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Review

Ghrelin in Alzheimer's disease: Pathologic roles and therapeutic implications

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ABSTRACT

Ghrelin, which has many important physiological roles, such as stimulating food intake, regulating energy homeostasis, and releasing insulin, has recently been studied for its roles in a diverse range of neurological disorders. Despite the several functions of ghrelin in the central nervous system, whether it works as a therapeutic agent for neurological dysfunction has been unclear. Altered levels and various roles of ghrelin have been reported in Alzheimer's disease (AD), which is characterized by the accumulation of misfolded proteins resulting in synaptic loss and cognitive decline. Interestingly, treatment with ghrelin or with the agonist of ghrelin receptor showed attenuation in several cases of AD-related pathology. These findings suggest the potential therapeutic implications of ghrelin in the pathogenesis of AD. In the present review, we summarized the roles of ghrelin in AD pathogenesis, amyloid beta (Aβ) homeostasis, tau hyperphosphorylation, neuroinflammation, mitochondrial deficit, synaptic dysfunction and cognitive impairment. The findings from this review suggest that ghrelin has a novel therapeutic potential for AD treatment. Thus, rigorously designed studies are needed to establish an effective AD-modifying strategy.

1. Introduction

Alzheimer's disease (AD) is the most common type of irreversible dementia and accounts for 50–77% of all cases of dementia (Barker et al., 2002; Francis et al., 1999; Holtzman et al., 2011). AD is a chronic progressive neurodegenerative disease that is characterized by cognitive impairment with pathological changes including the abnormal accumulation of amyloid plaques composed of amyloid beta (Aβ) and neurofibrillary tangles (NFT) containing aggregated tau protein in the brain (Brier et al., 2016; Haass and Selkoe, 2007; Roberson et al., 2011; Selkoe, 1991; Spires-Jones and Hyman, 2014). AD has been the focus of numerous researchers and studied extensively for over a century; numerous research has been conducted on the pathophysiology (Durazzo et al., 2014; Kumar et al., 2015; Lindsay et al., 2002; Swerdlow, 2007), clinical criteria (Cummings, 2004; Forstl, 1998; Nervi et al., 2008; Nestor et al., 2004), and genetic factors of AD (Bird, 2008; Van Cauwenberghe et al., 2016). So far, some extensively researched AD therapeutic approaches are including cholinesterase inhibitors, N-methyl D-aspartate (NMDA) receptor antagonists (Birks, 2006; Butterfield and Pocernich, 2003;

Abbreviations: AD, Alzheimer's disease; AChE, acetylcholinesterase; acyl-ghrelin, acylated ghrelin; AMPK, AMP-induced protein kinase; apo, apolipoprotein; APP, amyloid precursor protein; ARC, arcuate nucleus; Aβ, amyloid beta; AβO, Aβ oligomers; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; CaMKII, Ca2+/calmodulin-dependent protein kinase II; CDK, cyclin-dependent kinase; CNS, central nervous system; DG, dentate gyrus; DRN, dorsal raphe nucleus; ERK, extracellular-signal-regulated kinase; FACS, fluorescence activated cell sorting; GABA, γ-aminobutyric acid; GHS-R, growth hormone secretagogue-receptor; GHRP-6, growth hormone-releasing peptide 6; GKO, ghrelin knockout; GOAT, O-acyltransferase; GPCR, G-protein-coupled receptor; GSK, glycogen synthase kinase; i.c.v, intracerebroventricular; IGF-1, insulin-like growth factor 1; IL, interleukin; LPS, lipopolysaccharide; LRP, low density lipoprotein receptor-related protein; LTD, long-term depression; LTP, long-term potentiation; MACRO, macrophage receptor with collagenous structure; MAPK, mitogen-activated protein kinase; MCI, mild cognitive impairment; MPTP, 1-methyl-4-phenyl-12,3,6-tetrahydropyridine; MSG, monosodium L-glutamate; NSC, neural stem cell; NFT, neurofibrillary tangles; NMDA, *N*-methyl D-aspartate; p75NT, p75 neurotrophin; PD, Parkinson's disease; PI3-K, phosphoinositide 3-kinase; PLC, phospholipase C; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; SGZ, subgranular zone; UCP2, uncoupling protein 2; α2M, α2-macroglobulin

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McGleenon et al., 1999; Parsons et al., 2013), immunotherapies (Adolfsson et al., 2012; Imbimbo et al., 2012; Malpass, 2013; Panza et al., 2012), and preventive therapies (Bateman et al., 2011). Currently, the cholinesterase inhibitors and NMDA receptor antagonists are the only therapeutic approaches approved by the Food and Drug Administration. Unfortunately, they can only delay the progression of AD pathogenesis (Grossberg, 2003; Rountree et al., 2009). Moreover, studies have shown that the immunotherapies may lead to adverse effects such as meningoencephalitis (Gilman et al., 2005) and microhemorrhage in the brain (Wilcock et al., 2007, 2004). Despite the aforementioned efforts, a disease-modifying therapy has not been established yet (Huang and Mucke, 2012). Therefore, there is a need to establish a safe and substantial treatment strategy for AD.

Ghrelin is an orexigenic hormone that binds to its growth hormone secretagogue-receptor (GHS-R) and regulates food intake (Nogueiras et al., 2008). Ghrelin is a 28-amino-acid peptide that is mainly released from stomach when induced by hunger (Stengel and Tache, 2012). Although, several studies have reported the expression of ghrelin in the central nervous system (CNS), inconsistency exists among the findings regarding the expression of ghrelin in the CNS (Cabral et al., 2017). In the hypothalamus, ghrelin regulates energy homeostasis, metabolism, and body weight (Nogueiras et al., 2008). In addition, ghrelin has various extra-hypothalamic functions as well as pathophysiological roles (Andrews, 2011). As a multi-functional hormone, ghrelin is involved in the stimulation of growth hormone release, insulin sensitivity, muscle homeostasis, cardio-protection, and bone metabolism (Chollet et al., 2009; Pradhan et al., 2013). Native ghrelin (des-acyl-ghrelin) undergoes post-translational acylation by ghrelin O-acyltransferase (GOAT) to be converted into acylated ghrelin (acyl-ghrelin) (Al Massadi et al., 2011). Although the receptor of des-acyl-ghrelin is unknown, it is the most abundant form in the circulatory system (Delporte, 2013). Only acyl-ghrelin is an endogenous ligand for GHS-R1a (Delporte, 2013; Gauna et al., 2007; Staes et al., 2010), and the neuronal function of ghrelin is mediated by GHS-R1a (Lopez Soto et al., 2015; Ribeiro et al., 2014; Yang et al., 2011). In arcuate nucleus of the hypothalamus, ghrelin binds to GHS-R1a receptors and stimulates appetite (Cowley et al., 2003; Howick et al., 2017). Furthermore, while promoting the food intake, ghrelin modulates the synaptic input organization and activity of midbrain dopamine neurons (Abizaid et al., 2006). This stimulation is very similar to the ghrelin-induced interoceptive cues during the caloric restriction (Dhurandhar et al., 2013).

Interestingly, numerous studies have reported that ghrelin and ghrelin agonists improve diverse AD-related pathogenesis such as Aβ burden, tau hyperphosphorylation, synaptic loss, neuroinflammation, and cognitive dysfunction in several animal model of AD (Chen et al., 2010; Dhurandhar et al., 2013; Eslami et al., 2018; Jeong et al., 2018; Kang et al., 2015; Kunath et al., 2015; Moon et al., 2014; Santos et al., 2017). Therefore, therapeutic strategies using ghrelin are gaining considerable attention for their neuroprotective and possible additional beneficial effects on the AD pathogenesis (Dos Santos et al., 2013; Eslami et al., 2018; Gahete et al., 2010; Sevigny et al., 2008). Additionally, ghrelin modulates the tau phosphorylation, which is another major cause of AD pathogenesis in the hippocampal neurons (Chen et al., 2010). Most importantly, despite the accumulation of this evidence, no clinical trials have evaluated the efficacy of ghrelin on the AD pathogenesis (Collden et al., 2017; Seminara et al., 2018). Therefore, reviewing the effects of ghrelin in AD may provide an attainable treatment that affects the AD progression. In this review, we included and summarized recent discoveries regarding the roles of ghrelin and its receptor agonists in the attenuation of several AD-related pathologies. In addition, we discussed the potential therapeutic applications of ghrelin and its receptor agonists in the AD treatment.

2. The relevance of ghrelin and its receptor in AD

2.1. Ghrelin

Several studies have reported an association between ghrelin levels and AD pathology (Cao et al., 2018; Gahete et al., 2010). It has been clinically reported that ghrelin mRNA levels decrease in the temporal lobe of AD patients (Gahete et al., 2010). It has also been found that circulating acyl-ghrelin is associated with cognitive dysfunction in predementia AD. While total ghrelin level is not different between healthy controls and patients with mild cognitive impairment (MCI), the level of acyl-ghrelin in patients with MCI is significantly increased compared with that of the controls (Cao et al., 2018). Additionally, there is a sexual difference in basal ghrelin levels. Although male and female AD patients show similar levels compared with the controls, the male AD patients show significantly lower area-under-the-curve for ghrelin in the oral glucose tolerance test (Theodoropoulou et al., 2012). Notably, the patients with frontotemporal dementia show significantly lower levels of ghrelin the patients with AD do not show altered ghrelin levels (Woolley et al., 2014). In addition, a Japanese population study reports a genetic relationship between AD and ghrelin nucleotide polymorphisms (Shibata et al., 2011). Collectively, these findings imply the need to examine the levels of des-acyl-ghrelin and acyl-ghrelin separately in AD.

2.2. Growth hormone secretagogue-receptor (GHS-R)

In mice and rats, GHS-R is widely distributed in various organs including the spinal and dorsal vagal complexes and parasympathetic preganglionic neurons (Guan et al., 1997; Zigman et al., 2006). In addition, the expression of GHS-R mRNA is observed not only in the hippocampus, substantia nigra, and ventral tegmental area but also in multiple hypothalamic nuclei and the pituitary gland, which are important for food intake and maintaining body weight (Guan et al., 1997; Lattuada et al., 2013; Zigman et al., 2006).

In humans, GHS-R1a expression has been reported in the pituitary gland, hypothalamus, and hippocampus (Guan et al., 1997). Interestingly, unlike ghrelin and GHS-R1b, which are widely distributed in various peripheral tissues including the stomach, a functional receptor for acyl-ghrelin (GHS-R1a) is predominantly expressed in the pituitary gland (Gnanapavan et al., 2002; Guan et al., 1997; Liu et al., 2006; Zigman et al., 2006). A number of previous studies have suggested that ghrelin receptors are expressed in the CNS as well as in the peripheral organs (Fig. 1). When ghrelin binds to GHS-R1a (Bockaert and Pin, 1999; Lattuada et al., 2013), its α-helical transmembrane protein profoundly changes (Camina, 2006). Ghrelin-activated GHS-R1 activates the extracellular-signal-regulated kinase (ERK) 1/2 through phospholipase C (PLC) and protein kinase C (Mousseaux et al., 2006). The truncated ghrelin receptor polypeptide does not participate in ERK1/2, but attenuates the activation of phosphatidylinositol-specific PLC (Chu et al., 2007). Members of the seven transmembrane receptors are expressed in the ghrelinergic cells, and some ligands that inhibit the ghrelin secretion (Engelstoft et al., 2013). In addition, the β1-adrenergic receptors expressed in the ghrelinergic cells acts on sympathetic norepinephrine, causing the ghrelin secretion (Mundinger et al., 2006; Zhao et al., 2010). In particular, studies using the GHS-R-specific monoclonal antibody have provided evidence into the role of GHS-R in neurodegenerative diseases by showing that the expression of GHS-R is dependent on the developmental stage and brain region (Lattuada et al., 2013). Remarkably, the expression of GHS-R1a is significantly reduced in the inferior and superior region of the temporal lobe of AD patients when compared that of the controls (Gahete et al., 2010). These results suggest that ghrelin and its receptors may have important roles in AD.

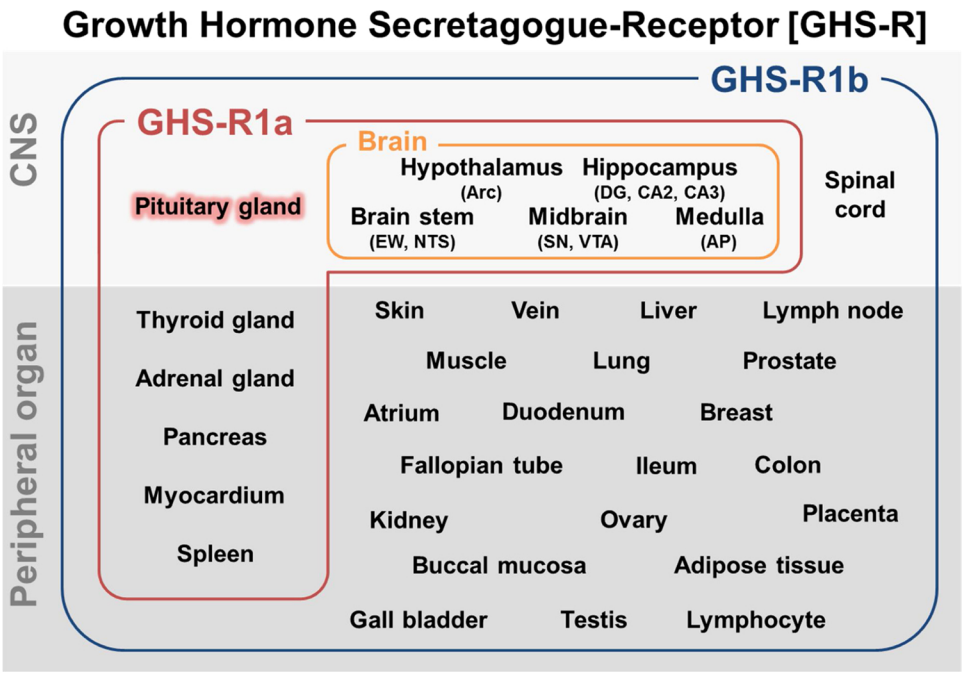

Fig. 1. Expression of Ghrelin Receptors.
Ghrelin receptors GHS-R1a and GHS-R1b are expressed in various cells throughout the central nervous system (CNS) and peripheral organs. In the CNS, GHS-R1a is expressed in the of the pituitary gland while the rest is weakly expressed in the hippocampus (DG, CA2, and CA3), hypothalamus (Arc), midbrain (SN, VTA), medulla oblongata (AP), and brain stem (EW, NTS). GHS-R1b is also expressed in the pituitary gland, midbrain, hypothalamus, medulla oblongata, brain stem, spinal cord. In the peripheral organs, GHS-R 1a is expressed in the thyroid gland, pancreas, spleen, myocardium, and adrenal gland. GHS-R 1b is also expressed in the skin, myocardium, thyroid, pancreas, ileum, colon, liver, breast, spleen, duodenum, placenta, lung, adrenal, buccal mucosa, lymph node, gall bladder, atrium, lymphocytes, kidney, prostate, fallopian tube, vein, muscle, ovary, testis, and adipose tissue. AP: Area postrema, Arc: Arcuate nucleus, DG: dentate gyrus, DVC: dorsal vagal complex, EW: Edinger–Westphal nucleus, GHS-R: growth hormone secretagogue-receptor, HIP: hippocampus, NTS: Nucleus of the solitary tract, SN: substantia nigra, TL: Temporal lobe, VTA: ventral tegmental area.

3. The association of ghrelin with AD-related pathologies

3.1. Aβ homeostasis

One of the most supported hypotheses for AD pathogenesis is the Aβ cascade hypothesis, which postulates that the Aβ peptide accumulates excessively to form Aβ plaques in the brain (Hardy and Higgins, 1992). Three proteases, α-, β-, and γ-secretases, are involved in the cleavage of the amyloid precursor protein (APP) into Aβ proteins. Sequential cleavages of APP by β- and γ-secretases are responsible for the Aβ protein generation (Cummings, 2004). Especially, the soluble Aβ oligomers (AβO) are deemed to be the primary triggers of AD-related pathology, such as inflammation, neuronal loss, synaptic dysfunction, and cognitive deficits (Haass and Selkoe, 2007; Kayed et al., 2003; Querfurth and LaFerla, 2010; Tanzi, 2005). The degradation or elimination of toxic Aβ is mediated by proteases such as neprilysin, insulin-degrading enzyme, matrix metalloproteinase, and plasmin (Querfurth and LaFerla, 2010; Wostyn et al., 2011). However, the autophagic pathway, one of the Aβ degradation mechanisms, is impaired in the brain of patients with AD and AD animal models; thus, Aβ-containing autophagosomes accumulate in the neurons without the Aβ degradation through autolysosome maturation (Banerjee et al., 2010; Nixon, 2007; Wolfe et al., 2013; Yu et al., 2005). Because the disruption of Aβ homeostasis is a risk factor for AD, the process of Aβ generation and degradation has been regarded as an important therapeutic target for AD (Cummings et al., 2018; Cummings, 2004; Querfurth and LaFerla, 2010).

