Alzheimer’s disease (AD) and diabetes are currently considered among the top threats to human health worldwide. Intriguingly, a connection between these diseases has been established during the past decade, since insulin resistance, a hallmark of type 2 diabetes, also develops in Alzheimer brains. In this article, the molecular and cellular mechanisms underlying defective brain insulin signaling in AD are discussed, with emphasis on evidence that Alzheimer’s and diabetes share common inflammatory signaling pathways. I put forward here a hypothesis on how a cross-talk between peripheral tissues and the brain might influence the development of AD, and highlight important unanswered questions in the field. Furthermore, I discuss a rational basis for the use of antidiabetic agents as novel and potentially effective therapeutics in AD.

Brain insulin signaling and clinical evidence linking AD and diabetes

Historically, skeletal muscle, adipose tissue, and liver were regarded as key insulin-sensitive organs involved in insulin-mediated regulation of peripheral carbohydrate, lipid, and protein metabolism. The consequences of impaired insulin action in those organs were deemed to explain the functional and structural abnormalities associated with insulin resistance. On the other hand, since the discovery of insulin in 1922 (1), the brain had been generally considered an insulin-insensitive organ. However, evidence of insulin actions in the brain emerged more than 30 years ago with the demonstration that i.c.v. infusion of insulin decreased food intake in baboons (2). This landmark finding was followed by several studies reporting that the hypothalamic actions of insulin regulate peripheral energy homeostasis (3, 4).

The effects of insulin in the brain are not restricted to the hypothalamus, as IRs are widely distributed throughout the encephalon (5). The hippocampus, a region that is fundamentally involved in the acquisition, consolidation, and recollection of new memories, presents particularly high levels of IRs (6), indicating that insulin might have additional targets in the CNS outside of the hypothalamus. Indeed, insulin has been shown to be neuroprotective (7–10) and to affect synaptic plasticity mechanisms (11, 12). Insulin has been proposed to regulate neuronal survival and to act as a growth factor (13), possibly by activating IGF receptors (14). In cultured hippocampal neurons, IRs show a punctate dendritic distribution (15, 16) consistent with the synaptic occurrence of IRs. IR signaling further regulates circuit function and plasticity by controlling synapse density (17). Nonetheless, knowledge of the precise roles of brain IRs is still limited. While studies indicate memory-improving effects of insulin and learning-associated changes in IR pathways (18–21), specific deletion of brain IRs did not lead to major learning and memory impairment in mice (22). However, compensatory mechanisms may operate to prevent memory deficits in such mice by stimulation of insulin signaling-related pathways via other receptors, including those for IGF and glucagon-like peptide 1 (GLP-1). These mechanisms may act to compensate for the absence of IR signaling.

Reflecting a major paradigm shift, recent evidence increasingly indicates that the brain is an important target for insulin actions. The challenge now is to identify in detail the signaling pathways used by insulin in the brain, as failure of those signals has been associated with brain disorders, including stroke, AD, and Parkinson disease (22). The incidence of these neurological disorders appears to be higher in individuals with type 2 diabetes (23), and type 2 diabetes patients can be more than twice as likely to develop AD than nondiabetics (24). In addition to clinical correlations, lower levels of insulin, IGF, and IRs in AD brains further implicate insulin resistance in AD neuropathology (25–27). Brain insulin signaling impairments were also described in animal models of AD (10, 28) and in rodents receiving intracerebral streptozotocin injections (29). A recent elegant study demonstrated that several biomarkers of peripheral insulin resistance are greatly increased in the hippocampus of nondiabetic AD patients (30). As a result of these studies, defective brain insulin signaling is now considered an important feature of AD pathology.

AD is the most common form of dementia in the elderly, and current estimates suggest it may affect more than 24 million individuals worldwide (31). In addition, recent assessments indicate that about 347 million individuals worldwide have type 2 diabetes (32). Both diseases are common causes of morbidity and mortality, thus underscoring the urgent need to unravel how insulin resistance develops in the brain and peripheral tissues.

