IRS molecules are known as **ADAPTERS**, because they do not activate anything alone.
- Phosphorylated IRS-1 substitutes as an attachment point, for lipid kinases, such as PI3K.
STEP THREE

- PI3K attaches to the one of the phosphorylated sites of the IRS molecule.
- Causes the phosphorylation of a molecule that exists within the membrane known as PIP2.
- WHY IS THIS IMPORTANT?
  - PIP2 contains a polar region that points towards the cytoplasmic side of membrane, and two tails inside the membrane.
STEP THREE cont’d

- The PI3K takes a phosphoryl group from an ATP molecule and places it onto PIP2 creating a PIP3.
- PIP3 travels along the membrane, and activates P-dependent protein kinase-1
- Which then activates AKT (protein kinase B): INACTIVE
  - WHY? BECAUSE IT’S NOT MEMBRANE BOUND, RESULTING IT IN DIFFUSING THROUGHOUT THE MEMBRANE
So, what happens if this doesn’t work?

“Juvenile” diabetes

Where the pancreas produces little to no insulin

- Muscle unable to use glucose due to low insulin
- Increased glucose due to low insulin
- Decreased insulin in the blood vessels
- Glycogen and protein breakdown, causing keto-acidosis

Affects the way the body processes sugar (glucose)

- Muscle unable to use glucose due to insulin resistance
- Increased glucose in the blood stream
- Obesity, inheritance & other factors leading to insulin resistance

TYPE-1 DIABETES

TYPE-2 DIABETES

Sufficient insulin secreted in the blood stream
Let’s take this one step further: MAP-K Pathway

Mitogen-activated protein kinase pathway:

- This starts with a GF: i.e epidermal growth factors, which is a primary messenger which initiates the cell division.
- Then RAS is the core (kinase) in this pathway, because once activated, it activates other molecules.
- The proteins SOS along with Grb2 will interact and activate RAS molecules.
MAPK PATHWAYS CONT’D

Why is this important?
- MAPK plays a vital role in the regulation of gene expression, cell growth, and survival. Any abnormalities can lead to increased/uncontrolled cell proliferation, and resistance to apoptosis.

- Which will then phosphorylate RAF activating it.
- Then MEK-1,2 will be activated
- Resulting in the activation of ERK1,2
- Ending up activating transcription factors
Alzheimer's Type 3 Diabetes?

- “AD represents a form of diabetes mellitus that selectively afflicts the brain.” Suzanne M. de la Monte, M.D., M.P.H.1,2,3 and Jack R. Wands, M.D.
- In a sense individuals who have Type 2 diabetes and later on develop dementia and alzheimers, are known as Type 3 diabetes

So insulin and the brain are more connected than we thought...
What happens when insulin binds to an IR?

Goal: Insulin hyperpolarizes and inactivates the glucose-responsive neurons.

Arcuate nucleus of the hypothalamus

Step 1: Insulin binds to an insulin receptor (IR)
What happens when insulin binds to an IR?

Goal: Insulin hyperpolarizes and inactivates the glucose-responsive neurons.

Step 2: P13K is activated
What happens when insulin binds to an IR?

Goal: Insulin hyperpolarizes and inactivates the glucose-responsive neurons.

Step 3: PIP2 is converted into PIP3
What happens when insulin binds to an IR?

Goal: Insulin hyperpolarizes and inactivates the glucose-responsive neurons.
Step 5: upregulation of CRH

P13K is important in mediating the intracellular effects of BOTH insulin and leptin.

Insulin hyperpolarizes the hypothalamus to give the signal to stop eating.

Leptin upregulates CRH, which also tells signal to stop eating.

Both are anorexigenic effects.
Melanocortin System

Goal: Mediate anorexigenic effects of insulin with α-MSH

Arcuate nucleus
What happens when there’s too much insulin in your body?

