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Integrating metabolism and longevity through insulin and IGF1 signaling

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Abstract

Understanding how metabolism integrates nutrient homeostasis with life span is a complicated undertaking. The insulin pathway coordinates growth, development, metabolic homeostasis, fertility and stress resistance, which ultimately influence lifespan. From a clinical perspective, compensatory hyperinsulinemia to overcome systemic insulin resistance is thought to be a healthy goal, because it circumvents the immediate catastrophic consequences of hyperglycemia; however, work in flies, nematodes and mice indicate that excess insulin signaling ultimately damages cellular function and accelerates aging. Maintenance of the central nervous system (CNS) has particular importance for lifespan. Depending upon the exact site, reduced insulin/IGF1 signaling in the CNS can dysregulate peripheral energy homeostasis and metabolism, promote obesity, and extend lifespan. In this review, we explore how genetic manipulations of insulin/IGF1 signaling components are beginning to reveal neuronal circuits which might resolve the central regulation of systemic metabolism from organism longevity.

Keywords

Aging; central nervous system; insulin/IGF signaling; lifespan; neurodegeneration; metabolism; leptin; energy balance; glucose homeostasis

Introduction

Insulin/IGF1 signaling has pleiotropic biological effects in virtually all tissues; however, the role of insulin/IGF1 signaling in peripheral tissues has been studied far more extensively than its role in the brain (1). Reduced insulin signaling—usually called insulin resistance in clinical circles—has serious detrimental effects that usually lead to excess circulating insulin and life-threatening metabolic disorders, including type 2 diabetes and cardiovascular disease (2). By comparison, genetic strategies to reduce insulin/IGF1 signaling in *Caenorhabditis elegans*, *Drosophila melanogaster*, and rodents has emerged as a reliable means of extending lifespan (3-7). Understanding the relation between insulin ‘resistance’ and ‘reduced’ insulin/IGF signaling might provide important insight into the pathology of metabolic disease, its sequelae, and strategies for treatment.

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Life expectancy in the industrialized world increased dramatically during the first two-thirds of the past century—from approximately 48 to about 70 years—owing largely to better nutrition, modern sanitation, antibiotics and immunization, and science-based medical diagnosis and treatment. Reaching old age in good health might involve a favorable balance between hundreds of disease causing and longevity-promoting genes and environmental factors—including the consequences of modern lifestyles and reduced activity (8-11).

Experiments with various long-lived animal models reveal general strategies to reduce the progression of age-related diseases and neuronal degeneration. In particular, insulin and IGF1 signaling has emerged as a conserved mechanism that regulates nutrient homeostasis, growth, and lifespan. But contrary to conventional clinical medicine where increased insulin signaling is a universal goal in the treatment of metabolic disease associated with obesity, type 2 diabetes and trauma, reduced insulin/IGF signaling can extend lifespan of experimental animals. Moreover, age-related diseases—including Alzheimer's and Huntington's—might be inversely related to the strength of brain insulin-like signaling (12-17).

While reduced insulin/IGF1 signaling in CNS extends life span and delays neurodegeneration processes, central insulin is also known to promote neuronal survival and memory, energy homeostasis, and reproduction (18-23). In this review we will discuss this complex biology with particular emphasis on insulin signaling as a central homeostatic signal with regard to energy and glucose homeostasis and its role in neurodegenerative diseases.

Insulin-like signaling pathway

1. Receptors

Insulin-like signaling is an inclusive term that includes three homologous receptors in mammals—two insulin receptor isoforms (InsRA and InsRB) and one receptor for IGF1 (IGF1R). By comparison, invertebrates express a single orthologous receptor that recognizes a broad array of insulin-like peptides that are differentially expressed throughout the organism (24). In mammals, the InsRs and IGF1R are encoded by 2 distinct genes that generate homologous precursors that are processed into α - and β -subunits that dimerize to form a ligand-regulated transmembrane receptor tyrosine kinase. InsRB has 12 additional amino acids at the carboxyl terminus of the α -subunit that are omitted from InsRA by alternative splicing of Exon-11 (25,26). The InsRA predominates in liver and adipose where it binds insulin much more strongly than the insulin like growth factors (IGF1 and IGF2). Unlike liver and adipose, most tissues express both InsRs and IGF1R, which form hybrid receptors with distinct insulin binding characteristics (27). Neurons express mainly InsRB and IGF1R, which can form InsRB•IGF1R hybrids that bind insulin and IGF1/2 with moderate affinity, revealing how insulin and IGF1/2 signaling might be integrated to play common and distinct functions in the CNS.

