Chapter

Diabetes Mellitus and Amyloid Beta Protein Pathology in Dementia

Teresa Ponce-López, Andrew Michael Sorsby-Vargas, Alma Patricia Bocanegra-López, José Luna-Muñoz, Miguel Angel Ontiveros-Torres, Ignacio Villanueva-Fierro, Parménides Guadarrama-Ortiz and Alejandra Martínez-Maldonado

Abstract

Amyloidosis is a pathological condition which consists on the accumulation of fibrillar proteins. This disease is characterized by extracellular amyloid deposits with a clinical variability depending on the affected tissue. Histopathological evidence indicates that diabetes mellitus type 2 (DM2) induces dementia development, specifically Alzheimer's disease (AD). It has been demonstrated in animal subjects that there is a possibility that aberrant signaling of insulin is a key factor in the induction of the pathology of AD. Recently, there has been newly emerged evidence regarding the relationship between the pathogenesis of Parkinson's disease (PD) and insulin resistance. On another note, the importance of the amyloid deposits in the patients' pancreas with DM2 was evidenced by the discovery of islets of amyloid polypeptide. This has generated interest in the search of the etiopathogenic role of DM2 in the carbohydrates' metabolism. Finally, it is important to consider DM2 as a risk factor essential for the formation of deposits of amyloid-β in patients' brains with dementia.

Keywords: diabetes mellitus, insulin resistance, β-amyloid, dementia, Alzheimer's disease, Parkinson's disease

1. Introduction

Dementia has become a worldwide public health issue that currently affects 50 million people. The impact of this disease not only affects the patient himself but also the family and caretaker. This neurodegenerative disorder is characterized by the loss of mental faculties in a progressive and irreversible way which includes language alterations, learning and memory, as well as loss of ethical judgment and social behavior.

Alzheimer's disease is the main cause of dementia, following vascular dementia, senil dementia, frontotemporal dementia, and even Parkinson's disease (P). Age is still the main risk factor to suffer from dementia, even though it is a multifactorial disorder. Smoking, alcoholism, lack of interest in education, and obesity are factors that can increase the risk of developing dementia in an old age [1].

Currently, obesity is another worldwide public health issue. According to the World Health Organization (WHO), the majority of the population lives in countries where overweight and obesity are the cause of more deaths than malnutrition. At the same time, obesity is one of the causes of diabetes mellitus (DM) which is a chronic disease derived from a failure in the pancreas to produce insulin, necessary hormone to process glucose [2].

Studies suggest that insulin is related with the formation of amyloid plaques which are histopathological structures, characteristics of some dementias such as Alzheimer's disease (AD) [3]. For this reason, in recent years, DM has been considered, specifically diabetes mellitus type 2 (DM2, in which the organism is unable to use insulin), as an important risk factor for the development of dementia. In this chapter, general data about DM and dementias, as well as the importance of DM in the formation of amyloid aggregates which converts it in a risk factor for AD and Parkinson's disease (PD), will be discussed.

2. Amyloidosis

Amyloidosis is a chronic disease that is characterized by the extracellular deposits of insoluble proteins in one or many organs (systematic amyloidosis). Such disease is due to the alteration in the metabolism of various proteins which is the origin of extracellular accumulation of material resistant to the digestion protein called amyloid fibrillar protein [4]. Generally, amyloid deposits are located in a systematic way. Amyloidosis can arise by itself (primary amyloidosis) or be a secondary effect of many infections, inflammatory disorders, or malignancies in diseases (secondary amyloidosis) (**Table 1**).

One of the most studied amyloid proteins is amyloid-β peptide (Aβ), which arises from the proteolictic processing (via amyloidogenic) of the precursor amyloid protein (APP) [5]. This peptide is added in an extracellular way and forms highly insoluble fibrils that give rise to the amyloid plaques which are found in patients' brains with neurodegenerative diseases such as Alzheimer's disease. Existing evidence has been suggested that monomers of Aβ do not generate a toxic environment in the brain parenchyma [6]; however, the oligomers of this peptide prevent the synapse and neuronal environment and generate an exacerbated inflammation associated with the glia and microgery favoring the production of

Primary Amyloidosis	*No alternate disease. Occurs by itself*		
Secondary Amyloidosis	*Originate in the bosom of another disease*	*Inflammatory diseases*	*Example: Rheumatoid arthritis*
		Infectious diseases	*Example: Tuberculosis*
		Neoplasias	*Example: Hodgkin's disease*

Table 1.
Amyloidosis classification.

interleukins triggering the formation of reactive oxygen species that have been shown to be toxic, causing neuronal death [7].

3. Definition, clinical characteristics, and epidemiology of diabetes mellitus

DM is a chronic metabolic disease characterized by hyperglycemia caused by a deficit of pancreas insulin production known as diabetes mellitus type 1 (DM1) or by insulin receptor dysfunction known as diabetes mellitus type 2 (DM2) [2]. DM is characterized by the presence of polyuria, polyphagia, and polydipsia. Patients present an unexplained weight loss; paresthesia of the extremities and foot pain may occur, as well as asthenia and recurrent or complicated infections. If the patients are not adequately treated, it can be associated with renal, visual, cardiac, intestinal, diabetic ketoacidosis, or diabetic coma complications, and it can lead to brain damage [8]. DM is currently considered a risk factor for the development of Alzheimer's disease (AD) and Parkinson's disease (PD) [3].