Amyloid-β oligomers: synaptotoxins that build up in the AD brain and impair neuronal IRs

In 1906, Alois Alzheimer noticed specific neuropathological alterations in the brain of a female patient who had died as a consequence of an atypical mental illness. Her symptoms included striking memory loss, language problems, and changes in personality. Upon postmortem examination of her brain, Alzheimer found many abnormal proteinaceous deposits, now known as amyloid plaques (33), in the parenchyma. Eight decades later, the chief component of the plaques was determined to be amyloid-β (Aβ) (34, 35), a peptide that exhibits a high propensity to self-associate in aqueous medium.
Several studies have demonstrated that the neurotoxicity of Aβ requires self-assembly of the 4 kDa Aβ peptide into aggregates of various sizes. The question of which specific aggregate species are responsible for degeneration has been vigorously debated. For decades, large insoluble Aβ fibrils that deposit as amyloid plaques, which can be easily detected in AD brains, were thought to cause neuronal death (hence, memory loss) in AD. More recent findings, however, indicate that fibrils are probably not the most harmful structures generated by self-association of Aβ. Of clinical relevance, individuals who died without any signs of cognitive and intellectual deterioration have been found to present abundant brain amyloid deposits while, conversely, individuals lacking deposits have been found to exhibit varying degrees of cognitive deterioration (36). Moreover, the best correlate of the extent of dementia is not amyloid burden, but rather synapse loss (37), suggesting a subcellular redistribution of IRs could be caused by a toxin other than fibrillar Aβ.

William Klein and coworkers first addressed this controversy, showing that Aβ self-aggregates to form neurotoxic-soluble oligomers, aggregates much smaller than fibrils (38) that are not easily observed in neuropathological examination. Oligomers were recently observed at the postsynapse in AD hippocampi (39), and their levels are elevated in the brain and cerebrospinal fluid of AD patients (40–42). Interestingly, the absence of Aβ oligomers at the postsynapse was reported in cognitively intact elderly individuals whose brains presented amyloid deposits (39). 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 impact of Aβ oligomers (43–45).

The impact of Aβ oligomers in the brain appears to be intimately related to defective insulin signaling. The first molecular clue to how the brain might become insulin resistant in AD came from studies demonstrating that Aβ oligomers bind to hippocampal neurons and trigger the removal of IRs from the plasma membrane (Figure 1) (15, 16), which was subsequently verified in AD brains (25, 46). Neurons with oligomers attached to their surface show elevated IR levels in their cell bodies, suggesting a subcellular redistribution of IRs (Figure 1). This leads to decreased responsiveness to insulin, revealed by impaired insulin-induced receptor protein tyrosine kinase activity in cultured neurons exposed to oligomers (15).

Besides IRs, other proteins important for synaptic plasticity, including NMDA- (47, 48) and AMPA-type glutamate receptors (49), are removed from the cell surface when neurons are exposed to oligomers, indicating a broad impact on synapses. Oligomer actions are thought to underlie other aspects of brain dysfunction in AD, activating signaling pathways that lead to abnormal tau phosphorylation (50–52) and oxidative stress (53–55), both hallmarks of AD pathology. Thus, altered neuronal IR function is an important aspect of the overall synaptic and neuronal pathology induced by Aβ oligomers. This provides a basis for brain insulin resistance in AD and is likely connected to impaired learning and memory in disease.

Roles of IRS-1, IRS-2, and IGF-1 signaling in the brain

IR substrate (IRS) proteins (IRS-1 and IRS-2) play key roles in transmitting signals from the insulin and IGF-1 receptors to several intracellular pathways, including the PI3K/AKT and ERK/MAP kinase pathways, in peripheral tissue (56, 57). In contrast, the spe-
cific roles of IRS-1, IRS-2, and IGF-1 in the brain with respect to cognitive function are still not completely understood, as knowledge of the precise roles of neuronal IRs is at present somewhat limited.

