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REVIEW ARTICLE

Systemic and Brain Metabolic Dysfunction as a New Paradigm for Approaching Alzheimer's Dementia*

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Abstract Since its definition Alzheimer's disease has been at the centre of consideration for neurologists, psychiatrists, and pathologists. With John P. Blass it has been disclosed a different approach Alzheimer's disease neurodegeneration understanding not only by the means of neurochemistry but also biochemistry opening new scenarios in the direction of a metabolic system degeneration. Nowadays, the understanding of the role of cholesterol, insulin, and adipokines among the others in Alzheimer's disease etiopathogenesis is clarifying approaches valuable not only in preventing the disease but also for its therapy.

Keywords Alzheimer's disease · Cholesterol · Insulin · Leptin · Ghrelin · Adiponectin

History

Frau Auguste D was 51-years old, when on 25th November 1901 was admitted to the Municipal Mental Asylum in Frankfurt-am-Main, where, at that moment, Alois Alzheimer covered the position of senior physician. By the time Frau Auguste passed away, four years later, Dr Alzheimer was a co-worker to Dr Emil Kraepelin at the Anatomical Laboratory of the Royal Psychiatric Clinic, Munich University, where Frau Auguste D's brain was sent for Alzheimer to perform the necroscopic exam, which he did on 8th April.

At the meeting of the South-West German Society of Alienists in Tűbingen, on the 3rd and 4th November 1906 Alois Alzheimer presented Frau Auguste D's clinic-pathologic case; which subsequently published, on 1907, in the journal Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin.

''A woman, 51-years old, showed (...) increasing loss of memory (...) she would think that someone wanted to kill her (...). Periodically she was totally delirious, and seemed to have auditory hallucinations. (...) The generalised dementia progressed (...) After 4 years of the disease death occurred.''

At necroscopy Alzheimer found that brain was atrophic with atherosclerotic large vessels, and ''peculiar changes of the neurofibrils (...) (*were*) clustering together in thick bundles which emerge (*d*) at the surface of the cell and miliary foci distinguishable by the deposit in the cerebral cortex of a peculiar substance (...) very refractory to staining'' [1, 2]. The later so called neurofibrillary tangles and amyloid plaques, respectively. A year later, a second case was described by Francesco Bonfiglio (1883–1966), and two years later, Gaetano Perusini (1879–1915), published four cases: including the above two. Alzheimer, Bonfiglio, and Perusini did not realize yet they were facing a new disease, they thought of an unusual variant of senile dementia. It was Emil Kraepelin firstly to introduce the term Alzheimer's disease, in the 8th edition of his textbook Compendium der Psychiatrie (1910) [2]. Until our days what has been mostly striking is that the certain diagnosis of Alzheimer's disease

* Special issue dedicated to John P. Blass.

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could not have been made but post-mortem by the clinic-pathologic corollary reported in the Kraepelin's Compendium der Psychiatrie referring mostly to Frau Auguste D's Alzheimer's case description; diagnosis depending on medical history, physical and neurological examinations, psychological testing, laboratory tests, brain imaging studies, and, possibly, brain tissue examination usually obtained at autopsy: namely too late!

Alzheimer's disease is a frightening and shocking progressive neurodegenerative disorder clinically characterized by loss of memory and deficits in other cognitive domains and intellectual functions steadily developing [3], with the neurotransmitters which permit cells to be in touch with one another, including acetylcholine, somatostatin, monoamine and glutamate, lowered down. Such a scenario, characterized by damage to the neural networks critical for attention, memory, learning and higher cognitive abilities, possibly underlies the devastating symptomatology. Therefore, alterations in behaviour, such as apathy, agitation, and psychosis, are also fundamental characteristics [4]. Memory loss (amnesia), the most remarkable early symptom, usually introduces itself as minor forgetfulness, and then it becomes steadily more pronounced as the illness progresses; while possibly older memories keep on relatively preserved. As the disorder goes further, cognitive (intellectual) impairment extends to the domains of language (aphasia), coordinated movement (apraxia), recognition (agnosia) and to those functions (such as decision-making and planning) closely related to the frontal lobe of the brain, reflecting extension of the underlying pathological process. Neuronal loss, together with deposition of beta-amyloid plaques, in the spaces around synapses (*neuritic plaques*) [5], and abnormal accumulation of tau protein modified form in the cell bodies of neurons (*neurofibrillary tangles*) [3, 6] are the main features of the pathological process.

Many efforts have been made in the evaluation of the above stigmata by autopsy and the searching for a correlation with quantitative measures of dementia by the means of scales, such as the Blessed Dementia Scale [7–9]. Moreover, other scales have been used to quantify cognitive impairment, like the Mini Mental State Examination (MMSE) [10, 11], which have been used also to relate the cerebral ventricular size and the cerebrospinal fluid acetylcholinesterase levels with the degree of Alzheimer's dementia disease [12]; or, also, the Assessment Scale for Cognition (ADAS-Cog) scores [13].

Disease mechanism(s)

Many efforts have been made in the understanding Alzheimer's disease causes and mechanism(s). From time by time a mechanistic *primum movens* have been evoked for Alzheimer's disease pathogenesis. It was 1965 when two different research groups have described experimentally induced Alzheimer's disease like lesions in rabbit brains by aluminium exposure [14, 15]. Afterwards, it has been established that excessive cortical intranuclear aluminium content is present in Alzheimer's disease patients, possibly relating to neurofibrillary degeneration [16–18]. Although the above observations arose into postulating aluminium neurotoxicity by induced immune-reactivity as etiologic issue in Alzheimer's disease, such a mechanism has remained unconfirmed and therapies with chelating agents have been not advisable [19]. Another of the oldest hypotheses to elucidate the mechanism(s) underlying Alzheimer's disease has been the ''cholinergic'' [20]. It is very well acknowledged the cholinergic neurotransmitter system quite critical role for the higher brain activities, such as the cognitive one [21]; besides, cholinergic neurons within the nucleus basalis of Meynert result nearly completely destroyed in Alzheimer's disease [22]; therefore, subsequently many investigators have postulated the cholinergic dysfunction as the primary/direct memory decline causative in Alzheimer's disease. Unfortunately, the first-generation Alzheimer's therapeutic approaches based on the above hypothesis using mostly acetylcholinesterases inhibitors, have not led to a cure, but only to the transitory symptomatic palliative treatment [23] being cognitive enhancers still a provocative and vague label for drugs used to treat demented of the Alzheimer type [24], and the cholinergic network not the only one to be injured (see above). Two other hypotheses, more exquisitely interrelated with an ''inflammatory'' context, quite often have been alternatively described as the ''baptist'' and ''tauist'' viewpoints by Alzheimer's disease dedicated scientific publications; stringently relating the beta-amyloid [5], and/or the tau proteins [25, 26] atypical physiopathology to the full disease cascade, respectively. Also Alpha synuclein, the protein involved in Parkinson's disease, has been connected with amyloid plaques in Alzheimer's disease [27]. Finally, pathological interactions among these three candidate proteins have been evoked [28, 29].

As a matter of fact, not all people who have pathologic classical Alzheimer's disease stigmata, such as plaques and/or tangles, are clinically manifesting disease symptoms; being synapses loss much better

related with the cognition decline than the mere presence of plaques and tangles [30, 31].

A great attention deal there have been regarding 'oxygen radicals', produced in an oxidative stress contest, as neurotoxic mediators processes behind Alzheimer's and other neurodegenerative diseases stigmata [32–35], leading to the key role of anti-oxidants such as of vitamin E (tocopherol) in the nervous system and their possible use in treating the above diseases [36]. Thus, several studies have been performed in search of altered vitamin E concentrations in cortex [37, 38], in plasma [39], and also in cerebrospinal fluid of patients with Alzheimer's disease [40, 41]. To date, disagreeing data do not sustain convincing vitamin E therapeutic effects on Alzheimer's disease progression by itself. For example, the Alzheimer's Disease Cooperative Study [42] showed that treatment with vitamin E could be helpful for a delay in the disease progression timing in moderately severe Alzheimer's disease patients; while in another clinical study the results did not go in the same direction [43]. Discouraging results have been obtained also in clinical trials with Vitamin C (for which almost same antioxidant principles could apply) and/or vitamin E [44]. Although another attractive hypothesis to be mentioned is the ''cobalaminergic'' [45] elaborated by the low CSF and serum vitamin B12 levels evidences in Alzheimer's patients [46, 47], vitamin B12 is biochemically, and nutritionally intimately related to folic acid [19], for which a specific chapter should be held. In fact, folates are essential for central nervous system development, and insufficient folate activity at the moment of conception and during early pregnancy can result in congenital neural tube defects. In adult life folate deficiency is often related to megaloblastic anaemia and, possibly, to high blood levels of homocysteine. Notably, elevated homocysteine blood levels, accompanied by low folate intake, have been linked with high arterial disease risk, but also with increased dementia and Alzheimer's disease risks [48]. In fact, in Alzheimer's disease experimental animal models folic acid deficiency homocysteine impairs DNA repair in hippocampal neurons and sensitize them to amyloid toxicity [49]. Furthermore, an Alzheimer's dementia pathogenesis hypothesis has been related to the defective DNA repair ability in Alzheimer's tissue cells, with consequential DNA damage, and cell functionality breakdown until death. Being cobalamin and folate dependently linked in a DNA and S-adenosylmethionine synthesis key position, cobalamin/folate deficiency (often featuring in Alzheimer's disclosed disease) would result in a concomitant slow down DNA and S-adenosylmethionine synthesis, possible common pathogenesis hallmarks for Alzheimer's disease, Down syndrome, and AIDS-related dementia [50].

