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Metabolic derangements mediate cognitive impairment and Alzheimer's disease: role of peripheral insulin resistance diseases

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Abstract

Herein, we review evidence that systemic insulin resistance diseases linked to obesity, type 2 diabetes, and non-alcoholic steatohepatitis promote neurodegeneration. Insulin resistance dysregulates lipid metabolism, which promotes ceramide accumulation with attendant inflammation and ER stress. Mechanistically, we propose that toxic ceramides generated in extra-CNS tissues, e.g. liver, get released into peripheral blood, and subsequently transit across the blood-brain barrier into the brain where they induce brain insulin resistance, inflammation, and cell death (extrinsic pathway). These abnormalities establish or help propagate a cascade of neurodegeneration associated with increased ER stress and ceramide generation, which exacerbate brain insulin resistance, cell death, myelin degeneration, and neuro-inflammation. The data suggest that a mal-signaling network mediated by toxic ceramides, ER stress, and insulin resistance should be targeted to disrupt positive feedback loops that drive the AD neurodegeneration cascade.

Key Phrases

Diabetes mellitus; insulin resistance; neurodegeneration; non-alcoholic steatohepatitis; ceramide; central nervous system

Crisis of insulin resistance

Insulin resistance diseases, including Alzheimer's disease (AD), obesity, type 2 diabetes mellitus (T2DM), non-alcoholic steatohepatitis (NASH), and metabolic syndrome are prevalent in modern high tech societies, and they are costly because they consume large percentages of healthcare budgets, lead to disability, and cause premature death . The unrelenting appetite for highly processed, high starch, high fat, and high caloric content foods is literally eroding health status across all age groups in the United States. Thanks to the robust domestic and international research efforts over the past decade, it is now clear that insulin resistance can afflict any organ and tissue in the body. The consequences include deficits in energy metabolism, increased inflammation and oxidative stress, and proneness to

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cellular degeneration and death. No thanks to commercial luring of the uninformed who seek the comfortable lifestyles of the West, insulin resistance diseases are quickly spreading throughout the world and beginning to bear their tolls on global health.

Insulin resistance disease states

Insulin stimulates lipogenesis and increases triglyceride storage in liver and adipose tissue [Capeau 2008; Leonard et al. 2005]. This process helps to maintain energy balance. Chronic high caloric intake disrupts homeostatic mechanisms and causes insulin resistance [Capeau 2008; de la Monte and Wands 2008; Kraegen and Cooney 2008; Lyn-Cook et al. 2009]. In liver, insulin resistance is associated with conversion of simple hepatic steatosis (lipid storage) to steatohepatitis (fatty liver with inflammation and cell injury). The accompanying inflammation, pro-inflammatory cytokine activation, oxidative stress, and increased cell death via mitochondrial or apoptotic mechanisms promote liver degeneration. Insulin resistance mediated lipolysis is yet another factor contributing to progression of liver disease in NASH [Kao et al. 1999]. Lipolysis leads to increased production of toxic lipids, including ceramides (see below), that further impair insulin signaling, mitochondrial function, and cell viability [Holland and Summers 2008; Kraegen and Cooney 2008; Langeveld and Aerts 2009]. Endoplasmic reticulum (ER) stress and mitochondrial dysfunction can worsen insulin resistance, lipolysis, and ceramide accumulation [Anderson and Borlak 2008; Kaplowitz et al. 2007; Malhi and Gores 2008; Sundar Rajan et al. 2007].

