WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 14, 20-41. Review Article ISSN 2277–7105

CAUSE OF NEURODEGENERATION THROUGH GABA RECEPTOR AND GAD ENZYME IN HYPERGLYCEMIC PATIENT

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Article Received on
22 May 2025,

Revised on 12 June 2025,
Accepted on 02 July 2025,

DOI: 10.20959/wjpr202514-37174

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ABSTRACT

Worldwide (6% of the population) suffers from diabetes mellitus (DM), the most prevalent endocrine condition. It is brought on by insufficient or insufficient insulin production by the pancreas, which increases blood glucose levels or falls. It has been demonstrated to harm numerous bodily systems, including the heart, kidneys, blood vessels, eyes, and nerves—insulin-dependent diabetes mellitus (IDDM, Type I). T1DM is caused by the autoimmune destruction of pancreatic beta cells where the hormone insulin is produced, which is essential for glucose metabolism. In diabetes, hyperglycemia is caused by inadequate insulin action. Numerous insulin receptors exist in the brain, particularly in the hippocampus and cerebral cortex, whose regions hold significance for memory and cognitive function, respectively. In the brain, insulin is broken down by the insulin-degrading enzyme (IDE). This enzyme also disassembles the amyloid beta protein. By encouraging the release of extracellular amyloid β peptide and upregulating IDE expression, insulin regulates the synthesis and elimination of amyloid β from the brain. Moreover, glucose and insulin can also affect the brain. Along with its impacts on acute metabolic effects, nutrition intake

regulation, and energy storage monitoring, insulin also affects cognition further, leading to various neurodegenerative diseases.

KEYWORDS: Diabetes Mellitus, Type 1 Diabetes Mellitus, Type 2 Diabetes Mellitus, Glutamic Acid Decarboxylase, Gamma-aminobutyric acid, Dementia, Neurocognitive Diseases.

INTRODUCTION

Definition of Diabetes Mellitus (DM)

A metabolic condition known as chronic hyperglycemia may be triggered by either insufficient insulin secretion, compromised insulin action, or both. Interestingly, as an anabolic hormone, insulin significantly impacts protein, lipid, and carbohydrate metabolism.[1] Because of insulin resistance, the metabolic problems linked to diabetes primarily impact tissues like the liver, skeletal muscles, and adipose tissue. The type and duration of diabetes can affect how severe the symptoms are. People with increased blood sugar levels, especially children who don't have any insulin at all, may have symptoms like weight loss, increased appetite, polydipsia, dysuria, and difficulties seeing. Certain individuals with diabetes might show no noticeable symptoms.[2] Unmanaged diabetes can lead to various problems if left untreated, including unconsciousness, disorientation, and in rare instances, death from nonketotic hyperosmolar syndrome or ketoacidosis.[1]

Classification of DM

Type 1 Diabetes

A continuous drop in insulin secretion begins at least two years before the evaluation of type 1 diabetes(T1D), which can be identified well before aberrant insulin secretion begins.[3] At around the same time, β-cell sensitivity to glucose decreases. The last insulin response increases while the first one falls, which may indicate a compensatory mechanism. The reduction in insulin responsiveness continues to accelerate in the early post-diagnosis phase. A biphasic decrease in the secretion of insulin has been noted in the initial years following diagnosis, with the first year being steeper than the second. After a diagnosis, there may be little to no insulin production for years consequently, due to the decline in insulin secretion. Even when blood sugar levels are within the normal range, elevated levels are indicative of T1DM diabetes. There are notable changes in glucose when T1D develops. Using metabolic markers like dysglycemia, it might be possible to more accurately forecast the onset of

diabetes in individuals who are at risk. To further enhance prediction, risk ratings can make use of changes in glucose and C-peptide levels.[4]

Type 2 Diabetes

Defective insulin production is a significant element in the underlying processes of type 2 diabetes (T2DM).[5] To maintain appropriate glucose levels, insulin sensitivity causes a wide range of variations in insulin output. The disposition index indicates the curvilinear relationship between insulin secretion and sensitivity. Additionally, individuals diagnosed with type 2 diabetes cannot effectively increase their insulin production to fight insulin resistance since they have a low disposition index. Given the severity of their insulin resistance, insulin-resistant obese T2D patients' absolute insulin levels are still unacceptably low, even if they superpass those of insulin-sensitive lean control individuals. Glucose stimulation causes a considerable reduction in or elimination of insulin production (initial phase). The proinsulin to insulin (C-peptide) ratio is elevated in T2D patients. The maximum amount of insulin produced and the potentiation of insulin responses to non-glucose stimuli caused by hyperglycemia are significantly reduced.[6] Over time, hyperglycemia usually gets worse and is harder to treat. Another characteristic of T2D progression is the ongoing reduction in β-cell function.[7]

GLUCOSE EFFECT ON THE BRAIN SYSTEM

We looked at interactions between glucose and medications that target particular neuropharmacological bases through which glucose may impact brain functions. Neurotransmitter systems, for instance, evaluate glucose's potential as a therapy to lessen drug-induced memory impairments. Glucose improves the effects of many ugs, according to studies involving systemic injections. These effects include reversing learning and memory impairments caused by opiate and y-aminobutyric acid (GABA) receptor agonists, as well as cholinergic (both muscarinic and nicotinic) and glutamatergic (N-Methyl-D-aspartate, NMDA) antagonists.[36]

Description of the transporters of glucose

The glucose transporters facilitating GLUTs, gene symbol SLC2, are energy independent because they function as many carriers of glucose and similar hexoses across the plasma membrane downhill their concentration and electrochemical gradient. Membrane-integrated proteins known as GLUTs share a structural characteristic: They have 12 membrane-spanning domains with cytosolic amino- and carboxy-terminal ends.[37] Conserved glycine

and tryptophan residues, critical for the facilitative transporter activity, were found in the amino acid sequence of individual GLUTs. Members of the GLUT family have been recognized up to this point. GLUT1, GLUT2, GLUT3, and GLUT4 are members of class I; GLUT5, GLUT7, GLUT9, and GLUT11 are members of class II; and HmIT (H+-myo inositol cotransporter) is a member of class III.[38]

Using a supplementary active transport mechanism, the sodium-dependent glucose transporters (SGLTs), also known by the gene name SLC5A (Solute Carrier Family 5A), transport glucose.

