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Inflammation, Defective Insulin Signaling, and Mitochondrial Dysfunction as Common Molecular Denominators Connecting Type 2 Diabetes to Alzheimer Disease

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A growing body of evidence supports an intriguing clinical/epidemiological connection between Alzheimer disease (AD) and type 2 diabetes (T2D). T2D patients have significantly increased risk of developing AD and vice versa. Recent studies have begun to reveal common pathogenic mechanisms shared by AD and metabolic disorders, notably obesity and T2D. In T2D and obesity, low-grade chronic inflammation is a key mechanism leading to peripheral insulin resistance, which progressively causes tissue deterioration and overall health decline. In the brain, proinflammatory signaling was recently found to mediate impaired neuronal insulin signaling, synapse deterioration, and memory loss. Here, we review evidence indicating that inflammation, insulin resistance, and mitochondrial dysfunction are common features in AD and T2D. We further propose the hypothesis that dementia and its underlying neuronal dysfunction are exacerbated or driven by peripheral inflammation. Identification of central and peripheral inflammation as potential mediators of brain dysfunction in AD may lead to the development of effective treatments for this devastating disease.

The incidence of metabolic disorders, including type 2 diabetes (T2D) and obesity-related insulin resistance, is increasing at alarming rates worldwide, largely due to poor lifestyle habits. Diabetes, for example, is now estimated to affect 382 million people worldwide, and this appalling figure may further rise to almost 600 million people in 2035 (1). In parallel, the prevalence of Alzheimer disease (AD), the most common form of dementia in the elderly, also increases as the world population ages. Thirty-five million people are now thought to be affected by AD worldwide, and this number is expected to double in the next few decades (2). Besides being major causes of morbidity and mortality, AD and metabolic diseases appear to be intimately connected. Since the original Rotterdam study (3), epidemiological/clinical observations have accumulated showing that diabetic patients are significantly more likely to develop cognitive deterioration and exhibit increased susceptibility to dementia, particularly AD (4). Indeed, studies by Ott and colleagues (3,5) have shown that dementia is twice as frequent in diabetic patients as in normal subjects. More generally, the incidence of other neurological disorders, such as vascular pathology and stroke, also appears to be doubled in T2D individuals compared with nondiabetic subjects (6,7).

Importantly, impaired metabolic parameters, such as hyperglycemia and hyperinsulinemia, positively correlate with development of AD-related pathology (8,9). Elevated blood glucose levels increase the hazard risk of dementia in both diabetic and nondiabetic individuals (by 40 and 18%, respectively) (4) and are associated with cognitive decline and reduced hippocampal volume (10). These findings indicate that persistently elevated blood glucose levels negatively

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impact the brain, even in the absence of overt T2D or impaired glucose tolerance. A new view is thus emerging according to which even a prediabetes state maintained throughout a long period of life may constitute a significant risk factor for dementia. In harmony with this concept, AD was recently proposed to be a form of dementia caused by metabolic dyshomeostasis that manifests in the elderly as a result of a cumulative, lifelong impact on peripheral tissues and on the brain (11,12). In addition to this metabolic hypothesis, it is important to note that prediabetic hyperglycemia may be accompanied by a state of low-grade peripheral inflammation, which might directly impact brain insulin signaling (as discussed below). Thus, from a mechanistic point of view, the connection between AD and T2D may comprise both inflammatory and metabolic components. A corollary of this proposal is that poor lifestyle habits (e.g., lack of or insufficient physical activity or inadequate nutrition) known to predispose to T2D and obesity are increasingly thought to play important roles in susceptibility to AD later in life (11,13).

Obesity is recognized as the most important epidemiological factor predisposing to T2D. Several studies have shown that high-fat feeding leads to important alterations in hypothalamic and peripheral systems that regulate food intake and energy expenditure (14). A recent study showed that the hypothalamus of obese humans and of experimental models of obesity presents signs of inflammation and dysfunction that precede the installation of increased adiposity and T2D (15). Obesity, often associated with consumption of diets that are high in fat, has also been proposed to increase the risk of dementia and AD later in life (16–18). Epidemiologic studies further suggest that diets high in saturated fats during midlife are a risk factor for development of AD later in life (19,20). Interestingly, induction of diabetes or obesity in animals triggers and/or accelerates AD-like pathology (21–23). Therefore, adopting a healthy lifestyle and strategies aimed at lifelong control of blood glucose levels, which are thought to prevent the development of metabolic diseases, may be of further benefit to preserve cognition in the elderly and to prevent AD development.

In the following sections, we discuss molecular events and pathways recently implicated in disrupted brain insulin signaling, inflammation, and cellular/metabolic stress in AD and review recent evidence indicating that inflammation, defective insulin signaling, and mitochondrial dysfunction are common molecular denominators connecting T2D to AD. We further highlight the need to unravel how metabolic disorders, especially T2D, negatively influence brain function, ultimately leading to dementia, and propose that peripheral inflammation and insulin resistance may be linked to clinical manifestation of AD.

DEFECTIVE INSULIN SIGNALING IN T2D AND AD

Insulin resistance, defined as a smaller than expected response to a given dose of insulin, is a pathological state characteristic of aging and of several disorders, including cancer, polycystic ovarian disease, infections, and trauma. Most significantly, insulin resistance is a major hallmark of obesity and T2D, two highly prevalent metabolic disorders. Knowledge of the molecular mechanism(s) of defective insulin signaling has increased tremendously during the past decades (24,25). Insulin exerts its actions via a complex signaling network that has multiple effects on metabolism and growth. Impaired insulin signaling can result, for example, from mutations or aberrant post-translational modifications in molecular components of the insulin signaling pathway (25–27). Major insight into the mechanisms by which insulin resistance develops in peripheral tissues has come from studies performed in the laboratories of Ronald Kahn, Bruce Spiegelman, and Gökhan Hotamisligil, among others (28–34). Seminal articles from these groups have demonstrated that prolonged metabolic stress and activation of proinflammatory pathways lead to attenuated insulin signaling and decreased cellular responsiveness to insulin.

Insulin resistance acutely impairs the ability of cells to maintain energy homeostasis. Intriguingly, AD brains present similar abnormalities as peripheral tissues in T2D, including metabolic stress and neuroinflammation (35–39). Thus, it is conceivable that similar mechanisms account for peripheral insulin resistance in T2D and impaired brain insulin signaling in AD. Recent studies have indeed demonstrated substantial commonalities between neuropathogenic mechanisms triggered by amyloid-β oligomers (AβOs), toxins that accumulate in the AD brain and are increasingly thought to underlie synapse failure and memory loss, and mechanisms involved in peripheral insulin resistance in diabetes (12,37,40).

