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Molecular links between early energy metabolism alterations and Alzheimer´s disease

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1. ABSTRACT

Recent studies suggest that the neurobiology of Alzheimer's disease (AD) pathology could not be explained solely by an increase in β-amyloid levels. In fact, success with potential therapeutic drugs that inhibit the generation of beta amyloid has been low. Therefore, due to therapeutic failure in recent years, the scientists are looking for alternative hypotheses to explain the causes of the disease and the cognitive loss. Accordingly, alternative hypothesis propose a link between AD and peripheral metabolic alteration. Then, we review in depth changes related to insulin signalling and energy metabolism in the context of the APPSwe/PS1dE9 (APP/PS1) mice model of AD. We show an integrated view of the changes that occur in the early stages of the amyloidogenic process in the APP/PS1 double transgenic mice model. These early changes affect several key metabolic processes related to glucose uptake and insulin signalling, cellular energy homeostasis, mitochondrial biogenesis and increased Tau phosphorylation by kinase molecules like mTOR and Cdk5.

2. INTRODUCTION

Alzheimer's disease, in the more common sporadic form (SAD), is one of the most common causes of senile dementia and the numbers of new cases of the disease are increasing exponentially. The AD progression is associated with the formation of senile β-amyloid (Aβ) plaques and cognitive decline. In the early 1980s, the biochemical characterization of senile plaques, in patients with Down's syndrome and AD, led to the identification of Aβ peptide as a major component. The Aβ is a product of the Aβ protein precursor (APP), and the relationship between APP and Aβ caused the formulation of the amyloid cascade hypothesis. Then, mutations in APP (or other genes) lead to an increase in Aβ and to disease (1,2).

The majority of AD research is carried out using animal models that have increased Aβ levels compared to controls, and while Aβ pathology is mimicked in these models, many other factors associated with AD pathology are not. The APP/PS1 double transgenic mouse is a genetically modified mouse model that has been generated to try to mimic human AD pathology. In the APP/PS1 line, two strategies are combined to reach elevated Aβ levels: overexpression of the mutant human amyloid precursor protein encoding gene, together with the mutant presenilin-1 gene, which additionally impairs amyloid protein processing leading to elevated Aβ42 levels (3-5).

Despite the existence of several mice models for AD, the early onset of pathological changes as the

cerebral amyloidosis present at 6–8 weeks old mice, allow to consider APP/PS1 mice a good model to study the familial form of AD. A detailed review concerning differential characteristics of the AD mice strains can be found in Bilkei-Gorzo (5). Among them, Tg2576, APP23, APP/PS1 and the triple transgenic 3xtg AD mice strains express the so called Swedish mutation. It consists in a 695-amino acid isoform of human Alzheimer Aβ precursor protein containing the substitution of Lys670 by Asn and Met671 by Leu. Whereas APP/PS1 mice is a good model to study the early onset of pathological changes, the Tg2576, APP23, and 3xtg strains express a late onset form of the disease. Loss of both noradrenergic and cholinergic neurons is unique to double transgenic APP/PS1 and 3xtg mice. By contrast, none of these models show massive neuronal loss in cortex and hippocampus. The APP/PS1 strain show amyloid plaques formation along with Tau protein hyperphosphorylation (3). Only in 3xtg mice strain neurofibrillary tangles can be observed (6).

It has been demonstrated that APP/PS1 mice show increased insoluble β-amyloid production accompanied by brain plaque pathology and early memory loss, becoming evident at the age of 6 months (7-9). Recent data demonstrated that cognitive decline occur early before amyloid plaque deposition in APP/PS1 mice and, then, in this experimental model soluble β-amyloid peptide should be involved in early cognitive impairment. Acutely administered soluble Aβ oligomers have recently been reported to induce impairments in memory function (10,11) possibly by disturbing acetylcholinesterase (ACh) or NMDA receptors signalling systems (12,13). In fact, several studies have demonstrated impaired function of ACh and NMDA receptors signalling systems in multiple transgenic mouse models of Alzheimer's disease like APP/PS1 (11,12). Since PS1/APP mice aggressively generate Aβ (14), excessive concentrations of soluble Aβ oligomers may lead to the observed memory deficits by functionally disrupting the ACh and NMDA receptors signalling pathways. Thus APP/PS1 mice are commonly used in AD research for behavioural tests and studying the molecular mechanisms in plaque formation and thus AD progression (8,9,15).

