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Review article

Inflammation and insulin/IGF-1 resistance as the possible link between obesity and neurodegeneration

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ABSTRACT

Obesity is a growing epidemic that contributes to several brain disorders including Alzheimer's, Parkinson's, and Huntington's diseases. Obesity could promote these diseases through several different mechanisms. Here we review evidence supporting the involvement of two recently recognized factors linking obesity with neurodegeneration: the induction of pro-inflammatory cytokines and onset of insulin and insulin-like growth factor 1 (IGF-1) resistance. Excess peripheral pro-inflammatory mediators, some of which can cross the blood brain barrier, may trigger neuroinflammation, which subsequently exacerbates neurodegeneration. Insulin and IGF-1 resistance leads to weakening of neuroprotective signaling by these molecules and can contribute to onset of neurodegenerative diseases.

Contents

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1. Introduction

Neurodegenerative disorders include an array of devastating diseases characterized by the loss of neuronal function and viability. This leads to a decline in brain functions including coordination of movement, memory and other cognitive abilities (Hanson and Clarke, 2013). According to the World Health Organization, 36.6 million people worldwide suffered from dementia in 2012, and the number of affected patients is rising at an alarming rate of 7.7 million new cases each year (World Health Organization, 2012). As the human population continues to age, the incidence of age-dependent dementia will increase, which is a major medical concern (Rollero et al., 1998; Puglielli, 2008; World Health Organization, 2012). With age, the brain undergoes physiological change, leading to decline in some cognitive abilities such as processing speed and memory; however, dementias that characterize Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD) are not a part of the normal aging process.

The human brain is comprised of an elaborate system of neuronal circuitry and supporting glial cells (astrocytes, microglia and oligodendrocytes), which perform protective and supportive roles towards neurons in the central nervous system (CNS). Glial cells play key roles in neuroinflammatory processes that contribute to the pathogenesis of neurodegenerative diseases (Block and Hong, 2005; Goll et al., 2013; Qin et al., 2013). The purpose of this review is to summarize published evidence on the role of obesity-induced inflammation and obesity-induced insulin/insulin like growth factor 1 (IGF-1) resistance in the onset and pathogenesis of neurodegenerative disorders. We will focus on AD, PD and HD (see Figs. 3–5), since evidence implicating brain inflammation as the potential initiator or aggravator in these diseases is most compelling (Uysal et al., 1997; Sathe et al., 2012; Hsiao et al., 2013).

2. Inflammatory response

Inflammation is part of the body's innate immune response to harmful stimuli, such as pathogens, damaged cells or noxious substances. The inflammatory process is a natural physiological response with three main functions: 1) wall off the infection, 2) call cells of the immune system to the area of injury, and 3) initiate the immune system response. Ultimately, the goal of inflammation is to clear the harmful substance and repair the associated damage (Davalos et al., 2005; Simard et al., 2006; Soczynska et al., 2011; Smith et al., 2012).

2.1. Inflammation in the periphery

Upon the appearance of inflammatory stimuli, the body responds quickly by increasing blood vessel diameter (vasodilatation), thus allowing for an increase in blood volume. Also, blood vessel permeability increases. This leads to the movement of leukocytes from the blood vessels into the site of tissue damage (Laskin, 2009). Neutrophils phagocytose the invading pathogen or damaged cells and release molecular mediators (cytokines and chemokines), which facilitate the inflammatory process via recruitment and activation of other immune cells (Bryant et al., 1966; Strieter et al., 1990). Upon arrival, activated macrophages engage in the process of phagocytosis, and simultaneously secrete an array of cytokines including tumor necrosis factor alpha (TNFα), interleukin (IL)-6 and IL-1β, all of which are pleiotropic pro-inflammatory cytokines. These cytokines are pyrogenic, they increase blood vessel permeability, induce synthesis of acute-phase response proteins, and activate both B and T lymphocytes (Duff and Durum, 1982; Kopf et al., 1994; Biffl et al., 1996; Sahan et al., 2013). Thus, the process of inflammation is self-perpetuating, and only ends when the injury is fully repaired or invading pathogens are removed.

2.2. Chronic inflammation

In chronic inflammation, the normal physiological process of defense and removal of unwanted noxious substances becomes disordered and persists even in the absence of the original stimuli; however, the mechanism by which acute self-resolving inflammation switches to chronic, persistent inflammation is not fully understood (Buckley, 2011). During the chronic inflammatory process, healthy neighboring cells suffer collateral damage as a result of the misdirected, unending immune attack (Frank-Cannon et al., 2009). Chronic inflammation proliferates several disease states in both the periphery and CNS including inflammatory bowel disease, arthritis, Crohn's disease, diabetes mellitus, Graves' disease, ulcerative colitis, multiple sclerosis (MS), arteriosclerosis and gastritis, to name a few (Naugler and Karin, 2008; Bende et al., 2009; Meijer et al., 2011). In addition to these previously well-characterized inflammatory diseases, obesity is now also regarded as a chronic pro-inflammatory disease state.

2.3. Neuroinflammation

Neurodegeneration is defined as the loss of neuronal cell structure and function, ultimately leading to neuronal death, and is an umbrella term for many disorders leading to dementia. Although several distinct mechanisms may trigger neurodegeneration, brain-specific inflammation is almost universally associated with this process (Block and Hong, 2005; Cunningham, 2013). Neuroinflammation is the state of an active immune system in the CNS, and is carried out by glial cells.

Astrocytes are involved in an array of significant functions, including maintenance of the blood brain barrier (BBB), physical support to neurons, modulation of synaptic transmission, and supplying neurons with nourishment (Dehouck et al., 1990; Rubin et al., 1991; Denis, 2013). Microglia are macrophages, which function as innate immune cells of the brain, continually monitoring the CNS for damaged cells, irregular proteins and infectious agents (Magnus et al., 2001; Jessen, 2004; Tambuyzer et al., 2009). Both glia and neurons benefit from the inflammatory process, since this response under normal physiological circumstances minimizes further cellular damage (Laroux, 2004). However, in chronic neuroinflammatory conditions, glial cells are constitutively activated, which may have detrimental effects.

Activation of glial cells leads to production of reactive oxygen and nitrogen species, initiation of phagocytosis and upregulation of anti-proliferative and pro-inflammatory mediators, all of which can contribute to neuronal damage and death (Mandrekar-Colucci and Landreth, 2010; Smith et al., 2012; Ruiz-Nunez et al., 2013). The damaged neurons are in-turn capable of further activating glial cells through release of soluble cellular factors, such as damage-associated molecular patterns (DAMPs) (Block and Hong, 2005; Lull and Block, 2010; Liu et al., 2012). This process leads to a vicious cycle of self-propelling inflammation and cell death that is sustained even after the removal of the initial stimuli (Block and Hong, 2005; Smith et al., 2012). This perpetual pro-inflammatory microenvironment is hypothesized to propagate conditions that lead to neurodegeneration (Pais et al., 2008; Frank-Cannon et al., 2009; Cunningham, 2013); it also sets the groundwork for several neurological diseases including: AD, PD, schizophrenia, major depressive disorder (MDD), bipolar disorder, amyotrophic lateral sclerosis and HD (Soczynska et al., 2011; Soulet and Cicchetti, 2011; Smith et al., 2012; Cai, 2013).