Interestingly, both ghrelin receptor agonist (LY444711)-treated and calorically restricted groups show significant decreases in Aβ accumulation and Iba-1 (marker of microglia) immunoreactivity in the hippocampus of APP^{Swe} transgenic mice (Dhurandhar et al., 2013). In addition, Aβ accumulation, neuroinflammation, and neuronal loss in the deep cortical layer in Aβ-overexpressing 5XFAD mice are alleviated by the administration of MK-0677, an agonist of GHS-R1a (Jeong et al., 2018). However, inconsistent findings are reported that the administration of the ghrelin receptor analog [D-Lys (3)]-growth hormone-releasing peptide 6 (GHRP-6) reduce the levels of $Aβ_{1-42}$ and acetylcholinesterase (AChE) that are increased in the hippocampus. [D-Lys (3)]-GHRP-6 also restores the abnormal levels of metabolites such as glucose and cholesterol and spatial disorientation in a monosodium L-glutamate (MSG)-treated obese rat model (Madhavadas et al., 2014). Unlike ghrelin mimetics, the administration of ghrelin in 5XFAD mice shows no significant difference in Aβ burden despite the increased hippocampal neurogenesis and reduced microgliosis (Moon et al., 2014). Remarkably, in several studies, ghrelin has been reported to exhibit beneficial effects via regulation of autophagy (Bonfili et al., 2013; Mao et al., 2015b; Tong et al., 2012). Especially, ghrelin deficient mice (*GOAT* gene knockout) have reduced microtubule-associated protein light chain 3-II (LC3-II), implying decreased autophagy (Zhang et al., 2015). In addition, treatment with ghrelin in the *APP* gene-transfected neuronal cell line restores proteasome function, which promotes the autophagy pathway (Cecarini et al., 2016). These studies suggest that ghrelin and its receptors may be involved directly or indirectly in reducing Aβ accumulation. However, the mechanism involved in Aβ accumulation and degradation in AD brains is unclear. Therefore, investigation of the role of ghrelin in Aβ homeostasis is necessary to enhance the therapeutic prospects of patients with AD (Fig. 2).

3.2. Tau hyperphosphorylation

Aggregates of hyperphosphorylated tau protein are one of the major pathological features of AD (Scheltens et al., 2016). Hyperphosphorylated tau proteins detach from the microtubules, resulting in the destabilization of microtubules and forming aggregated NFT (Avila, 2006; Iqbal et al., 2005). Similar to Aβ, hyperphosphorylated tau intermediates cause cytotoxicity and cognitive impairment (Khlistunova et al., 2006; Santacruz et al., 2005). Various kinases are involved in the tau phosphorylation, and these kinases interact closely with numerous factors including glucose metabolism, insulin, and ghrelin (Chen et al., 2010; Lesort et al., 1999; Planel et al., 2004). Furthermore, AD is associated with brain insulin-resistance that results in abnormal glucose utilization (de la Monte, 2012).

Ghrelin reduces abnormal phosphorylation of tau^{ser199} and modulates insulin sensitivity by phosphorylation of AKT, which is downstream of phosphatidylinositol 3-kinase (PI3-K), and glycogen synthase kinase (GSK)-3β in a normal or high glucose environment (Chen et al., 2010). In the AD rat model induced by intracerebroventricular (i.c.v)

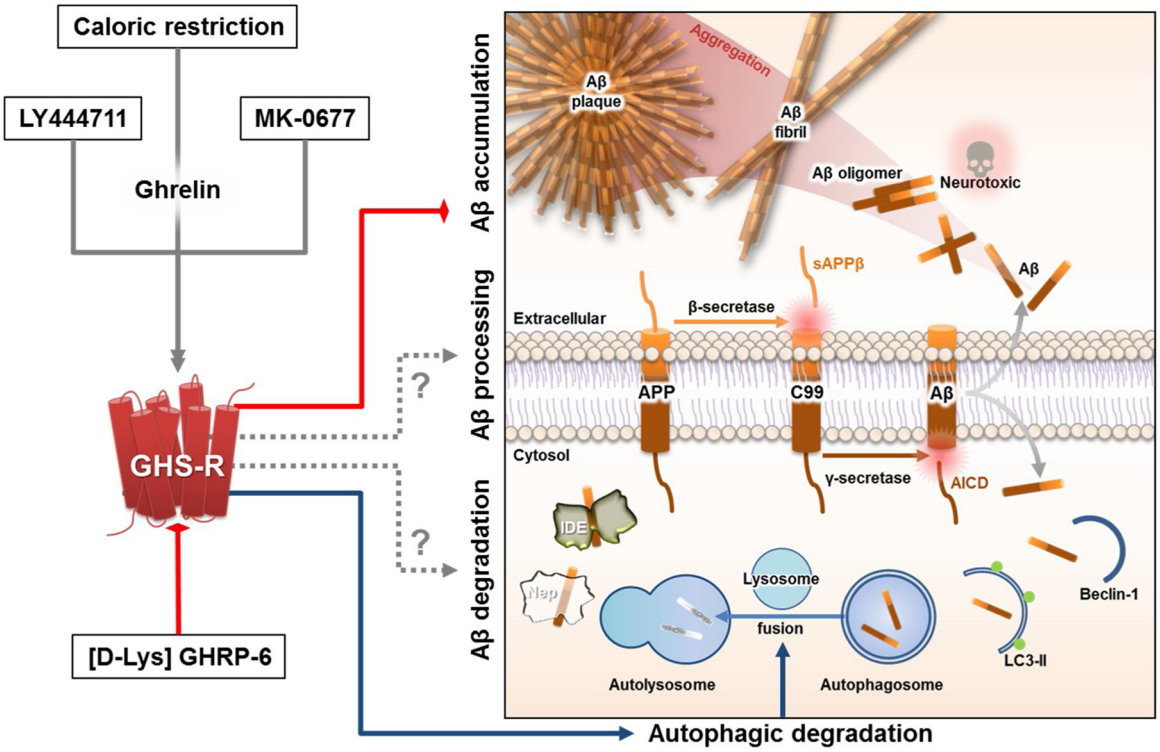

Fig. 2. The Effect of Ghrelin on Aβ homeostasis.
One of the primary causes of amyloid cascade in AD is considered to be the disruption of Aβ homeostasis, a constant process of production and elimination of Aβ. The Aβ production is mediated through a sequential cleavage of amyloid precursor protein (APP) by β-secretase and γ-secretase. Aβ aggregates into oligomers and fibril form and later becomes Aβ plaque, one of the histopathological features of AD. These oligomers and intermediates formed in the process are toxic to the synapse and neurons. Aβ is removed through autophagic degradation by beclin-1 and microtubule-associated protein light chain 3-II (LC3-II) and enzymatic proteolysis by insulin-degrading enzyme (IDE) and neprilysin (Nep). GHS-R stimulation through ghrelin and its analogs inhibits the accumulation of Aβ and promotes the autophagic degradation of Aβ-containing autophagosome. However, the role of ghrelin in the enzymes involved in Aβ degradation and amyloidogenic pathway is not known. AICD: amyloid intracellular domain.

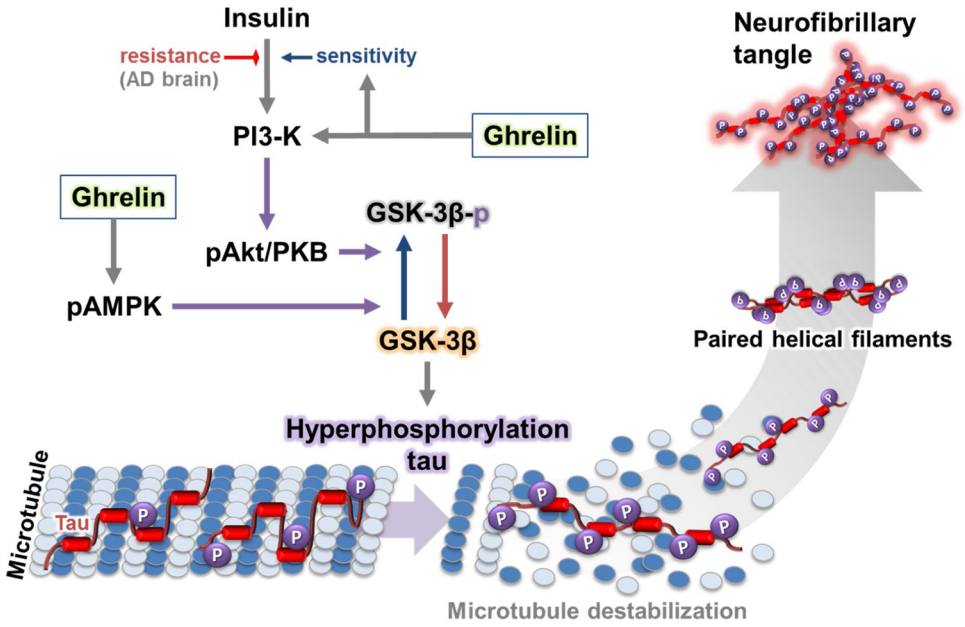

Fig. 3. The Effect of Ghrelin on Tau Accumulation.
Hyperphosphorylated tau and its aggregate neurofibrillary tangle are regarded as pathological features and causes of AD together with Aβ. Among the various kinases, glycogen synthase kinase-3β (GSK-3β) is a major mediator of tau hyperphosphorylation. Ghrelin inhibits hyperphosphorylation of tau by phosphorylating GSK-3β through the AMPK pathway and PI3-K/Akt pathway, respectively. AMPK: 5′ adenosine monophosphate-activated protein kinase, GSK-3β: glycogen synthase kinase-3β, PI3-K: phosphatidylinositol 3-kinase, PKB: protein kinase B.

infusion of Aβ and acyl-ghrelin, phosphorylation of AMP-induced protein kinase (AMPK) and GSK-3β and glucose metabolism are improved, and hyperphosphorylation of tau, Aβ deposition, and memory impairment are inhibited (Kang et al., 2015). In addition, an intravenous infusion of des-acyl-ghrelin in humans significantly improves glucose metabolism (Benso et al., 2012). These results suggest that ghrelin may regulate the activity of the kinases that are involved in phosphorylation (Fig. 3). Although several studies have reported the roles of ghrelin in regulating the activity of a variety of kinases such as mitogen-activated protein kinase (MAPK) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which are associated with tau phosphorylation and their neurotoxic ability, the direct mechanisms of effects of ghrelin on tau

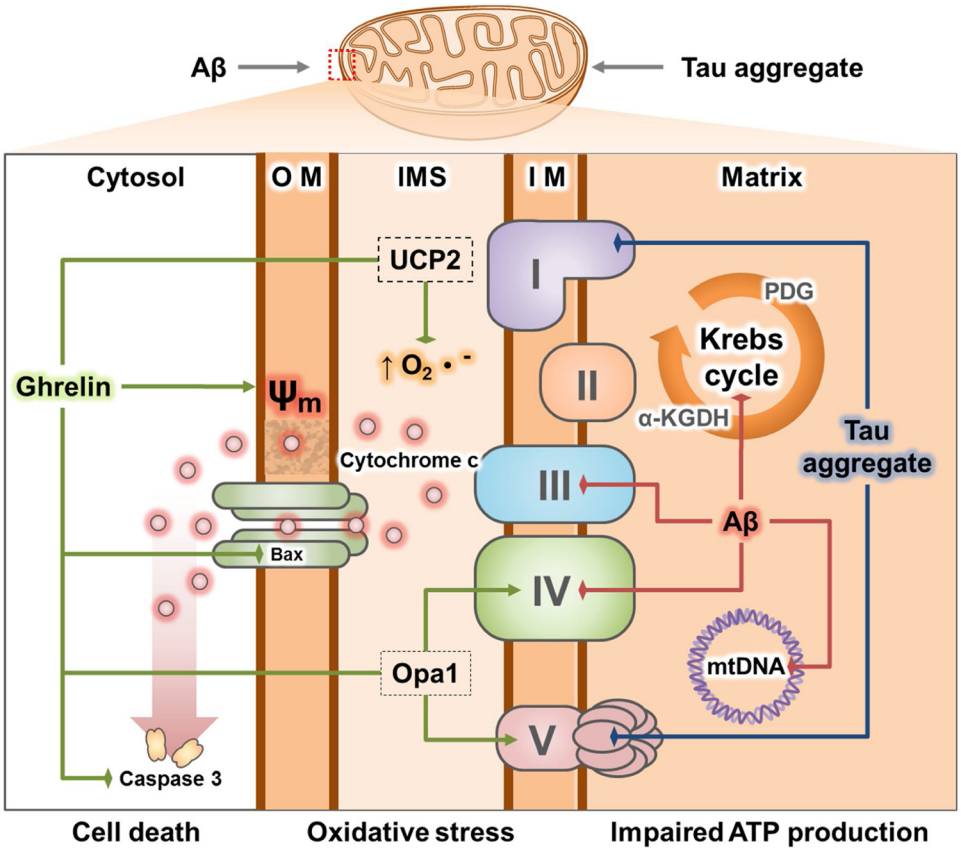

Fig. 4. The Effect of Ghrelin on Mitochondrial Dysfunction in Alzheimer's Disease.
Aβ attacks the electron transport complex III/IV (succinate-cytochrome c reductase/cytochrome c oxidase), and it is involved in DNA fragmentation and Krebs cycle impairment. Tau is involved in the dysfunction of complex I/V. These mitochondrial dysfunctions lead to defective ATP production and massive oxidative stress. The release of cytochrome c through permeability-transition (ψ_m) pores or Bax oligomeric pores activates caspase 3 and initiates apoptotic cell death. Ghrelin protects from mitochondrial dysfunction by inhibiting cytochrome c release and caspase 3 activity by increasing the Bcl-2/Bax ratio. In addition, ghrelin not only protects from the damage of the electron transport complex by mediating optic atrophy type 1 (Opa1), but also regulates oxidative stress through uncoupling protein 2 (UCP2). Bax: bcl-2-associated X protein, OM: outer membrane, IM: inner membrane, IMS: intermembrane space, αKGDH: α-ketoglutarate dehydrogenase, PDG: pyruvate dehydrogenase.

hyperphosphorylation is still not fully elucidated (Chen et al., 2011; Leugers et al., 2013; Wei et al., 2015; Yeh et al., 2005).

3.3. Mitochondrial dysfunction

Mitochondrial dysfunction and oxidative stress are well known as major causes of apoptosis (Chang et al., 2010; Joza et al., 2001; Kroemer and Reed, 2000; Wang and Youle, 2009). Notably, mitochondria isolated from patients with AD not only have structural damage with high levels of oxidative mitochondrial DNA damage but also have Aβ accumulation (Hirai et al., 2001; Pinho et al., 2014). Similarly, the distribution of mitochondrial Aβ in APP-expressing mice is correlated with the AD-related pathology (Caspersen et al., 2005). Aβ attacks the electron transport complex III/IV (succinate-cytochrome c reductase/cytochrome c oxidase) (Caspersen et al., 2005). In particular, Aβ induces potent mitochondrial dysfunction in synapses, leading to a decrease in synaptic vesicle protein (synaptophysin) and actin (Mungarro-Menchaca et al., 2002). In addition, tau^{P301L} transgenic mice also showed significantly reduced levels of mitochondrial complex I/V (NADH-ubiquinone oxidoreductase/ATP synthase) and impaired mitochondrial function in the brain (David et al., 2005). These key mitochondrial enzymes damaged by Aβ and tau impair ATP production and membrane potential. In addition, overload of superoxide radicals in the mitochondria cause oxidative stress and release of cytochrome c, which initiates apoptosis (Aleardi et al., 2005; Caspersen et al., 2005; Hauptmann et al., 2006; Rhein et al., 2009). These changes are accompanied by neuroinflammation and neuronal death that cause progression of AD.

