Chapter 10
Mammalian Target of Rapamycin at the Crossroad Between Alzheimer's Disease and Diabetes

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Abstract Accumulating evidence suggests that Alzheimer's disease may manifest as a metabolic disorder with pathology and/or dysfunction in numerous tissues. Adults with Alzheimer's disease suffer with significantly more comorbidities than demographically matched Medicare beneficiaries (Zhao et al, BMC Health Serv Res 8:108, 2008b). Reciprocally, comorbid health conditions increase the risk of developing Alzheimer's disease (Haaksma et al, PLoS One 12(5):e0177044, 2017). Type 2 diabetes mellitus is especially notable as the disease shares many overlapping pathologies observed in patients with Alzheimer's disease, including hyperglycemia, hyperinsulinemia, insulin resistance, glucose intolerance, dyslipidemia, inflammation, and cognitive dysfunction, as described in Chap. 8 of this book

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(Yoshitake et al, Neurology 45(6):1161–1168, 1995; Leibson et al, Am J Epidemiol 145(4):301–308, 1997; Ott et al, Neurology 53(9):1937–1942, 1999; Voisin et al, Rev Med Interne 24(Suppl 3):288s–291s, 2003; Janson et al. Diabetes 53(2):474–481, 2004; Ristow M, J Mol Med (Berl) 82(8):510–529, 2004; Whitmer et al, BMJ 330(7504):1360, 2005, Curr Alzheimer Res 4(2):103–109, 2007; Ohara et al, Neurology 77(12):1126–1134, 2011). Although nondiabetic older adults also experience age-related cognitive decline, diabetes is uniquely associated with a twofold increased risk of Alzheimer's disease, as described in Chap. 2 of this book (Yoshitake et al, Neurology 45(6):1161–1168, 1995; Leibson et al, Am J Epidemiol 145(4):301–308, 1997; Ott et al. Neurology 53(9):1937–1942, 1999; Ohara et al, Neurology 77(12):1126–1134, 2011). Good glycemic control has been shown to improve cognitive status (Cukierman-et al, Diabetes Care 32(2):221–226, 2009), and the use of insulin sensitizers is correlated with a lower rate of cognitive decline in older adults (Morris JK, Burns JM, Curr Neurol Neurosci Rep 12(5):520–527, 2012). At the molecular level, the mechanistic/mammalian target of rapamycin (mTOR) plays a key role in maintaining energy homeostasis. Nutrient availability and cellular stress information, both extracellular and intracellular, are integrated and transduced through mTOR signaling pathways. Aberrant regulation of mTOR occurs in the brains of patients with Alzheimer's disease and in numerous tissues of individuals with type 2 diabetes (Mannaa et al, J Mol Med (Berl) 91(10):1167–1175, 2013). Moreover, modulating mTOR activity with a pharmacological inhibitor, rapamycin, provides wide-ranging health benefits, including healthy life span extension in numerous model organisms (Vellai et al, Nature 426(6967):620, 2003; Jia et al, Development 131(16):3897–3906, 2004; Kapahi et al, Curr Biol 14(10):885–890, 2004; Kaeberlein et al, Science 310(5751):1193–1196, 2005; Powers et al, Genes Dev 20(2):174–184, 2006; Harrison et al, Nature 460(7253):392–395, 2009; Selman et al, Science 326(5949):140–144, 2009; Sharp ZD, Strong R, J Gerontol A Biol Sci Med Sci 65(6):580–589, 2010), which underscores its importance to overall organismal health and longevity. In this chapter, we discuss the physiological role of mTOR signaling and the consequences of mTOR dysregulation in the brain and peripheral tissues, with emphasis on its relevance to the development of Alzheimer's disease and link to type 2 diabetes.

10.1   Introduction to mTOR Signaling

mTOR is an evolutionarily conserved serine/threonine kinase, and member of the phosphoinositide-3-kinase (PI3K)-related kinases (PIKK) family; others include ATM, ATR, DNA-PK, and hSMG1. mTOR functions as the catalytic subunit of two independent multi-protein holoenzyme complexes, mTORC1 and mTORC2 (Fig. 10.1). Common to both core complexes are mTOR, mammalian lethal with Sec13 protein 8 (mLST8, also known as GβL), and both interact with DEP domain-containing mTOR-interacting protein (Deptor) and the Tel2/Tti1 complex. Furthermore, mLST8 is critical in promoting mTOR-mediated tumor progression
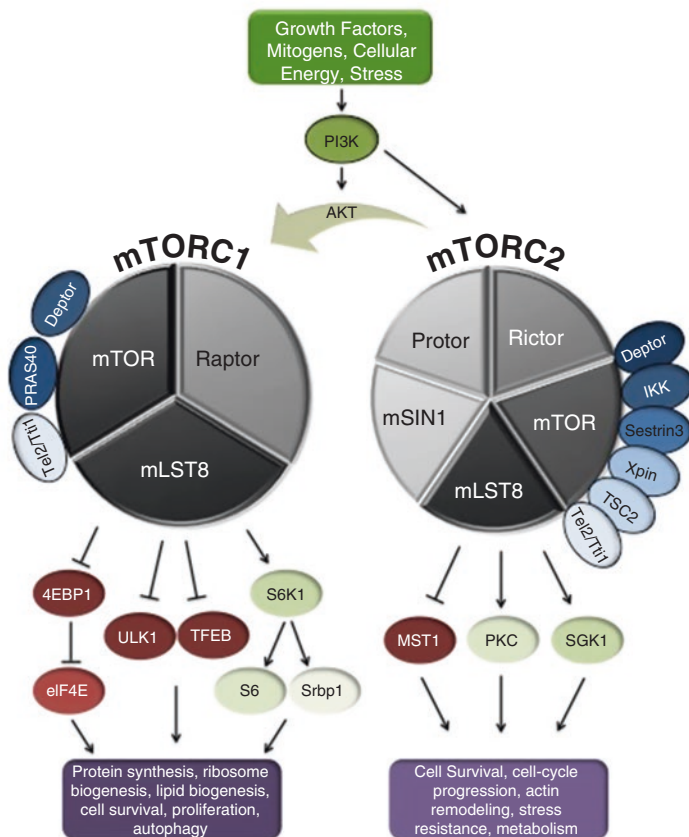
Fig. 10.1 mTOR complex proteins. Activation of both mTORC1 and mTORC2 occurs through growth factor and mitogen PI3K-dependent signaling. Active mTORC1 increases macromolecule biogenesis and suppress autophagy. Active mTORC2 promotes cell survival, proliferation, and cytoskeletal remodeling. AKT activates mTORC1 through PI3K signaling or downstream of mTORC2 activation and thus serves as a connecting node to these independent complexes. mTORC1 and mTORC2 share in common mTOR and mLST8 as core proteins and Tel2/Tti1 and Deptor as transient and/or nutrient-sensing regulatory proteins. Unique to mTORC1 is the scaffold protein Raptor and transient and/or nutrient-sensing proteins PRAS40. Rictor, Protor, and mSIN1 are unique to the mTORC2 core complex, as are the transient and/or nutrient-sensing proteins IKK, Sestrin3, Xpln, and TSC2

(Kakumoto et al. 2015), although it has no effect on physiological mTOR activity in vitro or in vivo (Guertin et al. 2006). Unique to the mTORC1 core complex is raptor and transient interactions with nutrient-sensitive proline-rich AKT substrate 40 kDa (PRAS40) (Wullschleger et al. 2006). Raptor has many functions that regulate mTORC1 assembly, substrate recruitment, subcellular localization, and amino acid sensing (Hara et al. 2002; Kim et al. 2002; Sancak et al. 2008). PRAS40 and Deptor are both substrates of mTORC1, whereby mTORC1-mediated phosphorylation weakens their association with the complex and promotes mTORC1

kinase activity (Oshiro et al. 2007; Sancak et al. 2007; Thedieck et al. 2007; Vander Haar et al. 2007; Wang et al. 2008; Peterson et al. 2009). Rictor, RPTOR-independent companion of mTOR, is the defining component of mTORC2. Rictor and raptor are mutually exclusive mTOR-binding partners and required for mTORC2 and mTORC1 activity, respectively (Jacinto et al. 2004; Sarbassov et al. 2004). The core protein complex of mTORC2 also consists of the mammalian stress-activated protein kinase-interacting protein (mSIN1); and protein observed with Rictor-1 (Protor-1, also known as PRR5). Proteins with nutrient-sensitive or transient interactions with the mTORC2 core are DEPTOR, IKK, Sestrin3, Xpln, and TSC2 (Fig. 10.1).