It is important to consider the toxic role of AβOs in AD, as their impact in the brain appears intimately related to defective neuronal insulin signaling. AβOs are soluble aggregates of Aβ, a 4 kDa peptide that exhibits a high propensity to self-associate in aqueous medium. Abnormal production, processing, and/or clearance of Aβ may lead to its accumulation and aggregation in the brain parenchyma and interstitial fluid. Early histopathological investigation of AD brains revealed the presence of fibrillar Aβ aggregates forming large, insoluble deposits known as amyloid plaques. Further in vitro biochemical and cell biology studies, as well as studies using a number of transgenic mouse models of AD, provided strong support to what initially seemed to be a solid concept, namely that Aβ fibrils/plaques played crucial roles in AD pathogenesis (reviewed in 41,42). However, a large body of evidence accumulated during the past 15 years indicates that fibrils are probably not the most harmful structures generated by self-association of Aβ. Of direct clinical relevance, postmortem analysis of the brains of individuals who died without signs of significant cognitive deterioration has revealed abundant brain amyloid deposits, whereas individuals lacking such deposits have been found to exhibit various extents of cognitive deterioration (e.g., 43). Moreover, the

best correlate of the extent of dementia is not brain amyloid burden but rather synapse loss (44,45), suggesting that synapse deterioration and cognitive impairment are caused by a toxin other than fibrillar Aβ.

Landmark studies by William L. Klein and colleagues (46) first addressed this controversy, showing that Aβ self-aggregates to form neurotoxic soluble oligomers, aggregates much smaller than fibrils that are not detected in classical neuropathological examination. Oligomers were recently detected at postsynaptic sites in AD hippocampi (47), and their levels are elevated in the brain and cerebrospinal fluid of AD patients (48,49). Interestingly, the absence of AβOs at the postsynapse was reported in cognitively intact elderly individuals whose brains presented amyloid deposits (47). Klein's discovery, confirmed and expanded by several groups, led to a novel hypothesis on how AD progression leads to dementia: synapse failure and neuronal dysfunction are now considered to derive from the accumulation and impact of AβOs in AD brains (41,42,50).

Recent evidence indicates that AD can be considered a brain-specific form of diabetes. AD brains exhibit defective insulin signaling, altered levels and/or aberrant activation of components of the insulin signaling pathway, and, importantly, decreased responsiveness to insulin (35,36,38). Molecular clues into how the brain becomes insulin resistant in AD came from studies demonstrating that AβOs trigger the removal of insulin receptors (IRs) from the plasma membrane in cultured hippocampal neurons (51,52), leading to reduced IR protein tyrosine kinase activity (52). IRs are widely distributed in the central nervous system (CNS), suggesting that insulin has important physiological roles in the brain. The hippocampus, a region that is fundamentally involved in the acquisition, consolidation, and recollection of new memories, presents particularly high levels of IRs. Insulin has been shown to be neuroprotective (37,51,53,54) and to modulate synapse plasticity mechanisms (55). IR signaling further regulates circuit function and plasticity by controlling synapse density (56). In cultured hippocampal neurons, IRs exhibit a punctate dendritic distribution (51,52) consistent with synaptic localization. Nonetheless, knowledge of the precise roles of brain IRs is still limited. Although a number of studies have reported learning-associated changes in IR pathways and beneficial actions of insulin on memory (57), specific deletion of brain IRs did not lead to major learning and memory impairment in mice (58). It is, nonetheless, possible that compensatory mechanisms may operate to prevent memory deficits in such mice by stimulation of insulin signaling–related pathways via other receptors, including IGF-1 and GLP-1 receptors (GLP-1Rs). Altered neuronal IR function thus appears to be an important aspect of the overall synaptic and neuronal pathology induced by AβOs.

In peripheral tissues, activated IRs recruit and phosphorylate members of a conserved family of adaptor proteins called IR substrates 1–4 (IRS1–4) (59). Upon phosphorylation at tyrosine residues, IRS proteins act as scaffolds that couple IR stimulation to downstream effectors, such as PI3K, Akt/PKB, and mTORC1 (59), allowing cellular metabolic and transcriptional reprogramming (60). On the other hand, inhibitory serine phosphorylation (pSer) of IRS-1 and IRS-2, the best studied components of the IRS family, causes their dissociation from the IR and decreases tyrosine phosphorylation (pTyr) (60). Therefore, the balance between IRS phosphorylation at serine or tyrosine residues (IRS-1pSer vs. IRS-1pTyr) determines the extent of insulin actions.

In T2D, activation of the stress kinase c-Jun NH_2-terminal kinase (JNK) phosphorylates IRS-1 at serine residues (IRS-1pSer), blocking downstream insulin signaling and causing peripheral insulin resistance (28). Similarly, AβOs instigate JNK activation and IRS-1 inhibition in primary hippocampal neurons (37,40) and in the hippocampi of cynomolgus monkeys that received intracerebroventricular infusions of AβOs (37). IRS-1 inhibition was also demonstrated in the brains of a transgenic mouse model of AD (37). Most important in establishing the clinical relevance of these findings was the demonstration of elevated IRS-1pSer (37,38) and activated JNK (37) in postmortem AD brains. Because AβOs trigger internalization and redistribution of neuronal IRs (52), it is possible that removal of IRs from the cell surface facilitates IRS-1pSer, a view consistent with our finding that insulin blocks both neuronal IR downregulation (51) and IRS-1pSer induced by AβOs (37).

INFLAMMATION AS A MAJOR LINK BETWEEN THE PATHOGENESIS OF AD AND METABOLIC DISORDERS

Inflammation is an important feature of diabetes and AD and is thought to play critical roles in the pathogenesis of both disorders (28,39,61). Inflammation is part of the body's mechanisms of defense against multiple challenges, including infections and injury, and involves both soluble factors and specialized cells that are mobilized to neutralize such threats and restore normal body physiology (62). Similar inflammatory processes are thought to occur in the brain and in peripheral tissues. Several studies have established the presence of inflammatory markers in the AD brain, including elevated levels of cytokines/chemokines and gliosis (notably microgliosis) (63). Moreover, blood concentrations of inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin 6 (IL-6), and IL-1β, are increased in AD patients (64). On the other hand, macrophage activation/infiltration into adipose tissue and overproduction of proinflammatory cytokines, including TNF-α, are key features of the pathophysiology of metabolic disorders. Elevated levels of TNF-α, overexpressed in adipose tissue of obese individuals, cause peripheral insulin resistance (30). Thus, both in the brain and in peripheral tissues, unchecked or chronic inflammation becomes deleterious, leading to progressive tissue damage in degenerative diseases (Fig. 1).