In hippocampal and hypothalamic cells, ghrelin exerts protective effects by mitigating mitochondrial dysfunction and oxidative stress induced by AβO in a GHS-R1a-dependent manner (Gomes et al., 2014; Martins et al., 2013). The molecular mechanisms of ghrelin on mitochondrial toxicity induced by Aβ or tau are still debated, but several mechanisms involved in ghrelin-mediated mitochondrial protection have been reported (Chung et al., 2007; Lee et al., 2011). In oxygen-glucose deprivation-induced mitochondrial damage of primary hypothalamic neurons, ghrelin not only increased the Bcl-2/Bax ratio but also inhibited the release of cytochrome c and the activity of caspase 3 (Chung et al., 2007). In hydrogen peroxide-treated primary oligodendrocytes, ghrelin treatment ameliorated apoptosis by increasing activation of ERK and inhibiting activation of p38MAPK (Lee et al., 2011). Similarly, des-acyl-ghrelin restored the expression of damaged electron transport system complexes IV/V via upregulation of optic atrophy type 1 protein in the liver of an ischemia/reperfusion rat model (Rossetti et al., 2017). In gastric ischemic injury, ghrelin alleviates tissue congestion and ulceration through antioxidant activity demonstrated by oxidative stress markers such as thiobarbituric acid reactive substance and glutathione (El Eter et al., 2007). Another study reported that the neuroprotective effect of ghrelin on the midbrain dopaminergic neurons in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced Parkinson's disease (PD) model is dependent on the regulation of mitochondria-derived oxidative stress via uncoupling protein 2 (UCP2) (Andrews et al., 2009). Furthermore, administration of ghrelin during ischemic injury of the forebrain protected the hippocampus accompanied with upregulation of UCP-2 (Liu et al., 2009). These results suggest that ghrelin may potentially mitigate mitochondrial dysfunction and oxidative stress in patients with AD through mitochondrial protection (Fig. 4). However, clearer demonstration of the molecular functions of ghrelin in mitochondria is required.

3.4. Neuroinflammation

Over-activated glial cells co-located with Aβ plaques are the biochemical markers for AD brains (Akiyama et al., 2000). Even prior to the development of AD symptoms, activated glial cells gather in Aβ aggregation sites and Aβ plaques (Boza-Serrano et al., 2018; Heneka

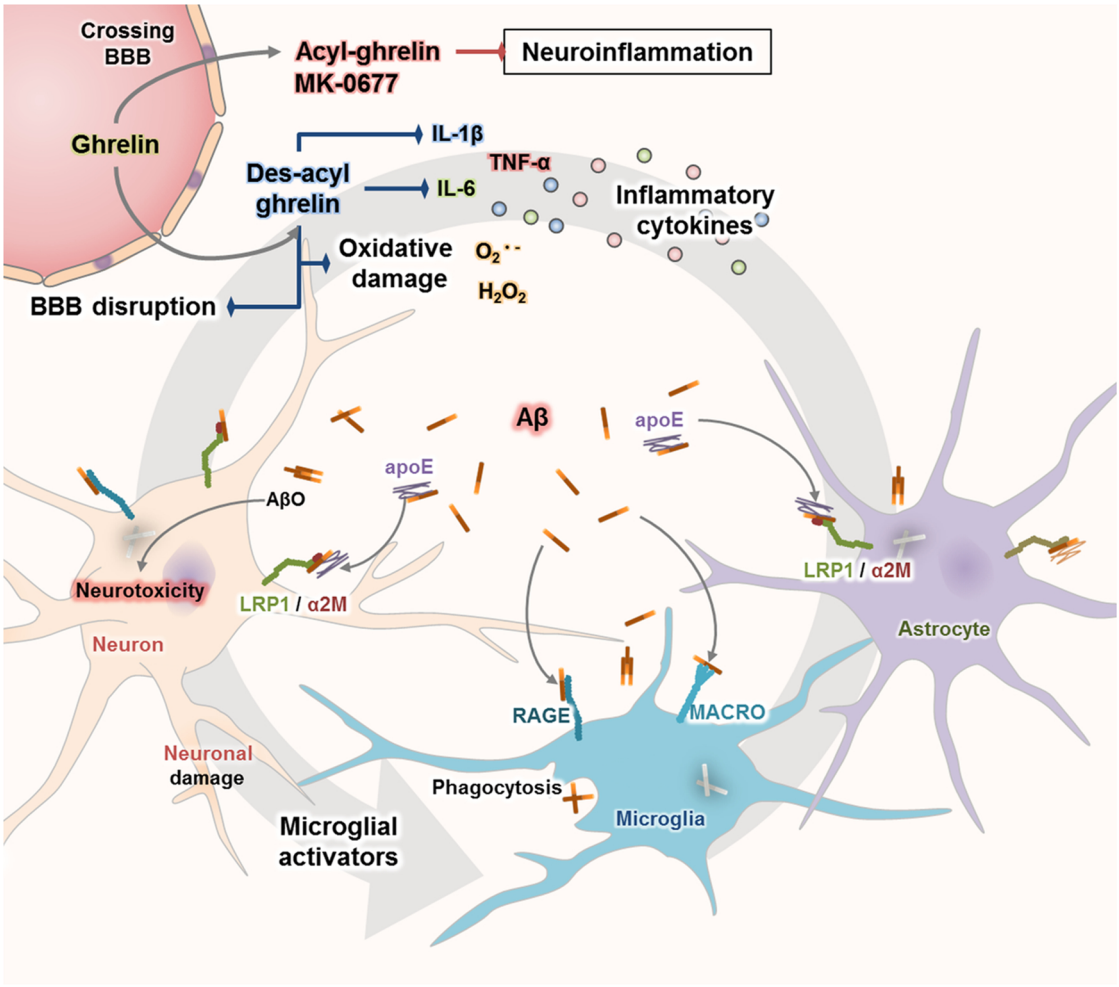

Fig. 5. The Effect of Ghrelin on Neuroinflammation in Alzheimer's Disease.
Microglia and astrocytes degrade and internalize Aβ through phagocytosis and receptors such as LRP, RAGE, and MACRO. However, chronic and excessive sensitization of glial cells by Aβ induces neuroinflammation though inflammatory cytokines and oxidative stress. Soluble oligomers of Aβ are known to be the most neurotoxic form. Neuronal death acts as an activator of glial cells and forms a positive feedback loop for neuroinflammation. Ghrelin, which can cross the blood–brain barrier (BBB), not only inhibits proinflammatory cytokines and oxidative damage, but also alleviates BBB disruption. α2M: α2-macroglobulin, apo: apolipoprotein, LRP: lipoprotein receptor-related protein, MACRO: macrophage receptor with collagenous structure, RAGE: receptor for advanced glycation end products.

et al., 2015; Kummer et al., 2014). Microglia and astrocytes that participate in neuroinflammation mediates the immune response, leading to either neuronal death or survival (Wyss-Coray and Mucke, 2002). Initially, the immune response of microglia degrades cytotoxic substances such as Aβ through phagocytosis (Streit, 2002). However, after chronic stimulation of inflammatory triggers, the activated glial cells release inflammatory cytokines, chemokines, and reactive oxygen species (ROS) (Akiyama et al., 2000). These neurotoxic factors are responsible for neuronal damage, which causes neuronal death and the release of microglial activators such as laminin, neuromelanin, matrix metalloproteinase 3, and α-synuclein to form positive feedback loops of neurotoxicity (Block et al., 2007). In glial cells, Aβ is directly taken up via the macrophage receptor with collagenous structure (MACRO) or the receptor for advanced glycation end products (RAGE), or it is complexed with apolipoprotein (apo) E to be internalized through the low density lipoprotein receptor-related protein (LRP)1/α2-macroglobulin (α2M) (Block et al., 2007; Thal, 2012). Moreover, Aβ and its aggregates act not only as microglia activators but also as direct neurotoxic factors (Mucke and Selkoe, 2012; Qin et al., 2002). Similarly, astrocytes stimulated by Aβ can secrete acute-phase reactants such as C-reactive protein, α1-antichymotrypsin, and α2M, which can either alleviate or aggravate AD (Querfurth and LaFerla, 2010).

Ghrelin, which can cross the blood-brain barrier (BBB) (Banks et al., 2002), exhibits anti-inflammatory effects in various disease models such as PD and ischemic stroke (Baatar et al., 2011; Bayliss and Andrews, 2013; Ku et al., 2016; Moon et al., 2009a; Spencer et al., 2013). Intraperitoneal administration of acyl-ghrelin alleviates neuroinflammation, neurodegeneration, and memory deficits induced by injection of AβO into the hippocampus of mice (Moon et al., 2011). Furthermore, the treatment with des-acyl-ghrelin in N9 microglia cells that does not express GHS-R1a significantly reduce interleukin (IL)-6 and IL-1β mRNA expression induced by insoluble fibrillary Aβ, whereas human ghrelin is ineffective (Bulgarelli et al., 2009). In addition, the administration of acyl-ghrelin and MK-0677 (a ghrelin receptor agonist), alleviates $A\beta_{1\text{-}40}$-induced acute neuroinflammation and Aβ-overexpressed chronic neuroinflammation in mice respectively (Jeong et al., 2018; Santos et al., 2017). Similarly, the ghrelin administration reduces secretion of pro-inflammatory cytokines in both chronic sciatic nerve injury model and acute lipopolysaccharide (LPS) challenge models (Beynon et al., 2013; Guneli et al., 2010). The administration of des-acyl-ghrelin, but not acyl-ghrelin, protect from BBB disruption and oxidative damage induced by ischemic stroke (Ku et al., 2016). Several studies have suggested that ghrelin reduces the amount of inflammatory cytokines through suppression of NF-kB (Li et al., 2004; Qu et al., 2019; Zhou and Xue, 2009), but another study reported that ghrelin is not involved in the nuclear translocation of NF-kB in LPS-

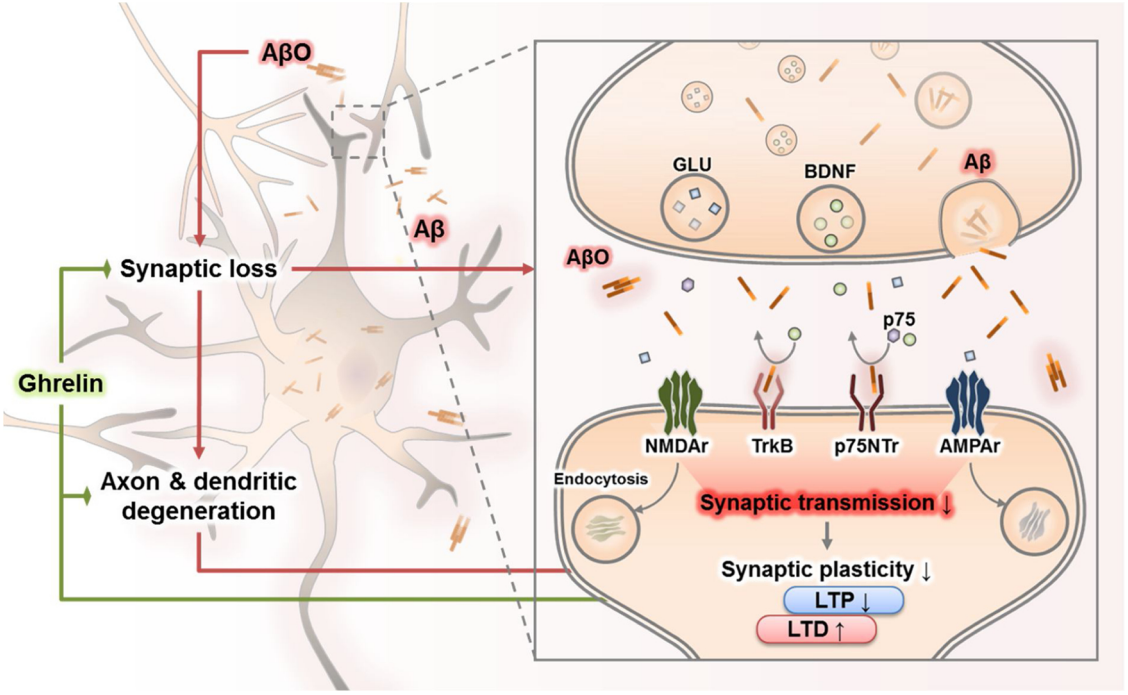

Fig. 6. The Effect of Ghrelin on Synaptic Dysfunction in Alzheimer's Disease.
Aβ and its intermediates disturb the action of neurotrophic factors and neurotransmitters on receptors. In particular, Aβ promotes endocytosis of AMPAr and NMDAr. Impaired synaptic transmission leads to synaptic loss and dendritic degeneration, and diminishes synaptic plasticity due to imbalance between LTP and LTD. Ghrelin enhances synaptic density, restores impaired synaptic plasticity and alleviates Aβ-induced synaptic degeneration. AMPAr: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, BDNF: brain-derived neurotrophic factor, GLU: glutamate, LTD: long-term depression, LTP: long-term potentiation, NMDAr: N-methyl-D-aspartate receptor, p75NT: p75 neurotrophin, p75NTr: p75 neurotrophin receptor, TrkB: tropomyosin receptor kinase B.

induced inflammatory responses (Beynon et al., 2013). Interestingly, in the carrageenan-induced inflammatory paw edema model, the central and peripheral administration of GHS-R1a agonist EP1572 is not effective at all while des-ghrelin significantly reduces hyperalgesia and paw edema in both central and peripheral administration (Sibilia et al., 2012). These results suggest that ghrelin has therapeutic potential against neuroinflammation and BBB damage induced by chronic inflammation during AD, but further studies on the detailed molecular mechanisms involved are required for therapeutic applications (Fig. 5).

3.5. Synaptic dysfunction

Synaptic dysfunction may be a major factor closely related to cognitive impairment in dementia including AD (Bereczki et al., 2018; Selkoe, 2002; Terry et al., 1991). Furthermore, altered synaptic content in the frontal lobe of AD patients has long been observed and is an early event in mild AD (Davies et al., 1987; DeKosky and Scheff, 1990; Masliah et al., 2001; Shankar and Walsh, 2009). Aβ not only reduces the action of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) but also promotes endocytosis of glutamate receptors (AMPAr and NMDAr), level of tropomyosin receptor kinase B (TrkB) and activation of p75 neurotrophin receptor (p75NTr)-mediated signaling pathway (Connor et al., 1997; Coulson, 2006; Forner et al., 2017; Hsieh et al., 2006; Snyder et al., 2005; Querfurth and LaFerla, 2010). In particular, AβO causes degeneration of dendritic spines and an imbalance between long-term potentiation (LTP) and long-term depression (LTD) (Shankar et al., 2007). These studies provide evidence of the impairment of synaptic transmission and synaptic plasticity by Aβ in AD.

Peripherally administered ghrelin enhances synaptic formation and LTP generation by binding to GHS-R in the hippocampus (Diano et al., 2006). Both subcutaneous and i.c.v injections of ghrelin enhance learning and memory (Diano et al., 2006; Ribeiro et al., 2014). The targeted disruption of ghrelin signaling decreases the number of spine synapses in the stratum radiatum and then increases rapidly after the ghrelin administration (Diano et al., 2006). In cultured rat hippocampal slices, ghrelin promotes the dendritic spine synapse formation. In addition, synaptic densities are significantly increased in neonate cortical cultures, in which acyl-ghrelin is treated chronically, and this increase is higher in the early development stages (Stoyanova and le Feber, 2014). These studies suggest that ghrelin can be a therapeutic target for the prevention of synaptic degeneration in AD (Dos Santos et al., 2013; Stoyanova, 2014). The administration of ghrelin in an acute AD mouse model induced by hippocampal AβO injection preventes synaptic loss and preserves cholinergic fibers (Moon et al., 2011). Furthermore, the long-term administration of ghrelin that restores synaptic plasticity and memory retention in the Aβ-treated animal model implying that this effect is mediated by a postsynaptic mechanism (Eslami et al., 2018). These reports suggest that chronic administration of ghrelin may mediate synaptic enhancement, improve memory impairment, and alleviate cognitive dysfunction in patients with AD (Fig. 6).

3.6. Adult hippocampal neurogenesis

The hippocampus, plays as important role in learning and memory, and it is affected by AD (Marlatt and Lucassen, 2010; Mu and Gage, 2011). Changes in adult hippocampal neurogenesis levels are under debate because the results from the studies examining the levels of neurogenesis in AD are not consistent. A number of studies have reported decreased neurogenesis in the hippocampus of AD animal models (Rodriguez and Verkhratsky, 2011). However, in both patients with AD and animal models, neurogenesis is enhanced in the hippocampus, which indicates a compensatory response (Jin et al., 2004a, b). Considering the impaired neurogenesis causes cognitive deficits in AD (Hollands et al., 2016), the stimulation of neurogenesis may be a novel therapeutic approach for the treatment of AD (Marlatt and Lucassen, 2010).

