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REVIEW ARTICLE

Putative Involvement of Endocrine Disruptors in the Alzheimer's Disease *Via* the Insulin-Regulated Aminopeptidase/GLUT4 Pathway

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Abstract: It has been well established that there is a connection between type II diabetes (DMTII) and Alzheimer's disease (AD). In fact, the increase in AD incidence may be an emerging complication of DMTII. Both pathologies are related to estradiol (E_2) exposure; on the one hand, estrogen receptors (ER) are emerging as important modulators of glucose homeostasis through ß-pancreatic cell function; on the other hand, brain bioenergetic and cognitive deficits have been related to the down regulation of brain ERs, contributing to women ageing and AD susceptibility, both related to the reduction in estradiol levels and the deficits in brain metabolism. Here we discuss that environmental contaminants with estrogenic capacity such as bisphenol A (BPA) could develop pharmacological effects similar to those of E_2, which could affect ß-pancreatic cell function by increasing the biosynthesis of glucose-induced insulin after extranuclear ER binding. BPA-induced hyperinsulinemia would promote the translocation of glucose transporter 4 (GLUT4), which is located next to insulin-regulated aminopeptidase (IRAP) in intracellular vesicles. In insulin-responsive tissues, IRAP and GLUT 4 are routed together to the cell surface after insulin stimulation. IRAP is also the angiotensin IV (AngIV) receptor, and AngIV associates the brain renin-angiotensin system (bRAS) with AD, since AngIV is related to learning, memory, emotional responses, and processing of sensory information not only through its inhibitory effect on IRAP but also through the stimulation of glucose uptake by increasing the presence of IRAP/GLUT4 at the cell surface. Thus, the IRAP/GLUT4 pathway is an emerging target for pharmacological intervention against AD.

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1. INTRODUCTION

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder characterized by cognitive impairment and consequent memory loss [1]. Pathological characteristics of AD embrace amyloid plaques, neurofibrillary tangles, and neuroinflammation, which are caused by deposits of Aß fragments, hyperphosphorylated TAU protein, as well as an important activation of microglia and astrocytes, respectively [2]. However, as Walker and Harrison state [3], a variety of studies are emerging suggesting a bidirectional relationship between brain dysfunction associated with AD and type 2 diabetes (DMTII), substantially increasing the prevalence of both in recent decades. In fact, both share symptoms such as inflammation, oxidative stress [4], low vitamin C levels [5], increased receptor for advanced glycation end products (RAGE)/Advanced glycation end products (AGES) [3], altered insulin signaling mechanisms and insulin resistance [6, 7], as well as glucose intolerance, and cognitive deficits [8-10].

The most common form of diabetes is type 2, which results mainly from the interaction of the individual's genetics with the environment. Both insulin resistance and pancreatic cell dysfunction contribute decisively to the pathogenesis of the disease [11]. In addition, estrogens may also mediate the development and appearance of DMTII, and thus, be involved in the onset of AD. In this context, exposure to estrogenic endocrine disruptors (EEDs) is particularly relevant. Conclusions from experimental models, clinical observations, and epidemiological studies converge to implicate exposure to EEDs as a major brain health concern to kids as well as adults because certain EEDs can alter neurogenesis,

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neural transmission, and the formation of neural networks Therefore implicating EEDs with an upsurge in neurological disorders, as well as autism, attention deficit, and hyperactivity disorder moreover, learning disabilities and aggressiveness [12-14].

In the light of these studies, we could therefore suggest that the striking increase in AD (particularly in perimenopausal women and patients with DMTII) [15] in recent decades could be influenced, at least in part, by continued exposure to different EDD-type compounds that could interfere with glucose homeostasis, as in the case of bisphenol A, leading to an increase in the incidence of DMTII and, ultimately, AD.

At the brain level, the IRAP/$GLUT_4$ system is involved in glucose homeostasis. IRAP, also known as the angiotensin IV receptor or AT4, ultimately involves the brain renin-angiotensin system (bRAS) in AD. In fact, its participation in the homeostasis of glucose at the brain level was already described through the translocation of the IRAP/$GLUT_4$ system [16, 17]. The connection between both processes on brain development and metabolism would fall on the modulation of the GLUT4/IRAP binomial translocation. The aim of this review is to break down each of the points of these possible relationships/interactions.

2. INSULIN, SIGNALLING MECHANISM AND CEREBRAL GLUCOSE TRANSPORT

As Banks explains [18, 19], correct insulin levels in the blood for the control of blood glucose do not ensure that brain insulin levels are at the appropriate concentrations for the development of its functions in the CNS. In mammals, insulin is released into the bloodstream from the pancreas [20] and reaches the brain by saturable transport to choroid plexus and cerebrospinal fluid (CSF) and the BBB by an active transport dependent on adenosine triphosphate ATP [21]. Transport through the choroid plexus involves the presence of the insulin receptors (IRs) themselves [22-24]. From here, insulin is released into the CSF [21] (Fig. **1**).

The critical role of brain insulin within the CNS function (and the whole organism) depends on the high and tightly controlled local expression of both insulin and IR downstream signaling pathways [27, 28]. IRs found in the brain have unique molecular characteristics compared to their peripheral counterparts [29, 30], being located mainly in brain areas involved in memory and learning processes, such as the cortex brain, entorhinal cortex, and hippocampus [31, 32], with its levels being higher in neurons compared to glial cells [33]. The transduction mechanism through IRs is mediated by the action of insulin receptor substrate (IRS) molecules through two established pathways, the phosphoinositide-3 kinase (PI3)/Akt and Ras/mitogen-activated kinase (MAPK) cascades. These pathways are fundamental in the mediation of insulin signaling in the CNS [34].

Normal glucose metabolism is crucial in improving and maintaining learning and memory [35-37], and the reduction of brain glucose metabolism caused the cognitive deficits [15, 38, 39]. Currently, the glucose transporter type 4 (GLUT4), present in the blood-brain barrier BBB and various brain cell types, is recognized as an insulin-sensitive glucose transporter. These transporters are very abundant in brain regions involved in memory and learning processes at a high rate [40, 41] since insulin-dependent glucose metabolism principally occurs in the hippocampus, and this process is mediated by GLUT4 [36, 42, 43]. This finding is relatively recent as glucose uptake had long been thought to be insulin-independent [35, 36].

