ELSEVIER

Alzheimer's & Dementia 10 (2014) S3–S11

Alzheimer's & Dementia

Review Article

The paradox of neuronal insulin action and resistance in the development of aging-associated diseases

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Abstract During past decades, ever-increasing life expectancy, despite the development of a sedentary lifestyle and altered eating habits, has led to a dramatic parallel increase in the prevalence of age-related diseases such as type 2 diabetes mellitus (T2DM) and neurodegenerative disorders. Converging evidence from animal and human studies has indicated that insulin resistance in the central nervous system (CNS) is observed in both T2DM and neurodegenerative disorders such as Alzheimer's disease (AD), leading to the hypothesis that impaired neuronal insulin action might be a unifying pathomechanism in the development of both diseases. This assumption, however, is in striking contrast to the evolutionary conserved, protective role of impaired insulin/insulin-like growth factor 1 signaling (IIS) in aging and in protein aggregation-associated diseases, such as AD. Thus, this review summarizes our current understanding of the physiological role of insulin action in various regions of the CNS to regulate neuronal function, learning, and memory, and to control peripheral metabolism. We also discuss mechanisms and clinical outcomes of neuronal insulin resistance and address the seeming paradox of how impaired neuronal IIS can protect from the development of neurodegenerative disorders.
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Keywords: Insulin; Brain; Insulin resistance; Diabetes; Aging; Dementia; Alzheimer's disease

1. Action of insulin within the central nervous system in control of metabolism and neurodegenerative diseases

During past decades, considerable progress in advanced modern medicine combined with greater quality of life in developing countries has extended one's life span markedly, and the elderly are expected to live even longer in the future [1]. Improvement of life expectancy is associated inevitably with a subsequent escalation in the prevalence of age-related diseases. Among them, type 2 diabetes mellitus (T2DM) and Alzheimer's disease (AD) are considered to be part of the leading health threats in old age [2,3].

Historically, T2DM and AD were considered unrelated disease entities, being characterized as either a metabolic disorder affecting primarily glucose homeostasis in skeletal muscle, liver, and fat, or a degenerative disease of the central nervous system (CNS), respectively. However, recent studies have raised the possibility that these diseases share similar molecular roots; recently, both diseases have been associated with impaired insulin action within the CNS. This notion is supported further by epidemiologic studies, which have uncovered an association between T2DM and AD [4]. However, other studies have failed to reveal this association [4]. Postmortem analyses of brain from patients with AD have demonstrated that insulin receptors (IRs) are downregulated [5], as is observed during aging [6,7]. This led to the hypothesis that neuronal insulin resistance may contribute to the etiology of AD. Thus, the close correlation between T2DM and AD is believed to originate mainly from the establishment of insulin resistance (i.e., one of the main hallmarks of T2DM) and the associated alterations of the pleiotropic effects of insulin on core physiological functions.

The authors have no conflicts of interest to report.

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1552-5260/$ - see front matter © 2014 The Alzheimer's Association. All rights reserved.
http://dx.doi.org/10.1016/j.jalz.2013.12.008

Nearly one century after the discovery of insulin as a pancreatic-secreted peptide [8], the classic view of insulin as one of the principal regulators of glucose homeostasis by promoting glucose uptake in muscle and fat, and by suppressing hepatic glucose production has been expanded to a large range of physiological and cellular effects, including its neuroprotective role and the regulation of learning and memory. After describing the molecular basis of insulin action in the CNS, this review provides an overview of the key regulatory roles of insulin in the CNS-dependent control of glucose and energy homeostasis, as well as cognition, both under physiological and pathological conditions. Last, we address the seeming paradox of the neuroprotective effect of insulin and the role of inflammatory signaling pathways that causes neuronal insulin resistance and are activated both in obesity/T2DM and AD.

2. CNS insulin signaling: Regional distribution and molecular mechanisms

IRs are distributed extensively throughout the CNS [9–11]. The expression of IRs in the brain displays a widespread but selective regional pattern, because the intensity of IRs varies in different regions of the CNS [9–11]. In rodents, the highest density of IRs is found in the olfactory bulb, hypothalamus, cerebral cortex, cerebellum, hippocampus, thalamus, and midbrain [9–11]. Thus, IRs are present abundantly in brain areas involved in both glucose and energy homeostasis as well as cognitive processes (i.e., the hypothalamus and the cortical/hippocampal regions, respectively) [9–11].