ER functions such as protein synthesis, modification, and folding, calcium signaling, and lipid biosynthesis are driven by glucose utilization. Impaired glucose uptake and metabolism in insulin resistance diseases such as obesity, T2DM, and NASH activates ER stress pathways [Kaplowitz, Than, Shinohara and Ji 2007; Malhi and Gores 2008; Sharma et al. 2008; Sundar Rajan, Srinivasan, Balasubramanyam and Tatu 2007]. ER stress contributes to lipid dyshomeostasis by activating pro-inflammatory, pro-ceramide, and pro-death pathways that lead to increased generation of toxic lipids, e.g. ceramides [Banerjee et al. 2008; de la Monte et al. 2009; Kaplowitz and Ji 2006; Ronis et al. 2008]. Correspondingly, ceramide levels and pro-ceramide gene expression are increased in livers with chronic steatohepatitis [Longato et al. 2012; Setshedi et al. 2011].

The consequences of insulin resistance, particularly the stress responses, themselves promote insulin resistance. Unchecked, the rates of injury eventually exceed those of repair. Organ-system degeneration is mediated by the combined effects of impaired energy balance, lipid dyshomeostasis, loss of membrane integrity, and ER stress, all of which contribute to increased ceramide generation [DeFronzo 2010; Eckardt et al. 2011; Holland et al. 2007; Kaplowitz, Than, Shinohara and Ji 2007; Lipina and Hundal 2011; Malhi and Gores 2008; Summers 2010], which itself causes insulin resistance (see below). Therefore, chronic insulin resistance initiates a harmful positive feedback loop that results in propagation of chronic diseases and tissue degeneration. Underlying pathophysiological mechanisms include increased ceramide generation, inflammation, tissue injury, ER stress, and mitochondrial dysfunction, all of which worsen insulin resistance.

Ceramides-the back story

Ceramides comprise a family of sphingolipids [Reynolds et al. 2004; Summers 2010] that regulates diverse functions including growth, motility, adhesion, differentiation, senescence, and apoptosis. Ceramides also contribute to cell membrane structure by participating in lipid microdomains, i.e. rafts [Sonnino and Prinetti 2010]. Ceramides differ in length of their fatty acid chains (up to C_{24}), and are formed via complex biosynthetic [Reynolds, Maurer and Kolesnick 2004; Stiban et al. 2010], catabolic [Clarke et al. 2011; Reynolds, Maurer and Kolesnick 2004], or salvage [Gault et al. 2010; Mullen and Obeid 2011; Reynolds, Maurer and Kolesnick 2004] mechanisms. The rapid turnover and short half-life of ceramides facilitate their role as second messengers for intracellular signaling.

Ceramides generated de novo regulate physiological functions, whereas those produced via catabolic pathways are generated in response to drugs, physical agents, chemotherapeutic agents, pro-inflammatory cytokines, trophic factor withdrawal, and ionizing radiation [Adibhatla and Hatcher 2008; Farooqui et al. 2010; Holland and Summers 2008; Liu et al. 1997; Nikolova-Karakashian and Reid 2011; Reynolds, Maurer and Kolesnick 2004; Summers 2006], indicating a link to stress and disease states. The salvage pathway accounts for 50% to 90% of sphingolipid biosynthesis in cells, and accomplishes this by recycling sphingoid bases released by acid ceramidases for use by ceramide synthases. Ceramide profiles in different organelles and cell types can shift as an adaptive or pathophysiological response. Accumulation of ceramides in lipid rafts [Sonnino and Prinetti 2010] causes small rafts to merge into larger units to modify membrane structure and protein function, including receptor responsiveness, signal transduction, and stress responses [Corre et al. 2010; Hajduch et al. 2001; Li et al. 2010; Lingwood et al. 2010; Lingwood et al. 2010].