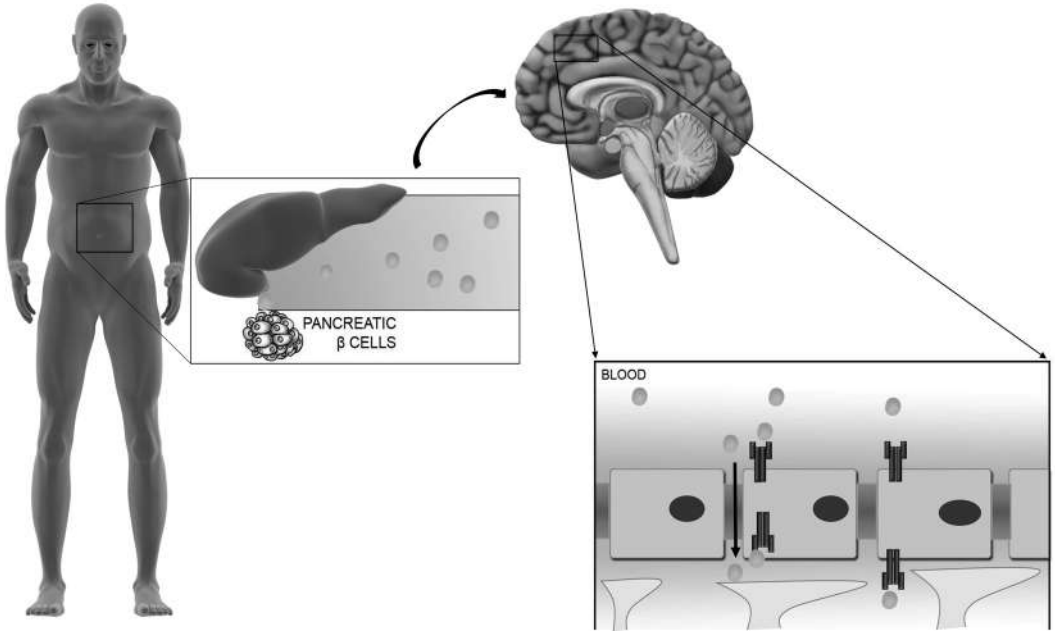

Fig. (1). Insulin enters the brain by traversing the BBB *via* receptor-mediated transport [21, 24, 25]. Peripheral insulin may also reach the brain interstitial fluid (bISF) directly *via* the microvascular endothelial cells that constitute the BBB [26]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Neurons express both GLUT4 isoforms and glucose transporter type 3 (GLUT3) [39], and astrocytes and endothelial cells express mostly GLUT1 [15, 39]. Regarding GLUT4, increasing glucose uptake by the brain/CNS would require an increased regulation of this transporter or insulin receptors [16, 41, 43-45].

Concerning the different brain cell types, it has been observed that not only the capability of neurons to transport glucose *via* GLUT3 and GLUT4 is higher than the astrocytic GLUT1 transporter [46], but that they also have greater demand for it, in order to provide energy in the brain because of the kinetic characteristics as well as the cellular concentration of glucose in both neurons and glia [47].

2.1. Insulin, Signalling Mechanism and Cerebral Glucose Transport in Alzheimer´s Disease

The alteration of glucose and insulin transport through the BBB has proven to be a crucial factor in the development of AD [48] since cognitive alterations, seizures, and ketosis, derived from disruptions, have been described in glucose transport through the BBB [49]. In patients with AD, low insulin levels are observed in the CSF, despite having an elevated level of serum insulin, and thus, a decreased CSF: serum ratio for insulin, which suggests an alteration in the insulin transport BBB [35]. In this context, the insulin-IRS-AKT pathway, aforecited, is highly relevant in DMTII since it is involved in the translocation of the main glucose transporter, insulin-dependent GLUT4, from intracellular vesicles to the plasma membrane, in muscle and fat cells [50]. In this line, DMTII may damage the BBB, which could lead to increased permeability to a variety of substances [51-53]. Thus, transport through the BBB is not only affected by blood glucose and consequently insulin concentrationbut also by factors such as obesity, inflammation, circulating triglyceride levels [54], or even steroid therapy that inhibits insulin transport through the BBB [18, 27, 55-57] (Fig. **2**).

This fact would lead to the conclusion that insulin resistance in the CNS can occur independently of peripheral insulin resistance [32]. However, the relationship between these two sides of insulin resistance is unknown. In humans, it has been reported that in CSF, the serum ratio of insulin levels is reduced in the presence of body insulin resistance [58, 59], as well as with ageing and in pathological situations such as AD [60, 61], again pointing to a decrease in insulin transport through the BBB. Furthermore, insulin also seems to influence the synthesis of amyloid precursors, showing differences between healthy and AD patients, even with respect to AD patients based on the presence of the apolipoprotein E (ApoE) genotype [42, 62, 63].

Hence, deficiency and resistance insulin could play an important role in the pathology of AD [64, 65], being proposed the AD as a brain-specific form of diabetes mellitus, a "type 3 diabetes"[66].

Duarte *et al.* [15] consider that the concept of AD has been changing from a perspective only as a neurodegenera-

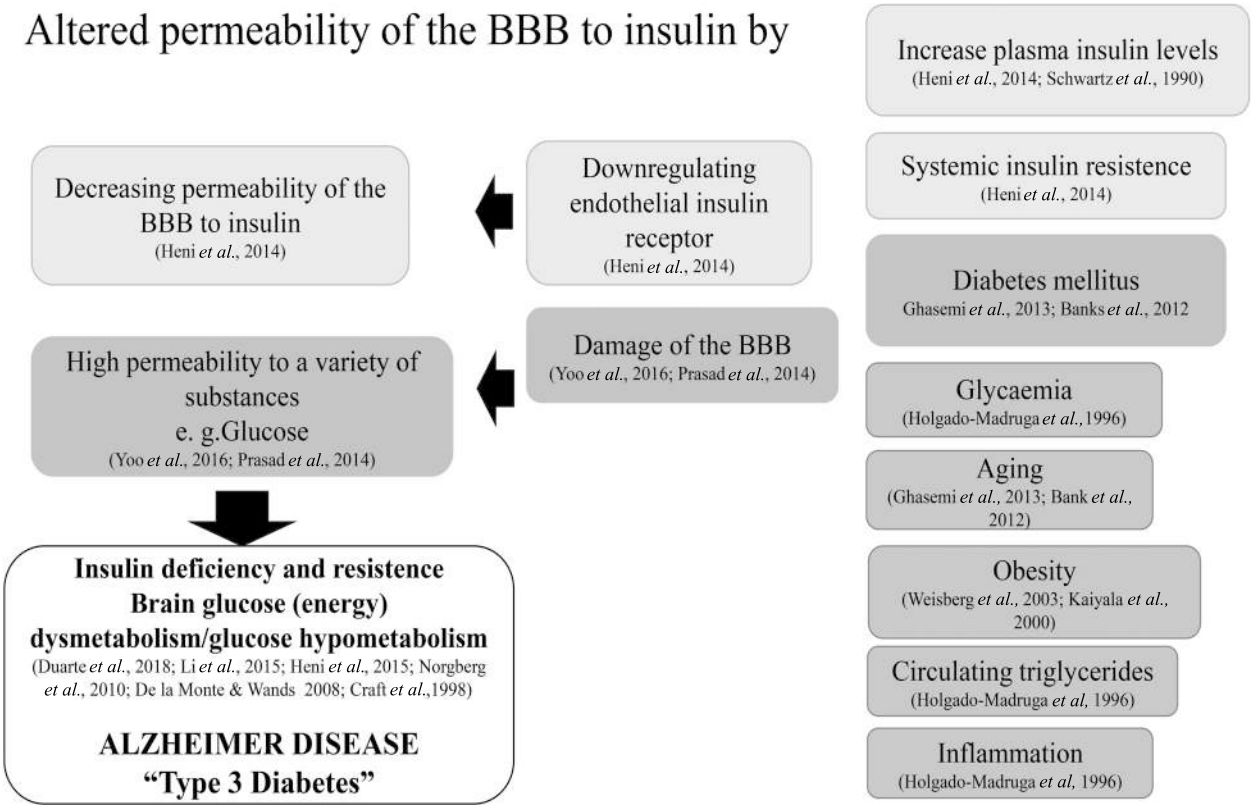

Fig. (2). Different factors lead to an alteration in the permeability of the BBB to insulin and the consequent changes in brain glucose metabolism and insulin levels. Such alterations are often associated with AD. In fact, AD has increasingly been faced as a (neuro) metabolic disorder and is often referred to as "type 3 diabetes." (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

tive disease to consider a disease with global involvement. This idea is supported by the fact that both Aß and P-Tau affect the CNS but also peripheral tissues, including pancreatic ß-cells, which would support the peripheral dysfunction and glucose dysfunction associated with AD. These alterations may limit the amount of insulin that enters CNS and, together, with the direct Aß and P-Tau-induced brain insulin resistance, would justify brain glucose (energy) hypometabolism and the shift ketone body's metabolism. So, more and more, AD is seen as a neurometabolic disorder known as "type 3 diabetes" [15].