Elevated cellular energy, nutrient availability, and mitogens activate mTOR signaling. Excess cellular resource availability, as in diabetes and obesity, increases mTOR signaling through the convergence of numerous signals. For example, hormones such as insulin and IGF1 activate mTOR through phosphoinositide 3-kinase (PI3K). In the presence of insulin, the transmembrane tyrosine kinase insulin receptor (IR) becomes activated and autophosphorylates tyrosine residues located in the intracellular portion of the receptor. The signal is rapidly transduced by the phosphorylation of tyrosine residues on insulin receptor substrate 1 through 4 (IRS-1 through IRS-4) (Sun et al. 1991, 1995; Lavan et al. 1997a, b). Among the distinct pathways next affected, the most prominent is mTORC2/AKT. Activated mTORC2 promotes cell survival, cytoskeletal remodeling, cell growth, and cell proliferation by activating AKT, SGK1, and PKC while inhibiting MST1 (Sarbassov et al. 2005; Cybulski and Hall 2009; Laplante and Sabatini 2012; Manning and Toker 2017). AKT also is an upstream activator of mTORC1 and an indirect substrate of mTORC1 during times of hyperactive mTOR signaling; thus, AKT serves as a signaling node between mTORC1 and mTORC2. Specifically, AKT activates mTORC1 through inhibitory phosphorylation of TSC1/2, an mTORC1 inhibitor (Figs. 10.1 and 10.2).

mTORC1 also responds to cellular energy, i.e., ATP/ADP ratio through AMPK (Hardie and Ashford 2014). During low cellular energy, AMPK inhibits mTORC1 through both direct and indirect mechanisms: direct phosphorylation of raptor disrupts the mTORC1 complex, and phosphorylation of the mTOR inhibitor TSC2 dampens mTORC1 activity. Increasing cellular amino acid (Wang and Proud 2009) or glucose concentration activates mTORC1 through the Rag family of GTPases. In response, mTORC1 localizes to the lysosome and stimulates macromolecule biosynthesis. In contrast, during starvation or low nutrient availability, mTORC1 negatively regulates autophagy by inhibiting autophagy initiation and lysosomal biogenesis through phosphorylation of the ULK complex and TFEB, respectively (Roczniak-Ferguson et al. 2012; Settembre et al. 2012). During high cellular energy resources, mTORC1 also promotes ribosome biogenesis and mRNA translation through phosphorylation and activation of downstream substrates: ribosomal S6 kinases (S6Ks) and the inhibitory eIF4E-binding proteins (4E-BPs). mTORC1-activated S6K phosphorylates substrates to promote translation and elongation (i.e., 40S ribosomal subunit proteins, eiF4B and eEF2K), while mTORC1-phosphorylated 4E-BPs promote cap-dependent translation through their participation in the eIF4F
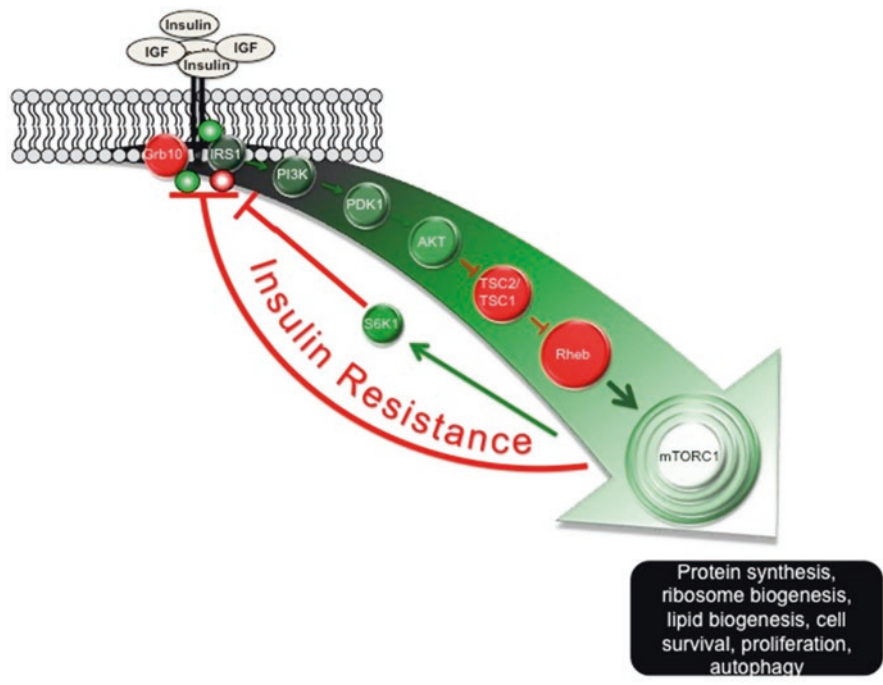
Fig. 10.2 Hyperactive mTORC1 signaling contributes to insulin resistance. Insulin signaling activates mTORC1 to promote macromolecule biogenesis and decrease autophagy. Activated mTORC1/S6K1 feeds back on the pathway to block insulin signaling through inhibitory phosphorylation of insulin receptor substrate 1 IRS1 (Ser307 and Ser636/639) and Grb10. Persistent nutrient availability induces insulin resistance through the sustained mTORC1/S6K1 inhibitory phosphorylation on IRS1 and Grb10 activation. Acute rapamycin releases the autoinhibitory signaling and prevents insulin resistance

complex (Laplante and Sabatini 2012; Saxton and Sabatini 2017a, b). Also, mTORC1 regulates lipid biosynthesis through activation of SREBP1, a major lipogenic transcription factor that controls genes involved in fatty acid and cholesterol synthesis, (Lamming and Sabatini 2013). In summary, mTOR is at the nexus of cellular metabolism, growth, and survival.

10.2   Physiological mTOR Signaling in the Brain

As in other cell types where mTOR regulates cell growth and proliferation, mTOR has an essential role in neuronal progenitor proliferation and in the temporal control of neuronal differentiation through insulin/IGF1-mediated PI3K/mTOR activation (Han et al. 2008; Fishwick et al. 2010; Malagelada et al. 2011). The principle growth factors that activate mTORC1 in neurons are brain-derived neurotrophic factor

(BDNF), insulin, insulin-like growth factor I (IGF-I), and vascular endothelial growth factor (VEGF) (Kim et al. 2008; Takei and Nawa 2014). The use of transgenic animal models and pharmacological approaches has provided strong evidence for the necessary role of mTOR signaling in the brain throughout life stages. Nestin-driven ablation of mTORC1 (raptor deletion) and mTORC2 (rictor deletion) activity was performed to determine the contribution of each complex on brain development (Cloetta et al. 2013; Thomanetz et al. 2013). Both studies found microcephaly, as well as reduced neuron cell number, size, morphology, and function indicating a necessary role of mTOR signaling during neuronal development. Interestingly, genetic upregulation of mTOR activity during forebrain development also resulted in microcephaly due to neural progenitor apoptosis in transgenic mice; in contrast upregulating mTOR in the adult brain resulted in cortical hypertrophy (Kassai et al. 2014). mTOR signaling is critical for axonal and dendritic sprouting, growth and regeneration during development (Inoki et al. 2006; Jossin and Goffinet 2007; Li et al. 2008; Nie et al. 2010), and in the mature nervous system. For example, in the adult central nervous system (CNS), neurons fail to regenerate; in contrast axonal sprouting and axonal growth can occur in response to injury in peripheral nervous system (PNS). This differential response to neuronal injury in the CNS and PNS is partially mediated through mTORC1 signaling. In the PNS, neuronal injury upregulates mTORC1; conversely, injury to CNS neurons causes mTORC1 downregulation (Park et al. 2008; Liu et al. 2010). In CNS neuron injury models, upregulation of mTORC1 by deleting negative regulators PTEN or TSC1 both enhanced axonal sprouting and regeneration retinal ganglion cells (Park et al. 2008); and PTEN deletion had the same benefits on corticospinal tract neuronal injury (Liu et al. 2010). Expression of constitutively active forms of mTOR pathway members, AKT and Rheb, also induce axonal regrowth. These studies indicate that mTORC1 activation is sufficient to promote axonal growth in both CNS and PNS neurons following injury and may have therapeutic importance to neurodegeneration and peripheral neuropathy in patients diagnosed with Alzheimer's disease and diabetes.

