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Review

Alzheimer's disease: Is there a relationship between brain renin-angiotensin system, estradiol and glucose transporter-4 (GLUT-4)?

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Abstract: One of the diseases more related to the continuous aging of the population is Alzheimer's disease, which is a type of dementia currently without either effective diagnosis biomarkers or treatments. Its higher prevalence in women makes it necessary to study pathways/systems that could participate and/or be involved in its development, as well as those that could be affected by hormonal factors, which, in this case, are estradiol levels. In this sense, one of the systems under study that is gaining special relevance in the scientific community is the brain renin-angiotensin system and its regulatory proteolytic enzymes. This system is strongly modulated by estrogens, and it is also connected with the cerebral glucose metabolism through the angiotensin IV receptor, also recognized as the insulin-regulated aminopeptidase (IRAP). Due to the fact that the cerebral glucose metabolism is highly compromised in patients with Alzheimer's disease, it is necessary to know the elements of the systems and their functions in this process, namely, the cerebral renin-angiotensin system, estradiol and IRAP, an enzyme and receptor co-localized in brain tissue with the insulin-dependent glucose transporter 4 (GLUT4). Knowledge of the connection between them could shed light on the molecular mechanisms of this disease and also provide new diagnostic and therapeutic targets.

Keywords: Alzheimer's disease; women; estrogen; insulin-regulated aminopeptidase; glucose transporter

1. Introduction

The complexity of Alzheimer's disease (AD) is mainly due to its multifactorial nature and the impossibility of finding biomarkers for early detection, which is mainly attributable to the complex differentiation between normal/physiological states of cognitive deterioration that are typical of aging and disease/pathological states, in addition to a non-specific and insidious onset of symptoms typical of this pathology [1].

These factors have a different implication, as they affect its diagnosis and progression. Two of them have received special attention; biological sex and, therefore, estrogens, are considered to constitute a risk factor for AD since most diagnoses are made in women in the perimenopausal stage; the second factor is energy metabolism, that is, glucose metabolism, which is found to be compromised in patients with AD. Both factors interact and/or modulate the brain renin-angiotensin system (bRAS), directly implicating this system in AD pathology.

Therefore, it is essential to investigate new potential targets and/or systems which could be involved in the process of the neuronal degeneration that is characteristic of this pathology. The bRAS is involved in brain energy homeostasis, and it is modulated by several factors, including estrogens. It must be taken into account that one important characteristic of this neurodegenerative pathology is that sex differences exist in relation to its development and progression. Thus, women tend to show a more powerful progression of mild cognitive impairment [2] and greater severity of clinical dementia [3,4] than men. Recent research on sex-specific pathophysiological mechanisms behind AD risk has implicated the menopausal transition, which is a state of neuroendocrine changes that occurs in midlife and is unique to women. Many symptoms of menopause, characterized as leading to reproductive senescence, are neurological, such as the presence of depression, impairment in multiple cognitive domains and disruption of the systems regulated by estrogens, thermoregulation, sleep and circadian rhythms [5].

In this context, the bRAS could be affected and involved in AD due to these sex differences, as it is modulated by steroid hormones. Also, the brain bioenergetic metabolism is regulated by angiotensin IV (AngIV), which is recognized by its receptor, the insulin-regulated aminopeptidase (IRAP), and colocalized with GLUT4, an insulin-dependent glucose transporter.

2. Brain renin-angiotensin system

The existence of a bRAS has been recognized in the scientific literature since its description by Ganten et al. in 1971 [6], as well as its involvement in neurodegenerative pathologies such as AD. Each of the bRAS components has been localized in the central nervous system (CNS) although no single cell type groups all of its components. This suggests a localized synthesis, whereas systemic renin-angiotensin system (RAS) components were found to only access brain tissue through the circumventricular organs with fenestrated capillaries [7]. In fact, angiotensin II (AngII) one of the major angiotensins produced by the RAS, does not cross the blood-brain barrier (BBB) [8], as do angiotensinogen (AGT) and renin, due to their molecular size; but, all of them have been localized in the brain.