Given the significant role of insulin in learning and memory, it would be logical to think that changes in the peripheral levels and/or in the CNS of insulin and the consequent subsequent brain regions are deeply affected by Alzheimer's disease [28, 67-68]. Brain IRSs are regulated differently depending on the cell type [69], thus, different behavior depending on the type of brain cell could help to understand how DMTII affects the brain function, as well as the different effects of insulin resistance in different tissues [65].

Once insulin binds with its receptor, autophosphorylation of many tyrosine residues occurs, which are important for IRS-1 / IRS-2 initiating various signaling cascades such as phosphatidylinositol 3-kinase (PI3K), GSK3ß signaling, mitochondrial regulation for energy production, and wnt signaling cascades. The PI3K pathway is associated with almost all metabolic functions of insulin [70-72], converting the phosphatidylinositol 4,5 bisphosphate (PIP2) to phosphatidylinositol 3,4,5 trisphosphate (PIP3). Then, PIP3 captures protein kinase B (PKB, also known as Akt) to the plasma membrane, where it is activated by phosphorylation carried out by specific kinases [73]. PKB would connect the IRs at the cell surface with enzymes of glycogen metabolism in the interior of the cell through GSK3ß phosphorylation, observing that inhibitors of GSK3ß mimic the action of insulin on glycogen synthesis [74].

One of the main features of insulin resistance is IRS-1 serine phosphorylation [75]. The mechanism associated with insulin resistance would be the following: insulin signaling is blocked by the activation of c-Jun NH2-terminal kinase (JNK) pathway by tumor necrosis factor-α (TNF-α), which then causes the serine phosphorylation of IRS-1 by various stress-sensitive kinases [76, 77]. Afterward, serine phosphorylation of IRS-1 inhibits the tyrosine phosphorylation of IRS-1 and, therefore, it is binding to PI3K, induced by insulin [78], blocking insulin signaling within the cell.

On the other hand, IRS-2 is involved in learning and memory processes, observing that total IRS-2 deficiency impaired N-Methyl-D-aspartate (NMDA) receptor-dependent long-term potentiation at the postsynaptic level in the hippocampus of IRS-2 knockout mice [79]. TNF-α, a pro-inflammatory cytokine, as we have shown above, is involved in the mechanism of insulin resistance and is a common component of inflammatory signalling in AD [80] and DMTII and obesity [81] (Fig. **3**). In this line, some authors describe that the hypo-metabolism of glucose in patients with AD, predates the onset of memory deficits and speculates that it may be a predictor of disease progression [82-84].

3. TYPE II DIABETES AND ALZHEIMER'S DISEASE ROLE OF ESTROGEN RECEPTORS

The increase in the incidence of AD could be associated with a complication of DMTII [85]. In pancreatic ß-cells, ER- α and ER-ß are present, and aside from the role that estrogen receptors may play in the physiology and survival of pancreatic ß-cells [86], we should bear in mind that any disruption of ß-cell physiology would be associated with the development of DMTII [87]. Therefore, the estrogen receptors should be considered important structures involved in glucose management [88]. In fact, ER-α knockout (ERαKO) mice are obese and insulin-resistant [89], considerations associated with DMTII. Supporting this idea, authors as Alonso-Magdalena *et al*. [87] showed that long-term exposure to physiological concentrations of 17ß-estradiol increased ß-cell insulin content, insulin gene expression, and insulin release, yet pancreatic ß-cell mass was unaltered. The receptor involved is ER-α, which increases the content of pancreatic insulin by activating the ERK1 / 2 dependent pathways [87]. In addition, activation of ER-ß triggers closure of ATP-dependent K+ channels, increasing glucose-induced [Ca^{2+}] oscillations and insulin release cooperatively with glucose [90].

This idea leads us to ask ourselves if environmental contaminants with estrogenic activity could influence this puzzle, which is AD. In this sense, the up-regulation of the insulin content of pancreatic beta cells for 17ß-estradiol was replicated by environmentally relevant doses of the Bisphenol-A (BPA) generalized endocrine disruptor [87]. These results may be highly relevant in explaining the effect of E_2 and environmental estrogens on endocrine pancreatic function and consequently on blood glucose homeostasis [87].

An interaction between genetics-environment in the development of AD becomes logical.

At the brain level, scientific evidence points to a possible protective role for estrogens linked to energy metabolism. The activation of brain estrogen receptors (ER)-α and -ß signaling, and the consequent up-regulation of nuclear (and mitochondrial) genes coding for glucose transport, metabolism, and mitochondrial function proteins, could be involved, whereas those from ketone body's metabolism, inflammation, and Aß formation may be down-regulated [15, 91-96]. Estrogens would inhibit brain fatty acid and ketone metabolism [97-98] therefore, in perimenopause state, the above mechanisms would be reversing, leading to brain hypometabolic state, increased fatty acid catabolism as well as Aß accumulation and synaptic deficits, increasing the risk for AD [15, 95, 98-101]. So, endocrine ageing could accelerate chronologic ageing in the female brain years before the onset of AD symptoms [102, 103] (Fig. **4**).

Brinton *et al*. [95] described that the brain bioenergetic deficits and cognitive deficits are due to the down-regulation of brain ERs, that may contribute to females' ageing and AD susceptibility [15, 95, 102, 103, 106-111].

In light of these works and the implication of estrogens both in the development of DMTII and in brain metabolism, it is logical to reason that estrogenic endocrine disruptors could be involved in increasing the incidence of this disease