Ceramides cause insulin resistance and insulin resistance increases ceramides

Ceramides are lipid signaling molecules that can be cytotoxic, cause insulin resistance [Arboleda et al. 2007; Chalfant et al. 1999; Chavez et al. 2005; Chavez et al. 2003; Delarue and Magnan 2007; Holland and Summers 2008; Kraegen and Cooney 2008; Liu, Obeid and Hannun 1997], and activate pro-inflammatory cytokines. Ceramides cause insulin resistance [DeFronzo 2010; Eckardt, Taube and Eckel 2011; Holland, Knotts, Chavez, Wang, Hoehn and Summers 2007; Kaplowitz, Than, Shinohara and Ji 2007; Lipina and Hundal 2011; Malhi and Gores 2008; Summers 2010] in obesity, T2DM, NASH [Alessenko et al. 2004; Han et al. 2008; Katsel et al. 2007; Summers 2010], and probably AD [de la Monte et al. 2012]. Ceramides cause insulin resistance by activating pro-inflammatory cytokines [Bryan et al. 2008; Summers 2006; Van Brocklyn 2007] and inhibiting insulin signaling at various levels in the pathway. For example, ceramides: 1) inhibit signaling through PI3 kinase-Akt [Bourbon et al. 2002; Hajduch, Balendran, Batty, Litherland, Blair, Downes and Hundal 2001; Nogueira et al. 2008; Powell et al. 2003]; 2) alter the phosphorylation states of proteins that regulate insulin signaling [Silveira et al. 2008]; 3) inhibit Akt [Arboleda, Huang, Waters, Verkhratsky, Fernyhough and Gibson 2007] by activating protein phosphatase 2A [Chalfant, Kishikawa, Mumby, Kamibayashi, Bielawska and Hannun 1999] and glycogen synthase kinase 3β (GSK-3β) [Arboleda et al. 2010; Stoica et al. 2003], and

recruiting phosphatase and tensin homologue deleted on chromosome 10 (PTEN) [Hajduch et al. 2008]; and 4) stimulate pro-apoptotic mechanisms such as interleukin-1β converting enzyme (ICE)-like proteases [Liu, Obeid and Hannun 1997]. Therefore, ceramide homeostasis is needed to maintain insulin responsiveness and minimize cell injury. Correspondingly, inhibition of ceramide synthesis and accumulation was shown to prevent obesity-associated insulin resistance [Chavez, Holland, Bar, Sandhoff and Summers 2005; Holland, Knotts, Chavez, Wang, Hoehn and Summers 2007].

In chronic obesity, T2DM and NASH, lipid dyshomeostasis results in increased generation of ceramide in adipose tissue and/or liver [Alessenko, Bugrova and Dudnik 2004; Han, Park, Shinzawa, Kim, Chung, Lee, Kwon, Lee, Park, Chung, Hwang, Yan, Song, Tsujimoto and Lee 2008; Katsel, Li and Haroutunian 2007; Summers 2010]. Pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) [Summers 2006], are activated in obesity, T2DM, NASH, and AD [Lieber et al. 2004; Rosenberg 2005; Sahai et al. 2004; Sastre et al. 2006; Satapathy et al. 2004; Tuppo and Arias 2005; Yalniz et al. 2006]. Inflammation and insulin resistance increase ceramide production, and ceramides promote oxidative and ER stress. Consequently, these interconnecting pathophysiological processes induce a positive feedback mal-signaling loops that establishes a cascade of progressive organ-system degeneration.

Brain metabolic derangements and insulin resistance in Alzheimer's disease

AD shares several features in common with systemic insulin resistance diseases including, reduced insulin-stimulated growth and survival signaling, increased oxidative stress, pro-inflammatory cytokine activation, mitochondrial dysfunction, and impaired energy metabolism [de la Monte 2012; de la Monte et al. 2009]. The concept that AD represents a metabolic disease stems from the findings that cerebral glucose utilization is impaired in the early stages of AD [Adolfsson et al. 1980; Caselli et al. 2008; Fujisawa et al. 1991; Langbaum et al. 2010; Mosconi et al. 2009; Mosconi et al. 2008], and that brain metabolic derangements worsen with AD progression [Hoyer and Nitsch 1989; Hoyer et al. 1991].

