Review

Insulin Peptides as Mediators of the Impact of Life Style in Alzheimer's disease

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Abstract. The search for the cause of Alzheimer's disease (AD), that affects millions of people worldwide, is currently one of the most important scientific endeavors from a clinical perspective. There are so many mechanisms proposed, and so disparate changes observed, that it is becoming a challenging task to provide a comprehensive view of possible pathogenic processes in AD. Tauopathy (intracellular neurofibrillary tangles) and amyloidosis (extracellular amyloid plaques) are the anatomical hallmarks of the disease, and the formation of these proteinaceous aggregates in specific brain areas is widely held as the ultimate pathogenic mechanism. However, the triggers of this dysproteostasis process remain unknown. Further, neurofibrillary tangles and plaques may only constitute the last stages of a process of still uncertain origin. Thus, without an established knowledge of its etiology, and no cure in the horizon, prevention –or merely delaying its development, has become a last-resort goal in AD research. As with other success stories in preventive medicine, epidemiological studies have provided basic knowledge of risk factors in AD that may contribute to understand its etiology. Disregarding old age, gender, and ApoE4 genotype as non preventable risk factors, there are diverse life-style traits –many of them closely related to cardiovascular health, that have been associated to AD risk. Most prominent among them are diet, physical and mental activity, exposure to stress, and sleep/wake patterns. We argue that all these life-style factors engage insulinergic pathways that affect brain function, providing a potentially unifying thread for life-style and AD risk. Although further studies are needed to firmly establish a link between faulty insulinergic function and AD, we herein summarize the evidence that this link should be thoroughly considered.

Keywords: Insulin peptides, life-style, risk of Alzheimer disease, diet, physical and mental activity, stress, sleep/wake cycle

INTRODUCTION

The first description of an AD patient was made over a hundred years ago [1]. In turn, the most accepted proposal of the origin of this disease -the "amyloid cascade" hypothesis [2], was made decades ago. However, this age-associated mental disorder is the only one among top causes of death that remains intractable. An important barrier to ameliorate the current worrying situation is chronic underfunding of AD research, as compared to other high-impact diseases such as cancer [3]. Probably, a profound re-thinking of what we actually know about this uniquely human disease is also required to lead us to new scenarios [4]. All AD researchers would agree that we need new animal models because available ones –that have been extraordinarily useful, do not mimic very important traits of the disease [5]. Even more dismaying, they have not helped to translate pre-clinical findings into clinically useful therapies. Brain pathology in AD is heterogeneous and somewhat blurs with closely related pathologies such as vascular dementia [6]. The latter aspect has not been

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faithfully captured by experimental modeling, and confronts us with the increasingly more recognized possibility that AD is not a single nosological entity.

From epidemiological studies we know that many life-style factors pose varying degrees of AD risk [7, 8]. Together with age -the main risk factor, ApoE genotype and sex -the main genetic risk factors (although many other genes are also associated to AD risk), behaviorally regulated factors such as diet, physical and mental activity (including social engagement and educational achievement), exposure to stress, and sleep patterns, are so far considered major modulators of AD pathology [9]. Accordingly, this knowledge has been used to implement intervention schemes that are now ongoing on a global scale, as reflected by the abundant literature on the topic [10–13]. An additional utility of this epidemiological information is that it may lead to a better understanding of the causes of AD. Based on this variety of risk factors two general questions arise. Are there many risk factors in AD because there are many potential causes for developing it? Alternatively, are all these risk factors affecting a common pathogenic pathway? Acknowledging that we still do not have enough data to favor any of these two general options and a combination thereof [4], we propose to explore the latter possibility in relation to the function of insulin-like peptides (ILPs), as there is enough evidence to entertain this notion. Vertebrate ILPs comprise three families of related hormones: insulin and its related insulin-like growth factor I and II (IGF-I and IGF-II), relaxins, and insulin-like peptides. For the purpose of this review we refer to insulin and IGFs as ILPs, as this family is the best studied in the central nervous system.