- You become hypoglycemic
- Your body is uptaking too much glucose
- Symptoms
  - Shakiness
  - Rapid heartbeat
  - Confusion
  - Anxiety
  - Blurred vision
  - Unconsciousness
  - Seizures
Central Insulin Action and Peripheral Glucose Metabolism
Overview

Interactions between the central nervous system and pancreatic islet secretions: a historical perspective

Denovan P. Begg and Stephen C. Woods
Department of Psychiatry and Behavioral Neuroscience, University of Cincinnati, Cincinnati, Ohio

- Insulin injected peripherally could act within the brain, led to the discovery of insulin and insulin receptors within the brain and the receptor mediated transport of insulin into the CNS from endothelial cells.
- Insulin has a diverse range of action
Insulin is best known action:

- Is its ability to reduce circulating glucose by **activating** glucose transporters on cell membranes, enabling the uptake of glucose into most peripheral tissues, where the glucose is used as FUEL or stored as glycogen.
- In 1972, insulin was discovered to be the key negative feedback molecule to prevent **hyperglycemia**
  - Cells responded by secreting insulin and consequently preventing further glucose increases and ultimately returning glucose to basal values.
Central Insulin Action and Peripheral Glucose Metabolism

- Insulin also modifies peripheral glucose metabolism through IRs localized in the hypothalamus.
- Research shows that central administration of insulin increases insulin sensitivity in peripheral tissues.
- By having peripheral insulin action, there is a **reduction** in hepatic glucose production.
- However, there is **NO increase** in glucose uptake in skeletal muscle and adipose tissue.
Central Insulin Action and Peripheral Glucose Metabolism

- Research shows that the reduction in hepatic glucose production is NOT mediated by insulin-induced activation of the melanocortin receptor system that is naturally activated by alpha-MSH.

*It's ok, let's talk it out!
If there is a Pharmacological inactivation of the main downstreams that target insulin signaling, research shows there is inhibition of PI3K pathway, but not inhibition of MAPK pathway,

What do you think this means?

- Intracerebroventricular administration of K-ATP blockers suppresses the effect of insulin on hepatic glucose production
- Causes a possible site of the central effects of insulin on peripheral glucose production.
If there is a Pharmacological inactivation of the main downstreams that target insulin signaling, this shows there is inhibition of PI3K pathway, but not inhibition of MAPK pathway,

*What do you think this means?*

- In contrast, in **chronic antagonism** of melanocortin receptor 4 (MC4R), this leads to an **increase** in food intake with more abdominal fat tissue, and **reduces** hepatic glucose production and the uptake of glucose into peripheral tissues in response to hyperinsulinemia.
Now, if there is chronic intracerebroventricular administration of the MC4R agonist α-MSH, what would be the results?

YOU WOULD HAVE OPPOSITE EFFECTS!
What does all of this mean?

The long-term modulation of the central melanocortin receptors have a role in:

1. Regulating body weight
2. Regulating body composition
3. Hepatic and Peripheral insulin sensitivity
Let’s talk about the brain!

- Hypothalamus is important for controlling compensatory responses of hypoglycemia + energy metabolism
- These compensatory responses comprise glucagon release from the pancreas and sympatho-adrenal activation, resulting in the secretion of epinephrine!
- In the ventromedial portion of the hypothalamus (VMH), specific neurons are influenced by glucose availability and affect the activity of the sympathetic nervous system.
What would happen if we have a focal lesion of the VMH?

- Focal lesioning in this area gets rid of the hormonal response to systemic hypoglycemia
- This suggests that the VMH might be the region in the CNS that is responsible for activating counter-regulatory mechanisms
Specific neurons in the lateral hypothalamus, and the VMH are capable of sensing changes in glucose concentrations

- These neurons are called
  - 1. Glucose-responsive neuron
  - 2. Glucose-sensitive neurons

- If glucose levels rise, the firing rate of glucose responsive neurons **INCREASES**, and the firing rate of glucose-sensitive neurons **DECREASES**.
Little is known about Glucose-sensitive neurons

- Glucose-responsive neurons seem to use K-ATP channels
  - Shows that IR is present, we know this because insulin has been shown to activate K-ATP channels

- Neurons expressing neuropeptide Y and pro-opiomelanocortin have been suggested to be important in glucose sensing because they show characteristics typical of glucose-responsive neurons, such as the expression of glucokinase (Figure 2).
What else does research say about these neurons?