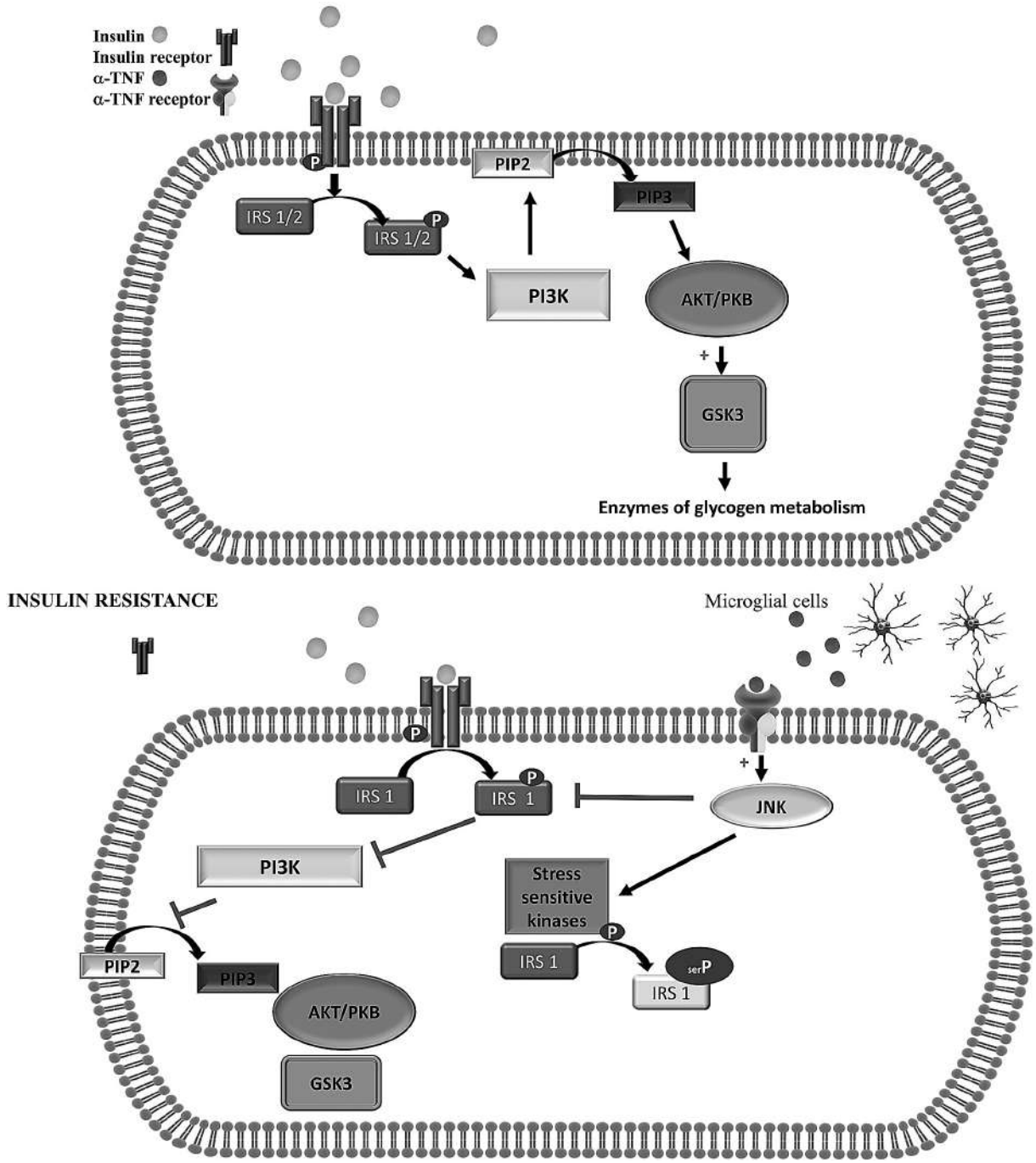

Fig. (3). After insulin binds with IR, the activation of many tyrosine residues occur by auto phosphorylation. These phospho-tyrosine residues are important for IRS-1/IRS-2, since they initiate several signaling cascades such as phosphatidylinositol 3-kinase (PI3K), GSK3ß signaling, mitochondrial regulation for energy production, and wnt signaling cascades. The PI3K pathway is associated with almost all metabolic functions of insulin [70-72], converting the phosphatidylinositol 4,5 bisphosphate (PIP2) to phosphatidylinositol 3,4,5 trisphosphate (PIP3). Then, PIP3 captures protein kinase B (PKB, also known as Akt) to the plasma membrane, where it is activated by phosphorylation carried out by specific kinases [73]. PKB would connect the IRs at the cell surface with enzymes of glycogen metabolism in the interior of the cell through GSK3ß phosphorylation, observing that inhibitors of GSK3ß mimic the action of insulin on glycogen synthesis [74]. One of the main features of insulin resistance is IRS-1 serine phosphorylation [75]. The mechanism associated with insulin resistance would be the following: insulin signaling is blocked by the activation of c-Jun NH2-terminal kinase (JNK) pathway by tumor necrosis factor-α (TNF-α), which then causes the serine phosphorylation of IRS-1 by various stress-sensitive kinases [76, 77]. Serine phosphorylation of IRS-1 then inhibits the tyrosine phosphorylation of IRS-1 and its subsequent binding of PI3K, which is normally induced by insulin stimulation [78], blocking insulin signaling within the cell. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

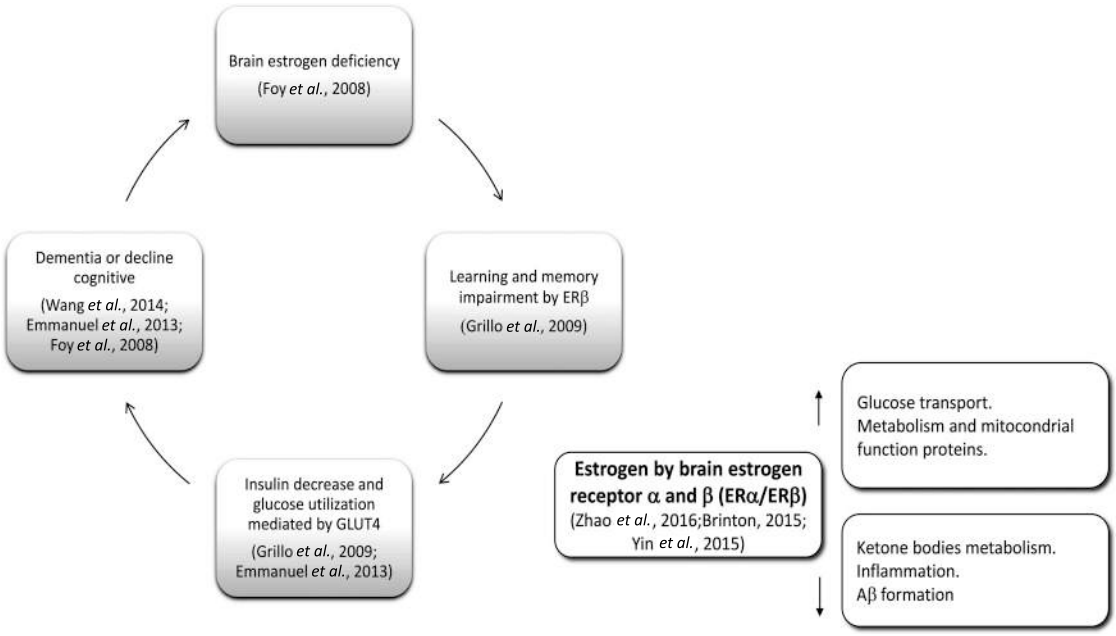

Fig. (4). Effects of estrogens on glucose metabolism and involvement in the onset of cognitive impairment and dementia. The activation of brain estrogen receptors (ER)-α and -ß signaling, and the consequent upregulation of nuclear (and mitochondrial) genes coding for glucose transport, metabolism, and mitochondrial function proteins, could be involved, whereas those from ketone body's metabolism, inflammation, and Aß formation may be down-regulated [91-96]. In perimenopause state, the above mechanisms would be reversed, leading to brain hypometabolic state, increased fatty acid catabolism as well as Aß accumulation and synaptic deficits, increasing the risk for AD [95, 98-101, 104-105]. In perimenopausal women, the metabolic shift was associated with brain insulin resistance and glucose dysmetabolism in estrogen-dependent areas, as well as with peripheral insulin resistance [15, 95, 102-111]. In the hippocampus, insulin-dependent glucose metabolism occurs mainly and is mediated by GLUT4. This mechanism seems to be intimately related to the appearance of dementia and/or cognitive impairment and is accompanied by decreased insulin level and GLUT4 expression in the hippocampus, indicating that estrogen blockade impaired the spatial memory of the female rats. The mechanisms by which estrogen blockade impairs memory partially also contribute to the decline in hippocampal insulin signals, which diminishes glucose consumption [112]. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

in two ways; firstly favoring an increase in the population with DMTII, acting on insulin signaling mechanisms; and secondly, acting on the brain's ERs involved to a greater or lesser extent in the development and/or progression of the disease.