3. METABOLIC SYNDROME, ADIPOKINES AND AD

Despite the genetic and cell biological evidence that supports the amyloid hypothesis, it is becoming clear that AD aetiology is complex and that Aβ alone is unable to account for all aspects of AD (16,17). For many years, it has been suspected that AD is a generalized metabolic disorder, but little evidence has emerged to confirm this suspicion. Published data have suggested metabolic syndrome as an independent risk factor for AD. Decades of fruitless search for effective therapies have led to the suggestion that the treatment usually starts too late in the course of the disease to be able to modify it, and can only be detected when pathology is already advanced (18).

There is evidence of a relationship between adipokines and AD. The adipokines, are cytokines secreted by adipose tissue. Among them, leptin, adiponectin, tumour necrosis factor (TNF)-alpha, interleukins (IL-6), and also molecules like Pituitary-derived prolactin (PRL), a well-known regulator of the lactating mammary gland, recently shown to be produced by human adipose tissue (19). Adipokines have come to be recognized for their contribution to the mechanisms by which obesity and related metabolic disorders influence diseases like cancer or AD. It has been observed that AD patients display increased circulating levels of anorexigenic adipokines, related to gender, that may contribute to the metabolic changes observed in AD patients (20).

Among the adipokine genes associated to AD, we can find the obese gene (ob) which is responsible of the synthesis of the adipostatic hormone leptin (Lep). Leptin is a hormone secreted by adipose tissue that acts to suppress appetite and regulate energy expenditure. In humans, recent studies have suggested an association between higher Lep levels and a reduced incidence of dementia and AD (21). In rodents, Lep modulates the production and clearance of Aβ (22). Mice with Lep receptor disruption show impaired long-term potentiation, synaptic plasticity and spatial learning, whereas treatment with Lep increases Aβ and tau clearance as well as amelioration of AD-like pathology (23-25). More recently it has been demonstrated that leptin resistance in the hippocampus may play a role in the characteristic changes associated with AD (26). In this study, whereas leptin mRNA was decreased in hippocampus, increased leptin was found and, then, suggesting a discontinuity in the leptin signalling pathway. The lack of leptin signalling within degenerating neurons may represent a novel neuronal leptin resistance in Alzheimer disease.

Similar to the ligand, the prolactin receptor (PRLR) has also been shown to be a member of the larger class of receptors, known as the class 1 cytokine receptor superfamily. Prolactin is secreted by the pituitary, decidua, and lymphoid cells, has been shown to have a regulatory role in reproduction, immune function, and cell growth in mammals. Elevated levels PRL, oxytocin, progesterone and glucocorticoids are characteristics of lactation and the pronounced fluctuation of these hormones occurring in this phase may play a role protecting the hippocampus. Indeed, it has been shown that PRL administration to ovariectomized rats significantly diminishes the deleterious effects of kainic acid (KA) in the dorsal hippocampus and reduces the progression of KA-induced seizures (27). Thus,

lactation is a natural model for neuroprotection because it effectively prevents acute and chronic cell damage of the hippocampus induced by excitotoxicity. Furthermore, it has been shown that PRLR affects energy balance and metabolic adaptation in rodents *via* effects on brown adipose tissue differentiation and function (28). In fact, recent findings show that circulating prolactin improves glucose homeostasis by increasing insulin action and secretion (29). It has been demonstrated that PRL loss resulted in learning and memory deficits in the PRL null mice, as indicated by significant deficits in the standard behavioural tests requiring input from the hippocampus (30).

Despite molecules like PRL have not been clearly associated to AD, it seems clear the presence of PRLR in several brain areas like cortex, hypothalamus and hippocampus, and identified in both astrocytes and glial cells (31). Then, changes downstream prolactin receptor involve key molecules related to fatty acid oxidation, mitochondrial biogenesis, inflammation and memory processes. Among them, we can point out the PPARγ coactivator-1α (PGC-1α) a molecular link between metabolic syndrome, Aβ generation and AD.