In recent years, the prevalence of this disease has increased in a progressive and alarming way, becoming a public health problem. The National Center for Chronic Disease Prevention and Health Promotion estimates that in 2017, 9.4% of the United States population suffers from diabetes, that is, 30.3 million people, of which 21.1 million people are diagnosed and 7.2 million people who have diabetes have not been diagnosed. On the other hand, the last report of the World Health Organization on the profiles of countries for diabetes in 2016 reports that in the United States, 3% of the population dies from this disease. **Table 2** highlights the figures on the number of deaths caused by this disease in the five countries with the highest number of patients according to the statistics portal Statista.

Year / Country	2016*					2017**
	Population (millions)	Age Range	DM cases		Deaths by DM	DM cases
			Men	Women		
China	1,376	30 – 69 years	16,000	10,600	3% of the population	114,441
		> 40 years	20,400	23,400		
India	1,311	30 – 69 years	75,900	51,700	2 % of the population	73,074
		> 40 years	46,800	45,000		
United States	322	30 – 69 years	16,600	10,600	3% of the population	30,357
		> 40 years	20,400	23,400		
Brazil	208	30 – 69 years	15,000	14,900	6% of the population	12,554
		> 40 years	16,900	25,900		
Mexico	127	30 – 69 years	23,100	22,000	14% of the population	12,056
		> 40 years	17,600	24,300		

**Data according to WHO 2016*

***Data according to Statista 2017*

Table 2.
Cases and deaths due to diabetes mellitus in the countries with the highest prevalence.

4. Amyloidosis' association with diabetes mellitus

Case studies have shown a deep connection in patients who suffer from amyloidosis and type 2 diabetes, especially in those with pancreatic damage [9, 10]. Studies have focused on a neuro pancreatic hormone called islet amyloid polypeptide (IAPP) or amylin, secreted along with insulin by β pancreatic cells, and its possible etiology in type 2 diabetes [11]. IAPP functions as a glucose homeostatic regulator, but once it suffers synthetic alterations, it starts to accumulate inside and outside the pancreatic cells resulting in apoptosis [12]. Although the specific etiology has remained unknown, there have been many hypotheses on what causes these pancreatic amyloid deposits. One of the most accepted hypotheses consists of a malfunctioning β pancreatic cell which is unable to correctly process amylin, resulting in the installment of amyloid proteins inside and outside the cells [13]. Another accepted theory indicates the genetic overexpression of amylin, which causes amyloid deposits, although there has not been a proven correlation (in humans) between high IAPP circulating levels and glucose intolerance [14]. It has been proved that the amino acids within the 26–29 sequence are a determinant factor proved in the development of amyloid deposits only in humans, simians, and felines, which are presumed to be the only three species to suffer from an amyloid deposit diabetes [9, 10, 15, 16]. It has been proved that in 9% of the diabetic population, there has been an identified mutation within the promoter region in the amyloid gene, increasing its transcription [17–19]. For years it has been proven that high blood glucose is not only toxic to β pancreatic cells, but it also generates an overexpression on the IAPP gene which contributes to pancreatic amyloid deposits, inducting cellular apoptosis [12]. It was never clear whether IAPP was the cause or the consequence of diabetes, but once the genetic mutation in the promoter region was finally identified, there is still more research to be done in order to be completely certain.

5. Definition and epidemiology of dementias

Dementia is a syndrome of generalized deterioration, since it involves cognitive-behavioral damage; is acquired, degenerative in most cases, and multi-etiological; and will have repercussions on the family, work, and social life of the person. Dementia is also characterized by a decrease in mental faculties of the individual, and clinical characteristics may vary depending on the neuropathological process of the disease and even the specific characteristics of each person. Symptoms may include short-term memory loss, temporary and spatial disorientation, and difficulty in communication and behavior alterations [20]. The most frequent types of dementia include vascular dementia, AD, and PD, although there are other forms of dementia such as frontotemporal dementia and dementia caused by Lewy body deposits. It usually affects older adults; however, it is not the result of normal aging.

Currently dementia is not considered a social priority in most countries, despite the increase in incidence. It is estimated that there are at least 50 million people in the world suffering from dementia, with 10 million new cases registered every year. WHO statistics indicates that it is expected that by the year 2030 and 2050, the figures will, respectively, increase to 76 million and 145 million cases. AD is the main cause of dementia, representing at least 60% of cases, with a prevalence of 10–30% in the population over 65 years of age [21–23]. On the other hand, PD is the second most common neurodegenerative disease after AD which frequently goes through a process of dementia. PD has a prevalence between 100 and 300/100,000 of the population [24], and it is expected that by 2030 the number of patients duplicates [25–27].

These numbers are alarming, and they represent a really serious situation that has not been given the attention and follow-up that is required, because as

already mentioned, it has not been a social priority for most countries yet has a great economic impact.

6. Diabetes mellitus as a risk factor for dementias

Dementia is a complex disorder of multifactorial etiology that results in alterations in health status changes in lifestyle. It is important to identify the risk factors, at an early age, to prevent this disease. There are several factors related to dementia such as age [28], ethnic group [29], gender [30], genetic factors [31], physical activity [32], smoking, alcoholism [33], education level [34], environmental factors, and obesity [35, 36]. In addition, in the last decade, DM has been associated as a risk factor for dementia, especially DM2, which is also related to obesity.