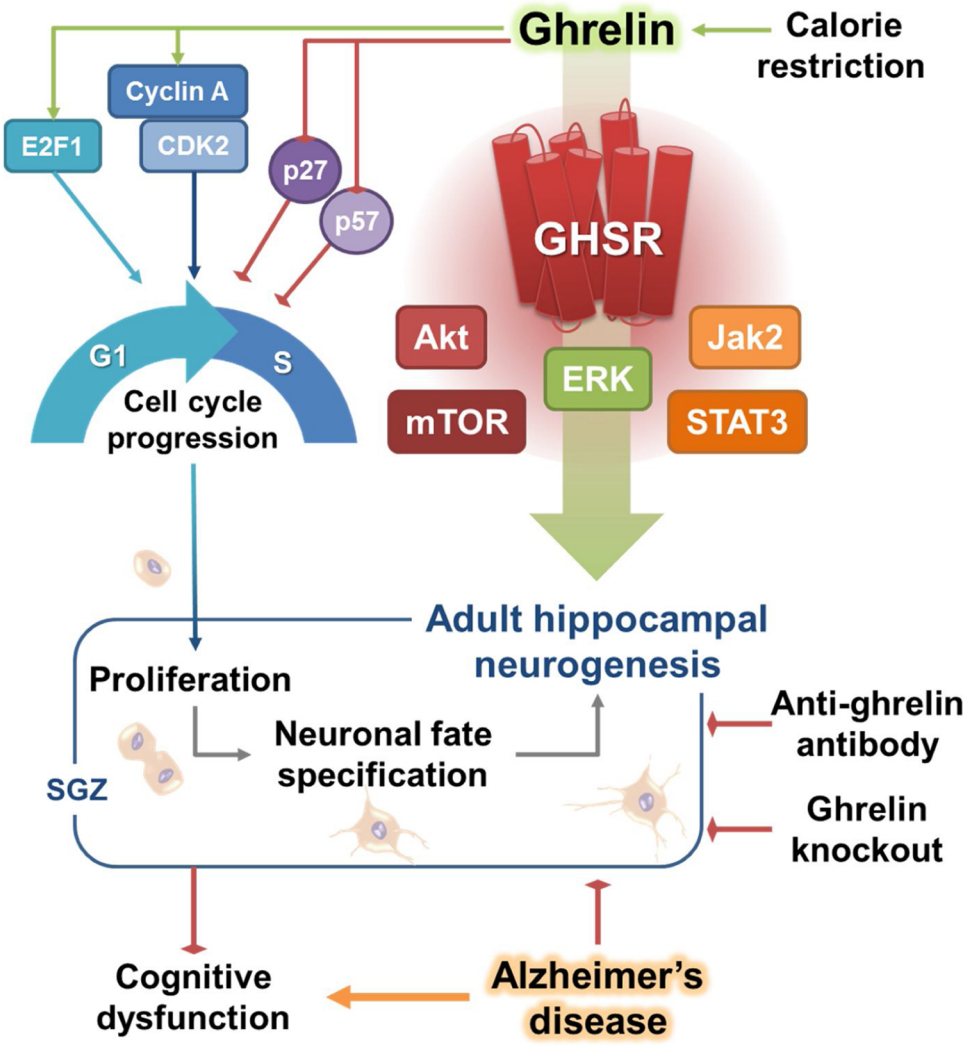

Fig. 7. The Effect of Ghrelin on Adult Hippocampal Neurogenesis in Alzheimer's Disease.
Diminished adult hippocampal neurogenesis in AD is considered a major cause of cognitive decline and is proposed as a therapeutic target. Surprisingly, administration of ghrelin was observed to increase proliferation and neuronal differentiation of hippocampal SGZ cells in an AD mouse model. The mechanism of ghrelin-mediated hippocampal neurogenesis includes several signaling pathways such as Akt, ERK, Jak2, and STAT3. In addition, ghrelin increased the expression of E2F1, cyclin A, and CDK2, which promote cell cycle progression to the S phase, and downregulated the expression of p27 and p57, which arrest the cell cycle. In contrast, the number of SGZ progenitor cells decreased when either the ghrelin gene was knocked-out or an anti-ghrelin antibody was administered. CDK2: cyclin-dependent kinase 2, SGZ: subgranular zone.

Several studies have reported about ghrelin-mediated hippocampal neurogenesis (Moon et al., 2014, 2009b). GHS-R1a-expressing hippocampal progenitor cells are co-localized with anti-Ki-67, a precursor cell proliferation marker of the subgranular zone (SGZ) (Moon et al., 2009b). In addition, the BrdU-positive cells, a mitotic biomarker in SGZ, are significantly decreased compared to the controls when animal models are treated with anti-ghrelin antibody (Moon et al., 2009b). Moreover, the DCX-positive cells, an early neuronal differentiation marker, are significantly increased in the ghrelin-treated adult mice in SGZ of the dentate gyrus (DG) (Christie and Cameron, 2006; Moon et al., 2009b). Notably, a study reported on the ameliorating effects of exogenous ghrelin on adult hippocampal neurogenesis in the AD animal model (Moon et al., 2014).

The targeted deletion of ghrelin reduces SGZ progenitor cell numbers in the ghrelin knockout (GKO) mice, which is restored after treating with ghrelin (Li et al., 2013). Ghrelin administration also restores the decreased number of immature neurons and newly generated neurons in the GKO mice (Li et al., 2013). Moreover, calorie restriction increases serum ghrelin levels (Lutter et al., 2008) and enhances adult neurogenesis in the mice (Lee et al., 2002). Furthermore, ghrelin levels decrease in elderly subjects compared to young subjects (Rigamonti et al., 2002), and patients with AD have decreased ghrelin production compared to the age-matched control individuals (Dos Santos et al., 2013). Therefore, low ghrelin levels can account for the high frequency of dementia and decreased hippocampal neurogenesis in the obese and elderly patients (Li et al., 2013; Lindqvist et al., 2006; Rigamonti et al., 2002; Tschop et al., 2001). Taken together, these results suggest the important role of ghrelin in the regulation of hippocampal neurogenesis

The mechanism of action of ghrelin on the hippocampal neurogenesis is not well understood, but there are some studies describing the mechanisms. Ghrelin seems to promote rapid activation of ERK1/2 and AKT, which is blocked by GHS-R1a antagonist (Xiang et al., 2011). The activation of STAT3 is also triggered after the ghrelin treatment (Chung et al., 2013). The specific inhibitors of MEK1, MEK1/2, Akt, mTOR, and Jak2/STAT3 suppressed the ghrelin-induced proliferation (Chung et al., 2013). This suggests that ghrelin is involved in the neurogenesis through several signaling pathways. Furthermore, fluorescence activated cell sorting (FACS) analysis reveals the cell cycle effects of ghrelin, as the cell progresses from G0/G1 phase to S phase by increasing the nuclear expression of E2F1 (Chung and Park, 2016). In addition, ghrelin increases cyclin A and CDK (cyclin-dependent kinase) 2, which promote the cell cycle progression, and it inhibits the expression of p27 and p57 that promotes an exit from the cell cycle (Chung and Park, 2016). As aberrant cell cycle re-entry markers can be observed in several stages in AD patients (Counts and Mufson, 2017) and the ghrelin-mediated cell cycle restoration can trigger the hippocampal neurogenesis (Kim et al., 2017), the ghrelin-induced hippocampal neurogenesis enhancement may be considered for the AD treatment (Fig. 7). Unlike the adult rats, acyl-ghrelin does not alter the neurogenesis or mitogenesis in the male juvenile rats but rather an increased immobility time in the tail suspension test (Jackson et al., 2019). In addition, ghrelin treatment suppresses the proliferation of

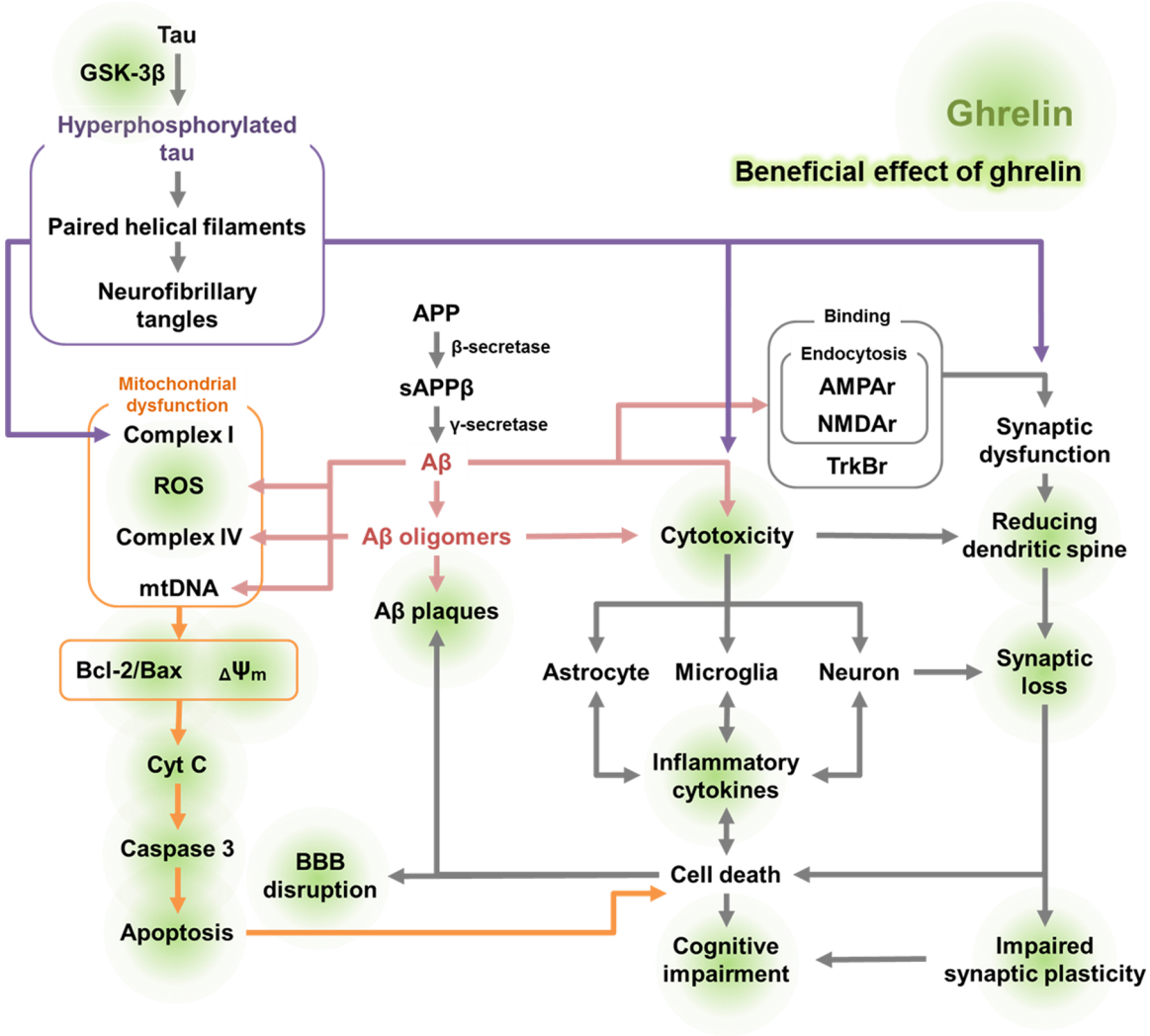

Fig. 8. Therapeutic Implication of Ghrelin in the Aβ/tau-mediated Pathological Cascade of Alzheimer's Disease.
Due to disruption of Aβ homeostasis, Aβ accumulation and tau phosphorylation produce hyperphosphorylated aggregates that induce cytotoxicity, synaptic dysfunction, and mitochondrial dysfunction. Inflammatory vicious cycle by excessive immunological reactions induced by glial cells and neurons, apoptotic cell death through cytochrome C (Cyt C) and caspase 3, and synaptic plasticity impair due to synaptic dysfunction ultimately lead to cognitive impairment. In this AD pathological cascade, ghrelin inhibits tau hyperphosphorylation through glycogen synthase kinase-3β (GSK-3β) inactivation and ameliorates Aβ burden through an unknown pathway. In addition, ghrelin reduces reactive oxygen species (ROS) and inhibits apoptotic mediators such as bcl-2-associated X protein (Bax), Cyt C, and caspase 3. Furthermore, ghrelin decreases Aβ-induced cytotoxicity and inflammatory cytokine. Moreover, ghrelin improves synaptic plasticity and cognitive function. In the AD pathogenesis diagram, the direct effects are colored: Aβ in red, tau in purple, mitochondrial dysfunction in yellow, and the cascade effect in gray. The beneficial effects of ghrelin are highlighted in green. Aβ: amyloid beta, AMPAr: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, APP: amyloid precursor protein, BBB: blood-brain barrier, NMDAr: N-methyl-D-aspartate receptor, TrkBr: Tropomyosin receptor kinase B, $_{\Delta}\psi_{m}$: mitochondrial membrane potential.

neural progenitor cells derived from fetal mice, whereas it induces neuronal differentiation of neural progenitor cells (Watanabe et al., 2015). Moreover, the subventricular zone (SVZ), another brain region in which adult neurogenesis is observed, does not express GHS-R, and SVZ neurogenesis is not modulated by acyl-ghrelin (Ratcliff et al., 2019). These results suggest that the role of ghrelin in neurogenesis may be dependent on age and brain area.

3.7. Cognitive dysfunction

The reputable AD pathological hallmarks, Aβ and Tau, contribute to cognitive decline due to neuronal alterations such as synaptic dysfunction, synaptic loss, and neuronal death (Brier et al., 2016; Haass and Selkoe, 2007; Roberson et al., 2011; Selkoe, 1991; Spires-Jones and Hyman, 2014). Initially, the episodic memory is affected followed by the deterioration of attention, executive functions, semantic memory, and visuospatial memory during the progression of AD (Grady et al., 1988; Hodges and Patterson, 1995; Perry and Hodges, 2000; Perry et al., 2000).

Ghrelin is a hypothalamus-targeting gastric hormone released during fasting, eliciting hunger; however, emerging evidence suggests that ghrelin may also affect memory function (Kang et al., 2015). Especially, serum ghrelin levels during fasting are positively associated with verbal learning and memory functions in fit and healthy elderly (Bellar et al., 2013). Injections of ghrelin into the rat hippocampus, amygdala, and dorsal raphe nucleus (DRN) increase memory retention (Carlini et al., 2004). Moreover, ghrelin increases dendritic synapse formation, LTP generation, and spatial learning and memory (Diano et al., 2006). Therefore, the ghrelin receptor signaling is suggested as a therapeutic target for cognitive dysfunction (Cong et al., 2010). In particular, ghrelin plays a role in the function of the temporal lobe, one of the most severely affected cognition-related regions in AD (Gahete et al., 2010). However, some studies suggest that the role of ghrelin in cognitive function may be controversial. The intra-hippocampal

Table 1
The role of ghrelin associated with Alzheimer's disease in CNS function.

Memory retrieval	**Experimental model**	**Main result**	**Ref.**
	Aβ i.c.v infused AD rat model	Infusion of acyl-ghrelin in AD-rat prevented the short retention memory loss and Aβ deposition	(Kang et al., 2015)
	Ghrelin or ghrelin receptor knockout animals	Administration of ghrelin restored performance of behavioral memory tests	(Diano et al., 2006)
	Fasting levels of serum ghrelin were positively associated with verbal learning and memory function		(Bellar et al., 2013)
LTP/LTD	**Experimental model**	**Main result**	**Ref.**
	Ghrelin administered peripherally in normal mice	Administration of ghrelin promoted neuronal dendritic spine formation and LTP in the hippocampus	(Diano et al., 2006)
	In vivo ghrelin microinjection into the CA1 subregion of the hippocampus of rats	Ghrelin reduced the threshold values to generate LTP in the DG	(Carlini et al., 2010b)
Synaptic Function	**Experimental model**	**Main result**	**Ref.**
	$A\beta_{1-42}$-induced AD model	Chronic ghrelin administration improves Aβ-induced synaptic dysfunction through postsynaptic mechanism	(Eslami et al., 2018)
	Ghrelin and ghrelin receptor knockout animals	Disruption of ghrelin signaling decreased the number of spine synapses in the stratum radiatum, and it was restored by ghrelin	(Diano et al., 2006)
	AβO- intrahippocampal injected rat	Ghrelin can attenuate synaptic loss mediated by AβO	(Moon et al., 2011)
	Cortical cells from neonatal brains of rats	AG affected synaptogenesis and accelerated synaptic activity	(Stoyanova and le Feber, 2014)
	Rat hippocampal neuron or slice	GHS-R1a activation enhanced excitatory synaptic transmission and plasticity	(Ribeiro et al., 2014)
Hippocampal neurogenesis	**Experimental model**	**Main result**	**Ref.**
	Anti-ghrelin antibody treated animal model	The number of proliferation and differentiation of cells in SGZ was significantly decreased in the anti-ghrelin group compared to that in the control group	(Moon et al., 2009b)
	Ghrelin treated animal model	The number of early neuronal differentiation marker DCX positive cells significantly increased in the SGZ	
	GKO mice	Ghrelin restored the decreased number of immature neurons and SGZ progenitor cells in GKO mice	(Li et al., 2013)
	Adult rat hippocampal NSCs	Treatment of ghrelin induced proliferation of adult rat NSCs through activation of Akt, ERK1/2, and STAT3 pathways	(Chung et al., 2013)
	Adult rat hippocampal NSCs	Ghrelin promoted cell cycle progression by upregulation of E2F1, cyclin A and CDK2, and downregulation of p27 and p57	(Chung and Park, 2016)

injection of ghrelin in the rats improves the long-term memory, but there is no significant change in the short-term memory (Carlini et al., 2010a). In addition, the systemic injection of ghrelin increases adult hippocampal neurogenesis but does not significantly improve spatial memory. On the other hand, the intra-hippocampal injection of ghrelin in the mice impairs spatial memory without changes in adult hippocampal neurogenesis (Zhao et al., 2014). Furthermore, the acute administration of acyl-ghrelin in young male participants does not affect cognitive test battery (Kunath et al., 2016). These studies suggest that the effects and mechanisms of ghrelin on cognitive function may be dependent on the administration route, dose, type of ghrelin, and species.