Please note that our proposal is entirely operational, as we consider that AD most likely is triggered by more than a single pathogenic event. Specifically, we propose that faulty ILP function in the brain is a main pathogenic pathway in AD because, as pointed out before [14], all major disturbances associated to the pathology can be explained by altered ILP activity (Fig. 1). For example, ILPs are major regulators of synaptic activity and number. Thus, insulin, IGF-I and IGF-II promote synapse formation and synaptic plasticity [15–17]. Insulin and IGF-I are also positive modulators of proteostasis [18–20], including amyloid β (Aβ) processing [21–24]. By inhibiting GSK-3β, a major Tau kinase, both insulin and IGF-I modulates Tau phosphorylation [25, 26]. Both ILPs are also important to preserve mitochondrial function [27, 28], combat oxidative stress [29, 30] and

inflammation [31, 32], and protect the brain vasculature [33]. Further, all three ILPs modulate mood in a positive fashion [34–36]. Importantly, a close connection between diabetes and AD has been suggested [37, 38], and numerous processes possibly connecting both diseases have been proposed [39–41]. Of note, diabetes not only alters insulin activity, but also reduces IGF-I levels [42]. Indeed, merely reducing insulin-like growth factor I (IGF-I) input to the brain elicited tauopathy, amyloidosis, cognitive deterioration and synaptic disturbances in rodents [43]. In addition, genome-wide analysis in pilot studies hint to a possible association of ILP-related genes with AD risk [44–46]. Finally, while there is still no evidence of a connection between ILPs and sex bias in AD incidence, many actions of ILPs in brain are sexually dimorphic [47–49]. Hence, this ILPs trait may also underlie varied AD incidence between both sexes [50]. In this regard, it is interesting to note that IGF-II is an X-linked imprinted gene and that epigenetic changes including alterations in genomic imprinting may affect the risk of AD [51].

However, it is important to point out that disturbed ILP function, as for example in diabetes, does not always originate cognitive disturbances. Maybe, altered ILP activity is necessary, but not sufficient to trigger AD pathology. Alternatively, diabetic patients with preserved brain function may have developed unknown protective mechanisms, similarly to what occurs with old individuals showing intact cognitive function despite displaying conspicuous AD-like neuropathology [52]. Additionally, it is important to remember that many studies in animal models, and even in humans, point to a deleterious role of ILPs, specifically insulin and IGF-I, in aging [53] and in age-related diseases, including AD [54]. The so called "insulin paradox" [55, 56] refers to the observation that reduction of insulin/IGF-I signaling promotes longevity in invertebrate species and in mammals [57], and protects against AD in mouse models [58, 59]. Conversely, IGF-I, IGF-II, and insulin display varied neuroprotective actions, including potentiation of learning and memory, and protection against AD [60].

ILPs constitute a well preserved family of hormones already present in primitive invertebrates. In the latter, ILPs share a common single receptor, whereas vertebrate insulin and IGFs share three receptors, with differing affinities. Insulin binds with highest affinity to its receptor –showing two isoforms, IR-A and IR-B [61], and with lower affinity to the IGF-I receptor (IGF-IR), and the hybrid insulin/IGF-I
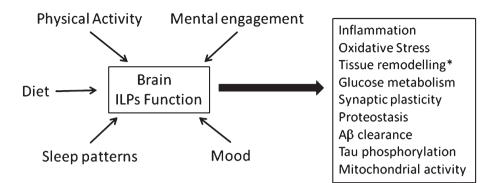
Fig. 1. Altered ILP function mediates the impact of life-style factors on pathological changes associated to Alzheimer's disease. Diet, mental and physical activity, sleep quality and mood can modulate ILP function that in turn intervene in many processes known to be altered in AD. Main ones include homeosteatic inflammation, protection against reactive oxygen species, tissue remodelling (including formation of new vessels, neurons and glia), glucose handling by brain cells, synaptic plasticity –that in turn impacts on mood, cognition, and sleep architecture, Aβ clearance, tau phosphorylation, proteostasis (autophagy, proteosome activity) and mitochondrial function. *New neuronal formation is an important aspect of ILPs function in the adult brain. However, recent controversial evidence in favor [192] or against [193] the presence of neurogenesis in the adult human brain puts somewhat in hold the significance of this ILP trait in human physiology.