After its transport into the brain via a saturable transporter expressed in the blood–brain barrier, insulin binds and activates its receptors [12]. IRs are tetrameric membrane receptors composed of two extracellular α subunits and two transmembrane β subunits, which constitute the binding region and tyrosine kinase activity, respectively [13–15] (Fig. 1). Insulin actions are mediated through a complex signaling profile that requires numerous second messengers that can be simplified into two major branches: the phosphatidylinositol 3 kinase (PI3K)/protein kinase B (AKT) pathway and the mitogen-activated protein kinase pathway (MAPK)/extracellular signal-regulated kinase cascade (for more details, see Kahn and Suzuki [15]). Binding of insulin to the IRs triggers a conformational change of the receptor, leading to activation of tyrosine kinase activity and, consequently, autophosphorylation of the receptor and phosphorylation of the insulin receptor substrate (IRS) protein family (mainly IRS-1 and IRS-2 in the CNS) [15]. Phosphorylation of IRSs induces the activation of various effector molecules, such as PI3K, which in turn activates the serine/threonine kinase AKT through phosphoinositide-dependent kinase 1 (Fig. 1). Once activated, AKT inhibits glycogen synthase kinase 3. Phosphorylated IRS also induces the activation of Ras, the initiator of the MAPK pathway, which results in the activation of extracellular signal-regulated kinase 1/2 (Fig. 1). One of the main targets of these pathways is the modulation of transcription and, therefore, gene expression. More important, based on their ability to form hybrid receptors, as well as their shared ligands and intracellular pathways, signaling of insulin and insulin-like growth factor 1 (IGF-1) are generally considered homologous as insulin/IGF-1 signaling (IIS) [16].

3. Insulin actions in neuronal control of energy and glucose homeostasis

Insulin action in the regulation of body weight, food intake, and glucose homeostasis is fine-tuned by its controlled secretion from pancreatic β cells via both short- and long-term regulation (i.e., acutely in response to hyperglycemia and directly proportional to adiposity in the long term). Intracerebroventricular (ICV) insulin administration leads to decreased food intake and body weight [17] (Fig. 2). The anorexigenic effect of insulin has been attributed primarily to its action in the two major antagonistic neuronal populations in the arcuate nucleus of the hypothalamus (ARH): the orexigenic neurons coexpressing neuropeptide Y (NPY) and agouti-related peptide (AgRP), and the anorexigenic neurons that produce proopiomelanocortin (POMC) and cocaine and amphetamine related-transcript (CART) [13,18,19]. Both NPY/AgRP neurons and POMC/CART neurons express IRs [20–22]. ICV insulin administration decreases the expression level of NPY/AgRP and increases that of POMC/CART, resulting in a decreased ratio of orexigenic-to-anorexigenic signals. ARH neurons then relay the signals to second-order neurons (for review see Vogt and Bruning [13] and Elmquist and colleagues [18]). More important, activation of these downstream pathways is dependent of the melanocortin system; co-infusion of insulin and melanocortin receptor (i.e., activated by the POMC-derived peptide α-melanocyte-stimulating hormone and inhibited by AgRP) antagonist blunts these effects [20]. Of note, in parallel to the insulin-induced reduction of food intake, the reduction in body weight after central infusion of insulin may also be linked to greater energy expenditure and locomotor activity, which is attributed to the action of insulin on POMC neurons [23,24].

In addition to its anorexigenic effect, insulin is a main player in CNS-dependent regulation of peripheral glucose fluxes (for a detailed review, see Grayson and colleagues [25]). Central insulin infusion results in suppression of hepatic glucose production (HGP) [21,26,27]. Accordingly, insulin fails to suppress HGP in CNS-restricted IR knockout mice (named NIRKO mice) [15,19] (Fig. 2). These defects are recapitulated by ablating the IR specifically in AgRP neurons, but not in POMC neurons [21], demonstrating that only 3000 AgRP neurons are required for insulin-induced suppression of HGP. In contrast to its anorexigenic effect, the antigluconeogenic effect of central insulin is not dependent of the melanocortin pathway [26].