Specifically, AGT has been described in astrocytes [7,9], as it also has been with renin [10]. Renin is an aspartyl protease that is expressed in neurons, astrocytes, oligodentrocytes and microglia in different brain regions [11] Therefore, there is a local and independent bRAS in which astrocytes

are the main source of brain AGT [12].

The oxidation of AGT confers a conformational change in the protein, which allows it to act on renin, generating angiotensin I (AngI). From this, through the action of the angiotensin-converting enzyme (ACE), AngII is formed. AngII is observed in areas of the brain that regulate blood pressure and other areas with a homeostatic function, such as the choroid plexus, vascular organ of the lamina terminalis, subfornical organ and area postrema [13]. AngII will be converted into angiotensin III (AngIII) and the latter into AngIV [14] by the action of several aminopeptidases that act as regulatory proteolytic enzymes. The regulatory mechanisms performed by these enzymes and their associated functions are delicately tuned to the cell or tissue in which they are involved [15–20]. Aspartyl aminopeptidase (ASAP) and aminopeptidase a (APA) act on AngII, removing its N-terminal aspartyl residue to generate AngIII [21,22]. AngIII can also be formed from AngI through the production of des-Asp1-AngI, which is converted to AngIII by the action of ACE. AngIII is rapidly converted to AngIV by the action of aminopeptidase B and N [23]. Unlike AngI, which is considered mainly inactive, AngII and AngIII exert their action through angiotensin type 1 and type 2 receptors. AngIV also binds to the aforementioned receptors but with lower affinity, showing much greater affinity for and specificity with the AngIV receptor (AT_4). This AT_4 receptor has been identified as IRAP [24,25], a receptor/enzyme regulator highly involved in the memory processes. As discussed above, AT_4 has been identified as the IRAP; in the brain, IRAP is colocalized with GLUT4, which is an insulin-dependent glucose transporter, thus establishing the relationship between the production and action of AngIV through its receptor with the insulin-dependent brain energy metabolism.

Therefore, the functions of bRAS go beyond those described for the systemic RAS. Evidence has demonstrated bRAS involvement in oxidative stress processes, endothelial dysfunction, microglial polarization, neuroinflammation, brain homestasis, altered neurotransmitter secretion, cognition and aging [11,26–30].

1.1. AT_4 receptor

The bRAS has been involved in the regulatory mechanisms involving functions such as memory, the learning of emotional responses and processing of sensory information. This role is attributed to AngIV peptide [31], although it was initially related to the action of AngII. The positive/favoring effect on the memory of angiotensins is probably due to the conversion of AngII to AngIV, exerting its effect by binding to its AT_4 receptor, which is responsible for cognitive facilitation [32].

In addition to regulating memory consolidation, the AT_4 receptor regulates physiological functions such as cerebral blood flow, neuroprotection and synaptogenesis. In fact, AngIV induces dose-dependent increases in cerebral blood flow without inducing significant changes in systemic blood pressure [33]. Therefore, the functions of AngIV, as mediated through its receptor AT_4, points to a protective profile of AngIV for brain tissue [29,33–35]. In this sense, AngIV levels would be determined by the catabolism of different substrates by the regulatory proteolytic enzymes involved in bRAS, as well as by the degradation of AngIV itself. AngIII and AngIV has been found to exert opposing functions in the regulation of IRAP catalytic activity and GLUT4-dependent glucose uptake [36]. In this sense, GLUT4 participates in the uptake of glucose during memory processing and other cognitive functions that are highly energy-demanding processes.

1.2. Insulin-regulated aminopeptidase

This zinc-dependent transmembrane metallopeptidase has important biological functions and is considered an emerging drug target. Ascher et al. [37] demonstrated that IRAP shows a second Zn^{2+} binding site that is not associated with the catalytic region but is lost (blocked) upon AngIV binding, precluding the binding of IRAP's own ligands. Thus, AngIV has been found to affect learning and memory through an inhibitory role in the enzymatic activity of IRAP [38]. The modulation of IRAP activity caused by domains 3 and 4 is consistent with a conformational change that regulates access to the active site of this enzyme. In this regard, Mpakali et al. [39] confirmed that IRAP has an open conformation in solution but undergoes conformational closure upon binding to an inhibitor. In fact, the development of IRAP inhibitors was already proposed a decade ago [37] as a promising approach in drug discovery for the treatment of memory loss, such as that associated with AD.