Damage to cognitive functions has been observed in patients with DM2 compared to healthy patients [37, 38]. Individuals with DM2 present alterations in their attention capacity, execution, processing speed, work memory, and verbal memory [39, 40]. Studies report a reduction of the gray matter in the frontotemporal cortex, as well as the decrease in glucose metabolism in patients with alterations in executive and memory functions [41], but it also has been associated to a white matter reduction [38]. On the other hand, the damages in verbal memory correlate with the integrity of the parahippocampal gyrus [42]. In other words, DM2 represents an important risk factor for dementia. Interestingly, in the five main countries with a high DM prevalence (see **Table 2**), there is also a significant prevalence of dementia (**Figure 1**).

DM2 is the most common type of diabetes in which autoimmune antibodies appear to be the cause. In this type of diabetes, insulin resistance is observed, which limits the ability to respond to hormones, both endogenous and exogenous [43]. In some cases, insulin resistance is a result of a lower number or a mutation of insulin receptors (IR). These receptors are expressed in the central nervous system (CNS), in the hypothalamus, olfactory bulb, cerebral cortex, cerebellum, and hippocampus [44–46]. Insulin can cross the blood-brain barrier and reach its target, generating anorexic effects by activating the satiety center. This happens because insulin and the insulin-like growth factor-1 (IGF-1) activate PI3K causing the opening of ATP-dependent potassium channels (ChK^{*}_{ATP}), thus hyperpolarizing the neuron which causes it to disrupt its activity, and thus, it stimulates the secretion of the

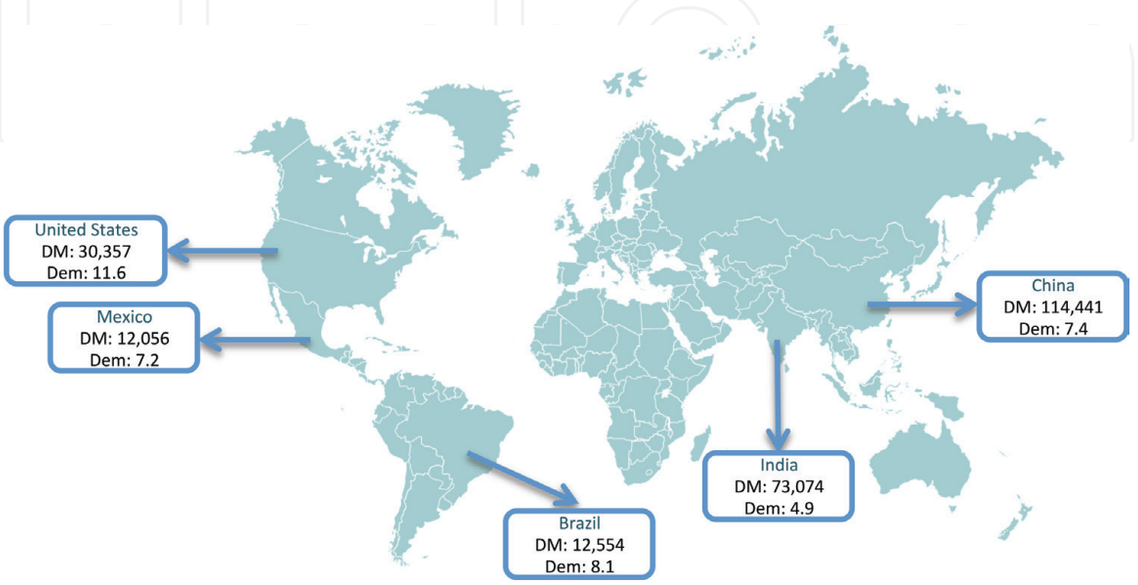

Figure 1.
Dementia prevalence in the five countries with the highest diabetes mellitus prevalence in 2017. DM, diabetes mellitus (thousands); Dem, dementia (for every 1000).

