Abstract

Type 3 diabetes is a new characterization of Alzheimer disease. The purpose of this comparative analysis is to outline and juxtapose Type 1 and Type 2 diabetes mellitus and Type 3 diabetes. This comparative analysis is based on published literature regarding both Type 1 and Type 2 diabetes mellitus, as well as literature on glucose metabolism and regulation, in addition to the literature on Type 3 diabetes and Alzheimer disease. This analysis includes a brief description and introduction to the history of diabetes, along with molecular descriptions and demonstrations of glucose metabolism and regulation. The regulation of gene expression, signaling, and mechanisms of action were investigated and demonstrated for both insulin and glucagon. Type 1 diabetes mellitus and Type 2 were discussed to the extent of manifestation of symptoms, molecular basis of the disease and pathophysiology of each type. Type 3 diabetes is also presented, including the molecular basis of the disease and the pathophysiology. Molecular mechanisms were compared and analyzed between both Type 1 and Type 2 diabetes mellitus and Type 3 diabetes. This paper reviews the evidence supporting the hypothesis that one form of Type 3 diabetes is related to Alzheimer disease, based on the molecular and clinical similarities between the mechanisms of vascular damage, insulin resistance, and formation of amyloid plaques contributing to the pathophysiology of both disorders.
Introduction

One could argue that diabetes is one of the most important diseases of our time. There is currently a pandemic-level problem that we have never faced before in human history. With the industrialization of food production as well as the continued rise in ‘fast food,’ we find ourselves with a record number of incidences for diabetes. It has become as important as ever to have a working knowledge of this disease given the ubiquity of it. Type 3 diabetes may be one of the newest scientific phenomena to be described, but it is still rooted in its ‘ancient’ predecessors, Type 1 and 2 diabetes. In order to understand the data giving rise to the hypothesis that Type 3 diabetes is related to Alzheimer disease, it is important to have a working knowledge of both Type 1 and Type 2 diabetes mellitus, along with the molecular basis of these diseases.

History of Diabetes

The first reference to diabetes is in the Ebers Papyrus: the famous papyrus acquired by the German Egyptologist Georg Ebers in 1872. Egyptian physicians were the first to treat and more importantly write about diabetes. In this document, written around 1550 BCE (with evidence that parts of it are much older), diabetes mellitus is detailed for the first time in human history. In particular, the Ebers Papyrus describes treatments for polyuria or to “eliminate urine which is too plentiful.” Other ancient characterizations of diabetes include the Ayurveda system of medicine in ancient India in the 5/6th Century BCE, as well as in Ancient Chinese medicine.

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1 “Papyros Ebers: Das Hermetische Buch Über Die Arzneimittel Der Alten Ägypter in Hieratischer Schrift (Band 1): Einleitung Und Text.”
2 Sanders, Lee J. “From Thebes to Toronto and the 21st Century: An Incredible Journey.”
3 Lakhtakia R. “The history of diabetes mellitus.”
around 475 BCE\textsuperscript{4}. The Hindu physicians Charaka and Susruta were the first to use the term “honey urine” by noticing the “attraction of flies and ants to the urine.”\textsuperscript{2}

As we get closer to the contemporary understanding of diabetes, Aretaeus, a disciple of Hippocrates, represented the Ancient Greek view of the disease. Not only is he responsible for the term ‘diabetes,’ he also described the disease: “Diabetes is a wonderful affection, not very frequent among men, being a melting down of the flesh and limbs into urine…”\textsuperscript{5} This characterization is a bit on the dramatic side, but nonetheless, Aretaeus officially detailed the polyuria and polydipsia symptoms of diabetes in the first century.

Prior to the Renaissance, most of the developments for diabetes took place under Muslim physicians during the Islamic golden age, where the disease began to be further distinguished from other diseases with similar symptoms (polyuria)\textsuperscript{6}. However, no real revolutionary change in the characterization of the disease occurred until the 19\textsuperscript{th} Century. Within a hundred years the disease was linked to the pancreas by Thomas Crawley\textsuperscript{7} in Britain, as well as the much anticipated differentiation of diabetes insipidus and diabetes mellitus in the medical literature in 1792\textsuperscript{8}. Past this point, diabetes and the study of its treatments started appearing at a rapid rate along the timeline and as such, a detailed description of every event far exceeds the scope of this paper. Diabetes is an ancient disease, and the timeline of it is fascinating, however to fully grasp the disease, the basis of normal glucose regulation in the body must be understood first.