- This observation provides a link between glucose sensing and feeding behavior at a cellular level.
- It highlights the role of the IR in the brain in controlling the complex network that regulates the energy needs of the body.
  - Remember Katie's Goal: When insulin binds to an IR, Insulin hyperpolarizes and inactivates the glucose-responsive neurons.
In summary,

#1 Neuronal IRs are NOT only involved in the regulation of feeding and energy expenditure, but also have an impact on peripheral glucose metabolism.

#2 The molecular mechanisms underlying these processes have not been completely unraveled, but they seem to involve the activation of PI3K and KATP channels.
Insulin receptors role in reproduction, learning and memory, ND disease and MetS
Insulin receptors role in regulation of reproduction

- Mild obesity linked to reduced fertility due to hypothalamic dysregulation of lutenizing hormone. (ovulation)
- IRS-2 knockout mice are obese, have small non-functioning ovaries with reduced number of follicles (potential eggs) due to impaired pituitary development and gonadotrophic insufficiency.

**Conclusion:** point to IR’s functional role in CNS specifically in energy homeostasis as well as reproductive endocrinology.

- Supported by data showing both insulin and insulin growth factor-1 both have a direct stimulatory effect on output of gonadotropin releasing hormone in hypothalamic cells
The role of IR signaling in learning and memory

- Conflicting information of insulin acting in CNS due to difficulty separating direct actions of insulin and effects for, hypoglycemia after administration of insulin.
- Infusion of insulin via euglycemic hyperinsulinemic conditions displayed significant improvement in verbal memory and selective attention.
- Intranasal administration of insulin leads to rapid concentration in CSF without affecting blood glucose levels (peripheral); this is used to treat processing of working memory (hypothalamus)
- **Conclusion:** insulin influences brain function directly, independently of changes in blood glucose
Learning and memory continued

- People with Alzheimer’s have reduced CSF (suggest inability to metabolize insulin properly) in addition to higher blood plasma (peripheral) insulin levels.
- Treating individuals with Alzheimer’s by administration of insulin has shown improvement in memory and performance

Speaking of Alzheimer’s....
Role of IR signaling in neurodegenerative diseases

- **Facts**: ND disease and Diabetes T2 are directly linked.
- Patients with Alzheimer’s and PD show reduced IR in brain.
- **Question**: is this a cause or consequence of neurodegeneration? Is neuronal insulin resistance a risk factor for these disorder?
Neurodegenerative disease Continued

Let’s talk tau....

- GSK-3 phosphorylates tau in neurons.... overproduction of GSK-3(beta) results in increased phosphorylation of tau (this is bad...)
- Insulin (and IGF-1) **reduce** phosphorylation of tau by inhibiting GSK-3B (yasss!)
- Guess what causes the lesions (tangles) in Alzheimer’s?
  Hyperphosphorylated tau (rude!)
- Why? The HP tau no longer shows affinity for microtubules ergo get tangled
Neurodegenerative disease continued

Let’s talk amyloid precursor protein...

- IR & IGF-1 mediated signals regulate secretion of APP
- Insulin resistance causes increase in beta-amyloid levels
- **Question**: why is this important?
- Insulin is involved in clearing the BAP indirectly: inhibits the breakdown of BAP by competitively blocking insulin degrading protein-a primary protease involved in degradation of BAP
Alzheimer’s Disease Is Type 3 Diabetes

Dr. De la Monte asserts:

- T2DM causes brain insulin resistance, oxidative stress, and cognitive impairment
- extensive disturbances in brain insulin and IGF signaling mechanisms could account for the majority of molecular, biochemical, and histopathological lesions in AD (tau!)
- experimental brain diabetes produced by intracerebral administration of streptozotocin shares many features with AD, including cognitive impairment and disturbances in acetylcholine homeostasis
- experimental brain diabetes is treatable with insulin sensitizer agents
### Metabolic Syndrome