In the stream of the redox failure, and, more in general, abnormalities in energy metabolism [51, 52], interest goes to the characterization of the mitochondrial injury [53], to the reduction of the key enzymes alpha-ketoglutarate dehydrogenase complex [54, 55], and carnitine acetyltransferase impairment [56], all leading to the clinical studies testing the therapeutic effects of acetyl-L-carnitine, which exerts also a cholinomimetic activity [57–64]. Noteworthy, it is remarkable to underline that, in Alzheimer's disease patients who carry Apolipoprotein(Apo)E4 allele of APOE gene, the clinical Dementia Rating (CDR) score correlates better with alpha-ketoglutarate dehydrogenase enzyme complex activity than with densities of neuritic plaques or neuritic tangles; however, in patients without ApoE4, the CDR correlated better with densities of neuritic plaques or neuritic tangles than with alpha-ketoglutarate dehydrogenase enzyme complex activity [65]. This suggests that mitochondrial dysfunctions may be more important for the development of Alzheimer's disease in patients who carry ApoE4 allele than in those who do not. ApoE, present in three common polymorphisms in the population: epsilon 2, epsilon 3, and epsilon 4, is a low density lipoprotein (LDL) associated lipoprotein involved in the plasmatic cholesterol transport and in the recognition by the LDL receptor; function which exerts also centrally where is involved in the brain cholesterol transport, has acquired very high importance for neurologists in 1993 when the association of the ApoE4 allele with familial and sporadic late-onset Alzheimer disease was reported [66–68]. ApoE involvement in Alzheimer's disease is strongly related to cholesterol involvement into the physiopathology of the process beginning from the observation that levels of high-density lipoprotein cholesterol are significantly lower in multi-infarct dementia than in Alzheimer's disease [69].

Cholesterol and ApoE

Cholesterol and apoE complex interplays are receiving greatest attention in Alzheimer's disease involvement, as already extensively described elsewhere in reason of many experimental and clinical supporting data [70, 71]. Cholesterol in the brain is almost totally synthesized *in loco* [72]; it covers more than two percent of brain weight, and it covers about 25% of the total cholesterol body amount [73, 74]. The majority of cholesterol in central nervous system is unesterified

and resides in two different pools: the myelin sheaths, and the plasma membranes of astrocytes and neurons. Brain cholesterol synthesis is very high during fetal development and declines in adult life being central cholesterol recycling quite efficient. In fact, in central nervous system cholesterol half-life could be as long as 5 years. But, still some excretion for central cholesterol steady state might be required. Thus, cholesterol exits the brain through the blood–brain barrier carried by ApoE or more properly by conversion into the polar oxisterol derivative 24(S)-hydroxycholesterol, also called cerebrosterol [75–77] to underline the fact that it is produced almost exclusively in the brain. 24(S)-hydroxycholesterol release into circulation reflects central cholesterol turnover with inverse age-dependent manner [78], then it could be considered a non-invasive marker for monitoring brain deregulated cholesterol turnover [79]. Not surprisingly, plasma (24(S)-hydroxycholesterol is very high in individuals with Alzheimer's disease, as a consequence of the dramatic increased brain cholesterol turnover [80]. Remarkably, 24S-hydroxycholesterol induces inflammatory gene expression in primary human neural cells [81]; and, also it shows an in vitro neurotoxic profile [82]. Inversely, the other oxysterol 27-hydroxycholesterol mostly produced in non-brain tissues, such as the liver, might cross the blood–brain barrier in the opposite direction towards the brain where accumulate in Alzheimer's disease patients [83].

The lipoproteins present in the cerebrospinal fluid, mostly represented by apoE [84, 85] function in brain cholesterol redistribution from producing cells, such as astrocytes, oligodendrocytes, and microglia to different cellular and subcellular sites of neurons [86] in the need of membrane remodelling during regeneration of neurites, axons, and synapses. ApoE is crucial for synaptic integrity by supplying cholesterol, stabilizing neural cytoskeleton, regulating intracellular calcium. ApoE is also a beta-amyloid scavenger by regulating extracellular beta-amyloid concentration through apoE receptor internalization to lysosomes. Increased neuronal cholesterol requirement for membrane regeneration induces glial apoE increased expression and secretion [87]. One of the 3 human isoforms of apoE, apoE4, is a very well documented risk factor for late-onset Alzheimer's disease possibly because of the lower affinity for the apoE receptor with reduction of the beta-amyloid scavenging whit consequent increased beta-amyloid lipid peroxidation. Moreover, compared to ApoE3 ApoE4 is less expressed during increased brain cholesterol requirement affecting neurites, axons, and synapses regeneration until neural degeneration [71].

Beta-amyloid extracellular plaques formation occur preferentially in the cholesterol-rich regions of membranes known as lipid rafts, and cholesterol level changes might alter the distribution of beta-amyloid precursor cleaving enzymes within the membrane such as the integral membrane proteases (secretases) [88].

Interactions between insulin and cholesterol

Rafts may be involved in the aggregation of beta-amyloid and also in its clearance by amyloid-degrading enzymes such as plasmin, neprilysin [89]; and insulin-degrading enzyme [88]. Not surprisingly, clinical and epidemiological studies have found that type 2 diabetes, and hyperinsulinaemia, increase the risk of developing Alzheimer's disease in the elderly. One of the links between hyperinsulinaemia and Alzheimer's disease may be, among the others, insulin-degrading enzyme. Insulin-degrading enzyme degrades both insulin and amylin, peptides related to the pathology of type 2 diabetes, along with beta-amyloid. The current evidences suggest that hyperinsulinaemia may elevate beta-amyloid through insulin's competition with beta-amyloid for insulin-degrading enzyme [88]. Genetic studies have also shown that insulin-degrading enzyme gene variations are associated with the clinical symptoms of Alzheimer's disease as well as the risk of type 2 diabetes [88]. The deficiency of insulin-degrading enzyme can be caused by genetic variation or by the diversion of insulin-degrading enzyme from the metabolism of beta-amyloid to the metabolism of insulin [88]. It is intriguing to notice that both hyperinsulinaemia and insulin-degrading enzyme gene variations are related to the risk of Alzheimer's disease when the Apolipoprotein E4 allele, the major risk factor of late-onset Alzheimer's disease, is not present [70].

It is very important to keep in mind that insulin exerts a strong activity on 3-hydroxy-3-methylglutaryl-CoA reductase [90], the 3-hydroxy-3-methylglutaryl-CoA into mevalonate converting enzyme in the rate-limiting step in cholesterol biosynthesis. Interestingly, 3-hydroxy-3-methylglutaryl-CoA reductase cholesterol-lowering drugs (statins) that are 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors also act to stabilize and promote increased transcription and translation. Cholesterol is a feedback inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase and also reduces expression of the enzyme. Another important strong relationship between cholesterol and insulin is evident in type 2 diabetes, and more in general in insulin-resistance,

where there is high synthesis of cholesterol with very low absorption [91, 92]. Insulin also down-regulates the expression of enzymes (cholesterol 7a-hydroxylase and sterol 27-hydroxylase) involved in the catabolism of cholesterol in oxysterols, which together with insulin are required for expression of sterol-regulatory-element-binding proteins [93]. Noteworthy, in Alzheimer's disease patients are present altered levels of plasma oxysterols [82]. The sterol-regulatory-element-binding proteins modulate insulin's ability to express genes involved in cholesterol and triacylglycerol synthesis. Finally, copper-oxidized LDL inhibits insulin-dependent phosphorylation of the signalling kinases ERK (extracellular-signal-regulated kinase) and PKB/Akt, suggesting that oxysterols may be involved in insulin resistance. For more specific details see ref [70].