2. IRS→AKT cascade

The InsRs and IGF1R phosphorylate tyrosine residues in cellular proteins, including the insulin receptor substrates Irs1 and 2 (1,28,29). IRS-proteins are adapter molecules that link the InsR and IGF1R to common downstream signaling cascades and heterologous regulatory mechanisms (**Fig. 1**). IRS-proteins are targeted to the activated receptors through an NH₂-terminal pleckstrin homology (PH) domain and a phosphotyrosine binding (PTB) domain (1). During insulin and IGF1 stimulation, tyrosine residues in the COOH-terminus are phosphorylated and bound to the SH2-domains in various signaling proteins (**Fig. 1**) (30). The interaction between IRS1 and the 85 kDa regulatory subunit (p85) of the class 1A PI3K

is key to insulin-mediated control of metabolism and cellular function (1). In addition to Irs1 and Irs2, the insulin receptor phosphorylates other proteins on tyrosine residues—including Shc, APS, and SH2B, Gab1/2, Dock1/2 and Cbl—and mass spectrometry reveals nearly 100 other tyrosyl phosphorylated proteins in insulin-stimulated cells (31). Moreover, quantitative interaction proteomics based upon SILAC technology reveals many proteins that might interact with Irs1 (32). Although the role of each of these substrates and binding proteins merit attention, work with knockout mice reveals that many insulin responses, especially those that are associated with somatic growth, carbohydrate, lipid and protein metabolism are regulated through Irs1- and 2-mediated activation of the PI 3K→Akt cascade (33-35).

3. AKT→mTORC cascade

The IRS1/2→PI3K→Akt1/2 cascade phosphorylates many proteins, including Tsc2 (activates mTORC1) and FoxO1 (inhibits its nuclear regulation of gene expression) (1,36-38) (**Fig. 1**). The TOR kinase is a principle signaling component regulated by nutrients in all cells. In yeast it is encoded by two homologous genes (TOR1 and TOR2). In mammals, a single mTOR kinase form two complexes called mTORC1 and mTORC2 owing to its association with Raptor or Rictor, respectively (39). mTORC1 promotes nutrient storage (protein and lipid synthesis) and inhibits autophagy (36-38,40). mTORC2 plays a role in organization of the actin cytoskeleton, and also phosphorylates the COOH terminal site in Akt and is required for mTORC1 activation and inhibition of FoxO nuclear localization (41,42) (**Fig. 1**). Inhibition of the TOR pathway extends life span in worms, flies and mice (43). Raptor and Rictor have both been linked to mammalian longevity (44), and treatment with rapamycin—an inhibitor of the mTOR pathway—significantly increases mouse life span (45).

4. AKT→FoxO cascade

FoxO transcription factors (mainly Foxo1 and 3) have broad tissue-specific functions linking gene expression to environmental stress—including glucose depletion, hypoxia, oxidative stress, and DNA damage (46). In the brain, FoxO1 is predominantly expressed in the striatum, dentate gyrus and ventral hippocampus, and FoxO3 is in the cortex, cerebellum and hippocampus (47,48). When starvation or insulin resistance are especially severe and cellular energy is depleted (increasing [NAD⁺]/[NADH]), Sirt1 (silent mating type information regulation 2 homolog/NAD-dependent deacetylase) deacetylates FoxO1, which might adapt it toward severe stress protection (49). By contrast while cellular energy is high (reducing the [NAD⁺]/[NADH]), Sirt1 is relatively less active and acetylated FoxO has less activity toward certain nuclear targets (46,49,50). Whether FoxO has beneficial or detrimental effects depends strongly upon the metabolic and tissue context. For example, FoxO ablation in the arcuate nucleus of the hypothalamus results in reduced food intake, leanness, improved hepatic glucose homeostasis and increased sensitivity to insulin and leptin (51). Hyperactivated FoxO contributes significantly to the negative effects of hepatic insulin resistance, whereas hyperactivated FoxO might mediate some of the beneficial effects of reduce insulin signaling during neurodegeneration. Regardless of this complexity, the activation of FoxO factors during acute starvation generally promotes mitochondrial function and life-sustaining metabolism under environmental or physiologic stress (52,53). However, during chronic insulin resistance, long term FoxO activity leads to genetic remodeling that can cause to cellular damage, even during nutrient excess.

Insulin/IGF1 signaling in CNS

1. Brain InsR and IGF1R localization

InsR is generally abundant in neurons—cell bodies and synapses—but it is less abundant in glia. InsR is expressed in regions that are linked to olfaction, appetite and autonomic

functions, such as the olfactory bulb, limbic system and hypothalamus, where it can influence feeding, body weight and reproduction. InsR is also present in the choroid plexus, circumventricular organs, and brain microvessels (54-56) suggesting it might contribute to the transport of insulin across the blood-brain barrier. IGF1R is expressed in the developing CNS and persists at high levels in the mature brain especially in the olfactory bulb, hippocampus, amigdala, parahippocampal gyrus, cerebellum, cortex and caudate nucleus. IGF1R is less abundant in the substantia nigra, white matter and cerebral peduncles, and glia cells (57-60).

2. Insulin/IGF1 in brain growth

Several mouse models demonstrate the importance of IGF1 signaling in brain growth and development (61). Mice lacking IGF1 or IGF2 display a small brain. The majority of IGF1-null mice die perinatally, whereas others demonstrate uniform growth retardation up to 38% (62,63). IGF2 is elevated in *IGF1*-null mice suggesting that it might partially compensate for the loss of IGF1 expression (64,65). Similarly, mice lacking *IGF1R* have smaller brains and die at birth (66). Reduced brain size was also observed in transgenic mice overexpressing human IGFBP1 (IGF binding protein 1) in the brain or other organs as it blocks IGF1 binding to its receptor (65). By contrast, neuron-specific disruption of the *InsR* gene (NIRKO mice) does not reduce brain size (18). Glial cell activation showed no differences between NIRKO and control mice, suggesting that InsR is not required for neuronal survival *in vivo*. Conversely, whole body or brain-specific *IRS2* deficiency uniformly reduces brain size between 30-40% (6,67). Brains of the *IRS1*-null mice are only moderately smaller and proportional to the smaller body and cranial volume, similar to the effect of growth hormone receptor knock-out (68). Thus the IGF1R→IRS2 pathway appears to play a crucial role in regulating neuronal growth and differentiation.