3.1. Energy metabolism and AD

Besides the role of adipokines *per se*, it has also been shown that alterations in energy metabolism also promote the development of AD. Mitochondrial structural and functional perturbations in AD have been recognized for some time, and led Swerdlow and Khan to propose the mitochondrial cascade hypothesis (32). This hypothesis proposes that inherited mutations in mtDNA determine the basal functional ability of mitochondria and their ability to respond to and recover from stress signalling. The histopathology of AD develops when the mitochondria loss their functions below a certain point, and includes neuronal apoptosis, β-amyloid deposition, and neurofibrillary tangles (33).

Mitochondrial biogenesis is the process by which cells generate new mitochondria and, if necessary, increase mitochondrial mass. PGC-1α is a member of a family of transcription co-activators that plays a central role in the regulation of cellular energy metabolism and stimulates mitochondrial biogenesis (34). PGC-1α participates in the regulation of both carbohydrate and lipid metabolism (35). Although the role of PGC-1α in peripheral disorders such as obesity and diabetes is well known, the role in neurons is currently a great interest because is a key regulator of energy metabolism (34). In addition, PGC-1α is also involved in the regulation of genes that protects neuronal cells from oxidative stress such as mitochondrial superoxide dismutase. Finally, PGC-1α coordinates mitochondrial biogenesis in at least some tissues such as muscle, heart, liver, and pancreas via co-activation of various transcription factors (33,34).

It has been recently shown that PGC-1α mRNA and protein levels are reduced in AD subject brains (36,37). As Selfridge and colleagues suggested (33), even if PGC-1α changes represent a consequence as opposed to cause of AD pathology, PGC-1α remains an attractive target for therapeutic intervention. Whether mitochondrial mass changes in AD, it is reasonable to postulate that increasing mitochondrial mass may alleviate bioenergetics-related stress in the AD brain.

PGC-1α is regulated by several metabolism-responsive elements like AMPK, which is activated by elevated AMP/ATP ratios. AMPK is a cellular energy sensor conserved in all eukaryotic cells. AMPK regulates the activities of a number of key metabolic enzymes through phosphorylation (38). It protects cells from stresses that cause ATP depletion by switching off ATP-consuming biosynthetic pathways. AMPK can phosphorylate and directly activate PGC-1α (39).

Furthermore, previous data suggest that AMPK, besides the important cellular functions such as cellular energy sensor, can also phosphorylate substrates like Tau protein and, thus, could favour its aggregation. Its phosphorylation makes it soluble and causes microtubule disassembly. In extreme situations as in AD, hyperphosphorylation of Tau leads to the formation of neurofibrillary tangles. It is well established that neurons are elongated cells. To maintain neuronal function they need efficient delivery of cellular organelles (such as mitochondria, endoplasmic reticulum, lysosomes, proteins, and lipids from soma to axons, dendrites and synapses. Hoover *et al*. (40) investigated the localization of abnormal Tau in dendritic spines using rTgP301L tau mice. They found that early Tau-related deficits develop not from the loss of synapses or neurons, but rather as a result of synaptic abnormalities caused by the accumulation of hyperphosphorylated Tau within intact dendritic spines.

PPARs are ligand-activated transcription factors of the nuclear receptors superfamily. The levels of PPARs have been reported to decline with age (41). PPARγ is highly expressed in adipose tissue and is a major regulator of insulin and glucose metabolism. PGC-1α is a PPAR transcriptional co-activator, and elevated levels of PGC1α change the composition of peroxisomes, so that they might exhibit decreased insulin degradation and purine metabolism. Then, it can be suggested that the link between energy metabolism and the amyloid cascade hypothesis can rely in the fact that PPARγ regulates the transcription of β-secretase (BACE1), a key enzyme involved in Aβ generation. In turn PGC-1α controls major metabolic functions through the co-activation of PPARγ and other transcription factors (42). In conclusion, since PGC-1α appears to decrease Aβ generation, therapeutic modulation of PGC-1α could have real potential as a treatment for AD.

3.2. Cholesterol, fatty acids and AD

Several strategies have proved to be effective in slowing down the pathological process or in improving the health status of the APP/PS1 mice (5) and, among them, can be pointed out the caloric restriction (43). From the 1930s it has been reported that caloric restriction (CR) mitigates neurological damage and, furthermore, rats submitted to CR live almost twice as long as non-restricted rats. Since that time, findings from a diverse range of species support the view that CR exerts beneficial effects on health and longevity, and is also able to reduce amyloid accumulation in middle-aged APP/PS1 mice. Then, excessive consumption of calories, particularly fat, opposes healthy brain aging though mechanisms that remain to be elucidated (43).