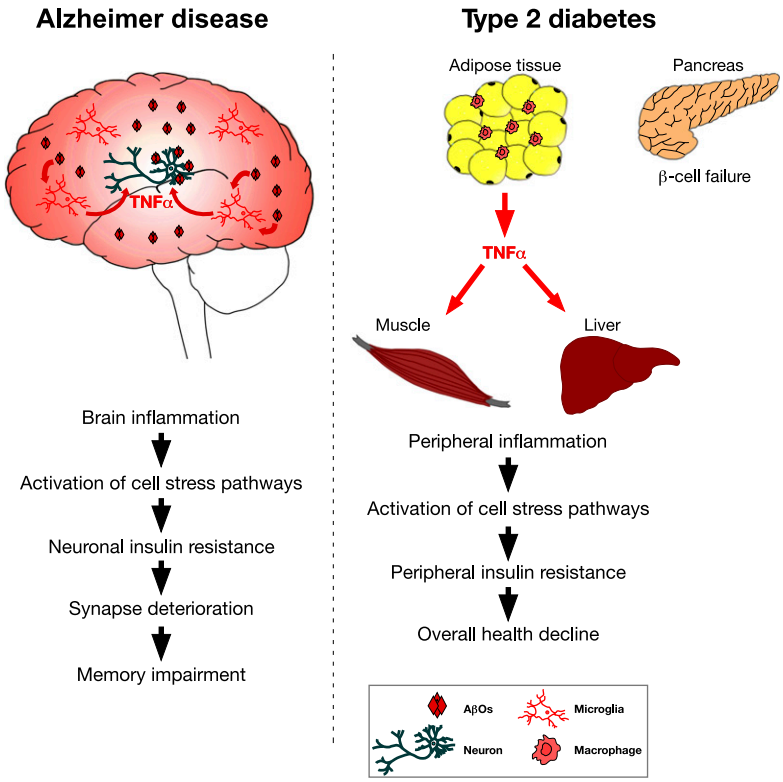

Figure 1—TNF-α–mediated inflammation underlies brain insulin resistance in AD and peripheral insulin resistance in T2D. An overview of parallel inflammatory mechanisms leading to brain insulin resistance and memory impairment in AD and to peripheral insulin resistance and overall health decline in T2D.

It is interesting to note that inflammation also underlies hypothalamic dysfunction in obesity. The hypothalamus plays a key role in neuroendocrine interaction between the CNS and the periphery (65). Emerging evidence indicates that inflammation and endoplasmic reticulum (ER) stress are critical pathogenic events in the establishment of hypothalamic and peripheral insulin resistance in metabolic disorders (15,66–68). In animal models of T2D and obesity, an inflammatory response in the hypothalamus, notably via activation of TNF-α and the IκBα kinase (IKK)-β/nuclear factor-κB pathway, is an important part of the mechanism underlying pathogenesis (69,70). Therefore, hippocampal dysfunction in AD and hypothalamic deregulation in obesity seem to share common inflammatory pathogenic pathways.

ACTIVATION OF PROINFLAMMATORY AND CELL STRESS SIGNALING PATHWAYS IMPAIRS NEURONAL INSULIN SIGNALING IN AD

In peripheral insulin resistance, aberrant TNF-α signaling leads to activation of JNK (71). Activation of the TNF-α/JNK pathway is linked to major inflammatory/stress signaling networks, including ER stress and the stress kinases IKK (IκBα kinase) and PKR (double-stranded RNA-dependent protein kinase) (72). In T2D, elevated TNF-α levels trigger serine phosphorylation of IRS-1 by stress kinases (30), blocking insulin signaling (71,72). In the brain, TNF-α is mainly secreted by microglial cells in response to trauma, infection, or abnormal accumulation of protein aggregates. TNF-α levels are elevated in brain microvessels and cerebrospinal fluid in AD (73), as well as in the brains of transgenic mouse models of AD (74). Initial evidence that impaired neuronal insulin signaling in AD was linked to proinflammatory signaling came from the finding that AβOs cause IRS-1 inhibition through TNF-α/JNK activation (37). Reinforcing the notion that common mechanisms underlie impaired peripheral insulin signaling in T2D and brain insulin resistance in AD, we recently showed that IKK and PKR, as well as ER stress, reported to be elevated in AD brains (75,76), mediate AβO-induced IRS-1 inhibition in hippocampal neurons (37,54).

IKK, a stress kinase activated by TNF-α signaling in peripheral insulin resistance (77), also mediates AβO-induced neuronal IRS-1 inhibition (37). Overnutrition induces an inflammatory response in peripheral metabolic tissues, a process referred to as “metaflammation” (78), which causes metabolic defects underlying T2D and obesity, including IKK activation (78). The recently established involvement of IKK in IRS-1 inhibition in AD provides additional evidence for a close parallel between inflammation-associated defective brain insulin signaling in AD and chronic inflammation–induced insulin resistance in peripheral tissues. Further studies aimed at exploring the role of IKK in neuronal dysfunction are

warranted and may bring novel clues on mechanisms underlying AD pathology.

The double-stranded RNA-dependent protein kinase (PKR), originally identified as a pathogen sensor and a regulator of the innate immune response against viral infections in higher eukaryotes (79), can regulate or act in conjunction with major inflammatory kinases/signaling pathways implicated in metabolic homeostasis, including JNK and IKK (80). Interestingly, PKR is involved in AβO-induced neuronal IRS-1 inhibition (37), further underlining the parallelism between peripheral insulin resistance in T2D and impaired brain insulin signaling in AD.

Current evidence thus indicates that proinflammatory TNF-α signaling and activation of cell stress pathways play key roles in peripheral and central IRS-1 inhibition and in neuronal dysfunction in AD (Fig. 2).

ANTIDIABETES AGENTS AS NOVEL THERAPEUTICS IN AD: UNRAVELING THE MECHANISMS OF NEUROPROTECTION

Evidence linking pathogenic mechanisms in the AD brain to mechanisms present in metabolic diseases provides a rationale for using antidiabetes agents as novel therapeutics in AD. As noted above, insulin actions seem to be important for proper function of the hippocampus, a memory-linked brain region that presents high levels of IRs (81). In cultured hippocampal neurons, IRs show a punctate dendritic synaptic distribution (51,52), and IR signaling regulates synaptic plasticity by controlling synapse density (56). In rodents, IR signaling contributes to long-term memory consolidation and improves spatial learning (81–84). Insulin has also been proposed to regulate neuronal survival and to act as a growth