Remarkably, the central ghrelin infusion almost completely prevents short term memory loss even though Aβ deposition in AD rats infused with acyl-ghrelin is higher than that of non-AD rats infused with saline (Kang et al., 2015). In addition, ghrelin also inhibits neuronal loss caused by AβO in the DG and increases the density of hippocampal synaptic and cholinergic nerve fibers; ghrelin also decreases AβO-induced microgliosis in the hippocampus (Moon et al., 2011). Furthermore, in rat model of obesity, the injection of ghrelin receptor antagonist [D-lys (3)]-GHRP-6 reduces hippocampal Aβ levels and restores ghrelin levels to the same level as that of the control (Madhavadas et al., 2014). A recent study using nuclear magnetic resonance for the identification of metabolites shows that the i.c.v ghrelin administration improves memory and cognitive functions by affecting oxidative stress, osteoporosis pathways, and vascular risk factors in the animal model of AD (Goshadrou et al., 2018). In this respect, ghrelin is able to play a beneficial role in the cognitive dysfunction, which is the major symptom of AD.

4. Potential of ghrelin receptor agonists as therapeutic agents for treatment of AD

A number of clinical trials have been conducted using ghrelin receptor agonists in various conditions (Ejskjaer et al., 2009, 2013; Garcia et al., 2013; Garin et al., 2013; Nass et al., 2008). Ghrelin mimetics such as pralmorelin, macimorelin, and tabimorelin have been tested in clinical trials for the diagnosis of growth hormone deficiency (Muller et al., 2015). Several studies have examined the effects of the ghrelin receptor agonists on the pathologies and symptoms of AD. Administration of LY444711, a ghrelin receptor agonist, enhances hippocampal dependent cognitive functions in AD mice. However, LY444711 does not change the microglial activation and Aβ burden (Kunath et al., 2015). In contrast, another study reports that LY444711 prevents cognitive decline and ameliorates AD pathologies including the level of Aβ and microglial activation (Dhurandhar et al., 2013). There are no changes in Aβ levels as well as cognitive functions after the MK-0677 administration in the AD patients (Sevigny et al., 2008). Interestingly, the ghrelin antagonist [D-Lys (3)]-GHRP-6 reduces Aβ and AChE levels in MSG-induced obese rats (Madhavadas et al., 2014). One recent study reported that MK-0677 administration reduces the Aβ-related pathologies such as Aβ deposition, neuroinflammation and neurodegeneration in mice at the early stage of AD (Jeong et al., 2018). Therefore, based on these findings that support the beneficial roles of ghrelin receptor agonists in AD, the ghrelin receptor agonists and ghrelin mimetics should be considered for therapeutic agents for AD (Fig. 8). Although the short-term safety of ghrelin administration has been verified in a number of studies in humans administered with ghrelin, there is still a lack of research on the long-term safety of ghrelin (Akamizu et al., 2004; Garin et al., 2013). The introduction of the ghrelin or ghrelin agonists for the treatment should consider the potential adverse effects since ghrelin can intervene universally in the pathological features of AD, which require the long-term administration.

5. Conclusion

Studies on the effects of ghrelin have changed their focus from its

Table 2
The association of ghrelin with Alzheimer's disease-related pathologies.

Aβ accumulation	**Experimental model**	**Main result**	**Ref.**
	Long-term administration of ghrelin agonist to APP transgenic mice (APPSwDI)	Significant reduction of Aβ in DG, and reduction of insoluble Aβ-40 and -42 levels in both groups	(Dhurandhar et al., 2013)
	Ghrelin receptor antagonist in MSG-induced obese rats	Reduction in Aβ level and increase in AChE level in MSG-induced obese rats	(Madhavadas et al., 2014)
Tau accumulation	**Experimental model**	**Main result**	**Ref.**
	Treatment of hippocampal neurons with ghrelin in neonatal Sprague-Dawley rats	Improving neuronal glucose uptake and Tau hyperphosphorylation partially via the PI3-K/Akt pathway Ghrelin improved neuronal insulin sensitivity and decreased Tau hyperphosphorylation in a normal or high glucose environment	(Chen et al., 2010)
	Aβ i.c.v infused AD rat models	Infusion of acyl-ghrelin activated AMPK pathways and then inhibited GSK-3b promoting hyperphosphorylation of Tau protein.	(Kang et al., 2015)
Mitochondrial deficits	**Experimental model**	**Main result**	**Ref.**
	Ghrelin injected into primary cultured hippocampal neurons	Attenuating Aβ induced superoxide production and mitochondrial membrane depolarization, eventually increasing cell survival rate. Preventing cell death through receptor dependent mechanisms	(Martins et al., 2013)
	Peripheral administration of ghrelin to rats	Increasing mRNA level of mitochondrial UCP2	(Barazzoni et al., 2005)
	Ghrelin administration to AβO treated hypothalamic cells	Inhibiting ROS production, calcium deregulation and mitochondrial dysfunction	(Gomes et al., 2014)
	Administration of ghrelin to acyl- and des-acyl-ghrelin to a mouse model of stroke	des-acyl-ghrelin decreased infarct, swelling and apoptosis, by inhibiting superoxide production, NOX activity, and expression of 3-nitrotyrosine	(Ku et al., 2016)
	Peripheral ghrelin administration to gastric ischemic injured rats	Ghrelin decreased levels of LDH, TNF-a, and thiobarbituric acid reactive substance, and increased glutathione level in gastric tissues Ghrelin reduced vascular mucosal permeability and INOS protein level	(El Eter et al., 2007)
	Isolated human polymorphonuclear (PMN) cells incubated with ghrelin	In human PMN cells, ghrelin attenuated ROS production in a dose-dependent manner	(El Eter et al., 2007)
	Ghrelin treatment of H_2O_2 treated oligodendrocytes	Ghrelin inhibited cytochrome c release and caspase 3 activation	(Lee et al., 2011)
	Ghrelin treatment of hypothalamic neurons exposed to oxygen-glucose deprivation	Ghrelin increased Bcl-2/Bax ratio leading to mitochondrial transmembrane potential stabilization and inhibition of apoptotic cell death	(Chung et al., 2007)
Neuro-inflammation	**Experimental model**	**Main result**	**Ref.**
	Des-acyl-ghrelin, hexarelin, EP 80317 (synthetic GH-secretagogue) administered into microglia activated by Aβ fibrils	Des-acyl ghrelin, hexarelin and EP80317 reduced mRNA expression of IL-1β and IL-6	(Bulgarelli et al., 2009)
	Ghrelin administration to chronic constriction injury model of sciatic nerve injury	Decreasing TNF-α and IL-1β levels	(Guneli et al., 2010)
	Pre-treatment of an LPS-stimulated dopaminergic SN4741 cell line with ghrelin	Ghrelin attenuated IL-6 secretion and prevented dopaminergic SN nerve cell destruction	(Beynon et al., 2013)
	Ghrelin administration to Aβ oligomer injected mice	Ghrelin significantly reduced AβO-induced neuroinflammation	(Moon et al., 2011)
Cerebral amyloid angiopathy	**Experimental model**	**Main result**	**Ref.**
	Administration of des-acyl-ghrelin in mice after transient middle cerebral artery occlusion	Des-acyl-ghrelin reduced BBB disruption and attenuated hyper-permeability	(Ku et al., 2016)
	Cobalt chloride-induced hypoxic condition in cardiac H9c2 cells	Ghrelin protected hypoxic injury by inducing autophagy and inhibiting oxidative stress	(Tong et al., 2012)
Autophagy	**Experimental model**	**Main result**	**Ref.**
	Treatment of a human colon adenocarcinoma cell line with ghrelin	Ghrelin inhibits proteasomes and induces autophagy as a pro-apoptotic factor	(Bonfili et al., 2013)
	C57BL/6 mice fed high-fat diet	Ghrelin upregulated autophagy via AMPK/mTOR	(Mao et al., 2015a)
	GH-infusion to ghrelin-deficient mice	Ghrelin-deficient mice exhibit decreased hepatic autophagy, and GH administration restores the decrease in autophagy	(Zhang et al., 2015)
	Ghrelin treatment in rat hippocampal neural stem cells inducing oxygen-glucose deprivation	Ghrelin suppressed production of autophagosomes and autophagy activity	(Chung et al., 2018)
Cognitive dysfunction	**Experimental model**	**Main result**	**Ref.**
	Injection of ghrelin in the rat hippocampus, amygdala, and DRN	Administration of ghrelin in the hippocampus, amygdala, and DRN promoted memory retention	(Carlini et al., 2004)
	Injection of [D-Lys (3)]-GHRP-6 in MSG-induced AD rats.	Administration of ghrelin receptor antagonist [D-Lys (3)]-GHRP-6 improved the spatial disorientation	(Madhavadas et al., 2014)
	Aβ i.c.v infused AD rat model	Ghrelin induced less Aβ deposition in the hippocampus and prevented cognitive dysfunction in rats infused with Aβ Infusion of acyl-ghrelin reduced Tau phosphorylation in AD rats	(Kang et al., 2015)
	APP-SwDI mouse model	Long-term administration of ghrelin mimetics LY444711 restored cognitive impairment.	(Dhurandhar et al., 2013)
	Aβ oligomer-injected mice	Ghrelin prevented neuroinflammation, neuronal and synaptic loss, attenuating cognitive impairment	(Moon et al., 2011)

well-known metabolic functions to the neuronal extra-hypothalamic functions. Roles of ghrelin on CNS functions associated with AD have been investigated (Table 1). The symptoms or physical responses of AD and the molecular and biochemical mechanisms involved in AD including the Aβ and tau functions are closely related to the ghrelin actions. Furthermore, ghrelin is involved in changes in the cell cycle, mitochondria, neuroinflammation, and cognitive functions in AD. Subsequently, these effects of ghrelin in AD have suggested that the

ghrelin receptor agonists and ghrelin mimetics may serve as the potential therapeutic agents for AD (Table 2). The experimental evidence supports the hypothesis that ghrelin and ghrelin receptors may serve as candidate drug targets. Yet, relatively few studies have examined the molecular and cellular mechanisms of the ghrelin involvement in AD. Therefore, future experiments should demonstrate the molecular and cellular responses underlying the physiological and behavioral responses. In addition, as the most predominant form of ghrelin in plasma is des-acyl-ghrelin rather than acyl-ghrelin and the effects of des-acyl-ghrelin are independent of those of GHS-R1a, future research should focus on the identification of des-acyl-ghrelin receptors and their endogenous functions. Furthermore, GOAT knockout mice, which lack acyl-ghrelin, will help confirm the neuronal functions of des-acyl-ghrelin and expand our knowledge in this area. The present review may have some limitations since the methodology used in this study was not a systematic methodology. Thus, it may not thoroughly assure the internal and external validity. A further study using the systematic methodology is needed to supplement this limitation. Nonetheless, this review can provide useful implications in establishing a treatment for AD by outlining the pathologic roles and therapeutic implications of ghrelin in patients with AD and related symptoms. A future assignment for researchers and clinicians is to translate highly promising basic research of ghrelin into clinical applications. Ghrelin has been demonstrated to be a prospective target for disease treatment and prevention in various respects. Particularly, no therapeutic drug that can substantially cure AD has been developed yet. Thus, as ghrelin is broadly associated with each step in the AD development, improving endogenous ghrelin secretion, stimulating GHS-R1a, or antagonizing ghrelin-restricting mechanisms may be great strategies to control the pathologies of AD. In addition, the neuroprotective effects of ghrelin (GHS-R1a agonists) may also improve age-induced neurological disorders. Nevertheless, the potential adverse effects caused by an increase in ghrelin should be considered. For instance, developing site-specific therapies are essential in controlling ghrelin levels during the AD treatment.

Declaration of Competing Interest

None.

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References

Abizaid, A., Liu, Z.W., Andrews, Z.B., Shanabrough, M., Borok, E., Elsworth, J.D., Roth, R.H., Sleeman, M.W., Picciotto, M.R., Tschop, M.H., Gao, X.B., Horvath, T.L., 2006. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J. Clin. Invest. 116, 3229–3239.

Adolfsson, O., Pihlgren, M., Toni, N., Varisco, Y., Buccarello, A.L., Antoniello, K., Lohmann, S., Piorkowska, K., Gafner, V., Atwal, J.K., Maloney, J., Chen, M., Gogineni, A., Weimer, R.M., Mortensen, D.L., Friesenhahn, M., Ho, C., Paul, R., Pfeifer, A., Muhs, A., Watts, R.J., 2012. An effector-reduced anti-beta-amyloid (Abeta) antibody with unique abeta binding properties promotes neuroprotection and glial engulfment of Abeta. J. Neurosci. 32, 9677–9689.

Akamizu, T., Takaya, K., Irako, T., Hosoda, H., Teramukai, S., Matsuyama, A., Tada, H., Miura, K., Shimizu, A., Fukushima, M., Yokode, M., Tanaka, K., Kangawa, K., 2004. Pharmacokinetics, safety, and endocrine and appetite effects of ghrelin administration in young healthy subjects. Eur. J. Endocrinol. 150, 447–455.

Akiyama, H., Barger, S., Barnum, S., Bradt, B., Bauer, J., Cole, G.M., Cooper, N.R., Eikelenboom, P., Emmerling, M., Fiebich, B.L., Finch, C.E., Frautschy, S., Griffin, W.S., Hampel, H., Hull, M., Landreth, G., Lue, L., Mrak, R., Mackenzie, I.R., McGeer, P.L., O'Banion, M.K., Pachter, J., Pasinetti, G., Plata-Salaman, C., Rogers, J., Rydel, R., Shen, Y., Streit, W., Strohmeyer, R., Tooyoma, I., Van Muiswinkel, F.L., Veerhuis, R., Walker, D., Webster, S., Wegrzyniak, B., Wenk, G., Wyss-Coray, T., 2000. Inflammation and Alzheimer's disease. Neurobiol. Aging 21, 383–421.

Al Massadi, O., Tschop, M.H., Tong, J., 2011. Ghrelin acylation and metabolic control. Peptides 32, 2301–2308.

Aleardi, A.M., Benard, G., Augereau, O., Malgat, M., Talbot, J.C., Mazat, J.P., Letellier, T., Dachary-Prigent, J., Solaini, G.C., Rossignol, R., 2005. Gradual alteration of mitochondrial structure and function by beta-amyloids: importance of membrane viscosity changes, energy deprivation, reactive oxygen species production, and cytochrome c release. J. Bioenerg. Biomembr. 37, 207–225.

Andrews, Z.B., 2011. The extra-hypothalamic actions of ghrelin on neuronal function. Trends Neurosci. 34, 31–40.

Andrews, Z.B., Erion, D., Beiler, R., Liu, Z.W., Abizaid, A., Zigman, J., Elsworth, J.D., Savitt, J.M., DiMarchi, R., Tschoep, M., Roth, R.H., Gao, X.B., Horvath, T.L., 2009. Ghrelin promotes and protects nigrostriatal dopamine function via a UCP2-dependent mitochondrial mechanism. J. Neurosci. 29, 14057–14065.

Avila, J., 2006. Tau phosphorylation and aggregation in Alzheimer's disease pathology. FEBS Lett. 580, 2922–2927.

Baatar, D., Patel, K., Taub, D.D., 2011. The effects of ghrelin on inflammation and the immune system. Mol. Cell. Endocrinol. 340, 44–58.

Banerjee, R., Beal, M.F., Thomas, B., 2010. Autophagy in neurodegenerative disorders: pathogenic roles and therapeutic implications. Trends Neurosci. 33, 541–549.

Banks, W.A., Tschop, M., Robinson, S.M., Heiman, M.L., 2002. Extent and direction of ghrelin transport across the blood-brain barrier is determined by its unique primary structure. J. Pharmacol. Exp. Ther. 302, 822–827.

Barazzoni, R., Bosutti, A., Stebel, M., Cattin, M.R., Roder, E., Visintin, L., Cattin, L., Biolo, G., Zanetti, M., Guarnieri, G., 2005. Ghrelin regulates mitochondrial-lipid metabolism gene expression and tissue fat distribution in liver and skeletal muscle. Am. J. Physiol. Endocrinol. Metab. 288, E228–235.

Barker, W.W., Luis, C.A., Kashuba, A., Luis, M., Harwood, D.G., Loewenstein, D., Waters, C., Jimison, P., Shepherd, E., Sevush, S., Graff-Radford, N., Newland, D., Todd, M., Miller, B., Gold, M., Heilman, K., Doty, L., Goodman, I., Robinson, B., Pearl, G., Dickson, D., Duara, R., 2002. Relative frequencies of Alzheimer disease, Lewy body, vascular and frontotemporal dementia, and hippocampal sclerosis in the State of Florida Brain Bank. Alzheimer Dis. Assoc. Disord. 16, 203–212.