- **Concept vs diagnosis:**
  - Common symptom is **insulin resistance**

### Table 1: Diagnostic criteria proposed for the clinical diagnosis of the MetS.

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<tr>
<td><strong>Insulin resistance</strong></td>
<td>IGT, IFG, T2DM, or lowered insulin sensitivity⁴ plus any 2 of the following</td>
<td>Plasma insulin &gt;75th percentile plus any 2 of the following</td>
<td>None, but any 3 of the following 5 features</td>
<td>IGT or IFG plus any of the following based on the clinical judgment</td>
<td>None</td>
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<td><strong>Body weight</strong></td>
<td>Men: waist-to-hip ratio &gt;0.96; women: waist-to-hip ratio &gt;0.85 and/or BMI &gt; 30 kg/m²</td>
<td>WC ≥94 cm in men or ≥80 cm in women</td>
<td>WC ≥102 cm in men or ≥88 cm in women</td>
<td>BMI ≥ 25 kg/m²</td>
<td>Increased WC (population specific) plus any 2 of the following</td>
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<td><strong>Lipids</strong></td>
<td>TGs ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TGs ≥150 mg/dL and/or HDL-C &lt;35 mg/dL in men or &lt;39 mg/dL in women</td>
<td>TGs ≥150 mg/dL and HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women</td>
<td>TGs ≥150 mg/dL or on TGs Rx, HDL-C &lt;40 mg/dL in men or &lt;50 mg/dL in women or on HDL-C Rx</td>
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<tr>
<td><strong>Blood pressure</strong></td>
<td>≥140/90 mm Hg</td>
<td>≥140/90 mm Hg or on hypertension Rx</td>
<td>≥130/85 mm Hg</td>
<td>≥130/85 mm Hg or ≥85 mm Hg diastolic or on hypertension Rx</td>
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<tr>
<td><strong>Glucose</strong></td>
<td>IGT, IFG, or T2DM</td>
<td>IGT or IFG (but not diabetes)</td>
<td>&gt;110 mg/dL (includes diabetes)</td>
<td>IGT or IFG (but not diabetes)</td>
<td>≥100 mg/dL (includes diabetes)</td>
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<tr>
<td><strong>Other</strong></td>
<td>Microalbuminuria: Urinary excretion rate of &gt;20 mg/min or albumin: creatinine ratio of &gt;30 mg/g.</td>
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<td></td>
<td>Other features of insulin resistance⁵</td>
</tr>
</tbody>
</table>

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⁴Insulin sensitivity measured under hyperinsulinemic euglycemic conditions, glucose uptake below lowest quartile for background population under investigation.

⁵Insulin resistance is not a feature of the MetS.
Metabolic syndrome continued

- Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome.
Metabolic syndrome continued

- **Question**: how is insulin resistance defined?
- It is defined as a pathophysiological condition in which a normal insulin concentration does not adequately produce a normal insulin response in the peripheral target tissues such as adipose, muscle, and liver.

- **Question**: so just make more right? Problem solved!
- Not quite: An inability of the pancreatic beta cells over time to produce a sufficient insulin to correct the worsening tissue insulin resistance leads to hyperglycemia and overt T2DM
Metabolic syndrome continued

- The PI3K-Akt pathway is affected, while, the MAP kinase pathway functions normally in insulin resistance.
- Inhibition of the PI3K-Akt pathway leads to a decreased skeletal muscle and fat glucose uptake.
Metabolic syndrome continued

So what can we do about it?