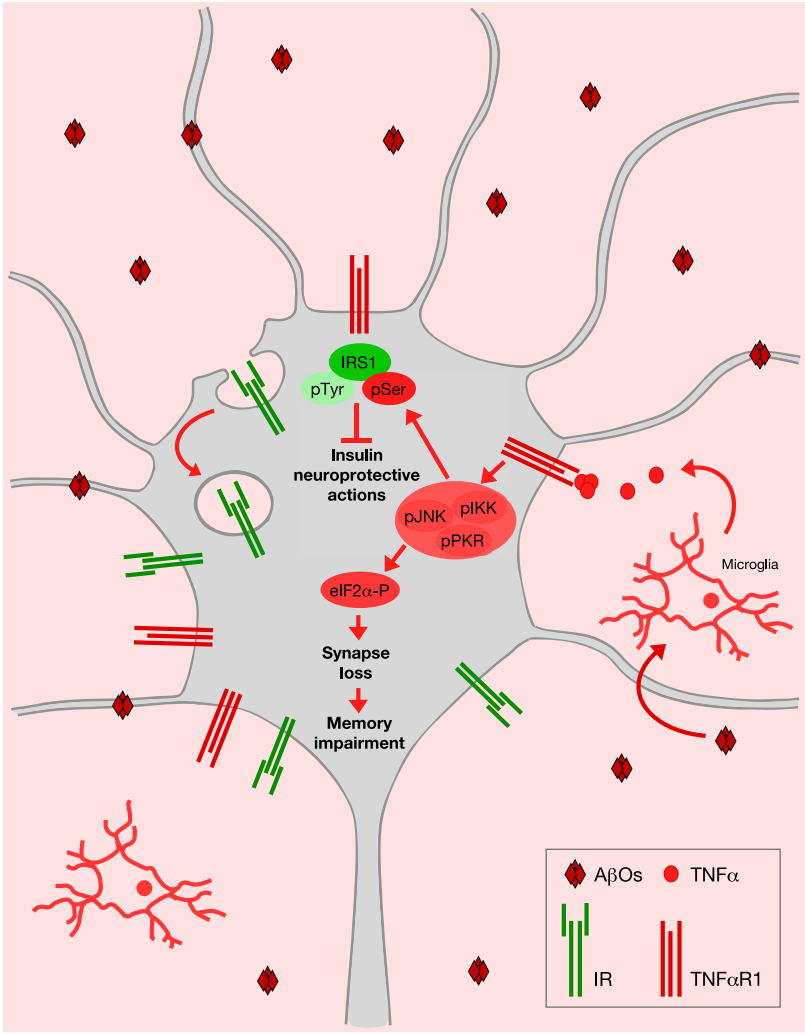

Figure 2—TNF-α–mediated signaling activates cell stress pathways and causes IRS-1 inhibition, synapse damage, and memory loss in AD. Microglial activation by AβOs results in increased production/release of TNF-α. Activation of neuronal TNF-α receptor induces aberrant activation of stress kinases (JNK, IKK, and PKR) (37,54) and ER stress (PKR-mediated phosphorylation of eIF2α-P) (54). Serine phosphorylation of IRS-1 inhibits insulin-induced IRS-1 tyrosine phosphorylation. This interferes with the ability of IRS-1 to engage in insulin signaling and blocks the intracellular actions of insulin. Reduced insulin signaling increases neuronal vulnerability to synapse damage induced by AβOs, ultimately leading to memory impairment.

factor (85), possibly by activating either its own receptor or IGF receptors (86).

Supporting the notion that insulin-related signaling plays a central role in learning and memory, impaired insulin sensitivity has been linked to cognitive deficits and structural and functional brain deficits in the elderly (87). Therefore, restoring brain insulin signaling might be beneficial to circumvent age-related dementia. Since to date most approaches proposed as possible treatments for AD have disappointingly failed in clinical trials (88), diabetes-based strategies have emerged as potentially effective therapies for AD. Intranasal insulin administration, a preferential route for CNS delivery, improves memory in healthy adults without affecting circulating levels of insulin or glucose (89). Intranasal insulin also enhances verbal memory in memory-impaired subjects and improves cognitive performance in early AD patients (12,90).

More recently, GLP-1R agonists have been proposed as an alternative therapeutic approach or as an addition to insulin-based therapies in AD. GLP-1R agonists, such as exendin-4 and liraglutide, are indeed an attractive option because they activate pathways common to insulin signaling through G protein–dependent signaling (91). GLP-1Rs are present and functional in cultured neurons as well as in rodent and human brains (92,93). In mice, GLP-1R analogs are stable in blood, with most of the injected peptide reaching the brain intact. Furthermore, recent evidence indicates that GLP-1R stimulation facilitates hippocampal synaptic plasticity, cognition, and cell survival (94–96).

An important step now is to understand if and how stimulation of insulin signaling in the brain might facilitate neuroprotection in AD, thereby preserving normal brain function. Molecular mechanisms underlying the protective actions of insulin signaling in the brain have recently started to be unraveled. Insulin and GLP-1R agonists were found to protect neurons against damage induced by AβOs in cellular and animal models of AD. Insulin was found to block IR downregulation (51), IRS-1pSer (37), eIF2α-P (54), and oxidative stress (51) induced by AβOs. Remarkably, insulin protects against synapse loss induced by AβOs (51). Insulin further favors nonamyloidogenic processing of the amyloid precursor protein in vitro (97) and reduces tau hyperphosphorylation in a rat model of T2D (98). Exendin-4 was recently found to block AβO-induced impairment in insulin signaling in hippocampal cultured neurons (37). Exendin-4 and liraglutide also restore impaired insulin signaling in the brains of a transgenic mouse model of AD, improving cognition, decreasing Aβ accumulation, and attenuating eIF2α-P (37,54,99). Importantly, liraglutide further protected the brain of nonhuman primates from AβO-induced eIF2α-P (54). Collectively, those studies provide a rational basis for use of insulin and/or GLP-1R agonists as therapeutics in AD.

Insulin and GLP-1R activation may thus provide novel strategies to resensitize impaired brain insulin signaling and to prevent or halt neurodegeneration in AD. Larger-scale clinical trials are now planned to determine the efficacy of insulin and GLP-1R agonists in improving memory and cognition in AD patients (www.adcs.org/studies/SNIFF.aspx; clinicaltrials.gov/ct2/show/NCT01843075), and results from such studies are highly expected in the field.

POSSIBLE IMPACT OF PERIPHERAL INFLAMMATION AND METABOLIC DEREGULATION IN AD

Aging, the single most important risk factor for AD, is often associated with a chronic state of low-grade inflammation resulting from deregulated levels of pro- and anti-inflammatory cytokines, a condition referred to as "inflamm-aging" (100). Increased levels of proinflammatory cytokines and markers, such as IL-1β, IL-6, TNF-α, and C-reactive protein, have been associated with "normal" aging. However, it is not yet clear whether increased levels of proinflammatory cytokines precede and play causal roles in the biochemical changes associated with aging, or whether they are a consequence of the aging process (101). Interestingly, it has been proposed that inflamm-aging is a result of lifetime exposure to acute and chronic infections (102,103), with human longevity at least partly related to the capacity to maintain inflammatory response at low levels (102).

Low-grade inflammation may persist throughout periods of life due to recurrent or persistent infections, and it is tempting to ask if chronically elevated peripheral inflammatory mediators could be associated with accelerated neuronal dysfunction and cognitive decline (11). Significantly, T2D induces changes in blood-brain barrier (BBB) permeability (104), and postmortem analysis of diabetic AD brains showed increased levels of IL-6 compared with nondiabetic AD brains (105). Moreover, the BBB of a transgenic mouse model of AD has been reported to be more permeable to peripheral inflammatory cytokines (106). These findings raise the possibility that AD brains could be more susceptible to peripheral inflammatory dyshomeostasis.

Peripheral (adipose tissue) inflammation is a major trait of diabetes and obesity (107), and both adipocytes and adipose-resident macrophages appear to participate in a cross-talk between the periphery and CNS. In obese patients, adipocytes react by producing proinflammatory cytokines, adipokines, and chemokines, while resident macrophages undergo a phenotypic change to a so-called M1 proinflammatory state (108). This leads to increased TNF-α, IL-1β, and IL-6 production, all of which can cross the BBB (109). Fat-derived inflammatory mediators could thus be an important addition to cytokines locally produced by CNS-resident microglia to generate a state of brain inflammation.