4. TYPE II DIABETES AND ALZHEIMER´S DISEASE; ENDOCRINE DISRUPTORS BISPHENOL A

As we have commented previously, we can talk about modifiable risk factors such as the level of education, life habits, as well as exposure to different environmental compounds and/or situations that may influence our health. Indeed, environmental, genetic, and biological factors contribute to the AD process [113], with most cases of late-onset.

In recent years it has been demonstrated that cognitive ageing in the absence of neurodegenerative disorders like AD, is not associated with significant neuronal loss in the human [114] or non-human primate neocortex [115]. Age-related cognitive decline is thought to result instead from more slight morphological and molecular differences in the neurons mediating these processes and in the connections between them [116, 117]. Therefore, in the appearance and development of AD, different factors must be interrelated with each other, such as environmental and genetic factors [118] (Fig. **5**).

There have been descriptions of genetic alterations such as mutations in the genes that encode amyloid precursor protein (APP), presenilin 1, and presenilin 2 associated with early-onset familial AD, and a small proportion of cases showing an autosomal dominant transmission of the disease. This is one of the better-described risk factors along with age, since more than one-third of patients with AD have one or more affected first-degree relatives.

Also, groups of individuals, such as elderly or women, may be more susceptible to certain environmental pollutants, have been described [119]. Other risk factors associated with the pathology of AD include the female gender, previous depression, lower levels of education, severe head injury and vascular factors [85, 120], as well as chronic stress [121] (Fig. **5**).

The most common definition of an endocrine-disrupting chemical (EDC) is "an exogenous chemical or a mixture of chemicals, that interferes with any aspects of hormone action" [122, 123]. However, a more comprehensive definition of EDC would be: "a structurally diverse class of synthetic and natural compounds that possess the ability to alter various components of the endocrine system and potentially induce adverse health effects in exposed individuals and populations" [124]. These compounds can modulate different components of the endocrine system through different

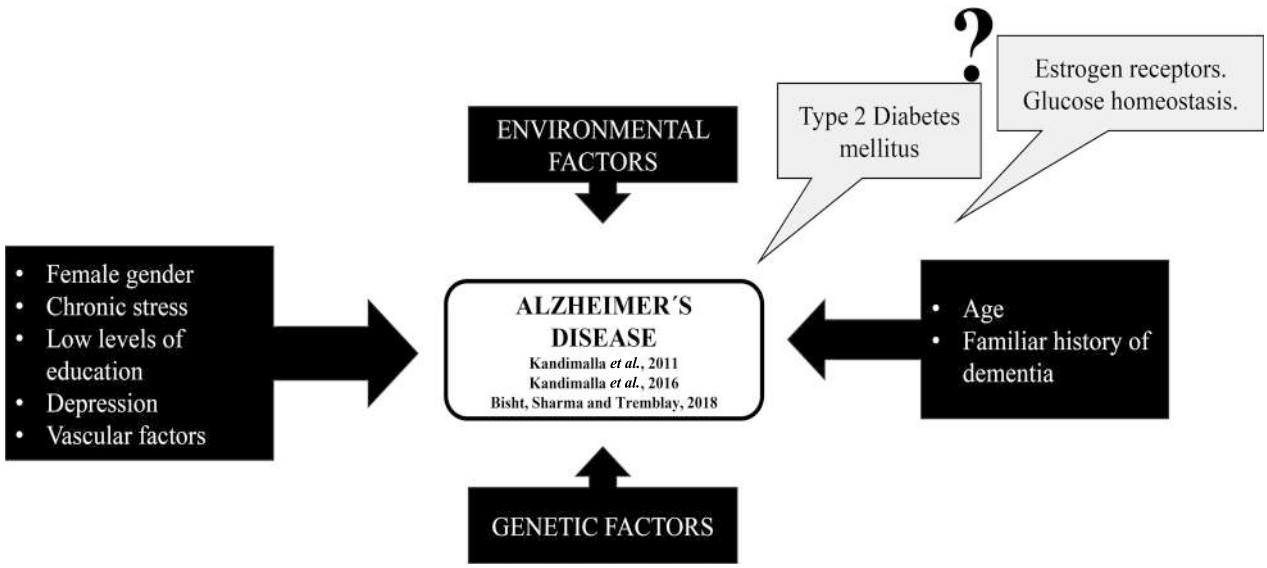

Fig. (5). Factors related to the development of AD.

mechanisms such as nuclear receptor-mediated and nonreceptor-mediated. The changes that they cause in the endocrine system may be related to pathologies such as breast cancer, ovarian problems, thyroid eruptions, testicular carcinoma or AD, and schizophrenia [124, 125]. The variety of EDCs is very wide, including organo-chlorinated pesticides, industrial wastes, plastics and plasticizers, fuels, and numerous other elements that exist in the environment or are in high use during daily life [126].

Although multiple environmental chemicals with EDC activity have been described, the most commonly studied is BPA; synthesized in 1891 and estrogenic capacity described in 1936 [127].

BPA is found in the coating of metal cans and as a plasticizer in other widely used plastics as it is the monomer used to make polycarbonate plastic and resins. Due to its location, this endocrine disruptor can leak into food and beverage containers [128, 129] and can be found in dental sealants as well [130]. Consequently, human exposure to significant amounts of BPA and the appearance of BPA in the urine of 95% of the US citizens [131] and human serum in ranges from 0.2-1.6 ng/ml serum (0.88-7.0 nM) [132, 133].

The mechanism proposed for BPA actions is based on its ability to bind to ER-α and ER-ß receptors, triggering estrogenic signals that modify gene expression. [134]. BPA regulates insulin content through ER-α. When receptor activation occurs at doses other than physiological or in situations where this activation is not required, such as exposure to environmental estrogens, adverse effects such as insulin resistance may be triggered [135]. In fact, Wang *et al*. [136] described a new mechanism for pathological protein expression mediated by BPA in the SH-SY5Y cell line. Through this pathway, there is an alteration of the transduction of IR, IRS-1, and AKT signaling, and the activation of downstream GSK3α / β, as well as an increase in the expressions of APP, BACE-1, Aβ1-42, and p-tau, culminating in disease similar to AD. BPA inhibits the tyrosine kinase phosphorylation site that is responsible for the transmission of insulin upstream signaling pathways [137], and also increases serine phosphorylation of IRS-1, a hallmark of insulin resistance [138]. Furthermore, BPA seems to be involved in the critical insulin signaling AKT, associating with p-tau regulation [136, 139, 140], being able to be associated with significant decreases described by the phosphorylation of mTOR and methylation level of PP2A, suggesting the adverse effects of BPA on insulin signaling pathway [136].

BPA concentrations as low as 1nM may trigger the actions as a release of insulin through its binding to extranuclear ER receptors or may affect β-pancreatic cell function by enhancing glucose-induced insulin biosynthesis of glucose-induced insulin after extranuclear ER-α binding [87, 90, 141], emphasizing the involvement of ER receptors in the context of AD.