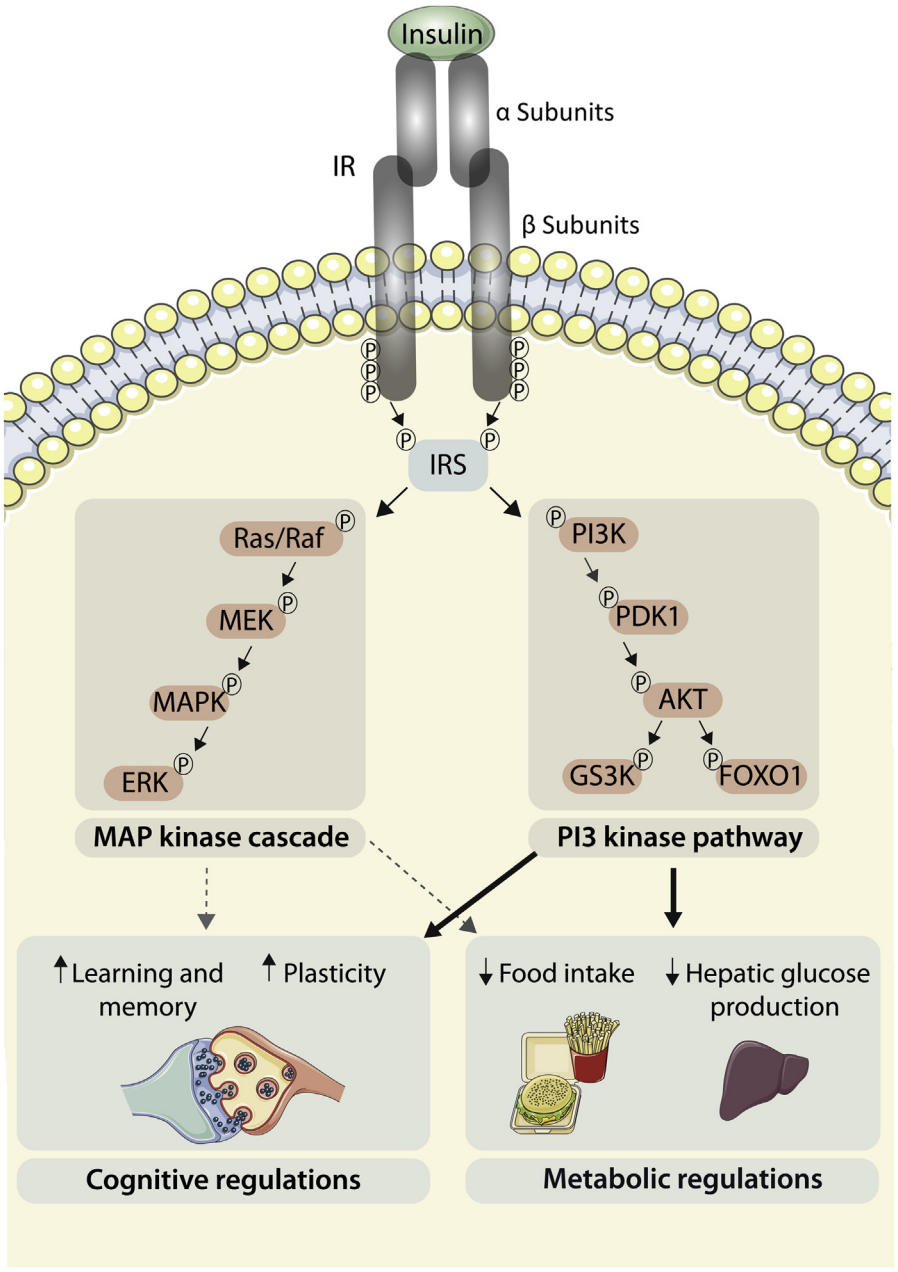

Fig. 1. Neuronal insulin signaling and associated physiological outcomes related to cognition as well as energy and glucose homeostasis. Insulin binds to the α subunits of the insulin receptor (IR) that activates tyrosine kinase activity of the β subunits. Autophosphorylation of the IR leads directly to phosphorylation of IRS. Activated the insulin receptor substrate (IRS) initiates the activation of two major signaling pathways: (*i*) the Ras–Raf–MEK–mitogen-activated protein kinase (MAPK) cascade, leading to the activation of extracellular signal-regulated kinase (ERK), and (*ii*) the phosphatidylinositol 3 kinase (PI3K) pathway that inhibits glycogen synthase kinase 3 (GSK3) activity and inactivates the transcriptional activity of forkhead box protein O1 (FOXO1) by its phosphorylation and subsequent nuclear exclusion. The PI3K pathway has been shown to be the main regulator of food intake and hepatic glucose production, as well as plasticity, learning, and memory. For corresponding references, please see the main text.

