Insulin resistance in the nervous system

Bhumsoo Kim and Eva L. Feldman

University of Michigan, Department of Neurology, Ann Arbor, MI 48109, USA

Metabolic syndrome is a cluster of cardiovascular risk factors including obesity, diabetes and dyslipidemia. Insulin resistance (IR) is at the core of metabolic syndrome. In adipose tissue and muscle, IR results in decreased insulin signaling, primarily affecting downstream phosphatidylinositol 3-kinase (PI3K)/Akt signaling. It was recently proposed that neurons can develop hyperinsulinemia-induced IR, which in turn results in injury to the peripheral and central nervous systems and is probably pathogenic in common neurological disorders such as diabetic neuropathy and Alzheimer’s disease (AD). This review presents evidence indicating that, similarly to insulin-dependent metabolically active tissues such as fat and muscle, neurons also develop IR and thus cannot respond to the neurotrophic properties of insulin, resulting in neuronal injury, subsequent dysfunction and disease states.

Metabolic syndrome and insulin resistance
Metabolic syndrome (MetS) is a constellation of disorders related to an increased risk of cardiovascular disease (CVD), and is the major contributor to the development of diabetes [1]. The National Cholesterol Education Program’s Adult Treatment Panel III (NCEP/ATP III) identified six components of MetS that relate to CVD: (i) abdominal obesity, (ii) atherogenic dyslipidemia, (iii) raised blood pressure, (iv) IR with or without glucose intolerance, (v) proinflammatory state, and (vi) prothrombotic state. A subject is diagnosed with MetS when he/she has central obesity plus any two of four additional factors (elevated triglycerides, reduced HDL-cholesterol, hypertension or abnormal fasting plasma glucose). The National Health and Nutrition Examination Survey study found that MetS affects 34% of adults in the US [2]. The incidence increases with both higher body mass index and advancing age.

IR is defined as a state of reduced responsiveness of target tissue(s) to normal circulating levels of insulin and is the central feature of type 2 diabetes (T2D) and MetS. Both genetic and environmental factors (lack of exercise, obesity, smoking, stress and aging) affect the development of IR [3].

Pathophysiology of IR
Abdominal fat accumulation is closely correlated to MetS and IR and increased risk of diabetes and CVD [1]. Visceral adipose tissue is a metabolically active endocrine organ whose dysfunction is responsible for increased plasma free fatty acids (FFAs) [4]. Inappropriate accumulations of lipids in muscle and liver due to abnormal fatty acid metabolism are the main features of IR. The resulting dyslipidemia is strongly correlated with increased CVD risk [5]. Visceral fat is also infiltrated with inflammatory cells and secretes proinflammatory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor-α (TNF-α) [6], which are implicated in the development of IR.

Insulin signaling and molecular basis of IR
Insulin is a major anabolic hormone that plays an essential role in glucose homeostasis by regulating the balance between hepatic glucose production and glucose uptake by muscle and adipose tissue, the two major sites of glucose uptake in man. Blood glucose levels are maintained by the balance between lipolysis in adipocytes and skeletal muscle and gluconeogenesis and glycogenolysis in liver. Insulin also regulates glucose transport in adipocytes and myocytes by controlling the translocation of glucose transporter (Glut) 4 between intracellular pools and the plasma membrane [7].

Insulin binds to the extracellular α-subunit of the insulin receptor (InsR), which results in the autophosphorylation and activation of the intracellular β-subunit [3] (Figure 1). Activated InsR phosphorylates several intracellular substrates including InsR substrate (IRS) family members (IRS1–IRS4) and Shc, which subsequently recruits downstream signaling molecules containing Src homology 2 (SH2) domains including the p85 subunit of PI3K and growth factor receptor-binding protein-2 (Grb-2) [8]. Activated PI3K phosphorylates phosphatidylinositol 4,5-bisphosphate (PIP2) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). Increased PIP3 stimulates phosphoinositide-dependent protein kinase (PDK), resulting in the activation of Akt.