3. Brain glucose homeostasis

Insulin has dominant and well-characterized effects upon glucose homeostasis in peripheral tissues; however, insulin also regulates glucose metabolism through specialized groups of glucose-sensing neurons in the arcuate nucleus of the hypothalamus. These neurons respond to peripheral signals to regulate feeding behavior and energy homeostasis. These signals include the anorexigenic peptides proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), as well as the orexigenic neuropeptide Y (NPY) and agouti-related peptide (AgRP) (69,70). Under high glucose levels, brain insulin signaling hyperpolarizes glucose sensing neurons to activate K⁺/ATP channels and reduce neuronal firing (probably due to the inactivation of POMC neurons), which decreases body weight (71). Conversely, impaired brain insulin signaling increases body weight (18). This orexigenic effect is mediated by the activation of arcuate neurons containing NPY, AgRP, and GABA. Hypothalamic insulin also suppresses hepatic glucose production. Decreased hypothalamic insulin signaling reduces hepatic insulin sensitivity, which stimulates hepatic glucose production (72). This suggests that central insulin can regulate a hypothalamus→liver axis to regulate hepatic glucose production (73,74).

4. Insulin/IGF1 signaling in neuronal survival and function

Insulin and IGF1 are neurotropic as they promote neuronal growth, survival and differentiation under various experimental conditions, especially in the absence of other growth factors (75,76). In the adult CNS, the activation of insulin/IGF1 signaling pathway by insulin and IGF1 is stimulatory to neuronal survival via the action of PI3K to directly inhibit apoptosis (77). However, high levels of insulin in the brain are associated with neurotoxicity, which is thought to be due to increased production of free radicals and elevated oxidative stress (78). Insulin has also been found to induce neuronal cell death at

physiologically high concentrations in an *in vitro* rat hippocampal culture system (79). IGF1 might inhibit neuronal survival by inhibiting SIRT1 expression: SIRT1 has been shown to have a protective effect on the survival of neuronal cells. The mechanism by which IGF1 regulates SIRT1 and its relevance to *in vivo* neuronal survival remains unsettled (80,81).

Invertebrate Insulin/IGF1 signaling and lifespan

At least three independent mechanisms regulate ageing and lifespan, including caloric restriction, insulin/IGF signaling, and mitochondrial function (82). The first studies demonstrating the involvement of the insulin-like pathway in determination of lifespan came from *C. elegans* (83). An insulin-like signaling pathway in *C. elegans*—consisting of proteins encoded by the genes *daf-2*, *age-1*, *akt-1*, *akt-2*, *daf-16*, and *daf-18*—regulates dauer diapause, reproduction and life span (84). Mutations that reduce the function of *daf-2*, *age-1* or *akt* can increase the life span of *C. elegans* (83,85,86). These effects depend upon the presence of the dauer formation protein *daf-16*—an ortholog of mammalian FoxOs (87). Inactivating mutations in *daf-16* suppress the phenotype of *daf-2* and *age-1* mutant (88). Thus, insulin/IGFIR-like signaling regulates aging by modulating gene expression.

In *Drosophila melanogaster*, a signaling pathway that includes the insulin/IGF1R, the insulin receptor substrate (CHICO), the PI3K (Dp110/p60), and the PI3K target PKB, regulates growth, size, and life span (89). Mutation of the fly IR significantly extends lifespan (90). Moreover, mutations of *CHICO* extend the life span of female flies by 48% (91). Heterozygous deletion of the *CHICO* gene can increase life span, which is not further extended by calorie restriction. However, *CHICO*^{+/-} flies are more easily starved by diluted food than are wild-type flies, whereas the maximal life span of *CHICO*^{+/-} is less sensitive to reduction by high-energy food (91). These results suggest that calorie restriction and reduced insulin-like signaling alter common downstream processes that extend life span. Regardless of the complexity, the informative genetic experiments with *C. elegans* and flies provide a solid molecular basis to investigate the role of insulin signaling in mammalian lifespan.