Proper mTOR regulation also is necessary for proper brain function. The use of rapamycin has elegantly demonstrated the requirement of mTORC1 activity for long-term potentiation (LTP) (Tang et al. 2002; Cammalleri et al. 2003; Banko et al. 2005; Ehninger et al. 2008; Stoica et al. 2011) and memory consolidation via mTORC1-mediated translational control (Stoica et al. 2011). mTORC1-dependent translational control also mediates changes in dendritic spine morphology that is required for memory storage and recall (Henry et al. 2017). Consolidation of memories also requires mTORC1 (Dash et al. 2006; Parsons et al. 2006; Schicknick et al. 2008; Stoica et al. 2011; Gafford et al. 2013) and mTORC2 activation for cytoskeletal remodeling (Costa-Mattioli and Monteggia 2013; Huang et al. 2013). While these studies collectively indicate the importance of mTOR in overall neuronal function, other experimental results contradict the necessity of mTOR in LTP (Antion et al. 2008), specifically in the dentate gyrus (Panja et al. 2009). Along these lines, mTORC1 hyperactivity induces seizures and epilepsy in rodent models (Sharma et al. 2010; Kassai et al. 2014; Rotschafer and Razak 2014; Russo et al. 2014), and genetic mutations resulting in hyperactive mTORC1 have been reported

in familial focal epilepsy (Dibbens et al. 2013). In models with hyperactive mTOR, such as aging and Alzheimer's disease, decreasing mTOR activity with rapamycin results in enhanced learning and memory (Zhou et al. 2009; Spilman et al. 2010; Majumder et al. 2011; Ehninger 2013; Neff et al. 2013; Ozcelik et al. 2013). Collectively these studies underscore that mTOR requires precise temporal regulation and level of activation for proper neuronal and brain function.

10.3   mTOR and Insulin Resistance in the Brain

In the late 1970s, the brain was deemed an insulin-insensitive organ; however, insulin now is well appreciated for its major physiological roles in the brain, as described in Chap. 1 of this book. While insulin is not a major regulator of glucose metabolism or transport of glucose in the brain (Marfaing et al. 1990; Hasselbalch et al. 1999; Seaquist et al. 2001), insulin and insulin-like growth factor type 1 (IGF-1) are important modulators of neurogenesis, neuronal growth, survival and differentiation, synaptic plasticity, lipid metabolism, and protein homeostasis (D'Ercole et al. 1996; Popken et al. 2004; Bedse et al. 2015). These processes are mediated through mTOR via the PI3K/mTOR axis of insulin signaling. Several studies report overactivation of the PI3K/mTOR pathway as an early feature of Alzheimer's disease (Pei et al. 2008; Caccamo et al. 2010; Tramutola et al. 2015) that can lead to aberrant glucose metabolism, energy production, and regulation of protein synthesis and degradation (Oddo 2012; O'Neill 2013; Tramutola et al. 2015). In Alzheimer's disease, neurons become increasingly resistant to insulin and IGF-1 (Moloney et al. 2010). Neuronal insulin resistance is maintained by overactivation of the PI3K/mTOR axis, which inhibits IRS1 activity via a negative feedback mechanism (Tramutola et al. 2015) (Fig. 10.2). In this way, insulin is both upstream and downstream of mTOR. The contribution of insulin-independent (e.g., oxidative stress, inflammation, protein accumulation, etc.,) chronic activation of mTORC1 signaling may be more responsible for the brain insulin resistance found in Alzheimer's disease and is discussed in the following sections.

10.4   mTOR in Alzheimer's Disease Pathogenesis

The human brain consumes ~20% of the body's glucose-derived energy to maintain its metabolic demands; compared to its modest 2% body weight, the brain's requirement is much higher than that of other tissues (Erbsloh et al. 1958). Neurons are the most energy-demanding cell type in the adult human brain and require continuous delivery of glucose from the blood (Howarth et al. 2012). Numerous clinical studies have shown that hypergylcemia causes cognitive impairment (Umegaki et al. 2008; Cukierman-Yaffe et al. 2009; Crane et al. 2013). Early stages of Alzheimer's disease are characterized by deficits in cerebral glucose utilization

(Caselli et al. 2008; Mosconi et al. 2008, 2009), brain insulin resistance, and insulin deficiency (Frolich et al. 1998) that continue to worsen as the disease progresses (Hoyer et al. 1991; Rivera et al. 2005). Furthermore, the impairment in insulin and IGF signaling is directly associated with neuropathological markers of Alzheimer's disease, including Aβ and phosphorylated tau (Orr et al. 2014). Aβ and tau pathologies are associated with mTOR hyperactivity in brains of patients with Alzheimer's disease and corresponding mouse models (An et al. 2003; Pei and Hugon 2008; Caccamo et al. 2010, 2011, 2013; Oddo 2012). Several groups have shown that Alzheimer's disease-associated pathology and cognitive deficits can be mitigated by using the mTOR inhibitor rapamycin to restore mTOR activity (Caccamo et al. 2010; Spilman et al. 2010; Majumder et al. 2011, 2012; Ozcelik et al. 2013), even in the presence of an insulin resistance-inducing diet (Orr et al. 2014). Since Alzheimer's disease is associated with increased mTOR activity, overactivation of both mTOR and insulin can contribute to brain insulin resistance in Alzheimer's disease through overlapping mechanisms.

Experimentally inducing insulin resistance in Alzheimer's disease models greatly exacerbates pathogenesis, cognitive decline, and insulin signaling (Cao et al. 2007; Ke et al. 2009; Jolivalt et al. 2010; Plaschke et al. 2010; Takeda et al. 2010; Bitel et al. 2012; Orr et al. 2014). Studies investigating the cellular mechanisms have found mTOR is a critical signaling molecule exacerbating cognitive deficits and pathogenic protein accumulation in diet (Ma et al. 2013; Orr et al. 2014) and pharmacological (i.e., use of a single streptozotocin injection to impair pancreatic β cells along with high-fat and/or high-carbohydrate diet) models of type 1/2 diabetes pathologies (Ma et al. 2015). Alzheimer's disease and type 2 diabetes rat models exhibit brain mTOR hyperactivity through oxidative stress, inflammation, protein accumulation, etc. (discussed below). When these diseases are combined, behavioral deficits are worsened coincident with increased mTOR and tau gene and protein expression levels (Ma et al. 2013, 2015). Administering 20% sucrose to drinking water of the 3xTgAD transgenic mouse model of Alzheimer's disease caused significant weight gain and insulin resistance (Orr et al. 2014). The peripheral phenotypes were accompanied by an increase in pathogenic Aβ, phosphorylated tau deposition, and mTORC1 pathway upregulation in the brain. The restoration of mTOR activity via rapamycin prevented the sucrose-induced exacerbation of Aβ and tau pathology, to strongly implicate disregulated mTORC1 as a nexus of peripheral insulin resistance and brain pathologies (Orr et al. 2014).

Neuronal autophagy is highly efficient and necessary for neuronal health. Loss of autophagy is neurotoxic even in the absence of disease and/or toxic protein accumulation (Hara et al. 2006; Komatsu et al. 2006). Disregulated autophagy (either hyper- or hypoautophagy) has been reported in neurodegenerative disease (Nixon 2013). In Alzheimer's disease mouse models with hyperactive mTOR, autophagic dysfunction is often cited as a contributing cellular mechanism responsible for the deleterious effects of protein accumulation (Caccamo et al. 2010, 2014; Majumder et al. 2011). Mechanistically, hyperactive mTOR decreases autophagy through ULK and TFEB inhibition (please refer to Fig. 10.1). In the rTg(tau$_{P301L}$)4510 mouse model of Alzheimer's disease-associated tau accumulation
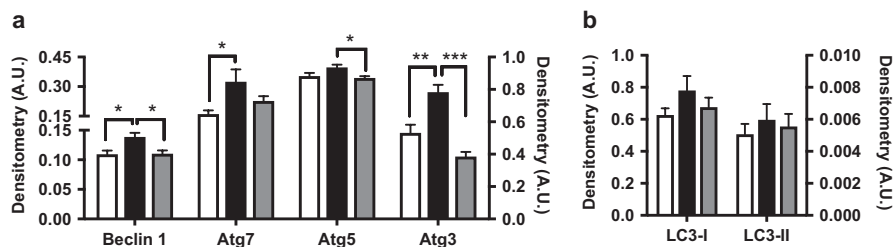
Fig. 10.3 Diet-induced insulin resistance caused autophagic impairment in the 3xTgAD Alzheimer's disease mouse model. (**a**) Protein expression analyses of brain tissue from 3xTgAD Alzheimer's disease mice indicate that dietary-induced insulin resistance increased autophagy-associated proteins. (**b**) The absence of concomitant LC3-II upregulation is indicative of autophagasome constipation. Treatment with rapamycin prevented the autophagasome accumulation and restored autophagic flux to control levels. (Open bar, control mice; solid bar, sucrose; gray bar, sucrose + rapamycin). $N = 8$ mice/group. One-way ANOVA Tukey's post hoc *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0001$

(Santacruz et al. 2005), TFEB is significantly downregulated (Polito et al. 2014). Experimentally increasing TFEB resulted in decreased pathogenic neurofibrillary tangle formation and brain atrophy concomitant with improved synaptic function and cognitive behavior (Polito et al. 2014). Maintaining proper autophagy in the Alzheimer's disease brain is especially critical in a diabetes-like condition. Experimentally inducing insulin resistance in 3xTgAD mice caused an upregulation of autophagy-associated proteins in the brain (Fig. 10.3). The upregulation of Beclin 1, Atg7, Atg5, and Atg3 occurred in the absence of increased LC3 II/I ratio, which suggests an accumulation of autophagasomes. A decrease in autophagic flux occurs when either autophagasome formation or lysosomal clearance mechanisms are impaired; the resulting accumulation of defective autophagasomes and autolysosomes is capable of exacerbating Alzheimer's disease pathogenesis (Orr and Oddo 2013). Notably, treatment with rapamycin restored autophagic flux deficits in these 3xTgAD insulin-resistant mice indicating that restoring brain mTOR activity can overcome the negative effective effects of peripheral obesity and insulin resistance.