In addition to cytokines, altered levels of fat-derived leptin and adiponectin have been reported in AD. Both leptin and adiponectin receptors are ubiquitously distributed, including in the brain, consistent with important central actions of these hormones in addition to their

roles in hypothalamic metabolic control (110,111). Initially described for its role in satiety and long-term body weight maintenance, leptin was recently proposed to regulate cognition, axonal growth, and synaptogenesis in extrahypothalamic regions (112). Moreover, leptin induces hippocampal neurogenesis (113), reduces Aβ generation in vitro (114), and improves cognitive performance (114) in transgenic mouse models of AD. Lower plasma levels of leptin have further been associated with increased risk of development of AD (115).

Plasma adiponectin levels are decreased in animal models of obesity and in obese patients (116,117). Surprisingly, recent studies found increased levels of adiponectin in mild cognitive impairment and AD patients (118). Although the possible action(s) of adiponectin in neuronal physiology are still unclear, it will be interesting to determine whether it plays any role in neuronal dysfunction in AD.

Dyslipidemia is another important trait of metabolic disorders. Cholesterol- and sphingolipid-enriched specialized cell membrane domains, called lipid rafts, appear to be preferential sites for Aβ generation via amyloidogenic cleavage of the amyloid precursor protein (119). Particular types of sphingolipids, namely ceramide and its metabolites, cause inflammation (120) and have been increasingly associated with T2D (121). Peripherally generated ceramides cross the BBB (122) and could contribute to AD pathogenesis in two ways: *1*) by changing the microenvironment of lipid rafts, thereby favoring Aβ generation, and *2*) by inducing central inflammation and disruption in neuronal insulin signaling (121).

Preclinical and clinical observations thus support the notion that peripheral mediators (cytokines, adipokines, and lipids) link peripheral and central metabolic/inflammatory dyshomeostasis in AD. Although effective therapeutic approaches to combat such deregulated signaling events are not yet available, current evidence supports encouragement of a healthier lifestyle and long-term metabolic control as a preventative measure to reduce the risk of AD (11,13).

MITOCHONDRIAL DYSFUNCTION AS A LINK BETWEEN PERIPHERAL/BRAIN INFLAMMATION AND DEFECTIVE INSULIN SIGNALING

Mitochondrial energy–transducing capacity is essential for maintenance of cellular function, and impaired mitochondrial energy metabolism/redox homeostasis is a hallmark of both brain and peripheral aging (123,124). Reactive oxygen species (ROS) are cytotoxic byproducts of normal mitochondrial metabolism generated by monoelectronic reduction of oxygen in the respiratory chain. In peripheral tissues, transient ROS generation in response to physiological stimuli such as insulin facilitates insulin signaling by inhibiting protein phosphatases, including PTEN (125). In the brain, transient production of ROS is implicated in synaptic signaling and facilitates long-term potentiation and memory-related mechanisms (126). However, chronically elevated ROS levels and/or an imbalance between ROS production and intracellular levels of antioxidant defenses lead to oxidative stress and mitochondrial dysfunction, a condition that has been associated with both T2D and AD (127,128).

Consumption of a high-fat diet causes increased mitochondrial ROS production and oxidative stress in skeletal muscle, leading to the development of peripheral insulin resistance in T2D (129). Similarly, elevated ROS levels in the brain can be detrimental. Excessive ROS levels are implicated in the molecular etiology of AD, with elevated markers of oxidative stress, including oxidized forms of lipids, proteins, and DNA present in an AD brain (128). In AD, aberrant stimulation of excitatory N-methyl-D-aspartate receptors (NMDA-Rs) by AβOs has been proposed as a key mechanism leading to excessive ROS production, likely as a consequence of Ca^{2+}-related mitochondrial dysfunction (130). Brain insulin signaling and oxidative stress appear to be intimately connected, as AβO-induced neuronal oxidative stress is blocked by insulin (51,131). The mechanism of protection by insulin appears to involve activation of Akt (131) and prevention of abnormal NMDA-R activation (132). NMDA-R deregulation indeed seems to play a role in oxidative stress and defective neuronal insulin signaling in AD, as AβO-induced inhibition of IR signaling is prevented by the NMDA-R blocker memantine (52). It is possible that mitochondrial dysfunction and chronically elevated ROS levels sustain a vicious cycle that impairs insulin signaling in AD.

Interestingly, mitochondrial dysfunction and increased ROS generation were recently found to activate JNK and to lead to insulin resistance in skeletal muscle and liver (133). As discussed in previous sections, AD and metabolic disorders have been associated with JNK activation and with reduced levels of insulin/IGF-1 and their receptors (37,38,40,121). Therefore, it is likely that a complex signaling network closely connected to mitochondrial dysfunction leads to impaired insulin signaling in both AD and diabetes. In fact, it has been recently proposed that a coordinated metabolic triad comprising mitochondria, insulin, and JNK signaling plays a key role in neuronal dysfunction in brain aging and AD (134). Since both the IR and the JNK signaling pathways affect mitochondrial function, it is conceivable that a similar triad operates in metabolic disorders, impairing mitochondrial bioenergetics and biogenesis and leading to redox dyshomeostasis.

CONCLUSION

AD and T2D are chronic, debilitating, and extremely costly for health programs in developed and developing countries. The emergence of molecular links between inflammatory, deregulated insulin signaling and mitochondrial dysfunction in AD and diabetes raises the prospect for development of novel therapeutic strategies for AD based on antidiabetes and/or anti-inflammatory agents (11,61). Further studies aimed to unravel novel pathways and mechanisms implicated in brain inflammation

and defective insulin signaling in AD as well as the effects of antidiabetes agents are highly anticipated in the field.