The anorexigenic effect of insulin as well as its ability to suppress gluconeogenesis are mediated by the PI3K/AKT pathway [26,28]. Downstream effectors of AKT that modulate food intake and HGP follow primarily two distinct nodes of the PI3K/AKT pathway: forkhead box protein O1 (FOXO1) and the activation of the adenosine triphosphate-dependent potassium channel [13,19]. Nuclear exclusion of FOXO1, secondary to its AKT-dependent phosphorylation, increases the transcription of POMC while decreasing that of AgRP. Recently, phosphorylated FOXO1 has been shown to blunt the transcription of the G-protein-coupled receptor 17 [29]. Ren and colleagues [29] proposed that the G-protein coupled receptor 17, specifically in AgRP neurons, correlates negatively with energy balance and may control food intake and HGP directly via the modulation of ion-channel activity and the subsequent increase in orexigenic neuropeptide

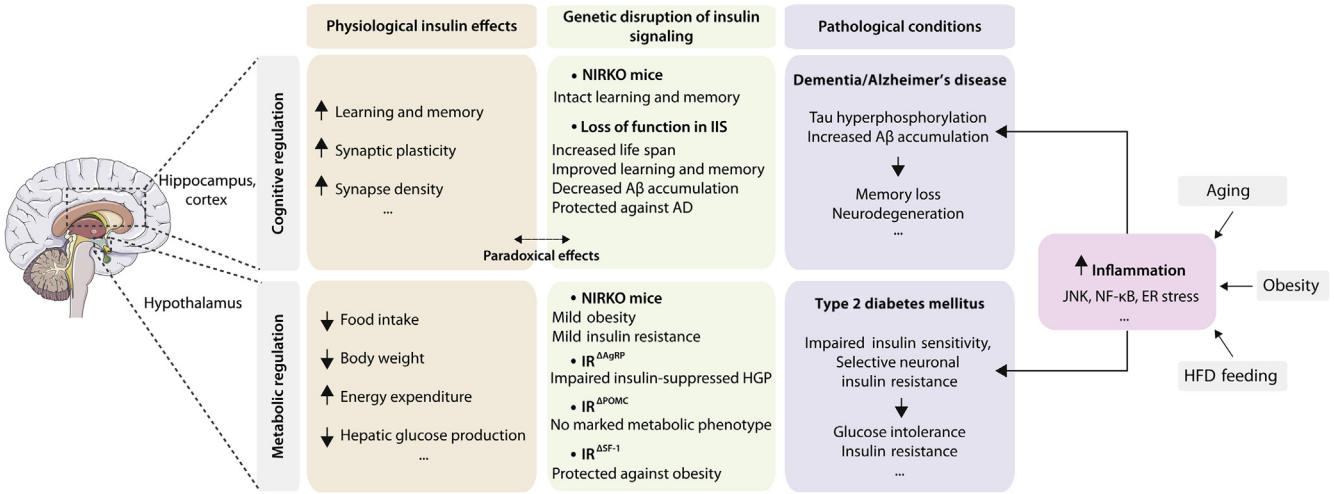

Fig. 2. Pathophysiological effects of insulin in metabolic regulation and its paradoxical action in cognition and associated diseases. Insulin acts within the hypothalamus and the cortex/hippocampus to regulate various processes of metabolism and cognition, respectively. On one hand, loss-of-function mutations in genes coding for insulin/insulinlike growth factor 1 signaling (IIS) elements highlight the critical role of insulin on glucose and energy homeostasis; on the other hand, they reveal paradoxical beneficial cognitive effects. Recent progress in the field argues that chronic, local, low-grade inflammation secondary to obesity, a high-fat diet (HFD) feeding, and/or aging could be the unifying mechanisms leading to the onset of both Alzheimer's disease (AD) and type 2 diabetes mellitus. For corresponding references, please see the main text. Aβ, amyloid-β; AgRP, Agouti-related peptide; ER, endoplasmic reticulum; IR, insulin receptor; JNK, c-Jun N-terminal kinase; NF-κB, nuclear factor-κB; NIRKO, CNS-restricted IR-knockout mice; POMC, proopiomelanocortin; SF-1, steroidogenic factor 1.

release. Another well-described intracellular route used by insulin to minimize neuropeptide release is the activation of the adenosine triphosphate-dependent potassium channel, leading to neuronal hyperpolarization and thereby inhibiting the secretory machinery [13,19].