Mammalian Insulin/IGF1 signaling and lifespan

1. Endocrine regulation of lifespan by Insulin/IGF1 signaling

In mammals, the first evidence that insulin/IGF1 signaling is related to life span came from experiments with Snell and Ames mice—naturally occurring loss-of-function mutations that cause dwarfism. Snell mice have mutations in pituitary factor 1 (PIT1) and Ames mice have a mutation in Prop-1 that is required for PIT1 expression (92). Compared with control mice, the life spans of Snell and Ames mice can increase 20 to 50%, depending upon genetic background and diet. These mice are deficient in serum GH (growth hormone), TSH (thyroid-stimulating hormone), and PRL (prolactin), and display low circulating concentrations of insulin and IGF1. The prolonged longevity of Ames and Snell dwarf mice is most likely due to GH deficiency, because comparable extension of life span was described in mice that cannot release GH in response to GH-releasing hormone due to a GH receptor/GH-binding protein knock-out (*GHRKO*) (92,93). Ames dwarf, Snell dwarf, and *GHRKO* mice share many phenotypic and physiological characteristics, which can contribute to the extended longevity (94). Moreover, the decrease in IR→IRS→PI3K pathway in the Snell dwarf mouse suggests that decreased activity of the insulin/IGF1 pathway might contribute to the longevity of the PIT1 mutant (95).

2. Insulin and IGF1 receptors and lifespan

Similar to *GHRKO* mice, IGF1 receptor-deficient mice are born 50% smaller than normal littermates, and die after a few days owing to developmental defects (66). However, a

moderate decrease in IGF1R levels can extend mouse longevity. The loss of one copy of the *Igf1r* gene increases life span of female mice by 33% and male mice by 16% (96). In contrast to the Ames and Snell dwarf mice, *Igf1r* heterozygous mice have no alteration in fertility. Interestingly, *Igf1r* heterozygous mice are more resistant to oxidative stress, suggesting a possible mechanism of their increased life span (96,97).

InsR-deficient mice die within a few days after birth owing to severe hyperglycemia (98). Mice retaining at least 20% of the normal InsR expression throughout the body can survive with severe postnatal growth retardation and hypoglycemia that resembles human leprechaunism (99). This growth defect arises, at least in part, from elevated hepatic IGFBP1 (IGF binding protein 1) that reduces IGF1 bioavailability. Thus, small mice with severely reduced insulin or IGF1 signaling have short life spans owing to developmental and metabolic defects. Whether the deletion of one allele of the InsR gene increases life span has not been investigated; however, as InsR^{+/−} mice develop hyperinsulinemia, and 5% of them develop diabetes by six months of age, their statistical life span might be reduced (100).

3. IRS proteins and lifespan

IRS1 null mice are small and insulin resistant with nearly normal glucose homeostasis, owing to β -cell expansion and compensatory hyperinsulinemia (68). Some reports indicate a small increase in longevity of global *Irs1*^{−/−} mice (101). By contrast, global knockout of IRS2 develop diabetes around 8 weeks of age, owing to reduced β -cell mass and insufficient compensatory insulin secretion (102,103). Owing to progressive diabetes, the life span of global *Irs2*^{−/−} mice is reduced to about 15 weeks. Mice without *Irs2* and only a single allele of *Irs1* (*Irs1*^{+/−}•*Irs2*^{−/−}) develop severe fasting hyperglycemia and die by 4 weeks of age (104). By contrast, mice retaining one allele of *Irs2*, (*Irs1*^{−/−}•*Irs2*^{+/−} mice) are small with nearly normal glucose tolerance and circulating insulin concentrations at six months of age (104); however, these very small animals are fragile and require extraordinary care to live beyond this age. Thus, healthy glucose tolerance and a small size are not definitive determinants of life span.

4. Mutations in insulin/IGF1 signaling and human longevity

Several reports document a correlation between lower insulin/IGF1 activity and extreme human longevity (105). Mutations in the *IGF1R* gene were found to be more abundant among Jewish Ashkenazi centenarians than in healthy controls (106). Similarly, mutations within FoxO3a (the closest *daf-16* mammalian orthologue) correlate with the long-lived Japanese-Hawaiian or German centenarians (107,108). In elderly women in the Leiden 85-plus study, polymorphisms of several genes related to insulin and somatotrophic signaling were associated with reduced mortality and improved cognitive function (109). IRS2 variants were also reported to correlate with longevity in an Italian population (110). Together these studies support the hypothesis that insulin/IGF1 signaling might influence human lifespan.

Insulin/IGF1 signaling in the CNS: metabolism and lifespan

1. Brain-specific inactivation of insulin/IGF1 signaling molecules and lifespan extension

Similarly to whole body heterozygous *IGF1R* mice (96), brain-specific heterozygous *IGF1R*-knockout mice with genetically-modified hyposensitivity for IGF1 in the CNS display increased life span (111). By contrast, NIRKO mice (neuron-specific disruption of the InsR gene) display a normal lifespan. However, NIRKO mice display peripheral insulin resistance and obesity, but have normal brain development and neuronal survival (18). A similar metabolic phenotype occurs in hypothalamic-specific *InsR* knockout mice (112). In addition, drug-inducible, brain-specific, *InsR* knockout mice suffer from hyperinsulinemia

and have an upregulation of hepatic leptin receptors (72). The deletion of murine InsR from midbrain dopamine neurons causes hyperphagia and increased body weight (113). Taken together, these results demonstrate the importance of InsR in the CNS regulation of feeding and energy homeostasis.