On a cellular level, the impaired energy metabolism maintained by mTOR-mediated inhibition of insulin and IGF-1 responses leads to oxidative stress and inflammation, which contributes to the pathogenesis of Alzheimer's disease, as described in Chap. 3 of this book (Craft and Watson 2004). Chronic overactivation of mTOR has been linked to systemic inflammation (Liu et al. 2016b; Paschoal et al. 2017), and there is evidence that mTOR also regulates neuroinflammation in several different disease models. For instance, high-fat diet-induced obesity is associated with increased neuroinflammation and overactivation of mTOR; and when neuroinflammation is reduced, mTOR activity also decreases (Dasuri et al. 2016).

However, much of the work showing mTOR-dependent regulation of neuroinflammation originates in models characterized by acute neuroinflammation. For instance, inhibiting mTOR after intracranial hemorrhage reduces neuronal death,

decreases expression of the proinflammatory cytokines TNF-α, IL1β, IL-6, and caspase-3, and reduces microglial activation (Li et al. 2016a; Wang and Zhang 2017). In fact, mTOR has been shown to specifically regulate cytokine-dependent microglial activation, such that pharmacological inhibition of mTOR reduces microglial, but not astrocytic, responses to inflammatory cytokine application (Dello Russo et al. 2009). Additionally, inhibition of mTOR with rapamycin also prevents proinflammatory M1 macrophage polarization and can shift macrophage polarization toward an anti-inflammatory M2 type (Xie et al. 2014b; Li et al. 2016b). In contrast, studies performed in cultured microglia indicate that rapamycin generally enhances proinflammatory activity (Xie et al. 2014b). This discrepancy suggests that mTOR regulates proinflammatory activity indirectly. Specifically, rapamycin likely acts on other cell types which then decrease proinflammatory markers in macrophages and microglia. Overall, these data indicate that mTOR regulates neuroinflammation through the activation of microglia and proinflammatory cytokines. However, since much of this work has been performed in disorders characterized by acute neuroinflammation, these results should be confirmed in disease states with chronic neuroinflammation, such as that found in neurodegenerative diseases.

Specific to Alzheimer's disease, neuronal insulin resistance is linked to neuroinflammation through activation of the TNF-α/JNK pathway, which inhibits IRS-1. Aβ oligomers (Bomfim et al. 2012; Lourenco et al. 2013) and misfolded tau (Kovac et al. 2011) activate TNF-α, which alters IRS-1/mTOR signaling. As insulin negatively regulates Aβ deposition and tau phosphorylation, dysregulation of insulin signaling increases these pathologies (de la Monte 2014). Additionally, Aβ oligomers inhibit the expression of neuronal surface insulin receptors (Zhao et al. 2008a) and IRS1 phosphorylation at Ser307 (Bomfim et al. 2012), which uncouples the interaction of IRS1 and IR (Harrington et al. 2004; Werner et al. 2004). Moreover, tau directly induces abnormal IRS-1 phosphorylation (Yarchoan et al. 2014), suggesting that Alzheimer's disease-associated pathologies can further contribute to aberrant insulin signaling in Alzheimer's disease. Therefore, Aβ and tau can influence abnormal insulin signaling both directly and indirectly through activation of the TNF-α/JNK pathway. Furthermore, dysregulation of brain insulin signaling in Alzheimer's disease is directly associated with increased Aβ accumulation, tau phosphorylation, and proinflammatory mediators (Di Domenico et al. 2017), as well as mTOR overactivation (Oddo 2012). Therefore, aberrant mTOR signaling is positioned at the crossroad of brain insulin resistance and neuroinflammation in Alzheimer's disease and acts as a vicious positive feed forward loop to accelerate disease progression.

Brain insulin resistance has been reported in nondiabetic Alzheimer's disease patients (Talbot et al. 2012), which is exacerbated by diabetes (Yoshitake et al. 1995; Leibson et al. 1997; Ott et al. 1999; Ohara et al. 2011). These reports indicate that brain insulin resistance in Alzheimer's disease can be a local disease process, as described in Chap. 3 of this book, but also is influenced by peripheral insulin resistance. For example, using rapamycin to reduce mTOR activity in Alzheimer's disease alleviates brain insulin resistance but simultaneously exacerbates peripheral

insulin resistance and obesity (Orr et al. 2014). Similarly, others have reported peripheral insulin resistance induced by rapamycin and rapalogs in wild-type mice, as well as an increased incidence of hyperglycemia and diabetes associated with pharmaceutical inhibition of the mTOR pathway in human clinical trials, indicating that physiological mTOR pathway activity levels are tissue specific (Johnston et al. 2008; Lamming et al. 2012; Geuna et al. 2015). Due to the promising therapeutic benefits of decreasing mTOR activity on various health conditions (Dazert and Hall 2011), recent work is now focused on intermittent dosing regimens to reduce the negative effects on peripheral insulin resistance and obesity while maintaining the benefits of decreasing mTOR activity in brain (Arriola Apelo et al. 2016a, b).

10.4.1   Peripheral Insulin Resistance

While the cause of elevated mTOR in Alzheimer's disease brain remains inconclusive, excess nutrient intake as seen in type 2 diabetes and obesity leads to the upregulation of mTORC1/S6K1 signaling in insulin-sensitive tissues (Um et al. 2004; Khamzina et al. 2005; Shigeyama et al. 2008). In response, the primary function of mTORC1 is to shift catabolism to growth-promoting anabolism through the synthesis of the major macromolecules (i.e., proteins, lipids, and nucleotides). In times of high nutrient availability, mTOR directly phosphorylates the insulin receptor leading to its internalization; this, in turn, results in a decrease of mTOR signaling (Wullschleger et al. 2006). However, chronic mTOR hyperactivity leads to pathogenic conditions including insulin resistance, a key feature of type 2 diabetes (Saha et al. 2011). Chronic mTORC1 activation by nutrient excess contributes to triacylglycerol or lipid deposition in white adipose tissue, liver, and muscle cells (Bentzinger et al. 2008; Cota et al. 2008; Polak et al. 2008; Sengupta et al. 2010). The induction of an S6K1-dependent negative feedback loop is one consequence from chronic mTORC1 hyper-activation and would lead to attenuation of AKT signaling in multiple tissues and insulin resistance (Harrington et al. 2004; Shah et al. 2004; Um et al. 2004; Khamzina et al. 2005). Therefore, it is conceivable that mTORC1 activation is required for an initial physiological adaptation of nutrient excess and obesity, but a negative feedback loop on IRS signaling caused by chronic and persistent hyper-activation could lead to development of insulin resistance.

10.4.1.1   Adipose Tissue

Obesity, defined as having a body mass index (BMI) of greater than 30 kg per m^2, greatly increases the risk of type 2 diabetes and has dichotomous effects on Alzheimer's disease risk depending on the individual's life stage. Specifically, obesity in midlife increases the risk of developing late-life Alzheimer's disease, whereas an increased BMI in older ages is protective (Whitmer et al. 2005, 2007; Emmerzaal et al. 2015; Rodriguez-Casado et al. 2017). As an exocrine organ,

adipose influences the activity and function of many tissues, including the brain. Through these neural connections, adipose tissue is well integrated in controlling whole-body glucose homeostasis in both normal and disease states. Mechanistically, mTOR signaling is hyperactive in numerous tissues derived from obese human and animal models due to the convergence of nutrients and growth factor stimuli (Um et al. 2004; Khamzina et al. 2005; Tremblay et al. 2007; Woods et al. 2008; Cota 2009; Kucejova et al. 2016; Tsai et al. 2016). Here we discuss the role of adipose tissue in type 2 diabetes and Alzheimer's disease, with particular focus on adipose-derived hormone signaling and how mTOR activity influences the interaction between obesity and cognition in Alzheimer's disease.