In general, IRS serine phosphorylation inhibits insulin signaling even though it can act as a positive regulator depending on the environment [8] (Box 1). Increased IRS serine phosphorylation prevents its interaction with the InsR and downstream signaling molecules, induces mislocalization of IRS and enhances its degradation by the ubiquitin–proteasome pathway. Enhanced proinflammatory states due to increased release of FFAs and proinflammatory cytokines from adipose tissue, also contribute to increased IRS serine phosphorylation by activating IRS serine kinases [8].

In normal conditions, insulin stimulates Glut4 activity in skeletal muscle via IRS tyrosine phosphorylation and downstream PI3K activation (Figure 1). Glut4 is the major
insulin-mediated glucose transporter in muscle and adipocytes [7]. Precise translocation of Glut4 from intracellular stores to the plasma membrane is crucial for insulin-regulated glucose transport. The PI3K-dependent signaling pathway is crucial for the metabolic effects of insulin, and this pathway is generally affected in individuals with the MetS and diabetes. Decreased association of the p85 subunit of PI3K and IRS is reported in obese and T2D patients. Decreased expression of IRS and the association and activation of PI3K are also evident in genetically obese and high-fat fed animals [9].

Akt (Box 1) is a serine/threonine kinase activated by PI3K and is responsible for glycogen, lipid and protein synthesis, for cell survival and for the anti-inflammatory response (Figure 1) [3]. Akt plays crucial roles in IR by regulating insulin-stimulated transport of Glut4 in muscle and adipose tissue [3], and therefore it is not surprising that alterations in Akt activity are found in various cells in diabetes and IR. Akt phosphorylation is reduced in adipocytes and skeletal muscle of T2D patients [10] and Akt2 activation is closely correlated to Glut4 translocation through insulin-activated PI3K signals in adipocytes [11]. Akt2 knockout mice, but not Akt1 or Akt3 knockout mice, develop diabetes with hyperglycemia, hyperinsulinemia, glucose intolerance, and impaired muscle glucose uptake [10], possibly because of impaired insulin action in liver and skeletal muscle. However some reports demonstrate a disparity between the activation of upstream signaling molecules (IRS–PI3K), Akt activation and glucose tolerance, arguing against the crucial role of Akt in the development of IR [12].

Other downstream substrates involved in the development of IR are the Akt substrate of 160 kDa (AS160, also termed TCB1D4) and glycogen synthase kinase 3 (GSK3) (Figure 1). Akt induces AS160 phosphorylation, which directly links insulin signaling to Glut4 trafficking [13]. Insulin-stimulated AS160 phosphorylation is reduced in T2D patients [14]. Insulin activates glycogen synthase, which is the rate-limiting enzyme in glycogen synthesis. Glycogen synthase is inactivated by GSK3, which itself is phosphorylated and inactivated by insulin stimulation in a PI3K/Akt-dependent manner [15]. An increase in the activity of GSK3 has been observed in diabetic animals and patients, and GSK3 inhibitor treatment reverses diabetes [16].

By contrast, phosphorylation of Shc by InsR activates the mitogen-activated protein kinase (MAPK) branch of insulin signaling [3]. MAPK pathway activation by insulin signaling is responsible for gene expression, cell growth and mitogenesis (Figure 1). In contrast to the decrease in
Box 1. IRS and Akt signaling

Activation of IRS by insulin stimulation results in the binding and phosphorylation of IRS proteins (IRS1–IRS4) [74]. Phosphorylated tyrosine residues on IRS serve as docking sites for downstream signaling molecules with SH2 domains such as PI3K, which is crucial for Akt activation. In addition to over 20 tyrosine residues, IRS proteins contain more than 50 potential serine/threonine phosphorylation sites. Because serine phosphorylation of IRS1 triggers its degradation, this step is generally considered a negative regulator of insulin signaling that contributes to the development of IR [8]. In an IR state, there is abnormal activation of the kinases that phosphorylate multiple serine residues on IRS proteins, resulting in impaired insulin signaling [8]. Multiple IRS serine kinases are activated during IR [8]. Increased IRS serine phosphorylation in IR states including obesity and T2D are reported in both animal and human studies [75]. Although IRS1 serine phosphorylation generally inhibits insulin signaling, recent reports suggest it may have positive roles for cell growth and mitogenesis [76].