receptor (IR/IGF-IR). IGF-I binds to highest affinity to its receptor and the hybrid IR/IGF-IR [62], and with lower affinity to IR and IGF-IIR. IGF-II binds with highest affinity to IGF-IIR and IR-A [63], and with lower affinity to IGF-IR and IR-B. An important feature of brain ILPs is their varied sources. Insulin is mostly produced in the pancreas, but low levels of expression are found in the adult brain [64]. This means that circulating insulin gets into the brain by crossing the cells of the blood-brain-barriers through a transcytosis process [65]. Despite its profound functional impact in brain physiology, the precise mechanism allowing serum insulin to transverse the BBB is still not well characterized. IGF-I is also locally produced by adult brain cells [66, 67], but a major proportion of brain IGF-I comes also from the periphery. Indeed, the adult brain expresses very low amounts of IGF-I as compared to the developing brain, but the amount of brain IGF-I is relatively constant throughout ontogeny (a decrease is seen at old age). In the case of serum IGF-I, the mechanisms involved in its passage into the brain are better characterized [68, 69]. Lastly, IGF-II is produced at high levels by the choroid plexus and meninges [70], so it is likely that brain IGF-II derives from these tissues. Greater detail of the different sources and mechanisms of transcytosis of brain ILPs is provided in Fernandez et al., 2012 [60].

Diet

A balanced diet is necessary for a healthy cardio-metabolic status. Evidence that a healthy diet may

also contribute to prevent or delay AD [71] is generally interpreted from the cardio-metabolic point of view. That is, preserved tissue perfusion -as a result of a healthy vasculature [72], and intact insulin sensitivity [72, 73] will explain the protective actions of a balanced diet on brain function. However, there is evidence that diet also affects brain function through a direct modulation of the actions of ILPs in the brain. Specifically, diet components such as lipids modulate the entrance of circulating IGF-I and insulin through the blood-brain-barrier [74, 75]. Furthermore, insulin resistance associated to imbalanced diets also reduces brain insulin sensitivity through mechanisms as yet unknown [76, 77], but that probably encompass reduced entrance of insulin into the brain. In turn, the known connection between metabolic status –which is highly diet-dependent, neuroinflammation [78], and oxidative stress [79], may be explained in part also by loss of the anti-inflammatory and anti-oxidant actions of insulin/IGF-I [80–82]. Thus, neuroinflammation and oxidative stress reduces insulin/IGF-I signaling in target cells [83, 84]. Therefore, a vicious cycle develops where deleterious actions of inflammation and oxidative stress on insulin/IGF-I sensitivity reduce their anti-inflammatory and anti-oxidant actions in the brain.

Formerly, the majority of reports identifying a proper diet as a protective factor in AD were cross-sectional studies generally using a relatively small sample size [85–89]. More recently, retrospective longitudinal studies with large populations have been implemented. Based on them, the favored idea is

that low-fat, low-sugar diets are protective [90, 91], although cholesterol intake has been shown not to influence AD risk [92]. The prototypical example of a beneficial diet is the so-called Mediterranean diet [87], but more work is needed to firmly establish its protective role [93]. A corollary of these observations is that obesity is a risk factor for AD. Indeed, many studies confirm an association of obesity with cognitive alterations [94], and increased AD risk [95, 96] These epidemiological studies comprise large populations and therefore their conclusions are more robust.

Many nutritional studies have focused on particular macro- and micro-nutrients to determine their influence in AD pathology. Among those analyzing large cohorts, high glycemic [97], or high-fat content [98] diets (but see [91] have proven deleterious. Conversely, diets rich in fish [99, 100] or B vitamins [101, 102] have been shown to be protective. For micro-nutrients such as vitamin E [103], omega-3 fatty acids [104], or folic acid [105], there is still insufficient evidence to determine their influence, if any, on AD pathology. However, AD patients show specific micronutrient deficiencies [106], and a micronutrient-based nutriceutical has shown promising protective effects in a small group of AD patients [85].

An important observation further reinforcing a link between metabolic status and AD is that AD patients often present weight loss [107–109]. Emaciation in AD patients has been ascribed to multiple factors, including an altered hypothalamus-pituitary-adrenal axis [110], which is closely related to IGF-I function in the brain (Santi, submitted). Further, since insulin is a key adiposity signal [111], it might be that faulty insulin function in the AD hypothalamus contributes to abnormal feeding behavior in these patients.