Human postmortem studies established that brain insulin resistance mediated by reduced insulin receptor expression and insulin receptor binding were consistent and fundamental abnormalities in AD [Rivera et al. 2005; Steen et al. 2005]. In AD, the deficits in brain insulin and IGF signaling involves pathways needed to maintain neuronal survival, energy production, gene expression, and plasticity [Frolich et al. 1998]. Correspondingly, nearly all of the critical features of AD, including increased: 1) activation of kinases that aberrantly phosphorylate tau and lead to the accumulation of neurofibrillary tangles, dystrophic neuritic plaques and neuorpil threads; 2) expression of amyloid-beta precursor protein (AβPP) and accumulation of AβPP-Aβ peptides that are neurotoxic and result in senile plaque formation; 3) oxidative and ER stress that propagate cell death cascades; 4) mitochondrial dysfunction which causes energy deficits; and 5) disruption of cholinergic homeostasis needed for neuronal plasticity, memory, and cognition, could represent consequences of brain insulin/IGF resistance.

In the central nervous system (CNS), insulin and insulin-like growth factor (IGF) signaling networks regulate a broad array of functions including cell growth and survival, metabolism, gene expression, protein synthesis, cytoskeletal assembly, synapse formation, neurotransmitter function, and plasticity [D'Ercole and Ye 2008; de la Monte and Wands 2005; Hoyer 2004]. Impairments in insulin and IGF signaling could be mediated by reduced ligand availability, reduced receptor rexponsiveness, or inhibition of downstream signaling. Chronic insulin/IGF-1 resistance has dire consequences on the functional integrity of the CNS [de la Monte and Wands 2005; Schubert et al. 2003; Schubert et al. 2004; Xu et al. 2003] due to impairments in neuronal survival, energy production, gene expression, and plasticity [Frolich, Blum-Degen, Bernstein, Engelsberger, Humrich, Laufer, Muschner, Thalheimer, Turk, Hoyer, Zochling, Boissl, Jellinger and Riederer 1998]. Moreover, inhibition of insulin/IGF signaling disrupts cholinergic homeostasis, thereby compromising one of the most important neurotransmitter systems utilized for neuronal plasticity, memory, and cognition.

Another major adverse effect of insulin/IGF resistance in the brain is chronically increased stress caused by oxidative and endoplasmic reticulum (ER) stress, generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS) that damage proteins, RNA, DNA, and lipids [Reddy et al. 2009], mitochondrial dysfunction; and activation of pro-inflammatory and pro-death cascades [de la Monte, Longato, Tong and Wands 2009; de la Monte and Wands 2005; de la Monte et al. 2008; Haan 2006; Lester-Coll et al. 2006; Rivera, Goldin, Fulmer, Tavares, Wands and de la Monte 2005; Steen, Terry, Rivera, Cannon, Neely, Tavares, Xu, Wands and de la Monte 2005; Tilg and Moschen 2008]. Oxidation of amino acid residues leads to formation of advanced glycation end products (AGEs) or advanced oxidation protein products. Oxidation of proteins causes them to become unfolded, inactivated, and more susceptible to cleavage. Moreover, oxidation of aliphatic side-chains leads to the formation of peroxides and carbonyls (aldehydes and ketone). Peroxides attack other molecules and produce radicals. Carbonyls are toxic and cause stress-induced AGE accumulation, which contributes to progressive impairment of cellular functions in aging, diabetes, AD, experimental models of AD, and degenerative diseases [Greilberger et al. 2010; Greilberger et al. 2008; Gu et al. 2008; Stadtman 2001]. In AD, elevated levels of AGE in amyloid plaques and neurofibrillary tangles [Gella and Durany 2009; Krautwald and Munch 2010; Rahmadi et al. 2011] quite likely contribute to the ongoing cell death and neurodegeneration [Gella and Durany 2009; Krautwald and Munch 2010; Reddy, Zhu, Perry and Smith 2009].