2.4. Glial cell activation in obesity

As already discussed, glial cells can be activated by many substances including such adipose tissue derived molecules as ceramide and the saturated fatty acid palmitate. These molecules are, for example, capable of inducing monocytic cell cytotoxicity (Little et al., 2012). High fat diet-fed obese pups express increased concentration of IL-1β in their hippocampus compared to their lean counterparts (Bilbo and Tsang, 2010).

Other studies have shown that diet-induced obesity (DIO) selectively increases IL-6 in cerebral amyloid angiopathy mice, while decreasing levels of TNFα in non-diseased control mice (Zhang et al., 2013). Chronic exposure of mice to the high fat 'western diet', results in exacerbated CNS (hypothalamus and hippocampus) TNFα, IL-6, IFNγ and IL-1β in response to peripheral lipopolysaccharide treatment when compared to normal chow-fed control mice (Milanski et al., 2009; Andre et al., 2014). Increase in cytokine expression in the brains of obese mice occurs through activation of toll-like receptor 4 (TLR4) by long-chain fatty acids (Milanski et al., 2009).

Studies have also shown that in rodent models of diet-induced obesity there is higher CNS macrophage infiltration and activation (up to 53% increase) compared to the lean control animals (Drake et al., 2011), as well as an increase in total number of microglia and astrocytes in the CNS (Koga et al., 2014). Markers of microglia activation, such as cluster of differentiation 11b (CD11b) and TLR4, are significantly upregulated (up to 2 fold and 1.8 fold respectively) in the hippocampus of maternal diet-induced obese pups as early as one day after birth (Bilbo and Tsang, 2010). Additionally, the ratio of activated vs. resting macrophages in the CNS of obese/high fat diet-fed mice is 30% higher compared to lean/normal chow-fed mice, reflecting either an increase in activation of resident microglia, or increased infiltration of monocytes/macrophages from the periphery (Buckman et al., 2014). However, others argue that the high fat diet-induced microglia activation in the hippocampus of mice is independent of body weight (Gao et al., 2014).

3. Epidemiological evidence linking obesity and neurodegenerative diseases

The relationship between obesity (excess body fat) and neurodegeneration is likely complex. High adiposity (fat) levels are associated with an environment of chronic low-grade inflammation in the periphery, which may contribute to neurological disorders through elevated levels of inflammatory cytokines, such as IL-6, IL-1β and TNFα (Iida et al., 2001; Weisberg et al., 2003; Brundage et al., 2008; Gregor and Hotamisligil, 2011). It is important to note that not all obese individuals exhibit an increase in systemic cytokine levels. Some studies report that up to 23% of people who are obese demonstrate no signs of inflamed adipose tissue (Farb et al., 2011). Other reports have identified gender differences with 92% of obese males and only 63% of obese females having inflamed adipose tissue (Bigornia et al., 2012). The cause for such difference is poorly understood.

In addition to increased secretion of pro-inflammatory mediators, obese and overweight individuals exhibit altered insulin/IGF-1 signaling (Polonsky et al., 1988; Bosello and Zamboni, 2000). Evidence supports association of more than twenty different neurological syndromes with insulin/IGF-1 signaling malfunctions and obesity. They include schizophrenia, bipolar disorder and MDD in addition to AD, HD and PD (Lopresti and Drummond, 2013); however, the cellular and molecular mechanisms linking obesity and neurodegenerative diseases are only beginning to be unraveled. Obesity-induced insulin and IGF-1 resistance, along with chronic low-grade inflammation, represent two of the possible mechanisms behind this. In addition, inflammation may induce or exacerbate insulin/IGF-1 resistance, compounding the impact of obesity on the neurodegenerative disease process (Fig. 1).

3.1. Epidemiological evidence linking obesity and Alzheimer's disease

AD is characterized by the gradual and progressive decline in cognitive ability and function. At the cellular level, AD possesses two characteristic hallmarks: amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) (Hauw et al., 1990; Pitt et al., 2013). NFTs consist of abnormally phosphorylated tau protein, which causes the cytoskeleton to disconnect and neurons to shrivel into disconnected cellular masses (Hauw et al., 1990). Aβ plaques are extracellular masses of aggregated Aβ that form due to the over production of abnormal Aβ protein, which cannot be cleared by proteases or immune defenses (Beach et al., 1989; Orre et al., 2013). Inflammation is fundamental to AD progression acting as a robust pathogenic force (Salminen et al., 2009; Tyagi et al., 2013). It is characterized by sustained glial cell activation in response to abnormal structures associated with the AD pathology: Aβ plaques, NFTs and necrotic cellular fragments (Beach et al., 1989; Hauw et al., 1990; Pitt et al., 2013).

Although the exact mechanisms are currently unclear, obesity is associated with changes in brain structure and function, a decline in cognitive ability leading to dementia and AD (Gustafson et al., 2003, 2012; Businaro et al., 2012; Arnoldussen et al., 2014). Body mass index (BMI), which is a measure of adiposity, declines with the progression of AD, especially at the late stages of the disease (Gilette-Guyonnet et al., 2000); however, it has been reported that an increase in BMI in mid-life correlates to an increased risk for the development of AD later on in life (Gustafson et al., 2003, 2012). This correlation was found to be particularly of concern for females (Gustafson et al., 2003). However, other studies have concluded that obesity negatively affects cognitive ability in men, but not women (Elias et al., 2003, 2005).

Obese males scored significantly lower than non-obese males in a variety of cognitive ability tests, including visual memory, verbal learning, visual organization, concentration and abstract reasoning (Elias et al., 2003). Others report that overweight individuals ($25 < BMI > 30$) have a 2-fold increase in risk for developing AD, and obese individuals ($BMI > 30$) have a 3-fold increase risk for AD, compared to normal weight controls ($BMI < 25$), regardless of gender (Whitmer et al., 2007). This epidemiological evidence indicates that one or possibly many factors related to obesity positively correlates with decreased cognitive ability and increased risk for developing AD. This association of obesity and neurodegeneration is not unique to AD, but also applies to other neuropathologies including HD and PD.

3.2. Epidemiological evidence linking obesity and Parkinson's disease

PD is an age-related neurodegenerative disease characterized by muscle rigidity, slowness of voluntary movement (bradykinesia), resting tremor and postural instability (Mahlknecht and Poewe, 2013; Santiago and Potashkin, 2013). PD brains are characterized by the aggregation of filamentous α-synuclein protein forming insoluble Lewy

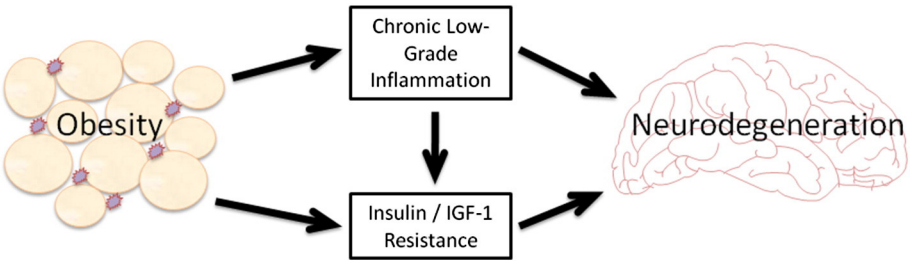

Fig. 1. Possible links between obesity and neurodegeneration. Obesity promotes chronic low-grade peripheral inflammation and insulin and IGF-1 resistance. Inflammation enhances insulin and IGF-1 resistance. Chronic inflammation, coupled with insulin and IGF-1 resistance, promotes neurodegenerative pathologies.

bodies, and also by selective loss of dopaminergic neurons especially in the substantia nigra pars compacta (SNpc) region of the brain (Morris et al., 2011; Marques and Outeiro, 2012; Mahlknecht and Poewe, 2013). α-Synuclein aggregates activate microglia by stimulating the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase-dependent production of reactive oxygen species (ROS), which induces oxidative stress in the microglia, and amplifies their activation (Zhang et al., 2005; Klegeris et al., 2008; Qin et al., 2013). Activated microglia can summon T lymphocytes to the site of inflammation, where they may become toxic towards dopaminergic neurons, resulting in neuronal cell death (Benner et al., 2008).