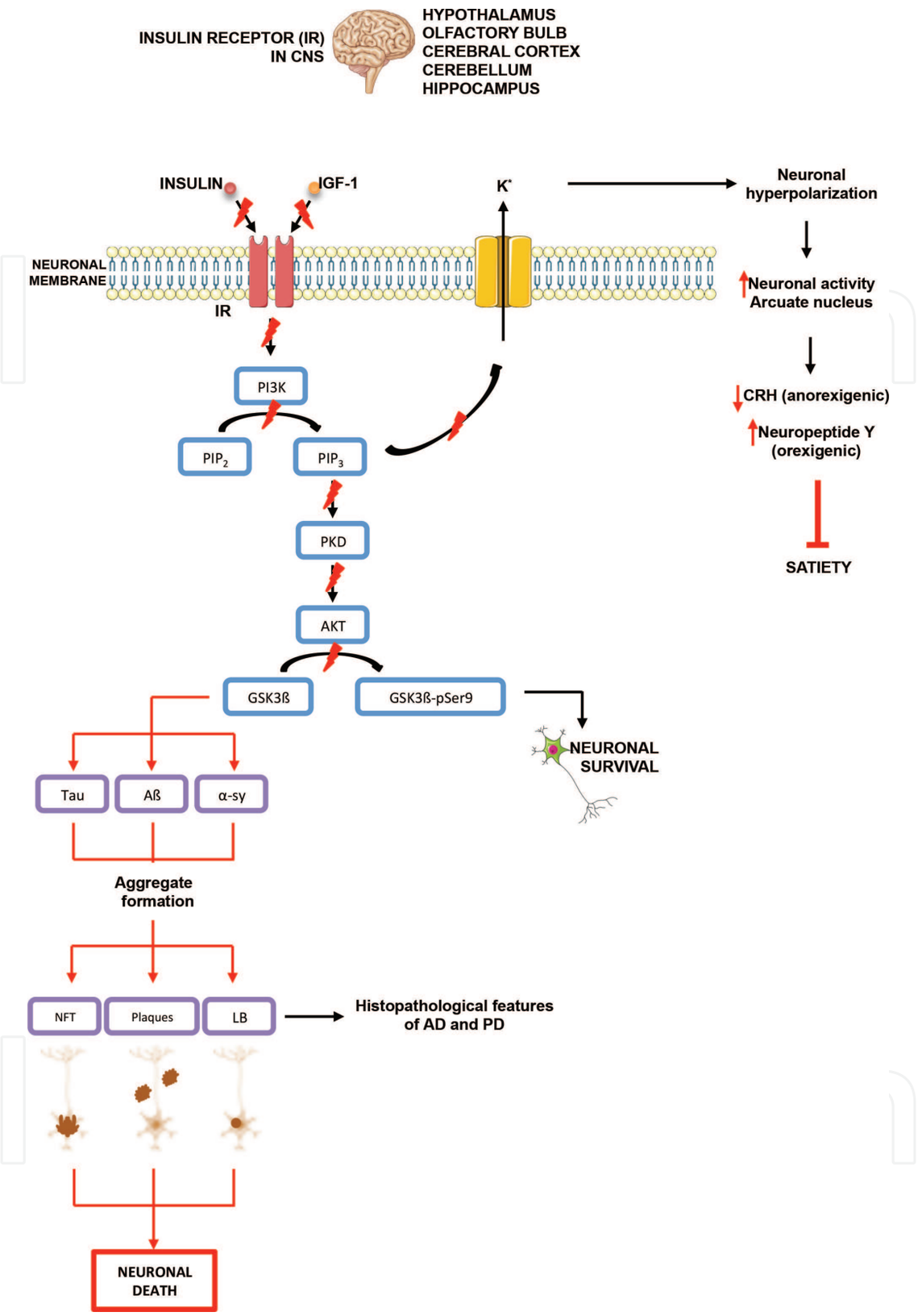

Figure 2.
Pathway of insulin/IGF-1/PI3K/AKT/GSK3β in respect to the neuronal function and its effect on satiety. Normally, this pathway of insulin/IGF-1 begins when it activates IR and it phosphorylates to begin the pathway for PI3K. Once PKD activates AKT, it will inhibit the activity of GSK3β by phosphorylating in Ser9, which is associated to neuronal survival. On another note, PI3K provokes the opening of potassium canals, via PIP2, hyperpolarizing the neuron which is what conducts the activation of the satiety center. When there is no suitable recognition of insulin, GSK3β will not inhibit; therefore, it will act upon proteins [tau, amyloid-β (Aβ) y α-synuclein (α-syn)] related to the formation of aggregates [neurofibrillary tangles (NFT), amyloid plaques, and Lewy bodies (LB), respectively] which lead to neuronal death and are histopathological characteristics of diseases such as AD and PD. Also, the opening of potassium canals will not be taken care of, inhibiting the satiety (in the presence of insulin, back arrows; lack of insulin, red arrows).

corticotropin-releasing hormone (CRH), which is anorexigenic and inhibits the secretion of neuropeptide Y, which is orexigenic. As mentioned above, insulin activates the PI3K/AKT/GSK3β pathway, where GSK3β is phosphorylated in Ser9 (GSK3β-pSer9) by means of AKT; being phosphorylated at this site inactivates it, resulting in neuronal survival. However, when there is insulin resistance as in the case of DM2 or there is no insulin production (DM1), this pathway does not activate; therefore GSK3β will not be inhibited and will act upon proteins involved in neuronal death such as tau, amyloid-β, and α-synuclein. These proteins will form intracellular (tau) and extracellular (tau, amyloid-β, and α-synuclein) deposits, which are histopathological features (neurofibrillary tangles, plaques, and Lewy bodies) of dementias such as AD and PD (**Figure 2**). Neuronal death caused by the lack of insulin is one of the reasons why DM is a risk factor for dementia.

7. Diabetes mellitus and amyloid-β protein pathology in Parkinson's disease

Clinically, Parkinson's disease is defined as a progressive disorder characterized by resting tremor, rigidity, and bradykinesia; however, there may be other manifestations less constant such as postural instability, propulsive gait, dysphagia, autonomic disorders, sebaceous sweating, salivation, and deteriorating superior functions that can lead up to dementia. This disease was described in 1817 by James Parkinson, who described the deficiency of dopamine in the brain of his patients in late 1950 and also described the treatment of this disease with L-dopa in the 1960s. Parkinson's disease is the second most frequent neurodegenerative disorder. It is a motor disease related with the disorder of the basal ganglia specifically via nigrostriatal which is formed by the axons of the dopaminergic neurons of the substance compact nigra which innervate the corpus striatum. This structure is considered the main target of dopaminergic innervation due to the high density of axons it receives and its large size. The main symptoms of Parkinson's disease are caused by the degeneration of dopaminergic neurons via nigrostriatal [47, 48]. A pathological hallmark of Parkinson's disease is the Lewy bodies (LB), eosinophilic inclusions of α-synuclein (α-syn) located in the neuronal soma especially in nigra substance [49]. Besides the (LB) there can be deposits of the protein tau (MNF) and of β-amyloid (plaques).