There are two main types of adipose tissue, white and brown. White adipose stores excess energy derived from food intake. In general, chronic nutrient stress signals resulting in uncontrolled white adipose tissue expansion promotes heart disease, diabetes, and metabolic syndrome. In contrast, brown adipose tissue is important for energy expenditure and non-shivering thermoregulation because it contains high mitochondrial content in the uncoupled state. This makes brown adipose tissue an attractive target for the treatment of obesity and type 2 diabetes. Interestingly, 3xTgAD Alzheimer's disease mice have impaired thermoregulation, which is exacerbated with age (Tournissac et al. 2017) and may suggest potential interactions between Alzheimer's associated protein aggregation and brown adipose tissue dysfunction. In line with this notion, cold exposure in these mice increases tau phosphorylation, full length APP, and soluble APP fragments; placing the animals in a thermoneutral environment reverses the effects on APP (Tournissac et al. 2017). In mice, white adipose tissue browning can alter whole-body energy expenditure, resulting in weight loss and increased insulin sensitivity. mTOR activity has a role in this cold stress-induced transition, resulting in an intermediate "beige" phenotype (Liu et al. 2016a). Furthermore, genetic activation of mTOR in white adipose tissue results in enhanced mitochondrial function and protection from high-fat diet-induced obesity and insulin resistance (Magdalon et al. 2016). In brown adipose tissue, genetically upregulating mTOR induces a transition to white adipose tissue, which can be reversed by pharmacologically decreasing mTOR with rapamycin treatment (Xiang et al. 2015). These dichotomous effects of mTOR in each adipose tissue type underscore its complexity.

Adipose tissue secretes numerous peptide hormones and cytokines (referred to as adipokines) including leptin, adiponectin, resistin, and lipoprotein lipase LPL allowing it to communicate with distant organs such as the brain (Ailhaud 2006). The effects of adipose-to-neuronal signaling have been demonstrated in vitro (Wan et al. 2015) and in vivo (Yamazaki et al. 2015). Human neuronal cells cultured with conditioned media from healthy female (males were not included in this study) adipocytes exhibit neuroprotection against toxic oxidative stress while increasing the activation of inflammatory proteins like JNK and ERK (Wan et al. 2015). In vivo, the systemic administration of adipocyte-conditioned media improved latency times in tail suspension and forced swim tasks in the 5xAD transgenic Alzheimer's disease mouse line (Yamazaki et al. 2015). In line with these findings, leptin treatment alone enhanced neural progenitor cell proliferation in transgenic APP/

PS1 mice, which is thought to confer some benefit to brain function in these mice (Perez-Gonzalez et al. 2011). Notably, leptin plasma concentration was positively associated with reduced incidence of Alzheimer's disease and whole brain and hippocampal weight in the Framingham Heart study, a large cohort study, to provide translational relevance of these in vitro and preclinical findings (Lieb et al. 2009; Paz-Filho et al. 2010).

The level of leptin in the CNS is dependent on the amount of body fat (Klein et al. 1996) and is correlated with BMI (Schwartz et al. 1996). Activation of mTOR is required for leptin biogenesis and is an important signaling event for healthy adipose tissue expansion (Roh et al. 2003). Like in the Alzheimer's disease brain, mTOR activity is elevated in adipose tissue from obese and insulin-resistant human subjects (Catalan et al. 2015). mTOR activation induces vascularization of white adipose tissue especially under nutrient replete conditions (Soumya et al. 2013). This process is critical for healthy adipose tissue expansion as evidenced by adipose tissue atrophy and insulin resistance in adipose-specific mTOR knockout mice (Shan et al. 2016). Though elevated mTOR is associated with obesity, it reduces adipose-derived inflammation, especially during high-fat diet feeding (Liu et al. 2016b; Paschoal et al. 2017).

Leptin receptors are highly expressed in several brain regions, highlighting the diversity and importance of leptin signaling in the brain. For example, leptin is involved in regulation of appetite and energy expenditure through its activity in the hypothalamus, satiety through signaling on neurons in the arcuate nucleus (Klein et al. 1996; Schwartz et al. 1996; Elmquist et al. 1998), and long-term potentiation, learning and memory in the hippocampus (Harvey et al. 2006). In Alzheimer's disease transgenic mice, leptin receptor expression is downregulated (Pedros et al. 2015), which lends support to the idea that patients with Alzheimer's disease have significant leptin resistance similar to obese and high-fat diet states. While leptin exerts many benefits to brain and neuronal health, a negative association between plasma leptin levels and brain region-specific volumes has been reported (Bentzinger et al. 2008). Obese individuals show greater brain atrophy in old age (Debette et al. 2010; Ho et al. 2010, 2011), which may result from alterations to leptin signaling (i.e., leptin resistance) as well as other adipose-derived molecules. For example, plasma and cerebral spinal fluid (CSF) levels of adipose-derived adiponectin are negatively correlated with cognitive acuity; specifically adiponectin levels increase in a stepwise fashion from control to mild cognitive impairment (MCI) and are even higher in patients with Alzheimer's disease (Une et al. 2011). However, like the inconsistent findings with leptin, other studies reported lower circulating adiponectin levels in patients with Alzheimer's disease than controls and concluded adiponectin levels provide no predictive value for disease progression (Teixeira et al. 2013). In vitro work further highlights the complexity of adiponectin signaling. For instance, globular adiponectin can increase the secretion of inflammatory cytokines in human astrocyte-like cells (Wan et al. 2014), but in cultured microglia, it can suppress Aβ-induced inflammatory signaling (Song et al. 2017). These studies have not been confirmed in vivo but underscore the diverse effects of adiponectin signaling dependent on cell type.

Adipose tissue also secretes non-peptide biologically active molecules such as activated lipids. One of the hallmarks of type 2 diabetes is elevated systemic free fatty acid (FFA) levels, which arises from resistance to insulin-induced suppression of lipolysis in adipose tissue (DeFronzo 2004). Furthermore, high levels of peripheral norepinephrine (NE) can also induce triacylglyceride (TAG) breakdown and release of FFA into circulation (Raclot and Groscolas 1993). In turn high levels of FFA can increase inflammation and induce insulin resistance (Liang et al. 2013) in a vicious cycle. Interestingly, one of the first brain regions to degenerate in Alzheimer's disease is the locus coeruleus, the primary producer of the NE to the brain (Grinberg et al. 2011). This decrease in central NE has been linked to elevated levels of NE in plasma and CSF of patients with Alzheimer's disease (Raskind et al. 1984). Increased peripheral NE may contribute to suppression of mTOR-mediated glucose uptake into fat cells and increased lipolysis (Mullins et al. 2014). Furthermore, NE mediates beta-adrenergic signaling-induced glucose uptake and mTOR activity in brown adipose tissue (Mullins et al. 2014). These findings suggest a potential link between Alzheimer's disease and increased susceptibility to insulin resistance. While elevated FFA levels have been shown to induce insulin resistance, FFAs have also been shown to accelerate the formation of Aβ and tau oligomers (Wilson and Binder 1997). Furthermore, Alzheimer's disease patients have increased CSF levels of the FFA shuttles (albumins) (Elovaara et al. 1985). CSF albuminuria is suggestive of blood-brain barrier leakage and elevated FFAs in the brain, which can facilitate toxic protein aggregation. Moreover, excess circulating FFAs cause accumulation of triglycerides and activated lipids in the form of long-chain fatty acyl-CoA esters in other tissues such as skeletal muscle, liver, and β-cells which disrupts the normal metabolic and secretory functions of these tissues. Thus, adipose tissue is the primary organ responsible for controlling systemic lipid levels, which greatly impacts the modulation of both glucose and lipid homeostasis and underscores the importance of maintaining proper BMI in preventing systemic metabolic dysfunction as in type 2 diabetes and Alzheimer's disease. It is generally accepted that two features are critical for obesity to elicit type 2 diabetes: skeletal muscle insulin resistance and the failure of pancreatic β cells to secrete the required levels of insulin needed to maintain euglycemia, which will be discussed below.

10.4.1.2 Skeletal Muscle

Skeletal muscle is the largest organ in the human body and comprises 30–50% of an individual's total body weight. It is classically known for its roles in the generation of power, locomotion, metabolism, and thermogenesis. Skeletal muscle is critically important in the regulation of metabolic homeostasis; it is the major site of glucose disposal (~80%), and muscle insulin resistance is considered one of the major hallmarks of type 2 diabetes (DeFronzo and Tripathy 2009). The risk for sarcopenia, the progressive decline in skeletal muscle mass resulting in decreased muscle strength and physical performance (Cruz-Jentoft et al. 2010), and physical disability increases in older patients with type 2 diabetes mellitus (Kalyani et al. 2010).

Sarcopenia negatively impacts cognition (Canon and Crimmins 2011), overall health and quality of life. Motor, sensory, and coordination deficits are not common early in Alzheimer's disease; however, abnormal weight and muscle loss are clinical features of Alzheimer's disease progression (McKhann et al. 1984; Burns et al. 2010; Takagi et al. 2017). Moreover, acquired resistance to insulin signaling and action in skeletal muscle is associated with obesity and promotes the development of type 2 diabetes mellitus. In this section, we will discuss the role of skeletal muscle in metabolic homeostasis, dysfunctions in type 2 diabetes and Alzheimer's disease, and the role of mTOR signaling in these processes.