This cumulative evidence highlights the critical importance of AgRP/NPY and/or POMC neurons in control of energy and glucose homeostasis. However, although these two target neuronal populations are necessary, they do not appear to be the exclusive mediators of insulin's metabolic actions in the CNS. Although the classic view of the arcuate-based circuitry in which first-order neurons (i.e., NPY/AgRP and POMC neurons) receive insulin signals and then relay the information to second-order neurons is undoubtedly critical, it is important to note that insulin may also act directly on additional neuronal populations. The fact that IRs are expressed widely in other hypothalamic regions, suggests strongly that insulin may act directly on other neurons located outside the ARH. For instance, insulin signaling specifically in the ventromedial nucleus of the hypothalamus (VMH) is involved in the onset of obesity upon high-fat diet (HFD) feeding [30], and insulin action in catecholaminergic neurons also controls body weight, presumably via regulation of hedonic feeding circuits [31]. Therefore, despite a clear evolution in our understanding of mechanisms underlying insulin's metabolic effects, the exact neuronal wiring mediating insulin's actions, including its defined cellular targets and the associated neuronal circuitries, remain to be elucidated further.

4. Insulin actions in cognitive processes

The role of insulin in the modulation of cognition is a newly emerging field that is not yet fully understood. The abundance of IRs in the hippocampus, amygdala, and cerebral cortex suggests that insulin could participate in the regulation of synaptic activity and cognitive processes. Many studies have highlighted the effects of insulin on learning and memory, proposing that insulin regulates cognition by modulating synaptic plasticity, density, and neurotransmission, and also by regulating adult neurogenesis (for a detailed review, see Fernandez and Torres-Aleman [16]) (Fig. 2). Indeed, altering insulin levels in the brain affects spatial memory and associative conditioning [32,33]. Insulin administration has been shown to improve memory/learning in rats [34] and in healthy humans (after intranasal administration) [35]. Moreover, systemic insulin infusion also improved verbal memory and attention in humans [36], and ICV administration of insulin in rodents has been shown to enhance performance during a passive-avoidance memory task [37]. Accordingly, cognitive activity recruits insulin signaling in the brain. For instance, spatial memory training increases IRs expression in the hippocampal dentate gyrus and CA1 field [38].

Although the molecular mechanisms underlying these processes are not clearly understood, they seem to involve mainly the PI3K signaling pathway because central insulin administration increases memory in a PI3K-dependent manner [39] (Fig. 1). In addition, insulin also modulates neuronal plasticity (i.e., the processes through which neurons adapt constantly to changing functional demands). Emerging evidence suggests that insulin signaling plays a role in synaptic plasticity both by modulating activities of excitatory and inhibitory receptors such as glutamate and γ-aminobutyric acid receptors, and by triggering signal transduction cascades that alter the expression of genes involved in long-term memory consolidation [40]. However,

the unaltered performance of NIRKO mice during a Morris water maze task puts in question the requirement of insulin signaling for memory formation [41] (Fig. 2).