\textsuperscript{4} Zhang, Hui, et al. “Study on the History of Traditional Chinese Medicine to Treat Diabetes.”
\textsuperscript{5} Henschen, Folke. “On the Term Diabetes in the Works of Aretaeus and Galen: Medical History.”
\textsuperscript{6} Eknoyan, Garabed, and Judit Nagy. “A History of Diabetes Mellitus or How a Disease of the Kidneys Evolved into a Kidney Disease.”
\textsuperscript{7} Cawley, Thomas. “A Singular Case of Diabetes, Consisting Entirely in the Quality of the Urine; with an Inquiry into the Different Theories of That Disease.”
\textsuperscript{8} Lindholm, Jörgen. “Diabetes Insipidus: Historical Aspects.”
Glucose Regulation

To understand the mechanism of both Type 1 and Type 2 diabetes mellitus, it is first important to understand how the body functions normally in terms of glucose regulation. The two main hormones that participate in glucose metabolism are glucagon and insulin. Glucagon is a peptide hormone that is secreted by pancreatic alpha cells as well as intestinal L Cells\(^9\). Glucagon release and production is encoded by the pro-glucagon gene. This gene shown in Figure 1, contains 5 DNA response elements (G1-G5) as well as a cyclic-AMP-Response element (CRE)\(^10\). The regulation of this gene’s expression includes various transcription factors, one of the more relevant being Pax6.

Figure 1: Schematic diagram of the glucagon gene promoter (rat) regulating expression in α-cells. (From: Diagram of the glucagon gene promoter. Adapted [reprinted] from Gosmain, Y., et al. “Glucagon Gene Expression in the Endocrine Pancreas: the Role of the Transcription Factor Pax6 in α-Cell Differentiation, Glucagon Biosynthesis and Secretion.”)

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\(^10\) Gosmain, Y., et al. “Glucagon Gene Expression in the Endocrine Pancreas: the Role of the Transcription Factor Pax6 in α-Cell Differentiation, Glucagon Biosynthesis and Secretion.”
Pax6, is a transcriptional regulator of glucagon secretion. Although there are many factors that regulate transcription of this gene, Pax6 gives us a general idea on how this gene is regulated. A study out of the University of Geneva Medical School in 2012\textsuperscript{11} showed how critical Pax6 is to glucagon expression. This study utilized “rat primary enriched-α cells with specific small interfering RNA leading to a 70% knockdown of Pax6 expression\textsuperscript{12}” to demonstrate the importance of Pax6. Using glucagon secretion assays, they were able to show in these rat model α cells that there was a 42% decrease\textsuperscript{13} in relative glucagon levels in the partial Pax6 knockout models (see Figure 2C). These data were interpreted to show that in the absence of Pax6, glucagon secretion decreased significantly. This mechanism has also been shown to be applicable to human models for the same transcription factors, in terms of glucagon concentrations.\textsuperscript{14} While this is only a ‘surface-level’ analysis of this extremely complicated system, it is still a representative model on how this gene is regulated by its transcription factors.

\textsuperscript{11} Yvan Gosmain, Claire Cheyssac, Mounia Heddad Masson, Audrey Guérardel, Caroline Poisson, Jacques Philippe, “Pax6 Is a Key Component of Regulated Glucagon Secretion.”
\textsuperscript{12} Yvan Gosmain, Claire Cheyssac, Mounia Heddad Masson, Audrey Guérardel, Caroline Poisson, Jacques Philippe, “Pax6 Is a Key Component of Regulated Glucagon Secretion.”
\textsuperscript{13} Yvan Gosmain, Claire Cheyssac, Mounia Heddad Masson, Audrey Guérardel, Caroline Poisson, Jacques Philippe, “Pax6 Is a Key Component of Regulated Glucagon Secretion.”
Figure 2: Representation of the effect of Pax6 gene silencing on glucagon synthesis and release. (From: Glucagon content relative to total protein amounts. Adapted [reprinted] from Yvan Gosmain, Claire Cheyssac, Mounia Heddad Masson, Audrey Guérardel, Caroline Poisson, Jacques Philippe, “Pax6 Is a Key Component of Regulated Glucagon Secretion.”)

Glucagon signaling takes place via a specific seven transmembrane G protein-coupled receptor. This receptor is most prevalent in the tissues of the liver and pancreas given the role of both organs in blood glucose regulation. The activation of the glucagon receptor or GPCR is a typical representation of a G-protein signaling cascade. Once glucagon binds its receptor, it triggers a conformational change that activates the heterotrimeric G protein complex. Specifically, this conformational change allows the receptor to act as a guanine nucleotide exchange factor (GEF) and exchange GDP for GTP on the α subunit of the complex. This transfer activates the complex and cause the dissociation of the α subunit (αGTP) from the β and γ subunit as well as the receptor itself. The activated Gα subunit then activates adenylyl cyclase (AC), an effector enzyme, which produces cyclic adenosine monophosphate (cAMP) from ATP. cAMP is an extremely important intracellular signaling transducer and involved in many
signaling cascades. For glucagon secretion, there is evidence that modulation of cAMP levels can influence secretion independent of any paracrine signaling\textsuperscript{15}. After its synthesis, cAMP then binds to Protein Kinase A (PKA) activating it and allowing for PKA to phosphorylate the enzyme phosphorylase kinase (PPK) (\textbf{Figure 3}). This enzyme then phosphorylates glycogen phosphorylase (PYG) which is the enzyme that breaks down glycogen to yield glucose-1-phosphate\textsuperscript{16}. PKA also phosphorylates the glycogen synthase enzyme (GYS), inactivating it. Under normal conditions, glycogen synthase is the enzyme that synthesizes glycogen from glucose-1-phosphate.