The downhill Na+ gradient produced by the Na+/K+ ATPase pump facilitates the transfer of glucose. Two K+ and three Na+ are pumped into the cells by this ATPase. Following their binding on the SGLT, glucose, and Na+ are carried by an electrochemical gradient against the gradient. SGLTs and GLUTs have different structures. Both the amino and carboxyl termini of the 14 transmembrane helices that make up SGLTs face the extracellular space. Sugar binding and translocation are made possible by Na+'s binding to the amino-terminal region of the transport protein, which alters its conformation. Through the carboxy-terminal domain, sugar enters.[39]

Importance of Insulin in the Brain

The brain can respond to insulin as well as glucose. Insulin has an impact on cognition in addition to its effects on acute metabolic effects, regulating nutrition intake, and monitoring energy storage. The brain's amount of insulin could be 10–100 times more than plasma. Additionally, it varies throughout development and then falls in the adult brain (around 32 ng/g).[40] The pancreatic β cells are the primary source of insulin in the brain. A protein transporter known as an insulin receptor protein facilitates the transport of insulin across the blood-brain barrier (BBB) and into the brain. This is corroborated by research showing that long-term peripheral hyperinsulinemia, which is a symptom of insulin resistance, may cause the BBB's insulin receptors to be downregulated, which would hinder the brain's ability to absorb insulin.[41]

Insulin in the central nervous system can also be produced locally within pyramidal neurons of the olfactory bulb, hypothalamus, and amygdala, but not in glial cells (CNS). Both neurons and glia in the human brain have insulin downstream signaling molecules, insulin transporters, and insulin receptors. The medial temporal lobe, hippocampus, and prefrontal

cortex—areas of the brain linked to cognition, specifically working memory and long-term memory—have a high concentration of insulin receptors.[40]

Insulin, glucocorticoid, and glutamate receptors are most abundant in the hippocampus.
The proteins known as insulin-like growth factors (IGFs)possess a significant level of sequence similarity with insulin. Neurogenesis, myelination, synaptogenesis, dendritic branching, and neuroprotection following neuronal injury are all regulated by IGF-1. IGF-1 is necessary for memory and learning and supports synapses. There is a correlation between greater IQ and elevated IGF-I blood levels in children. In both neurons and glia, IGF-1 receptors (IGF-1Rs) are found.[42]

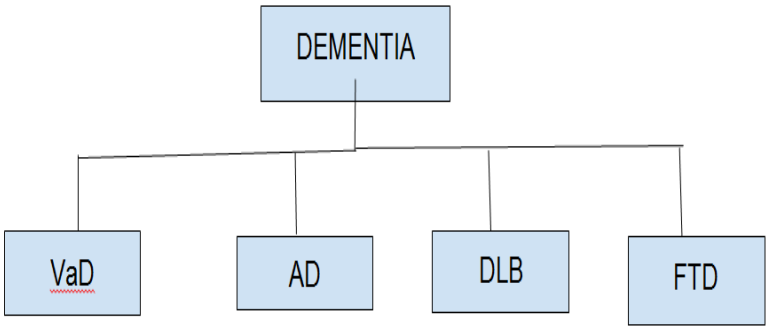
Insulin degrading enzyme (IDE) breaks down insulin in the brain. Amyloid β protein is also broken down by this enzyme. Insulin controls the production and removal of amyloid β from the brain by promoting the release of extracellular amyloid β peptide and upregulating IDE expression. Patients with low-level Alzheimer's disease may be driven to clinical disease if they have type 2 diabetes because elevated peripheral insulin may lower brain insulin levels through feedback at the blood-brain barrier. This would downregulate IDE and let amyloid β protein build up.[43]

Dementia

The state known as dementia is brought on by brain disease, which is either progressive or chronic. Memory, reasoning, comprehension, computation, learning, language, and judgment are among advanced cortical functions that are compromised.[44] These disabilities frequently coexist with shifts in motivation, social behavior, or emotional regulation. Alzheimer's, vascular, Lewy body, mixed dementia (typically a combination of Alzheimer's and vascular dementia), and frontotemporal dementia are the most prevalent of the more than 200 subtypes of dementia.

In the UK, there are currently an estimated 944,000 persons with dementia; estimates suggest that number will rise to 1 million by 2025 and almost 2 million by 2050. Although being older is believed to be a risk factor for dementia in later life, dementia can strike anyone at any age. An estimated 70,800 individuals, or 7.5% of the overall number of dementia patients in the UK, had young onset dementia, meaning that their symptoms started before the age of 65.[45]

TYPES OF DEMENTIA



Alzheimer's Disease

The most prevalent type of dementia is Alzheimer's disease. The extracellular buildup of senile plaques made of Amyloid beta peptide and the intraneuronal buildup of neurofibrillary tangles (NFTs) made of hyperphosphorylated microtubule-binding protein-tau (p-tau) are the neuropathologic hallmarks of AD. Neuronal degeneration, neuroinflammation, microglia activation, BBB dysfunction, and cognitive decline are all pathologic markers. Additionally, the three stages of NFT pathology in AD—transentorhinal, limbic, and isocortical—form the foundation of the Braak and Braak staging system of AD and are a more accurate indicator of cognitive decline than Amyloid beta pathology.[46]

Cerebrovascular effects of amyloid

According to recent research, vascular alterations and AD-related alterations frequently overlap, which may have a synergistic impact on cognitive decline. Blood vessel morphological changes, decreased vascular density, and increased vessel tortuosity have been fully examined and observed in pathologic examinations of Alzheimer's brain microcirculation. Amyloid beta, a cleaved fragment of the amyloid precursor protein, or APP, is known to have potent vascular effects and is a significant contribution to AD-mediated cerebrovascular injury. In human postmortem investigations, it has also been explained that the A1–40 fragment is deposited in the cerebral blood vessels.[46]

There is also evidence of A deposition on cerebral blood vessel walls (CAA), which causes smooth muscle atrophy and lumen constriction. Increased cerebrovascular resistance has been linked to the direct effects of soluble A1-40 and A1-42 on cerebrovascular vasomotor control in rodent penetrating arterioles.36 It has been shown that even soluble A1–40 causes the endothelium wall to generate reactive oxygen species that are dependent on Nicotinamide adenine dinucleotide phosphate oxidase, leading to A-induced neurovascular dysfunction.