5. CNS insulin resistance

5.1. Selective insulin resistance in the onset of T2DM and obesity

The critical involvement of abnormal insulin signaling in the etiology of metabolic diseases has been emphasized by the onset of mild obesity and altered glucose metabolism in NIRKO mice [42] (Fig. 2). Although the exact molecular mechanisms driving the onset of insulin resistance are not yet fully understood, it is evident that two of the main risk factors for development of T2DM are overweight/obesity and aging. Experiments performed in rodents, and in humans, have demonstrated that central administration of insulin (via ICV and intranasal administration, respectively) fail to reduce food intake under obese conditions [43–45]. Obesity-induced central insulin resistance seems to be associated mainly with the ingestion of a fat-rich diet, rather than a secondary effect of increased adiposity. Indeed, similarly to chronic HFD feeding, acute exposure to an HFD is sufficient to initiate hypothalamic insulin resistance independent of adiposity [46]. Recent progress in the field has led to the emerging concept of selective insulin resistance, in which central insulin resistance is not uniform, but rather is restricted to specific neuronal populations, and even affects distinct intracellular pathways selectively within the same cell. For instance, AgRP/NPY and POMC neurons develop insulin resistance on HFD feeding, whereas adjacent neurons located in the VMH expressing steroidogenic factor 1, remain insulin sensitive [30]. Interestingly, the suppression of insulin action within the ARH, and enhanced action in another nucleus (VMH), cooperate functionally to deteriorate whole-body energy and glucose homeostasis. Another noteworthy characteristic of selective insulin resistance resides in the specific pattern of intracellular insulin signaling in insulin-resistant neurons. The reduced ability of insulin to activate its downstream cascades is not generalized to all signaling pathways, rather appearing to affect specifically the PI3K/AKT pathway while leaving the MAPK cascade intact [28]. Thus, against expectation, insulin resistance in the CNS does not develop uniformly on obesity, nor it is likely to occur during aging.

5.2. Disruption of brain insulin signaling in aging and dementia

Insulin sensitivity within the CNS is regulated in an age-dependent fashion. Numerous steps governing insulin action are altered during aging—from changes in the level of insulin itself to its intracellular signaling pathways. Indeed, along with the general gradual loss of core physiological functions in old age, decline in insulin action appears to be an inevitable consequence of aging (for a review, see Kushner [47]). Aging is associated with marked alterations in insulin secretion, which commonly leads to hyperinsulinemia [6]. The expression of IRs in the brain also succumbs to an aged-dependent decline [38]. Notably, the messenger RNA level of IRs is decreased dramatically in the hypothalamus, cortex, and hippocampus of aged rats [38]. In addition to the lower expression of IRs in the CNS during aging, the pathogenesis of central insulin resistance is believed to be multifactorial in origin, including reduced accessibility of insulin to the brain and lower affinity of insulin binding sites, as well as alterations in intracellular signaling pathways [6,7].

The age-related decreases in CNS insulin signaling seem to be pronounced even further in neurodegenerative diseases. Possible defects in insulin signaling have been investigated in postmortem AD brains. Frolich and colleagues [5] first identified a reduction in IR expression in brains from an AD patient. This initial finding has been confirmed and extended by other investigators, who demonstrate reduced insulin levels in the cerebrospinal fluid in patients with AD and in those with mild cognitive impairment [48], in addition to reduced insulin signaling in the brain of those subjects [49]. However, the mechanisms underlying this reduced insulin signaling in AD remain unknown. It is still yet to be elucidated whether impaired central insulin action is a direct consequence of decreased insulin transport to the brain through the blood–brain barrier and/or if the neurons per se become insulin resistant. Although the concept of decreased brain insulin signaling in AD is widely accepted, there is a lack of strong evidence demonstrating neuronal insulin resistance in the cortex or hippocampus, and therefore this remains a hypothesis to be tested directly.

Several studies have demonstrated a tight link between insulin and the two main neuropathological hallmarks of AD: tau hyperphosphorylation and amyloid-β (Aβ) accumulation. Many of the protein kinases that can phosphorylate tau on residues known to exhibit increased phosphorylation in AD are regulated by insulin. For example, insulin-induced activation of PI3K reduces tau phosphorylation by inhibiting glycogen synthase kinase 3. Upon insulin resistance, impaired PI3K activation leads to conditions that are permissive for tau phosphorylation [50]. Insulin is also in close relationship with Aβ, the peptide produced by cleavage of the Aβ precursor protein [40]. Insulin reduces accumulation of toxic species of Aβ, the so-called oligomers, and protects against Aβ-induced synaptotoxicity and long-term potentiation disruption [51]. In contrast, Aβ also regulates brain insulin signaling. Soluble Aβ reduces insulin's ability to induce the PI3K/AKT pathway in cultured hippocampal neurons [52], whereas oligomers have been proposed to be responsible for the reduction in plasma membrane IRs in primary hippocampal neurons, promoting synaptic spine loss [51]. Interestingly, these effects were prevented by insulin pretreatment [51]. Taking into consideration the ability of Aβ to impair insulin action, decreased insulin signaling in AD could

also be considered a downstream consequence of Aβ accumulation. Paradoxically, despite the hypothesis that development of AD is driven by decreased insulin signaling, it has been reported clearly that decreased insulin signaling displays neuroprotective effects (as discussed later).