Not without controversy, high BMI (>30) has been identified as one of the risk factors for PD (Abbott et al., 2002; Hu et al., 2006; Palacios et al., 2011). A recent meta-analysis determined that being overweight (BMI > 25) is a risk factor (up to 1.39 relative risk) for PD (J. Chen et al., 2014). Others have reported that the prevalence of obesity is higher in individuals with PD compared to the prevalence of obesity in the general population in Italy (Barichella et al., 2003; Cereda et al., 2013). More specifically, it has been determined that obese individuals demonstrate depletion of striatal dopamine receptors compared to non-obese controls (Wang et al., 2001). Both central (abdominal) and total obesity have been shown to negatively impact performance on motor speed and manual dexterity tests (Waldstein and Katzel, 2006), which could also contribute to the observed link between obesity and PD.

3.3. Epidemiological evidence linking obesity and Huntington's disease

HD is an inherited neurodegenerative disease characterized by abnormal involuntary and voluntary movements including jerky limb movements; bradykinesia; irregular movements of the face, neck or respiratory muscles, referred to as choreoathetosis; interference with vocalization, chewing and swallowing; apathy; irritability; lack of impulse control; intellectual impairment; and decrease in memory and learning ability (Cummings and Benson, 1988; Podoll et al., 1988; Rothlind et al., 1993; Purdon et al., 1994). As the disease progresses, symptoms become increasingly worse.

The two main pathological features of HD are selective loss of neurons in the striatum and cortex of the brain, and aggregation of huntingtin protein (Htt) (Hsiao and Chern, 2010). Irregular Htt arises from the expanding CAG triplet repeat in the huntingtin gene (HTT) (Ha and Fung, 2012). The length of CAG repeat has approximately a 70% contribution to the variability in the age of HD onset (Wexler et al., 2004), which indicates that there are other genetic and environmental factors contributing to the disease (Byars et al., 2012).

Although cachexia is well characterized in HD, this symptom appears after the disease onset due to persistent involuntary movements causing excess energy expenditure, difficulty swallowing, malabsorption or underlying metabolic defects (Fain et al., 2001; Marder et al., 2013). Thus, cachexia and weight loss are an aftermath of HD progression. Obesity, on the other hand, has been identified as one of the potential causes of earlier age of HD onset (Lundh et al., 2012). Other studies argue, however, that early onset of HD is due to an increase in caloric intake, independent of BMI (Marder et al., 2009). Moreover, increased BMI in HD patients does not correlate with increase in leptin, the satiety hormone, as it does in control subjects matched for elevated BMI (Aziz et al., 2010). This indicates that irregularities in adipose tissue function are present in HD patients, which may include insulin resistance and heightened inflammatory response (Lundh et al., 2012).

4. Pathophysiological mechanisms of inflammation in adipose tissue

Adipose tissue represents loose connective tissue comprised mainly of adipocytes (fat cells), but also containing pre-adipocytes (adipocytes not yet containing lipids), leukocytes, T-cells and macrophages (Doyle et al., 2012; Little et al., 2012). Adipose tissue functions primarily as an energy storage reservoir. It is also an endocrine organ secreting cytokines and inflammatory mediators, known as adipokines, which are capable of acting locally as well as systemically. Obese individuals generally have higher amounts of hypoxic adipocytes, which attract infiltrating macrophages leading to peripheral inflammation (Olli et al., 2013). Adipocytes themselves are a known source of IL-6, TNFα, and IL-1β, and most of obese individuals secrete superfluous amounts of this pro-inflammatory cocktail (Hotamisligil et al., 1993; Stenlof et al., 2003; Nov et al., 2013). Adipocytes also secrete the anti-inflammatory adipokine adiponectin (Scherer et al., 1995), which is inversely associated with adiposity (Arita et al., 1999; Cnop et al., 2003). Thus obese individuals have lower circulating levels of this anti-inflammatory signal. The chronic low-grade inflammatory state of obesity may contribute to neurological disorders, through the secretion of specific mediators (Hotamisligil et al., 1993; Banks et al., 1995; Cai, 2013). Moreover, both an increase in BMI and a decrease in insulin sensitivity lead to release of free fatty acids, which upregulate pro-inflammatory cytokines that have been implicated in exacerbation of neuroinflammation (Suganami et al., 2005; Little et al., 2012).

The pro-inflammatory mixture of excess TNFα, IL-6 and IL-1β elicits a variety of systemic responses (Duff and Durum, 1982; P.A. Kern et al., 2001; Meijer et al., 2011). TNFα is central to the inflammatory response. TNFα impacts immune responses via activation of macrophages and neutrophils, induction of apoptosis, regulation of lipid metabolism and insulin signaling within adipose tissue (Simons et al., 2007). Additionally, TNFα suppresses the release of the anti-inflammatory molecule adiponectin, while inducing the secretion of the pro-inflammatory cytokine IL-6 from adipose tissue (Berg et al., 1994; P.A. Kern et al., 2001; Simons et al., 2007).

IL-6 is a powerful pro-inflammatory cytokine, which regulates B and T cell functions, induces hematopoiesis, stimulates platelet production, immunoglobulin synthesis and acute-phase response (Kopf et al., 1994; Yamashita et al., 1994; Biffl et al., 1996). IL-6 affects energy homeostasis, and controls appetite and nutrient consumption via hypothalamic regulation (Stenlof et al., 2003). When left unchecked, IL-6 promotes chronic inflammatory conditions, such as those involved in the perpetuation of obesity, insulin resistance, inflammatory bowel disease and inflammatory arthritis (Naugler and Karin, 2008). More specifically, IL-6 is critical in the transition from acute to chronic inflammation by promoting the changeover from neutrophil to monocyte recruitment at the site of inflammation (Hurst et al., 2001; Marvin et al., 2001).

IL-1β regulates fibroblast proliferation, platelet production and the induction of pro-inflammatory cytokines (e.g., IL-6) and chemokines (e.g., IL-8) (Zetterstrom et al., 1998; Chiaretti et al., 2013). Since IL-1β is secreted by adipose tissues and induces secretion of other pro-inflammatory molecules, IL-1β has emerged as a central molecule in obesity-induced systemic inflammation (Stienstra et al., 2012).