The section under "Cerebrovascular risk elements and neuropathological correlates of dementia" contains more details on BBB permeability in AD. Additionally, thickening of the basement membrane, disruption of vascular smooth muscle cells, and decreased drainage are effects of A deposition on vessel structure and function.

Leaky vessels and/or Cerebral hemorrhages can occur due to weakened blood vessel walls. Collectively, these observations suggest that CAA and A restrict the blood vessels' capacity to respond appropriately to physiological stimuli and provide a danger of hemorrhages and BBB opening due to A-induced vessel wall weakening.[47]

Dementia with Lewy Bodies

The second most frequent cause of neurodegenerative dementia in older adults is dementia with Lewy bodies. It has histological and clinical similarities to other dementias that can develop in Parkinson's disease and other neurological disorders. In terms of pathology, DLB is distinguished by aberrant synaptic protein synuclein aggregation in neurons linked to brain atrophy, known as "Lewy bodies," which is less pronounced than in AD.[48]

Cerebrovascular dysfunction and neuroinflammation in dementia with Lewy bodies

There is increasing proof that vascular hemodynamic changes and hypoxia contribute to DLB. In the occipital cortex of DLB patient brains compared to controls, reductions in cerebral blood flow and decreased microvessel density linked to vascular endothelial growth factor deficiency, secondary to the buildup of synuclein, were seen. According to a recent study, human SH-SY5Y neuroblastoma cells' synuclein levels rise following oxygen-glucose deprivation, supporting the idea that protein aggregation may be encouraged by hypoperfusion. There is significant proof that the neurodegenerative processes associated with DLB also involve altered inflammatory responses, specifically concerning glial activation. The cerebrospinal fluid (CSF) in individuals with dementia was discovered to have autoantibodies against glial-derived and amyloid formations.

Interestingly, DLB had considerably greater serum autoantibody levels against synuclein, Amyloid beta 1–42 myelin oligodendrocyte glycoprotein, and myelin basic protein than tau-associated dementias (AD, FTD), VaD, and controls. It was regularly noted that the patient with DLB had greater CSF and plasma concentrations of hyaluronic acid, an adhesion molecule known to affect both vascular and inflammatory processes, in comparison to cognitively normal and age-matched controls. When these findings are put together, they

suggest that patients have vascular anomalies and a strong inflammatory response, both of which worsen Lewy body-induced neuropathology.[49]

Frontotemporal Dementia

With a diverse clinical and pathological appearance, frontotemporal dementia is a neurodegenerative category of non-AD dementia. A variety of genes contribute to the familial autosomal dominant types of FTD. But we'll concentrate on sporadic FTD, which accounts for 60% of instances.53 The sixth decade of life is when the sporadic type of disease usually manifests in older adults.54 The neuropathology of FTDs is referred to as frontotemporal lobar degeneration (FTLD). In contrast to the diffuse atrophy of AD, the pathological features of FTLDs include atrophy of the frontal and temporal lobes (lobar atrophy) and a portion or the entirety of the following microscopic findings: ballooned neurons, vacuolization of the superficial cortex (spongiosis), and neuronal loss and gliosis.[50]

FTD-tauopathies (including progressive supranuclear palsy, Pick's disease, corticobasal degeneration, and argyrophilic grain disease, etc.); FTD-ubiquitin with ubiquitin-positive tau-negative neuronal inclusions (such as motor neuron disease and sporadic amyotrophic lateral sclerosis); and FTD-without tau- or ubiquitin-positive inclusion (such as amyotrophic lateral sclerosis, and in certain cases of AD, Pick's disease, and DLB).56 The damaged brain regions, cognitive impairment, and clinical presentation of these variations vary.57 This classification is logically widely accepted.[51]

Vascular Dementia

VCI encompasses both dementia and cognitive impairment without dementia, and it refers to the diverse collection of cognitive illnesses that have a suspected vascular origin. Large vessel disease, cardioembolic disease, and small-vessel disease are examples of vascular dysfunctions that are thought to be causal in patients with VaD as opposed to having additive or synergistic effects in conjunction with the other dementias previously discussed. As per the vascular hypothesis, VaD is brought on by decreased blood flow, which results in hypoxia and BBB permeability from long-term neurotoxic and vasculotoxic effects that encourage amyloid buildup and neurodegeneration. The six subgroups of vascular dementia are as follows: (1) hemorrhagic dementia, (2) strategic infarction dementia, (3) multi-infarction dementia, (4) mixed dementia, and (5) subcortical ischemic vascular dementia (SIVD).

Certain cortical or subcortical symptoms associated with stroke-affected brain regions may be paralleled by the abrupt onset of infarction and hemorrhagic stroke dementia subtypes linked to acute cerebrovascular disorders. The remaining VaD subtypes, which go beyond the main classifications of large vessel disease, cardioembolic disease, and small-vessel disease, reflect diverse etiologies such as vasculitis, CAA, and hereditary diseases like CADASIL (cerebral autosomal dominant arteriopathy with leukoencephalopathy).[52]

Morphological alteration in the brain in Patients with Diabetes Mellitus

In the initial phase of Alzheimer's disease, the hippocampus, amygdala, and medial temporal lobe exhibit morphologic alterations. A reliable indicator of the extent of Alzheimer's neuropathology is the measurement of the brain's hippocampus and amygdala volume on magnetic resonance imaging (MRI), which reveals that individuals with the initial phase of illness have smaller MRI volumes of the hippocampus and amygdala than healthy control patients.[53]

In the Rotterdam Scan Study, the link between diabetes mellitus and hippocampal and amygdalar atrophy on MRI was investigated in elderly people without dementia. Individuals diagnosed with diabetes mellitus experienced smaller volumes of the hippocampus and amygdala on MRI than people without DM. The associations were not due to vascular morbidity being more pronounced in persons with diabetes mellitus. The pathologic studies that examined the link between diabetes-related variables and Alzheimer's disease neuropathology also produced encouraging results. Neurofibrillary tangles and hippocampal neuritic plaques were more prevalent among individuals with diabetes mellitus and the APOEe4 genotype in the Honolulu Heart Program than in participants without either of these risk factors.[54]