Peripheral insulin resistance states are linked to cognitive impairment and Alzheimer's disease

The molecular and biochemical abnormalities in brains with AD closely mimic those in T2DM and NASH, and until recently, the vast majority of sporadic AD had no association with diabetes. In fact, prior to 1980, the epidemiological trends for AD (increasing prevalence) were opposite those for diabetes mellitus (declining as a cause of death) [de la Monte, Neusner, Chu and Lawton 2009]. Within the past 2-3 decades, morbidity and mortality rates have trended upward for diabetes and other insulin resistance diseases,

including metabolic syndrome (dyslipidemic states), non-alcoholic steatohepatitis (NASH), and obesity, despite improvements in medical care [de la Monte, Neusner, Chu and Lawton 2009]. At the same time, the increasing overlap between cognitive impairment or AD and peripheral insulin resistance diseases has raised concerns about the potential contributions or even causal roles of obesity and diabetes mellitus in neurodegeneration and dementia [de la Monte, Neusner, Chu and Lawton 2009; Qiu et al. 2007].

Epidemiologic studies showed that people with glucose intolerance, deficits in insulin secretion, T2DM, obesity/dyslipidemic disorders, and NASH had significantly higher risks for developing MCI or AD-type dementia [Craft 2005; Craft 2006; Craft 2007; de la Monte, Longato, Tong and Wands 2009; Hoyer 2004; Luchsinger et al. 2007; Martins et al. 2006; Pasquier et al. 2006]. For example, obese individuals were found to have higher rates of MCI [Lokken et al. 2009] and impaired performance on executive function tests [Gunstad et al. 2007; Lokken, Boeka, Austin, Gunstad and Harmon 2009]. In adition, their risk for developing dementia or AD was at least two-fold higher than for the general population [Yaffe 2007]. These results were corroborated by experimental data showing that chronic high fat feeding and diet induced obesity with T2DM impair spatial learning and memory [Winocur and Greenwood 2005; Winocur et al. 2005] and cause atrophy, insulin resistance, inflammation, oxidative stress, and cholinergic dysfunction in the brain [Lyn-Cook, Lawton, Tong, Silbermann, Longato, Jiao, Mark, Wands, Xu and de la Monte 2009; Moroz et al. 2008]. Moreover, in NASH, which is associated with hepatic insulin resistance, the rates of neuropsychiatric diseases such as depression and anxiety [Elwing et al. 2006], and risks for developing cognitive impairment [Felipo et al. 2011] are significantly increased. On the other hand, weight loss leading to reduced peripheral insulin resistance improves cognitive performance [Baker et al. 2010; Baker et al. 2010] and enhances neuropsychiatric function including mood and behavior [Bryan and Tiggemann 2001].

Several studies have shown that cognitive impairment and neuropsychiatric dysfunction occur with liver disease caused by various agents, including alcohol abuse, obesity, chronic Hepatitis C virus infection, Reyes syndrome, and nitrosamine exposure [Elwing, Lustman, Wang and Clouse 2006; Karaivazoglou et al. 2007; Kopelman et al. 2009; Loftis et al. 2008; Perry et al. 2008; Schmidt et al. 2005; Weiss and Gorman 2006]. These diseases are linked because they are all associated with hepatic steatosis or steatohepatitis and hepatic insulin resistance, endoplasmic reticulum (ER) stress, and increased generation of cytotoxic sphingolipids, including ceramides [de la Monte et al. 2006; Lester-Coll, Rivera, Soscia, Doiron, Wands and de la Monte 2006; Lyn-Cook, Lawton, Tong, Silbermann, Longato, Jiao, Mark, Wands, Xu and de la Monte 2009; Moroz, Tong, Longato, Xu and de la Monte 2008; Tong et al. 2010; Tong et al. 2009]. Mechanistically, inflammation, superimposed on disease states that promote lipid storage in hepatocytes promotes ER stress, oxidative damage, mitochondrial dysfunction, and lipid peroxidation, which together drive hepatic insulin resistance [Capeau 2008; Kraegen and Cooney 2008].