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References

1. International Diabetes Federation. *IDF Diabetes Atlas*. 6th ed. Brussels, International Diabetes Federation, 2013
2. Alzheimer's Association. 2013 Alzheimer's disease facts and figures. Alzheimers Dement 2013;9:208–245
3. Ott A, Stolk RP, van Harskamp F, Pols HAP, Hofman A, Breteler MMB. Diabetes mellitus and the risk of dementia: the Rotterdam Study. Neurology 1999;53:1937–1942
4. Crane PK, Walker R, Hubbard RA, et al. Glucose levels and risk of dementia. N Engl J Med 2013;369:540–548
5. Ott A, Stolk RP, Hofman A, van Harskamp F, Grobbee DE, Breteler MMB. Association of diabetes mellitus and dementia: the Rotterdam Study. Diabetologia 1996;39:1392–1397
6. Patrone C, Eriksson O, Lindholm D. Diabetes drugs and neurological disorders: new views and therapeutic possibilities. Lancet Diabetes Endocrinol 2014;2:256–262
7. Peters SAE, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775 385 individuals and 12 539 strokes. Lancet. 6 March 2014 [Epub ahead of print]
8. Baker LD, Cross DJ, Minoshima S, Belongia D, Watson GS, Craft S. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol 2011;68:51–57
9. Matsuzaki T, Sasaki K, Tanizaki Y, et al. Insulin resistance is associated with the pathology of Alzheimer disease: the Hisayama study. Neurology 2010; 75:764–770
10. Kerti L, Witte AV, Winkler A, Grittner U, Rujescu D, Flöel A. Higher glucose levels associated with lower memory and reduced hippocampal microstructure. Neurology 2013;81:1746–1752
11. De Felice FG. Alzheimer's disease and insulin resistance: translating basic science into clinical applications. J Clin Invest 2013;123:531–539
12. Craft S. Alzheimer disease: insulin resistance and AD—extending the translational path. Nat Rev Neurol 2012;8:360–362
13. Mattson MP. Energy intake and exercise as determinants of brain health and vulnerability to injury and disease. Cell Metab 2012;16:706–722
14. Velloso LA, Schwartz MW. Altered hypothalamic function in diet-induced obesity. Int J Obes (Lond) 2011;35:1455–1465
15. Thaler JP, Yi C-X, Schur EA, et al. Obesity is associated with hypothalamic injury in rodents and humans. J Clin Invest 2012;122:153–162
16. Beydoun MA, Beydoun HA, Wang Y. Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis. Obes Rev 2008;9:204–218
17. Hassing LB, Dahl AK, Thorvaldsson V, et al. Overweight in midlife and risk of dementia: a 40-year follow-up study. Int J Obes (Lond) 2009;33:893–898
18. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. Arch Neurol 2005;62: 1556–1560
19. Eskelinen MH, Ngandu T, Helkala EL, et al. Fat intake at midlife and cognitive impairment later in life: a population-based CAIDE study. Int J Geriatr Psychiatry 2008;23:741–747
20. Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Dietary fat intake and the risk of incident dementia in the Rotterdam Study. Ann Neurol 1997;42:776–782
21. Ho L, Qin W, Pompl PN, et al. Diet-induced insulin resistance promotes amyloidosis in a transgenic mouse model of Alzheimer's disease. FASEB J 2004; 18:902–904
22. Takeda S, Sato N, Uchio-Yamada K, et al. Diabetes-accelerated memory dysfunction via cerebrovascular inflammation and Abeta deposition in an Alzheimer mouse model with diabetes. Proc Natl Acad Sci U S A 2010;107:7036–7041
23. Bitel CL, Kasinathan C, Kaswala RH, Klein WL, Frederikse PH. Amyloid-β and tau pathology of Alzheimer's disease induced by diabetes in a rabbit animal model. J Alzheimers Dis 2012;32:291–305
24. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell 2012;148:852–871
25. Biddinger SB, Kahn CR. From mice to men: insights into the insulin resistance syndromes. Annu Rev Physiol 2006;68:123–158
26. Gesta S, Blüher M, Yamamoto Y, et al. Evidence for a role of developmental genes in the origin of obesity and body fat distribution. Proc Natl Acad Sci U S A 2006;103:6676–6681
27. Gunton JE, Kulkarni RN, Yim S, et al. Loss of ARNT/HIF1β mediates altered gene expression and pancreatic-islet dysfunction in human type 2 diabetes. Cell 2005;122:337–349
28. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol 2011;29:415–445
29. Taniguchi CM, Emanuelli B, Kahn CR. Critical nodes in signalling pathways: insights into insulin action. Nat Rev Mol Cell Biol 2006;7:85–96
30. Hotamisligil GS, Peraldi P, Budavari A, Ellis R, White MF, Spiegelman BM. IRS-1-mediated inhibition of insulin receptor tyrosine kinase activity in TNF-α- and obesity-induced insulin resistance. Science 1996;271:665–668
31. Peraldi P, Hotamisligil GS, Buurman WA, White MF, Spiegelman BM. Tumor necrosis factor (TNF)-alpha inhibits insulin signaling through stimulation of the p55 TNF receptor and activation of sphingomyelinase. J Biol Chem 1996;271: 13018–13022
32. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409–2415
33. Hotamisligil GS, Budavari A, Murray D, Spiegelman BM. Reduced tyrosine kinase activity of the insulin receptor in obesity-diabetes. Central role of tumor necrosis factor-α. J Clin Invest 1994;94:1543–1549
34. Hotamisligil GS. Inflammation and metabolic disorders. Nature 2006;444: 860–867
35. Steen E, Terry BM, Rivera EJ, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease—is this type 3 diabetes? J Alzheimers Dis 2005;7:63–80
36. Moloney AM, Griffin RJ, Timmons S, O'Connor R, Ravid R, O'Neill C. Defects in IGF-1 receptor, insulin receptor and IRS-1/2 in Alzheimer's disease indicate possible resistance to IGF-1 and insulin signalling. Neurobiol Aging 2010;31:224–243

37. Bomfim TR, Forny-Germano L, Sathler LB, et al. An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease-associated Aβ oligomers. J Clin Invest 2012;122:1339–1353

38. Talbot K, Wang HY, Kazi H, et al. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J Clin Invest 2012;122:1316–1338

39. Clark I, Atwood C, Bowen R, Paz-Filho G, Vissel B. Tumor necrosis factor-induced cerebral insulin resistance in Alzheimer's disease links numerous treatment rationales. Pharmacol Rev 2012;64:1004–1026

40. Ma QL, Yang F, Rosario ER, et al. β-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. J Neurosci 2009;29:9078–9089

41. Ferreira ST, Vieira MNN, De Felice FG. Soluble protein oligomers as emerging toxins in Alzheimer's and other amyloid diseases. IUBMB Life 2007;59:332–345

42. Ferreira ST, Klein WL. The Aβ oligomer hypothesis for synapse failure and memory loss in Alzheimer's disease. Neurobiol Learn Mem 2011;96:529–543

43. Negash S, Bennett DA, Wilson RS, Schneider JA, Arnold SE. Cognition and neuropathology in aging: multidimensional perspectives from the Rush Religious Orders Study and Rush Memory And Aging Project. Curr Alzheimer Res 2011;8:336–340

44. Terry RD, Masliah E, Salmon DP, et al. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann Neurol 1991;30:572–580

45. Gylys KH, Fein JA, Yang F, Wiley DJ, Miller CA, Cole GM. Synaptic changes in Alzheimer's disease: increased amyloid-beta and gliosis in surviving terminals is accompanied by decreased PSD-95 fluorescence. Am J Pathol 2004;165:1809–1817

46. Lambert MP, Barlow AK, Chromy BA, et al. Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. Proc Natl Acad Sci U S A 1998;95:6448–6453

47. Björklund NL, Reese LC, Sadagoparamanujam VM, Ghirardi V, Woltjer RL, Taglialatela G. Absence of amyloid β oligomers at the postsynapse and regulated synaptic Zn2+ in cognitively intact aged individuals with Alzheimer's disease neuropathology. Mol Neurodegener 2012;7:23

48. Gong Y, Chang L, Viola KL, et al. Alzheimer's disease-affected brain: presence of oligomeric A β ligands (ADDLs) suggests a molecular basis for reversible memory loss. Proc Natl Acad Sci U S A 2003;100:10417–10422

49. Fukumoto H, Tokuda T, Kasai T, et al. High-molecular-weight β-amyloid oligomers are elevated in cerebrospinal fluid of Alzheimer patients. FASEB J 2010;24:2716–2726