Adiponectin, which is diminished in obese individuals, is typically regarded as an anti-inflammatory mediator inhibiting the production of the pro-inflammatory cytokines TNFα and IL-6 by adipocytes (Folco et al., 2009), and suppressing IL-6 release from endothelial cells at the BBB (Spranger et al., 2006). Thus, excessive adiposity not only increases the number of pro-inflammatory molecules, such as IL-1β, TNFα and IL-6, but also leads to decreased anti-inflammatory signal, adiponectin (Arnoldussen et al., 2014). A number of other adipokines including leptin, ghrelin, resistin, and visfatin have been implicated as regulators of neuroinflammation and their CNS effects have been highlighted in several recent reviews (Al-Suhaimi and Shehzad, 2013; Park and Ahima, 2013; Arnoldussen et al., 2014; Prodam and Filigheddu, 2014).

Given the excess levels of inflammatory adipose tissue secretions, it is understandable that overweight and obese individuals are in a chronic state of low-grade inflammation (Xu et al., 2003; Mathis, 2013). The adipose tissue of obese individuals could be a trigger or a risk factor for many illnesses, including: type 2 diabetes (T2D), cardiovascular disease (Hubert et al., 1983), stroke (Kurth et al., 2002), and certain cancers, such as breast and prostate cancers (Weisberg et al., 2003; Doyle

et al., 2012). Elevated levels of circulating cytokines are also a risk factor for neurodegenerative diseases including AD, PD and HD (Sun et al., 2003; Bjorkqvist et al., 2008; Cai, 2013; Trager and Tabrizi, 2013). Cytokines can cross the BBB and activate the Jun N-terminal kinase (JNK), protein kinase C (PKC) and IkappaB kinase β (IKKβ) pathways, which ultimately lead to transcription of pro-inflammatory cytokines and chemokines within the CNS (Solinas and Karin, 2010). These pathways inhibit insulin receptor substrates (IRS) 1 and 2, which are critical for initiating insulin signaling and propagating it from the extracellular space to intracellular targets (He et al., 2006; Solinas and Karin, 2010). Therefore, chronic low-grade peripheral inflammation could be one of the key mechanisms linking obesity with several disease states, but obesity-induced insulin/IGF-1 resistance represents another distinct possible mechanism.

5. Pathophysiological mechanisms of insulin/IGF-1 in obesity

It is now widely accepted that the state of obesity leads to insulin/IGF-1 resistance (Bosello and Zamboni, 2000; P.A. Kern et al., 2001; Mallea-Gil et al., 2012). Insulin/IGF-1 resistance is a state of weakened cellular response to these hormones, which is highly consequential since insulin and IGF-1 are critical for a number of peripheral functions as well as for the CNS health. The exact molecular mechanisms are still under investigation, but pro-inflammatory cytokines have been shown to directly alter insulin/IGF-1 signaling in a wide range of cell and tissue types (Hotamisligil et al., 1993; Xu et al., 2003).

5.1. Insulin in the periphery

Insulin is a 51 amino acid peptide hormone mainly produced by pancreatic β-cells (Harfenist and Craig, 1952). Insulin belongs to the family of insulin-like hormones, which also includes IGF-1 and IGF-2. Insulin is most recognized for its role in regulation of blood glucose levels (Duarte et al., 2012). In addition to its effects on glucose metabolism, insulin down-regulates gluconeogenesis, increases glycogen synthesis, increases adiposity, promotes lipid synthesis, and inhibits lipolysis and fatty acid esterification (Wagle et al., 1975; Beynen et al., 1980; Baskin et al., 1999).

Insulin resistance initially results in increased insulin secretion from the pancreatic β-cells, in a compensatory effort to maintain normal blood glucose levels. Over time, however, the pancreatic β-cells begin to fail and start to produce less insulin. Insulin resistance itself is not recognized as a disease state, but can lead to the development of T2D (Santiago and Potashkin, 2013). This transition from insulin resistance to T2D is due to partial loss of pancreatic β-cell function. Recent studies indicate that T2D is a significant risk factor for certain forms of dementia, most notably AD (Li and Holscher, 2007) and PD (Hu et al., 2007).

5.2. IGF-1 in the periphery

IGF-1 is a 70 amino acid peptide hormone primarily synthesized in the liver and secreted in response to increased concentrations of growth hormone (a.k.a somatotrophin). IGF-1 production is influenced by several other factors, including nutritional status and age (Marcovecchio and Chiarelli, 2013). The secretion of IGF-1 requires adequate nutrition, as it has been shown that during states of malnourishment, even in the presence of growth hormone, IGF-1 secretion does not occur (Corpas et al., 1993; Moloney et al., 2010). IGF-1 has many functions, including acting as a mitogenic growth factor, cell survival stimulant, apoptosis inhibitor, as well as inducing fat breakdown and glucose uptake by muscle cells (Rollero et al., 1998; Chen et al., 2000; Trumper et al., 2000; Troncoso et al., 2012). Concentrations of circulating IGF-1 as a growth factor rise and fall at different developmental stages. IGF-1 production and secretion is increased during periods of growth and development, such as during puberty, and is decreased during times of stasis (Clark et al., 1998; Lacau-Mengido et al., 2000).

5.3. Insulin in the brain

Originally, the brain was considered to be an insulin insensitive organ. It has since been discovered that insulin performs many functions in the CNS critical to neuronal survival. Insulin affects CNS metabolism by triggering glucose uptake by glial cells (Werner et al., 1989; Duarte et al., 2012). It is also a neuromodulator, which enhances serotonin (5-HT) synthesis and inhibits reuptake of norepinephrine by presynaptic neurons (Crandall et al., 1981; Chen and Yang, 1991). Insulin promotes cell survival through the inhibition of apoptosis-inducing peptides, facilitates neuronal growth and differentiation by enhancing neurite outgrowth and synapse formation, and regulates learning and memory through its effects on synaptic function (Schulingkamp et al., 2000; W. Kern et al., 2001; Banks, 2004; Benedict et al., 2007; Soczynska et al., 2011). Thus, insulin positively regulates synaptic plasticity by inducing internalization of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors leading to upregulation of activity-regulated cytoskeleton-associated protein (Arc). Arc is one of several proteins responsible for the balance between the long-term potentiation and long-term depression, two of the phenomena responsible for synaptic plasticity (T.J. Chen et al., 2014). Due to its importance in neuronal survival and cognitive functions, insulin has moved to the forefront of neurodegeneration research.

5.4. IGF-1 in the brain

IGF-1 has long been recognized for its role in the periphery as a metabolic and anabolic hormone. It was not until recently, however, that IGF-1 was deemed a neurotrophic peptide. In the CNS, IGF-1 plays a key role in brain development, maturation and function (Landi et al., 2009; Castilla-Cortazar et al., 2014). IGF-1 acts as a pro-survival signal responsible for activation of anti-apoptotic cascades, enhancement of nerve cell growth and promotion of synaptic plasticity (Chen et al., 2000; Trumper et al., 2000; Castilla-Cortazar et al., 2014). IGF-1 induces myelination both in vivo (Mozell and McMorris, 1991) and in vitro (McMorris et al., 1986), and enhances survival of cultured rat oligodendrocytes (Barres et al., 1993). These combined functions are critical for protection of nerve cells against toxic insults associated with neurodegenerative processes. Decrease in IGF-1 concentration and resulting signaling errors have been associated with such pathological states as AD, PD, HD, MS and depressive disorders (Rollero et al., 1998; Humbert et al., 2002; Talbot et al., 2012; Pellecchia et al., 2014). It is, therefore, of critical importance to study the role of IGF-1 signaling in neurodegenerative disease onset and progression.