Hepatic insulin resistance stimulates lipolysis [Kao, Youson, Holmes, Al-Mahrouki and Sheridan 1999], and lipolysis leads to increased generation of toxic lipids e.g. ceramides, which further impair insulin signaling, mitochondrial function, and cell viability [Holland and Summers 2008; Kraegen and Cooney 2008; Langeveld and Aerts 2009]. Moreover, with

steatohepatitis, hepatic and peripheral insulin resistance are accompanied by increased local and peripheral levels of ceramides [de la Monte, Tong, Lester-Coll, Plater and Wands 2006; Lester-Coll, Rivera, Soscia, Doiron, Wands and de la Monte 2006; Moroz, Tong, Longato, Xu and de la Monte 2008; Tong, Longato and de la Monte 2010; Tong, Neusner, Longato, Lawton, Wands and de la Monte 2009], suggesting that distant target organs may be susceptible to their toxic effects. Experimentally, molecular and biochemical abnormalities associataed with AD can be produced by in vitro exposure to short-chain cytotoxic ceramides [Adibhatla and Hatcher 2008; Alessenko, Bugrova and Dudnik 2004]. In addition, in vivo administration (i.p.) of toxic ceramides causes cognitive-motor deficits, brain insulin resistance, oxidative stress, metabolic abnormalities, and neurodegeneration, similar to AD-type neurodegeneration [Tong and de la Monte 2009]. Further investigations showed that toxic ceramides delivered into peripheral blood by i.p. injection localize in brain membranes and therefore cross the blood brain barrier [de la Monte 2012].

Toxic lipids produced in peripheral insulin resistance states contribute to brain insulin-resistance and neurodegeneration

In obesity, adipose tissue, skeletal muscle, and liver have abnormal sphingolipid metabolism results in increased ceramide production, inflammation, and activation of pro-inflammatory cytokines, with impairments in glucose homeostasis and insulin responsiveness [Delarue and Magnan 2007; Shah et al. 2008; Summers 2006]. In human [Kolak et al. 2007] and experimental models of NASH [Cong et al. 2008], ceramide levels in adipose tissue are elevated due to increased activation of serine palmitoyl transferase, and acidic and neutral sphingomyelinases [Liu, Obeid and Hannun 1997]. In addition, liver ceramide synthase and serine palmitoyl transferase mRNA levels are increased in the early stages of hepatic steatosis, but with the development of NASH and neurodegeneration, ceramide synthase mRNA transcripts decline while sphingomyelinase gene expression increases [Lyn-Cook, Lawton, Tong, Silbermann, Longato, Jiao, Mark, Wands, Xu and de la Monte 2009]. Since neurodegeneration in models of obesity and diabetes have not been associated with increased CNS expression of pro-ceramide genes, we suspect that the AD-type neurodegeneration with brain insulin/IGF resistance is mediated by secondary effects of peripheral insulin resistance, i.e. dysregulated lipid metabolism, increased production of cytotoxic ceramides, and increased trafficking of cytotoxic ceramides from peripheral blood to brain.

Corresponding with the above concept, mass spectrometry-based lipidomics analysis of plasma detected elevated levels of saturated sphingolipids (N16:0 and N21:0) in AD relative to control subjects, and linked severity of cognitive impairment with altered levels of specific very long chain ceramides [Han 2010]. In addition, elevated plasma levels of very long-chain saturated ceramides (C22:0 and C24:0) were found to be predictive of memory loss and hippocampal atrophy in patients with MCI [Mielke et al. 2010], whereas increased ratios of dihydrosphingomyelin to dihydroceramide and sphingomyelin to ceramide were shown to be correlated with slower progression of AD [Mielke et al. 2011]. Although these studies did not interrogate the sources of plasma sphingolipids and ceramides or the presence of underlying peripheral insulin resistance diseases, they provide evidence that

shifts in plasma spingolipid profiles and levels could be used as peripheral biomarkers for individuals at risk for progression from MCI to dementia. Ideally, it would be beneficial to determine the degree to which peripheral blood very long chain ceramide profiles shift with treatment of AD with insulin, insulin sensitizers, or measures to support neurotransmitter function and metabolic homeostasis in the CNS.