Several reports indicate memory-enhancing effects of insulin, learning-associated changes in IR pathways, and impairment of memory and long-term potentiation (LTP) in diabetic animals (6, 8, 11, 58). IRS-1 seems to be particularly important for proper brain function, and is found to be inhibited in AD brains (10, 30, 46) and in an animal model (10). Additionally, attenuation of IRS-1 inhibition is accompanied by improved cognition in transgenic mice (10, 52). On the other hand, IRS-2 signaling impairs dendritic spine formation (59). Deletion of IRS-2 further reduces amyloid deposition, cognitive deficits, and premature mortality in a transgenic mouse model of AD (60). The beneficial effects of IRS-2 deletion in AD pathology parallel the effects on lifespan, with less IRS-2 signaling resulting in extended lifespan in mice (61). IRS-2 levels are also decreased in the amyloid precursor protein-presenilin 1 (APP/PS1) transgenic mouse model of AD (10) and in AD brains (46), which may indicate a compensatory mechanism to decrease IRS-2 signaling (62). However, whether this is an active neuroprotective response or a secondary response to the neurodegenerative process remains unclear. Recently, physiological doses (1 nM) of insulin and IGF-1 were demonstrated to activate different IRS signaling pathways in ex vivo AD brain slices (30); impaired IR signaling was associated with dysfunctional IRS-1, while IGF-1 resistance was associated with dysfunctional IRS-2 signaling (30). Therefore, an apparent dichotomy exists between the neuroprotective effects of brain insulin signaling and its deleterious actions on lifespan and memory. Conceivably, IRS-1 positively regulates memory, while IRS-2 acts as a negative regulator of memory formation, but the roles of neuronal IRS-1, IRS-2, and IGF signaling in health and disease certainly need further exploration.

Molecular basis for brain insulin resistance in AD

As several pathological features, including impaired insulin signaling and inflammation, appear to be shared by diabetic and AD patients, mechanisms analogous to those that account for peripheral insulin resistance in type 2 diabetes likely underlie impaired brain insulin signaling in AD. Indeed, recent findings link pathogenic mechanisms triggered by Aβ oligomers in AD brain to mechanisms present in diabetes (10, 27, 52). In type 2 diabetes, TNF-α signaling activates c-Jun N-terminal kinase (JNK) (63). This results in IRS-1 serine phosphorylation (IRS-1pSer), blocking downstream insulin signaling and triggering peripheral insulin resistance (15). Similarly, Aβ oligomers cause abnormal activation of the TNF-α/JNK pathway and IRS-1 inhibition in cultured hippocampal neurons (10, 52). JNK activation and IRS-1 inhibition are further present in the hippocampi of cynomolgus monkeys given i.c.v. injections of Aβ oligomers, as well as in the brains of a transgenic mouse model of AD (10). Likewise, postmortem AD brains showed elevated IRS-1pSer (10, 30) and activated JNK levels (10). Because oligomers instigate internalization and redistribution of neuronal IRs (15), IR removal from the cell surface may underlie, or facilitate, IRS-1pSer. Insulin consistently blocks both IR downregulation (16) and IRS-1pSer induced by Aβ oligomers (10).

Downstream of IRS-1 and PI3 kinase, oligomers induce inhibitory phosphorylation of AKT, a central signaling molecule of the IR pathway. Elevated AKT-pSer473 levels are associated with inflammation and peripheral insulin resistance (64, 65). Notably, stimulation of AKT-pSer473 by oligomers occurs whether or not insulin is present (15), suggesting the involvement of a pathway independent of IRS, and possibly involving TNF-α signaling. Recently, elevated TNF-α and APP levels were observed in the hippocampus of a mouse model of high-fat diet–induced obesity (66), mechanistically linking the pathophysiology of obesity to AD.

In peripheral insulin resistance, TNF-α/JNK activation is linked to major inflammatory and stress signaling networks, including ER stress and the stress kinases JNK and AKT, and protein kinase regulated by RNA (PKR) (67, 68). Interestingly, JNK and PKR appear to mediate oligomer–induced neuronal IRS-1 inhibition (10). Therefore, ER stress, which is reported to occur in AD brains (69), likely further underlies Aβ oligomer–induced defective neuronal insulin signaling. If confirmed, this observation would reinforce the notion that common mechanisms underlie impaired peripheral insulin signaling in type 2 diabetes and brain insulin resistance in AD (10).

Oxidative stress: a link between AD and diabetes

ROS are minor cytotoxic products of normal mitochondrial metabolism. In the brain, the transient production of ROS plays a role in synaptic signaling, with ROS acting as messenger molecules in LTP (70). Similarly, moderate ROS levels are thought to enhance peripheral insulin sensitivity (71). However, the imbalance between mitochondrial ROS production and intracellular levels of antioxidant defenses leads to mitochondrial dysfunction, abnormally elevated ROS levels, and oxidative stress, which is associated with both peripheral insulin resistance and AD (71, 72). The transcriptional activity of FoxO proteins has been proposed to underlie defective insulin signaling in AD and diabetes, as insulin resistance and oxidative stress may promote the FoxO response that leads to JNK activation (73).