- Clinical identification and management is first step to reduce comorbidities.
- Effective preventive approaches include lifestyle changes, primarily weight loss, diet, and exercise, and the treatment comprises the appropriate use of pharmacological agents to reduce the specific risk factors.
- Drugs should be used only for those with risk factors not adequately reduced by lifestyle changes.
- Clinical management difficult because there is no recognized method to prevent or improve the whole syndrome, the background of which is essentially insulin resistance; so we treat everything à la carte.
Questions?
Alzheimer’s Disease Is Type 3 Diabetes—Evidence Reviewed
Suzanne M. de la Monte, M.D., M.P.H.1,3 and Jack R. Wands, M.D.3

Abstract
Alzheimer’s disease (AD) has characteristic histopathological, molecular, and biochemical abnormalities, including cell loss; abundant neurofibrillary tangles; dystrophic neurites; amyloid precursor protein, amyloid-β (APP-β) deposits; increased activation of prodeath genes and signaling pathways; impaired energy metabolism; mitochondrial dysfunction; chronic oxidative stress; and DNA damage. Gaining a better understanding of AD pathogenesis will require a framework that mechanistically interlinks all these phenomena. Currently, there is a rapid growth in the literature pointing toward insulin deficiency and insulin resistance as mediators of AD-type neurodegeneration, but this surge of new information is riddled with conflicting and unresolved concepts regarding the potential contributions of type 2 diabetes mellitus (T2DM), metabolic syndrome, and obesity to AD pathogenesis. Herein, we review the evidence that (1) T2DM causes brain insulin resistance, oxidative stress, and cognitive impairment, but its aggregate effects fall far short of mimicking AD; (2) extensive disturbances in brain insulin and insulin-like growth factor (IGF) signaling mechanisms represent early and progressive abnormalities and could account for the majority of molecular, biochemical, and histopathological lesions in AD; (3) experimental brain diabetes produced by intracerebral administration of streptozotocin shares many features with AD, including cognitive impairment and disturbances in acetylcholine homeostasis; and (4) experimental brain diabetes is treatable with insulin sensitizer agents, i.e., drugs currently used to treat T2DM. We conclude that the term “type 3 diabetes” accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type 1 diabetes mellitus and T2DM.


Review Article
A Comprehensive Review on Metabolic Syndrome
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Metabolic syndrome is defined by a constellation of interconnected physiological, biochemical, clinical, and metabolic factors that directly increases the risk of cardiovascular disease, type 2 diabetes mellitus, and all cause mortality. Insulin resistance, visceral adiposity, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, elevated blood pressure, hypercoagulable state, and chronic stress are the several factors which constitute the syndrome. Chronic inflammation is known to be associated with visceral obesity and insulin resistance which is characterized by production of abnormal adipocytokines such as tumor necrosis factor α, interleukin-1 (IL-1), IL-6, leptin, and adiponectin. The interaction between components of the clinical phenotype of the syndrome with its biological phenotype (insulin resistance, dyslipidemia, etc.) contributes to the development of a proinflammatory state and further a chronic, subclinical vascular inflammation which modulates and results in atherothrombotic processes. Lifestyle modification remains the initial intervention of choice for such population. Modern lifestyle modification therapy combines specific recommendations on diet and exercise with behavioural strategies. Pharmacological treatment should be considered for those whose risk factors are not adequately reduced with lifestyle changes. This review provides summary of literature related to the syndrome’s definition, epidemiology, underlying pathogenesis, and treatment approaches of each of the risk factors comprising metabolic syndrome.

1. Introduction
The metabolic syndrome (MetS) is a major and escalating years) risk is better calculated using the classical algorithms (Framingham, REGICOR [Registre Gironi del COR]), as they include age, sex, total cholesterol or LDL, and smoking [4].
The role of insulin receptor signaling in the brain

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The insulin receptor (IR) is expressed in various regions of the developing and adult brain, and its functions have become the focus of recent research. Insulin enters the central nervous system (CNS) through the blood-brain barrier by receptor-mediated transport to regulate food intake, sympathetic activity and peripheral insulin action through the inhibition of hepatic glucoseogenesis and reproductive endocrinology. On a molecular level, some of the effects of insulin converge with those of the leptin signaling machinery at the point of activation of phosphatidylinositol 3-kinase (PI3K), resulting in the regulation of ATP-dependent potassium channels. Furthermore, insulin inhibits neuronal apoptosis via activation of protein kinase B \textit{in vitro}, and it regulates phosphorylation of tau, metabolism of the amyloid precursor protein and clearance of \(\beta\)-amyloid from the brain \textit{in vivo}. These findings indicate that neuronal IR signaling has a direct role in the link between energy homeostasis, reproduction and the development of neurodegenerative diseases.