6. Pathophysiological mechanisms of insulin/IGF-1 signaling in neurodegenerative diseases

There is a growing body of evidence to support the hypothesis that irregular insulin and IGF-1 hormone levels and resulting impaired insulin/IGF-1 signaling contribute to neurodegenerative processes. Obesity is one of the main causes of insulin/IGF-1 resistance in the periphery, which correlates with central insulin/IGF-1 resistance (P.A. Kern et al., 2001; Bigornia et al., 2012).

Insulin and IGF-1 CNS signaling cascades share a remarkable amount of overlap (de la Monte and Wands, 2005; Moloney et al., 2010). This similarity likely stems from significant homology in their amino acid sequences and the similar receptor structures. Both the IGF-1 receptor (IGF-1R) and insulin receptor (INSR) are receptor tyrosine kinases, which are tetrameric in structure, and comprised of two extracellular α-subunits disulfide-linked to two transmembrane β-units (Lawrence et al., 2007; Glendorf et al., 2011). In addition to binding its own receptor, insulin is capable of binding (and activating) the IGF-1R. Conversely, IGF-1 is able to bind (and activate) the INSR (Fujita et al., 2013). However, each ligand has a 100–500 fold higher affinity for its own receptor (Conejo and Lorenzo, 2001). The functional and structural similarity

between these two receptors is best illustrated by the fact that their subunits can combine (Li and Holscher, 2007; Duarte et al., 2012) by one INSR α- and β-subunit binding to an IGF-1R α- and β-subunit forming a hybrid heterotetrameric receptor (Lawrence et al., 2007). The functional significance of this phenomenon is not understood.

The INSR and the IGF-1R interact with several common receptor substrates, which are responsible for the initial transduction of the signal once the receptor has been activated. INSR and IGF-1R share IRS-1, IRS-2, and the Src homologous and collagenous protein (Shc) as common receptor substrate molecules (Ariga et al., 2000; Strack et al., 2000). Thus, binding of IGF-1 and insulin to their corresponding receptors leads to parallel pathway activation and subsequent identical downstream responses (Yu et al., 2003). In the CNS, IRS-1 and IRS-2 are redundant proteins as they are used interchangeably in the same signaling pathway (Moloney et al., 2010). Activation of IRS-1/2 sets off the main signaling cascade common to insulin and IGF-1: the phosphatidylinositol 3-kinase (PI3K)-dependent pathway (Yu et al., 2003; Moloney et al., 2010). Protein kinase B (Akt) is central to the PI3K pathway (Banfic et al., 1998); it is pivotal to cell survival, as it phosphorylates proteins subsequently initiating several critical cross talking pathways including: 1) activation of γ-aminobutyric acid (GABA) A receptors, which are responsible for synaptic signaling (Wan et al., 1997; Ma et al., 2003); 2) phosphorylation of IkappaB kinase α (IKKα), which activates the nuclear factor kappa B (NFkB) leading to transcription of apoptosis regulators, cytokines, chemokines and growth factors (Ghosh et al., 1998; Nomura et al., 2000); 3) phosphorylation of huntingtin protein, which blocks aggregation of mutant huntingtin, thus promoting neuronal survival (Humbert et al., 2002; Rangone et al., 2004); and 4) activation of glycogen synthase, which induces glycogen synthesis, to name just a fraction of the molecules and resulting signaling cascades affected by Akt activation (Delcommenne et al., 1998).

Activation of the Shc receptor substrate, on the other hand, leads to initiation of the mitogen-activated protein kinase (MAPK) pathway. This pathway facilitates cellular growth, proliferation and differentiation (Delafontaine et al., 2004; Yoon and Seger, 2006), promotes pro-inflammatory cytokine transcription (Soczynska et al., 2011; Stienstra et al., 2012), and regulates protein translation (Yoon and Seger, 2006; Soczynska et al., 2011). Thus, induction of the insulin/IGF-1 signaling cascades leads to complex cellular responses (Fig. 2).

Although insulin and IGF-1 share a remarkable homology in their receptor structure and signaling cascades, the physiological responses triggered by these two hormones differ. Several mechanisms have been proposed to explain this paradox including differential tissue and sub-cellular distribution of the INSR and IGF-1R resulting in distinct biological effects (Bondy et al., 1990; Zapf et al., 1994). In addition, the ligand–receptor interaction affinities for insulin and IGF-1 are different (Mastick et al., 1998), which is particularly relevant since peripheral insulin typically circulates at concentrations in the order of pg/ml (Craft et al., 1998), while IGF-1 circulates at ng/ml concentrations (Karabulut et al., 2014). Experiments using INSR and IGF-1R isolated from kidney cells showed that affinity of IGF-1 towards its receptor is much higher relative to insulin-INSR binding affinity (Hansen et al., 2012). Insulin dissociates from its receptor more readily than IGF-1 from IGF-1R (Zapf et al., 1994), and INSR activation leads to higher phosphorylation of IRS-1, while activation of IGF-1R leads to higher phosphorylation of IRS-2 (Urso et al., 1999). INSR-induced phosphorylation of IRS-1 favors activation of the PI3K pathway, while IGF-1R-induced phosphorylation of IRS-1 leads to preferential activation of the MAPK pathway (Amoui et al., 2001). The above observations identify molecular mechanism that could explain why deficit of insulin or IGF-1 could not be fully compensated in those cases where the other hormone is present in normal quantities, even though the receptors and signaling cascades engaged by both of these hormones overlap heavily (Boulware et al., 1994; Russell-Jones et al., 1995; de la Monte and Wands, 2005; Moloney et al., 2010).

Insulin/IGF-1 signaling outcomes are major factors in the biological aging process (Rollero et al., 1998; Aimaretti et al., 2008). Up- or down-regulation of the insulin/IGF-1 signaling cascades could result from changes in brain insulin and IGF-1 levels (Bondy and Cheng, 2004), change in INSR and IGF-1R distribution (Schulingkamp et al.,