Physical activity

Together with a balanced diet, proper amount of physical activity is probably the most modifiable lifestyle factor for populations at risk worldwide, particularly in developed countries. However, it is as difficult to implement in the general population, as it is to promote balanced diets [112]. This explains the current intense search for drug mimetics of exercise [113]. Increasing physical activity to reduce risk of AD is one of the few behaviors widely acknowledged to be effective [114], including organizations such as The Alzheimer's Association [9]. Again, reported beneficial effects of physical activity in AD prevention are

usually ascribed to its cardio-protective actions, with gender posing different effects [115, 116].

A steadily increasing number of reports document protective actions of physical activity on AD risk. Currently, the focus is to delineate the minimal amount of activity that is protective [117, 118], and whether it will also be therapeutic [119, 120]. An ancillary effect of these increasingly generalized analyses is the wide use of exercise regimes for treatment of AD patients [121]. Thus, exercise is not only preventive but may also be beneficial for treatment, once AD pathology is established.

Because exercise improves brain insulin sensitivity [122], and increases brain uptake of circulating IGF-I [68], a direct connection of neuroprotection by exercise with enhanced brain activity of ILPs is straightforward. Intensity, type, length, and frequency of exercise, all may affect ILP function in target tissues [123–125], including the brain. Direct proof of IGF-I-dependent neuroprotection by exercise in animal models [126, 127] has widened to include many other trophic signals [128], which allow us to consider that the main neuroprotective action of exercise is to maintain appropriate levels of trophic support, in many cases arising from the periphery.

Why is exercise required? As pointed out many times, the problem is the abnormally low level of physical activity that is the norm in the modern world [129, 130]. Thus, sedentarism impedes proper trophic support to the brain, essential for homeostatic maintenance of brain function.

Stress

A substantial proportion of patients with mild cognitive impairment (MCI) present depressive symptoms. In addition, AD patients frequently have depression as co-morbidity [131, 132]. While the proportion of affected patients differ depending on the study, it is clear that psychiatric co-morbidities are of great impact in the disease [133, 134]. Depression often antecedes the appearance of overt cognitive deterioration [135, 136], and it is generally assumed that exposure to stress is a main triggering mechanism of depression [137]. Therefore, altered mood regulation can be considered an integral part of the disease. Indeed, AD patients are usually prescribed with psychoactive drugs [133], a component of current medical treatment that requires further insight due to its multiple unwanted effects [110].

Retrospective epidemiological studies indicate that exposure to stress is a risk factor for AD

[135], but whether depression is related to the origin of the disease, or it is a consequence of it, is still unknown. Several reports document a link between AD and brain changes elicited by stress. These include tau missorting [138], altered pro-inflammatory cytokines profile [139], disturbed hypothalamic-pituitary-adrenal (HPA) axis [140], or impaired mitochondrial function [141]. An additional question that merits further study is that mood is regulated by sex-specific mechanisms not yet entirely understood [142]. The fact that women show a greater AD incidence may be related to this gender trait.

All the above stress-related mechanism impact on ILPs actions in the brain. In general terms we should consider that stress hormones such as glucocorticoids -that are dysregulated in chronic stress conditions [143], may elicit ILP resistance [144–146]. And as discussed above, ILP resistance may account for many of the pathological changes in AD. A less evident aspect of stress effects on ILP activity is that they may interrupt the connection between peripheral ILPs and the brain by hampering their entrance in response to increased brain activity. Indeed, stress exposure reduces activation of hippocampal IGF-I receptors in response to environmental enrichment (Fig. 2), a well-established stimulator of the entrance of ILPs in the brain [69], and widely documented in experimental studies as a protection against AD pathology [147–150].

Mental activity

Resilience to AD and other neurodegenerative diseases has been related to cognitive reserve [151]. This is a concept coined to explain individual differences in brain aging trajectories and in the responses to brain damage [152]. Cognitive reserve will rely in the amount of neuronal resources that each individual has available, which theoretically may be reflected in brain architecture. Neuronal resources are the sum of inherited intelligence traits and of the extent each individual has used them. The latter is a reflection of the level of education of each individual. Thus, cognitive reserve is in part genetically acquired, and in part, environmental-dependent. Accordingly, the amount of cognitive reserve individually determined would account for the degree of functional compensation underlying individual differences in healthy and pathological brain aging. In this regard it is important to note that during healthy aging, functional compensation is the norm, as the aged brain utilizes resources that differed from young ones [153]. Hence,

age-related functional compensation should be more effective in individuals with larger cognitive reserve.