Insulin functions in brain regions involved in cognition, and insulin dysfunction in these areas can result in memory loss and even Alzheimer's disease [70, 94, 95]. In CNS there is high expression of insulin receptors mostly localized to synapses. The expression of insulin receptors, increased in postmortem brain tissues from patients with sporadic Alzheimer's disease, shows a significant reduction in the kinase activity, suggesting an insulin signalling dysfunction in Alzheimer's disease [96]. Consistent with this, a severe reduction in cerebral glucose utilization is found in late-onset sporadic Alzheimer's disease, although their glucose supply to the brain is normal [97]. Also, it has been shown that the increase in blood insulin, not glucose level, significantly improves memory in Alzheimer's disease, suggesting that insulin has a glucose-independent mechanism of regulating cognition [98]. Moreover, insulin and insulin-like growth factor I (IGF-I) (see below) are involved in tau phosphorylation. Old insulin receptor substrate 2 knockout mice show in the hippocampus neurofibrillary tangles deposits containing phosphorylated tau [98]. Insulin is a strong negative modulator of intracellular accumulation of beta-amyloid by accelerating beta-amyloid precursor protein/beta-amyloid transfer from Golgi to plasma membrane. Insulin degrading enzyme, the extracellular protease involved in insulin, IGF-I, and IGF-II degradation, as described above, is also involved in beta-amyloid cleavage. Not surprisingly, insulin degrading enzyme transgenic neuronal overexpressing mice present reduced brain beta-amyloid levels, and retarded or completely absent amyloid plaque formation; while, mice with insulin degrading enzyme deficit show increased cerebral accumulation of endogenous beta-amyloid [98].

Thus, insulin dysregulation may strongly contribute to Alzheimer's disease pathology by several mechanisms, from reduced brain glucose utilization, to neurofibrillary tangle formation, and increased beta-amyloid aggregation by insulin degrading enzyme inhibition. Insulin effects on neuronal cognition and memory could act at several levels by regulating ion channels, neurotransmitter receptors and synaptic transmission. Being the memory improvement insulin-mediated very fast (~30 min), it is quite possible an insulin receptor-mediated signal on substrates directly involved in synaptic transmission and plasticity, rather than targets that take much longer time to modify (e.g. beta-amyloid clearance) [98].

Given the above insulin activities, it is still very important to keep in mind that insulin, besides regulating glucose metabolism, stimulates lipogenesis, diminishes lipolysis, increases amino acid transport into cells, modulates transcription and stimulates growth, DNA synthesis and cell replication. Thus, distinguishing between insulin's effects on glucose levels and insulin's possible role as a neurohormone might be difficult, because changes in peripheral insulin produce a variety of effects unrelated to memory. For example, animals with streptozotocin-induced diabetes have impaired memory and insulin-enhancing therapeutic agents enhance memory [70].

Given relationship between non-insulin diabetes type 2 and Alzheimer's disease [99], glucose itself has been shown to be toxic in several cell types such as endothelial [100], cardiomyocytes [101]; but also in critically ill patients with mortal effects [102]. It is already very well described 'toxic' effects of hyperglycaemia and the brain diabetic end-organ damage [99]. In fact, hyperglycaemic rodents, not only express cognitive impairments but also functional and structural alterations in the brain [103]. High glucose levels might exert toxic effects by an enhanced glucose flux through the polyol and hexosamine pathways, disturbances of intracellular second messenger pathways, an imbalance in the generation and scavenging of reactive oxygen species, and by advanced glycation of important structural and functional proteins. It is important also to underline how high glucose levels, as discussed above, might inhibit cholesterol intestinal absorbance, and increase cholesterol biosynthesis, peripherally [91, 92], and, possibly, centrally (brain).

Insulin and IGF-1

Emerging evidences underline the relationship between insulin and IGF-1 on important functions in the brain, such as on metabolic, neurotrophic, neuromodulatory and neuroendocrine activities. Also IGF-1,

like insulin (see above), is present in brain by active transport through the blood–brain barrier and possibly by locally production in the brain. Insulin and IGF-1 share a high degree of structural and functional homology and both bind to, and activate the receptor of the other, thus sharing several physiological functions [104]. The insulin–IGF-1 pathway in Alzheimer's disease shows perturbations overlapping with those above descript for insulin itself [94, 104], with IGF-1 also involved in the metabolism and clearance of beta-amyloid. Serum IGF-1 levels strictly relate with cerebral levels of beta-amyloid in animals: in old rats injected with IGF-1 beta-amyloid levels are decreased in the brain. While, in IGF-1 defective mice is present an increase in beta-amyloid cerebral levels. IGF-1 and insulin might also influence the development of neurofibrillary tangles by regulating the phosphorylation of tau as described elsewhere [104].

Metabolic system degeneration

Given all the above, when considering the involvement of single metabolic dysfunction and/or factor in Alzheimer's dementia, many other metabolic pathways and factors should require to be taken into account for simultaneous/contemporaneous scientific investigations. Consequently, we might assist to the contours disclosure of predominant systemic metabolic dysfunctional representations in which Alzheimer's disease is meant to play the tragic and horrifying leading role [105], contextualized to the above mentioned factors (plus many others) which participate and contribute in a (in)decorous way. Such an approach has been very useful in making an allowance for looking at Alzheimer's disease as late-onset system degeneration, involving certain populations of cholinergic neurons but also many other cell populations. Thus, John P. Blass have been the enthusiastic protagonist, promoter, and catalyser of an outstanding scientific journey, spending most of his energies in searching, identifying and characterizing peripheral (nonneural) markers [106, 107] meant to be helpful for testing pathophysiological hypotheses and for the diagnosis of Alzheimer's disease [108]. Accordingly, he has contributed, among others, to describe the reduced pyruvate dehydrogenase complex activity in Alzheimer brain and eventually in periferic fibroblasts [109, 110]; fibroblasts altered calcium uptake [111], changed metabolic properties [112], affected glucose metabolism [113], replicative life span [114], phosphofructokinase activity [115] compared to brain [116], expression of ''Alzheimer antigens'' [117], abnormality of the alpha-ketoglutarate dehydrogenase complex [118], altered oxidation and signal transduction systems [119]; red blood cell abnormalities [120], choline uptake [121]; the diminished mitogen-induced calcium uptake by lymphocytes [122]; the impairment of the mitochondrial function [123]; the reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues [124]; transketolase abnormality [125]; brain carnitine, carnitine acetyltransferase, and glutathione [56], in Alzheimer's disease patients; enriching the complex chapter of the metabolic alterations common to neural and non-neural cells in Alzheimer's disease [126].

Multifactoriality and complexity

Alzheimer disease, like most chronic diseases, is probably best considered in a life course framework, with a journey started at patient's conception and early foetal life. The epidemiological, preclinical, and clinical studies conducted over the past several decades strongly suggest that what lies beneath the disease, usually flaming much later in life [127], is a very slow chronic process involving risk factor constellations with neuropathologic alterations starting many decades before, at the lighting of the patient's life [128, 129], in the stream of the thrifty phenotype hypothesis which claim the activation during the ontogenesis of adaptive mechanisms preventively activated in prevision of altered nutritional environment signalled by altered maternal nutrition [130]. For example, some risk factors such as genes inheritance and/or nutritional deprivation/excess altering brain formation and growth may have their major effects in early life; others related to socioeconomic status, such as smoking, malnutrition, and obesity in childhood, as well as in adulthood, may set the stage for later adulthood influences such as insulin resistance, obesity, hyperlipidemia, hypertension, diabetes, metabolic syndrome, cardiovascular, and cerebrovascular disease, all related to Alzheimer's disease's increased incidence [128–132].

Metabolic syndrome

The metabolic syndrome is characterized by clustering risk factors for cardiovascular diseases, but also for Alzheimer's disease. Non insulin diabetes type 2 [99], hyperinsulinemia [133, 134], insulin resistance [135], atherosclerosis [136], inflammation, and inflammatory cytokines [137] have been identified as independent predictors of cerebrovascular disease, ischaemic stroke and accelerated cognitive decline and dementia, which,

if combined, inside metabolic syndrome, might powerfully reinforce these effects [99]. Given the clustering of hyperinsulinemia, insulin resistance, hypertension, dyslipidaemia, hyperglicemia in metabolic syndrome the effort to determine which factor might be the *primum movens* in the development of Alzheimer's disease cognitive dysfunction is becoming an empty exercise. Moreover, new evidences relate other factors, which are disrupted in the metabolic syndrome, with the cognitive impairment and Alzheimer's disease development: leptin, adiponectin, and ghrelin.