Hyperlipidemia, hypercholesterolemia, and obesity are all associated with increased accumulation of amyloid in AD and mouse models that form AD-type amyloid plaques. The brain is rich in cholesterol and substantial *in vitro* and animal evidence indicates that cholesterol levels in the brain affect the synthesis, clearance, and toxicity of Aβ (44). Then, elevated cerebral Aβ levels can be associated with cholesterol fractions in a pattern analogous to that found in coronary artery disease. In fact, a large amount of evidence suggests a pathogenic link between cholesterol homeostasis dysregulation and AD, where altered cholesterol metabolism and hypercholesterolemia appear to play fundamental roles in amyloid plaque formation and tau hyperphosphorylation (45). Experiments carried out with the use of low density lipoprotein receptor (LDLR)-deficient mice link hypercholesterolemia with cognitive dysfunction, potentially mediated by increased neuroinflammation and APP processing (46). Furthermore, it has been demonstrated, using an Aβ25-35-injected AD-like pathological mouse model, that hypercholesterolemia accelerated Aβ accumulation and tau pathology, which was accompanied by microglial activation and subsequent aggravation of memory impairment (47).

By contrast, it is unknown if a specific fatty-acid composition influences the development of AD, and published results are controversial. For instance, an study based on the Uppsala Longitudinal Study of Adult Men (ULSAM) cohort show that serum levels of saturated FAs were inversely associated with risk of AD, in sharp contrast to experimental studies (48). By contrast, research carried out in the APP/PS1 mice model show that AD increases susceptibility to body weight gain induced by short-term high-fat diet (HFD) feeding, and to the associated glucose intolerance and insulin resistance (49).

Nevertheless, protective effects of omega-3 fatty acids have been hypothesized (50-52). This can be supported on epidemiologic results and on the evidence that decreased levels of omega-3 fatty acids have been observed in brain tissue of people with AD, specifically in areas that mediate learning and memory. Thus, these observations reinforce an innovative approach that focuses on the protective action exerted by molecules naturally occurring in food and, at higher content, in dietary supplements (52,53).

Then, recognition of the correlation between AD and dyslipemia could be an important step forward for our understanding of AD pathogenesis and, possibly, for the development of new therapeutic strategies. However, the underlying mechanisms remain unknown.

3.3. Alzheimer's disease or "brain diabetes"

It has been described that obesity and diabetes significantly increase cognitive decline and AD risk, supporting the notion that molecular mechanisms of cellular energy homeostasis are linked to AD pathogenesis. Furthermore, biological plausibility for this relationship has been framed within the *metabolic cognitive syndrome* concept. Thus, several early biomarkers have been proposed and many of them rely on the definition of AD as a "Cognitive Metabolic Syndrome" or "Diabetes 3" (54). Then, AD would be a degenerative metabolic disease in which brain glucose uptake and utilization are impaired. Furthermore, a growing body of epidemiological evidence suggested that metabolic syndrome and its components (impaired glucose tolerance, abdominal or central obesity, hypertension, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol) may be important in the development of age-related cognitive decline, mild cognitive impairment, vascular dementia, and AD (55). In fact, results from hippocampal gene expression studies in normal mice, show several aging-dependent up-regulated processes and, among them, lipid catabolism, proteolysis, cholesterol transport, and myelinogenesis (56,57). Additionally, a consistent observation is that persons with AD, despite unchanged eating habits, begin to lose weight several years prior to the onset of clinical symptoms, suggesting the link between adipose tissue metabolism and AD (25,58,59).

Epidemiological, clinical, and basic studies have shown a relationship between AD and Type 2 Diabetes Mellitus (T2DM), and that the main physiological link between both conditions is peripheral and central insulin signalling impairment (60). T2DM triggers a condition of "diabetic encephalopathy" characterized by electrophysiological, structural and neurochemical changes leading to cognitive impairments (61). In fact, results from the so called "Hisayama Study" indicate that altered expression of genes related to diabetes mellitus in AD brains is a result of AD pathology, which may thereby be exacerbated by peripheral insulin resistance or diabetes mellitus (62). These cognitive deficits associated to T2DM have been argued to be due in large part to an impaired central insulin modulation in

the hippocampus, which is a critical region for memory processing (63). In fact, adults with newly diagnosed pre-diabetes or T2DM show insulin resistance associated with reductions in regional cerebral glucose metabolism and subtle cognitive impairments (64). Interestingly, the insulin signalling overlaps with pathways that regulate both synaptic plasticity and memory processes (63). Therefore, insulin has effects on memory storage and synaptic physiology (65,66).