Skeletal muscle is a major determinant of the basal metabolic rate (Zurlo et al. 1990, 1994; Janssen et al. 2000), which is the amount of energy that an individual requires for the body to maintain function while at rest. These basic processes include breathing, blood circulation, and controlling body temperature. The basal metabolic rate accounts for about 60–75% of the daily calorie expenditure by individuals and determines whether an individual maintains, gains, or loses weight. As in most tissues of the adult human body, mTOR signaling in skeletal muscle is critical for protein synthesis. Since muscle mass is regulated by the balance between protein synthesis and degradation, mTOR signaling in skeletal muscle is paramount for maintaining muscle mass. Furthermore, skeletal muscle mTOR activity is key to integrating nutrient, growth factor, and stress signaling, as well as promoting muscle mass accrual after exercise (Saxton and Sabatini 2017a, b). Both mTORC1 and mTORC2 are highly expressed in skeletal muscle. mTORC1 signaling is essential for maintaining muscle mass and has been associated with muscle hypertrophy (Bodine et al. 2001). Moreover, muscle-specific raptor knockout mice with diminished mTORC1 signaling exhibited severe muscle atrophy leading to early death (Bentzinger et al. 2008). Paradoxically, sustained activation of mTORC1 in muscle-specific TSC1 knockout mice also led to myopathy and reduced survival due to an inability of the body to remove damaged cells as a result of impaired autophagy (Castets et al. 2013). Similar to brain mTOR signaling, these data suggest that proper mTORC1 activity is important for maintaining optimal tissue health, and subsequently an individual's overall metabolic rate.

In contrast to mTORC1, the major function of mTORC2 in the muscle is the regulation of glucose uptake through PI3K/AKT signaling. Consistent with this notion, muscle-specific rictor knockout mice showed impaired insulin-stimulated glucose transport (Kumar et al. 2008). Injecting mice with the mTOR inhibitor, AZD8055, suppressed insulin-stimulated glucose disposal in the muscle (Kleinert et al. 2014). However, in muscle-specific Rictor knockout mice, AZD8055 did not cause further defects in glucose regulation, suggesting that AZD8055 impairs glucose metabolism in the muscle, in part by blocking mTORC2. These findings support the notion that mTORC2 signaling critically regulates glucose metabolism in muscle and subsequently whole-body metabolism.

Similar to brain and adipose tissue, muscle mTORC1 signaling is elevated in obesity and diabetes (Khamzina et al. 2005). It has been demonstrated that mTORC1 activation of S6K1 results in serine phosphorylation of IRS-1, leading to suppressed insulin signaling (Tzatsos and Kandror 2006) and subsequently insulin resistance

(Khamzina et al. 2005). Furthermore, rodent studies showed that mice with constitutive 4E-BP1 activity in the muscle, i.e., reduced downstream mTORC1 signaling, were resistant to age and diet-induced insulin resistance (Tsai et al. 2015). These studies suggest that downstream targets of mTORC1 signaling in the muscle play important roles in glucose metabolism.

In the brain during Alzheimer's disease pathogenesis, elevated mTOR activity is associated with dysregulation of insulin signaling and the accumulation of pathogenic proteins (Caccamo et al. 2014; Orr et al. 2014). Experimental evidence suggests that skeletal muscle of obese and/or Alzheimer's disease animal models may develop similar pathogenic protein accumulation and lead to disruptions in glucose regulation. Specifically, a high-cholesterol diet given to rabbits induced Aβ and phosphorylated tau deposition in skeletal muscle (Sparks et al. 1994). In transgenic Alzheimer's disease mice, mutant APP was found within skeletal muscle as well (Monteiro-Cardoso et al. 2015). These findings are also relevant to human patients: amyloid beta 42 (Aβ42) expression is detectable in skeletal muscle from cognitively normal older adults and is elevated in the skeletal muscle from patients with Alzheimer's disease as assessed during autopsy (Arai et al. 1991; Kuo et al. 2000). Collectively these findings suggest that hyperactive mTOR may be common to numerous tissues in patients with Alzheimer's disease and even produce similar protein accumulation pathologies, which could contribute to the muscular dysfunction that is present in Alzheimer's disease.

Skeletal mass and function have critical roles in the overall health of an organism. Gait speed, primarily governed by muscle function, is one of the closest predictors of mortality in older individuals (Studenski et al. 2011; Toots et al. 2013). Muscle atrophy and dysfunction in patients with Alzheimer's disease has been confirmed in several independent studies (McKhann et al. 1984; Burns et al. 2010; Takagi et al. 2017). Reduced motor function and grip strength have been associated with an increased risk of mild cognitive impairment (MCI), a diagnosis which often progresses to Alzheimer's disease (Boyle et al. 2009). Moreover, poor swallowing function in patients with Alzheimer's disease has been directly attributed to skeletal muscle dysfunction (Takagi et al. 2017). A loss of the homeostatic control of energy metabolism has been implicated as the common cause underling both brain and skeletal muscle dysfunctions detected in Alzheimer's disease subjects and is attributed to mitochondrial dysfunction (Hauptmann et al. 2009; Du et al. 2010; Boncompagni et al. 2012; Ding et al. 2013). Transgenic Alzheimer's disease mice recapitulate defects in skeletal muscle function similar to patients with Alzheimer's disease (Schuh et al. 2014). Specifically decreased skeletal muscle maximal respiratory capacity (Schuh et al. 2014), acetylcholinesterase and catalase activity, and altered skeletal muscle mitochondrial membrane composition (Monteiro-Cardoso et al. 2015) have all been reported in mouse models of Alzheimer's disease. Of note, acetylcholinesterase inhibitors are used as a standard treatment for Alzheimer's disease, although they provide little benefit (Kaduszkiewicz et al. 2005). Given that acetylcholinesterase activity in skeletal muscle is impaired in Alzheimer's disease (Monteiro-Cardoso et al. 2015), using acetylcholinesterase

inhibitors may also affect skeletal muscle function, which could impact systemic metabolism.

Muscle is increasingly recognized as an endocrine organ that communicates with other tissues, including the brain, through the secretion of myokines, soluble factors that regulate metabolism and other biological processes in a systemic manner (Henningsen et al. 2010; Pedersen and Hojman 2012; Schnyder and Handschin 2015). Myokines include cytokines, peptides, and other metabolites, which are released by muscle primarily in response to exercise (Schnyder and Handschin 2015). BDNF is predominantly expressed in the brain (Matthews et al. 2009) and is a recently identified myokine (Matthews et al. 2009). BDNF is a member of the neurotrophin family and is essential in regulating the survival, growth, and maintenance of neurons (Hofer and Barde 1988). BDNF plays a key role in learning and memory (Tyler et al. 2002) and in the regulation of body mass and energy homeostasis (Wisse and Schwartz 2003). Patients with Alzheimer's disease showed lower levels of BDNF in the brain and circulation (Connor et al. 1997; Laske et al. 2006). Interestingly, reduced plasma BDNF levels were also found in obesity and type 2 diabetes (Krabbe et al. 2007). Muscle contractions during exercise produce BDNF mRNA and protein in skeletal muscle, where it seems to play a role in enhancing glucose metabolism. Whether BDNF acts as a myokine that can improve Alzheimer's disease, however, is currently under debate. Muscle-derived BDNF does not appear to be released into the circulation suggesting that BDNF primarily acts locally in the muscle (Miura et al. 2012). Other neurotrophin family members such as neurotrophin 3 (NT-3) and NT-4/5 have also been found in the skeletal muscle (Omura et al. 2005). While the systemic effects of these aforementioned myokines is not yet understood, evidence for improved memory in Rhesus monkeys and humans due to the upregulation of muscle-derived cathepsin B has been elegantly demonstrated (Moon et al. 2016). Upregulated cathepsin B also improves learning and memory in Alzheimer's disease mouse models (Embury et al. 2017). Because skeletal muscle release of cathepsin B is increased with exercise, myokines may be directly contributing to the exercise-associated cognitive benefits reported in Alzheimer's disease (Brandt and Pedersen 2010).

Sarcopenia is associated with a proinflammatory state and lower cognitive function in older adults (Mazure and Swendsen 2016). Systemic inflammation was found to mediate the negative relationship between sarcopenia and cognitive function, especially in females (Mazure and Swendsen 2016). Interestingly, exercise training has been shown to lower all-cause mortality partially because it exerts an anti-inflammatory effect. Chronic "sterile" low-grade systemic inflammation has been implicated in the pathogenesis of a number of aging-related chronic illnesses including both Alzheimer's disease and type 2 diabetes. The etiology of sterile inflammation is still not clear and likely is a result of several factors, including physical inactivity, altered immune cell function, and somatic cell damage, among others, that can be largely abrogated by exercise. Exercise training reduces visceral fat mass, which is a major source of inflammation (please refer to the section on adipose). The production of anti-inflammatory cytokines, such as IL-1ra, IL-10, and sTNFR, increases after exercise training (Ostrowski et al. 1999). Also, contracting

muscle releases myokines that may create a systemic anti-inflammatory environment to improve the function of distant organs (Brandt and Pedersen 2010). Therefore, regular exercise offers protection against Alzheimer's disease and type 2 diabetes, as well as other chronic diseases, through decreasing adiposity, improving insulin sensitivity, and releasing myokines, many of which are regulated through the mTOR signaling axis.