There is existing evidence that α-syn, tau and Aβ act in a synergistic way in the pathology of AD and PD [50, 51] accelerating the aggregation of each [52]. The presence of tau and Aβ was found in patients with PD, and the cognitive function was lower than healthy patients' [53]. It has also been demonstrated that when these three proteins are found in high concentrations, as in PD, it generates changes in CFS tau levels [54], and if these patients are obese as well, they present insulin resistance [55, 56] even though they do not suffer from DM. These patients have deficits of cognitive functions. It is possible that the resistance to insulin accelerates the demential process in patients with PD, and it can lead to more serious motor symptoms.

As described before, insulin/IGF-1 activates the route PI3K/AKT/GSK3β, which, besides being involved in the glucose metabolism and the ingestion of food, also plays an important role in the learning and memory process associated with long-term potential (LTP) in the hippocampus [57]. Apparently, insulin stabilizes the production of dopamine and decreases the alterations in movement in a PD model [58–61]. When insulin acts over IR in a suitable way, the result is neuronal survival; however, the lack of insulin provokes that the GSK3β will not be inactivated (when it is phosphorylated in Ser9 by AKT), which leads to the favoring of the formation of MNF, LB, and amyloid plaques (see **Figure 2**). These pathological structures are found frequently coexisting in the hippocampus and cerebral cortex in patients

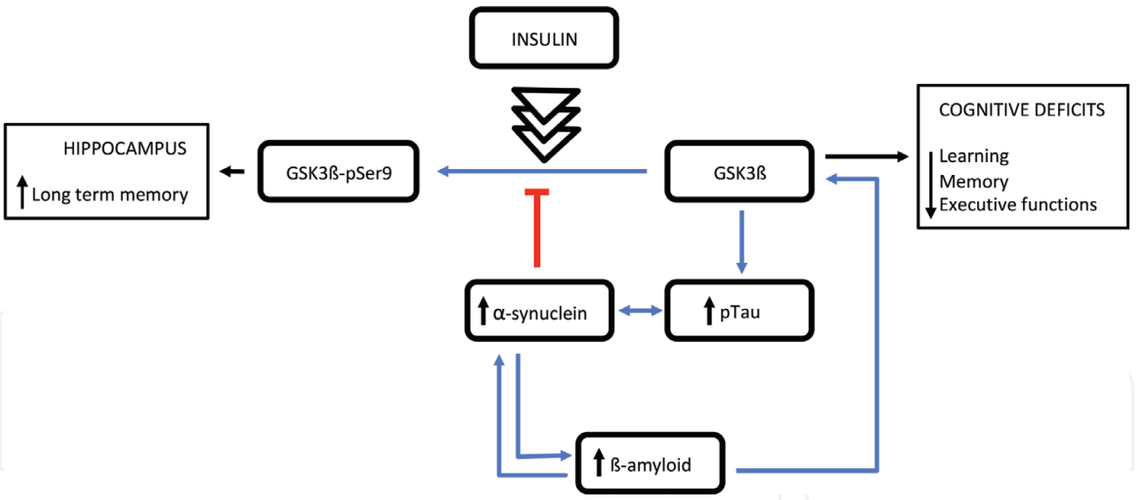

Figure 3.
GSK3β activation regulated by synergistic action of α-synuclein (α-syn), phosphorylated tau (pTau), and β-amyloid (Aβ). In the presence of insulin, a GSK3β inhibition occurs that has as a result, the improvement of long-term memory in the hippocampus. When there are alterations in the recognition of the insulin or there is simply no production, no GSK3β inhibitions occur which promoted the augmentation of α-sy, pTau, and Aβ aggregates which at the same time act synergistically, augmenting GSK3β activity. Therefore, cognitive deficits that include alterations in the learning and memory processes as well as executive functions are favored.

with PD [62]. The negative regulation of GSK3β is extremely important in the neurodegenerative disorders such as PD [63] and even more in the function of α-syn, having as consequences cognitive deficits [64, 65] which include learning and memory alterations as well as executive functions. If this negative regulation of GSK3β does not happen due to the lack of insulin, then there will be a tau phosphorylation increase which will favor the accumulation of α-syn amyloid. These aggregates of α-syn have a positive feedback over the accumulation of phosphorylated tau and facilitate the formation of Aβ deposits. The accumulation of aβ and α-syn (amyloid) activates GSK3β, even though α-syn does so by inhibiting the formation of GSK3β-pSer9 (**Figure 3**).

It is possible that patients with DM-PD deteriorate rapidly due to the favoring of the accumulation of Aβ due to the lack of insulin, since this could generate more oxidative stress and thereby damage dopaminergic neurons. However, more studies are needed regarding the interaction between Aβ and α-syn in the demential process of PD caused by the failure in recognition of insulin such as in DM2.