In the brain, IRAP is found in highly specialized vesicles also containing GLUT4. These vesicles appear mainly within hippocampal neurons, but also in other brain regions, such as the hypothalamus, pyriform cortex, entorhinal cortex, pituitary gland, olfactory bulb, in most neocortical areas and in different nuclei of the limbic and motor regions, including the basal ganglia [40–45]. In response to certain stimuli, both IRAP and GLUT4 are translocated from these vesicles to the cell surface. One such stimuli is insulin [46]. However, as reported by Fernando et al. [46] (and reviewed in [47]), this translocation does not imply the functioning of GLUT4 due to these vesicles having to integrate adequately into the plasma membrane [48,49]. Thus, GLUT4 participates in the uptake of glucose during memory processing and other cognitive functions that are highly energy-demanding processes [50,51].

3. Brain renin-angiotensin system and Alzheimer's disease

The activation of the bRAS can be promoted by different molecules, as it is a system with multiple and diverse functions. Recently, scholars [52] have described the activation of bRAS through the acetylcholine receptor [53,54]. An increase in this receptor's level was found to lead to activation of the bRAS, ultimately increasing AngIV levels and glucose uptake in hippocampal neurons [52].

In AD, the bRAS effector peptides, including AngII, have been implicated in its development. The latter is associated with cognitive deficits and impairment, as it promotes the accumulation of amyloid β1-42 and induces AD-like tau phosphorylation, which further increases amyloid neurotoxicity [55].

Another bRAS modulating factor is estradiol, which is a steroid hormone with important implications in AD in relation to glucose metabolism. In situations of estrogen suppression, activation of the bRAS has been observed; it is presumed to be involved in the processes of neurodegeneration and pathogenesis of AD through amyloidogenesis and cognitive impairment [11].

In this context, we could consider that, in the case of AD-type dementia, where the decrease in acetylcholine levels is characteristic, the bRAS activation pathway could be affected, affecting glucose intake and favoring glucose-rich environments. In this sense, the elevation of angiotensin receptors has been described in situations of hyperglycemia, which contributes to neurodegeneration, elevated oxidative stress and the pathogenesis of AD [56]. On the other hand, states of estradiol suppression, such as menopause, could favor states of neurodegeneration through the bRAS, a point

that we will develop below.

4. Alzheimer's disease and estrogens

The impact of estradiol on brain structures and in terms of cognition is profound [57]. One of the brain's master regulatory systems is the estrogen receptor network. Under its influence, the brain effectively responds at proper timescales to regulate the brain energy metabolism, such as in the ovarian-neural estrogen axis. Changes in either the availability of estrogen or its receptor network can affect intracellular signaling, neural circuit function and energy availability [58].

Estrogen receptors at the brain level are abundant in those structures affected by menopause. Such receptors are located in various cellular compartments, such as the mitochondria, plasma membranes and cell nucleus, being especially abundant in the hypothalamus, thermoregulatory and sleep and circadian cycle centers [59–61]. In addition, fundamental regions for learning and memory such as the prefrontal cortex, hippocampus, amygdala and posterior cingulate cortex also contain estrogen receptors [61].

Estrogen receptors also participate at the brain level in the modulation of neural differentiation, neuroinflammation, synaptic plasticity, proliferation, behavior and cholesterol metabolism since brain tissue performs de novo synthesis of estrogens through neurosteroidogenesis, mainly in neurons.

One of the most compelling pieces of evidence linking systemic estrogen loss during menopause to neurological changes is the increased risk of depression associated with the menopausal transition [62]. In fact, the treatment of perimenopausal women with estrogens significantly reduced its probability [63–65]. This statement additionally supports the hypothesis regarding the influence of systemic estradiol on behavior. These results have not been found in postmenopausal women, probably because they are older when they initiate the therapy with estrogens [62]. In this sense, estrogens have neuroprotective effects that would be eliminated with the drastic systemic decrease in estradiol during menopause. In this context, the use of hormone therapy would not only alleviate the symptoms of depression and cognitive impairment associated with menopause, but it would also prevent the risk of dementia.