Expression of the IR in the CNS and source of cerebral insulin

In 1978, Havrankova \textit{et al.} \cite{2} localized the IR in the CNS for the first time by ligand autoradiography. The presence and localization of IRSs in the CNS were subsequently confirmed by immunohistochemistry and autoradiography \cite{3,4}. IRSs are widely distributed in the brain with highest concentrations in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum and hippocampus. Moreover, downstream effectors of insulin, such as IRS proteins and PDK1 isoforms, show distinct patterns of expression in the CNS that partly overlap with expression of the IR \cite{5}.

To initiate signaling in the CNS, insulin has to reach its receptor, which is separated from the circulation by the blood-brain barrier. In the 1960s, Margolis \textit{et al.} \cite{6} showed that peripheral infusion of insulin leads to an increase in insulin levels in cerebrospinal fluid, suggesting that insulin can indeed cross the blood-brain barrier. These findings were later confirmed in studies indicating that less than 1% of the peripherally administered insulin reaches the CNS in rodents \cite{7}. The amount of insulin missing the blood-brain barrier has been subsequently
References

Interactions between the central nervous system and pancreatic islet secretions: a historical perspective

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Begg DP, Woods SC. Interactions between the central nervous system and pancreatic islet secretions: a historical perspective. Adv Physiol Educ 37: 53–60, 2013; doi:10.1152/advan.00187.2012.—The endocrine pancreas is richly innervated with sympathetic and parasympathetic projections from the brain. In the mid-20th century, it was established that α-adrenergic activation inhibits, whereas cholinergic stimulation promotes, insulin secretion; this demonstrated the importance of the sympathetic and parasympathetic systems in pancreatic endocrine function. It was later established that insulin injected peripherally could act within the brain, leading to the discovery of insulin and insulin receptors within the brain and the receptor-mediated transport of insulin into the central nervous system from endothelial cells. The insulin receptor within the central nervous system is widely distributed, reflecting insulin’s diverse range of actions, including acting as an adiposity signal to reduce food intake and increase energy expenditure, regulation of systemic glucose responses, altering sympathetic activity, and involvement in cognitive function. As observed with central insulin administration, the pancreatic hormones glucagon, somatostatin, pancreatic polypeptide, and amylin can each also reduce food intake. Pancreatic and also gut hormones are released cephalically, in what is an important mechanism to prepare the body for a meal and prevent excessive postprandial hyperglycemia.

cephalic response; conditioning; insulin; islets; pancreatic innervation

are discussed, the primary focus throughout this review is upon insulin.

The Endocrine Pancreas and Insulin

Of the many hormones produced in and excreted by cells in the islets, the first identified and best known is insulin. Two decades after the discovery of the islets, Minkowski and von Mering (133) reported that removal of the pancreas produced a diabetic phenotype, and it was subsequently reported that aqueous pancreatic extracts produced moderate reductions in glycosuria (92). The isolation of insulin from pancreatic islets was first performed by Banting and Best (13) in 1922, and exogenous insulin soon became the only effective treatment for insulin-deficient (type 1) diabetes mellitus (123).

Insulin is a 51-amino acid peptide hormone cleaved by proteases from proinsulin and subsequently from proinsulin in the secretory vesicles of β-cells (104, 105). Insulin’s best known action is its ability to reduce circulating glucose by activating glucose transporters on cell membranes, enabling the uptake of glucose into most peripheral tissues, where the glucose is used as a fuel or stored as glycogen (72). Insulin is secreted from β-cells in response to increases of local glucose levels, and both its basal and stimulated levels are directly proportional to body fat, with leaner individuals having reduced insulin secretion relative to individuals with greater...