GAD ENZYMES

Gamma-aminobutyric acid (GABA) is a crucial neurotransmitter in the CNS. It is created on demand rather than spontaneously in nature when the amino acid glutamic acid, occurs naturally Glutamic acid decarboxylase (GAD) is an enzyme that decarboxylates glutamate. There are two isoforms of this enzyme, each with a slightly different molecular weight (65 and 67 kDa).[14]

GAD65

GAD65 is a 585 amino acid protein that is encoded at chromosome 10p11. The brain contains GABAa and GABAb, a minimum of two different GABA receptors for inhibitory transmission. GABA and GAD enzymes are involved during the development of the brain before the differentiation of several neuronal types from stem cells. Typically, GAD65 targets particular intracellular vesicles where it converts glutamate into GABA.[15]

A decrease in GAD activity, along with a decline in the synthesis of GABA from glutamate, may result in diminished GABAergic control over signaling. This alteration can trigger hyperactivity and seizures since GABA functions as an inhibitory neurotransmitter. Patients with stiff-person syndrome show that to have lower amounts of GABA, a neurotransmitter that has been crucial in the motor cortex. Muscle stiffness and recurrent spasms affecting the axial and limb musculature are hallmarks of the uncommon condition known as stiff-person syndrome. Neurologic examination results are typically normal, except for muscle stiffness. The brain's magnetic resonance imaging and standard computed tomography results are normal. It is uncertain what causes stiff-person syndrome. However, the existence of antibodies against GAD, its immunogenetic relationship, its connection with other autoimmune disorders, and the existence of numerous additional auto-antibodies raise the chances of an autoimmune pathophysiology. Most patients have high titers of anti-GAD antibodies.[16]

However, some findings suggest that the individuals diagnosed with type 1 diabetes and stiff person syndrome differ in their humoral (isotype pattern) and cellular (epitope identification) reactions to GAD65. In addition, if anti-GAD antibodies contributed to the pathogenesis of neurological disorders, one would expect to see some cases of stiff-person syndrome in the tens of thousands of children and adolescents with type 1 diabetes, many of whom have very high anti-GAD antibodies. However, to date, there are no indications of any such cases documented in the literature.[17]

GAD67

Long ago, the pancreatic GAD enzymes were identified. Human beta cells only express GAD65, whereas mouse beta cells typically express GAD67. In addition to increasing insulin secretion, elevated glucose concentrations that stimulate beta cells also enhance the release of GAD. Nevertheless, it is still unclear how GAD and its byproduct GABA work in the pancreatic islets. It has been suggested that GABA regulates hormone release in the pancreas

and/or acts as a paracrine signaling molecule that aids communication between beta cells and other endocrine cells in the islets. Islet alpha and delta cells express GABAa receptors, which control chloride conductance and can suppress cell hyperpolarization, whereas beta cells do not.[18]

There are indications that the pancreatic islets possess GABAb receptors, which may mediate the opening of Ca2+ channels and the closure of K+ channels. It has been documented that a GABAb receptor agonist inhibits insulin release. Subsequent research indicates that GABA produced by GAD65 might act as a negative modulator of insulin secretion during the early stage when responding to glucose.[19]

GABA

Glutamic acid decarboxylase (GAD) converts glutamate into GABA, a key neurotransmitter in the central nervous system.[8] GABA mediates the rapid and gradual regulation of excitability at central synapses the CNS by acting on two different types of receptors: ligand-gated ionotropic GABAA receptors and G protein-linked metabotropic GABAB receptors.[9] GABA quickly inhibits neurons in the adult brain, mostly via the GABAA receptor (GABAAR). GABAA activation opens the ligand-gated Cl− ion channel, which in turn promotes membrane hyperpolarization due to Cl− influx and controls the proliferation and maturation of neuronal cells.[10]

Pancreatic β-cells also generate GABA.[18] By affecting the immune system and islet β-cells, it has anti-diabetic, protective, and regenerative actions. It also inhibits the generation of systemic inflammatory cytokines and insulitis. The immune inhibitory and β-cell regeneration properties of GABA shed light on how GABA controls glucose homeostasis and islet cell activity. In the islets of Langerhans, β-cells release GABA, which prevents α cells from releasing glucagon.[19,20] It is thought that GABAAR mediates this inhibition.[11]

GABA produced from β-cells can interact with GABAAR in α-cells, resulting in membrane hyperpolarization and glucagon secretion suppression. Insulin-Akt-GABBAR-glucagon dysfunction secretory route in the islet could be the fundamental reason for diabetic persons' unsuppressed glucagon secretion despite hyperglycemia. GABA synthesis and release from β-cells may be inhibited by persistently high glucose or higher cytoplasmic ATP levels. In diabetic individuals, trophic activities and therapeutic effects would result from activation of GABA–GABA signaling in pancreatic β-cells. Beta-cells produce ATP as a consequence of

the metabolism of glucose. The ATP-dependent K+ channels (KATPC) are closed by the elevated ATP/ADP, which causes the plasma membrane to depolarize and opens voltage-dependent rise in [Ca2+]i and Ca2+ channels (VDCC). Increased intracellular [Ca2+]ions cause beta cells to produce more GABA and insulin.[12]

VARIOUS MECHANISMS OF GABA IN DIABETES

1) GABA Prevents Apoptosis and Encourages β-Cell Proliferation

GABA considerably lowers streptozotocin (STZ)-induced death in clonal INS-1 cells and may shield β-cells from apoptosis. These findings imply that GABA stimulates β-cell survival and replication.

2) GABA Starts the Ca2+-PI3-K/Akt Pathway and Has Depolarizing Effects.

GABAAR antagonist bicuculline, PI3K inhibition, or calcium channel blockers such as nifedipine prevented GABA-stimulated Akt phosphorylation. This implies that the Ca2+-dependent PI3K/Akt pathway in β-cells mediates the GABAAR-mediated trophic effect. Researchers discovered that muscimol, a GABA and GABAAR agonist, increased Ca2+ influx in β-cells. These findings showed that the mechanism behind GABA's in vivo actions in supporting β-cell growth and survival may be related to membrane depolarization, following Ca2+ entry, and PI3K/Akt pathway activation.

3) GABA Boosts Regulatory T-cell counts and Reduces Inflammation.