8. Diabetes mellitus and amylin and amyloid-β protein pathologies in Alzheimer's disease

AD is one of the most prevalent dementias in older people and is characterized by the progressive loss of memory and deterioration of cognitive functions such as judgment and behavior [66]. AD develops through mutations in the chromosomes (presenilin 2), chromosome 14 (presenilin 1) and chromosome 21 (PPA) [67]. Only 5% of patients with AD associate to this genetic factor. It has an early appearance in people around 45 years old; however, the most common form of appearance of this neurodegenerative disease is "sporadic" where there are no mutations and it develops in people around 65 years [68]. There is still doubt regarding the genesis of sporadic AD; risk factors that can lead to the development of AD have been described. One of these risk factors is aging and poor eating habits where it involves ingesting large quantities of fat and sugar. Therefore, obesity is a risk factor for diabetes mellitus type 2.

Histopathologically, the brains of these patients present in great abundance neuritic plaques (NP) and neurofibrillary tangles. (NFT) [69, 70]. Neuritic plaques are constituted by extracellular deposits of the fibrillar beta-amyloid peptide, and associated to these, dystrophic neurites (DN), neuritic plaques bordered by astroglial cells and associated with the amyloid peptide, the tight microglial cells can be observed (**Figure 4**). Together, they unleash the inflammatory cell process observed in a brain with AD [71]. NFT are constituted by highly soluble filaments (paired helical filaments, PHF) inside the neuronal soma. The PHF are constituted by tau protein; in normal conditions, tau protein favors the stability to the microtubules and the organelles and vesicles along the axon. The genesis of PHF has been associated with posttranslational mechanisms of tau protein as in hyperphosphorylation and truncation. Recent studies have suggested that the tau protein plays a dual role in protection and toxicity upon the neurodegenerative process and neuronal death. The phosphorylation of the tau protein could be involved in processes of neuronal protection to degeneration