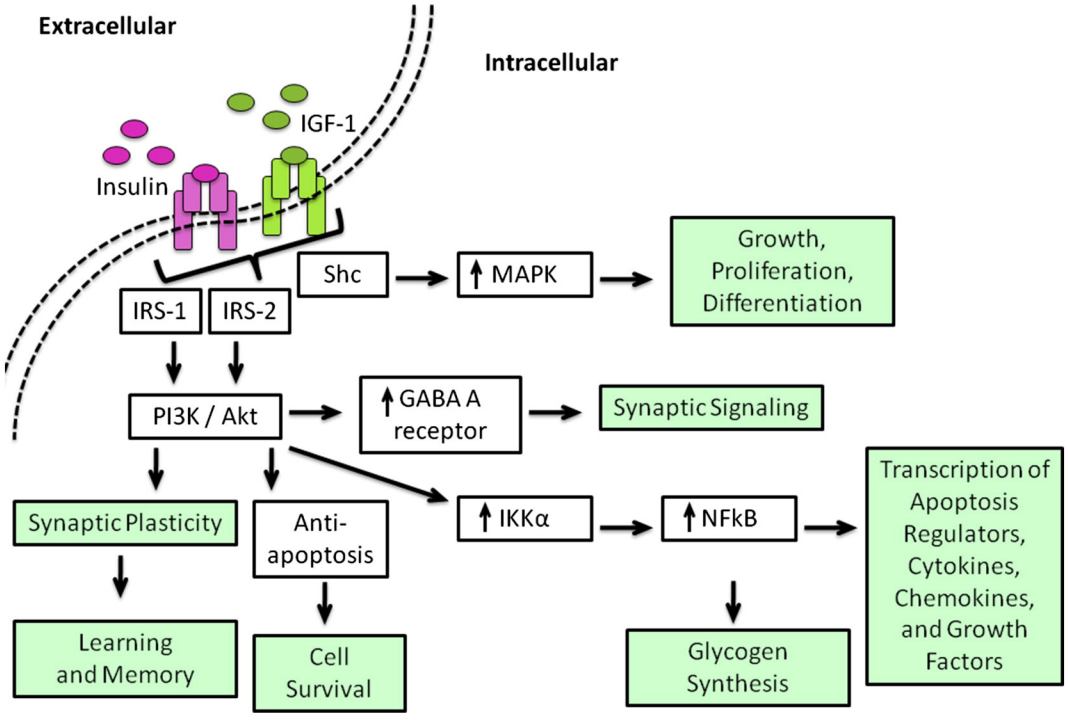

Fig. 2. The overlapping pathways and functions of insulin and IGF-1. IRS-1, insulin receptor substrate 1; IRS-2, insulin receptor substrate 2; Shc, the Src homologous and collagenous protein; MAPK, mitogen activated protein kinase; GABA A, gamma-aminobutyric acid A; IKKα, IkappaB kinase alpha; NFkB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase.

2000; Bondy and Cheng, 2004) or receptor activity (Moloney et al., 2010), and change in IRS-1/2 and Shc protein levels or activity (Nemoto et al., 2009). Such alterations, depending on the cell type and brain region affected, could also contribute to several CNS diseases (Humbert et al., 2002; Altar et al., 2008; Moloney et al., 2010). For example, individuals with schizophrenia have higher circulating levels of insulin, compared to healthy control patients (Venkatasubramanian et al., 2007; Guest et al., 2011). This correlates with lower circulating levels of IGF-1 in schizophrenia patients, which may be due to compensatory mechanism responding to the elevated levels of insulin (Guest et al., 2011). AD patients show an increase in IGF-1R in astrocytes, and a decrease in IGF-1R in neurons, compared to healthy controls (Moloney et al., 2010). IGF-1 is reduced in the brains of HD patients, and addition of IGF-1 to striatal neurons, can block the formation of mutant huntingtin-induced cell death and formation of intranuclear inclusions (Humbert et al., 2002). In addition, tissue-specific knock-out mice studies show that decrease in hippocampal IGF-1 levels leads to lower serum IGF-1 levels, which correlates with depression-like phenotype in the affected mice (Mitschelen et al., 2011). Positive correlation between insulin resistance and severity of symptoms in MDD has also been reported (Timonen et al., 2005; Shomaker et al, 2010), which may be due in part to the role that insulin signaling plays in regulating dopamine neurotransmission (Speed et al., 2010; Williams et al., 2010).

The role of IGF-1 in MS and its animal model, experimental autoimmune encephalomyelitis (EAE), was first investigated due to the observations that IGF-1 promotes myelination (McMorris et al., 1986; Mozell and McMorris, 1991) and oligodendrocyte survival (Barres et al., 1993). The initial EAE studies in rodents showed that administration of IGF-1 decreased disease symptoms, diminished lesions and reduced inflammation (Liu et al., 1997). However, studies exploring the role of IGF-1 in MS, showed that IGF-1R expression levels were similar in the brains of healthy individuals and patients with MS (Wilczak and De Keyser, 1997). IGF-1 treatment was also ineffective in EAE model and in clinical studies involving MS patients (Cannella et al., 2000; Andreassen et al., 2010).

The above diseases could be provoked at least in part by obesity-induced insulin and IGF-1 resistance (Morris et al., 2010; Kwon and Pessin, 2013), and the resulting insulin/IGF-1 signaling impairment. Insulin/IGF-1 resistance typically goes hand-in-hand with inflammation since obese adipose tissue chronically secretes a cocktail of pro-inflammatory mediators. Thus, insulin/IGF-1 resistance and chronic neuroinflammation could help mechanistically explain the links between obesity and neurodegenerative conditions. The role of insulin and IGF-1 signaling alterations in three such pathologies (AD, PD and HD) is discussed below.

6.1. Obesity, insulin/IGF-1 resistance and Alzheimer's disease

The role of insulin, IGF-1 and obesity in the onset and pathogenesis of AD has been the subject of a series of recent studies. Insulin and IGF-1 resistance has moved to the forefront of AD research. Some experts consider AD to be a direct result of brain insulin resistance, even naming AD "Type 3 Diabetes" (Duarte et al., 2012; Vagelatos and Eslick, 2013). In a normal brain, insulin signaling hinders the formation of Aβ plaques and abnormal phosphorylation of tau protein. However, in an insulin resistant AD brain this signaling cascade is diminished, thus contributing to the formation of Aβ plaques and NFTs (Hauw et al., 1990; Goll et al., 2013) (Fig. 3). Since binding of insulin and IGF-1 to their corresponding receptors sets off almost identical signaling cascades (Bondy and Cheng, 2004), reduced levels of IGF-1, the down-regulation of its receptor and the ensuing signaling cascade could also contribute to the formation of Aβ plaques and NFTs in a manner similar to insulin resistance. Decreased activation of the insulin/IGF-1 signaling