50. Haass C, Selkoe DJ. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid β-peptide. Nat Rev Mol Cell Biol 2007;8:101–112

51. De Felice FG, Vieira MNN, Bomfim TR, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. Proc Natl Acad Sci U S A 2009;106:1971–1976

52. Zhao WQ, De Felice FG, Fernandez S, et al. Amyloid beta oligomers induce impairment of neuronal insulin receptors. FASEB J 2008;22:246–260

53. Plum L, Schubert M, Brüning JC. The role of insulin receptor signaling in the brain. Trends Endocrinol Metab 2005;16:59–65

54. Lourenco MV, Clarke JR, Frozza RL, et al. TNF-α mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's β-amyloid oligomers in mice and monkeys. Cell Metab 2013;18:831–843

55. Wan Q, Xiong ZG, Man HY, et al. Recruitment of functional GABA(A) receptors to postsynaptic domains by insulin. Nature 1997;388:686–690

56. Chiu S-L, Chen C-M, Cline HT. Insulin receptor signaling regulates synapse number, dendritic plasticity, and circuit function in vivo. Neuron 2008;58:708–719

57. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol 2012;69:29–38

58. Schubert M, Gautam D, Surjo D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. Proc Natl Acad Sci U S A 2004;101:3100–3105

59. Cheng Z, Tseng Y, White MF. Insulin signaling meets mitochondria in metabolism. Trends Endocrinol Metab 2010;21:589–598

60. White MF. Insulin signaling in health and disease. Science 2003;302:1710–1711

61. Ferreira ST, Clarke JR, Bomfim TR, De Felice FG. Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease. Alzheimers Dement 2014;10(Suppl.):S76–S83

62. Brown KL, Cosseau C, Gardy JL, Hancock REW. Complexities of targeting innate immunity to treat infection. Trends Immunol 2007;28:260–266

63. Perry VH, Nicoll JAR, Holmes C. Microglia in neurodegenerative disease. Nat Rev Neurol 2010;6:193–201

64. Swardfager W, Lanctôt K, Rothenburg L, Wong A, Cappell J, Herrmann N. A meta-analysis of cytokines in Alzheimer's disease. Biol Psychiatry 2010;68:930–941

65. Schwartz MW, Porte D Jr. Diabetes, obesity, and the brain. Science 2005;307:375–379

66. De Souza CT, Araujo EP, Bordin S, et al. Consumption of a fat-rich diet activates a proinflammatory response and induces insulin resistance in the hypothalamus. Endocrinology 2005;146:4192–4199

67. Arruda AP, Milanski M, Coope A, et al. Low-grade hypothalamic inflammation leads to defective thermogenesis, insulin resistance, and impaired insulin secretion. Endocrinology 2011;152:1314–1326

68. Purkayastha S, Zhang H, Zhang G, Ahmed Z, Wang Y, Cai D. Neural dysregulation of peripheral insulin action and blood pressure by brain endoplasmic reticulum stress. Proc Natl Acad Sci U S A 2011;108:2939–2944

69. Zhang X, Zhang G, Zhang H, Karin M, Bai H, Cai D. Hypothalamic IKKbeta/NF-kappaB and ER stress link overnutrition to energy imbalance and obesity. Cell 2008;135:61–73

70. Milanski M, Degasperi G, Coope A, et al. Saturated fatty acids produce an inflammatory response predominantly through the activation of TLR4 signaling in hypothalamus: implications for the pathogenesis of obesity. J Neurosci 2009;29:359–370

71. Hirosumi J, Tuncman G, Chang L, et al. A central role for JNK in obesity and insulin resistance. Nature 2002;420:333–336

72. Nakamura T, Furuhashi M, Li P, et al. Double-stranded RNA-dependent protein kinase links pathogen sensing with stress and metabolic homeostasis. Cell 2010;140:338–348

73. Grammas P, Ovase R. Inflammatory factors are elevated in brain microvessels in Alzheimer's disease. Neurobiol Aging 2001;22:837–842

74. Ruan L, Kang Z, Pei G, Le Y. Amyloid deposition and inflammation in APPswe/PS1dE9 mouse model of Alzheimer's disease. Curr Alzheimer Res 2009;6:531–540

75. Hoozemans JJM, van Haastert ES, Nijholt DAT, Rozemuller AJM, Eikelenboom P, Scheper W. The unfolded protein response is activated in pretangle neurons in Alzheimer's disease hippocampus. Am J Pathol 2009;174:1241–1251

76. Chang RC, Suen K-C, Ma C-H, Elyaman W, Ng H-K, Hugon J. Involvement of double-stranded RNA-dependent protein kinase and phosphorylation of eukaryotic initiation factor-2alpha in neuronal degeneration. J Neurochem 2002;83:1215–1225

77. Cai D, Yuan M, Frantz DF, et al. Local and systemic insulin resistance resulting from hepatic activation of IKK-β and NF-kappaB. Nat Med 2005;11:183–190

78. Calay ES, Hotamisligil GS. Turning off the inflammatory, but not the metabolic, flames. Nat Med 2013;19:265–267

79. Thomis DC, Samuel CE. Mechanism of interferon action: evidence for intermolecular autophosphorylation and autoactivation of the interferon-induced, RNA-dependent protein kinase PKR. J Virol 1993;67:7695–7700

80. Takada Y, Ichikawa H, Pataer A, Swisher S, Aggarwal BB. Genetic deletion of PKR abrogates TNF-induced activation of IkappaBalpha kinase, JNK, Akt and