Bateman, R.J., Aisen, P.S., De Strooper, B., Fox, N.C., Lemere, C.A., Ringman, J.M., Salloway, S., Sperling, R.A., Windisch, M., Xiong, C., 2011. Autosomal-dominant Alzheimer's disease: a review and proposal for the prevention of Alzheimer's disease. Alzheimers Res. Ther. 3, 1.

Bayliss, J.A., Andrews, Z.B., 2013. Ghrelin is neuroprotective in Parkinson's disease: molecular mechanisms of metabolic neuroprotection. Ther. Adv. Endocrinol. Metab. 4, 25–36.

Bellar, D., Glickman, E.L., Judge, L.W., Gunstad, J., 2013. Serum ghrelin is associated with verbal learning and adiposity in a sample of healthy, fit older adults. Biomed. Res. Int. 2013, 202757.

Benso, A., St-Pierre, D.H., Prodam, F., Gramaglia, E., Granata, R., van der Lely, A.J., Ghigo, E., Broglio, F., 2012. Metabolic effects of overnight continuous infusion of unacylated ghrelin in humans. Eur. J. Endocrinol. 166, 911–916.

Bereczki, E., Branca, R.M., Francis, P.T., Pereira, J.B., Baek, J.H., Hortobagyi, T., Winblad, B., Ballard, C., Lehtio, J., Aarsland, D., 2018. Synaptic markers of cognitive decline in neurodegenerative diseases: a proteomic approach. Brain 141, 582–595.

Beynon, A.L., Brown, M.R., Wright, R., Rees, M.I., Sheldon, I.M., Davies, J.S., 2013. Ghrelin inhibits LPS-induced release of IL-6 from mouse dopaminergic neurones. J. Neuroinflammation 10, 40.

Bird, T.D., 2008. Genetic aspects of Alzheimer disease. Genet. Med. 10, 231–239.

Birks, J., 2006. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst. Rev. Cd005593.

Block, M.L., Zecca, L., Hong, J.S., 2007. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. Nat. Rev. Neurosci. 8, 57–69.

Bockaert, J., Pin, J.P., 1999. Molecular tinkering of G protein-coupled receptors: an evolutionary success. EMBO J. 18, 1723–1729.

Bonfili, L., Cuccioloni, M., Cecarini, V., Mozzicafreddo, M., Palermo, F.A., Cocci, P., Angeletti, M., Eleuteri, A.M., 2013. Ghrelin induces apoptosis in colon adenocarcinoma cells via proteasome inhibition and autophagy induction. Apoptosis 18, 1188–1200.

Boza-Serrano, A., Yang, Y., Paulus, A., Deierborg, T., 2018. Innate immune alterations are elicited in microglial cells before plaque deposition in the Alzheimer's disease mouse model 5xFAD. Sci. Rep. 8, 1550.

Brier, M.R., Gordon, B., Friedrichsen, K., McCarthy, J., Stern, A., Christensen, J., Owen, C., Aldea, P., Su, Y., Hassenstab, J., Cairns, N.J., Holtzman, D.M., Fagan, A.M., Morris, J.C., Benzinger, T.L., Ances, B.M., 2016. Tau and Abeta imaging, CSF measures, and cognition in Alzheimer's disease. Sci. Transl. Med. 8, 338ra366.

Bulgarelli, I., Tamiazzo, L., Bresciani, E., Rapetti, D., Caporali, S., Lattuada, D., Locatelli, V., Torsello, A., 2009. Desacyl-ghrelin and synthetic GH-secretagogues modulate the production of inflammatory cytokines in mouse microglia cells stimulated by beta-amyloid fibrils. J. Neurosci. Res. 87, 2718–2727.

Butterfield, D.A., Pocernich, C.B., 2003. The glutamatergic system and Alzheimer's disease: therapeutic implications. CNS Drugs 17, 641–652.

Cabral, A., Lopez Soto, E.J., Epelbaum, J., Perello, M., 2017. Is ghrelin synthesized in the central nervous system? Int. J. Mol. Sci. 18.

Camina, J.P., 2006. Cell biology of the ghrelin receptor. J. Neuroendocrinol. 18, 65–76.

Cao, X., Zhu, M., He, Y., Chu, W., Du, Y., Du, H., 2018. Increased serum acylated ghrelin levels in patients with mild cognitive impairment. J. Alzheimers Dis. 61, 545–552.

Carlini, V.P., Ghersi, M., Schioth, H.B., de Barioglio, S.R., 2010a. Ghrelin and memory: differential effects on acquisition and retrieval. Peptides 31, 1190–1193.

Carlini, V.P., Perez, M.F., Salde, E., Schioth, H.B., Ramirez, O.A., de Barioglio, S.R.,

2010b. Ghrelin induced memory facilitation implicates nitric oxide synthase activation and decrease in the threshold to promote LTP in hippocampal dentate gyrus. Physiol. Behav. 101, 117–123.
Carlini, V.P., Varas, M.M., Cragnolini, A.B., Schioth, H.B., Scimonelli, T.N., de Barioglio, S.R., 2004. Differential role of the hippocampus, amygdala, and dorsal raphe nucleus in regulating feeding, memory, and anxiety-like behavioral responses to ghrelin. Biochem. Biophys. Res. Commun. 313, 635–641.
Caspersen, C., Wang, N., Yao, J., Sosunov, A., Chen, X., Lustbader, J.W., Xu, H.W., Stern, D., McKhann, G., Yan, S.D., 2005. Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. FASEB J. 19, 2040–2041.
Cecarini, V., Bonfili, L., Cuccioloni, M., Keller, J.N., Bruce-Keller, A.J., Eleuteri, A.M., 2016. Effects of ghrelin on the proteolytic pathways of Alzheimer's disease neuronal cells. Mol. Neurobiol. 53, 3168–3178.
Chang, J.C., Kou, S.J., Lin, W.T., Liu, C.S., 2010. Regulatory role of mitochondria in oxidative stress and atherosclerosis. World J. Cardiol. 2, 150–159.
Chen, J.H., Huang, S.M., Chen, C.C., Tsai, C.F., Yeh, W.L., Chou, S.J., Hsieh, W.T., Lu, D.Y., 2011. Ghrelin induces cell migration through GHS-R, CaMKII, AMPK, and NF-kappaB signaling pathway in glioma cells. J. Cell. Biochem. 112, 2931–2941.
Chen, Y., Cao, C.P., Li, C.R., Wang, W., Zhang, D., Han, L.L., Zhang, X.Q., Kim, A., Kim, S., Liu, G.L., 2010. Ghrelin modulates insulin sensitivity and tau phosphorylation in high glucose-induced hippocampal neurons. Biol. Pharm. Bull. 33, 1165–1169.
Chollet, C., Meyer, K., Beck-Sickinger, A.G., 2009. Ghrelin—a novel generation of anti-obesity drug: design, pharmacomodulation and biological activity of ghrelin analogues. J. Pept. Sci. 15, 711–730.
Christie, B.R., Cameron, H.A., 2006. Neurogenesis in the adult hippocampus. Hippocampus 16, 199–207.
Chu, K.-M., Chow, K.B., Leung, P.-K., Lau, P.-N., Chan, C.-B., Cheng, C.H., Wise, H., 2007. Over-expression of the truncated ghrelin receptor polypeptide attenuates the constitutive activation of phosphatidylinositol-specific phospholipase C by ghrelin receptors but has no effect on ghrelin-stimulated extracellular signal-regulated kinase 1/2 activity. Int. J. Biochem. Cell Biol. 39, 752–764.
Chung, H., Choi, J., Park, S., 2018. Ghrelin protects adult rat hippocampal neural stem cells from excessive autophagy during oxygen-glucose deprivation. Endocr. J. 65, 63–73.
Chung, H., Kim, E., Lee, D.H., Seo, S., Ju, S., Lee, D., Kim, H., Park, S., 2007. Ghrelin inhibits apoptosis in hypothalamic neuronal cells during oxygen-glucose deprivation. Endocrinology 148, 148–159.
Chung, H., Li, E., Kim, Y., Kim, S., Park, S., 2013. Multiple signaling pathways mediate ghrelin-induced proliferation of hippocampal neural stem cells. J. Endocrinol. 218, 49–59.
Chung, H., Park, S., 2016. Ghrelin regulates cell cycle-related gene expression in cultured hippocampal neural stem cells. J. Endocrinol. 230, 239–250.
Collden, G., Tschop, M.H., Muller, T.D., 2017. Therapeutic potential of targeting the ghrelin pathway. Int. J. Mol. Sci. 18.
Cong, W.N., Golden, E., Pantaleo, N., White, C.M., Maudsley, S., Martin, B., 2010. Ghrelin receptor signaling: a promising therapeutic target for metabolic syndrome and cognitive dysfunction. CNS Neurol. Disord. Drug Targets 9, 557–563.
Connor, B., Young, D., Yan, Q., Faull, R.L., Synek, B., Dragunow, M., 1997. Brain-derived neurotrophic factor is reduced in Alzheimer's disease. Brain Res. Mol. Brain Res. 49, 71–81.
Coulson, E.J., 2006. Does the p75 neurotrophin receptor mediate Abeta-induced toxicity in Alzheimer's disease? J. Neurochem. 98, 654–660.
Counts, S.E., Mufson, E.J., 2017. Regulator of cell cycle (RGCC) expression during the progression of Alzheimer's disease. Cell Transplant. 26, 693–702.
Cowley, M.A., Smith, R.G., Diano, S., Tschop, M., Pronchuk, N., Grove, K.L., Strasburger, C.J., Bidlingmaier, M., Esterman, M., Heiman, M.L., Garcia-Segura, L.M., Nillni, E.A., Mendez, P., Low, M.J., Sotonyi, P., Friedman, J.M., Liu, H., Pinto, S., Colmers, W.F., Cone, R.D., Horvath, T.L., 2003. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron 37, 649–661.
Cummings, J., Lee, G., Ritter, A., Zhong, K., 2018. Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement. (New York, N. Y.) 4, 195–214.
Cummings, J.L., 2004. Alzheimer's disease. N. Engl. J. Med. 351, 56–67.
David, D.C., Hauptmann, S., Scherping, I., Schuessel, K., Keil, U., Rizzu, P., Ravid, R., Drose, S., Brandt, U., Muller, W.E., Eckert, A., Gotz, J., 2005. Proteomic and functional analyses reveal a mitochondrial dysfunction in P301L tau transgenic mice. J. Biol. Chem. 280, 23802–23814.
Davies, C.A., Mann, D.M., Sumpter, P.Q., Yates, P.O., 1987. A quantitative morphometric analysis of the neuronal and synaptic content of the frontal and temporal cortex in patients with Alzheimer's disease. J. Neurol. Sci. 78, 151–164.
de la Monte, S.M., 2012. Brain insulin resistance and deficiency as therapeutic targets in Alzheimer's disease. Curr. Alzheimer Res. 9, 35–66.
DeKosky, S.T., Scheff, S.W., 1990. Synapse loss in frontal cortex biopsies in Alzheimer's disease: correlation with cognitive severity. Ann. Neurol. 27, 457–464.
Delporte, C., 2013. Structure and physiological actions of ghrelin. Scientifica (Cairo) 2013, 518909.
Dhurandhar, E.J., Allison, D.B., van Groen, T., Kadish, I., 2013. Hunger in the absence of caloric restriction improves cognition and attenuates Alzheimer's disease pathology in a mouse model. PLoS One 8, e60437.
Diano, S., Farr, S.A., Benoit, S.C., McNay, E.C., da Silva, I., Horvath, B., Gaskin, F.S., Nonaka, N., Jaeger, L.B., Banks, W.A., Morley, J.E., Pinto, S., Sherwin, R.S., Xu, L., Yamada, K.A., Sleeman, M.W., Tschop, M.H., Horvath, T.L., 2006. Ghrelin controls hippocampal spine synapse density and memory performance. Nat. Neurosci. 9, 381–388.
Dos Santos, V.V., Rodrigues, A.L., De Lima, T.C., de Barioglio, S.R., Raisman-Vozari, R., Prediger, R.D., 2013. Ghrelin as a neuroprotective and palliative agent in Alzheimer's and Parkinson's disease. Curr. Pharm. Des. 19, 6773–6790.
Durazzo, T.C., Mattsson, N., Weiner, M.W., 2014. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimer's Dement. 10, S122–145.
Ejskjaer, N., Vestergaard, E.T., Hellstrom, P.M., Gormsen, L.C., Madsbad, S., Madsen, J.L., Jensen, T.A., Pezzullo, J.C., Christiansen, J.S., Shaughnessy, L., Kosutic, G., 2009. Ghrelin receptor agonist (TZP-101) accelerates gastric emptying in adults with diabetes and symptomatic gastroparesis. Aliment. Pharmacol. Ther. 29, 1179–1187.
Ejskjaer, N., Wo, J.M., Esfandyari, T., Mazen Jamal, M., Dimcevski, G., Tarnow, L., Malik, R.A., Hellstrom, P.M., Mondou, E., Quinn, J., Rousseau, F., McCallum, R.W., 2013. A phase 2a, randomized, double-blind 28-day study of TZP-102 a ghrelin receptor agonist for diabetic gastroparesis. Neurogastroenterol. Motil. 25, e140–150.
El Eter, E., Al Tuwaijiri, A., Hagar, H., Arafa, M., 2007. In vivo and in vitro antioxidant activity of ghrelin: attenuation of gastric ischemic injury in the rat. J. Gastroenterol. Hepatol. 22, 1791–1799.
Engelstoft, M.S., Park, W.M., Sakata, I., Kristensen, L.V., Husted, A.S., Osborne-Lawrence, S., Piper, P.K., Walker, A.K., Pedersen, M.H., Nohr, M.K., Pan, J., Sinz, C.J., Carrington, P.E., Akiyama, T.E., Jones, R.M., Tang, C., Ahmed, K., Offermanns, S., Egerod, K.L., Zigman, J.M., Schwartz, T.W., 2013. Seven transmembrane G protein-coupled receptor repertoire of gastric ghrelin cells. Mol. Metab. 2, 376–392.
Eslami, M., Sadeghi, B., Goshadrou, F., 2018. Chronic ghrelin administration restores hippocampal long-term potentiation and ameliorates memory impairment in rat model of Alzheimer's disease. Hippocampus 28, 724–734.
Forner, S., Baglietto-Vargas, D., Martini, A.C., Trujillo-Estrada, L., LaFerla, F.M., 2017. Synaptic impairment in Alzheimer's disease: a dysregulated symphony. Trends. Neurosci. 40, 347–357.
Forstl, H., 1998. Alzheimer's disease: the size of the problem, clinical manifestation and heterogeneity. J. Neural Transm. Suppl. 54, 1–8.
Francis, P.T., Palmer, A.M., Snape, M., Wilcock, G.K., 1999. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J. Neurol. Neurosurg. Psychiatr. 66, 137–147.
Gahete, M.D., Rubio, A., Cordoba-Chacon, J., Gracia-Navarro, F., Kineman, R.D., Avila, J., Luque, R.M., Castano, J.P., 2010. Expression of the ghrelin and neurotensin systems is altered in the temporal lobe of Alzheimer's disease patients. J. Alzheimers Dis. 22, 819–828.
Garcia, J.M., Friend, J., Allen, S., 2013. Therapeutic potential of anamorelin, a novel, oral ghrelin mimetic, in patients with cancer-related cachexia: a multicenter, randomized, double-blind, crossover, pilot study. Support. Care Cancer 21, 129–137.
Garin, M.C., Burns, C.M., Kaul, S., Cappola, A.R., 2013. Clinical review: the human experience with ghrelin administration. J. Clin. Endocrinol. Metab. 98, 1826–1837.
Gauna, C., van de Zande, B., van Kerkwijk, A., Themmen, A.P., van der Lely, A.J., Delhanty, P.J., 2007. Unacylated ghrelin is not a functional antagonist but a full agonist of the type 1a growth hormone secretagogue receptor (GHS-R). Mol. Cell. Endocrinol. 274, 30–34.
Gilman, S., Koller, M., Black, R.S., Jenkins, L., Griffith, S.G., Fox, N.C., Eisner, L., Kirby, L., Rovira, M.B., Forette, F., Orgogozo, J.M., 2005. Clinical effects of Abeta immunization (AN1792) in patients with AD in an interrupted trial. Neurology 64, 1553–1562.
Gnanapavan, S., Kola, B., Bustin, S.A., Morris, D.G., McGee, P., Fairclough, P., Bhattacharya, S., Carpenter, R., Grossman, A.B., Korbonits, M., 2002. The tissue distribution of the mRNA of ghrelin and subtypes of its receptor, GHS-R, in humans. J. Clin. Endocrinol. Metab. 87, 2988.
Gomes, S., Martins, I., Fonseca, A.C., Oliveira, C.R., Resende, R., Pereira, C.M., 2014. Protective effect of leptin and ghrelin against toxicity induced by amyloid-beta oligomers in a hypothalamic cell line. J. Neuroendocrinol. 26, 176–185.
Goshadrou, F., Arefi Oskouie, A., Eslami, M., Nobakht Mothlagh Ghoochani, B.F., 2018. Effect of ghrelin on serum metabolites in Alzheimer's disease model rats; a metabolomics studies based on 1H-NMR technique. Iran. J. Basic Med. Sci. 21, 1245–1254.
Grady, C.L., Haxby, J.V., Horwitz, B., Sundaram, M., Berg, G., Schapiro, M., Friedland, R.P., Rapoport, S.I., 1988. Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. J. Clin. Exp. Neuropsychol. 10, 576–596.
Grossberg, G.T., 2003. Cholinesterase inhibitors for the treatment of Alzheimer's disease:: getting on and staying on. Curr. Ther. Res. Clin. Exp. 64, 216–235.
Guan, X.M., Yu, H., Palyha, O.C., McKee, K.K., Feighner, S.D., Sirinathsinghji, D.J., Smith, R.G., Van der Ploeg, L.H., Howard, A.D., 1997. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Res. Mol. Brain Res. 48, 23–29.
Guneli, E., Onal, A., Ates, M., Bagriyanik, H.A., Resmi, H., Orhan, C.E., Kolatan, H.E., Gumustekin, M., 2010. Effects of repeated administered ghrelin on chronic constriction injury of the sciatic nerve in rats. Neurosci. Lett. 479, 226–230.
Haass, C., Selkoe, D.J., 2007. Soluble protein oligomers in neurodegeneration: lessons from the Alzheimer's amyloid beta-peptide. Nat. Rev. Mol. Cell Biol. 8, 101–112.
Hardy, J.A., Higgins, G.A., 1992. Alzheimer's disease: the amyloid cascade hypothesis. Science 256, 184–185.
Hauptmann, S., Keil, U., Scherping, I., Bonert, A., Eckert, A., Muller, W.E., 2006. Mitochondrial dysfunction in sporadic and genetic Alzheimer's disease. Exp. Gerontol. 41, 668–673.
Heneka, M.T., Carson, M.J., El Khoury, J., Landreth, G.E., Brosseron, F., Feinstein, D.L., Jacobs, A.H., Wyss-Coray, T., Vitorica, J., Ransohoff, R.M., Herrup, K., Frautschy, S.A., Finsen, B., Brown, G.C., Verkhratsky, A., Yamanaka, K., Koistinaho, J., Latz, E., Halle, A., Petzold, G.C., Town, T., Morgan, D., Shinohara, M.L., Perry, V.H., Holmes, C., Bazan, N.G., Brooks, D.J., Hunot, S., Joseph, B., Deigendesch, N., Garaschuk, O., Boddeke, E., Dinarello, C.A., Breitner, J.C., Cole, G.M., Golenbock, D.T., Kummer, M.P., 2015. Neuroinflammation in Alzheimer's disease. Lancet Neurol. 14, 388–405.
Hirai, K., Aliev, G., Nunomura, A., Fujioka, H., Russell, R.L., Atwood, C.S., Johnson, A.B., Kress, Y., Vinters, H.V., Tabaton, M., Shimohama, S., Cash, A.D., Siedlak, S.L., Harris,