Interestingly, Aβ oligomer–induced neuronal oxidative stress (53, 54, 74) is blocked by insulin (16, 75). The mechanism of protection by insulin appears to involve activation of AKT (75) and prevention of abnormal NMDA receptor (NMDA-R) activation (76). NMDA-R dysfunction indeed seems to play a role in oxidative stress and defective neuronal insulin signaling in AD, as Aβ oligomer–induced inhibition of IR signaling is prevented by the NMDA-R blocker memantine (15). Memantine and an anti–NMDA-R antibody further attenuate the oligomer–induced increase in intraneuronal calcium, which is essential in causing neuronal oxidative stress (53, 74). A mechanism involving aberrant calcium influx and oxidative stress may underlie insulin resistance in AD, as glutamate and neuronal depolarization reduce the responsiveness of IRs to insulin (15), and chelation of intracellular calcium with BAPTA-AM prevents both oligomer–induced IR inhibition (15) and oxidative stress (53). NMDA-R signaling itself is affected by Aβ oligomers (48). These effects are concordant with existing IR regulatory mechanisms and suggest a possible physiological feedback between neuronal activity and insulin signaling. Thus, abnormal ROS levels may trigger a vicious cycle that impairs insulin signaling in AD.

A cumulative hypothesis for AD

Appealing hypotheses have been proposed to explain how AD develops, undoubtedly providing major contributions to our understanding of AD pathogenesis. The revised amyloid cascade hypothesis (77), which includes Aβ oligomers as synaptotoxins in AD, has received major attention. In familial forms of AD, muta-
tions in the APP and/or presenilin genes lead to increased Aβ production (78), strongly suggesting a causative relationship between Aβ generation and pathogenesis in AD. However, in sporadic AD (which corresponds to greater than 90% of AD cases), the exact mechanism that leads to oligomer-amyloid accumulation in AD brain remains a mystery. The discovery that insulin resistance develops in AD brains might be seen as an additional complication, because insulin resistance itself is a complex metabolic disorder (79). Nevertheless, this new link between AD and diabetes may in fact shed light on how sporadic AD develops.

Here, an alternative hypothesis is proposed in which a cross-talk between brain and peripheral tissues plays a central role in triggering the onset of sporadic AD (Figure 2). Similar hypotheses have been put forward based on work from Craft and de la Monte (80, 81), providing important advances in elucidating the connection between AD and diabetes. In the hypothesis presented here, I highlight the central role of peripheral inflammation in causing sporadic AD and propose that such events can start very early in life. An unhealthy lifestyle (e.g., lack of or insufficient physical activity, inadequate nutrition), which may start in the first years of life and increase the prevalence of type 2 diabetes in youth (82), might have an important role in susceptibility to AD later in life, as pointed out by Mark Mattson (83). An unhealthy lifestyle triggers deleterious processes in peripheral tissue, leading to the activation of pathways related to chronic metabolic syndrome (including obesity, insulin resistance, and type 2 diabetes). Notably, an unhealthy lifestyle exerts several detrimental effects on brain aging (84). Furthermore, poor sleep quality, as occurs in aging and in many obese individuals, may contribute to an increased risk of type 2 diabetes and AD (85, 86). According to this proposal, a cumulative impact on peripheral organs eventually results in defective brain metabolic homeostasis (see below), ultimately leading to AD (Figure 2).