Hypothesis: Peripheral insulin resistance diseases can cause MCI and contribute to progressive AD-type neurodegeneration

The aggregate results from several studies suggest that peripheral, including hepatic insulin resistance with associated chronic injury, inflammation, and metabolic dysfunction leads to dysregulated lipid metabolism with increased ceramide production. Intra-hepatic (or visceral fat) accumulation of cytotoxic ceramides promotes ER stress, which exacerbates insulin resistance, inflammation, and oxidative stress. Consequences include increased DNA damage, mitochondrial dysfunction, energy depletion, ROS production, and eventually the formation lipid, protein, and DNA adducts, which further impair cellular functions. Finally, a reverberating cascade of mal-signaling and insulin resistance with impaired cell survival gets established, resulting in leakage of toxic ceramides from liver (visceral fat) to peripheral blood [de la Monte, Longato, Tong and Wands 2009]. Toxic lipids, including ceramides can cross the blood-brain barrier and cause insulin resistance by interfering with critical phosphorylation events [Arboleda, Huang, Waters, Verkhratsky, Fernyhough and Gibson 2007; Chalfant, Kishikawa, Mumby, Kamibayashi, Bielawska and Hannun 1999; de la Monte et al. 2010; Liu, Obeid and Hannun 1997; Tong and de la Monte 2009] and activating pro-inflammatory cytokines [Bryan, Kordula, Spiegel and Milstien 2008; Summers 2006; Van Brocklyn 2007], CNS Therefore, brain insulin resistance, which is an early and important feature of AD, may be mediated by chronic exposure to cytotoxic ceramides generated in extra-CNS sources [de la Monte, Tong, Nguyen, Setshedi, Longato and Wands 2010] and capable of penetrating the blood brain barrier. cause CNS insulin resistance, oxidative stress, and pro-inflammatory cytokine activation, which ultimately result in dysregulated lipid metabolism, myelin breakdown, increased endogenous ceramide generation, and ER stress.

The epidemic of peripheral insulin resistance diseases which includes obesity, T2DM, and NAFLD/NASH, is likely responsible for the staggering increases in morbidity and mortality rates from AD across all age groups, 50-years and older [de la Monte, Neusner, Chu and Lawton 2009]. Mechanistically, we propose that this extrinsic pathway of brain insulin/IGF resistance with attendant ER stress is initiated through insults arising from toxic ceramides generated in peripheral tissues, e.g. liver, and traffic through peripheral blood to the CNS to exert their neurotoxic and degenerative effects. Future therapeutic strategies for restoring cognitive function and preventing progression to AD should consider the inclusion of agents that block toxic ceramide and other toxic lipid production in both peripheral tissues and the brain.