Regulation of IRS2 signaling in the brain reveals a link between the life span extension and metabolic regulation. Reduced IRS2 signaling in all tissues or just in the brain can increase the life span of mice maintained on a high-energy diet by nearly six months (6). However, brain-specific, long-lived *IRS2* knockout mice consume approximately the same or slightly more food than the short-lived controls. At 22 months of age, brain *IRS2* knockout mice are overweight, hyperinsulinemic, and glucose intolerant (6). Thus, less brain IRS2 signaling is associated with an increased life span regardless of the peripheral insulin sensitivity. The exact location of IRS2 signaling is important to investigate. Recent studies indicate that inhibiting IRS2 in the mouse midbrain attenuates the morphine reward (114). Moreover, IRS2 in a subpopulation of hypothalamic neurons plays a role in energy homeostasis and growth (115). It is possible that the impact of altered insulin/IGF1 signaling in the brain upon aging and metabolism will prove to be related to its action in a specific site or set of neurons.

2. Targeting Nutrient-sensing neural circuits

The role of insulin-like signaling has focused upon distinct populations of neurons in the hypothalamic arcuate nucleus (ArcN) that express pro-opiomelanocortin (POMC) or agouti-related peptide (AgRP); however, deletion of IRS2 or InsR from these neurons in mice negligibly impacts metabolic homeostasis (115-117). Similarly, disruption of the PI3K/Akt→FoxO1 pathway in POMC and AgRP neurons produces relatively subtle alterations in energy balance and glucose homeostasis (118-120). While insulin signaling in TH (tyrosine hydroxylase)-expressing catecholaminergic neurons is important for the control of mesolimbic dopamine (DA) signaling, lack of InsR signaling in these neurons has no effect upon peripheral adiposity or glucose homeostasis (113). By comparison, deletion of the InsR from SF1 (steroidogenic factor 1) neurons—a specific set of neurons of the ventromedial hypothalamus (VMH)—promotes modest weight gain on a high-fat diet without altering energy balance or insulin sensitivity in chow-fed animals (121). Thus, the relevant site at which insulin signaling contributes to metabolic regulation must be a distinct, or broader, set of neurons.

Whereas the mammalian CNS is far more complicated than that of worms and flies, recent advances provide insight into the neural circuitry that controls metabolism in mammals (69). The peripheral hormone leptin signals the status of body energy stores to the central nervous system by binding and activating the leptin receptor (LepRb) on neurons that control energy balance and metabolism (122). The dysregulation of all aspects of metabolism, from glucose and lipid homeostasis to energy balance, in humans and rodents null for leptin or LepRb reflect the centrality of leptin→LepRb signaling to the regulation of metabolism (123,124). LepRb neurons include those that express AgRP (as well as subsets of POMC, SF-1, and TH neurons), but also include other metabolically important neurons in the ARC and elsewhere (70). Recently we have demonstrated that LepRb neurons represent the crucial mediators of brain insulin/IGF1 signaling in the control of energy balance and glucose homeostasis (125). Thus, deletion of IRS2 from this restricted subset of CNS neurons dysregulates gene expression within the hypothalamic melanocortin system—which increases feeding, decreases energy expenditure, and promotes insulin resistance. Whereas this crucial set of neurons that mediates the metabolic effects of IRS2 signaling in the brain is by definition the same one that mediates leptin action, IRS2 was not required for leptin action. Furthermore, while interference with leptin action in these LepRb neurons promotes reproductive

dysfunction, obesity and insulin resistance (123), deletion of IRS2 and interference with insulin/IGF1 signaling in LepRb neurons did not alter the thyroid, adrenal, or reproductive axes (125). While leptin can promote some IRS2→PI3K signaling (126), leptin barely stimulates this pathway by comparison to insulin, suggesting that IRS2 functions primarily to mediate insulin/IGF1 rather than LepRb signaling in these neurons. Indeed, while the hypothalamic application of PI3K inhibitors or the genetic blockade of PI3K in some leptin responsive neurons impairs the acute anorectic response to leptin, these manipulations have little effect on baseline leptin action or energy balance (71,126,127). Thus, while IRS2 signaling in LepRb neurons modulates metabolism, it does not appear to interact directly with leptin signaling.

Interestingly, attenuation of the insulin/IGF1 pathway via IRS2 signaling in these nutrient-sensing leptin receptor expressing neurons had no effect on IRS2-associated increase in lifespan (Sadagurski M., Dong X., Miller R.A., Myers M.G., White M.F., unpublished). These results clearly dissect the set of LepRb neurons that are responsible for the metabolic effects of the insulin/IGF1 signaling in CNS from yet unidentified neuronal circuits that underlie mammalian lifespan extension due to altered insulin/IGF1 signaling. Additional work will reveal new strategies to extend lifespan without causing undesirable metabolic side effects.

Insulin/IGF1 signaling and neurodegenerative diseases

1. Link between insulin/IGF1 signaling and neurodegeneration

Neurodegenerative diseases—including Alzheimer's (AD), Parkinson's (PD), and Huntington's (HD)—are associated with advanced age (128-130). Most AD and PD cases appear sporadically, and not earlier than the seventh decade of life. HD is a familial, monogenic disease that presents in middle age (130). The adult onset of these neurodegenerative diseases might be related to progressive metabolic stress of aging. In humans, aging is associated with a decline in plasma levels of IGF1, which is suggested to contribute to disease progression (131). By contrast, plasma insulin levels tend to increase with age, owing to peripheral insulin resistance associated with weight gain and inactivity. Although the molecular link is controversial, neurodegeneration might be exacerbated by hyperinsulinemia and reduced peripheral IGF1 (33,78).