Leptin

Adipose tissue secretes a variety of proteins with important roles in metabolism, reproduction, immunity and cardiovascular function. The endocrine function of adipose tissue, especially that exerted through leptin, could be simplistically linked to adaptive metabolic mechanisms to energy availability, leading to storage or mobilization of fat, in relationship to food intake and fasting energy storage providing insights into obesity and other diseases associated with energy imbalance [138, 139]. It is very important to underline the discovering of very well documented activities of leptin in the brain, with particular emphasis on transport across the blood–brain barrier, signal transduction, neuropeptide targets and roles during fasting and obesity [140]. In fact, leptin is released into the blood stream and circulates to the brain crossing the blood–brain barrier; to act through the leptin receptors (ObR), which is widely expressed in the central nervous system as multiple forms [141]. Leptin primarily acts on the hypothalamus arcuate nucleus neurons, but also hippocampal and peripheral neurons [142]. Very recent data disclose also the leptin involvement in memory function by synapses inducing mechanisms [143]. The CA1 hippocampal region of Zucker and db/db mice, neither of which expresses functional leptin receptors, shows impairments of long-term potentiation and long-term depression [144]. These mice present also impaired spatial memory further supporting an involvement of leptin and/or its receptor in Alzheimer's disease. Spatial memory consolidation requires ERK activity in entorhinal cortex, a cerebral area affected by neurodegeneration in preclinical Alzheimer's disease. Interestingly, leptin restores the increase in ERK1/2 phosphorylation which is lost in Leprdb/db mice pyriform and entorhinal cortex [145].

It has been also demonstrated leptin ability to regulate in vitro and in vivo beta-amyloid levels, the major proteinateous component of the amyloid plaques in Alzheimer's disease patients' brains. Leptin modulates beta-amyloid kinesis in a bidirectional way, reducing its extra-cellular levels, by reducing beta-secretase activity in neuronal cells possibly by altering the lipid composition of membrane lipid rafts; and by increasing apoE-dependent beta-amyloid uptake [146]. Finally, most strikingly, chronic administration of leptin to Alzheimer disease-transgenic animals reduces the brain beta-amyloid load [146]. Moreover, galanin, which together with its receptors (GALR) is overexpressed in limbic brain regions associated to cognition impairment in Alzheimer disease [147], results highly modulated in the mRNA expression by leptin [148]. Thus, a complex direct and indirect action in leptin deregulated conditions might be evoked in Alzheimer's disease, taking into account also leptin involvement in the general metabolism with obvious consequences on the central nervous system (CNS) metabolism and performance.

As a matter of fact, a disturbed dual relationship between leptin and cortisol has been detected in Alzheimer's patients [149], a weight loss associated to inappropriate leptin levels [150], or more related to gender dimorphism [151] probably due to the fact that the disease was already acclaimed at the leptin evaluation moments [152]; while, in some cases, the change in eating behaviour could be significantly more common in the frontotemporal dementia than in Alzheimer's disease [153] or weight loss despite an increased intake of calories [154].

Ghrelin

Ghrelin, the endogenous ligand of growth hormone secretagogue (GHS) receptors, is gut hormone and neuropeptide, recognized for several years to influence pituitary hormone secretion, appetite, body weight, metabolism, and gastrointestinal, cardiovascular and immune systems, functions with a grossly direct and inverse relationship to adiponectin and leptin, respectively [155–160]. By looking at how ghrelin binds to parts of the brain that regulate food intake such as hippocampus, it has been found that it also binds to other parts like the pyramidal neuron of layer V in the sensorimotor area of cerebral cortex, in the cingulate gyrus, as well as in the neurons of lateral, paraventricular, and arcuate nuclei hypothalamus [161]. In Alzheimer's, the hippocampus is the area that shows the most atrophy. It has also to be underlined the link between Alzheimer's disease, as described elsewhere, and obesity, and insulin resistance and how obesity increases the progression of dementia, like in Alzheimer's disease. Ghrelin binding is also present in other

brain areas, including the telencephalon. Very recently it has been reported that circulating ghrelin going through the blood–brain barrier enters the hippocampus, and binding to neurons of the hippocampal formation promotes dendritic spine synapses formation and generation of long-term potentiation [162]. Ghrelin is highest in the circulation during the day and when the stomach is empty, these results also indicate that brain activity may be most effective before meal-time. The ghrelin-induced synaptic changes are paralleled by enhanced spatial learning and memory. Targeted disruption of the gene that encodes ghrelin results in decreased numbers of spine synapses in the CA1 region and impaired performance of mice in behavioural memory testing, both of which rapidly reversed by ghrelin administration [163]. Those observations disclose an endogenous/complex function of ghrelin linking once again metabolic activity controls with higher brain functions which when disrupted could disclose Alzheomer's disease (-like symptoms).

Adiponectin

Adiponectin is, with (an inverse function compared to) leptin, another important adipocyte hormone involved in glucose and lipid metabolism generating a negative energy balance by increasing energy expenditure. Adiponectin, also known as Acrp30, is an adipose tissue-derived hormone with anti-atherogenic, anti-diabetic and insulin sensitizing properties [164–167]. In mice, targeted deletion of the adiponectin gene leads to insulin resistance [168, 169]. In addition, administration by continuous systemic infusion of adiponectin significantly increases insulin sensitivity in type 2 diabetic mice [170]. In humans, a reduced serum concentration of adiponectin has been shown to correlate with obesity [171], insulin resistance [171, 172] and type 2 diabetes [172–174]. Collectively, these findings suggest that adiponectin not only has an essential function in regulating whole-body energy homeostasis, but also it could strongly counteract the most of the risk factors for sporadic Alzheimer's disease such as insulin resistance, diabetes, obesity, vascular injury, atherosclerosis, and, more in general the metabolic syndrome. It is possible that adiponectin's protective effects could be played mostly indirectly due to the fact that neither radiolabelled nonglycosylated nor glycosylated globular adiponectin crosses the blood–brain barrier in mice; and, in addition, adiponectin is not detectable in human cerebrospinal fluid using various established methods. Interestingly, it has been shown adiponectin receptors expression in brain endothelium, upregulated during fasting [175]. The above phenomena might account for a further adiponectin (indirect) regulatory mechanism on brain metabolism-activity; regulatory mechanism probably affected in Alzheimer's disease. In this sense, it is noticeable that treatment with adiponectin reduces secretion of the centrally active interleukin-6 (IL-6) [176] in the above brain endothelial cells, phenomenon paralleled by a similar trend of other proinflammatory cytokines. It is remarkable that IL-6, and proinflammatory cytokines, has not only been involved in immune dysfunction but also in Alzheimer's disease pathogenesis [176].

Conclusions

In the '80s John P. Blass, by focusing his attention by a metabolic approach to the neurodegenerative diseases, made a cultural/scientific revolution in the understanding of Alzheimer's disease. Only nowadays such an approach is reaching the critical mass useful for lightening a real revolution in the understanding the physiopathology of Alzheimer's disease for an efficacious therapy which until now has been examined through the residual phenotype represented by a damaged brain.

References

1. Alzheimer A, Alzheimer A (1907) Über eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift für Psychiatrie und psychisch-gerichtliche Medizin, Berlin 64:146–148
2. Pearce JM (2000) Alzheimer's disease. J Neurol Neurosurg Psychiatry 68(3):348
3. Abdul HM, Calabrese V, Calvani M, Butterfield DA (2006) Acetyl-L-carnitine-induced up-regulation of heat shock proteins protects cortical neurons against amyloid-beta peptide 1–42-mediated oxidative stress and neurotoxicity: implications for Alzheimer's disease. J Neurosci Res 84(2):398–408
4. Levy ML, Cummings JL, Fairbanks LA, Bravi D, Calvani M, Carta A (1996) Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. Am J Psychiatry 153(11):1438–1443
5. Schwartz P (1975) Amyloidosis, expression and cause of presenile and senile mental and physical regression. A revision of the amyloid problem. Zentralbl Allg Pathol 119(6):533–548
6. Wisniewski HM, Narang HK, Terry RD (1976) Neurofibrillary tangles of paired helical filaments. J Neurol Sci 27(2):173–181
7. Roth M, Tomlinson BE, Blessed G (1966) Correlation between scores for dementia and counts of 'senile plaques' in cerebral grey matter of elderly subjects. Nature 209(18):109–110