P.L., Jones, P.K., Petersen, R.B., Perry, G., Smith, M.A., 2001. Mitochondrial abnormalities in Alzheimer's disease. J. Neurosci. 21, 3017–3023.
Hodges, J.R., Patterson, K., 1995. Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. Neuropsychologia 33, 441–459.
Hollands, C., Bartolotti, N., Lazarov, O., 2016. Alzheimer's disease and hippocampal adult neurogenesis; exploring shared mechanisms. Front. Neurosci. 10, 178.
Holtzman, D.M., Morris, J.C., Goate, A.M., 2011. Alzheimer's disease: the challenge of the second century. Sci. Transl. Med. 3, 77sr71.
Howick, K., Griffin, B.T., Cryan, J.F., Schellekens, H., 2017. From belly to brain: targeting the ghrelin receptor in appetite and food intake regulation. Int. J. Mol. Sci. 18.
Hsieh, H., Boehm, J., Sato, C., Iwatsubo, T., Tomita, T., Sisodia, S., Malinow, R., 2006. AMPAR removal underlies Abeta-induced synaptic depression and dendritic spine loss. Neuron 52, 831–843.
Huang, Y., Mucke, L., 2012. Alzheimer mechanisms and therapeutic strategies. Cell 148, 1204–1222.
Imbimbo, B.P., Ottonello, S., Frisardi, V., Solfrizzi, V., Greco, A., Seripa, D., Pilotto, A., Panza, F., 2012. Solanezumab for the treatment of mild-to-moderate Alzheimer's disease. Expert Rev. Clin. Immunol. 8, 135–149.
Iqbal, K., Alonso Adel, C., Chen, S., Chohan, M.O., El-Akkad, E., Gong, C.X., Khatoon, S., Li, B., Liu, F., Rahman, A., Tanimukai, H., Grundke-Iqbal, I., 2005. Tau pathology in Alzheimer disease and other tauopathies. Biochim. Biophys. Acta 1739, 198–210.
Jackson, T.M., Ostrowski, T.D., Middlemas, D.S., 2019. Intracerebroventricular ghrelin administration increases depressive-like behavior in male juvenile rats. Front. Behav. Neurosci. 13, 77.
Jeong, Y.O., Shin, S.J., Park, J.Y., Ku, B.K., Song, J.S., Kim, J.J., Jeon, S.G., Lee, S.M., Moon, M., 2018. MK-0677, a ghrelin agonist, alleviates amyloid beta-related pathology in 5XFAD mice, an animal model of Alzheimer's disease. Int. J. Mol. Sci. 19.
Jin, K., Galvan, V., Xie, L., Mao, X.O., Gorostiza, O.F., Bredesen, D.E., Greenberg, D.A., 2004a. Enhanced neurogenesis in Alzheimer's disease transgenic (PDGF-APPSw, Ind) mice. Proc. Natl. Acad. Sci. U. S. A. 101, 13363–13367.
Jin, K., Peel, A.L., Mao, X.O., Xie, L., Cottrell, B.A., Henshall, D.C., Greenberg, D.A., 2004b. Increased hippocampal neurogenesis in Alzheimer's disease. Proc. Natl. Acad. Sci. U. S. A. 101, 343–347.
Joza, N., Susin, S.A., Daugas, E., Stanford, W.L., Cho, S.K., Li, C.Y., Sasaki, T., Elia, A.J., Cheng, H.Y., Ravagnan, L., Ferri, K.F., Zamzami, N., Wakeham, A., Hakem, R., Yoshida, H., Kong, Y.Y., Mak, T.W., Zuniga-Pflucker, J.C., Kroemer, G., Penninger, J.M., 2001. Essential role of the mitochondrial apoptosis-inducing factor in programmed cell death. Nature 410, 549–554.
Kang, S., Moon, N.R., Kim, D.S., Kim, S.H., Park, S., 2015. Central acylated ghrelin improves memory function and hippocampal AMPK activation and partly reverses the impairment of energy and glucose metabolism in rats infused with beta-amyloid. Peptides 71, 84–93.
Kayed, R., Head, E., Thompson, J.L., McIntire, T.M., Milton, S.C., Cotman, C.W., Glabe, C.G., 2003. Common structure of soluble amyloid oligomers implies common mechanism of pathogenesis. Science (New York, N.Y.) 300, 486–489.
Khlistunova, I., Biernat, J., Wang, Y., Pickhardt, M., von Bergen, M., Gazova, Z., Mandelkow, E., Mandelkow, E.M., 2006. Inducible expression of Tau repeat domain in cell models of tauopathy: aggregation is toxic to cells but can be reversed by inhibitor drugs. J. Biol. Chem. 281, 1205–1214.
Kim, C., Kim, S., Park, S., 2017. Neurogenic effects of ghrelin on the Hippocampus. Int. J. Mol. Sci. 18.
Kroemer, G., Reed, J.C., 2000. Mitochondrial control of cell death. Nat. Med. 6, 513–519.
Ku, J.M., Taher, M., Chin, K.Y., Barsby, T., Austin, V., Wong, C.H., Andrews, Z.B., Spencer, S.J., Miller, A.A., 2016. Protective actions of des-acylated ghrelin on brain injury and blood-brain barrier disruption after stroke in mice. Clin. Sci. (Lond.) 130, 1545–1558.
Kumar, A., Singh, A., Ekavali, 2015. A review on Alzheimer's disease pathophysiology and its management: an update. Pharmacol. Rep. 67, 195–203.
Kummer, M.P., Hammerschmidt, T., Martinez, A., Terwel, D., Eichele, G., Witten, A., Figura, S., Stoll, M., Schwartz, S., Pape, H.C., Schultze, J.L., Weinshenker, D., Heneka, M.T., Urban, I., 2014. Ear2 deletion causes early memory and learning deficits in APP/PS1 mice. J. Neurosci. 34, 8845–8854.
Kunath, N., Muller, N.C.J., Tonon, M., Konrad, B.N., Pawlowski, M., Kopczak, A., Elbau, I., Uhr, M., Kuhn, S., Repantis, D., Ohla, K., Muller, T.D., Fernandez, G., Tschop, M., Czisch, M., Steiger, A., Dresler, M., 2016. Ghrelin modulates encoding-related brain function without enhancing memory formation in humans. Neuroimage 142, 465–473.
Kunath, N., van Groen, T., Allison, D.B., Kumar, A., Dozier-Sharpe, M., Kadish, I., 2015. Ghrelin agonist does not foster insulin resistance but improves cognition in an Alzheimer's disease mouse model. Sci. Rep. 5, 11452.
Lattuada, D., Crotta, K., Tonna, N., Casnici, C., Benfante, R., Fornasari, D., Bianco, F., Longhi, R., Marelli, O., 2013. The expression of GHS-R in primary neurons is dependent upon maturation stage and regional localization. PLoS One 8, e64183.
Lee, J., Seroogy, K.B., Mattson, M.P., 2002. Dietary restriction enhances neurotrophin expression and neurogenesis in the hippocampus of adult mice. J. Neurochem. 80, 539–547.
Lee, J.Y., Oh, T.H., Yune, T.Y., 2011. Ghrelin inhibits hydrogen peroxide-induced apoptotic cell death of oligodendrocytes via ERK and p38MAPK signaling. Endocrinology 152, 2377–2386.
Lesort, M., Jope, R.S., Johnson, G.V., 1999. Insulin transiently increases tau phosphorylation: involvement of glycogen synthase kinase-3beta and Fyn tyrosine kinase. J. Neurochem. 72, 576–584.
Leugers, C.J., Koh, J.Y., Hong, W., Lee, G., 2013. Tau in MAPK activation. Front. Neurol. 4, 161.
Li, E., Chung, H., Kim, Y., Kim, D.H., Ryu, J.H., Sato, T., Kojima, M., Park, S., 2013. Ghrelin directly stimulates adult hippocampal neurogenesis: implications for learning and memory. Endocr. J. 60, 781–789.
Li, W.G., Gavrila, D., Liu, X., Wang, L., Gunnlaugsson, S., Stoll, L.L., McCormick, M.L., Sigmund, C.D., Tang, C., Weintraub, N.L., 2004. Ghrelin inhibits proinflammatory responses and nuclear factor-kappaB activation in human endothelial cells. Circulation 109, 2221–2226.
Lindqvist, A., Mohapel, P., Bouter, B., Frielingsdorf, H., Pizzo, D., Brundin, P., Erlanson-Albertsson, C., 2006. High-fat diet impairs hippocampal neurogenesis in male rats. Eur. J. Neurol. 13, 1385–1388.
Lindsay, J., Laurin, D., Verreault, R., Hebert, R., Helliwell, B., Hill, G.B., McDowell, I., 2002. Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. Am. J. Epidemiol. 156, 445–453.
Liu, Y., Chen, L., Xu, X., Vicaut, E., Sercombe, R., 2009. Both ischemic preconditioning and ghrelin administration protect hippocampus from ischemia/reperfusion and upregulate uncoupling protein-2. BMC Physiol. 9, 17.
Liu, Y., Wang, P.S., Xie, D., Liu, K., Chen, L., 2006. Ghrelin reduces injury of hippocampal neurons in a rat model of cerebral ischemia/reperfusion. Chin. J. Physiol. 49, 244–250.
Lopez Soto, E.J., Agosti, F., Cabral, A., Mustafa, E.R., Damonte, V.M., Gandini, M.A., Rodriguez, S., Castrogiovanni, D., Felix, R., Perello, M., Raingo, J., 2015. Constitutive and ghrelin-dependent GHSR1a activation impairs CaV2.1 and CaV2.2 currents in hypothalamic neurons. J. Gen. Physiol. 146, 205–219.
Lutter, M., Sakata, I., Osborne-Lawrence, S., Rovinsky, S.A., Anderson, J.G., Jung, S., Birnbaum, S., Yanagisawa, M., Elmquist, J.K., Nestler, E.J., Zigman, J.M., 2008. The orexigenic hormone ghrelin defends against depressive symptoms of chronic stress. Nat. Neurosci. 11, 752–753.
Madhavadas, S., Kutty, B.M., Subramanian, S., 2014. Amyloid beta lowering and cognition enhancing effects of ghrelin receptor analog [D-Lys (3)] GHRP-6 in rat model of obesity. Indian J. Biochem. Biophys. 51, 257–262.
Malpass, K., 2013. Alzheimer disease: plaque-specific anti-A[beta] antibody shows promise in model of AD. Nat. Rev. Neurol. 9, 61.
Mao, Y., Cheng, J., Yu, F., Li, H., Guo, C., Fan, X., 2015a. Ghrelin attenuated lipotoxicity via autophagy induction and nuclear Factor-kappaB inhibition. Cell. Physiol. Biochem. 37, 563–576.
Mao, Y., Zhang, S., Yu, F., Li, H., Guo, C., Fan, X., 2015b. Ghrelin attenuates liver fibrosis through regulation of TGF-beta1 expression and autophagy. Int. J. Mol. Sci. 16, 21911–21930.
Marlatt, M.W., Lucassen, P.J., 2010. Neurogenesis and Alzheimer's disease: biology and pathophysiology in mice and men. Curr. Alzheimer Res. 7, 113–125.
Martins, I., Gomes, S., Costa, R.O., Otvos, L., Oliveira, C.R., Resende, R., Pereira, C.M., 2013. Leptin and ghrelin prevent hippocampal dysfunction induced by Abeta oligomers. Neuroscience 241, 41–51.
Masliah, E., Mallory, M., Alford, M., DeTeresa, R., Hansen, L.A., McKeel Jr., D.W., Morris, J.C., 2001. Altered expression of synaptic proteins occurs early during progression of Alzheimer's disease. Neurology 56, 127–129.
McGleenon, B.M., Dynan, K.B., Passmore, A.P., 1999. Acetylcholinesterase inhibitors in Alzheimer's disease. Br. J. Clin. Pharmacol. 48, 471–480.
Moon, M., Cha, M.Y., Mook-Jung, I., 2014. Impaired hippocampal neurogenesis and its enhancement with ghrelin in 5XFAD mice. J. Alzheimers Dis. 41, 233–241.
Moon, M., Choi, J.G., Nam, D.W., Hong, H.S., Choi, Y.J., Oh, M.S., Mook-Jung, I., 2011. Ghrelin ameliorates cognitive dysfunction and neurodegeneration in intrahippocampal amyloid-beta1-42 oligomer-injected mice. J. Alzheimers Dis. 23, 147–159.
Moon, M., Kim, H.G., Hwang, L., Seo, J.H., Kim, S., Hwang, S., Kim, S., Lee, D., Chung, H., Oh, M.S., Lee, K.T., Park, S., 2009a. Neuroprotective effect of ghrelin in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease by blocking microglial activation. Neurotox. Res. 15, 332–347.
Moon, M., Kim, S., Hwang, L., Park, S., 2009b. Ghrelin regulates hippocampal neurogenesis in adult mice. Endocr. J. 56, 525–531.
Mousseaux, D., Le Gallic, L., Ryan, J., Oiry, C., Gagne, D., Fehrentz, J.A., Galleyrand, J.C., Martinez, J., 2006. Regulation of ERK1/2 activity by ghrelin-activated growth hormone secretagogue receptor 1A involves a PLC/PKCvarepsilon pathway. Br. J. Pharmacol. 148, 350–365.
Mu, Y., Gage, F.H., 2011. Adult hippocampal neurogenesis and its role in Alzheimer's disease. Mol. Neurodegener. 6, 85.
Mucke, L., Selkoe, D.J., 2012. Neurotoxicity of amyloid beta-protein: synaptic and network dysfunction. Cold Spring Harb. Perspect. Med. 2, a006338.
Muller, T.D., Nogueiras, R., Andermann, M.L., Andrews, Z.B., Anker, S.D., Argente, J., Batterham, R.L., Benoit, S.C., Bowers, C.Y., Broglio, F., Casanueva, F.F., D'Alessio, D., Depoortere, I., Geliebter, A., Ghigo, E., Cole, P.A., Cowley, M., Cummings, D.E., Dagher, A., Diano, S., Dickson, S.L., Dieguez, C., Granata, R., Grill, H.J., Grove, K., Habegger, K.M., Heppner, K., Heiman, M.L., Holsen, L., Holst, B., Inui, A., Jansson, J.O., Kirchner, H., Korbonits, M., Laferrere, B., LeRoux, C.W., Lopez, M., Morin, S., Nakazato, M., Nass, R., Perez-Tilve, D., Pfluger, P.T., Schwartz, T.W., Seeley, R.J., Sleeman, M., Sun, Y., Sussel, L., Tong, J., Thorner, M.O., van der Lely, A.J., van der Ploeg, L.H., Zigman, J.M., Kojima, M., Kangawa, K., Smith, R.G., Horvath, T., Tschop, M.H., 2015. Ghrelin. Mol. Metab. 4, 437–460.
Mundinger, T.O., Cummings, D.E., Taborsky Jr., G.J., 2006. Direct stimulation of ghrelin secretion by sympathetic nerves. Endocrinology 147, 2893–2901.
Mungarro-Menchaca, X., Ferrera, P., Moran, J., Arias, C., 2002. Beta-Amyloid peptide induces ultrastructural changes in synaptosomes and potentiates mitochondrial dysfunction in the presence of ryanodine. J. Neurosci. Res. 68, 89–96.
Nass, R., Pezzoli, S.S., Oliveri, M.C., Patrie, J.T., Harrell Jr., F.E., Clasey, J.L., Heymsfield, S.B., Bach, M.A., Vance, M.L., Thorner, M.O., 2008. Effects of an oral ghrelin mimetic on body composition and clinical outcomes in healthy older adults: a randomized trial. Ann. Intern. Med. 149, 601–611.