5.3. *Evolutionary conserved protection of reduced IIS in the CNS to prevent aging and neurodegenerative disorders*

IIS is a highly conserved signaling pathway across many phyla that regulates life span in worms as well as in mice [53]. Indeed, despite increasing experiments focusing on the putative role of decreased CNS insulin signaling in the etiology of neurodegenerative disorders, it is critical to state that decreased insulin signaling has also been reported to have a beneficial effect on life span regulation, and even to delay age-related processes (Fig. 2). Notably, a mutation in the *Caenorhabditis elegans* homolog of the IGF-1 receptor (Daf-2) results in a twofold increase of life span [54]. Similarly, in rodents, increased longevity is induced by loss-of-function mutations in genes encoding for IRS-1 [55], IRS-2 [56,57], and IGF-1 receptor [56,58] (Fig. 2). Specific deletion of IRS-2 in the brain is sufficient to extend the life span to a similar extent as the whole-body mutant [57], strongly highlighting the importance of IIS signaling in the CNS in life span regulation. Decreased IIS has not only been associated with longevity but also with a significant improvement in behavioral and intracellular age-related events associated with neurodegenerative disorders and, therefore, cognitive decline. Notably, ablation of IRS-2 [59] or IGF-1 receptor [56,60] in a genetic model of AD, improved behavioral defects and even reversed further the premature mortality associated with AD. These beneficial effects on cognitive processes are associated with a delay of age-related biomarkers such as decreased Aβ toxicity and/or accumulation, as well as prevention of neuronal loss and neuroinflammation [56,59,60].

Therefore, based on evidence that decreased insulin signaling triggers neuroprotective effects and protects against AD-like symptoms, it is tempting to speculate that the decreased insulin signaling described in aging brains, or in cases of neurodegenerative diseases, may in fact be a controlled protective mechanism aiming to counter neuroanatomic and behavioral impairments. Based on the paradoxical effects of insulin signaling, the state of our actual knowledge in the field is not sufficient to differentiate firmly between the beneficial vs. the detrimental effects of decreased insulin signaling on aging and neurodegenerative disease. This controversy raises a main concern, particularly considering the increased interest in intranasal application of insulin as AD therapy [35,61], which may actually challenge neuroprotective mechanisms and lead even further to neuronal damage. Indeed, in a provocative view, taking into consideration the beneficial neuroprotective effect of minimized IIS signaling in the brain, we may even further envisage tackling the onset of AD by boosting neuroprotective mechanism via application of an IIS inhibitor.

6. Is inflammation the common mechanism driving the onset of obesity/T2DM and neurodegenerative diseases?

Given that genetic insulin resistance protects from AD progression, one can hypothesize the involvement of another molecular mechanism that, on one hand, leads to insulin resistance and, on the other hand, contributes to AD progression, thus explaining the clinical link between T2DM and AD. Cumulative evidence has demonstrated that the existing crosstalk between insulin signaling and low-grade inflammatory tone associated with HFD feeding and/or obesity may be one of the leading processes toward the onset of neuronal insulin resistance (as reviewed by others [13,62–64]). Hence, activation of inflammatory cascades within the hypothalamus, either secondary to elevated saturated free fatty acid or associated with increased release of obesity-induced proinflammatory cytokines, impairs insulin signaling directly [13,62,63]. Hypothalamic inflammation has been associated mainly with the activation of inflammatory kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of κB-kinase-β (IKKβ), which activates nuclear factor-κB (NF-κB) [65–67]. Obesity and/or activation of the IKKβ/NF-κB pathways also trigger endoplasmic reticulum (ER) stress, which enhances NF-κB activity even further. JNK, IKKβ/NF-κB, and ER stress are all increased in the hypothalamus on HFD feeding, and independent central inhibition of these key intracellular proinflammatory signals improves peripheral metabolism and/or restores hypothalamic insulin sensitivity [65–67]. In addition to the detrimental effect of low-grade inflammation per se on cellular physiology, activation of inflammatory cascades blunt IR signaling directly, notably by interfering with the phosphorylation events downstream of IR activation [13]. For instance, activation of JNK leads to inhibition of IRS phosphorylation, and therefore to desensitization of insulin action [13,68].