Akt (Akt1, Akt2 and Akt3), also known as PKB (PKBα, PKBβ and PKBγ), is a serine/threonine kinase activated downstream of growth factors and various cellular stimuli. Many molecules involved in Akt signaling are key therapeutic targets for various human diseases including T2D and cancer. Akt1 and Akt2 are ubiquitously expressed, even though Akt2 is more concentrated in insulin-sensitive tissues such as liver, muscle and adipose tissue. Akt3 expression is restricted to the brain, testis, lung and pancreatic islets, with virtually no expression in visceral organs and muscle. Targeted deletion of Akt demonstrates the unique roles of each isoform. Akt2−/− mice develop IR and mild glucose intolerance, implying that Akt2 plays a crucial role in energy homeostasis. Akt1−/− mice display mild growth retardation and increased apoptosis, suggesting the important role of Akt in cell growth and survival. Interestingly, Akt1−/− mice display improved insulin sensitivity and reduced blood glucose levels. Akt3−/− mice have smaller brains. Full activation of Akt requires the phosphorylation of a threonine residue in the catalytic domain, and of a serine residue in the hydrophobic motif by PKD1 and the mTORC2 complex, respectively (Figure 1). Once activated, Akt phosphorylates various substrates, leading to their activation or inactivation. These substrates contribute to the regulation of cellular processes such as cell cycle control, growth and proliferation, survival, protein synthesis and glucose metabolism. Detailed reviews are given in [10,12].

PI3K/Akt activity, MAPK activity remains relatively normal in IR [17]. MAPK can phosphorylate IRS1 at specific serine residues and interfere with its signaling [8]; therefore, inappropriately high MAPK activity when IRS1 function is already impaired could lead to worsening of IR.

Proper insulin signaling is crucial to maintaining glucose homeostasis. In IR, insulin signaling is impaired at multiple levels, resulting in imbalance between glucose uptake and production in peripheral tissues. Most studies of IR, however, have focused on metabolically active tissues such as muscle or adipocytes, and there is surprisingly little knowledge about IR in neurons. In the following sections we discuss insulin signaling in neurons and neuronal IR as a potential contributor to the development of neurodegenerative diseases.

The role of insulin receptor signaling in neurons

Although neurons are not insulin-dependent, they are insulin-responsive [18]. The InsR and downstream signaling molecules including IRS are expressed throughout the peripheral and central nervous systems (PNS and CNS) (Figure 2). Both InsR mRNA and protein are detected in peripheral sensory neurons of dorsal root ganglion (DRG) neurons [19]. InsR expression is especially high in small-diameter sensory DRG neurons and lateral laminae V and X of the spinal cord, suggesting the involvement of insulin signaling in nociceptive pathways. Immunohistochemistry demonstrates preferential expression of InsRs at the perikarya of DRG neurons [20]. Intrathecal injection of insulin rescues and regenerates sural nerves after crush injury, demonstrating a direct neurotrophic effect of insulin in peripheral neurons [20]. Systemic insulin injection also accelerates reinnervation of motor axons after sciatic nerve transection [21]. With direct injury to the PNS, neuronal regeneration or reinnervation is associated with increased InsR expression.