cell proliferation but potentiates p44/p42 MAPK and p38 MAPK activation. Oncogene 2007;26:1201–1212
81. Zhao WQ, Chen H, Quon MJ, Alkon DL. Insulin and the insulin receptor in experimental models of learning and memory. Eur J Pharmacol 2004;490:71–81
82. Zhao WQ, Alkon DL. Role of insulin and insulin receptor in learning and memory. Mol Cell Endocrinol 2001;177:125–134
83. Haj-ali V, Mohaddes G, Babri SH. Intracerebroventricular insulin improves spatial learning and memory in male Wistar rats. Behav Neurosci 2009;123: 1309–1314
84. Francis GJ, Martinez JA, Liu WQ, et al. Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy. Brain 2008;131:3311–3334
85. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev 2007;56:384–402
86. Fernandez AM, Torres-Alemán I. The many faces of insulin-like peptide signalling in the brain. Nat Rev Neurosci 2012;13:225–239
87. Benedict C, Brooks SJ, Kullberg J, et al. Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly. Diabetes Care 2012;35:488–494
88. Selkoe DJ. Resolving controversies on the path to Alzheimer's therapeutics. Nat Med 2011;17:1060–1065
89. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. Neurology 2008;70:440–448
90. Freiherr J, Hallschmid M, Frey WH 2nd, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. CNS Drugs 2013;27:505–514
91. Vilsbøll T, Krarup T, Madsbad S, Holst JJ. Both GLP-1 and GIP are insulinotropic at basal and postprandial glucose levels and contribute nearly equally to the incretin effect of a meal in healthy subjects. Regul Pept 2003;114:115–121
92. Mattson MP, Perry T, Greig NH. Learning from the gut. Nat Med 2003;9: 1113–1115
93. Göke R, Larsen PJ, Mikkelsen JD, Sheikh SP. Distribution of GLP-1 binding sites in the rat brain: evidence that exendin-4 is a ligand of brain GLP-1 binding sites. Eur J Neurosci 1995;7:2294–2300
94. During MJ, Cao L, Zuzga DS, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med 2003;9:1173–1179
95. Abbas T, Faivre E, Hölscher C. Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: interaction between type 2 diabetes and Alzheimer's disease. Behav Brain Res 2009;205:265–271
96. Yusta B, Baggio LL, Estall JL, et al. GLP-1 receptor activation improves β cell function and survival following induction of endoplasmic reticulum stress. Cell Metab 2006;4:391–406
97. Pandini G, Pace V, Copani A, Squatrito S, Milardi D, Vigneri R. Insulin has multiple antiamyloidogenic effects on human neuronal cells. Endocrinology 2013; 154:375–387
98. Yang Y, Ma D, Wang Y, et al. Intranasal insulin ameliorates tau hyperphosphorylation in a rat model of type 2 diabetes. J Alzheimers Dis 2013;33: 329–338
99. McClean PL, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci 2011;31:6587–6594
100. Vitale G, Salvioli S, Franceschi C. Oxidative stress and the ageing endocrine system. Nat Rev Endocrinol 2013;9:228–240
101. Salvioli S, Capri M, Valensin S, et al. Inflamm-aging, cytokines and aging: state of the art, new hypotheses on the role of mitochondria and new perspectives from systems biology. Curr Pharm Des 2006;12:3161–3171
102. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci 2000;908:244–254
103. Herrup K. Reimagining Alzheimer's disease—an age-based hypothesis. J Neurosci 2010;30:16755–16762
104. Acharya NK, Levin EC, Clifford PM, et al. Diabetes and hypercholesterolemia increase blood-brain barrier permeability and brain amyloid deposition: beneficial effects of the LpPLA2 inhibitor darapladib. J Alzheimers Dis 2013;35: 179–198
105. Sonnen JA, Larson EB, Brickell K, et al. Different patterns of cerebral injury in dementia with or without diabetes. Arch Neurol 2009;66:315–322
106. Takeda S, Sato N, Ikimura K, Nishino H, Rakugi H, Morishita R. Increased blood-brain barrier vulnerability to systemic inflammation in an Alzheimer disease mouse model. Neurobiol Aging 2013;34:2064–2070
107. Xu H, Barnes GT, Yang Q, et al. Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance. J Clin Invest 2003; 112:1821–1830
108. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007;117:175–184
109. Banks WA. Blood-brain barrier transport of cytokines: a mechanism for neuropathology. Curr Pharm Des 2005;11:973–984
110. Yamauchi T, Kamon J, Ito Y, et al. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. Nature 2003;423:762–769
111. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. Nat Med 2001;7:947–953
112. Paz-Filho G, Wong ML, Licinio J. The procognitive effects of leptin in the brain and their clinical implications. Int J Clin Pract 2010;64:1808–1812
113. Pérez-González R, Antequera D, Vargas T, Spuch C, Bolós M, Carro E. Leptin induces proliferation of neuronal progenitors and neuroprotection in a mouse model of Alzheimer's disease. J Alzheimers Dis 2011;24(Suppl. 2):17–25
114. Greco SJ, Sarkar S, Johnston JM, et al. Leptin reduces Alzheimer's disease-related tau phosphorylation in neuronal cells. Biochem Biophys Res Commun 2008; 376:536–541
115. Lieb W, Beiser AS, Vasan RS, et al. Association of plasma leptin levels with incident Alzheimer disease and MRI measures of brain aging. JAMA 2009;302: 2565–2572
116. Hotta K, Funahashi T, Bodkin NL, et al. Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. Diabetes 2001;50:1126–1133
117. Yatagai T, Nagasaka S, Taniguchi A, et al. Hypoadiponectinemia is associated with visceral fat accumulation and insulin resistance in Japanese men with type 2 diabetes mellitus. Metabolism 2003;52:1274–1278
118. Une K, Takei YA, Tomita N, et al. Adiponectin in plasma and cerebrospinal fluid in MCI and Alzheimer's disease. Eur J Neurol 2011;18:1006–1009
119. Osenkowski P, Ye W, Wang R, Wolfe MS, Selkoe DJ. Direct and potent regulation of gamma-secretase by its lipid microenvironment. J Biol Chem 2008; 283:22529–22540
120. Holland WL, Bikman BT, Wang L-P, et al. Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid-induced ceramide biosynthesis in mice. J Clin Invest 2011;121: 1858–1870
121. de la Monte SM. Triangulated mal-signaling in Alzheimer's disease: roles of neurotoxic ceramides, ER stress, and insulin resistance reviewed. J Alzheimers Dis 2012;30(Suppl. 2):S231–S249
122. Smith QR, Nagura H. Fatty acid uptake and incorporation in brain: studies with the perfusion model. J Mol Neurosci 2001;16:167–172; discussion 215–221
123. Petersen KF, Befroy D, Dufour S, et al. Mitochondrial dysfunction in the elderly: possible role in insulin resistance. Science 2003;300:1140–1142
124. Cadenas E, Davies KJ. Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med 2000;29:222–230
125. Loh K, Deng H, Fukushima A, et al. Reactive oxygen species enhance insulin sensitivity. Cell Metab 2009;10:260–272
126. Serrano F, Klann E. Reactive oxygen species and synaptic plasticity in the aging hippocampus. Ageing Res Rev 2004;3:431–443

127. Petersen KF, Dufour S, Befroy D, Garcia R, Shulman GI. Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes. N Engl J Med 2004;350:664–671
128. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature 2004;430:631–639
129. Anderson EJ, Lustig ME, Boyle KE, et al. Mitochondrial H2O2 emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. J Clin Invest 2009;119:573–581
130. De Felice FG, Velasco PT, Lambert MP, et al. Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. J Biol Chem 2007; 282:11590–11601
131. Picone P, Giacomazza D, Vetri V, et al. Insulin-activated Akt rescues Aβ oxidative stress-induced cell death by orchestrating molecular trafficking. Aging Cell 2011;10:832–843
132. Decker H, Jürgensen S, Adrover MF, et al. N-methyl-D-aspartate receptors are required for synaptic targeting of Alzheimer's toxic amyloid-β peptide oligomers. J Neurochem 2010;115:1520–1529
133. Sebastián D, Hernández-Alvarez MI, Segalés J, et al. Mitofusin 2 (Mfn2) links mitochondrial and endoplasmic reticulum function with insulin signaling and is essential for normal glucose homeostasis. Proc Natl Acad Sci U S A 2012;109: 5523–5528
134. Yin F, Jiang T, Cadenas E. Metabolic triad in brain aging: mitochondria, insulin/IGF-1 signalling and JNK signalling. Biochem Soc Trans 2013;41:101–105