\textbf{Figure 3}: Schematic of glucagon mechanism of action. (From: Pathway of glucagon action. Adapted [reprinted] from Man, Frozen. “Image/PNG.”)

\textsuperscript{15} Yu, Qian, et al. “Glucose Controls Glucagon Secretion by Directly Modulating CAMP in Alpha Cells.”
\textsuperscript{16} Berg, Jeremy M. “Phosphorylase Is Regulated by Allosteric Interactions and Reversible Phosphorylation.”
This signaling cascade can also act on glucagon in terms of promoting gene expression. Activated PKA acts to phosphorylate/activate, as well as localize to the nucleus, molecules like CREB (cAMP response element-binding protein) (Figure 4). CREB can independently promote expression of the glucagon gene. However, through the effector IP3 (inositol 1,4,5-triphosphate), which enhances calcium release, other downstream signaling effectors can be activated like CRTC2 (Figure 4). CRTC2 is a transcriptional co-activator for CREB and acts to enhance overall gene expression. Consequently, there is a positive feedback loop where an increase in glucagon-mediated signaling pathways results in increased expression of the glucagon gene.

Figure 4: Schematic representation of glucagon signaling cascade. (From: Glucagon Signaling cascade. Adapted [reprinted] from Rix, Iben. “Glucagon Physiology.”)

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17 Rix, Iben. “Glucagon Physiology.”
The main action of glucagon is the raising of the concentration of blood glucose. The hormone accomplishes this goal through two processes, gluconeogenesis and glycogenolysis. Glycogenolysis, or the breakdown the glycogen is accomplished by the glycogen phosphorylase enzyme, which as previously stated, breaks down glycogen to yield glucose-1-phosphate. Gluconeogenesis is the metabolic pathway in which glucose is formed de novo. This pathway (shown below) (Figure 5) consists of 11 steps starting with pyruvate and ending with glucose. One of the most important steps in this reaction is the last step, the conversion of glucose-6-phosphate into glucose. This reaction occurs via the hydrolysis action of glucose-6-phosphatase, a membrane bound enzyme. For glucose to diffuse out of the cell, it must lose the attached phosphate. This is an important decision point for the cell, as leaving the phosphate on glucose relegates it to the inside of the cell where it can be used in the formation of glycogen. Consequently, the enzyme glucose-6-phosphatase is mainly found in tissues where maintenance of blood glucose levels is a priority (i.e. liver).
Figure 5: Gluconeogenesis pathway. Four enzymes in red are used in the gluconeogenesis pathway, along with other enzymes in blue also used in glycolysis. (From: Gluconeogenesis pathway. Adapted [reprinted] from Berg, Jeremy M. “Glucose Can Be Synthesized from Noncarbohydrate Precursors.”)
Glucagon secretion is a tightly regulated process with glucagon secretion being influenced by several different molecules (Figure 6). Obviously, low blood glucose levels are the most direct positive regulators on glucagon secretion. When blood sugar is low, hypoglycemia, glucagon secretion is stimulated and under hyperglycemic conditions, glucagon secretion is inhibited. In the past, the predominant model proposed that glucagon secretion was in response directly to the variation in blood glucose levels. At present, the thought is that the regulation of glucagon is not only influenced by fluctuating blood glucose levels, but also by various paracrine/autocrine/endocrine molecules.\textsuperscript{18}

**Figure 6:** Diagram of glucagon regulation, including negative and positive regulators. (From: Factors that regulate glucagon secretion, as well as the action of glucagon. Adapted [reprinted] from Kate, Nilesh. “PDF.”)