An example that illustrates the concept of cognitive reserve as a protective trait is that individuals with higher education, or greater mental activity in general, show reduced incidence of dementia [154, 155]. This means that the brain can be stimulated to build cognitive reserve, probably throughout life. Thus, even at late stages of life, cognitive activity likely protects against AD [156]. This is because cognitive reserve is probably built through activity-dependent processes. Numerous neuroprotective mechanisms are activated in response to neuronal activity. These include antioxidant [157, 158], inflammatory [159], cytoprotective [160], neurogenic [161, 162], and synaptogenic [163] processes, to name a few. In turn, all these protective traits can be explained by enhanced ILPs activity. Accordingly, it is important to point out that brain activity in general stimulates uptake of circulating IGF-I by the brain on demand, through processes that we have labeled as "neurotrophic coupling" [69]. In turn, local increases in ILPs will favor antioxidant [30, 81], anti-inflammatory [80, 164], cytoprotective [60], neurogenic [165] and synaptogenic actions [17, 166]. Although it is clear that the protective actions of increased brain activity cannot be solely ascribed to increased entrance of IGF-I into the brain, it is highly likely that it forms part of the pro-cognitive mechanisms underlying cognitive reserve.

Sleep/wake patterns

Altered sleep/wake pattern is an early disturbance in AD patients that seems to present a bidirectional relationship. That is, altered sleep is associated to AD, whereas amyloidosis related to AD alters sleep patterns [167]. Although increased sleep fragmentation is linked to normal aging [168], AD patients present more profound alterations in sleep architecture [169]. While the causal connection with the pathology is under intense scrutiny [170, 171], it is well recognized that maintaining a minimal amount of sleep is protective against AD [172]. Furthermore, better sleep consolidation attenuates the effect of ApoE genotype on AD risk [173]. This poses sleep therapy as an important potential target for AD prevention [174].

Since the brain flux of beta-amyloid (Aβ) is controlled by the sleep/wake cycle [175], a direct link with brain amyloidosis has been suggested [174].
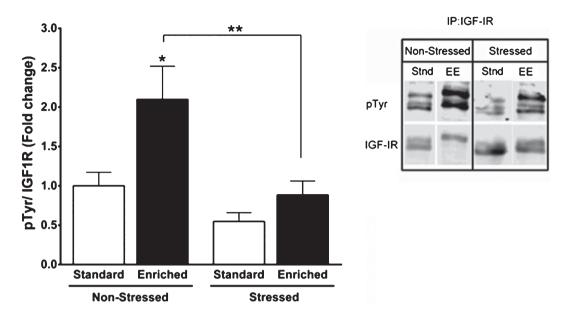
Fig. 2. Stress reduces IGF-I signaling in brain. C57BL/6 mice were exposed to a predator (a rat) or a sham predator (a toy rat) for 10 minutes. An environmental enrichment (EE) protocol was used 24 hours later in half of the animals to increase the entrance of IGF-I into the brain [69], while the rest stayed at their home cages (Stand: standard housing). After 2 hours of EE, animals where sacrificed and their hippocampi collected to determine levels of phosphorylated IGF-I receptor. Both the enrichment and the immunoprecipitation + western blot protocols were performed as described [194].

Because an important regulator of sleep patterns are orexin neurons of the lateral hypothalamus [176], and a connection between orexin and Aβ dynamics was demonstrated [177], orexinergic dysfunction was also proved to be associated to AD [178]. Furthermore, a correlation between CSF levels of orexin and CSF biomarkers of AD such as Tau has been described [179].

The lateral hypothalamus where orexin neurons reside is a classical feeding center where integration of energy availability and arousal takes place [180]. Not surprisingly, orexinergic function is modulated by insulin [181, 182], as the sleep/wake cycle is considered to support optimal energy allocation [183]. Thus, insulin signals the fed state to suppress orexinergic activity, leading to reduced physical activity [181]. Conversely, orexin is activated by hunger signals to promote arousal necessary for food-seeking [184].