In addition, different types of injuries may impact the brain and/or peripheral organs throughout life. Such events may start very early in life, with stress caused by maternal separation or physical or emotional child abuse, including shaken infant syndrome associated with cerebral contusions. Although the long-term outcomes of mild brain injury in infants still need to be fully understood, learning difficulties and memory problems have been reported to occur in affected children (87). Mild brain injury accelerates Aβ deposition, tau pathology, and cognitive deficits in transgenic AD mice (88, 89) and further leads to neurodegeneration and cognitive deficits in immature rats (90). In any period of life, traumatic brain injury may further lead to AD, as evidenced by elevated production of Aβ in such events (91). Additionally, brain insulin signaling declines with age (92). This deficiency may be a consequence of decreased insulin uptake into the brain following sustained peripheral hyperinsulinemia (93). This point, however, is still somewhat unclear, as an earlier study reported that AD patients have elevated insulin levels in their cerebrospinal fluid (CSF) under fasting conditions (94). However, more recent studies demonstrated that CSF insulin levels are decreased in patients with mild AD (95). Furthermore, a high saturated fat and high

Figure 2
A “cumulative hypothesis” for development of sporadic AD. Listed are the different types of injuries that may impact the brain (yellow), peripheral organs (pink), or both systems (orange) throughout life and increase the risk of sporadic AD. The cross-talk between brain and peripheral tissues may eventually result in defective brain metabolic homeostasis, which might be closely linked to elevated Aβ production and progressive accumulation of AβOs in the brain. AD, which could thus be considered a form of dementia caused by metabolic dyshomeostasis, would manifest in the elderly as a result of the cumulative, lifelong impact in the peripheral tissues and the brain.
glicemic diet was found to lower CSF insulin concentrations in healthy adults (96), corroborating the possibility that physiological mechanisms result in decreased brain insulin levels following peripheral hyperinsulinemia. Interestingly, impaired insulin sensitivity has been linked to cognitive deficits and structural and functional brain deficits in the elderly (97).

Inflammation plays a key role in metabolic disorders, particularly in obesity and type 2 diabetes (98). It is important to consider the causes of inflammation in peripheral tissues and to determine how this process could impact the brain, as activation of inflammatory signaling pathways is closely linked to the development of ER stress and insulin resistance (79, 99). A common pathway leading to peripheral insulin resistance involves lipid accumulation (e.g., palmitic acid, ceramides) in liver and skeletal muscle (100, 101). Prolonged consumption of food rich in saturated fatty acids is thought to be deleterious, as saturated fatty acids exert adverse health effects and are more likely to cause peripheral insulin resistance than unsaturated fatty acids. In fact, saturated fatty acids activate JNK and induce peripheral insulin resistance (102), abnormalities that are also observed in AD brains (10, 30). Interestingly, enhanced brain fatty acid uptake and accumulation have recently been reported in patients with metabolic syndrome, a process reversed by weight reduction (103). Also, ceramides, which are generated in the liver, have been proposed to cross the blood-brain barrier and cause brain insulin resistance and neurodegeneration (81). A mechanism linking lipid homeostasis and Aβ production was recently demonstrated, as microRNAs were found to regulate an enzyme involved in ceramide synthesis and, in turn, Aβ generation (104). Furthermore, cholesterol depletion inhibits Aβ generation (105), and growing evidence suggests that other lipids may have important roles in AD (106).

Moreover, microglial activation and inflammation-mediated neurotoxicity are suggested to be important in the pathogenesis of AD (107, 108). As disease progresses, Aβ deposits, neurofibrillary tangles, and damaged neurons, along with brain insulin resistance and ER stress (109), are thought to provide stimuli for inflammation.

Thus, inflammatory processes related to insulin resistance, such as inflammation caused by an unhealthy diet and physical inactivity, likely play a decisive role in linking peripheral and brain dyshomeostasis. The accumulation of and imbalance in certain lipids in peripheral tissues could lead to their continued release into the systemic circulation and their subsequent transport across the blood-brain barrier, which may affect the brain. In fact, nutritional inflammation impacts the hypothalamus (110, 111). Therefore, in brain regions that are affected in AD (e.g., hippocampus, frontal cortex), inflammation could lead to elevated Aβ production and to the progressive accumulation of Aβ oligomers in the brain. AD, which could thus be considered a form of dementia caused by metabolic dyshomeostasis, would manifest in the elderly as a result of this cumulative, lifelong impact on the periphery and the brain (Figure 2).

**Stimulation of brain insulin signaling as a therapeutic approach in AD**

AD is a catastrophic disease that demands effective treatment. Molecular links between dysregulated insulin signaling in AD and diabetes (10) raise the prospect for novel therapeutic strategies for AD based on antidiabetes agents. Conversely, diabetes therapy may affect the brain in other ways, as disruptions in the mechanisms of hypothalamic nutrient sensing alter homeostatic responses and contribute to the pathophysiology of obesity and type 2 diabetes (110).