\textsuperscript{18} Jesper Gromada, Isobel Franklin, Claes B. Wollheim, $\alpha$-Cells of the Endocrine Pancreas: “35 Years of Research but the Enigma Remains.”
Glucagon is positively regulated by an increase in amino acids as well as an increase in parasympathetic and sympathetic nerve activity. An increase in amino acids usually parallels a decrease in blood glucose, usually indicating a need for nutritional energy. The autonomic nervous system also plays a role in the regulation of glucagon, especially the neurotransmitter epinephrine. Glucose is incredibly important in terms of brain activity, so when declining blood glucose levels are sensed, epinephrine (in addition to glucagon) is released. Functionally, epinephrine acts like a coactivator of the glycogenolysis process. In the liver, epinephrine can bind its α2-adrenergic receptor, along with its β2-adrenergic receptor\textsuperscript{19}. This binding triggers a signaling cascade called the phosphoinositide cascade. Through the effector phospholipase C, inositol 1,4,5-trisphosphate is produced, promoting the release of Ca2+ from the ER\textsuperscript{20}. Phosphorylase kinase is the enzyme that phosphorylates glycogen phosphorylase, the enzyme that breaks down glycogen to yield glucose-1-phosphate. The δ subunit of this enzyme is calmodulin\textsuperscript{21}, which senses the increase Ca2+ levels, thus partially activating the enzyme. This increase in Ca2+ levels also assists in the exocytosis of glucagon\textsuperscript{22}. Overall, glucagon secretion is regulated by a myriad of molecules, both positively and negatively. One of the most powerful negative regulators of glucagon secretion is insulin.

Insulin is the other major hormone involved in glucose regulation. Insulin is a peptide hormone that is secreted by the pancreatic beta cells. Insulin production is encoded by the INS gene. Much like the glucagon gene, the INS gene is highly regulated for the production of

\textsuperscript{19} Brian T. Layden, M.D., Ph.D., Vivek Durai & William L. Lowe, Jr., M.D. “G-Protein-Coupled Receptors, Pancreatic Islets, and Diabetes.”

\textsuperscript{20} Berg, Jeremy M. “Epinephrine and Glucagon Signal the Need for Glycogen Breakdown.”


\textsuperscript{22} Gromada, J, et al. “Adrenaline Stimulates Glucagon Secretion in Pancreatic A-Cells by Increasing the Ca2 Current and the Number of Granules Close to the L-Type Ca2 Channels.”
insulin. The gene’s promoter comprises 3 main sites, A3, E1 and the C1 site (Figure 7). There are three main transcription factors acting on the promoter region of the gene, Pdx-1, MafA and NeuroD1. While the specific mechanism of action for these transcription factors remains unknown, in general they “act in a coordinated and synergistic manner to stimulate insulin gene expression in response to increased glucose levels.”

Insulin, like most peptide hormones requires some post-translational modifications. Unlike other peptide hormones, the post-translational modifications for insulin are clinically significant based on their products. Once the insulin gene begins to be expressed, preproinsulin is produced, and via its signal peptide is translocated to the ER. Once in the ER, the signal peptide is cleaved, creating proinsulin. Proinsulin folds and forms disulfide bonds and is then transported to the Golgi apparatus. To become active insulin, proinsulin gets cleaved by various endopeptidases, leaving the B and A chains disulfide-bonded together and releasing the C peptide fragment. C peptide levels are clinically significant as a low C-peptide level means that the body is not producing enough insulin, a marker of diabetes mellitus.

Figure 7: Schematic view of the promoter region of the INS gene encoding insulin. (From: Schematic of INS gene. Adapted [reprinted] from Sreenath S. Andrali, Megan L. Sampley, Nathan L. Vanderford, Sabire Özcan; “Glucose regulation of insulin gene expression in pancreatic β-cells.”)
Insulin release is a multi-step pathway that is critical to the regulation of plasma glucose levels. Glucose enters pancreatic beta cells through GLUT2 transporters, which are only present in beta cells as they have a much lower affinity for glucose relative to GLUT4 transporters, which are found in muscle and adipose cells. This low affinity of GLUT2 ensures that there must be a high enough glucose concentration to warrant insulin release. Once glucose enters the cell it is phosphorylated by glucokinase and proceeds to enter glycolysis to produce ATP. This increase in ATP levels coincides with a “closure of $K_{ATP}$ channels, [a] depolarization of the plasma membrane, [and a] opening of voltage-dependent Ca2+ channels.” This increase in intracellular Ca2+ levels causes the release of insulin from its secretory vesicles (Figure 8).  

**Figure 8:** Mechanism of insulin release and action within the cell. (From: Insulin release pathway and mechanism of action. Adapted [reprinted] from Fu, Zhuo, et al. “Regulation of Insulin Synthesis and Secretion and Pancreatic Beta-Cell Dysfunction in Diabetes.”) 