Indirect evidence also supports an influence of insulin/IGFs on orexin neurons. For example, IGF-binding protein 3, the major IGF-binding protein, is expressed by orexin neurons, and modulate their function [185]. Also, insulin activity modulates the sleep/wake cycle [186]. In addition, hypothalamic neuronal loss have been found in aged individuals with fragmented sleep [187], which may also be associated to reduced ILPs neuroprotection during aging [188, 189]. Collectively, these data indicate that ILPs affect orexinergic activity and in this way affects the sleep/wake cycle. Whether dysregulated ILP activity originates orexinergic dysfunction leading to disrupted sleep archichecture in AD is a possibility that merits further attention.

Context-dependent actions of insulin peptides in the brain

Although reductionist approaches have been very useful to analyze complex systems, we have to keep in mind their limitations. Nevertheless, we still tend to disregard contextual nuances when addressing complex biological processes. For instance, insulin resistance is generally considered a pathological disturbance, although it is known that insulin resistance develops in response to different conditions as part of the homeostatic response [159]. Conceivably, physiological resistant states to the action of insulin peptides in the brain may go awry and trigger a cascade of pathological changes. Maladaptive perpetuation of resistant states may be related to life-style, which provides an individual context to disease progression (see Table 1). For example, while glucocorticoid release in response to stress produces insulin resis-

Table 1
Main lifestyle factors associated to risk of Alzheimer's disease

Life-style factor	Relevant mechanisms	References
Diet	Diet components such as lipids interfere with brain entrance of insulin/IGF-I.	[74, 75]
	Inflammation and oxidative stress produced by unhealthy diets.	[78, 79]
Physical Activity	Exercise increases brain sensitivity to insulin and stimulates brain uptake of circulating IGF-I.	[68, 122]
Stress	High glucocorticoids elicit insulin/IGF-I resistance.	[144–146]
	Stress reduces brain IGF-I signalling.	Figure 2
Mental Activity	Increased mental activity will increase brain uptake of IGF-I.	[69]
Sleep/Wake Cycle	Insulin modulation of orexin neurons may impact on activity patterns.	[181]

tance as part of the homeostatic repertoire to prepare the body to a life-threatening situation [144], chronic stress in susceptible individuals may cause chronic disruption of insulin signaling in the brain and lead to pathology.

Another key contextual aspect is that the actions of inter-cellular messengers are strictly cell-dependent. It is becoming increasingly clear that each type of brain cell responds to ILPs in specific ways that may even be antagonistic [190], and are strongly driven by cell context [191]. Therefore, it is the sum of cell- and context-specific responses to ILPs what should be considered. In other words, it would not be the same to modulate ILP activity in astrocytes or neurons for example, or in damaged or intact brain areas. In our effort to understand cellular and molecular pathways driving pathology, these nuances are somewhat overlooked. Administering anti-inflammatory drugs to AD patients based on epidemiological studies of their protective effects may be a typical case of precluding the context.

CONCLUSIONS

AD is an age-associated disease of profound incidence in modern societies. It has been argued that AD prevalence has increased in the last century because the age of the population has steadily raised, and now we live enough for the disease to manifest. This may be true, but life-style has also drastically changed in parallel. We may consider that AD is in part an unwanted cultural by-product and as such, it can theoretically be fought. Until the drug industry develops compounds mimicking or potentiating the protective effects of a healthy life style, it is imperative that public health agencies implement salutary behaviors.

Accordingly, we envisage two main ways to potentiate brain ILPs function through healthy habits. First, by influencing the amount of circulating ILPs input to the brain, as diet, together with physical/mental activity and stress seem to do.

Second, by modulating local ILPs actions. The latter can be brought about by adaptive changes in the sensitivity of brain circuits to ILPs, such as during neuronal plasticity processes involved in mental activity, mood regulation, and sleep/wake cycles.

Compounds modulating ILP actions in the brain in a cell-context dependent fashion may be of therapeutic utility, as they may ameliorate pathological changes associated to AD. Thus, we need to develop new drugs that will counteract ILP imbalances in the proper brain cell type and at the correct time during the course of the disease. For the former, we have to understand better the differences in ILP signaling among brain cell types; for the latter, we need to develop greater insight into the stages that define AD progress.

CONFLICT OF INTEREST

The authors state no conflict of interests.

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