About its metabolism, BPA is metabolized to non-bioactive compounds and has a short lifespan of approximately 4-5 hours in adult humans, with lower metabolic rates in the fetus and infants [142, 143]. However, recent studies point to the BPA accumulation in the adipose tissue, with detectable levels on 50% of the mammary adipose tissue samples [144], and that daily exposition to BPA might come from different sources [145, 146]. Also, we must not lose sight that due to the high presence of BPA in our daily lives, the total elimination of this compound is considered complicated [147, 148].

Therefore, exposure to persistent organic pollutants, such as BPA, is particularly relevant in relation to the appearance of metabolic pathologies such as DMTII and the development of AD [136].

5. BRAIN RENIN ANGIOTENSINS SYSTEM AND ALZHEIMER'S DISEASE

In brain functions such as sensory information processing, emotional responses as well as learning and memory, the bRAS has an important implication, mainly through the

AngIV peptide [149] since AngIV may facilitate cognitive processing by promoting glucose uptake into hippocampal neurons [150]. Possibly the memory-facilitating effects associated with bRAS are due to the binding of AngIV to its AT4 receptor, although initially, this function was attributed to angiotensin II (Ang II) [17, 151-155]. Authors as Ismail *et al*. [156] described that AngIII and AngIV show a different role in the regulation of IRAP catalytic activity and GLUT4-dependent glucose uptake [156]. However, the equilibrium levels of AngIV would depend as much on the aminopeptidases, angiotensin regulatory enzymes, which synthesize it from its precursors such as AngIII, if not also on those that degrade AngIV. In this sense, in patients with AD, the decrease in A and N brain aminopeptidases, fundamental for the synthesis of AngIV, has been described, as well as in receptor numbers AT4 [155]. This fact would be in line with those obtained by Puertas *et al*. [157], which describe a decrease in aminopeptidase A activity in patients with AD, supporting the fact that AngII levels would be increased due to a decreased metabolism from AngII to AngIII. In addition, this study supports the hypothesis of a reduction in the conversion of AngIII to AngIV due to the decrease in the activities of enzymes regulating the metabolism of angiotensins, aminopeptidase N, and aminopeptidase B [157]. This study increases the evidence of a putative implication of AngII and AngIV in AD.

In the case of AD, the functions that angiotensins mediate through their receptors are also clearly differentiated, as established by Wright and Harding [155]. Thus, the AngII and its AT1 receptor have been associated with the alterations that predispose the development of AD, unlike the AngIII / AT2 receptor systems, the insulin-regulated aminopeptidase / AngIV (IRAP), the AngIV / AT4 receptor, and the Ang (1-7) / More receptor [155]. In fact, these authors point out the most damaging contributions of angitontesin II (AngII) as hypertension, facilitation of neuroinflammation and oxidative stress, reduced cerebral blood flow, tissue remodeling, and disruption of memory consolidation and retrieval (Fig. **6**).

Several studies demonstrate an increase in the levels of AngII and AngII receptor binding in the brain of people with AD [158, 159]. However, AngIV binds at the AT4 receptor subtype, the number of receptors being decreased in AD patients, in parallel with the decrease in brain aminopeptidases A and N, enzymes essential for the synthesis of AngIV [155].

Therefore, the implication of angiotensin II in the inflammatory process is also related to the degenerative processes associated with ageing [160, 161]. In fact, ageing tissues, including brain tissue, are characterized by a pro-inflammatory and pro-oxidant state that causes exacerbated responses to injuries and increased vulnerability to neurodegeneration [162]. In this context, several studies demonstrate an increase in the levels of AngII and AngII receptor binding in the brain of people with AD [158, 159].

5.1. Insulin-related Aminopeptidase (IRAP) and GLUT4

Insulin-regulated aminopeptidase (IRAP, oxytocinase, EC 3.4.11.3) is known in relation to the insulin-responsive glucose transporter GLUT4 in fat and muscle cells [163] and as the enzyme responsible for the metabolism of the hor-

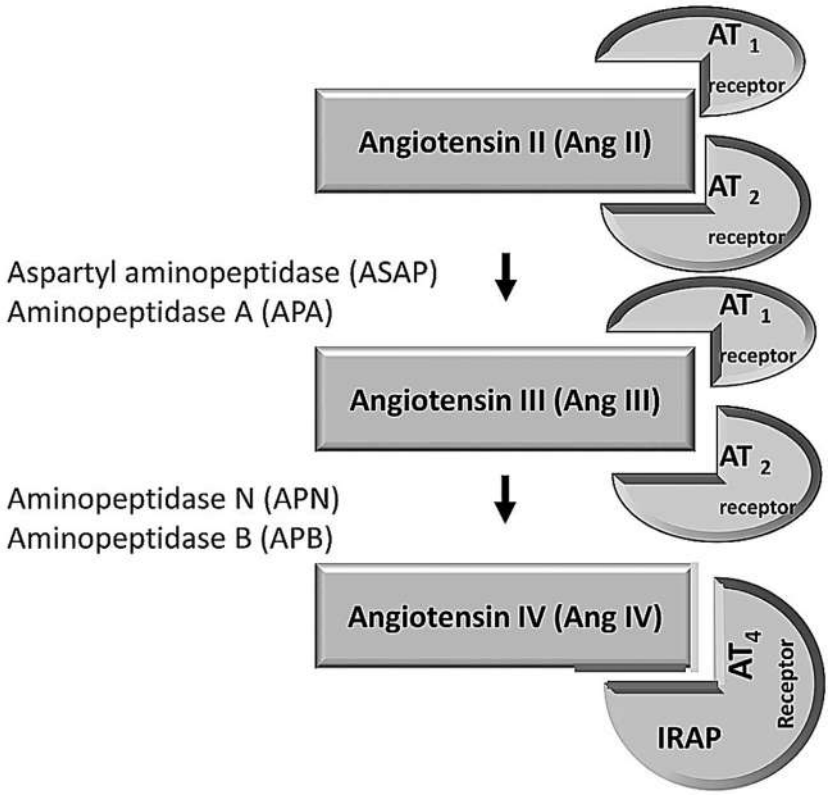

Fig. (6). bRAS associated receptors and active peptides.

mone oxytocin in the placenta [164]. However, its localization in specific cell types [165] may be related with particular roles as maintenance of glucose homeostasis by the regulation of the trafficking of GLUT4 in insulin-responsive cells, control of oxytocin concentrations in pregnancy, regulation of brain oxytocin and vasopressin levels, as well as participating in cognitive and memory processing in the brain [166]. Therefore, a higher proteolytic activity of IRAP on neuropeptides could be involved in impaired memory processing [167].

In addition, IRAP shows a multitude of possible substrates [168, 169], so a pathological increase in its activity would have diverse consequences such as hypertension [170], reduced levels of somatostatin [171], or arginine vasopressin [172, 173]. Also, IRAP has been implicated in diabetes andimmune system function [174].

IRAP is located mainly in areas of the brain involved in cognitive, sensory, and motor functions, showing a differential distribution. In fact, IRAP is located in intracellular vesicles containing GLUT4, in neurons of the hippocampus, as well as in the hypothalamus, piriform and entorhinal cortices, pituitary, olfactory bulb, and most neocortical areas, and also in different nuclei of the limbic and motor systems, including the basal ganglia [16, 44, 175-179], signifying a similar system that exists for IRAP and GLUT4 in neurons as has been described for fat and muscle cells [166].