The serum levels of cytokines, such as IL-1β, TNF-α, IFN-γ, IL-12, IL-6, and IL-10, were noticeably higher in STZ-treated animals than in normal mice, who had undetectable or very low levels. However, certain studies indicated that MDSD mice treated with GABA exhibited significantly reduced levels of circulating inflammatory cytokines, such as IL-1β, TNF-α, IFN-γ, and IL-12. Interestingly, there was no suppression of the concentrations of the anti-inflammatory cytokine IL-10. These results suggest that GABA reduces inflammation and creates a more favorable cytokine profile, which may be related to the decreased insulitis observed in MDSD and NOD animals treated with GABA.[13]

BETA CELLS

The islets generate GABA, a non-proteinogenic amino acid and neurotransmitter, in quantities comparable to those found in the brain. Glutamic acid decarboxylase (GAD) produces GABA.[8] Glutamate is the source of GABA. The TCA cycle in the pancreatic islets is involved in its metabolism, which is primarily dependent on three enzymes: succinic

semialdehyde dehydrogenase (SSADH), the catabolic enzyme GABA transaminase (GABA-T), and the synthetic enzyme GAD. The primary sources of glutamate, the substrate for GAD, are glucose and glutamine. Glutamic acid is then broken down by GAD to produce GABA.

GABA-T and SSADH break down GABA into succinctly in two stages. GABA is transferred to α-KG by transamination in the first catabolic step, forming glutamate and succinic semialdehyde in the process. Nicotinamide adenine dinucleotide (NAD) is reduced to NADH in the second step, which oxidizes succinic semialdehyde to succinate.

During membrane depolarization, β cells release GABA via Ca2+-dependent exocytosis, a mechanism controlled by synaptic-like microvesicles (SLMV). GABA has been demonstrated to have anti-apoptotic and proliferation-stimulating actions in human β cells. α and β cells can be affected by GABA produced by islet β cells via the paracrine and autocrine routes. The PI3K/Akt signaling pathway was activated by GABA-induced β-cell membrane depolarization and VDCC-induced Ca2+ influx. As a downstream mediator of the insulin receptor-2 signaling cascade, PI3K/Akt is essential for promoting the proliferation and differentiation of β cells while preventing their death.[20]

GABA METABOLISM-

Nitrogen metabolism and GABA production are closely related (Figure 4). The breakdown of glutamine's amide group to produce glutamate and ammonia can be facialted by glutaminase [91]. The opposite process, which is ATP-dependent and produces glutamine from glutamic acid and ammonia, is catalyzed by glutamine synthase (GS). In the glutamic acid–glutamine cycle, GS is a crucial enzyme. It is crucial to the brain's equilibrium of ammonia, glutamine, and glutamic acid. GABA is produced when GAD transforms glutamic acid through decarboxylation.[21]

Glutamate is essential for producing GABA, produced by two pathways: glutamine and α-KG, which is derived from the TCA cycle (tricarboxylic acid). Glutamate dehydrogenase (GDH) uses NAD+ or NADP+ as coenzymes to catalyze the interaction between glutamate, α-KG, and ammonia. Because it directly controls glutamic acid concentrations and indirectly controls GABA levels by altering the availability of precursors, GDH plays an important role in glutamic acid and GABA neurotransmission. GTP may inhibit GDH, while ADP may activate it.[22]

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Two different GAD isoenzymes, homocarnosine and pyrrolidinone, hold a considerable influence on GABA metabolism in the human brain. Thus, new avenues for the management of GABA-linked metabolic diseases may be opened by altering the GABA biosynthesis and metabolic pathways.[23]

GABAERGIC SIGNALING IN PATHOLOGICAL STATES

There are two types of GABAergic inhibition: tonic and phasic. High-affinity perisynaptic or extrasynaptic GABA receptors mediate a persistent inhibitory current that is triggered by extracellular or ambient GABA levels. This mechanism is referred to as tonic inhibition. Simultaneous activation of GABA receptors mostly takes place in the glia and is independent of neuronal activity, phasic activation of these receptors is crucial for regulating the rhythm of neuronal activity. Inhibition can be shifted to regulate the increase in neuronal excitability thanks to the tonic current. Furthermore, because tonic GABAergic inhibition is influenced by GABA binding to high-affinity GABA receptors, its effects may be more subdued.[24]

GABAergic neurotransmission

Glutamate decarboxylase (GAD) transforms glutamate into GABA for GABA production. Some peripheral tissues and GABAergic neurons, particularly the pancreatic islets, are the sole areas where GAD is present in its two isoforms, GAD67 and GAD65. After being released into the synapse, presynaptic neurons can also take up GABA. However, the GABA pathway route is mostly used to digest this GABA that has been recycled to produce ATP.

whereas SVs preferentially absorb newly produced GABA. Since both transporter VGAT form a protein complex, and CaMKII, which indicates that GABA into synaptic vesicles is closely tied to its production.[49] When GAD65 is absent, cytosolic GABA may reach the VGAT active site, and the vesicular transport of GABA.[25]

Additionally, GAD65 plays a critical function in GABAergic vesicle trafficking to presynaptic clusters. The delivery of GAD65 to synaptic terminals relies on the palmitoylation of cysteine residues at its N-terminus, and Huntington's disease is characterized by reduced palmitoylation, which compromises GABAergic neurotransmission.[52] Likewise release of GABA in a manner that relies on Ca2+ when the presynaptic ndergoes depolarization.[26]

Quick inhibitory postsynaptic potentials are caused by ionotropic GABA receptors, while delayed inhibitory postsynaptic potentials are caused by metabotropic GABA B receptors. α, β, and γ are the three main subunits that make up GABAA receptors, which are multi-subunit proteins. The primary ion pore is surrounded by five subunits in total. Three subunits make up the main receptor isoform: Two α1 subunits, two β2 subunits, and one γ2 subunit are present. When GABA attaches to GABAA receptors on the postsynaptic neuron, GABAA receptor Cl channels open rapidly and briefly. Following this, the membrane experiences hyperpolarization due to the influx of anions (phasic inhibition). Extrasynaptic GABAA receptors may be activated by GABA overspill, resulting in a longer ion channel opening (tonic inhibition).[27]