Studies on estrogen receptors, and specifically on the ERα subtype, have demonstrated its overexpression in several brain regions, including the neuronal nuclei of the basal forebrain, mammillary body and hypothalamus in AD patients when compared with sex- and age-matched healthy brains [66–69]. In contrast, it is decreased in hippocampal neurons [70]. Results regarding the linkage of its expression with tau phosphorylation, an anatomopathological feature of AD, are contradictory, with some relating ERα overexpression to increased tau phosphorylation, and others showing opposite results [71]. These conflicting results do not help to determine the neuroprotective role of ERα. However, it has been described that ERα gene polymorphisms are related to cognitive impairment in women after menopause [72,73], and they have been localized in AD patient populations [74,75], supporting a promising role for ERα in AD risk and progression [76]. Specifically, the signaling processes dependent on estrogen receptors and their involvement as a protector or facilitator of this disease have received special attention. Thus, estrogen action through its alpha receptor has been found to be involved in cognitive impairment after menopause [77]. Therefore, the study of this pathway and its possible modulation is of importance in relation to disease progression.

4.1. Estrogens and glycogen metabolism

As described by Brinton [59,78,79], the effect/implication of estrogens on glucose metabolism and mitochondrial protein function through the activation of their brain receptors reverses during perimenopause. This reversion favors brain hypometabolic states and ketone body metabolism [58,59,78–80], in addition to modulating insulin sensitivity [61]. During perimenopause, due to the process of estrogen withdrawal, brain glucose metabolism regulation by estrogens is dismantled, which promotes a hypometabolic condition [59,80,81]. Preclinical studies show that, during perimenopause, when brain estrogen substantially decreases, rates of cerebral glucose metabolism and suppression of ketogenic pathways are disabled [82]. Subsequently, an adaptive starvation reaction occurs to increase mitochondrial fatty acid metabolism for the generation and utilization of ketone bodies as an alternative energy source [58,82–84]. In a situation of hypometabolism, impaired and/or failed mitochondrial function results in the formation of free radicals and leads to oxidative damage that can promote the accumulation of ß-amyloid and neuronal malfunctioning [85], which increases the risk of developing AD later in life.

Therefore, the reduction in estradiol levels during the fifth and subsequent decades of life may be responsible for deficits in cerebral metabolism and vascular pathologies, mainly among women, as men of the same age could aromatize testosterone into estrogen.

The hypothesis developed in relation to women being more affected by this pathology has focused on the idea of a greater life expectancy or sociocultural detection bias [86]. However, there is evidence that the faster progression is due to neurobiological vulnerability in postmenopausal women [87]. In fact, at the level of gene expression, the changes observed during aging at the perimenopausal stage in women would start earlier [88] than in men.

Thus, endocrine aging has been found to accelerate chronological aging in the brain of women years before the onset of AD symptoms [89]. The brain tissue of perimenopausal women depends on ketone bodies as a primary energy source. Although this has an immediate beneficial impact on ATP synthesis and cell function, the long-lasting transition to menopause may exacerbate the catabolism of brain white matter to generate ketones, resulting in neuronal loss and AD pathology [58,80,90,91]. Furthermore, this metabolic change has been found to be associated with brain insulin resistance in perimenopausal women, as well as with peripheral insulin resistance [58,89,91,92]. As reviewed by Ramirez-Expósito et al., [47], CNS insulin resistance can occur independently of peripheral insulin resistance, although the relationship between the two is unknown. It has been found that the serum ratio of insulin levels in cerebrospinal fluid (CSF) is reduced in the presence of resistance to body insulin, as well as in the case of aging and in pathological situations such as AD, pointing to a decrease in insulin transport through the BBB. In addition, insulin seems to influence the synthesis of amyloid precursors, showing differences between healthy and AD patients. Therefore, insulin deficiency and insulin resistance could play important roles in AD pathology, suggesting AD as a brain-specific form of diabetes mellitus, i.e., a “type 3 diabetes” [93]

Despite enormous advancement in the knowledge of AD pathogenesis, the molecular basis that is hidden in the sex-dependent differences in AD is still unknown. Therefore, this is a major impediment to finding new sex-based molecular targets for this illness. For example, hormone replacement and anti-estrogen therapies take into account the circulating blood levels of estrogens, but they do not provide any information about the estrogen brain levels and how brain functions are affected by their alteration. The consequence is that such endocrine therapies do not help against

AD [94], whereas experimental data, including animal models (transgenic mice with amyloid precursor protein), clearly support the idea that, not only does brain estrogen deficiency induce AD, but also that early treatment with estradiol, not late treatment, prevents AD [95–97]. Recent studies show that women at genetic risk for AD appear to particularly benefit from hormone therapy replacement [98].