A common problem in the PNS is distal-to-proximal loss of nerve function, a condition known as neuropathy. The most common cause of neuropathy in the Western world is diabetes, with an estimated 60% of patients with diabetes afflicted with diabetic neuropathy (DN) (discussed in detail below). Intrathecal, but not subcutaneous, infusion of low-dose insulin for 1 month significantly improves the function of motor and sensory nerves, measured by electrophysiology, in a type 1 diabetes (T1D) rat model [22]. Intrathecal insulin infusion also prevents axonal atrophy of sensory nerves. These results suggest that lack of proper trophic support by insulin on peripheral neurons might be one mechanism for the development of PNS dysfunction, especially neuropathy. Unfortunately, there is very little knowledge about the neuronal signaling mechanisms downstream of InsR in the PNS (Figure 2). It was only recently reported that DRG neurons predominantly express IRS2 [23]. IRS2 serine phosphorylation is significantly increased in DRG neurons from both type 1 and 2 diabetic mice with neuropathy. In addition, insulin-stimulated Akt phosphorylation and neurite outgrowth are decreased in DRG neurons from a model of T2D and neuropathy, the ob/ob mouse [23].

InsRs are widely expressed in the brain, including the olfactory bulb, cerebral cortex, hippocampus, hypothalamus and amygdala [24]. InsRs are more concentrated in neurons compared to glial cells and are especially high in postsynaptic densities [25]. Along with leptin, insulin in the brain is best known for its role in the control of energy homeostasis [26]. Direct administration of insulin to the brain reduces food intake and body weight. By contrast, both insulin antibody infusion to hypothalamus [27] and neuron-specific deletion of InsR (NIKKO) in mice [28] give rise to hyperphagia and obesity. Insulin also regulates peripheral glucose metabolism and increases insulin sensitivity by reducing hepatic glucose production. This effect is mainly regulated through InsR signaling in the ventromedial portion of the hypothalamus [26].

Although controversial, there is evidence that insulin may play important roles in learning and memory. Intranasal insulin administration improved working memory in both human and animal studies [29]. Intrahippocampal delivery of insulin, but not IGF-I, improves hippocampus-dependent spatial working memory [30]. InsR mRNA and protein levels are upregulated in the hippocampus in association with short-term memory formation after a spatial learning experience [31]. Furthermore, poor cognitive
performance in diabetes or AD is associated with IR and/or decreased InsR signaling [26]. Similarly, the anti-diabetic drugs and peroxisome proliferator-activated receptor gamma (PPARγ) agonists, pioglitazone and rosiglitazone, demonstrate mixed results for improvements in memory in both human and animal studies [32]. However, NIRKO mice, despite the complete loss of neuronal InsRs and signaling, demonstrate little alteration in spatial learning [33]. A recent report demonstrates that brain-specific IRS2 knockout mice have enhanced hippocampal spatial memory, suggesting that IRS2 acts as a negative regulator of memory formation [34].

As discussed above, the important role of insulin in many aspects of neuronal function in both the PNS and CNS suggests that the development of IR may play a role in the pathogenesis of neurological diseases [21]. The following sections summarize current evidence indicating that IR is instrumental in the development of diseases of the PNS and CNS, using DN and AD, respectively, as the best-studied examples.

**Diabetic neuropathy**

Diabetes is a complex metabolic disorder characterized by hyperglycemia and associated microvascular and macrovascular complications, including retinopathy, nephropathy, neuropathy and CVD. According to recent data from the Centers for Disease Control and Prevention (http://www.cdc.gov/diabetes/pubs/), 25.8 million people (8.3% of the US population) are diagnosed with diabetes, with another 79 million adults with prediabetes. Diabetes costs $174 billion in direct and indirect expenses (22% of total medical expenses). Diabetes is the leading cause of kidney failure and new cases of blindness among adults and is a major cause of heart disease and stroke in the USA.

DN is the most common and costly complication of both T1D and T2D. It is defined as ‘the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes’ [35]. The onset of DN correlates with the duration of diabetes; 50% of patients develop DN after 25 years of diabetes [35]. In a cross-sectional study in the UK the overall prevalence of DN was 28.5% of diabetic patients, which increased to 44% in patients over 70 years of age [36]. DN is the leading cause of non-traumatic lower limb amputations and costs for the treatment of DN and associated morbidities in the US exceed $11 billion annually (up to 27% of the direct medical cost of diabetes).