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Once insulin is released from its secretory vesicle, it is free to begin its own signaling cascade. Unlike glucagon, insulin signaling takes place via a single transmembrane receptor tyrosine kinase, or RTK. Upon insulin binding to the β subunit of the RTK, autophosphorylation occurs and begins the signaling cascade starting with insulin receptor substrates (IRS). There are two main signaling pathways for insulin, the PI3K pathway and the Ras-MAPK pathway. For the purposes of this review, the PI3K pathway will be discussed. Once the IRS are phosphorylated, they activate various kinases, in particular the phosphoinositol 3 kinase or PI3K. This enzyme then converts PIP2 (phosphatidylinositol 4,5-bisphosphate) to PIP3 (phosphatidylinositol 3,4,5-triphosphate). PIP3 then binds to and activates protein kinase B (PKB) (also called AKT).27 Once PKB is activated, it promotes the fusion of GLUT4 glucose transporters within the cell membrane. GLUT4 transporters transport glucose into muscle and adipose tissues where the glucose is either converted into glycogen, or broken down by glycolysis to yield ATP. PKB also inactivates glycogen synthase kinase (GSK), which activates glycogen synthase, via phosphorylation.28 This inactivation means that GSK cannot deactivate the glycogen synthase enzyme and thus glycogen continues to be produced. The overall goal of the peptide hormone insulin is to reduce plasma glucose levels, by either producing glycogen or by producing ATP.

Insulin production, like glucagon is tightly regulated, most directly by elevated plasma glucose levels. When blood sugar is low, hypoglycemia, insulin secretion is inhibited, as there is not enough glucose being transported through GLUT2 transporters to warrant a significant depolarization effect. Under hyperglycemic conditions, insulin secretion is stimulated via the action previously discussed. Other molecules that positively regulate insulin include

27 Meyts, Pierre De. “The Insulin Receptor and Its Signal Transduction Network.”
28 Fang, X, et al. “Phosphorylation and Inactivation of Glycogen Synthase Kinase 3 by Protein Kinase A.”
acetylcholine. Acetylcholine positively regulates insulin via “moderate membrane depolarization and increased β-cell electrical activity.” Negative regulators of insulin release include somatostatin and epinephrine, which both exhibit “strong membrane repolarization and … inhibition of action potential firing.”

Both glucagon and insulin and glucagon work in harmony to regulate blood glucose levels in the body (Figure 9). The mechanisms required to maintain this harmony are complicated and thus can become disrupted in a multitude of ways to yield pathology.

**Figure 9:** Diagram of the overall plasma glucose regulation mechanism in the body. (From: Diagram of plasma glucose regulation. Adapted [reprinted] from Jesper Gromada, Isobel Franklin, Claes B. Wollheim, “α-Cells of the Endocrine Pancreas: 35 Years of Research but the Enigma Remains.”)

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29 Rorsman, Patrik, and Matthias Braun. “Regulation of Insulin Secretion in Human Pancreatic Islets.”
30 Rorsman, Patrik, and Matthias Braun. “Regulation of Insulin Secretion in Human Pancreatic Islets.”
31 Jesper Gromada, Isobel Franklin, Claes B. Wollheim, “α-Cells of the Endocrine Pancreas: 35 Years of Research but the Enigma Remains.”
Type 1 Diabetes Mellitus

Type 1 diabetes mellitus was often referred to as juvenile diabetes, given that childhood was often when it was diagnosed. However, as Type 1 diabetes is also diagnosed in adult patients, the name ‘juvenile diabetes’ has been abandoned by the medical community. Symptoms of Type 1 diabetes mellitus include “excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes, and fatigue.”32 The unfortunate reality of Type 1 diabetes is that the cause is still largely unknown, with genetics and environment being the predominant theories. However, be it genetics or environment, the pathophysiology of the disease is the same. Type 1 diabetes mellitus is an autoimmune disorder in which the beta cells of the pancreas are destroyed which results eventually in no insulin production. Specifically, an increase in autoreactive CD4+ and CD8+ T cells, along with an overall activation of the innate immune system, work together to destroy the pancreatic beta cells. In a normally functioning immune system, the system can distinguish between ‘self’ and ‘not self.’ However, in autoimmune disorders like Type 1 diabetes, these immune cells react to ‘self’ and seek to destroy pancreatic beta cells. Specifically these CD4+ and CD8+ T cells are activated in the pancreatic draining lymph nodes because of a “high turnover of β-cells in the islets leading to antigen presentation.”33 Once the T cells are ‘made aware’ of the pancreatic islets, a multiplication effect takes place, making the destruction even more wide spread and leading to the insulitis, an overall destruction of the beta cells (Figure 10).

32 “Diabetes.” World Health Organization
33 Bluestone, Jeffrey A, et al. “Genetics, Pathogenesis and Clinical Interventions in Type 1 Diabetes.”
Figure 10: Process of destruction of pancreatic beta cells via autoimmune induced insulitis. (From: Mechanism of destruction of pancreatic beta cells via insulitis. Adapted [reprinted] from Bluestone, Jeffrey A, et al. “Genetics, Pathogenesis and Clinical Interventions in Type 1 Diabetes.”)