Published results indicate that there is a close link between insulin deficient diabetes and cerebral amyloidosis in the pathogenesis of AD (67,70). Despite the active research on this field in recent years, the molecular mechanisms involved in the pathophysiology observed in both diseases remain unclear. It has been shown that β-amyloid peptide and phosphorylated tau accumulation also occur in T2DM rat models that exhibit neurite degeneration and neuronal loss (71). These changes appear to be associated with insulin resistance and hypercholesterolemia, and emphasize the role of energy metabolism control in the etiopathology of the AD. Results from Chua and colleagues have demonstrated an alteration in brain insulin proteins in APP/PS1 females, and the alteration of this pathway is responsible of the increase in brain β42 level in APP/PS1 mice (72). Thus, authors suggest that the brain insulin signalling impairment is involved in the amyloid accumulation in female APP/PS1 mice. Sadowski and colleagues demonstrated a correlation between the hippocampal levels of amyloid plaques and glucose utilization at 22 months of age (73).

It has been suggested from human brain imaging studies that impaired glucose utilization in AD precedes the onset of cognitive deficits and, thus, it will be the cause of AD. Therefore, brain glucose metabolism defects are strongly associated with memory impairment in AD brain. In agreement with that, early markers related to insulin function, like circulating insulin-like growth factor I (IGF-I) have been recently proposed (18). Furthermore, it has been shown that insulin tolerance tests revealed significant hyperglycaemia in mice overexpressing mutant amyloid precursor protein and presenilin-1 (APdE9), either by cross-breeding them with pancreatic insulin like growth factor 2 (IGF-2) overexpressing mice, or by feeding them with high-fat diet (74). In fact, it has been shown that local and systemic levels of IGF1 are altered in such CNS diseases as Alzheimer. IGF1 has emerged as a crucial factor in the CNS; it is involved in normal cognitive function and successful aging, in addition to development. In this context, insulin binds to the insulin receptor and insulin receptor substrates 1 and 2 (IRS-1 and IRS-2), and is involved in the modulation of hippocampal synaptic plasticity and memory consolidation (75).

Then, it can be concluded that the association between obesity and altered signalling mechanisms of insulin implies a greater susceptibility to neurodegenerative processes.

3.4. The "missing link" between T2DM and AD

Several studies have shown that AD and T2DM may share another common pathways to pathology, both kinases involved in Tau phosphorylation and microtubule stability: the mammalian target of rapamycin (mTOR) and the cyclin dependent kinase 5 (Cdk5). The kinase mTOR plays a key role in maintaining energy homeostasis in the brain and other tissue types (76,77). As an energy sensor, mTOR regulates numerous cellular pathways including protein translation, cell growth and proliferation. In fact, mTor mediates the synthesis and aggregation of Tau, resulting in compromised microtubule stability (78). Furthermore, the authors describe that changes of mTOR activity cause fluctuation of the level of a battery of Tau kinases such as protein kinase A, v-Akt murine thymoma viral oncogene homolog-1, glycogen synthase kinase 3β, cyclin-dependent kinase 5, and Tau protein phosphatase 2A. In addition, compelling evidence indicated that the sequential molecular events such as the synthesis and phosphorylation of Tau can be regulated through p70 S6 kinase, the well characterized immediate downstream target of mTOR. A common pattern observed in both post-mortem AD brains and drug-oriented *in vitro* and *in vivo* models, is an aberrant accumulation of mTOR. Recently, rapamycin has been shown to be neuroprotective in models for Alzheimer's disease in an autophagy-dependent manner. Caccamo and colleagues (79) and Spilman and colleagues (80) showed that rapamycin rescued cognitive deficits by suppressing extracellular Aβ deposition and intracellular Tau accumulation (81). In fact, treatment with rapamycin has proved to reduce Aβ42 levels and to improve cognitive function through inhibition of mTOR signalling in two independent mouse models of AD (77,79,80). Finally, it has been shown that rapamycin exerts neuroprotection via a novel mechanism that involves presynaptic activation (82) and rapamycin-treated hippocampal neurons are resistant to the synaptotoxic effect induced by Aβ oligomers, suggesting that enhancers of presynaptic activity can be therapeutic agents for Alzheimer's disease.