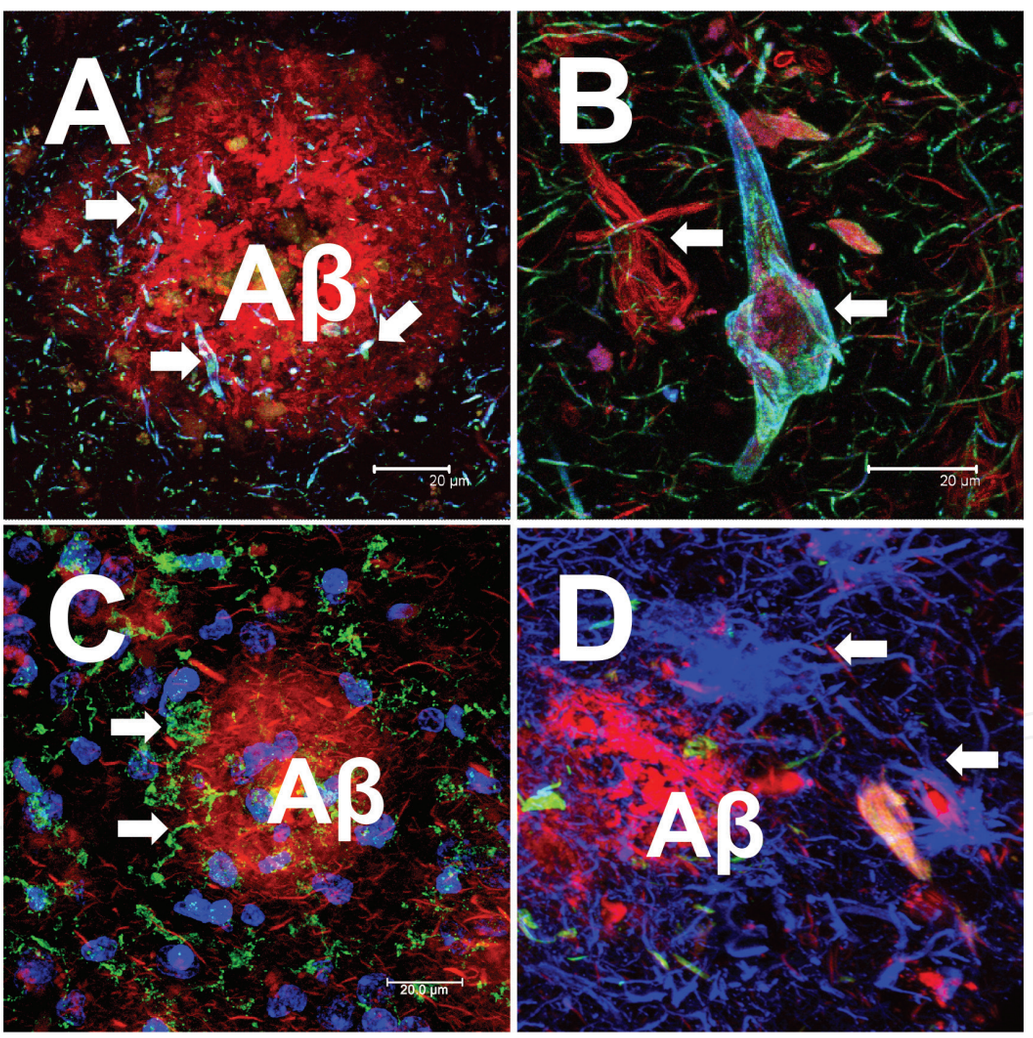

Figure 4.
Characteristic lesions of a brain with Alzheimer's disease. (A) Neuritic plaque. Dystrophic neuritis (green and blue channels) are observed in the periphery of the Aβ deposit (red channel). (B) Neurofibrillary tangles recognized by antibodies directed against phosphorylated tau protein, in the vicinity there is a neurofibrillary tangle evidenced only in the red channel, the dystrophic neuritis in the periphery show different degrees of co-localization. (C) Neuritic plaque evidenced in the red channel, the nuclei are observed in blue color. The microglial cells are closely associated with the Aβ deposit (green channel). (D) Neuritic plaque in the periphery glial cells (blue channel) are observed. And in the channel see observed neuritic dystrophic positive tau protein. Double immunostaining with antibodies directed against the phosphorylated tau protein (A, B), IBA1 (C), and GFAP (D), counterstained with triazine red dye A-D and ToPro (C). Images taken with confocal microscope (SP8, Leica).

upon the fragment of the minimal filament (92–95 amino acids culminating in Glu391). The process of proteolysis in the asp-421 of tau favors in the beginning its polymerization, and the truncation in glu391 favors the stability and insolubility of the PHF [72].

8.1 Amyloid formation is the pathological hallmark of T2D and AD

The incidence of both AD and T2D is increasing at an alarming rate at present and has become a major public health concern in many industrialized countries [73]. Many epidemiological studies have shown that diabetic individuals have a significantly higher risk of developing AD [74]. Recently, it has become increasingly recognized that there is an overlap between the pathology of AD and vascular dementia and cerebrovascular dysfunction plays a role not only in vascular dementia but also in AD [75]. Nevertheless, clinical observations suggest that the association is independent of vascular factors [76], which raises the possibility that diabetic conditions such as insulin resistance and hyperglycemia may affect the fundamental pathogenesis of AD. Many neuronal functions are affected by changes in the insulin signaling pathway; therefore diabetes mellitus may have an important role in the progression of AD ([77]; see **Figure 2**).

Another possible mechanism that has been involved is the **amyloid deposition** in islets composed primarily of islet amyloid polypeptide (IAPP or amylin) that is a common feature in T2D. IAPP amyloid deposition has been correlated with disease severity, reduced β-cell mass, the development of hyperglycemia, and islet inflammation. Similarly, Aβ plays a central role in synaptic dysfunction and in the cognitive deficiencies associated with AD pathogenesis [78]. Evidences from clinical and animal studies associate the pancreatic amyloid, amylin in mediating neuronal loss in AD, suggesting its role as a potential link between AD and T2D pathogenesis [79–81]. The presence of amyloid deposits in pancreas and brain has been demonstrated in patients with T2D, which can serve as seed to increase the aggregation of these deposits. This suggests that pancreatic IAPP can potentiate amyloid beta misfolding in patients with AD [81]. Previously, de la Monte and colleges, 2008, reported that IAPP enters the brain, augments Aβ misfolding, and associates with Aβ plaques, and plasma levels correlate with AD diagnosis [82]. Interestingly, amylin has been identified in human cerebrospinal fluid and brains of diabetic patients with vascular dementia or AD and nondiabetic patients with AD. Furthermore, co-localization of amylin and Aβ deposits was also observed in postmortem human brains [81]. Likewise, amylin deposits were observed in the temporal lobe gray matter in diabetic patients [79]. Therefore, the co-existence of Aβ and amylin in the brain suggests the potential ability of amylin to infiltrate the brain and induce amyloid deposition in the brain [81].

8.2 Potential mechanisms of amylin-Aβ-induced toxicity in neurons and pancreatic β cells

Several studies have showed that amyloid aggregates have been found to be associated with disruption of several cellular functions, including mitochondrial activity [83, 84], oxidative stress [85], receptor mediated functions [86, 87], disruption of Ca^{2+} homeostasis [88], and membrane depolarization and disorder [89]. Possibly there is a toxic interaction between Aβ and tau that together with insulin resistance participate in the progression of AD. Similarly, the accumulation of amylin in the brain and its ability to induce neurotoxicity and form "cross-seeding" aggregates with Aβ provide a role for this pancreatic amyloidogenic protein in neurodegeneration [89].