One of the most indicative conditions associated with Type 1 diabetes is a condition called diabetic ketoacidosis (DKA). DKA is drastic example of the complications associated with Type 1 diabetes. DKA is characterized by an extremely high blood glucose level as a result of a lack of insulin action. As a result of a lack of insulin and a consequential lack of glucose transport into cells, the body begins to rely on other sources of energy. This includes the breakdown of fatty acids, a process called lipolysis. This breakdown of fats via beta oxidation yields ketone bodies (acetoacetate and β-hydroxybutyrate). These ketone bodies are partially acidic and begin to lower the plasma pH level. The body can initially compensate through the use of bicarbonate buffering, but eventually the system becomes overwhelmed and the body enters acidosis. To compensate, patients often exhibit Kussmaul breathing, which is hyperventilation in order to lower blood carbon dioxide levels\textsuperscript{34}. DKA can eventually progress to

\textsuperscript{34}Kitabchi, Abbas E., et al. “Hyperglycemic Crises in Adult Patients With Diabetes.”
cerebral edema and eventually death if left untreated. DKA is not unique to patients with Type 1 diabetes, as patient with Type 2 diabetes can develop the condition as well, although it is significantly rarer.

**Type 2 Diabetes Mellitus**

The second type of diabetes mellitus is often referred to as ‘late-onset’ or ‘adulthood’ diabetes as it usually develops later in life. However, as this disease is also diagnosed in teens or younger children, the former names have been replaced with Type 2 diabetes. (There are also other rare types of diabetes mellitus that will not be discussed in this paper.) While Type 1 is characterized by a complete destruction of pancreatic beta cells and a complete lack of insulin production, Type 2 is characterized by ‘insulin resistance.’ Some of the symptoms of Type 2 diabetes mellitus are the same as Type 1, including, “excessive excretion of urine (polyuria), thirst (polydipsia), constant hunger, weight loss, vision changes, and fatigue.”35 The main difference between the two is that the symptoms for Type 2 tend to come on slower and are less abrupt.36 The causes of Type 2 diabetes mellitus are much better characterized than those of Type 1. Type 2 can develop from long term diet issues/obesity along with contributing genetic factors. A meta-analysis done in 2010 looked at multiple studies on the disease and concluded that “the relative risk of developing Type 2 diabetes for obese persons, compared to those with normal weight was 7-fold, and the risk for overweight people was almost 3-fold.”37 A social

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35 “Diabetes.” World Health Organization
perspective would also be helpful in looking at the cause of Type 2 diabetes. Simply put, the world today has seen an enormous rise in cheap, high calorie foods which are being consumed at a rapid rate. ‘Fast’ and low quality food is being utilized as a band-aid on social issues like poverty and hunger. Unfortunately, the result is the highest level of obesity in the history of the mankind. This has contributed to the almost meteoric rise in Type 2 diabetes. Looking past the social influences on Type 2 diabetes, genetics may also play a role.

Single nucleotide polymorphisms are the basis for some of the genetic contributions to the development of Type 2 diabetes. In 2010, at the Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, it was determined via GWAS (genome-wide association studies) that “at least 36 gene loci have been identified that contribute to the genetic risk of type 2 diabetes.”38 These genes vary in responsibility from encoding for islet ATP-sensitive potassium channels to transcription factors for the proglucagon gene.39

The pathophysiology of Type 2 diabetes begins with the notion of insulin resistance as well as dysfunction in pancreatic beta cells. In normal functioning pancreatic beta cells, glucose is transported into the cell via GLUT2, triggering the activation of glucokinase, and the release of insulin. However, in some patients with Type 2 diabetes, the action of glucokinase is severely reduced, not as a result of the efficacy of the enzyme itself, but rather because glucose transport is severely reduced.40 Type 2 diabetes is more of a generalized term that describes multiple different disease processes. All the mechanisms have in common the insulin resistance property, which is a disruption in the ‘second step’ of insulin action. If the body’s cells are not responding to insulin production as they normally should, then that is considered insulin resistance. Unlike

38 Roden, Michael. “Genetics of Type 2 Diabetes: Pathophysiologic and Clinical Relevance.”
39 Rother, Kristina I. “Diabetes Treatment--Bridging the Divide.”
Type 1, in Type 2 the beta cells of the pancreas are functioning properly and producing insulin; however, that insulin is not being recognized by cells in their normal capacity. This disruption can be caused by several things. Most patients with Type 2 diabetes struggle with either obesity, or a long-term poor diet. This can cause chronic hyperglycemia which consequentially causes long-term hyperinsulinemia. This long-term elevation of insulin inhibits its action as well as production through its own feedback system.\(^1\) Specifically, it is thought to inhibit insulin action through a process usually present before pathogenesis. The studies on non-diabetic relatives of patients with diabetes have been found to have “decreased stimulation of [the] tyrosine kinase activity of the insulin receptor.”\(^2\) Having elevated blood glucose levels long-term can also cause the development of a phenomenon called “glucose toxicity.” This is where chronic hyperglycemia begins to change the normal insulin response to glucose just based on oversaturation,\(^3\) or more specifically by the “accumulation of glucose within the β-cell.”\(^4\) Similar to Type 1 diabetes, patients with Type 2 diabetes can also experience beta cell loss as a result of autoimmune activation. This makes up only about 10% of Type 2 diabetes cases in specific populations.\(^5\) Overall, Type 2 diabetes is characterized by both insulin resistance as well as insulin insufficiency.