GABAB receptors are a type of metabotropic G-protein coupled receptor can be present both pre- post-synaptically and are primarily found extra-synaptically. GABA can bind to the GABAB1 subunit, whereas GABAB2 is attached to the G-protein. The components of the linked G-protein dissociate when GABAB receptors become activated. The Gβ/γ-subunit complex causes the cell to become hyperpolarized and inhibits neurotransmission by activating inwardly rectifying K+ channels and inhibiting voltage-activated Ca2+ channels.[28] As previously mentioned, the Gαi-subunit prevents adenylyl cyclase activation for mGluR. Inhibiting voltage-activated Ca2+ channel opening, which lowers neurotransmitter release. GABAB receptors on GABAergic axons allow discharge via a negative feedback cycle.[60] Postsynaptic GABA B activation decreases plasma membrane depolarization, which in turn modifies excitatory impulses. GABA transporter protein, which

is found in presynaptic nerve terminals (GAT-1) and adjacent glial cells (GAT-3), mediates GABA reuptake.[29]

Neurological disorders linked to glutamate and GABA receptors and the release of GABA mechanisms

Neurological disorders linked to impairments in GABA receptors

The clinical presentation of anti-GABAB receptor Ab-associated limbic encephalitis is comparable to that of Anti-GluRAb-mediated limbic encephalitis can occur in some individuals. Certain patients may develop CAs as well. Neoplastic conditions, especially small-cell lung cancer, impact approximately 50% of those affected.[30]

The link between GAD65 impairment and neurological issues

CAs and stiff-person syndrome (SPS) are linked to anti-GAD65Abs. In both cases, antiGAD65Ab titers are high (>1000 U/ml). Clinically, SPS is characterized by painful muscle spasms in the axial and limb muscles as well as increasing rigidity. Both the antagonistic and agonistic muscles are simultaneously active, according to electromyography (EMG). Women in their 50s to 60s are primarily affected by anti-GAD65Ab-associated CAs, which can be either subacute or chronic. Occasionally linked to epilepsy or SPS.[31] First, anti-GAD65Ab formulations have shown their harmful effects both in vitro and in vivo. For instance, the cerebrospinal fluid (CSF) of SPS patients blocked GABA production. Additionally, IgGs extracted from the CSF of CA and SPS patients were administered intrathecally, intraventricularly, or intracerebral into experimental rats and mice, reproducing SPS-like symptoms.[32]

Specifically, rats with anti-GAD65Ab-associated CA experienced ataxic gait due to cerebellar control of the motor cortex, which was impacted by intracerebral injection of IgGs from the CSF of these patients. In slices of the cerebellar brain, IgGs also reduced the release of GABA. These results were reproduced by human anti-GAD65 monoclonal Ab b78, which bound to an epitope similar to that present in SPS patients with anti-GAD65Ab tests.[33]

Second, research on animals has revealed that cerebellar neurons internalize antibodies proving that anti-GAD65Ab can reach its intracellular target. All of these findings point to the potential that anti-GAD65Ab could harm enough GABAergic neurons to cause overt neurological symptoms.[34]

Numerous cytokines can be released by microglia in response to elevated glutamate levels. that encourage glutamate release, on microglia, and restrict glutamate uptake by EAATs on astrocytes. Consequently, neuroinflammation triggers a series of events that aggravate the imbalance and lead to severe excitotoxicity. Cerebellar neurons are completely lost in patients with advanced-stage CAs, according to this view. In conclusion, Deficits in glutamate- and GABA-mediated synaptic processes cause disruptions in the glutamate/GABA ratio. Because of several factors, including damage-induced depolarization-induced glutamate release, exaggerated glutamate release, attenuated glutamate uptake via EAATs, or a decrease in GABA release followed by an increase in glutamate release. Excitotoxicity is a way through which neurons can die, and it can be caused by an imbalance between glutamate and GABA.[35]

CONCLUSION

The central nervous system (CNS) and pancreatic islets depend on GABA (gamma-aminobutyric acid) and its related enzyme systems, especially glutamic acid decarboxylase (GAD65 and GAD67), to maintain excitatory-inhibitory balance. Numerous clinical conditions, such as neurological, metabolic, and immunological diseases, are linked to changes in GABAergic transmission. Neuronal inhibition, β-cell function, and glucose homeostasis all depend on the interaction of GABA synthesis, receptor activation, and metabolism.

Anti-GAD antibodies highlight a possible role for immune-mediated dysfunction in GABAergic systems in autoimmune diseases such as stiff-person syndrome (SPS) and type 1 diabetes. Similarly, in illnesses such as limbic encephalitis, cerebellar ataxias, and other GABA-receptor-associated disorders, glutamate and GABA signaling abnormalities lead to excitotoxicity, neuroinflammation, and neuronal degeneration.

GABA's dual function in metabolic and neurological settings emphasizes its potential for treatment. GABA is an interesting target for diabetes control because of its capacity to stimulate proliferation, inhibit β-cell apoptosis, and alter immunological responses. Furthermore, knowing the processes behind GABAergic dysregulation opens the door to therapeutic approaches for neurological disorders associated with pathophysiology mediated by anti-GAD antibodies or GABA receptor dysfunction.

To sum up, future studies should concentrate on identifying the specific processes by which GABAergic signaling is disrupted in diseased conditions, investigating GABA receptor modulators, and creating plans to prevent antibody-mediated interference. This may open the door to new therapeutic strategies that maintain cellular homeostasis in the central nervous system and peripheral tissues while reestablishing the delicate balance between excitatory and inhibitory neurotransmission.

REFERENCES

1. Poznyak A, Grechko AV, Poggio P, Myasoedova VA, Alfieri V, Orekhov AN. The diabetes mellitus–atherosclerosis connection: The role of lipid and glucose metabolism and chronic inflammation. International journal of molecular sciences, 2020 Mar 6; 21(5): 1835.
2. Rossi MC, Nicolucci A, Ozzello A, Gentile S, Aglialoro A, Chiambretti A, Baccetti F, Gentile FM, Romeo F, Lucisano G, Giorda CB. Impact of severe and symptomatic hypoglycemia on quality of life and fear of hypoglycemia in type 1 and type 2 diabetes. Results of the Hypos-1 observational study. Nutrition, Metabolism and Cardiovascular Diseases, 2019 Jul 1; 29(7): 736-43.
3. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Gaglia JL, Hilliard ME, Isaacs D, Johnson EL. 2. Classification and diagnosis of diabetes: standards of care in diabetes—2023. Diabetes care, 2023 Jan 1; 46(Supplement_1): S19-40.
4. Kahanovitz L, Sluss PM, Russell SJ. Type 1 diabetes—a clinical perspective. Point of care, 2017 Mar 1; 16(1): 37-40.
5. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of type 2 diabetes mellitus. International journal of molecular sciences, 2020 Aug 30; 21(17): 6275.
6. Dufurrena Q, Amjad FM, Scherer PE, Weiss LM, Nagajyothi J, Roth J, Tanowitz HB, Kuliawat R. Alterations in pancreatic β cell function and Trypanosoma cruzi infection: evidence from human and animal studies. Parasitology research, 2017 Mar; 116: 827-38.
7. Wysham C, Shubrook J. Beta-cell failure in type 2 diabetes: mechanisms, markers, and clinical implications. Postgraduate Medicine, 2020 Nov 16; 132(8): 676-86.
8. Kittler JT, Moss SJ. Modulation of GABAA receptor activity by phosphorylation and receptor trafficking: implications for the efficacy of synaptic inhibition. Current opinion in neurobiology, 2003 Jun 1; 13(3): 341-7.