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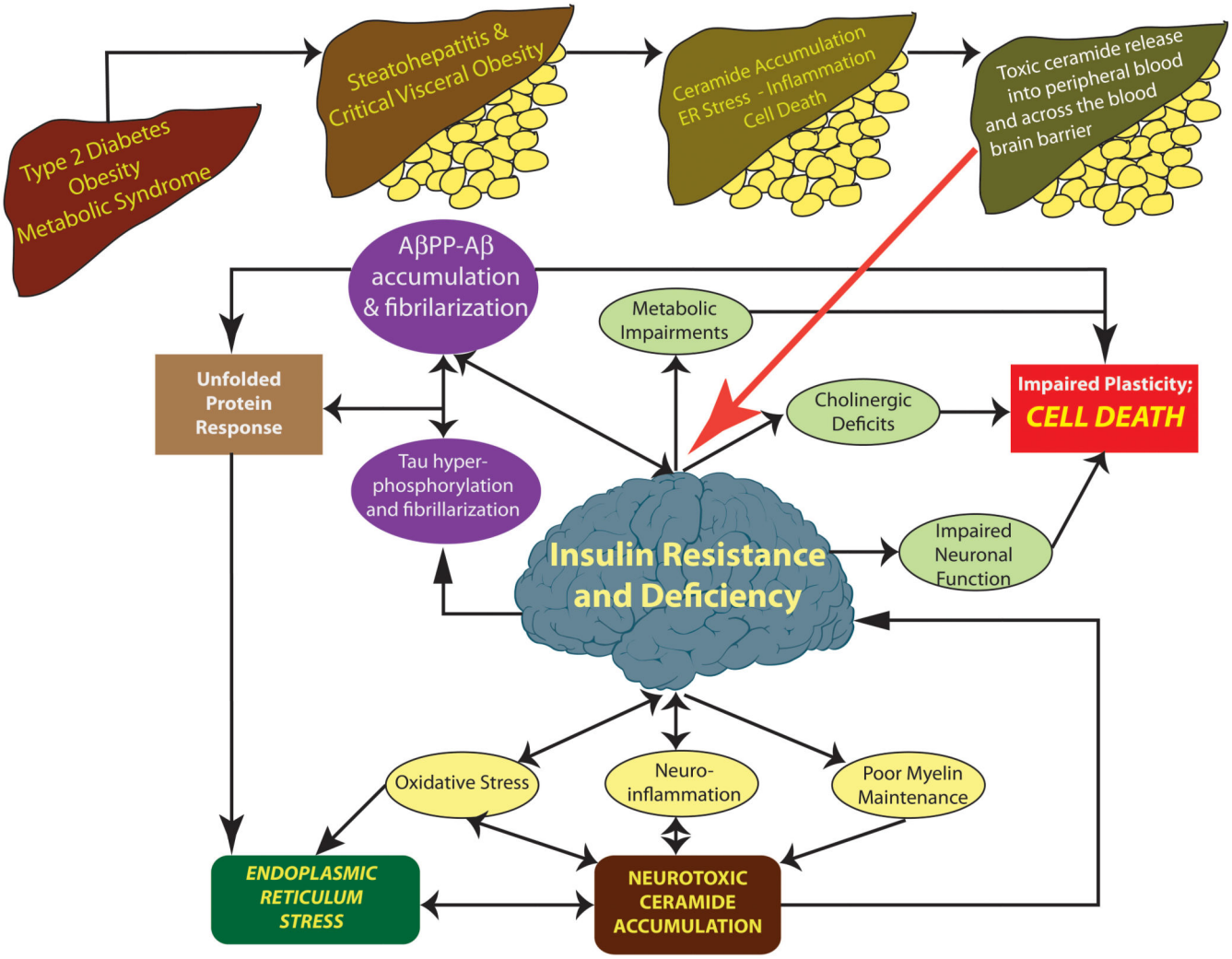

Figure 1.

Extrinsic mechanisms of brain insulin/IGF resistance and neurodegeneration. In Type 2 diabetes, non-alcoholic steatohepatitis, and visceral obesity (visceral obesity shown as yellow discs below livers), excess lipid accumulation leads to insulin resistance, which promotes inflammation, ER stress, and oxidative injury. This process establishes a positive feedback cycle of mal-signaling and insulin resistance with impaired cell survival that results in leakage of toxic ceramides from liver (or visceral fat) to peripheral blood. Toxic ceramides capable of penetrating the blood brain barrier, cause CNS insulin resistance, oxidative stress, and pro-inflammatory cytokine activation, which ultimately result in dysregulated lipid metabolism, myelin breakdown, increased endogenous ceramide generation, and ER stress.