8. Roth M, Tomlinson BE, Blessed G (1967) The relationship between quantitative measures of dementia and of degenerative changes in the cerebral grey matter of elderly subjects. Proc R Soc Med 60(3):254–260
9. Blessed G, Tomlinson BE, Roth M (1968) The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. Br J Psychiatry 114(512):797–811
10. Rabins PV, Folstein MF (1983) The dementia patient: evaluation and care. Geriatrics 38(8):99–103
11. Tune L, Gucker S, Folstein M, Oshida L, Coyle JT (1985) Cerebrospinal fluid acetylcholinesterase activity in senile dementia of the Alzheimer type. Ann Neurol 17(1):46–48
12. Pearlson GD, Tune LE (1986) Cerebral ventricular size and cerebrospinal fluid acetylcholinesterase levels in senile dementia of the Alzheimer type. Psychiatry Res 17(1): 23–29
13. Burch EA Jr, Andrews SR (1987) Comparison of two cognitive rating scales in medically ill patients. Int J Psychiatry Med 17(2):193–200
14. Klatzo I, Wisniewski H, Streicher E (1965) Experimental production of neurofibrillary degeneration 1, light microscopic observations. J Neuropathol Exp Neurol 24:187–199
15. Terry RD, Pena C (1965) Experimental production of neurofibrillary degeneration 2, electron microscopy, phosphatase histochemistry and electron probe analysis. J Neuropathol Exp Neurol 24:200–210
16. Crapper DR, Krishnan SS, Dalton AJ (1973) Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Trans Am Neurol Assoc 98:17–20
17. Crapper DR, Krishnan SS, Dalton AJ (1973) Brain aluminum distribution in Alzheimer's disease and experimental neurofibrillary degeneration. Science 180(85):511–513
18. Crapper DR, Krishnan SS, Quittkat S (1976) Aluminium, neurofibrillary degeneration and Alzheimer's disease. Brain 99(1):67–80
19. Vatassery GT, Maletta GJ (1983) Relationship between nutrition and dementia in the elderly. Psychiatr Med 1(4):429–443
20. Davies P, Maloney AJ (1976) Selective loss of central cholinergic neurons in Alzheimer's disease. Lancet 2(8000):1403
21. Perry E, Walker M, Grace J, Perry R (1999) Acetylcholine in mind: a neurotransmitter correlate of consciousness?. Trends Neurosci 22:273–280
22. Whitehouse PJ, Price DL, Clark AW, Coyle JT, DeLong MR (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. Ann Neurol 10(2):122–126
23. Bales KR, Tzavara ET, Wu S, Wade MR, Bymaster FP, Paul SM, Nomikos GG (2006) Cholinergic dysfunction in a mouse model of Alzheimer disease is reversed by an anti-A beta antibody. J Clin Invest 116(3):825–832
24. Calvani M, Carta A (1991) Clinical issues of cognitive enhancers in Alzheimer disease. Alzheimer Dis Assoc Disord 5(S1):25–31
25. Chapel HM, Esiri MM, Wilcock GK (1984) Immunoglobulin and other proteins in the cerebrospinal fluid of patients with Alzheimer's disease. J Clin Pathol 37(6):697–699
26. Wolozin BL, Pruchnicki A, Dickson DW, Davies P (1986) A neuronal antigen in the brains of Alzheimer patients. Science 232(4750):648–650
27. Jakes R, Spillantini MG, Goedert M (1994) Identification of two distinct synucleins from human brain. FEBS Lett 345(1):27–32
28. Mudher A, Lovestone S (2002) Alzheimer's disease-do tauists and baptists finally shake hands? Trends Neurosci 25(1):22–26
29. Trojanowski JQ (2002) Tauists, Baptists, Syners, Apostates, and new data. Ann Neurol 52(3):263–265
30. Masliah E, Terry RD, Mallory M, Alford M, Hansen LA (1990) Diffuse plaques do not accentuate synapse loss in Alzheimer's disease. Am J Pathol 137(6):1293–1297
31. Honer WG (2003) Pathology of presynaptic proteins in Alzheimer's disease: more than simple loss of terminals. Neurobiol Aging 24(8):1047–1062
32. Butterfield DA (1997) Beta-Amyloid-associated free radical oxidative stress and neurotoxicity: implications for Alzheimer's disease. Chem Res Toxicol 10(5):495–506
33. Butterfield DA, Hensley K, Cole P, Subramaniam R, Aksenov M, Aksenova M, Bummer PM, Haley BE, Carney JM (1997) Oxidatively induced structural alteration of glutamine synthetase assessed by analysis of spin label incorporation kinetics: relevance to Alzheimer's disease. J Neurochem 68(6):2451–2457
34. Subramaniam R, Roediger F, Jordan B, Mattson MP, Keller JN, Waeg G, Butterfield DA (1997) The lipid peroxidation product, 4-hydroxy-2-trans-nonenal, alters the conformation of cortical synaptosomal membrane proteins. J Neurochem 69(3):1161–1169
35. Koppal T, Drake J, Yatin S, Jordan B, Varadarajan S, Bettenhausen L, Butterfield DA (1999) Peroxynitrite-induced alterations in synaptosomal membrane proteins: insight into oxidative stress in Alzheimer's disease. J Neurochem 72(1):310–317
36. Halliwell B, Gutteridge JMC (1985) Oxygen radicals and the nervous system. Trends in Neurosciences 8:22–26
37. Muller DP, Metcalfe T, Bowen DM (1986) Vitamin E in brains of patients with Alzheimer's disease and Down's syndrome. Lancet 1(8489):1093–1094
38. Metcalfe T, Bowen DM, Muller DP (1989) Vitamin E concentrations in human brain of patients with Alzheimer's disease, fetuses with Down's syndrome, centenarians, and controls. Neurochem Res 14(12):1209–1212
39. Zaman Z, Roche S, Fielden P, Frost PG, Niriella DC, Cayley AC (1992) Plasma concentrations of vitamins A and E and carotenoids in Alzheimer's disease. Age Ageing 21(2):91–94
40. Tohgi H, Abe T, Nakanishi M, Hamato F, Sasaki K, Takahashi S (1994) Concentrations of alpha-tocopherol and its quinone derivative in cerebrospinal fluid from patients with vascular dementia of the Binswanger type and Alzheimer type dementia. Neurosci Lett 174(1):73–76
41. Jimenez-Jimenez FJ, de Bustos F, Molina JA, Benito-Leon J, Tallon-Barranco A, Gasalla T, Orti-Pareja M, Guillamon F, Rubio JC, Arenas J, Enriquez-de-Salamanca R (1997) Cerebrospinal fluid levels of alpha-tocopherol (vitamin E) in Alzheimer's disease. J Neural Transm 104(6–7):703–710
42. Sano M, Ernesto C, Thomas RG et al (1997) A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 336:1216–1222
43. Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, van Dyck CH, Thal LJ (2005) Vitamin E and donepezil for the treatment of mild cognitive impairment. N Engl J Med 352(23):2379–2388
44. Fillenbaum GG, Kuchibhatla MN, Hanlon JT, Artz MB, Pieper CF, Schmader KE, Dysken MW, Gray SL (2005) Dementia and Alzheimer's disease in community-dwelling elders taking vitamin C and/or vitamin E. Ann Pharmacother 39(12):2009–2014