Studies in different invertebrate models suggests that genetic manipulations that reduce insulin-like signaling have the potential to reduce neurodegeneration and improve neuronal function with age (24,132). In worms, long-lived *age-1* mutants show improved thermotaxis learning with age, which might be due to increased resistance to neuronal stresses and disease (12,14). This protective effect was apparent in the worm model even when the alteration of insulin-like signaling was applied late in life (14). In flies the mutation *CHICO* slows age-related decline in motor function, suggesting that lowered insulin-like signaling has the potential to ameliorate CNS-based declines (24,90).

Contemporary work suggests that it might be possible to slow the progression of neurodegeneration by modulating insulin-like signaling. Studies in rats demonstrate that infusion of IGF1 can protect against A β -mediated toxicity (133). Injection of IGF1 into AD-model mice reduces the typical behavioral impairments that are associated with increased A β levels (134). Furthermore, IGF1 treatment of mouse primary neuronal cells transfected with mutant Huntington protein (HTT) inhibits polyQ-HTT aggregation and reduces cell death—presumably via the activation of the PI3K→AKT cascade (135). In the cell-based functional genetic screen, it was found that activation of IRS2 led to a macroautophagy-mediated aggregate clearance of the accumulated HTT. However, the polyQ-toxicity-

protective effect was AKT-independent, suggesting that unknown signals downstream of IRS2 diverge and more than one mechanism might be involved (136).

These studies raise the possibility that insulin/IGF1 signaling might influence the progression of different stages of neurodegeneration. For example, hyperinsulinemia could exacerbate oxidative stress and the accumulation of damaged proteins, whereas reduced IGF1 might facilitate apoptosis and reduce the generation of new neurons (82,137). However, increased peripheral signaling can attenuate the acute effects of insulin resistance and hyperglycemia. Thus it remains controversial whether more or less insulin/IGF1 signaling can be expected to protect from progressive neurodegenerative disease.

2. Insulin/IGF1 signaling in AD

AD is a chronic and progressive neurodegenerative disease and the most common form of dementia leading to the loss of cognitive abilities and finally to death (138). The disease is characterized by β -amyloid accumulation, formation of extracellular amyloid plaques as well as neurofibrillary tangles. The β -amyloid plaques mainly contain aggregated amyloid- β (A β) peptides generated by proteolytic cleavage of the amyloid precursor protein (APP). The aggregation of A β is thought to be the principle cause of neurodegeneration in AD (139). The removal or attenuated production of A β is an important clinical goal.

Recent studies suggest that CNS insulin resistance—sometimes called type 3 diabetes (140)—is associated with AD progression (141). Two recent studies reveal an association between AD pathology and Ser/Thr phosphorylation (pS616^{IRS1} and pS636^{IRS1}/pS639^{IRS1}) of IRS1. Phosphorylation at these sites has been found to be associated with reduced insulin sensitivity in cell culture experiments and in peripheral tissues (142). Inflammation, excess nutrients or chronic hyperinsulinemia are often linked to Ser/Thr phosphorylation of IRS1, so the exact profile of phosphorylation sites that accumulate might reveal the underlying cause of insulin resistance (143,144). However, it is not clear what patterns of IRS1 Ser/Thr phosphorylation might reflect attenuated insulin/IGF1 signaling that contribute to disease pathology, or reflect a molecular counter regulation to promote insulin/IGF signaling under stressful conditions (143,144). For example, recent work suggests that Ser307—one of the principle phosphorylation sites on IRS1—might promote systemic insulin action (IRS1 tyrosine phosphorylation). In this scenario Ser/Thr phosphorylation of IRS1 might be part of a mechanism to protect neurons by augmenting IGF signaling. It is also possible that reduced insulin signaling caused by Ser/Thr phosphorylation of IRS1 might protect neurons from proteotoxicity and decrease the A β load, in which case efforts to normalize Ser/Thr phosphorylation should be avoided (15,16,145,146).

3. The protective effects of the reduced insulin/IGF1 signaling in AD

Several studies have focused upon effects of reduced insulin/IGF1 signaling in AD mouse models (15,16,145). The models include a transgenic mouse that accumulates A plaques, owing to the Swedish mutation (APP^{sw}) in APP (*Tg2576*-mice). Intercrosses between *Tg2576*-mice and mice lacking *IRS2* (*Tg2576•Irs2*^{-/-} mice) display a reduced A β plaque burden in the brain. Moreover, *Tg2576•Irs2*^{-/-} mice exhibit better learning and memory when compared against the *Tg2576* mice (15). A similar study shows that female *Tg2576•Irs2*^{-/-} mice benefit most from the deletion of *IRS2*, as male mice develop early onset life threatening diabetes owing to the rapid and complete loss of beta cells. The deletion of *IGF1R* predominantly from the hippocampus of *Tg2576* mice by cre-recombinase under control of the synapsin-1 promoter (*Tg2576•nIGF1R*^{-/-}) protects both female and male mice against APP^{sw}-induced lethality (16). Furthermore the reduction in A β was observed specifically in hippocampus, but not in other brain regions. These results

suggest an important role for neuron-autonomous IGF1R→IRS2 pathway in hippocampus in the control of APP metabolism.