Brain insulin signaling declines with age (92), a major risk factor for AD, suggesting that the beneficial effects of insulin signaling could be extended to AD patients. In agreement with the proposed role of insulin signaling in brain regions associated with cognition, especially in the hippocampus (5), intranasal insulin treatment improves memory in healthy adults, without changing blood levels of insulin or glucose (19, 112). Intranasal insulin administration further regulates peripheral energy homeostasis in humans (113, 114).

Moreover, intranasal insulin enhances verbal memory in memory-impaired subjects (20) and, importantly, improves performance in early AD patients (18, 19). Beneficial effects on cognitive functions have been reported for acute and long-term intranasal insulin administration. Although potential adverse side effects might be expected from the use of intranasal insulin (113), no treatment-related severe adverse events occurred in a 4-month period of treatment, and most adverse events were minor, such as mild rhinitis (21). The beneficial effects of acute insulin administration were not observed in APOE e4 carriers (116, 117), who have a higher risk for developing AD, but further studies are needed to confirm this association.

The mechanism of protection by insulin seems to involve downregulation of sites where Aβ oligomers bind (16), consequently preventing synapse loss, IR internalization, oxidative stress, and impairment of synaptic plasticity (16, 118). Notably, insulin fails to block oligomer binding to neurons when IR tyrosine kinase activity is inhibited (16). The protective role of insulin thus derives from IR signaling–dependent downregulation of oligomer-binding sites in neuronal processes, indicating the occurrence of cellular mechanisms that physiologically protect synapses against Aβ oligomers (16). Such active synaptic protection mechanisms could contribute to preserved cognitive function in normal individuals, while impaired mechanisms might render neurons vulnerable to oligomer-induced synaptotoxicity. Indeed, insulin may have important therapeutic implications in early and/or intermediate phases of AD (20, 119), preventing oligomer binding and blocking the pathology of IRs in cultured neurons (15, 16) and in AD brains (46). However, at later disease stages, when surface IRs dwindle, insulin might stimulate other receptors (e.g., IGF-1R) and thus improve AD-related deficits.

Nevertheless, alternative approaches to bypass IRs and boost insulin-related signaling pathways might provide an improved therapeutic approach or an addition to insulin-based therapies in AD. Glucagon-like peptide-1 receptor (GLP-1R) agonists are an attractive option because they activate pathways common to insulin signaling through G-protein–dependent signaling (120). GLP-1Rs are present and functional in cultured neurons as well as in rodent and human brains (121, 122). Exendin-4 and liraglutide are GLP-1R agonists that were recently approved for the treatment of type 2 diabetes. In mice, GLP-1R analogs are stable in blood, with most of the injected peptide reaching the brain (115), no treatment-related severe adverse events occurred in a 4-month period of period of treatment, and most adverse events were minor, such as mild rhinitis (21). The beneficial effects of acute insulin administration were not observed in APOE e4 carriers (116, 117), who have a higher risk for developing AD, but further studies are needed to confirm this association.

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A genic mouse model of AD, improving cognition and decreasing Aβ accumulation (10, 126). As recently suggested, an agent that chronically decreases Aβ levels should be beneficial in APOE ε4 carriers (127). If the beneficial effect of GLP-1R agonists is found to translate to primates, APOE ε4 carriers may possibly benefit from the use of GLP-1R agonists. GLP-1R activation may thus provide a novel strategy to resensitize impaired brain insulin signaling and prevent or halt neurodegeneration in AD.

In conclusion, the link between AD and diabetes may have profound implications for our understanding of the mechanisms underlying neuronal dysfunction in AD. Indeed, novel effective and safe therapeutic opportunities for AD are likely to arise from efforts aimed at unraveling the mechanisms that account for brain insulin resistance, as well as from a deeper understanding of the connection between AD and diabetes (Figure 3) (21, 27). The upcoming results from recently implemented clinical trials using both insulin (128) and GLP-1R agonists in AD are highly anticipated in the field. These studies will hopefully demonstrate a benefit for AD therapeutics targeting insulin signaling to treat this devastating disease.
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