It has been proposed that mTOR modulate insulin signalling in times of high nutrient exposure. mTOR directly phosphorylates the insulin receptor leading to its internalization; this, in turn, results in a decrease of mTOR signalling (83, 77). However, through the same mechanisms, chronic mTOR hyperactivity leads to insulin resistance, a key feature of T2DM (84). Then, as Orr and colleagues propose (77), since mTOR hyperactivity is common to both diabetes and AD, mTOR signalling could be considered a molecular link between these two age-related diseases.

In addition to mTOR, the hyper-activation of Cdk5/p25 can be related to AD and T2DM (85). Cdk5

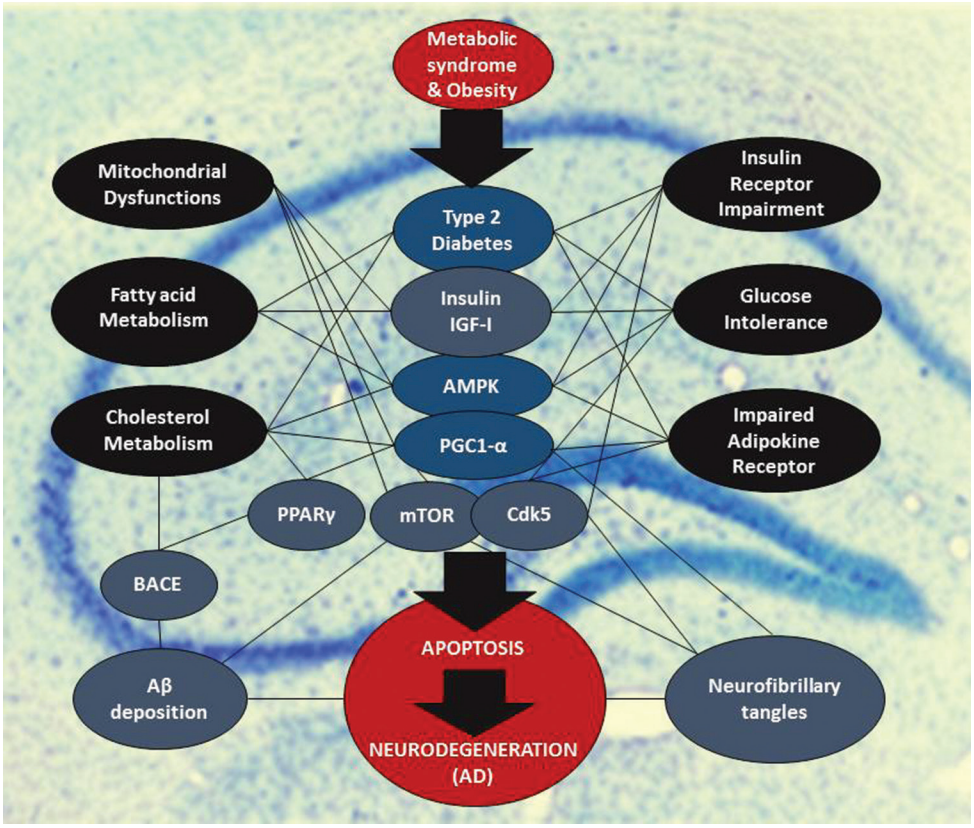

Figure 1. The image shows a complex grid of interactions resulting from the correlations that can be found among metabolic processes and key molecules involved in AD. Results from animal models of AD, like APPswe/PS1dE9, show early down-regulation of glucose and insulin signalling pathways and energy metabolism. The observed changes are complex and are related to insulin and adipokine receptors signalling impairment, all along with alterations in cholesterol and fatty acids metabolism. All together cause changes that affect the activity of key molecules like AMPK and PGC-1α, involved in mitochondrial biogenesis, PPAR and BACE activity regulation and Aβ deposition. Since Tau expression is regulated by insulin/IGF-I, and by AMPK, changes in neurofibrillary tangles can be related to energy impairment. Finally, an increased activity of mTOR, Cdk5 and p35 could be responsible of increased Tau phosphorylation and neurofibrillary tangles formation.