10.4.1.3 Pancreas

Regulation of glucose homeostasis by insulin depends on pancreatic β cell growth and function. A primary characteristic of type 2 diabetes pathogenesis is the slowly progressive pancreatic β cell failure which results in impaired insulin secretion, decreased β cell mass, decreased insulin action on peripheral tissues, and ultimately β cell death. In general, the pancreas serves two main roles: an exocrine function that aids in digestion and an endocrine function that controls blood glucose level. The endocrine component of pancreatic regulation is controlled by the islet cells (islets of Langerhans), which create and release important metabolic hormones directly into the bloodstream. The two main pancreatic hormones are insulin, which is secreted from islet β cells to suppress catabolic processes and stimulate glucose uptake. Conversely, glucagon is secreted from islet α cells and stimulates hepatic gluconeogenesis. Each β cell contains over 10,000 secretory vesicles filled with insulin (Dean 1973; Olofsson et al. 2002), which are under close regulation to ensure tight control of blood glucose levels. During type 2 diabetes pathogenesis, individuals exhibit a progressive decline in β cell function, with gradual β cell degeneration and worsening of glycaemia over time (1995; Kahn et al. 2006); eventually pancreatic islets fail to compensate for insulin resistance in peripheral tissues. Great effort has focused on understanding mechanisms responsible for pancreatic dysfunction; mTOR signaling has emerged as a key molecular regulator of interest. In this section, we will highlight cellular processes that overlap between type 2 diabetes, β cell pathology, and brain pathogenesis in Alzheimer's disease with emphasis on hyperactive mTOR and protein accumulation.

Numerous studies highlight a positive role of mTORC1 activation in regulating β cell health in physiological conditions (Tremblay and Marette 2001; Khamzina et al. 2005; Teutonico et al. 2005; Ueno et al. 2005; Di Paolo et al. 2006; Sarbassov et al. 2006; Krebs et al. 2007; Fraenkel et al. 2008; Rachdi et al. 2008; Elghazi et al. 2010; Gu et al. 2011; Yang et al. 2011; Blandino-Rosano et al. 2012). Carbohydrate- and fat-rich Western diets provide chronic nutrient overload (Fig. 10.4). The Western diet results in chronic exposure of β cells to persistent glucose and FFAs resulting in obesity, β cell failure, and type 2 diabetes. This nutrient excess in type 2 diabetes and obesity drives elevated blood glucose, amino acids, proinflammatory cytokines, and insulin, all of which activate mTORC1 (Wellen and Thompson 2010; Zoncu et al. 2011; Efeyan et al. 2015; Kennedy and Lamming 2016). Indeed, pancreatic islets isolated from patients with type 2 diabetes and various type 2 diabetes mouse models (i.e., hyperglycemic obese high-fat diet-fed mice and leptin receptor-deficient
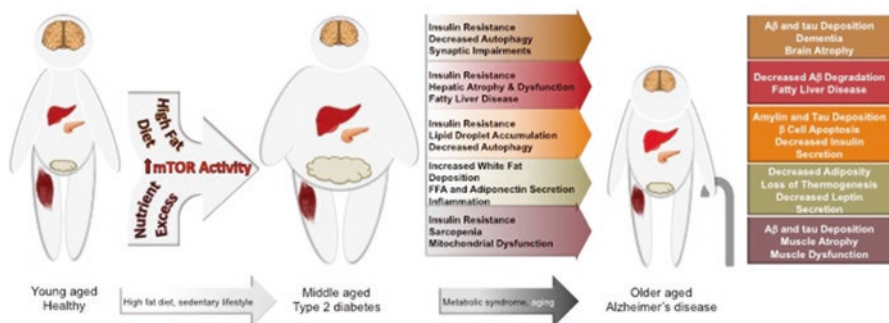
Fig. 10.4 Causes and consequences of mTOR hyperactivity in mid- and older ages. Carbohydrate- and fat-rich Western diets increase blood glucose and mTOR activity in several tissues, leading to obesity, insulin resistance, and type 2 diabetes in middle ages. With advanced age, the persistent mTOR hyperactivity contributes to tissue dysfunction and Alzheimer's disease. Brown, brain; red, liver; orange, pancreas; beige, adipose; purple, muscle

db/db mice) display elevated mTORC1 activity (Shigeyama et al. 2008; Bartolome et al. 2014; Hatanaka et al. 2014; Yuan et al. 2017) but reduced mTORC2/AKT signaling (Wang et al. 2010; Ardestani et al. 2014; Yuan et al. 2017). Genetically and pharmacologically modulating mTOR signaling have provided compelling evidence for a critical role of both mTORC1 and mTORC2 complexes in the regulation of glucose homeostasis by modulating β cell mass and function (Tremblay and Marette 2001; Khamzina et al. 2005; Teutonico et al. 2005; Ueno et al. 2005; Di Paolo et al. 2006; Sarbassov et al. 2006; Krebs et al. 2007; Fraenkel et al. 2008; Rachdi et al. 2008; Elghazi et al. 2010; Gu et al. 2011; Yang et al. 2011; Blandino-Rosano et al. 2012).

mTORC1 regulates several pancreatic islet functions including β cell size, growth, and proliferation, insulin secretion, and protein translation by modulating mRNA translation through phosphorylation of 4E-BPs and S6K1 (McDaniel et al. 2002; Briaud et al. 2003; Kwon et al. 2004; Zahr et al. 2007; Rachdi et al. 2008; Shigeyama et al. 2008; Mori et al. 2009; Barlow et al. 2013; Rhodes et al. 2013; Xie et al. 2014a; Stamateris et al. 2016). Whole-body mTOR loss-of-function/deletion was found to be lethal (Gangloff et al. 2004; Murakami et al. 2004; Guertin et al. 2006; Jacinto et al. 2006; Shiota et al. 2006; Yang et al. 2006); however, whole-body depletion of S6K1 caused hypoinsulinemia and reduced β cell size but improved insulin sensitivity (Pende et al. 2000; Ruvinsky et al. 2005). To further gain insight into pancreatic mTOR function, transgenic mice have been created with tissue-specific mTOR modulation. Overexpressing S6K1 in β cells increases insulin secretion without affecting β cell mass (Elghazi et al. 2010). Activation of mTORC1 by targeted deletion of mTORC1 repressors, tuberous sclerosis 1 (TSC1), or tuberous sclerosis 2 (TSC2) (Rachdi et al. 2008; Shigeyama et al. 2008; Mori et al. 2009; Blandino-Rosano et al. 2012) or overexpressing Rheb (Hamada et al. 2009) significantly increases islet β cell function (Saxton and Sabatini 2017a, b). In contrast, transgenic mice with decreased mTOR function exclusively in β cells

displayed reduced mTORC1 and mTORC2 signaling and developed β cell dysfunction and glucose intolerance (Alejandro et al. 2017; Blandino-Rosano et al. 2017; Chau et al. 2017; Elghazi et al. 2017; Ni et al. 2017; Sinagoga et al. 2017). While one model displayed normal β cell mass (Alejandro et al. 2017), others display reduction in β cell mass, smaller islets, and/or pancreas size (Blandino-Rosano et al. 2017; Chau et al. 2017; Elghazi et al. 2017; Ni et al. 2017; Sinagoga et al. 2017). Similarly, mTORC2 loss of function causes hyperglycemica, glucose intolerance, reduced β cell mass and proliferation, as well as reduced pancreatic insulin level and secretion (Gu et al. 2011). These studies underscore that proper regulation of mTOR signaling in β cells is critical for pancreatic function and whole-body glycemic control.

The chronic exposure of human and rodent β cells to persistent glucose and FFAs, as occurs in obesity and type 2 diabetes, causes β cell failure (Robertson et al. 2004; Prentki and Nolan 2006; Muoio and Newgard 2008; Leibowitz et al. 2010; Alejandro et al. 2015) and apoptosis through hyperactive mTORC1 signaling and mTORC1-dependent lipid drop accumulation (Bachar et al. 2009; Vernier et al. 2012; Mir et al. 2015; Yang et al. 2015; Varshney et al. 2017; Yuan et al. 2017). Additional mTORC1-mediated cytotoxicity occurs through inhibition of autophagy (Jung et al. 2008; Masini et al. 2009; Stienstra et al. 2014; Riahi et al. 2016) and compensatory downregulation of cytoprotective mTORC2 signaling (Gu et al. 2011; Blandino-Rosano et al. 2012; Ardestani et al. 2014; Ardestani and Maedler 2016). Rapamycin treatment significantly decreased triglyceride accumulation and β cell toxicity (Vernier et al. 2012), and mTORC1-S6K1 inhibition restored insulin secretion in human islets derived from type 2 diabetic patients providing further evidence that upregulated mTORC1 activity is responsible for these pathologies (Yuan et al. 2017).