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\(^1\) DeFronzo, R A, et al. “Sensitivity of Insulin Secretion to Feedback Inhibition by Hyperinsulinemia.”


\(^3\) Yki-Järvinen, H. “Glucose Toxicity.”

\(^4\) Richard J. Mahler, Michael L. Adler, “Type 2 Diabetes Mellitus: Update on Diagnosis, Pathophysiology, and Treatment.”

\(^5\) Richard J. Mahler, Michael L. Adler, “Type 2 Diabetes Mellitus: Update on Diagnosis, Pathophysiology, and Treatment.”
**Type 3 Diabetes**

To put it simply, Type 3 diabetes does not present as Type 1 and Type 2 diabetes mellitus, at least not yet in the clinical sense. Type 3 diabetes is a characterization of insulin resistance in Alzheimer disease. Initially, the connection between traditional pancreatic diabetes and Alzheimer disease was not clear. Granted, the connection has only been theorized since 2008 from researchers at Brown University.\(^{46}\) Alzheimer disease is a chronic neurodegenerative disorder and is the prevailing cause of dementia. The cause of Alzheimer disease has long escaped researchers, with the prevailing theories being that 70% of the risk of the disease is attributable to genetics,\(^{47}\) with head injuries and chronic hypertension following closely behind.\(^{48}\)

The pathophysiology of Alzheimer disease is based on the misfolding of proteins in the brain, specifically the misfolding of amyloid β peptide (Aβ), which is a part of the larger amyloid precursor protein (APP). APP is a transmembrane protein in neurons. It functions in “adhesion, neurotrophic and neuroproliferative activity”\(^{49}\) along with intercellular communication. One of the theories on the pathology of Alzheimer disease is the “possibility that Aβ peptide and α-synuclein might interact to cause mitochondrial and plasma membrane damage.”\(^{50}\) This damage could trigger an apoptosis (cytochrome c) cascade which explains the overall neurodegenerative effect of the disease. Characterizations of Alzheimer disease lack any significant mechanism in

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46 Editor. “Type 3 Diabetes Is a Title That Has Been Proposed for Alzheimers Disease Which Results from Resistance to Insulin in the Brain.”
49 Turner, Paul R, et al. “Roles of Amyloid Precursor Protein and Its Fragments in Regulating Neural Activity, Plasticity and Memory.”
50 Hashimoto, Makoto, et al. “Role of Protein Aggregation in Mitochondrial Dysfunction and Neurodegeneration in Alzheimers and Parkinsons Diseases.”
terms of what gives rise to the disease. The Type 3 diabetes characterization of Alzheimer disease may finally be suggesting a significant mechanism for the disease.

There are 3 main connections between Alzheimer disease and diabetes, the first of which being the vascular dementia connection. Chronic hyperglycemia in Type 2 diabetes can lead to oxidative stress via PKC activation. PKC or Protein kinase C, is a universal signaling molecule, and its upregulation in diabetes contributes to vascular damage via reactive oxygen species from the activation of the NOX1 Enzyme (Figure 11). These reactive oxygen species (ROS) contribute to the overall endothelial dysfunction. Overall, vascular damage can contribute to neurodegeneration via a “disruption of white matter networks.”

**Figure 11:** Mechanisms of NOX activation in hyperglycemic conditions. (From: Mechanism and pathway of NOX activation. Adapted [reprinted] from Meza, et al. “Endothelial Dysfunction: Is There a Hyperglycemia-Induced Imbalance of NOX and NOS?”)

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52 Cholerton, Brenna, et al. “Type 2 Diabetes, Cognition, and Dementia in Older Adults: Toward a Precision Health Approach.”
The next major connection between Alzheimer disease and diabetes is the formation of amyloid plaques. Much like in Alzheimer disease, there is formation of amyloid polypeptide, or plaques in Type 2 diabetes. Insulin is regulated by an islet amyloid polypeptide called amylin, also known as IAPP. IAPP is co-secreted with insulin and assists in the slowing of gastric motility, as well as promoting satiety.53 The specific mechanism for the increase in IAPP in Type 2 diabetes patients is not yet known, however the predominant hypothesis is based on insulin resistance.54 As a result of pancreatic beta cell loss, there is a compensatory increase in insulin and IAPP secretion, and this compensatory increase is thought to lead to the accumulation of aggregated, oligomer IAPP proteins and extracellular plaques.55 The progression of Type 2 diabetes generates an increase in apoptosis of pancreatic beta cells. In Alzheimer disease, the accumulation of the amyloid β peptides are thought to also initiate an increase in apoptosis in neurons. However, in Type 2 diabetes there is evidence to suggest that the toxic oligomer form of IAPP is more responsible for apoptosis than the extracellular amyloid plaques.56 The accumulation of IAPP in Type 2 diabetes, much like the accumulation of amyloid β peptides in Alzheimer disease and the resulting pathology of both mechanisms, gives rise to the strong connection between diabetes and Alzheimer disease.