Studies by the Diabetes Control and Complications Trial (DCCT) research group provide a clear connection between chronic hyperglycemia and the development of DN [37]. Currently, strict glycemic control is one of the very few available treatment options for DN. Studies focused on the glucose metabolic pathway suggest that overproduction of sorbitol and amino sugars due to activation of the polyl and hexosamine pathways, excess or inappropriate activation of protein kinase C (PKC) and accumulation of advanced glycation endproducts, among others, contribute to the pathogenesis of DN. All of these pathways are related to the metabolic and/or redox state of the cells. Readers are encouraged to refer to recent reviews for more detailed biochemical and molecular pathophysiology, and their application to therapeutic strategies for DN [38,39].

**IR and DN**

Studies in the last 10 years clearly suggest that insulin is a neurotrophic factor responsible for regulating neuronal growth, survival and differentiation [20,21]. As discussed above, InsR and IRS are widely expressed in peripheral
neurons in both the cell body and axons [19,20,23]. There are a variety of opinions concerning the pathogenesis of DN [39]. Considering the important neurotrophic role of insulin, it is possible that perturbation of insulin signaling during IR (both insulin deficiency in T1D and hyperinsulinemia in T2D) result in neurodegeneration and contribute to the pathogenesis of DN. Insulin administration relieves painful DN [40] and reverses slowing of motor and sensory conduction velocities [22] in animal models of T1D, suggesting a direct role of insulin on neurons.

Nevertheless, the direct effect of IR on the development of DN remains poorly understood. It was recently demonstrated that neurons indeed develop IR following hyperinsulinemia in a manner similar to that in metabolic tissues [41]. Development of IR on chronic insulin treatment is accompanied by a decrease in insulin stimulation of Akt, p70S6K and GSK3β, but does not affect MAPK-mediated signaling pathways, a result mimicking that seen in muscle and adipocytes [17,42]. Similarly, insulin-induced Akt stimulation is also reduced in DRG neurons from animal models of T2D that develop DN: db/db and ob/ob mice [23,41]. Interestingly, hyperinsulinemia-mediated decreases in Akt phosphorylation are reversed by PI3K, but not MAPK, inhibition [41]. However, there are conflicting reports on the roles of IRS proteins in decreased Akt phosphorylation in neurons [25,41].

One of the key pathological features of diabetes and IR in metabolic tissues is increased oxidative stress due to mitochondrial dysfunction, and this is characterized by smaller mitochondrial size and decreased mitochondrial DNA content [43]. Similar disruption of mitochondrial fission–fusion machinery is present in several neurological disorders [44,45]. In addition to a role in cellular energy (ATP) production, mitochondria are important mediators of cellular function by integrating glucose and lipid metabolism [43]. Insulin regulates mitochondrial metabolism and oxidative capacity through PI3K/Akt signaling [43,46]. Therefore, decreased Akt signaling by hyperinsulinemia-mediated IR may have profound effects on mitochondrial function in neurons and result in subsequent increased oxidative stress. It was recently demonstrated that glucose-mediated oxidative stress contributes to the development and progression of DN by inducing an imbalance in mitochondrial biogenesis and fission [47,48]. Similarly, chronic insulin treatment induces mitochondrial dysfunction by increasing expression of the fission protein Drp1 in adult DRG neurons [41]. These studies suggest that chronic insulin stimulation in vivo and in vitro results in the disruption of Akt signaling and mitochondrial biogenesis, a result of IR in DRG neurons. We contend that disruption of insulin signaling due to IR makes PNS neurons more vulnerable to metabolic insults such as hyperglycemia and contributes to the development of DN [41,49].