9. Vicini S. New perspectives in the functional role of GABA A channel heterogeneity. Molecular neurobiology, 1999 Apr; 19: 97-110.
10. 10) Ludwig A, Li H, Saarma M, Kaila K, Rivera C. Developmental up-regulation of KCC2 in the absence of GABAergic and glutamatergic transmission. European Journal of Neuroscience, 2003 Dec; 18(12): 3199-206.
11. Rorsman P, Berggren PO, Bokvist K, Ericson H, Möhler H, Östenson CG, Smith PA. Glucose inhibition of glucagon secretion involves the activation of GABAA-receptor chloride channels. Nature, 1989 Sep 21; 341(6239): 233-6.
12. Winnock F, Ling Z, De Proft R, Dejonghe S, Schuit F, Gorus F, Pipeleers D. Correlation between GABA release from rat islet β-cells and their metabolic state. American Journal of Physiology-Endocrinology and Metabolism, 2002 Apr 1; 282(4): E937-42.
13. Tritt M, Sgouroudis E, d'Hennezel E, Albanese A, Piccirillo CA. Functional waning of naturally occurring CD4+ regulatory T-cells contributes to the onset of autoimmune diabetes. Diabetes, 2008 Jan 1; 57(1): 113-23.
14. Christgau S, Schierbeck H, Aanstoot HJ, Aagaard L, Begley K, Kofod H, Hejnaes K, Baekkeskov S. Pancreatic beta cells express two autoantigenic forms of glutamic acid decarboxylase, a 65-kDa hydrophilic form and a 64-kDa amphiphilic form which can be both membrane-bound and soluble. Journal of Biological Chemistry, 1991 Nov 5; 266(31): 21257-64.
15. Barker JL. GABA as a Neurotransmitter and Neurogenic Signal. eLS. 2001 May 30.
16. LM L. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. Ann Intern Med., 1999; 1310: 522-30.
17. Lohmann T, Hawa M, Leslie RD, Lane R, Picard J, Londei M. Immune reactivity to glutamic acid decarboxylase 65 in stiff-man syndrome and type 1 diabetes mellitus. The Lancet, 2000 Jul 1; 356(9223): 31-5.
18. Kämpe O, Andersson A, Björk E, Hallberg A, Karlsson FA. High-glucose stimulation of 64,000-M r islet cell autoantigen expression. Diabetes, 1989 Oct 1; 38(10): 1326-8.
19. Shi Y, Kanaani J, Menard-Rose V, Ma YH, Chang PY, Hanahan D, Tobin A, Grodsky G, Baekkeskov S. Increased expression of GAD65 and GABA in pancreatic β-cells impairs first-phase insulin secretion. American Journal of Physiology-Endocrinology and Metabolism, 2000 Sep 1; 279(3): E684-94.
20. Yi Z, Waseem Ghani M, Ghani H, Jiang W, Waseem Birmani M, Ye L, Bin L, Cun LG, Lilong A, Mei X. Gimmicks of gamma-aminobutyric acid (GABA) in pancreatic β-cell

regeneration through transdifferentiation of pancreatic α-to β-cells. Cell Biology International, 2020 Apr; 44(4): 926-36.

21. Roberts E, Frankel S. γ-Aminobutyric acid in brain: its formation from glutamic acid.
22. Plaitakis A, Zaganas I. Regulation of human glutamate dehydrogenases: implications for glutamate, ammonia, and energy metabolism in the brain. Journal of Neuroscience Research, 2001 Dec 1; 66(5): 899-908.
23. Walls AB, Waagepetersen HS, Bak LK, Schousboe A, Sonnewald U. The glutamine–glutamate/GABA cycle: function, regional differences in glutamate and GABA production and effects of interference with GABA metabolism. Neurochemical research., 2015 Feb; 40: 402-9.
24. Stell BM, Mody I. Receptors with different affinities mediate phasic and tonic GABA (A) conductances in hippocampal neurons. The Journal of Neuroscience: the official journal of the Society for Neuroscience, 2002 May 10; 22(10): RC223-.
25. Jin H, Wu H, Osterhaus G, Wei J, Davis K, Sha D, Floor E, Hsu CC, Kopke RD, Wu JY. Demonstration of functional coupling between γ-aminobutyric acid (GABA) synthesis and vesicular GABA transport into synaptic vesicles. Proceedings of the National Academy of Science, 2003 Apr 1; 100(7): 4293-8.
26. Rush DB, Leon RT, McCollum MH, Treu RW, Wei J. Palmitoylation and trafficking of GAD65 are impaired in a cellular model of Huntington's disease. Biochemical Journal, 2012 Feb 15; 442(1): 39-48.
27. Brickley SG, Mody I. Extrasynaptic GABAA receptors: their function in the CNS and implications for disease. Neuron, 2012 Jan 12; 73(1): 23-34.
28. Ong J, Kerr DI. Recent advances in GABAB receptors: from pharmacology to molecular biology. Acta Pharmacologica Sinica, 2000 Feb 1; 21(2): 111-23.
29. Schousboe A. Pharmacological and functional characterization of astrocytic GABA transport: a short review. Neurochemical research, 2000 Oct; 25: 1241-4.
30. Höftberger R, Titulaer MJ, Sabater L, Dome B, Rózsás A, Hegedus B, Hoda MA, Laszlo V, Ankersmit HJ, Harms L, Boyero S. Encephalitis and GABAB receptor antibodies: novel findings in a new case series of 20 patients. Neurology, 2013 Oct 22; 81(17): 1500-6.
31. Honnorat J, Saiz A, Giometto B, Vincent A, Brieva L, de Andres C, Maestre J, Fabien N, Vighetto A, Casamitjana R, Thivolet C. Cerebellar ataxia with anti-glutamic acid decarboxylase antibodies: a study of 14 patients. Archives of neurology, 2001 Feb 1; 58(2): 225-30.