45. McCaddon A, Kelly CL (1992) Alzheimers disease: a 'cobalaminergic' hypothesis. Med Hypotheses 37:161–165
46. Cole MG, Prchal JF (1984) Low serum vitamin B12 in Alzheimer-type dementia. Age Ageing 13(2):101–105
47. Ikeda T, Furukawa Y, Mashimoto S, Takahashi K, Yamada M (1990) Vitamin B12 levels in serum and cerebrospinal fluid of people with Alzheimer's disease. Acta Psychiatr Scand 82(4):327–329
48. Malouf M, Grimley EJ, Areosa SA (2003) Folic acid with or without vitamin B12 for cognition and dementia. Cochrane Database Syst Rev 4:CD004514
49. Kruman II, Kumaravel TS, Lohani A, Pedersen WA, Cutler RG, Kruman Y, Haughey N, Lee J, Evans M, Mattson MP (2002) Folic acid deficiency and homocysteine impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. J Neurosci 22(5):1752–1762
50. Regland B, Gottfries CG (1992) Slowed synthesis of DNA and methionine is a pathogenetic mechanism common to dementia in Down's syndrome, AIDS and Alzheimer's disease?. Med Hypotheses 38(1):11–19
51. Blass JP, Sheu RK, Gibson GE (2000) Inherent abnormalities in energy metabolism in Alzheimer disease. Interaction with cerebrovascular compromise. Ann N Y Acad Sci 903:204–221
52. Bubber P, Haroutunian V, Fisch G, Blass JP, Gibson GE (2005) Mitochondrial abnormalities in Alzheimer brain: mechanistic implications. Ann Neurol 57(5):695–703
53. Cash AD, Perry G, Ogawa O, Raina AK, Zhu X, Smith MA (2002) Is Alzheimer's disease a mitochondrial disorder? Neuroscientist 8(5):489–496
54. Gibson GE, Sheu KF, Blass JP (1998) Abnormalities of mitochondrial enzymes in Alzheimer disease. J Neural Transm 105(8–9):855–870
55. Gibson GE, Park LC, Sheu KF, Blass JP, Calingasan NY (2000) The alpha-ketoglutarate dehydrogenase complex in neurodegeneration. Neurochem Int 36(2):97–112
56. Makar TK, Cooper AJ, Tofel-Grehl B, Thaler HT, Blass JP (1995) Carnitine, carnitine acetyltransferase, and glutathione in Alzheimer brain. Neurochem Res 20(6):705–711
57. Rai G, Wright G, Scott L, Beston B, Rest J, Exton-Smith AN (1990) Double-blind, placebo controlled study of acetyl-l-carnitine in patients with Alzheimer's dementia. Curr Med Res Opin 11(10):638–647
58. Passeri M, Cucinotta D, Bonati PA, Iannuccelli M, Parnetti L, Senin U (1990) Acetyl-L-carnitine in the treatment of mildly demented elderly patients. Int J Clin Pharmacol Res 10(1–2):75–79
59. Carta A, Calvani M (1991) Acetyl-L-carnitine: a drug able to slow the progress of Alzheimer's disease? Ann N Y Acad Sci 640:228–232
60. Spagnoli A, Lucca U, Menasce G, Bandiera L, Cizza G, Forloni G, Tettamanti M, Frattura L, Tiraboschi P, Pomelli M et al (1991) Long-term acetyl-L-carnitine treatment in Alzheimer's disease. Neurology 41(11):1726–1732
61. Sano M, Bell K, Cote L, Dooneief G, Lawton A, Legler L, Marder K, Naini A, Stern Y, Mayeux R (1992) Double-blind parallel design pilot study of acetyl levocarnitine in patients with Alzheimer's disease. Arch Neurol 49(11):1137–1141
62. Carta A, Calvani M, Bravi D, Bhuachalla SN (1993) Acetyl-L-carnitine and Alzheimer's disease: pharmacological considerations beyond the cholinergic sphere. Ann N Y Acad Sci 695:324–326
63. Thal LJ, Calvani M, Amato A, Carta A (2000) A 1-year controlled trial of acetyl-l-carnitine in early-onset AD. Neurology 55(6):805–810
64. Montgomery SA, Thal LJ, Amrein R (2003) Meta-analysis of double blind randomized controlled clinical trials of acetyl-L-carnitine versus placebo in the treatment of mild cognitive impairment and mild Alzheimer's disease. Int Clin Psychopharmacol 18(2):61–71
65. Gibson GE, Haroutunian V, Zhang H, Park LC, Shi Q, Lesser M, Mohs RC, Sheu RK, Blass JP (2000) Mitochondrial damage in Alzheimer's disease varies with apolipoprotein E genotype. Ann Neurol 48(3):297–303
66. Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci USA 90(5):1977–1981
67. Strittmatter WJ, Weisgraber KH, Huang DY, Dong LM, Salvesen GS, Pericak-Vance M, Schmechel D, Saunders AM, Goldgaber D, Roses AD (1993) Binding of human apolipoprotein E to synthetic amyloid beta peptide: isoform-specific effects and implications for late-onset Alzheimer disease. Proc Natl Acad Sci USA 90(17):8098–8102
68. Roses AD (1996) Apolipoprotein E in neurology. Curr Opin Neurol 9(4):265–270
69. Muckle TJ, Roy JR (1985) High-density lipoprotein cholesterol in differential diagnosis of senile dementia. Lancet 1(8439):1191–1193
70. Nelson TJ, Alkon DL (2005) Insulin and cholesterol pathways in neuronal function, memory and neurodegeneration. Biochem Soc Trans 33(5):1033–1036
71. Lane RM, Farlow MR (2005) Lipid homeostasis and apolipoprotein E in the development and progression of Alzheimer's disease. J Lipid Res 46(5):949–968
72. Kabara JJ (1973) A critical review of brain cholesterol metabolism. Prog Brain Res 40:363–382
73. Bjorkhem I (2002) Do oxysterols control cholesterol homeostasis? J Clin Invest 110(6):725–730
74. Bjorkhem I, Meaney S (2004) Brain cholesterol: long secret life behind a barrier. Arterioscler Thromb Vasc Biol 24(5):806–815
75. Ercoli A, Di Frisco S, De Ruggeri P (1953) Isolation, constitution and biological significance of cerebrosterol, a companion of cholesterol in the horse brain. Boll Soc Ital Biol Sper 29(4):494–497
76. Di Frisco S, De Ruggieri P, Ercoli A (1953) Isolation of cerebrosterol from human brain. Boll Soc Ital Biol Sper 29(7):1351–1352
77. Dhar AK, Teng JI, Smith LL (1973) Biosynthesis of cholest-5-ene-3beta, 24-diol (cerebrosterol) by bovine cerebral cortical microsomes. J Neurochem 21(1):51–60
78. Lutjohann D, Breuer O, Ahlborg G, Nennesmo I, Siden A, Diczfalusy U, Bjorkhem I (1996) Cholesterol homeostasis in human brain: evidence for an age-dependent flux of 24S-hydroxycholesterol from the brain into the circulation. Proc Natl Acad Sci USA 93(18):9799–9804
79. Papassotiropoulos A, Lutjohann D, Bagli M, Locatelli S, Jessen F, Rao ML, Maier W, Bjorkhem I, von Bergmann K, Heun R (2000) Plasma 24S-hydroxycholesterol: a peripheral indicator of neuronal degeneration and potential state marker for Alzheimer's disease. Neuroreport 11(9):1959–1962