**AD**

AD is a progressive neurodegenerative disease characterized by loss of memory and other cognitive functions necessary to perform complex daily activities [50]. It is the most common form of dementia, accounting for over 70% of all cases. The most prominent neuropathological features of AD are the appearance of senile plaques composed of amyloid β (Aβ) peptides and neurofibrillary tangles (NFTs) derived from the aggregation of microtubule-associated protein tau (Box 2). Aging is the most definitive risk factor for AD, with the incidence doubling every 5 years in the population over 65 years of age; 50% of people over 85 years of age are affected by various degrees of AD. AD currently affects 5.4 million Americans and the incidence is expected to reach over 16 million by 2050 (http://www.alz.org/downloads/Facts_Figures_2011.pdf). It is estimated to cost $183 billion in direct medical expenses, with another $202.6 billion accounting for unpaid economic expenses for care-givers; the medical expense is estimated to increase to $1.1 trillion by 2050.

**MetS and AD**

Multiple studies report that patients with MetS have an increased risk of developing AD compared to age- and gender-matched controls. Accumulating evidence suggests that AD is closely related to dysfunction of both insulin signaling and glucose metabolism in the brain, prompting some investigators to refer to AD as type 3 diabetes or an insulin-resistant brain state [51,52]. The Rotterdam study suggests that IR, but not blood glucose, is associated with a higher risk of AD [53]. Another study demonstrates that...
both hyperinsulinemia and hyperglycemia are associated with an increased risk of senile plaque formation, but not NFTs, after adjustment for age, sex, systolic blood pressure, total cholesterol, body mass index, habitual smoking, regular exercise and CVD [54]. IR is associated with reduced cerebral glucose metabolism (CMRglu) in various brain regions in cognitively normal adults with prediabetes and T2D, and is suggested as a marker for AD even before the onset of mild cognitive impairment [55]. A detailed analysis of 14 high-quality longitudinal studies from MEDLINE and EMBASE searches [56] demonstrates that individuals with T2D have a greater than twofold increased risk of developing AD compared to individuals without T2D, adjusted for age and sex, education and vascular risk factors (including a history of stroke, hypertension, and heart disease).

The role of MetS and IR in AD is also evident from animal studies. Control animals fed with a high-fat diet performed poorly in a cognitive test, which correlated well with the development of IR but not with weight gain [57]. Similarly, development of IR on drinking fructose water is correlated with increased Aβ production, which is prevented by treatment with the insulin sensitizer pioglitazone [58]. Age-dependent increases in tau phosphorylation and cleavage are observed in the best-characterized T2D mouse model, the db/db mouse [59]. Furthermore, inducing diabetes and IR by streptozotocin (STZ) or a high-fat diet in AD animal models exacerbates both amyloid and tau accumulation [60,61].

The converse is also true, because patients with AD are also more likely to develop diabetes. The Mayo Clinic AD Patient Registry reveals that 80% of AD patients have either T2D or an impaired fasting glucose level [62]. Many features of MetS, including obesity, dyslipidemia and IR, are risk factors not only for diabetes and CVD but also for AD [63].

**Molecular mechanism for the role of IR in AD**

Brain insulin signaling plays crucial roles in the regulation of food intake, body weight and reproduction, as well as in learning and memory [64]. Defective insulin signaling is associated with decreased cognitive ability and development of dementia, including AD [65]. A recent study demonstrated a decrease in the phosphorylation of similar insulin signaling molecules in both AD and T2D patient brains. The decrease was more severe in the brains of patients with both AD and T2D [66]. Disruption of insulin signaling makes neurons more vulnerable to metabolic stress, thus accelerating neuronal dysfunction.

As in peripheral tissues, IR predominantly affects PI3K/Akt signaling in the brain. It was demonstrated that insulin-stimulated Akt phosphorylation is decreased in hyperinsulinemic conditions in cortical neuron cultures [49]. Furthermore, db/db cortical slice cultures display increased basal Akt phosphorylation and insulin cannot further stimulate Akt phosphorylation as it does in non-diabetic control (db−) cortex. One of the key signaling molecules activated downstream of Akt is GSK3αβ [67]. GSK3α increases Aβ production by stimulating amyloid precursor protein (APP) γ-secretase activity, whereas GSK3β is the major tau kinase responsible for its hyperphosphorylation and the formation of NFT [68] (Box 2). Impaired insulin signaling reduces GSK3α/β phosphorylation, and thus constitutively activates these molecules, which affects both Aβ and tau accumulation. It is also reported that decreased insulin-stimulated Akt phosphorylation resulting from chronic hyperinsulinemia reduces GSK3β phosphorylation, in other words, activation [49]. In addition, constitutively active Akt inhibits APP trafficking and Aβ secretion through feedback inhibition of IRS and PI3K [69]. Therefore, precise regulation of Akt signaling is crucial for both amyloid and tau neuropathology in AD.