32. Hansen N, Grünewald B, Weishaupt A, Colaço MN, Toyka KV, Sommer C, Geis C. Human Stiff person syndrome IgG-containing high-titer anti-GAD65 autoantibodies induce motor dysfunction in rats. Experimental neurology, 2013 Jan 1; 239: 202-9.
33. Hampe CS, Petrosini L, De Bartolo P, Caporali P, Cutuli D, Laricchiuta D, Foti F, Radtke JR, Vidova V, Honnorat J, Manto M. Monoclonal antibodies to 65kDa glutamate decarboxylase induce epitope-specific effects on motor and cognitive functions in rats. Orphanet Journal of Rare Diseases, 2013 Dec; 8: 1-0.
34. Mitoma H, Manto M, Hampe CS. Pathogenic roles of glutamic acid decarboxylase 65 autoantibodies in cerebellar ataxias. Journal of immunology research, 2017; 2017(1): 2913297.
35. Ishida K, Mitoma H, Wada Y, Oka T, Shibahara J, Saito Y, Murayama S, Mizusawa H. Selective loss of Purkinje cells in a patient with anti-glutamic acid decarboxylase antibody-associated cerebellar ataxia. Journal of Neurology, Neurosurgery & Psychiatry, 2007 Feb 1; 78(2): 190-2.
36. Gold PE. Role of glucose in regulating the brain and cognition. The American journal of clinical nutrition, 1995 Apr 1; 61(4): 987S-95S.
37. Thorens MU. The SLC2 family of facilitated hexose and polyol transporters. Pflugers Arch-Eur J Physiol, 2004; 448: 259-60.
38. Joost HG, Thorens B. The extended GLUT family of sugar/polyol transport facilitators: nomenclature, sequence characteristics, and potential function of its novel members. Molecular membrane biology, 2001 Jan 1; 18(4): 247-56.
39. Wood IS, Trayhurn P. Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. British journal of nutrition, 2003 Jan; 89(1): 3-9.
40. Wozniak M, Rydzewski B, Baker SP, Raizada MK. The cellular and physiological actions of insulin in the central nervous system. Neurochemistry international, 1993 Jan 1; 22(1): 1-0.
41. Freude S, Plum L, Schnitker J, Leeser U, Udelhoven M, Krone W, Bruning JC, Schubert M. Peripheral hyperinsulinemia promotes tau phosphorylation in vivo. Diabetes, 2005 Dec 1; 54(12): 3343-8.
42. van der Heide LP, Ramakers GM, Smidt MP. Insulin signaling in the central nervous system: learning to survive. Progress in neurobiology, 2006 Jul 1; 79(4): 205-21.
43. Fishel MA, Watson GS, Montine TJ, Wang Q, Green PS, Kulstad JJ, Cook DG, Peskind ER, Baker LD, Goldgaber D, Nie W. Hyperinsulinemia provokes synchronous increases

in central inflammation and β-amyloid in normal adults. Archives of neurology, 2005 Oct 1; 62(10): 1539-44.

44. Castellano, J. M., Garcia-Rodriguez, S., Espinosa, J. M., Millan-Linares, M. C., Rada, M., and Perona, J. S. (2019). Oleanolic acid exerts a neuroprotective effect against microglial cell activation by modulating cytokine release and antioxidant defense systems. Biomolecules 9 (11): 683. doi:10.3390/biom9110683
45. Carter J. Prevalence of all-cause young onset dementia and time lived with dementia: analysis of primary care health records. Journal of Dementia Care, 2022 May 9; 30(3): 1-5.
46. Nelson PT, Alafuzoff I, Bigio EH, Bouras C, Braak H, Cairns NJ, Castellani RJ, Crain BJ, Davies P, Tredici KD, Duyckaerts C. Correlation of Alzheimer disease neuropathologic changes with cognitive status: a review of the literature. Journal of Neuropathology & Experimental Neurology, 2012 May 1; 71(5): 362-81.
47. Thomason LA, Stefanovic B, McLaurin J. Cerebrovascular contributions to Alzheimer's disease pathophysiology and potential therapeutic interventions in mouse models. European Journal of Neuroscience, 2013 Jun; 37(12): 1994-2004.
48. Mg S. α-synuclein in Lewy bodies. Nature, 1997; 388: 839-40.
49. Han Y., Yuan C., Zhou X., Han Y., He Y., Ouyang J., Zhou W., Wang Z., Wang H., Li G. (2021). Anti-inflammatory activity of three triterpene from Hippophae rhamnoides L. in lipopolysaccharide-stimulated RAW264.7 cells. Int. J. Mol. Sci, 22: 12009.
50. Pan XD, Chen XC. Clinic, neuropathology and molecular genetics of frontotemporal dementia: a mini-review. Translational neurodegeneration, 2013 Dec; 2: 1-9.
51. Raz L, Knoefel J, Bhaskar K. The neuropathology and cerebrovascular mechanisms of dementia. Journal of Cerebral Blood Flow & Metabolism, 2016 Jan; 36(1): 172-86.
52. Pendlebury ST, Rothwell PM. Prevalence, incidence, and factors associated with pre-stroke and post-stroke dementia: a systematic review and meta-analysis. The Lancet Neurology, 2009 Nov 1; 8(11): 1006-18.
53. Schott JM, Fox NC, Frost C, Scahill RI, Janssen JC, Chan D, Jenkins R, Rossor MN. Assessing the onset of structural change in familial Alzheimer's disease. Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society, 2003 Feb; 53(2): 181-8.
54. Peila R, Rodriguez BL, Launer LJ. Type 2 diabetes, APOE gene, and the risk for dementia and related pathologies: The Honolulu-Asia Aging Study. Diabetes, 2002 Apr 1; 51(4): 1256-62.