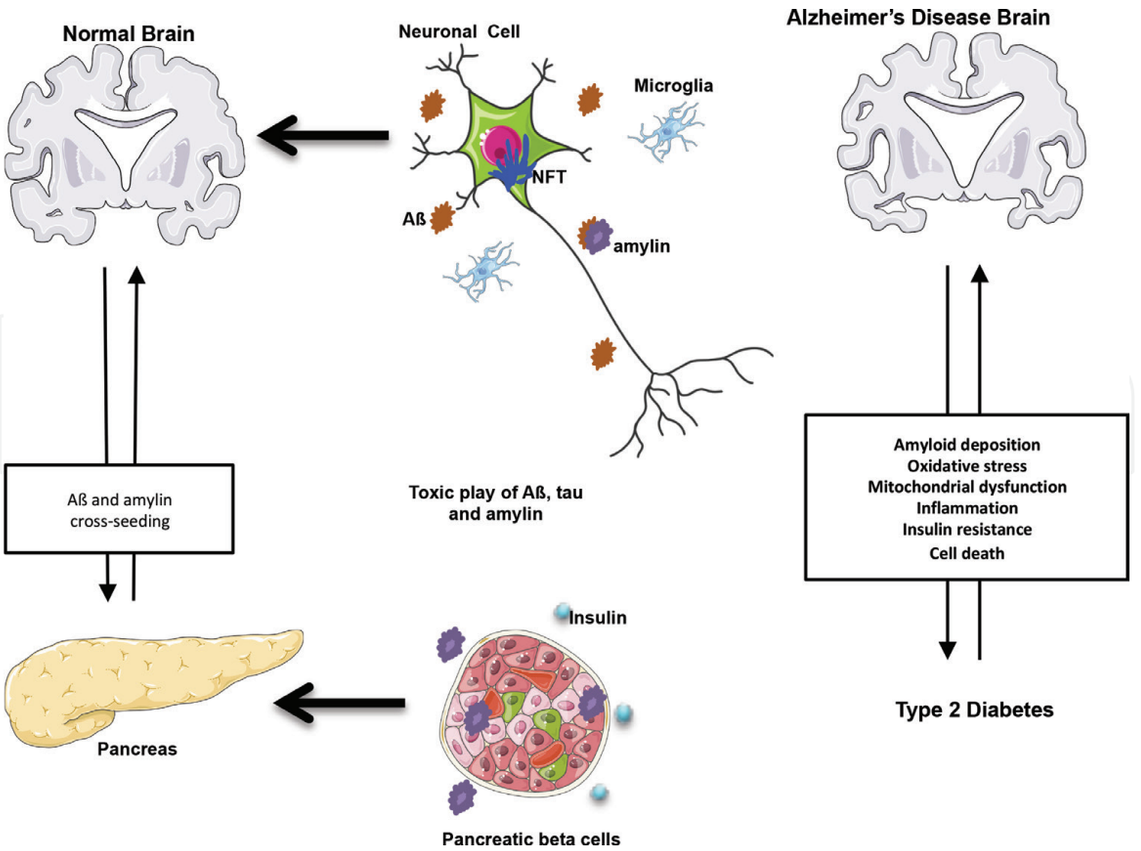

Figure 5.
Association between AD and T2D. Both AD and T2D present cellular loss and abnormal deposition of Aβ, tau, and amylin. These aggregates have the ability to promote the accumulation of amyloid by cross-seeding in neurons and pancreatic cells. The aggregation of amyloid deposits is favored by the presence of aggregates of tau and amylin, which in turn leads to oxidative stress, mitochondrial dysfunction, inflammation, insulin resistances, and finally cell death.

On the other hand, it is likely that there is also a synergistic interaction between the accumulation of amylin in the pancreas and the insulin secretion decrease, which will lead to abnormalities in glucose metabolism, promoting the development of neurodegenerative diseases (**Figure 5**). It is suggested that amylin mediates neurotoxicity by crossing the blood-brain barrier and binding to its receptors [90–92]. This leads to the hyperamulinemia of insulin resistance and to the accumulation of amyloid deposits in the brain.

Both in the animal models and in the clinical trials of AD, those drugs related to production of insulin have been observed or have focused on improving the mechanisms of insulin and improving the condition of patients with cognitive impairment [93]. Analogues of amylin, for example, pramlintide, have been used as adjunctive therapy with insulin for diabetes [94] and are also being evaluated for their ability to prevent neurodegeneration [90, 95, 96].

9. Conclusions

The advantages of studying therapies for T2D in diseases that occur with an insane process are evident. However, no one has questioned whether targeted therapies for dementias could be useful in the treatment of T2D. Immunotherapy targeting Aβ has been shown to improve blood glucose by increasing sensitivity to insulin [97, 98]. Thus, we believe that amyloid deposits as therapeutic targets could be key in the treatment of dementias and alterations in glucose metabolism. But more studies about this issue are needed.

Acknowledgements

Authors want to express their gratitude to Oskar Soto for his support with microglial confocal images and to Ashley Rose Sorsby Vargas for her assistance. We also want to express our gratitude to the Mexican families who donated the brain of their loved ones affected with Alzheimer's disease and made possible our research.

Conflict of interest

The authors declare no conflict of interest.

Author details

Teresa Ponce-López[1], Andrew Michael Sorsby-Vargas[1], Alma Patricia Bocanegra-López[1], José Luna-Muñoz[2], Miguel Angel Ontiveros-Torres[3], Ignacio Villanueva-Fierro[4], Parménides Guadarrama-Ortiz[5] and Alejandra Martínez-Maldonado[1,2*]

1 Anahuac University North Mexico, Mexico City, Mexico

2 National Brain Bank, Laboratorio Nacional de Servicios Experimentales (LaNSE), Centro de Investigación y Estudios Avanzados del IPN (CINVESTAV-IPN), Mexico City, Mexico

3 Bioengineering Department, Engineering and Sciences School, Tecnológico de Monterrey, Mexico

4 Instituto Politécnico Nacional, Becario COFAA, CIIDIR Durango, Mexico

5 Neurosurgery, Specialized Center in Neurology and Neurosciences, México City, México

*Address all correspondence to: alemartinez13@gmail.com

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