Impaired glucose metabolism due to IR affects AD neuropathology by dysregulation of O-GlcNAcylation, a protein modification by O-linked N-acetyl-D-glucosamine (GlcNAc). Similar to phosphorylation, O-GlcNAcylation is a dynamic post-translational modification involving the attachment of GlcNAc moieties to the hydroxyl groups of serine and threonine residues [70]. In some cases O-GlcNAc may occur at or near residues that can also be phosphorylated, thereby modulating each other. APP is modified by O-GlcNAc in a region that may affect its degradation, and a recent report demonstrates that O-GlcNAcylation of APP encourages non-amyloidogenic processing of APP, thus decreasing Aβ production and secretion [71]. Tau has at least 12 O-GlcNAcylation sites, which are mostly inversely correlated with phosphorylation status [70]. Recent reports demonstrate that reduced brain glucose metabolism and O-GlcNAcylation result in increased tau phosphorylation in both in vivo and in vitro models [72]. Therefore, disruption of glucose metabolism due to IR may affect both amyloid and tau pathology.

Conversely, Aβ can inhibit insulin signaling. All forms of Aβ, including monomers, oligomers and Aβ-derived diffusible ligands (ADDLs), directly bind to InsR and prevent insulin signaling [73]. Intracellularly, Aβ prevents the interaction of PDK1 with Akt and inhibits Akt activation [51]. Therefore, there may be a feed-forward mechanism between impaired insulin signaling and increased Aβ production to further exacerbate AD pathology in the presence of IR.

**Concluding remarks and future perspectives**

IR is the core pathogenic feature of MetS, a cluster of disorders including diabetes, obesity, dyslipidemia and hypertension, all of which lead to increased CVD. Until recently, the study of IR was mainly focused on metabolic tissues such as muscle and adipose tissue; recent data, however, suggest that IR also develops in the nervous system. IR in sensory neurons makes cells respond inappropriately to growth factor signals, and this impairment may contribute to the development of neurodegeneration and subsequent DN. IR in diabetes is tightly correlated with the increased risk of AD by making cortical and hippocampal neurons more vulnerable to Aβ and tau toxicity. In both systems, decreased Akt signaling is the common feature of neuronal dysfunction. Akt signaling is crucial for cell survival and normal cell function. We speculate that IR accelerates neuronal dysfunction by preventing neurons from responding to the neurotrophic properties of insulin and rendering them more susceptible to a variety of injurious stimuli (Figure 3).
This new theory requires more investigation and there are many unanswered questions. Even though Akt plays crucial roles in mediating IR-induced neuronal dysfunction, there are no studies addressing the mechanism (i.e. the upstream or downstream signaling pathways responsible for the effects of Akt during this process). Studies will be needed to understand the contribution of hyperinsulinemia, hyperglycemia and/or hyperlipidemia on the development of neuronal IR. Inflammation probably contributes to the development of IR in both the PNS and CNS, but there are virtually no studies addressing this idea, which could provide a new therapeutic target for disease states. Whether or not IR develops in PNS or CNS glia (Schwann cells and oligodendrocytes, respectively) is not known, and it is highly likely that IR in glia could play an important role in nervous system disorders. In summary, IR in the PNS and CNS is an intriguing new idea that may lead to not only a better understanding of disease states but also new therapeutic targets for some of the most common and disabling neurologic disorders.

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