The brain has the highest energy requirement of all tissues in the body; in fact, it is well established that glucose improves cognitive performance [180]. In fact, GLUT4 contributes substantially to the uptake of most of the blood glucose required for cognitive function [38, 181]. IRAP is localized along with GLUT4 in specialized vesicles, and both are translocated from these vesicles to the cell surface in response to stimuli as insulin [16], although this translocation does not guarantee GLUT4 activity [16]. Therefore, the authors propose that GLUT4 requires translocation to the plasma membrane, as well as activation at the plasma membrane, to initiate glucose uptake, and to start the process requires the PI3-kinase activation [45, 182] (Fig. **7**).

In AD, the commitment of GLUT4 or insulin receptors, could cause functional hypoglycemia in the brain and consequently decreases the rate of brain glucose metabolism [39, 41]. Insulin and IR are co-localized with GLUT4 in the hippocampus, choroid plexus neurons, the cerebellum, hypothalamus, and hippocampus [15, 183-186], suggesting a role for GLUT4 in memory formation [15, 37, 40, 41, 187, 188] and therefore in AD, since it has been described that lower GLUT4 levels were accompanied with the down-regulation of IR and Akt in cells overexpressing Tau protein [15, 189]. Also, the chronic inhibition of brain GLUT4 deteriorated hippocampal metabolism and cognitive performance [15, 40]. Besides, we must consider that deficient glucose transport due to insulin deficiency would increase the glycation process in the brain. Patients with advanced AD who present high levels of insulin in plasma show lower levels in CSF, compared to healthy people [35], which would indicate that the glucose present in the brain could not be metabolized (insulin resistance), leading to the formation of AGE, affecting cognitive function. In this context, chronic administration of

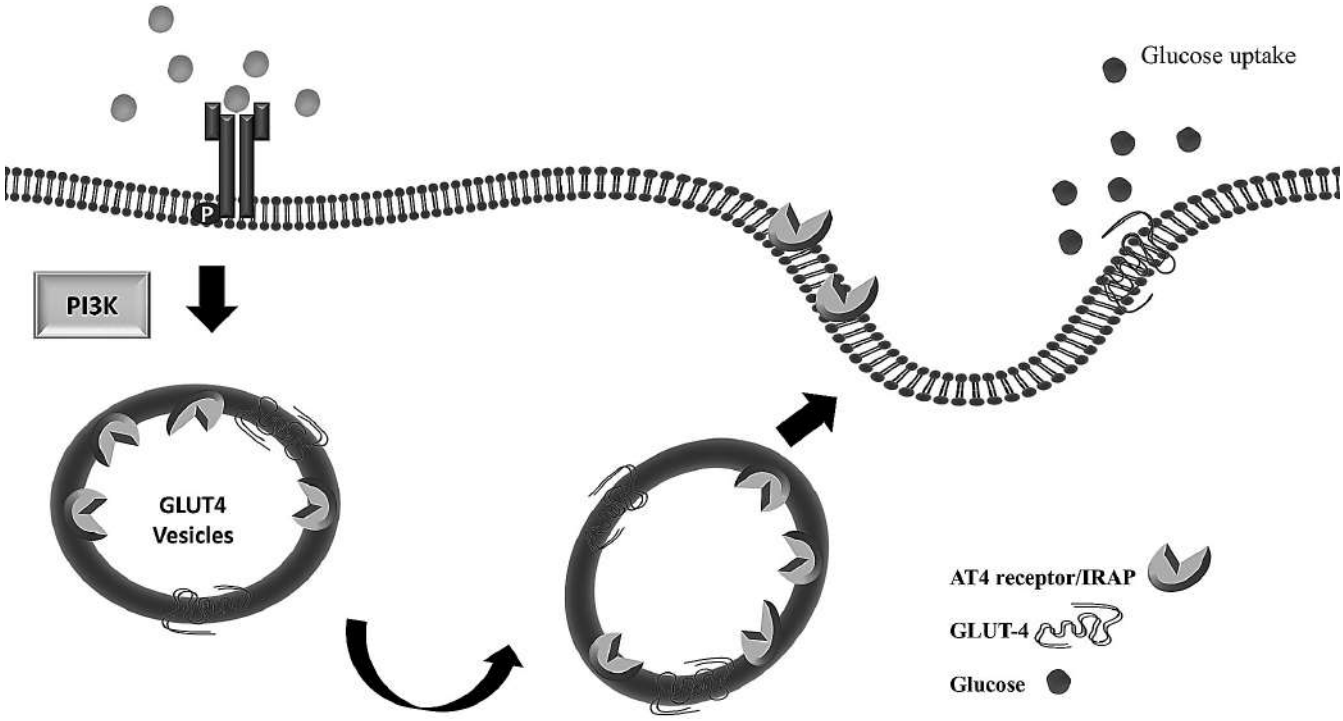

Fig. (7). IRAP and GLUT4 translocation in insulin-responsive tissues. IRAP is supposed to contribute to deteriorating memory processing [167] since this enzyme is found in regions associated with cognitive function as well as sensory and motor function. In neurons of the hippocampus and cerebral cortex, IRAP is present in intracellular vesicles containing GLUT4 [16], suggesting a similar system as has been described for fat and muscle cells. In insulin-responsive tissues, IRAP and the glucose transporter are translocated together to the cell surface after insulin stimulation [166, 180].

insulin would negatively affect the results of memory and cognition tests, unlike acute administration, where favorable results would be observed in cognition [190-193].

For that reason, a parallel could be drawn with DMTII, in which acute administration of insulin normalized glucose uptake, but chronically administration leads to insulin resistance, hyperglycemia, as well as inflammation and vascular damage. In our organism, in the absence of a fuel source, brain cells starve, and neurons will decrease in their metabolic activity for the physiological functions [85]. In both situations, the fuel, glucose, is inside the body, but the cells, specifically brain cells, are not able to obtain energy from it. The close similarity between AD and DMTII is striking, establishing the term "type 3 diabetes" [85].

5.2. IRAP/GLUT4 and AT4 Receptor

AngIV is involved in learning and memory by the inhibitory role described for IRAP activity [17]. Authors such as Mustafa *et al*. [194, 195] point out the possibility that the union of AngIV to IRAP could directly activate a system of second messengers that can be antagonized by divalinal-AngIV. Therefore, a possible mechanism of action by which AT4 ligands facilitate memory is by inhibiting the degradation of IRAP substrates [196] (Fig. **8**). Thus, studies in rodents have shown that IRAP substrates such as vasopressin and somatostatin, facilitate learning and memory in aversion conditioning tasks and/or spatial learning in rodents [197].