Acute rapamycin treatment improves insulin sensitivity in humans and rodents through inhibition of mTORC1 (Tremblay and Marette 2001; Khamzina et al. 2005; Ueno et al. 2005; Krebs et al. 2007). In contrast, chronic rapamycin exposure exacerbates insulin resistance in wild type (Sarbassov et al. 2006) and Alzheimer's disease mouse models (Orr et al. 2014). The negative effects of long-term treatment occur, in part, through inhibition of mTORC2. While mTORC1 is sensitive to low-dose and short-term exposure to rapamycin, chronic rapamycin exposure also inhibits mTORC2; thus through the mTORC2/AKT signaling pathway, β cell proliferation and survival are negatively affected (Sarbassov et al. 2006). The relative contributions of long-term rapamycin-induced β cell dysfunction and insulin resistance from mTORC1 and mTORC2 signaling are not fully understood, but both complexes influence these phenotypes (Teutonico et al. 2005; Di Paolo et al. 2006). While rapamycin treatment has been proposed as a therapeutic strategy for metabolic diseases, more research is required to unravel the tissue-specific effects after acute versus chronic treatment in different metabolically active tissues. For example, negative effects of chronic mTOR inhibition have been reported in several studies using mTOR inhibitors; therefore, it is conceivable that rapamycin therapy could impair the adaptation of β cells to insulin resistance or have yet

unrecognized off-target effects, resulting in diabetes (Fraenkel et al. 2008; Yang et al. 2011).

In the brain, chronic mTOR activation contributes to Aβ and tau protein aggregation; evidence continues to suggest a role of protein accumulation contributing to pancreatic dysfunction in type 2 diabetes as well. Amylin, also known as islet amyloid polypeptide (IAPP), is a 37 amino acid peptide hormone that is derived by proteolytic cleavage of a precursor protein, called islet amyloid precursor protein, and is co-secreted with insulin from pancreatic β cells (Opie 1901; Westermark et al. 1986, 1987; Cooper et al. 1987a, b). Amylin plays a role in glycemic regulation by inhibiting insulin and glucagon secretion, slowing gastric emptying and promoting satiety. Amylin accumulates in pancreatic islets forming amyloid deposits that are present in ~95% of type 2 diabetes patients (Lopes et al. 2004). Aggregated amylin is cytotoxic and is positively correlated with the clinical severity of type 2 diabetes, β cell loss, and negatively correlated with insulin secretion and glucose metabolism (Cooper et al. 1987a, b; Hull et al. 2004) suggesting a causal role in the islet dysfunction. The proteolytic processing of amylin is akin to Aβ production by amyloid precursor protein in Alzheimer's disease brain tissue. Moreover, Aβ and amylin deregulate similar proteins in their respective tissues, of which about 25% are associated with mitochondrial dysfunction (Lim et al. 2010). Collectively, these studies suggest that pathophysiology of protein aggregation is similar between these diseases. Moreover, in 2010, autopsy performed on patients with Alzheimer's disease found hyperphosphorylated tau, as well as amyloid protein, in pancreatic tissue (Miklossy et al. 2010).

A common feature of Alzheimer's disease and type 2 diabetes is APP accumulation and tau hyperphosphorylation co-localizing with components of the JNK pathway in neurons and islet cells, respectively (Thedieck et al. 2007; Tramutola et al. 2015). Hyperphosphorylated tau accumulation, along with Aβ, is hallmark of Alzheimer's disease pathogenesis (Orr et al. 2017). Studies have since characterized the biochemistry of tau protein in β cell lines and revealed six unique tau isoforms with a balanced 1:1 ratio of 3R and 4R tau isoforms (Maj et al. 2016), but with higher molecular weight than that of cerebral cortex tau isoforms (Maj et al. 2010). Human insulinomas, pancreatic tumors comprised of β cells that overproduce insulin, display elevated tau expression with an imbalance in isoforms, specifically increased 3R isoforms (Maj et al. 2016), which is hallmark of many neurodegenerative tauopathies (Orr et al. 2017). Because tau protein stabilizes microtubules, elevated tau expression in pancreatic β cells would presumably decrease insulin secretion. Experimental evidence indeed supports this notion: exposing pancreatic cell lines to sera derived from diabetic patients modestly increased tau expression (Maj et al. 2010), and overexpressing tau in vitro significantly increases β cell proliferation and decreases insulin secretion (Maj et al. 2016). In neurons, tau is primarily expressed in axons where it stabilizes microtubules to allow for proper delivery of cargo throughout the cell. The microtubules are nucleated at the centrosome-based microtubule organizing center and extend to the cell periphery. However, in pancreatic β cells, microtubules form a dense meshwork with the Golgi acting as the microtubule organizing center. This microtubule configuration limits

granule density at the cell periphery and subsequently glucose-stimulated insulin secretion (Zhu et al. 2015). High glucose destabilizes microtubules and decreases microtubule density allowing for glucose-stimulated insulin secretion (Zhu et al. 2015). In diabetic mice, dysfunctional β cells display elevated microtubule density, which decreases insulin secretion. These data indicate that tau expression and microtubule regulation in β cells plays an important role in pancreatic dysfunction and type 2 diabetes pathogenesis.

10.5   Concluding Remarks

Dr. Alois Alzheimer initially described Alzheimer's disease as the histological accumulation of Aβ-containing plaques and tau-containing neurofibrillary tangles concomitant with neurodegeneration and dementia. Since this seminal report in 1906, basic scientists and physicians have primarily approached Alzheimer's disease as a brain-specific disease. However, Alzheimer's disease increasingly is being recognized as a complex systemic disorder involving numerous tissues that manifest extensive comorbid health conditions. The finding that type 2 diabetes doubles the risk for developing Alzheimer's disease is one such example that has prompted scientists to investigate pathological changes in peripheral tissues and systems. This slowly emerging change in dogma is accompanied by a new vision for therapeutic treatment. Instead of targeting a single aberrant gene or protein, biomedical researchers are beginning to witness benefits of modulating molecules that are highly integrated into numerous cellular pathways across tissues. Pathologically hyperactive mTOR activity is a common mechanism linking Alzheimer's disease and type 2 diabetes across multiple tissue types. Therefore, targeting mTOR epitomizes this new strategy: therapeutic modulation improves Alzheimer's disease pathogenesis (Caccamo et al. 2010, 2013) while simultaneously delivering numerous health benefits, most notably extended life span (Vellai et al. 2003; Jia et al. 2004; Kapahi et al. 2004; Kaeberlein et al. 2005; Powers et al. 2006; Harrison et al. 2009; Selman et al. 2009; Sharp and Strong 2010).

Embarking on this new treatment era does not come without challenges. Therapeutic approaches to precisely alter only pathological, but not physiological, mTOR signaling have not yet been developed. Since mTOR is a highly integrated signaling pathway that regulates cellular metabolism and physiology across multiple tissues, maintaining a physiological level of mTOR signaling will be critical to the success of mTOR inhibitors as a pharmacotherapeutic intervention in Alzheimer's disease. While rapamycin has celebrated numerous successes, a major obstacle is that chronic rapamycin treatment induces insulin resistance in animal models (Sarbassov et al. 2006; Orr et al. 2014) and human subjects (Teutonico et al. 2005; Blagosklonny 2013), likely through the inhibition of mTORC2 (Sarbassov et al. 2006). Nonetheless, investigators are continuing to devise strategies to overcome these pitfalls. For instance, since mTORC1 is more sensitive to low-dose and short-term rapamycin treatment, intermittent rapamycin dosing strategies are being

employed to circumvent the negative effects of mTORC2 inhibition, and this dosing strategy has had success in both animal models (Arriola Apelo et al. 2016a, b) and humans (Mannick et al. 2014).

While the need for research and therapeutics targeting brain-specific pathologies in Alzheimer's disease remains relevant, expanding the research focus to include common signaling pathways that are affected across organ systems offers a complementary approach to therapeutic discovery. Moreover, identifying and targeting the common molecular mechanisms linking Alzheimer's disease with common comorbidities, such as type 2 diabetes, may provide further insight into the role of mTOR and potentially uncover additional molecules for therapeutic intervention. This promising research approach offers hope to identify treatments that mitigate brain pathologies while simultaneously alleviating comorbid medical conditions that plague patients with Alzheimer's disease.

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