The last major connection between Alzheimer disease and diabetes is the insulin resistance in the brain connection. Although the effects of insulin binding the insulin receptor in so-called “insulin-dependent tissues,” such as muscle, adipose and liver tissues, are well understood, insulin binding a different insulin receptor in the brain is extremely important for

53 Gupta, Dhananjay, and Jack L Leahy. “Islet Amyloid and Type 2 Diabetes: Overproduction or Inadequate Clearance and Detoxification?”
54 Haataja, Leena, et al. “Islet Amyloid in Type 2 Diabetes, and the Toxic Oligomer Hypothesis.”
many neurological effects. The major glucose transport mechanisms in the brain utilizing the GLUT-1 and GLUT-3 glucose transporters are independent of insulin. However, recent research has provided a glimpse into the role of insulin binding the insulin receptor in the brain and the effect on insulin-dependent glucose transport via GLUT-4.\textsuperscript{57} Glucose transport in the brain is paramount to achieve normal neuronal function. Past that, insulin also assists with neuronal growth as well as being involved in the regulation of synaptic plasticity and genes related to long term memory.\textsuperscript{58} As previously discussed, the mechanism for insulin resistance in Type 2 diabetes is essentially defective insulin signaling, or tissue cells not responding to insulin production as they normally should. The mechanism is similar for Alzheimer disease. The presence of misfolded amyloid β peptide (Aβ) in hippocampal neurons has been shown to be associated with insulin insensitivity.\textsuperscript{59} Specifically, the inhibition of IRS (\textbf{Figure 12}) has “major impact on synaptic dysfunction, impaired synaptic plasticity, and synapse loss.”\textsuperscript{60} After the activation of the insulin receptors, an autophosphorylation cascade occurs, with IRS1, Akt and GSK-3 molecules being phosphorylated by c-Jun N-terminal kinases (p-JNK). Insulin resistance decreases the effect of the p-JNK which reduces the overall effect of the signaling cascade. The decrease of p-JNK causes the IRS1 that is phosphorylated at its serine residue to become favored over the normal tyrosine phosphorylation, inhibiting the IRS enzyme.\textsuperscript{61} The presence of insulin resistance in diabetes as well as Alzheimer disease further establishes a strong connection between the two diseases.

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\textsuperscript{58} Vieira, Marcelo N.N., et al. “Connecting Alzheimers Disease to Diabetes: Underlying Mechanisms and Potential Therapeutic Targets.”
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Conclusion

Diabetes is an extremely complicated disease. Not only is the pathophysiology of diabetes mellitus multifaceted, the genetic basis is extremely intricate and not yet characterized. Looking past the science to the more social aspect of the disease, it is easy to get lost in a complicated structure of influences on not only the prevalence of the disease but the actual manifestation. With the sheer prevalence of diabetes in our world today, it is no surprise that the disease is beginning to find its way into other disease in terms of pathophysiology. Recent data is consistent with the connection between Type 3 diabetes and Alzheimer disease. Whether it be
through the common mechanism of insulin resistance, vascular damage, or through the formation of amyloid plaques, there is significant data that shows a connection. Not only that, but the risk for developing Alzheimer disease is 1.5-fold higher among patients with Type 2 diabetes. The one major difference between the two diseases is that there is a much clearer path to management and treatment for diabetes mellitus than there is for Alzheimer disease. Type 3 diabetes may be a new avenue for treating Alzheimer disease. In fact, intranasal insulin is already being used to treat the disease. While the literature does not (currently) think that Type 3 diabetes is a cause of Alzheimer disease, it is at the very least intimately involved in terms of pathology.

While researching Type 3 diabetes, the question had to be asked, did Type 3 arise purely out of a massive cultural presence of diabetes in general? Or has the rampant diabetes epidemic begun to influence our characterization of other diseases? While the characterization may have begun that way, the research that has been done since has provided much more validity to the argument. The avenue for treatment is undoubtedly the most exciting part of Type 3 diabetes. At least for now, there is a gap between the knowledge of a connection of diabetes and Alzheimer disease and a lack of an understanding of the mechanism of Alzheimer disease itself. But the future is hopeful.

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