80. Lutjohann D, Papassotiropoulos A, Bjorkhem I, Locatelli S, Bagli M, Oehring RD, Schlegel U, Jessen F, Rao ML, von Bergmann K, Heun R (2000) Plasma 24S-hydroxycholesterol (cerebrosterol) is increased in Alzheimer and vascular demented patients. J Lipid Res 41(2):195–198
81. Alexandrov P, Cui JG, Zhao Y, Lukiw WJ (2005) 24S-hydroxycholesterol induces inflammatory gene expression in primary human neural cells. Neuroreport 16(9):909–913
82. Kolsch H, Ludwig M, Lutjohann D, Rao ML (2001) Neurotoxicity of 24-hydroxycholesterol, an important cholesterol elimination product of the brain, may be prevented by vitamin E and estradiol-17beta. J Neural Transm 108(4):475–488
83. Heverin M, Bogdanovic N, Lutjohann D, Bayer T, Pikuleva I, Bretillon L, Diczfalusy U, Winblad B, Bjorkhem I (2004) Changes in the levels of cerebral and extracerebral sterols in the brain of patients with Alzheimer's disease. J Lipid Res 45(1):186–193
84. Boyles JK, Pitas RE, Wilson E, Mahley RW, Taylor JM (1985) Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. J Clin Invest 76(4):1501–1513
85. Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH (1987) Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E(LDL) receptors in the brain. J Biol Chem 262(29):14352–14360
86. Boyles JK, Zoellner CD, Anderson LJ, Kosik LM, Pitas RE, Weisgraber KH, Hui DY, Mahley RW, Gebicke-Haerter PJ, Ignatius MJ et al (1989) A role for apolipoprotein E, apolipoprotein A-I, and low density lipoprotein receptors in cholesterol transport during regeneration and remyelination of the rat sciatic nerve. J Clin Invest 83(3):1015–1031
87. Petegnief V, Saura J, de Gregorio-Rocasolano N, Paul SM (2001) Neuronal injury-induced expression and release of apolipoprotein E in mixed neuron/glia co-cultures: nuclear factor kappaB inhibitors reduce basal and lesion-induced secretion of apolipoprotein E. Neuroscience 104(1):223–2334
88. Cordy JM, Hooper NM, Turner AJ (2006) The involvement of lipid rafts in Alzheimer's disease. Mol Membr Biol 23(1):111–122
89. Pappolla MA, Bryant-Thomas TK, Herbert D, Pacheco J, Fabra Garcia M, Manjon M, Girones X, Henry TL, Matsubara E, Zambon D, Wolozin B, Sano M, Cruz-Sanchez FF, Thal LJ, Petanceska SS, Refolo LM (2003) Mild hypercholesterolemia is an early risk factor for the development of Alzheimer amyloid pathology. Neurology 61(2):199–205
90. Osborne AR, Pollock VV, Lagor WR, Ness GC (2004) Identification of insulin-responsive regions in the HMG-CoA reductase promoter. Biochem Biophys Res Commun 318(4):814–818
91. Simonen P, Gylling H, Howard AN, Miettinen TA (2000) Introducing a new component of the metabolic syndrome: low cholesterol absorption. Am J Clin Nutr 72(1):82–88
92. Simonen PP, Gylling HK, Miettinen TA (2002) Diabetes contributes to cholesterol metabolism regardless of obesity. Diabetes Care 25(9):1511–1515
93. Twisk J, Hoekman MF, Lehmann EM, Meijer P, Mager WH, Princen HM (1995) Insulin suppresses bile acid synthesis in cultured rat hepatocytes by down-regulation of cholesterol 7 alpha-hydroxylase and sterol 27-hydroxylase gene transcription. Hepatology 21(2):501–510
94. Carro E, Torres-Aleman I (2004) Insulin-like growth factor I and Alzheimer's disease: therapeutic prospects? Expert Rev Neurother 4(1):79–86
95. de la Monte SM, Wands JR (2005) Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. J Alzheimers Dis 7(1):45–61
96. Frolich L, Blum-Degen D, Riederer P, Hoyer S (1999) A disturbance in the neuronal insulin receptor signal transduction in sporadic Alzheimer's disease. Ann N Y Acad Sci 893:290–293
97. Hoyer S (1998) Is sporadic Alzheimer disease the brain type of non-insulin dependent diabetes mellitus? A challenging hypothesis. J Neural Transm 105(4–5):415–422
98. Yan Z, Feng J (2004) Alzheimer's disease: interactions between cholinergic functions and beta-amyloid. Curr Alzheimer Res 1(4):241–248
99. Biessels GJ, Kappelle LJ (2005) Increased risk of Alzheimer's disease in Type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 33(Pt 5):1041–1044
100. Zhang J, Slevin M, Duraisamy Y, Gaffney JA, Smith C, Ahmed N (2006) Comparison of protective effects of aspirin, d-penicillamine and vitamin E against high glucose-mediated toxicity in cultured endothelial cells. Biochim Biophys Acta 1762(5):551–557
101. Li SY, Fang CX, Aberle NS 2nd, Ren BH, Ceylan-Isik AF, Ren J. 2005 Inhibition of PI-3 kinase/Akt/mTOR, but not calcineurin signaling, reverses insulin-like growth factor I-induced protection against glucose toxicity in cardiomyocyte contractile function. J Endocrinol 186(3):491–503
102. der Voort PH, Feenstra RA, Bakker AJ, Heide L, Boerma EC, der Horst IC (2006) Intravenous glucose intake independently related to intensive care unit and hospital mortality: an argument for glucose toxicity in critically ill patients. Clin Endocrinol 64(2):141–145
103. Gispen WH, Biessels GJ (2000) Cognition and synaptic plasticity in diabetes mellitus. Trends Neurosci 23(11):542–549
104. Gasparini L, Xu H (2003) Potential roles of insulin and IGF-1 in Alzheimer's disease. Trends Neurosci 26(8):404–406
105. Blass JP, Zemcov A (1984) Alzheimer's disease. A metabolic systems degeneration? Neurochem Pathol 2(2):103–114
106. Blass JP, Gibson GE (1992) Nonneural markers in Alzheimer disease. Alzheimer Dis Assoc Disord 6(4):205–224
107. Blass JP, Gibson GE, Sheu KF (1997) Peripheral markers of Alzheimer's disease. Aging 9(4S):55–56
108. Gasparini L, Racchi M, Binetti G, Trabucchi M, Solerte SB, Alkon D, Etcheberrigaray R, Gibson G, Blass J, Paoletti R, Govoni S (1998) Peripheral markers in testing pathophysiological hypotheses and diagnosing Alzheimer's disease. FASEB J 12(1):17–34
109. Sorbi S, Bird ED, Blass JP (1983) Decreased pyruvate dehydrogenase complex activity in Huntington and Alzheimer brain. Ann Neurol 13(1):72–78

110. Sheu KF, Kim YT, Blass JP, Weksler ME (1985) An immunochemical study of the pyruvate dehydrogenase deficit in Alzheimer's disease brain. Ann Neurol 17(5):444–449
111. Peterson C, Gibson GE, Blass JP (1985) Altered calcium uptake in cultured skin fibroblasts from patients with Alzheimer's disease. N Engl J Med 312(16):1063–1065
112. Sims NR, Finegan JM, Blass JP (1987) Altered metabolic properties of cultured skin fibroblasts in Alzheimer's disease. Ann Neurol 21(5):451–457
113. Sims NR, Finegan JM, Blass JP (1985) Altered glucose metabolism in fibroblasts from patients with Alzheimer's disease. N Engl J Med 313(10):638–639
114. Balin AK, Baker AC, Leong IC, Blass JP (1988) Normal replicative lifespan of Alzheimer skin fibroblasts. Neurobiol Aging 9(2):195–198
115. Sims NR, Blass JP (1986) Phosphofructokinase activity in fibroblasts from patients with Alzheimer's disease and age- and sex-matched controls. Metab Brain Dis 1(1):83–90
116. Sims NR, Blass JP, Murphy C, Bowen DM, Neary D (1987) Phosphofructokinase activity in the brain in Alzheimer's disease. Ann Neurol 21(5):509–510
117. Blass JP, Baker AC, Ko L, Sheu RK, Black RS (1991) Expression of 'Alzheimer antigens' in cultured skin fibroblasts. Arch Neurol 48(7):709–717
118. Sheu KF, Cooper AJ, Koike K, Koike M, Lindsay JG, Blass JP (1994) Abnormality of the alpha-ketoglutarate dehydrogenase complex in fibroblasts from familial Alzheimer's disease. Ann Neurol 35(3):312–318
119. Gibson G, Martins R, Blass J, Gandy S (1996) Altered oxidation and signal transduction systems in fibroblasts from Alzheimer patients. Life Sci 59(5–6):477–489
120. Blass JP, Hanin I, Barclay L, Kopp U, Reding MJ (1985) Red blood cell abnormalities in Alzheimer disease. J Am Geriatr Soc 33(6):401–405
121. Sherman KA, Gibson GE, Blass JP (1986) Human red blood cell choline uptake with age and Alzheimer's disease. Neurobiol Aging 7(3):205–209
122. Gibson GE, Nielsen P, Sherman KA, Blass JP (1987) Diminished mitogen-induced calcium uptake by lymphocytes from Alzheimer patients. Biol Psychiatry 22(9):1079–1086
123. Sims NR, Finegan JM, Blass JP, Bowen DM, Neary D (1987) Mitochondrial function in brain tissue in primary degenerative dementia. Brain Res 436(1):30–38
124. Gibson GE, Sheu KF, Blass JP, Baker A, Carlson KC, Harding B, Perrino P (1988) Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease. Arch Neurol 45(8):836–840
125. Sheu KF, Clarke DD, Kim YT, Blass JP, Harding BJ, DeCicco J (1988) Studies of transketolase abnormality in Alzheimer's disease. Arch Neurol 45(8):841–845
126. Blass JP (1993) Metabolic alterations common to neural and non-neural cells in Alzheimer's disease. Hippocampus 3S:45–53
127. Giaquinto S, Nolfe G, Calvani M. 1985 Cluster analysis of cognitive performance in elderly and demented subjects. Ital J Neurol Sci 6(2):157–165
128. Borenstein AR, Copenhaver CI, Mortimer JA (2006) Early-life risk factors for Alzheimer disease. Alzheimer Dis Assoc Disord 20(1):63–72
129. Whalley LJ, Dick FD, McNeill G. 2006 A life-course approach to the aetiology of late-onset dementias. Lancet Neurol 5(1):87–96
130. Hales CN, Barker DJ (1992) Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis. Diabetologia 35(7):595–601
131. Luchsinger JA, Mayeux R (2004) Cardiovascular risk factors and Alzheimer's disease. Curr Atheroscler Rep 6(4):261–266
132. Messier C, Teutenberg K (2005) The role of insulin, insulin growth factor, and insulin-degrading enzyme in brain aging and Alzheimer's disease. Neural Plast 12(4):311–328
133. Kuusisto J, Koivisto K, Mykkanen L, Helkala EL, Vanhanen M, Hanninen T, Pyorala K, Riekkinen P, Laakso M (1993) Essential hypertension and cognitive function. The role of hyperinsulinemia. Hypertension 22(5):771–779
134. Kuusisto J, Koivisto K, Mykkanen L, Helkala EL, Vanhanen M, Hanninen T, Kervinen K, Kesaniemi YA, Riekkinen PJ, Laakso M (1997) Association between features of the insulin resistance syndrome and Alzheimer's disease independently of apolipoprotein E4 phenotype: cross sectional population based study. BMJ 315(7115):1045–1049
135. Kernan WN, Inzucchi. SE, Viscoli CM, Brass LM, Bravata DM, Horwitz RI (2002) Insulin resistance and risk for stroke. Neurology 24;59(6):809–815
136. Golden SH, Folsom AR, Coresh J, Sharrett AR, Szklo M, Brancati F (2002) Risk factor groupings related to insulin resistance and their synergistic effects on subclinical atherosclerosis: the atherosclerosis risk in communities study. Diabetes 51(10):3069–3076
137. Yaffe K, Kanaya A, Lindquist K, Simonsick EM, Harris T, Shorr RI, Tylavsky FA, Newman AB (2004) The metabolic syndrome, inflammation, and risk of cognitive decline. JAMA 292(18):2237–2242
138. Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG (2000) Central nervous system control of food intake. Nature 404:661–671
139. Calvani M, Benatti P, Mancinelli A, D'Iddio S, Giordano V, Koverech A, Amato A, Brass EP (2004) Carnitine replacement in end-stage renal disease and hemodialysis. Ann N Y Acad Sci 1033:52–66
140. Ahima RS (2005) Central actions of adipocyte hormones. Trends Endocrinol Metab 16(7):307–313
141. Couce ME, Burguera B, Parisi JE, Jensen MD, Lloyd RV (1997) Localization of leptin receptor in the human brain. Neuroendocrinology 66:145–150
142. Shanley LJ, Irving AJ, Rae MG, Ashford ML, Harvey J (2002) Leptin inhibits rat hippocampal neurons via activation of large conductance calcium-activated K+ channels. Nat Neurosci 5:299–300
143. Harvey J, Shanley LJ, O'Malley D, Irving AJ (2005) Leptin: a potential cognitive enhancer?. Biochem Soc Trans. 33(Pt 5):1029–1032
144. Li XL, Aou S, Oomura Y, Hori N, Fukunaga K, Hori T (2002) Impairment of long-term potentiation and spatial memory in leptin receptor-deficient rodents. Neuroscience 113(3):607–615
145. Valerio A, Ghisi V, Dossena M, Tonello C, Giordano A, Frontini A, Ferrario M, Pizzi M, Spano P, Carruba MO, Nisoli E (2006) Leptin increases axonal growth cone size in developing mouse cortical neurons by convergent signals inactivating glycogen synthase kinase-3beta. J Biol Chem. 281(18):12950–12958
146. Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD, Tezapsidis N (2004) Obesity-related leptin regulates Alzheimer's Abeta. FASEB J 18(15):1870–1878