Indeed, Hermans and colleagues [166] define it as a membrane-bound zinc-metallopeptidase that cleaves neuroactive peptides in the brain and produces memory-enhancing effects when inhibited. Therefore, and as Ascher *et al*. [174] consider, the development of IRAP inhibitors represents a promising approach for the discovery of drugs for the treatment of memory loss, such as that associated with AD. These authors demonstrate that IRAP presents a second Zn^{2+}

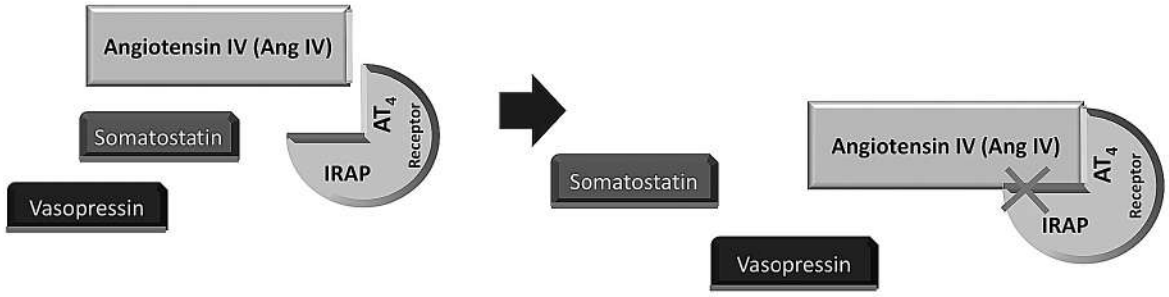

Fig. (8). Scheme of the possible modulation of the activity of the IRAP and the AT4 receptor through its substrates: AngIV, somatostatin, and vasopressin.

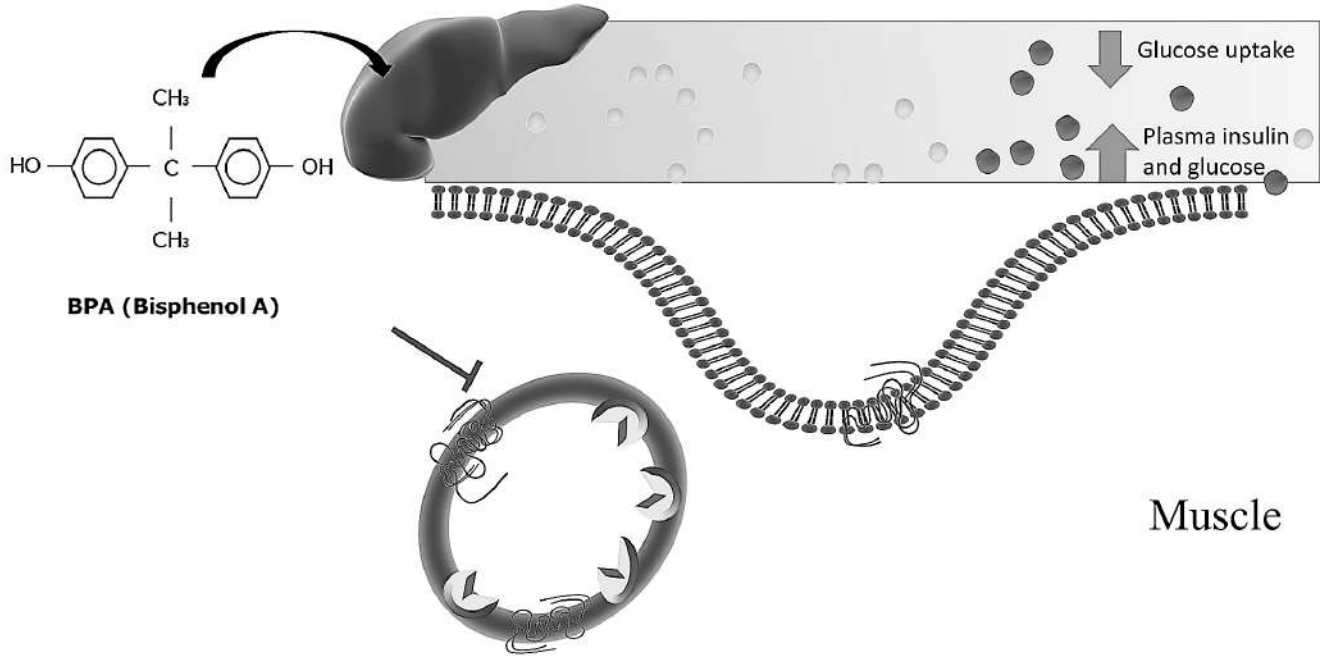

Fig. (9). Effect of BPA on the translocation of GLUT4 in muscle. The administration of BPA alters the proteins involved in the translocation of GLUT4, resulting in a lower disposition of glucose. BPA alters the insulin-dependent dose translation signaling and therefore alters the translocation of GLUT4 from the cytosol to plasma, making the gastrocnemius muscle an insulin-resistant tissue and consequently generates an elevation of blood glucose and the consequent increase in circulating insulin levels [200].

binding site not associated with the catalytic region, which is lost with AngIV binding.

Several mechanisms have been proposed to explain the role of IRAP in mediating the actions of AT4 receptor ligands, with particular relevance to those who believe that competitive inhibition of IRAP catalytic activity results in increased availability of AT4 receptor endogenous ligands [167, 198]. That is, AT4 ligands are believed to block the enzymatic activity of IRAP, which prevents degradation of substrates, or that IRAP is involved in the modulation of glucose absorption by influencing intracellular vesicular traffic through GLUT4 [16]. Therefore, these findings confirm a role for IRAP and GLUT4 in activity-dependent glucose uptake in hippocampal neurons.

5.3. BPA and IRAP/GLUT4

One of the undisputed effects of BPA is hyperinsulinemia. Exposure to BPA has shown to cause ß-pancreatic cells to produce more insulin, leading to this condition [87, 135, 199]. The condition of BPA-induced hyperinsulinemia influences the translocation of GLUT4 to the muscle level. In other words, the administration of BPA alters the proteins involved in the translocation of GLUT4, resulting in a lower disposition of glucose. BPA alters the insulin-dependent dose translation signaling and therefore alters the translocation of GLUT4 from the cytosol to plasma, making the gastrocnemius muscle an insulin-resistant tissue and hence generates an elevation of blood glucose and the subsequent increase in circulating insulin levels [200] (Fig. **9**).

These results are supported by the work developed by Provvisiero *et al*. [201], which conclude that both *in vivo* and *in vitro* studies show that exposure to BPA induces a decrease in adiponectin production by adipose cells and alters the signaling mechanism through insulin receptors and GLUT4 expression in muscle and liver inducing insulin resistance. To date, we have not located studies on the implication of BPA exposure on GLUT4 and its relationship with glucose availability at the brain level, although it is true that authors such as Wang *et al*. [112] establish a relationship between ER receptor blockade and GLUT4 translocation.

CONCLUSION

In view of the data presented in the literature and the complexity of the pathways, as well as the ignorance of their interaction points in AD, we consider it necessary to deepen the role of EDCs, particularly relevant in relation to the appearance of metabolic pathologies such as DMTII and the development of AD, and due to the involvement of estrogens in both insulin-dependent and bRAS pathways through the IRAP / GLUT4 binomial, since they could have an important role in the incidence, ultimately of AD. A possible treatment strategy in order to reduce the likelihood of AD occurring due to an endocrine disruption could be through an IRAP receptor antagonist that crosses the BBB. According to the theory offered by the Albiston group, this would be a small molecule-based on AngIV.

AUTHOR'S CONTRIBUTION

MJR-E; Investigation, Methodology, Writing-Review & Editing, JMM-M, Visualization, Writing - Review & Editing, VC-H: Writing-Review & Editing, Resources. MdPC-G, Conceptualization, Visualization, Investigation, Writing-Original Draft, Writing-Review & Editing. All authors read and approved the final document.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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