Mice harboring only one copy of the IGF1R gene were also crossed to transgenic AD mice. These mice were protected from AD-associated memory and orientation impairments and had reduced rates of neuro-inflammation, and neuronal and synaptic losses in the aged brain. Owing to the appearance of smaller and highly dense A β plaques, it is suggested that reduced IGF1 signaling protects the brain by sequestering highly-toxic A β oligomers (145). Although no data was reported on the metabolic status of these animals, based on the phenotype of the *IGF1R* heterozygous mice, it is reasonable to assume that glucose metabolism was not affected in these animals.

4. The protective effects of the reduced insulin/IGF1 signaling in mouse model of Huntington's disease

Compared to the lengthy degenerative processes associated with mortality in AD, neurodegeneration in Huntington's disease (HD) progresses predictably to death that depends upon the length of an expanded CAG triplet repeat in the HD gene that encodes a mutant form of the protein huntingtin (HTT) (147). Mutant HTT produces intranuclear and cytoplasmic inclusions, and kills cells in the striatum and cerebral cortex—although other areas are also affected (148). We investigated the relation between IRS2 signaling and the progression of HD in R6/2 mice (17). We selected the R6/2-mice because it displays a rapid and highly-reproducible phenotype of neurodegeneration used frequently as a model of HD (149). We hypothesized that HD might represent a suitable model to examine the effects of IRS2 signaling upon degenerative processes in the CNS. Two experiments show that the levels of IRS2 signaling can modulate HD progression in the R6/2 mice. Increasing IRS2 levels by 50% with a neuron-specific enolase transgene (*R6/2•Irs2^{mg}*) accelerates the progression of neurodegeneration and significantly reduces the life span of R6/2 mice. By contrast, reducing IRS2 levels throughout the body—except in β cells, where IRS2 expression is needed to prevent diabetes onset—extends life span of the R6/2 mice (17). These results are consistent with the hypothesis that reduced IRS2 signaling (insulin/IGF1 resistance) might be protective against the effects of proteotoxicity.

PolyQ-HTT causes pathological sequela in R6/2-mice that develop progressively until death—including mitochondrial dysfunction and oxidative stress, accumulation of protein aggregates in the CNS, neuroinflammation, and abnormal behavior and movement (149-151). However, only mitochondrial dysfunction and oxidative stress increase significantly in the CNS of *R6/2•Irs2^{mg}*-mice, revealing a major consequence of excess insulin/IGF signaling upon acute neurodegeneration and early death of these HD mice (17). The slower progression of HD-like symptoms in R6/2 mice with less IRS2 expression is associated with increased nuclear localization of the transcription factor FoxO1. Some FoxO1 target genes are expressed at higher levels in the CNS of these mutant mice, including *Ppargc1 α* and *SOD2*, both of which have strong effects on energy homeostasis and prevention of oxidative stress (152,153). Whether neuronal mitochondrial damage and oxidative stress during normal aging is modulated by IRS2 signaling is an interesting disease model to establish, as it might have broad consequences upon the progression of debilitating disease in an aging population. Our previous work shows that less neuronal IRS2 signaling preserves a youthful diurnal transition between glucose and fat oxidation, which is ordinarily lost in old wild type mice (6). Thus the negative effects of IRS2 signaling upon energy homeostasis in HD mice might exacerbate a common mechanism that contributes to the slow progressive neurodegeneration of normal aging.

R6/2 mice with reduced IRS2 signaling accumulate fewer polyQ-HTT aggregates in the brain (17). Aggregate accumulation is thought to reflect cellular damage, as cells that form

aggregates earlier tend to die earlier (154). Aggregates might impair mitochondrial oxidative phosphorylation and contribute to free radical damage (155); however, other modes of protection, such as increased autophagy might facilitate the clearance of protein aggregates (156). Autophagy sequesters damaged organelles, including soluble and aggregate forms of mutant HTT, into double-membrane structures (autophagosomes) for degradation (156,157). Increased nuclear FoxO-mediated gene expression, owing to less IRS2 signaling might increase the expression of genes that mediate autophagy and promote autophagosomes formation. Thus increased autophagy might be responsible for the reduced HTT aggregates and slower HD progression in mice with reduced IRS2 expression levels.

Mutant HTT leads to the dysregulation of a number of different cellular pathways, including gene transcription, mitochondrial function, oxidative stress resistance and protein degradation pathways (147). Decreased IRS2 signaling slows the progression of several of these pathogenic abnormalities, which attenuates the disease phenotypes in R6/2 mice (**Fig 2**). Our results suggest that attenuation of the insulin/IGF1 signaling cascade, as a regulator of multiple cellular pathways, can slow the disease progression, and thus, represent a potential therapeutic strategy to optimize neuroprotection during progressive genetic stress. While increasing insulin signaling in peripheral tissues might be necessary to avoid the consequences of peripheral metabolic disease—insulin resistance, dyslipidemia and cardiovascular disease—it is equally important to appreciate the potential life-threatening consequences of increased insulin/IGF1→IRS2 signaling in the brain.