4.2. Estrogens and GLUT4

As we have seen, situations of the absence of brain estrogens affect the glycemic metabolism, giving rise to situations of hypometabolism, cerebral hyperglycemia and insulin resistance. Specifically, according to recent research, glucose hypometabolism, i.e. a glucose-rich brain environment, strongly favor the formation of Aβ-42 oligomers, even suggesting that high glucose concentrations within the range observed in diabetic patients (10 mM) facilitate their formation [99].

In this regard, a link has been established between ERß receptor blockade and GLUT4 vesicle translocation [100]. Indeed, previous studies have indicated that hippocampal neurons rapidly increase insulin-mediated glucose utilization during learning, which was reversed after ovariectomy or tamoxifen treatment. Insulin levels and GLUT4 expression in the hippocampus were lower in ovariectomized and non-ovariectomy-plus-tamoxifen (10 mg/kg, i.p.) rats than in normal rats. These effects were associated with reduced translocation of GLUT4 to the plasma membrane in rats [101].

Thus, in the hippocampus, glucose metabolism is insulin-dependent and mediated by GLUT4 [102]. In fact, the onset of dementia and/or cognitive impairment occurs in parallel with a decrease in hippocampal insulin level and GLUT4 expression. Furthermore, estrogen blockade impaired spatial memory in female rats. Probably, these effects are related, at least in part, by the decrease in hippocampal insulin signaling, which in turn decrease glucose consumption [100]. Thus, it has been suggested that decreased glucose metabolism predates amyloid peptide deposition. That is, bioenergetic deficits may be driving amyloid deposition in at least some women [89]. Also, from a molecular point of view, the absence of estrogen is related to the increase of apoptosis in the process of neurodegeneration [103]. Worsening AD is associated with increased apoptotic markers under hyperglycemia [104].

4.3. Estrogens, GLUT4 and IRAP/AT4

The involvement of GLUT4 in estrogen-mediated glycemic metabolism, as well as its colocalization with IRAP/AT_4 in conjunction with the insulin-dependent translocation, is of great significance in the context of AD.

As pointed out previously, due to the activation of the bRAS and the activity of the proteolytic regulatory enzymes, AngIV levels and its binding to its receptor AT_4/IRAP will be determined. Its colocalization with the GLUT4 transporter, its response to estrogens and the presence of insulin, which determines its translocation, has been shown to affect glucose metabolism. On the other hand, the activity of IRAP substrates, in the case that the IRAP catalytic domain was hidden by AngIV, has been found to favor the memory process. On the contrary, the non-binding of AngIV would favor the catalytic activity of IRAP.

One explanation of the role of IRAP in mediating the actions of AT_4 receptor ligands is to consider that the competitive inhibition of IRAP catalytic activity promotes the availability of

endogenous AT_4 receptor ligands [105,106]. These AT_4 ligands block their enzymatic activity and prevent substrate degradation. Alternatively, IRAP has been shown to be directly involved in modulating glucose uptake by regulating intracellular vesicular trafficking and GLUT4 function [46]. It is also important to reflect that the brain distribution of IRAP generally agrees with the AngIV binding site distribution [24,32,107,108].

5. Conclusions

AD is a puzzle with multiple pieces. But, two of them have become particularly relevant; sex—and, therefore, estrogen—is considered to be a risk factor for AD; the second factor is energy metabolism, i.e., glucose metabolism, which is compromised in patients with AD. Both factors interact and/or modulate the bRAS. Therefore, the bRAS must be investigated as a target of study in the context of AD, particularly in view of the clear increase in the diagnosis of this pathology, mainly in women in the perimenopausal stage.

Conflict of interest

The authors declare no conflict of interest.

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