is an atypical cyclin-dependent kinase localized in the brain, and its activity is dependent upon binding to p35/p39. In addition, while cdk5 has important physiological functions related to brain development, the breakdown of cdk5/p35 into cdk5/p25 increases its kinase activity and neurotoxicity. Interestingly, in recent years increased cdk5/p25 expression has been demonstrated in the brains of patients with Alzheimer's and Parkinson's diseases. Experimental studies performed in neuronal cell cultures indicate that cdk5/p25 plays a prominent role in apoptosis. In fact, The Cdk5-p25 forms a more stable and hyperactive complex, causing aberrant phosphorylation of cytoskeletal components like Tau and neurofilaments, and induces cell death. It has been shown that cells treated with high glucose concentrations exhibit an induction of p25, the p35-derived truncated fragment which hyper activates Cdk5 in neurons. Cdk5/p35 has been implicated in cytoskeletal protein phosphorylation in normal brain and in many human neurodegenerative disorders (86). Significant increases in Cdk5 activity and the localization of Cdk5 in neurodegenerative lesions have been demonstrated in several diseases, including AD (87). Studies illustrate that p35 regulates the subcellular distribution of Cdk5 and cytoskeletal proteins in neurons and that Cdk5 has a hierarchical role in regulating the phosphorylation and function of cytoskeletal proteins. All these data supports the hypothesis that cdk5/p25 acts as a master regulator of neuronal cell death. In addition, cdk5/p25 might also interact with other pathways such as GSK-3β and c-JUN kinase.

Recent studies have identified P5, a truncated 24-aa peptide derived from the Cdk5 activator p35, later modified as TFP5, so as to penetrate the blood-brain barrier after intraperitoneal injections in AD model mice (84). Since this treatment inhibited abnormal Cdk5 hyperactivity and significantly rescued AD pathology in these mice, the authors suggest that TFP5 peptide may be a novel candidate for type 2 diabetes therapy.

4. CONCLUDING REMARKS

In summary, the reviewed results show early down-regulation of glucose and insulin signalling pathways

and energy metabolism in an APPswe/PS1dE9 model of Alzheimer disease (Figure 1). These changes affect the activity of key molecules like AMPK and PGC-1α, involved in mitochondrial biogenesis. It reinforces the hypothesis that the preceding events in the amyloidogenesis are related with both insulin signalling and energy metabolism impairment. Then, initial hypothesis of insoluble Aβ fibrils as main responsible of AD is currently changing because Aβ soluble oligomers truly may be the responsible of a synapse failure, neuronal dysfunction and also cognitive deficits. Likewise, experimental data in APP transgenic animal models reinforce this hypothesis because it was demonstrated that cognitive impairment in AD occurs early before amyloid plaque deposition. Since Tau expression is regulated by insulin/IGF-I, and by AMPK, changes in neurofibrillary tangles can be related to energy impairment. Finally, an increased activity of mTOR, Cdk5 and p35 could be responsible of increased Tau phosphorylation and neurofibrillary tangles formation in the APP/PS1 mice model.

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Abbreviations: AD: Alzheimer's disease; APP/PS1: APPSwe/PS1dE9 mice; SAD: Alzheimer's sporadic form; Aβ: β-amyloid; APP: Aβ protein precursor; Ach: acetylcholinesterase; PRL: Pituitary-derived prolactin; ob: obese gene; Lep: leptin; PRLR: prolactin receptor; PGC-1α: PPARγ coactivator-1α; BACE1: β-secretase; CR: caloric restriction; LDLR: low density lipoprotein receptor; ULSAM: Uppsala Longitudinal Study of Adult Men; HFD: short-term high-fat diet; T2DM: Type 2 Diabetes Mellitus; APdE9: overexpressing mutant amyloid precursor protein and presenilin-1 mice; IGF-2: insulin like growth factor 2; IRS-1/2: insulin receptor substrates 1 and 2; mTOR: mammalian target of rapamycin; Cdk5: cyclin dependent kinase 5

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