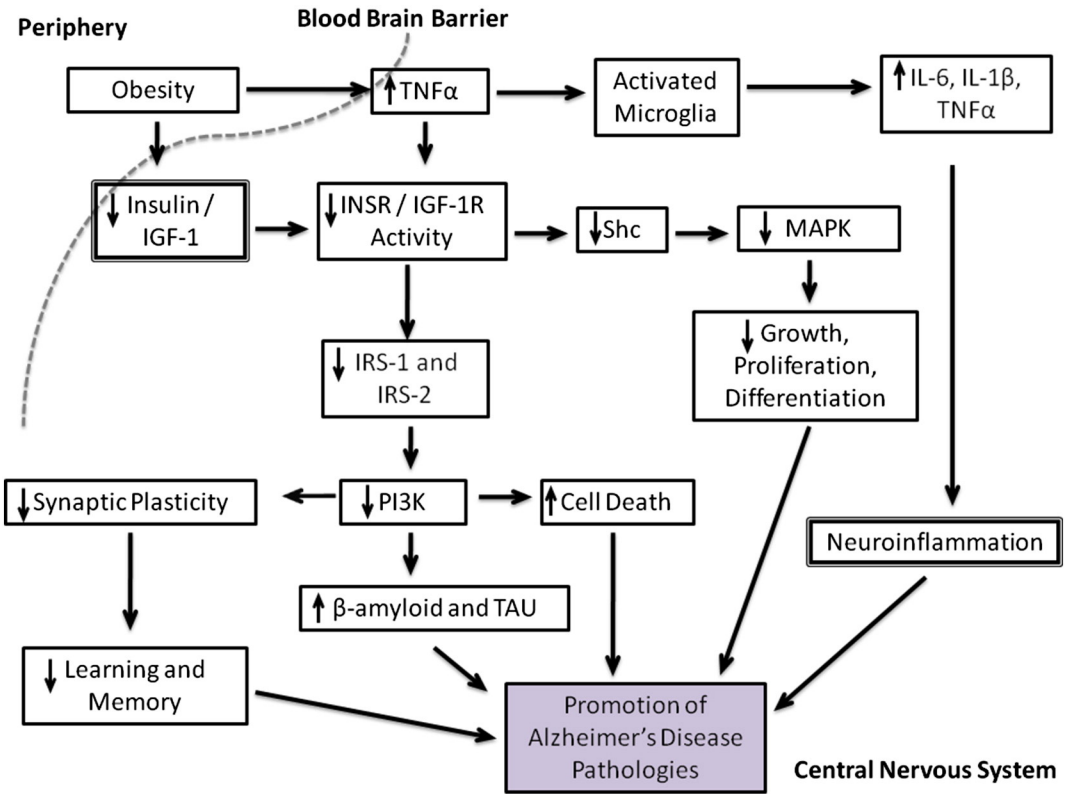

Fig. 3. Obesity and obesity-induced insulin/IGF-1 resistance contribute to the Alzheimer's disease pathology. TNFα, tumor necrosis factor alpha; IL-6, interleukin 6; IL-1β, interleukin 1 beta; INSR, insulin receptor; IGF-1R, IGF-1 receptor; Shc, the Src homologous and collagenous protein; MAPK, mitogen activated protein kinase; IRS-1, insulin receptor substrate 1; IRS-2, insulin receptor substrate 2; PI3K, phosphatidylinositol 3-kinase.

pathway has been detected in AD (Andreassen et al., 2002; Solas et al., 2013; Pellecchia et al., 2014).

Individuals with chronic peripheral hyperinsulinemia, such as many obese individuals, experience decreased brain insulin signaling. This decrease in signaling is mainly due to lower CNS insulin concentrations as a direct result of down-regulated transport of insulin into the brain (Stein et al., 1987; Kaiyala et al., 2000). Moreover, IGF-1R and INSR are upregulated in areas surrounding Alzheimer Aβ plaques (Jafferali et al., 2000). Receptor upregulation is a common compensatory mechanism observed when their ligand, in this case insulin and IGF-1, is low or absent. In addition to the decrease in the CNS insulin levels, individuals with AD demonstrate decreased levels of IRS-1/2, which further amplifies insulin/IGF-1 resistance (Moloney et al., 2010).

The chronic low-grade inflammation in most obese individuals leads to increased levels of local and circulating cytokines such as TNFα, which have an inhibitory effect on the tyrosine kinase activity of the INSR and IGF-1R, thus reducing the insulin/IGF-1 signaling cascade and associated down-stream mechanisms (Hotamisligil et al., 1996; P.A. Kern et al., 2001).

It has been demonstrated that peripheral pro-inflammatory cytokines are capable of crossing the BBB by distinctive saturable transport systems, and therefore can act in the CNS (Banks et al., 1995; Erickson et al., 2012). The central effects of TNFα could be responsible for the observed positive association between an increased systemic level of this cytokine and accelerated cognitive decline in AD patients (Holmes et al., 2009). Moreover, high fat diet studies involving mice have shown increase in brain cytokine levels associated with obesity (Zhang et al., 2013). It is possible that decreased insulin/IGF-1, combined with actions of pro-inflammatory cytokines, inhibits insulin/IGF-1 signaling systemically as well as in the CNS and therefore exacerbates AD pathogenesis in obesity (Fig. 3). This process is not exclusive to AD; similar errors contribute to other neurodegenerative conditions, including PD and HD.

6.2. Obesity, insulin/IGF-1 resistance and Parkinson's disease

It has also been discovered that insulin receptors are decreased in the SNpc region of the PD brains (Moroo et al., 1994; Takahashi et al., 1996), thus reducing the beneficial growth and proliferation promoting effects of the insulin signaling cascade, and thereby contributing to PD. Decreased insulin concentration has been shown in PD brains (Duarte et al., 2011), and could contribute to α-synuclein deposition, which is the characteristic feature of PD (Frank-Cannon et al., 2009). Huang et al. (2003) showed that insulin promotes normal function of CNS mitochondria. Absence of insulin causes depolarization of mitochondria, which leads to the generation of excess ROS, which may contribute to PD pathology (Gao et al., 2008).

Impaired insulin signaling may decrease glucose uptake in the brain, and specifically in the SNpc region of the brain, which could lead to a decrease in the intracellular ratio of ATP to ADP (Levin, 2000). Such imbalance is known to trigger the activation of ATP-sensitive potassium (K_{ATP}) channels. Dopamine release from dopaminergic neurons is affected by glucose levels and is under control of K_{ATP} channels (Santiago and Potashkin, 2013). Studies have shown that depending on its severity, insulin resistance decreases both the release of DA from dopaminergic neurons and clearance of DA following synaptic release (Morris et al., 2011). Likewise, IGF-1 has been shown to protect DA neurons, but CNS levels of IGF-1 are decreased in PD patients (Ebert et al., 2008). IGF-1 resistance has also been observed in patients experiencing neurodegeneration associated with PD (Trejo et al., 2004). Thus, the inflammation, as well as insulin and IGF-1 resistance caused by obesity, contributes to the pathogenesis of PD in a multifaceted manner (Fig. 4).

6.3. Obesity, insulin/IGF-1 resistance and Huntington's disease

Obesity may provoke HD onset through insulin resistance and decreased circulating IGF-1 levels (Podolsky and Leopold, 1977; Lalic