5. Autophagy as a Therapeutic Target

What candidate mechanism can be a potential therapeutic target that will contribute to the lifespan extension and neuronal survival due to reduced insulin/IGF1 signaling? One of the potential therapeutic targets is the autophagy mechanism (158,159). Autophagy is crucial for cell survival under extreme conditions, by removing damaged organelles and using the components for energy or repair. Autophagy might have a direct impact to reduce progressive aging and especially neurodegeneration (159).

Autophagy was first associated with longevity because it is required for the lifespan extension of insulin-like signaling mutant worms (160). Promoting autophagy in neurons is sufficient to extend lifespan and increase resistance to oxidative stress, possibly via the prevention of age-dependent accumulation of neuronal damage (161-163). As autophagy is predominantly regulated by the TOR pathway, lowered insulin/IGF1 signaling can induce autophagy by attenuating the IRS→AKT→mTOR cascade (164). Rapamycin is highly effective in inducing autophagy, reducing the load of misfolded proteins *in vitro* and in mouse models (165). Thus, rapamycin or other mTORC1 inhibitors might serve to slow the accumulation of misfolded proteins (166). However, the risk of diabetes due to rapamycin-induced suppression of insulin signaling components has diminished enthusiasm for its long term use (167).

The development of small molecules that can activate autophagy without cytotoxicity could emerge as novel therapeutic approaches to ameliorate brain pathologies associated with aging. For example, Psammalyse A increases nuclear localization of FoxO3 *in vitro* and *in vivo*, which seems to protect motor neurons and fly eyes from toxic protein aggregation (168). This study provides evidence that manipulating this longevity-promoting signaling pathway can effectively block neurodegeneration. Although it is not obvious how to modulate IRS2 signaling in specific neurons, compounds that reduce IRS2 levels in brain without similar effects in peripheral tissues (especially pancreatic beta cells) would seem to be worth investigating. A strategy to reduce IRS2 signaling in a specific set of neurons might clear misfolded proteins to slow the progression of neurodegenerative diseases without undesirable peripheral metabolic effects.

Future perspectives

Although insulin and IGF signaling are well known for their system-wide effects upon metabolism and organism growth, their effects upon longevity might be non-autonomous and emanate from the CNS (82,169). In mammalian CNS, genetic manipulations in insulin/IGF1 signaling, while extending longevity also cause insulin resistance and hyperglycemia, as in cases of long-lived brain specific IGFR^{+/−} mice and IRS2 brain specific knock-out mice (6,111). However, with further analysis it might be possible to resolve the effects of insulin/IGF signaling upon metabolism and lifespan. As we dissect the neuronal population that is responsible for the metabolic effects of insulin/IGF1 signaling pathway, we can concentrate our efforts on identifying neural circuits that mediate beneficial effects of the reduced insulin/IGF1 signaling on life span and neurodegeneration while maintaining CNS energy homeostasis and peripheral glucose metabolism.

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KEY POINTS

- Understanding how metabolism integrates nutrient homeostasis with life span is a complicated undertaking.
- The insulin pathway coordinates growth, development, metabolic homeostasis, fertility and stress resistance, which ultimately influence lifespan.
- Maintenance of the central nervous system (CNS) has particular importance for lifespan.
- Depending upon the exact site, reduced insulin/IGF1 signaling in the CNS can dysregulate peripheral energy homeostasis and metabolism, promote obesity, and extend lifespan.

Figure 1.

Insulin regulated PI 3-kinase→PDK1→Akt and Grb2/Sos→ras kinase cascades. Insulin (INS) stimulates tyrosine phosphorylation of IRS-proteins (pY) that promotes PI3K [p85•p110] and Grb2/SOS binding. Grb2/SOS stimulates the ras→MAPK (ERK1/2) cascade, which stimulates transcription factors. The PI3K produces PI_{3,4}P₂ and PI_{3,4,5}P₃ (antagonized by the action of PTEN or SHIP2), which recruits PDK1 and AKT to the plasma membrane where AKT1 is activated by phosphorylation at T308 by PDK1 and S473 by mTORC2. AKT phosphorylates many cellular proteins including TSC2 that inhibits a Rheb-specific GTPase that activates mTORC1-dependent protein synthesis, and activation of SREBP1c that stimulates lipogenic gene expression. AKT-mediated phosphorylation of FOXO1 results in cytoplasmic sequestration, which alters the expression of many genes in liver, muscle, brain and other tissues. Akt, mTORC1 and S6K1, mediate ‘homologous’ feedback inhibition of IRS-dependent signaling by Ser/Thr phosphorylation of IRS1/2, while circulating factors (TNFa) activate ‘heterologous’ pathways that phosphorylate IRS on S/T-sites.

Figure 2.

Decreased IRS2 signaling slows the progression of HD by manipulating several cellular pathways, including gene transcription, mitochondrial function, oxidative stress resistance, autophagy and protein degradation pathways in R6/2 mice.