147. Counts SE, Perez SE, Ginsberg SD, De Lacalle S, Mufson EJ (2003) Galanin in Alzheimer disease. Mol Interv 3(3):137–156
148. Cheung CC, Hohmann JG, Clifton DK, Steiner RA (2001) Distribution of galanin messenger RNA-expressing cells in murine brain and their regulation by leptin in regions of the hypothalamus. Neuroscience 103:423–432
149. Olsson T, Nasman B, Rasmuson S, Ahren B (1998) Dual relation between leptin and cortisol in humans is disturbed in Alzheimer's disease. Biol Psychiatry 44(5):374–376
150. Power DA, Noel J, Collins R, O'Neill D (2001) Circulating leptin levels and weight loss in Alzheimer's disease patients. Dement Geriatr Cogn Disord 12(2):167–170
151. Intebi AD, Garau L, Brusco I, Pagano M, Gaillard RC, Spinedi E. 2002–(2003) Alzheimer's disease patients display gender dimorphism in circulating anorectic adipokines. Neuroimmunomodulation 10(6):351–358
152. Koivisto AM, Helisalmi S, Pihlajamaki J, Moilanen L, Kuusisto J, Laakso M, Hiltunen M, Keijo K, Hanninen T, Helkala EL, Kervinen K, Kesaniemi YA, Soininen H (2005) Interleukin-6 promoter polymorphism and late-onset Alzheimer's disease in the Finnish population. J Neurogenet 19(3):155–161
153. Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR (2002) Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry Oct;73(4):371–376
154. Wang PN, Yang CL, Lin KN, Chen WT, Chwang LC, Liu HC (2004) Weight loss, nutritional status and physical activity in patients with Alzheimer's disease. A controlled study. J Neurol 251(3):314–320
155. Kojima M, Hosoda H, Date Y, Nakazato M, Kangawa K (1999) Ghrelin is a growth-hormone-releasing acylated peptide from stomach. Nature 402:656–660
156. Tschop M, Smiley DL, Heiman ML (2000) Ghrelin induces adiposity in rodents. Nature 407:908–913
157. van der Lely AJ, Tschop M, Heiman ML, Ghigo E (2004) Biological, physiological, pathophysiological, and pharmacological aspects of ghrelin. Endocr Rev 25:426–457
158. Horvath TL, Castañeda T, Tang-Christensen M, Pagotto U, Tschop MH (2003) Ghrelin as a potential anti-obesity target. Curr Pharm Des 9:1383–1395
159. Kojima M, Kangawa K (2005) Ghrelin: structure and function. Physiol Rev 85:495–522
160. Valera Mora ME, Scarfone A, Valenza V, Calvani M, Greco AV, Gasbarrini G, Mingrone G (2005) Ghrelin does not influence gastric emptying in obese subjects. Obes Res 13(4):739–744
161. Hou Z, Miao Y, Gao L, Pan H, Zhu S (2006) Ghrelin-containing neuron in cerebral cortex and hypothalamus linked with the DVC of brainstem in rat. Regul Pept 134(2–3):126–131
162. Yamada KA, Sleeman MW, Tschop MH, Horvath TL (2006) Ghrelin controls hippocampal spine synapse density and memory performance. Nat Neurosci 9(3):381–388
163. Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, Gaskin FS, Nonaka N, Jaeger LB, Banks WA, Morley JE, Pinto S, Sherwin RS, Xu L, Yamada KA, Sleeman MW, Tschop MH, Horvath TL (2006) Ghrelin controls hippocampal spine synapse density and memory performance. Nat Neurosci 9(3):381–388
164. Berg AH, Combs TP, Scherer PE (2002) ACRP30–adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab 13:84–89
165. Calvani M, Scarfone A, Granato L, Mora EV, Nanni G, Castagneto M, Greco AV, Manco M, Mingrone G (2004) Restoration of adiponectin pulsatility in severely obese subjects after weight loss. Diabetes 53(4):939–947
166. Kadowaki T, Yamauchi T (2005) Adiponectin and adiponectin receptors. Endocr Rev 26:439–451
167. Tsao TS, Lodish HF, Fruebis J (2002) ACRP30, a new hormone controlling fat and glucose metabolism. Eur JPharmacol 440:213–221
168. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, Eto K, Yamashita T, Kamon J, Satoh H, Yano W, Froguel P, Nagai R, Kimura S, Kadowaki T, Noda, Tl (2002) Disruption of adiponectin causes insulin resistance and neointimal formation. J Biol Chem 277:25863–25866
169. Maeda NShimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, Furuyama N, Kondo H, Takahashi M, Arita Y, Komuro R, Ouchi N, Kihara S, Tochino Y, Okutomi K, Horie M, Takeda S, Aoyama T, Funahashi T, Matsuzawa Y (2002) Diet-induced insulin resistance in mice lacking adiponectin–ACRP30. Nature Med 8:731–737
170. Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, Mori Y, Ide T, Murakami K, Tsuboyama-Kasaoka N, Ezaki O, Akanuma Y, Gavrilova O, Vinson C, Reitman ML, Kagechika H, Shudo K, Yoda M, Nakano Y, Tob K, Nagai R, Kimura S, Tomita M, Froguel P, Kadowaki T (2001) The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. Nature Med 7:941–946
171. Hu E, Liang P, Spiegelman BM (1996) AdipoQ is a novel adipose-specific gene dysregulated in obesity. J BiolChem 271:10697–10703
172. Weyer C et al (2001) Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 86:1930–1935
173. Statnick MA et al (2000) Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. Int J Exp Diabetes Res 1:81–88
174. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y (2000) Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 20:1595–1599
175. Spranger J, Verma S, Gohring I, Bobbert T, Seifert J, Sindler AL, Pfeiffer A, Hileman SM, Tschop M, Banks WA (2006) Adiponectin does not cross the blood–brain barrier but modifies cytokine expression of brain endothelial cells. Diabetes 55(1):141–147
176. Zuliani G, Ronzini M, Guerra G, Rossi L, Munari MR, Zurlo A, Volpato S, Atti AR, Ble A, Fellin RJ (2006) Plasma cytokines profile in older subjects with late onset Alzheimer's disease or vascular dementia. Psychiat Res (in press)