Interestingly, these aforementioned inflammatory pathways are also enhanced in the hypothalamus during normal aging [69,70]. Recently, Zhang and colleagues [69] showed that the basal hypothalamic level of activated NF-κB increases gradually during aging, and furthermore, inhibiting IKK activation in the CNS prolongs life span in mice. Age-dependent activation of inflammatory signals appears to be a general process that affects numerous regions of the aging brain as the shift from innate immunity toward a proinflammatory status also occurs in the cortex and hippocampus of aged mice (for detailed review, see Krstic and Knuesel [71]).

The age-related increase in inflammatory tone is exacerbated even further in AD brains [71]. Interestingly, induction of chronic neuroinflammation in rodents reproduces both cellular damage associated with neurodegenerative disorders and a decline in cognition [72]. This study, as well as

others [71], suggest that the activation of inflammatory cascades may be an upstream mediator of AD pathogenesis rather than a downstream consequence. Indeed, proinflammatory mediators that are released under inflammatory states, such as tumor necrosis factor-α, could be associated with an increased production of Aβ peptides [73]. A recent study published by Yoon and colleagues [74] highlighted that JNK is involved directly in Aβ production, and they also show that JNK is necessary for the onset of AD. On the flip side, extracellular deposition of Aβ in the form of amyloid plaques in sporadic AD cases triggers chronic inflammatory reactions in the CNS [75], and there is ample evidence from in vitro studies to demonstrate that Aβ aggregates can activate a variety of inflammatory pathways. For instance, these toxic aggregates per se are able to induce ER stress [76], which in turn activates the JNK pathway. In in vitro and animal models, Aβ was also found to interact with Toll-like receptors to promote an inflammatory response mediated by microglia and astrocytes, which activate proinflammatory signaling pathways further and enhance neurodegeneration, thus initiating a vicious circle and perpetuation of the disease [71]. Taken together, innate immune responses are activated in the CNS during aging and can cause neuronal insulin resistance on the one hand, and contribute to AD progression on the other.

7. Concluding remarks

In the past decades, brain insulin signaling has faced a new and increasing interest in neuroscience research because of to its multifaceted and spatially compartmentalized actions. Within this wide spectrum of actions, insulin is clearly a significant regulator of glucose and energy homeostasis. The causal effects of CNS insulin in cognitive function, however, are less well supported. Although neuronal insulin resistance is contributing undeniably to the development of T2DM and obesity, the significant role of decreased insulin signaling in the pathogenesis of neurodegenerative diseases is still under debate. This debate is fed by two main arguments: (*i*) the paucity of data demonstrating clearly the detrimental effect of reduced insulin signaling to cause AD and (*ii*) the seemingly paradoxical findings of neuroprotective effects of attenuated IIS in *C. elegans*, *Drosophila*, and mice, while under physiological conditions, insulin exerts beneficial effects on cognition. However, the onset of both T2DM and AD appears to be associated with and driven by neuroinflammation. In this regard, blunting inflammatory cascades may be more relevant to treat AD [75] because this may not only halt disease progression, but also bypass the paradoxical actions of insulin in the CNS. One of the main challenges for upcoming years will be to clarify these discrepancies and to delineate the exact mechanisms that lead independently and synergistically to the onset of T2DM and AD. This will ultimately open new avenues in the development of more efficient preventive and therapeutic strategies.

Acknowledgments

We thank Servier Medical Art for their permission to use their illustration for our review. We apologize to those colleagues whose important contributions we could not cite because of space limitations. We thank Hayley Nicholls for critical reading, and Gisela Schmall and Tanja Rayle for excellent secretarial assistance. This work was supported by the Center for Molecular Medicine Cologne, University of Cologne (TVA1 to JCB), the European Union (FP7/2007-2013 under grant agreement no. 241592, EurOCHIP, to JCB), the German Research Foundation (BR 1492/7-1 to JCB), and the Competence Network for "Adipositas" (Neurotarget) funded by the Federal Ministry of Education and Research (FKZ01GIO845 to JCB).

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