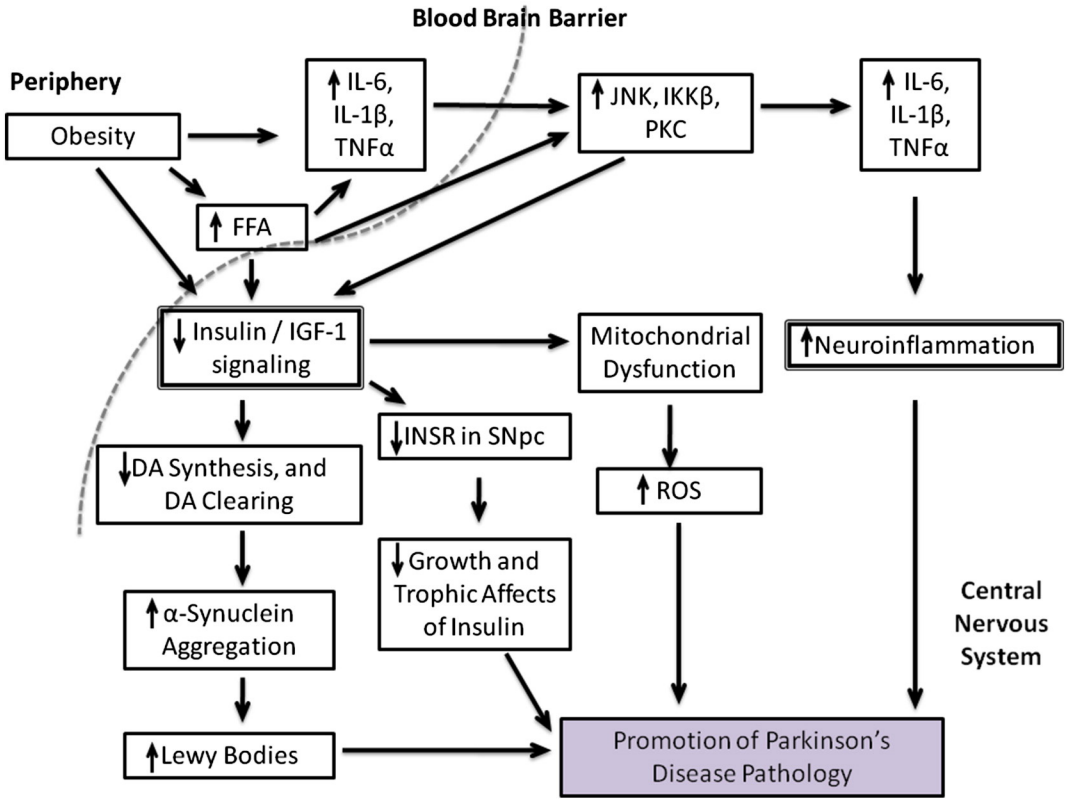

Fig. 4. Obesity and obesity-induced insulin/IGF-1 resistance contribute to the Parkinson's disease pathology. IL-6, interleukin 6; IL-1β, interleukin 1 beta; TNFα, tumor necrosis factor alpha; FFA, free fatty acids; DA, dopamine; SNpc, substantia nigra pars compacta; INSR, insulin receptor; ROS, reactive oxygen species.

et al., 2008; Hsiao and Chern, 2010; Lundh et al., 2012). This accelerates HD pathology, as insulin participates in the regulation of several HD-related genes (Crocker et al., 2006). For example, insulin signaling promotes clearance of abnormal Htt aggregates (Yamamoto et al., 2006). Animal models of HD have demonstrated that Akt protein, which is central in the insulin/IGF-1 signaling cascade, is down-regulated in HD (Colin et al., 2005) and its down-regulation is associated with early onset of HD (Andreassen et al., 2002). As previously discussed, the PI3K/Akt signaling cascade promotes neuronal survival through a number of different mechanisms including phosphorylation of huntingtin protein (Humbert et al., 2002).

Chronic peripheral inflammation has also been noted in patients with HD, and may be a contributing factor (Frank-Cannon et al., 2009). Elevated circulating and CNS cytokine levels, particularly of IL-6, have been observed in HD patients several years prior to onset of classical HD symptoms (Bjorkqvist et al., 2008). Since excess adipose tissue is a trigger for early onset of HD and is a source of IL-6 and other cytokines, it is possible that obesity-induced earlier onset of HD is a result of increased pro-inflammatory mediators (Fig. 5). Even though obesity, insulin and IGF-1 disturbances do not cause HD, high adiposity may induce earlier disease onset and exacerbation of HD progression.

7. Conclusions

Compelling evidence indicates that excess adiposity contributes to several neurodegenerative diseases including AD, PD and HD (Kaiyala et al., 2000; Sun et al., 2003; Beydoun et al., 2008; Bjorkqvist et al., 2008; Trager and Tabrizi, 2013). One possible mechanism responsible for this link involves excess secretion of pro-inflammatory cytokines in the periphery, leading to their brain uptake and resulting exacerbation of neuroinflammation (Gonzales et al., 2012; Hsuchou et al., 2012). A second mechanism linking obesity to neurodegeneration is insulin/IGF-1 resistance, which has far-reaching effects in the CNS (Hallschmid and Schultes, 2009; Gregor and Hotamisligil, 2011). These two mechanisms may interact; obesity-related insulin resistance and reduced insulin signaling in the brain may be exacerbated by the chronic peripheral and CNS inflammatory environment associated with obesity (Fig. 1). Studies investigating use of intranasal insulin as a treatment for mild cognitive impairment have shown promising results (Benedict et al., 2007; Craft et al., 2012). Intranasal IGF-1 treatment regimen has been investigated for treatment of depression (Paslakis et al., 2012) and also as a treatment for brain injury (Lin et al., 2009). These therapies could show promise in other neurodegenerative conditions associated with defective insulin/IGF-1 signaling. Further investigation into the role of obesity-induced insulin and IGF-1 resistance as the possible contributor to neurodegeneration is required. Elucidation of the role of these hormones in neurodegeneration will strengthen our understanding of the pathogenic mechanisms of neurodegeneration and may ultimately lead to identification of novel targets for effective treatment strategies in AD, PD and HD.

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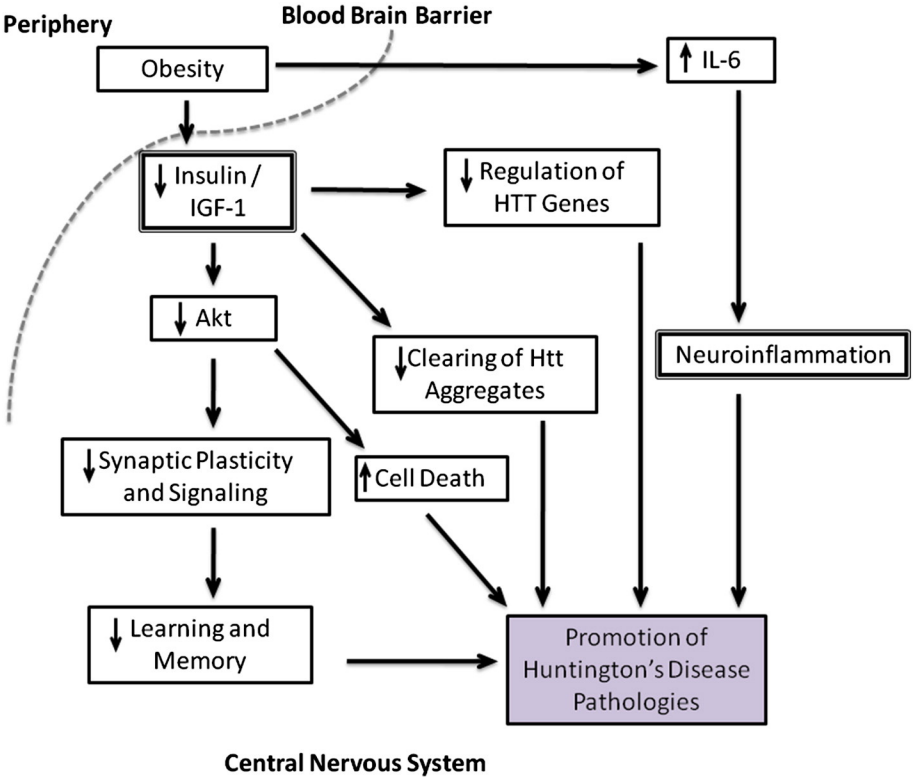

Fig. 5. Obesity-induced insulin/IGF-1 resistance contributes to Huntington's disease pathology. IL-6, interleukin 6; Htt, huntingin protein; HTT, huntingtin gene; Akt, serine/threonine kinase.

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