Nervi, A., Reitz, C., Tang, M.-X., Santana, V., Piriz, A., Reyes, D., Lantigua, R., Medrano, M., Jimenez, I., Lee, J.H., Mayeux, R., 2008. Comparison of clinical manifestation in familial Alzheimer's disease and dementia with Lewy bodies. Arch. Neurol. 65, 1634–1639.
Nestor, P.J., Scheltens, P., Hodges, J.R., 2004. Advances in the early detection of Alzheimer's disease. Nat. Med. 10 (Suppl), S34–41.
Nixon, R.A., 2007. Autophagy, amyloidogenesis and Alzheimer disease. J. Cell. Sci. 120, 4081–4091.
Nogueiras, R., Tschop, M.H., Zigman, J.M., 2008. Central nervous system regulation of energy metabolism: ghrelin versus leptin. Ann. N. Y. Acad. Sci. 1126, 14–19.
Panza, F., Frisardi, V., Solfrizzi, V., Imbimbo, B.P., Logroscino, G., Santamato, A., Greco, A., Seripa, D., Pilotto, A., 2012. Immunotherapy for Alzheimer's disease: from anti-beta-amyloid to tau-based immunization strategies. Immunotherapy 4, 213–238.
Parsons, C.G., Danysz, W., Dekundy, A., Pulte, I., 2013. Memantine and cholinesterase inhibitors: complementary mechanisms in the treatment of alzheimer's disease. Neurotox. Res. 24, 358–369.
Perry, R.J., Hodges, J.R., 2000. Fate of patients with questionable (very mild) Alzheimer's disease: longitudinal profiles of individual subjects' decline. Dement. Geriatr. Cogn. Disord. 11, 342–349.
Perry, R.J., Watson, P., Hodges, J.R., 2000. The nature and staging of attention dysfunction in early (minimal and mild) Alzheimer's disease: relationship to episodic and semantic memory impairment. Neuropsychologia 38, 252–271.
Pinho, C.M., Teixeira, P.F., Glaser, E., 2014. Mitochondrial import and degradation of amyloid-beta peptide. Biochim. Biophys. Acta 1837, 1069–1074.
Planel, E., Miyasaka, T., Launey, T., Chui, D.H., Tanemura, K., Sato, S., Murayama, O., Ishiguro, K., Tatebayashi, Y., Takashima, A., 2004. Alterations in glucose metabolism induce hypothermia leading to tau hyperphosphorylation through differential inhibition of kinase and phosphatase activities: implications for Alzheimer's disease. J. Neurosci. 24, 2401–2411.
Pradhan, G., Samson, S.L., Sun, Y., 2013. Ghrelin: much more than a hunger hormone. Curr. Opin. Clin. Nutr. Metab. Care 16, 619–624.
Qin, L., Liu, Y., Cooper, C., Liu, B., Wilson, B., Hong, J.S., 2002. Microglia enhance beta-amyloid peptide-induced toxicity in cortical and mesencephalic neurons by producing reactive oxygen species. J. Neurochem. 83, 973–983.
Qu, R., Chen, X., Hu, J., Fu, Y., Peng, J., Li, Y., Chen, J., Li, P., Liu, L., Cao, J., Wang, W., Qiu, C., Guo, L., Vasilev, K., Chen, J., Zhou, G., Li, W., Zhao, Y., 2019. Ghrelin protects against contact dermatitis and psoriasiform skin inflammation by antagonizing TNF-alpha/NF-kappaB signaling pathways. Sci. Rep. 9, 1348.
Querfurth, H.W., LaFerla, F.M., 2010. Alzheimer's disease. N. Engl. J. Med. 362, 329–344.
Ratcliff, M., Rees, D., McGrady, S., Buntwal, L., Hornsby, A.K.E., Bayliss, J., Kent, B.A., Bussey, T., Saksida, L., Beynon, A.L., Howell, O.W., Morgan, A.H., Sun, Y., Andrews, Z.B., Wells, T., Davies, J.S., 2019. Calorie restriction activates new adult born olfactory-bulb neurones in a ghrelin-dependent manner but acyl-ghrelin does not enhance subventricular zone neurogenesis. J. Neuroendocrinol. e12755.
Rhein, V., Song, X., Wiesner, A., Ittner, L.M., Baysang, G., Meier, F., Ozmen, L., Bluethmann, H., Drose, S., Brandt, U., Savaskan, E., Czech, C., Gotz, J., Eckert, A., 2009. Amyloid-beta and tau synergistically impair the oxidative phosphorylation system in triple transgenic Alzheimer's disease mice. Proc. Natl. Acad. Sci. U. S. A. 106, 20057–20062.
Ribeiro, L.F., Catarino, T., Santos, S.D., Benoist, M., van Leeuwen, J.F., Esteban, J.A., Carvalho, A.L., 2014. Ghrelin triggers the synaptic incorporation of AMPA receptors in the hippocampus. Proc. Natl. Acad. Sci. U. S. A. 111, E149–158.
Rigamonti, A.E., Pincelli, A.I., Corra, B., Viarengo, R., Bonomo, S.M., Galimberti, D., Scacchi, M., Scarpini, E., Cavagnini, F., Muller, E.E., 2002. Plasma ghrelin concentrations in elderly subjects: comparison with anorexic and obese patients. J. Endocrinol. 175, R1–5.
Roberson, E.D., Halabisky, B., Yoo, J.W., Yao, J., Chin, J., Yan, F., Wu, T., Hamto, P., Devidze, N., Yu, G.Q., Palop, J.J., Noebels, J.L., Mucke, L., 2011. Amyloid-beta/Fyn-induced synaptic, network, and cognitive impairments depend on tau levels in multiple mouse models of Alzheimer's disease. J. Neurosci. 31, 700–711.
Rodriguez, J.J., Verkhratsky, A., 2011. Neurogenesis in Alzheimer's disease. J. Anat. 219, 78–89.
Rossetti, A., Togliatto, G., Rolo, A.P., Teodoro, J.S., Granata, R., Ghigo, E., Columbano, A., Palmeira, C.M., Brizzi, M.F., 2017. Unacylated ghrelin prevents mitochondrial dysfunction in a model of ischemia/reperfusion liver injury. Cell Death Discov. 3, 17077.
Rountree, S.D., Chan, W., Pavlik, V.N., Darby, E.J., Siddiqui, S., Doody, R.S., 2009. Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. Alzheimers Res. Ther. 1, 7.
Santacruz, K., Lewis, J., Spires, T., Paulson, J., Kotilinek, L., Ingelsson, M., Guimaraes, A., DeTure, M., Ramsden, M., McGowan, E., Forster, C., Yue, M., Orne, J., Janus, C., Mariash, A., Kuskowski, M., Hyman, B., Hutton, M., Ashe, K.H., 2005. Tau suppression in a neurodegenerative mouse model improves memory function. Science 309, 476–481.
Santos, V.V., Stark, R., Rial, D., Silva, H.B., Bayliss, J.A., Lemus, M.B., Davies, J.S., Cunha, R.A., Prediger, R.D., Andrews, Z.B., 2017. Acyl ghrelin improves cognition, synaptic plasticity deficits and neuroinflammation following amyloid beta (Abeta1-40) administration in mice. J. Neuroendocrinol. 29.
Scheltens, P., Blennow, K., Breteler, M.M., de Strooper, B., Frisoni, G.B., Salloway, S., Van der Flier, W.M., 2016. Alzheimer's disease. Lancet 388, 505–517.
Selkoe, D.J., 1991. The molecular pathology of Alzheimer's disease. Neuron 6, 487–498.
Selkoe, D.J., 2002. Alzheimer's disease is a synaptic failure. Science 298, 789–791.
Seminara, R.S., Jeet, C., Biswas, S., Kanwal, B., Iftikhar, W., Sakibuzzaman, M., Rutkofsky, I.H., 2018. The neurocognitive effects of ghrelin-induced signaling on the Hippocampus: a promising approach to Alzheimer's disease. Cureus 10, e3285.
Sevigny, J.J., Ryan, J.M., van Dyck, C.H., Peng, Y., Lines, C.R., Nessly, M.L., Group, M.K.P.S., 2008. Growth hormone secretagogue MK-677: no clinical effect on AD progression in a randomized trial. Neurology 71, 1702–1708.
Shankar, G.M., Bloodgood, B.L., Townsend, M., Walsh, D.M., Selkoe, D.J., Sabatini, B.L., 2007. Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. J. Neurosci. 27, 2866–2875.
Shankar, G.M., Walsh, D.M., 2009. Alzheimer's disease: synaptic dysfunction and Abeta. Mol. Neurodegener. 4, 48.
Shibata, N., Ohnuma, T., Kuerban, B., Komatsu, M., Arai, H., 2011. Genetic association between ghrelin polymorphisms and Alzheimer's disease in a Japanese population. Dement. Geriatr. Cogn. Disord. 32, 178–181.
Sibilia, V., Pagani, F., Mrak, E., Dieci, E., Tulipano, G., Ferrucci, F., 2012. Pharmacological characterization of the ghrelin receptor mediating its inhibitory action on inflammatory pain in rats. Amino Acids 43, 1751–1759.
Snyder, E.M., Nong, Y., Almeida, C.G., Paul, S., Moran, T., Choi, E.Y., Nairn, A.C., Salter, M.W., Lombroso, P.J., Gouras, G.K., Greengard, P., 2005. Regulation of NMDA receptor trafficking by amyloid-beta. Nat. Neurosci. 8, 1051–1058.
Spencer, S.J., Miller, A.A., Andrews, Z.B., 2013. The role of ghrelin in neuroprotection after ischemic brain injury. Brain Sci. 3, 344–359.
Spires-Jones, T.L., Hyman, B.T., 2014. The intersection of amyloid beta and tau at synapses in Alzheimer's disease. Neuron 82, 756–771.
Staes, E., Absil, P.A., Lins, L., Brasseur, R., Deleu, M., Lecouturier, N., Fievez, V., Rieux, A., Mingeot-Leclercq, M.P., Raussens, V., Preat, V., 2010. Acylated and unacylated ghrelin binding to membranes and to ghrelin receptor: towards a better understanding of the underlying mechanisms. Biochim. Biophys. Acta 1798, 2102–2113.
Stengel, A., Tache, Y., 2012. Gastric peptides and their regulation of hunger and satiety. Curr. Gastroenterol. Rep. 14, 480–488.
Stoyanova, I.I., 2014. Ghrelin: a link between ageing, metabolism and neurodegenerative disorders. Neurobiol. Dis. 72 (Pt A), 72–83.
Stoyanova, I.I., le Feber, J., 2014. Ghrelin accelerates synapse formation and activity development in cultured cortical networks. BMC Neurosci. 15, 49.
Streit, W.J., 2002. Microglia as neuroprotective, immunocompetent cells of the CNS. Glia 40, 133–139.
Swerdlow, R.H., 2007. Pathogenesis of Alzheimer's disease. Clin. Interv. Aging 2, 347–359.
Tanzi, R.E., 2005. The synaptic Abeta hypothesis of Alzheimer disease. Nat. Neurosci. 8, 977–979.
Terry, R.D., Masliah, E., Salmon, D.P., Butters, N., DeTeresa, R., Hill, R., Hansen, L.A., Katzman, R., 1991. Physical basis of cognitive alterations in Alzheimer's disease: synapse loss is the major correlate of cognitive impairment. Ann. Neurol. 30, 572–580.
Thal, D.R., 2012. The role of astrocytes in amyloid beta-protein toxicity and clearance. Exp. Neurol. 236, 1–5.
Theodoropoulou, A., Metallinos, I.C., Psyrogiannis, A., Vagenakis, G.A., Kyriazopoulou, V., 2012. Ghrelin and leptin secretion in patients with moderate Alzheimer's disease. J. Nutr. Health Aging 16, 472–477.
Tong, X.X., Wu, D., Wang, X., Chen, H.L., Chen, J.X., Wang, X.X., Wang, X.L., Gan, L., Guo, Z.Y., Shi, G.X., Zhang, Y.Z., Jiang, W., 2012. Ghrelin protects against cobalt chloride-induced hypoxic injury in cardiac H9c2 cells by inhibiting oxidative stress and inducing autophagy. Peptides 38, 217–227.
Tschop, M., Weyer, C., Tataranni, P.A., Devanarayan, V., Ravussin, E., Heiman, M.L., 2001. Circulating ghrelin levels are decreased in human obesity. Diabetes 50, 707–709.
Van Cauwenberghe, C., Van Broeckhoven, C., Sleegers, K., 2016. The genetic landscape of Alzheimer disease: clinical implications and perspectives. Genet. Med. 18, 421–430.
Wang, C., Youle, R.J., 2009. The role of mitochondria in apoptosis. Annu. Rev. Genet. 43, 95–118.
Watanabe, J., Matsumoto, M., Kageyama, H., Murai, N., Sasaki, S., Hirako, S., Wada, N., Arata, S., Shioda, S., 2015. Ghrelin suppresses proliferation of fetal neural progenitor cells, and induces their differentiation into neurons. Peptides 69, 40–46.
Wei, Y., Han, C., Wang, Y., Wu, B., Su, T., Liu, Y., He, R., 2015. Ribosylation triggering Alzheimer's disease-like Tau hyperphosphorylation via activation of CaMKII. Aging Cell 14, 754–763.
Wilcock, D.M., Jantzen, P.T., Li, Q., Morgan, D., Gordon, M.N., 2007. Amyloid-beta vaccination, but not nitro-nonsteroidal anti-inflammatory drug treatment, increases vascular amyloid and microhemorrhage while both reduce parenchymal amyloid. Neuroscience 144, 950–960.
Wilcock, D.M., Rojiani, A., Rosenthal, A., Subbarao, S., Freeman, M.J., Gordon, M.N., Morgan, D., 2004. Passive immunotherapy against Abeta in aged APP-transgenic mice reverses cognitive deficits and depletes parenchymal amyloid deposits in spite of increased vascular amyloid and microhemorrhage. J. Neuroinflammation 1, 24.
Wolfe, D.M., Lee, J.H., Kumar, A., Lee, S., Orenstein, S.J., Nixon, R.A., 2013. Autophagy failure in Alzheimer's disease and the role of defective lysosomal acidification. Eur. J. Neurosci. 37, 1949–1961.
Woolley, J.D., Khan, B.K., Natesan, A., Karydas, A., Dallman, M., Havel, P., Miller, B.L., Rankin, K.P., 2014. Satiety-related hormonal dysregulation in behavioral variant frontotemporal dementia. Neurology 82, 512–520.
Wostyn, P., van Dam, D., Audenaert, K., de Deyn, P.P., 2011. Genes involved in cerebrospinal fluid production as candidate genes for late-onset Alzheimer's disease: a hypothesis. J. Neurogenet. 25, 195–200.
Wyss-Coray, T., Mucke, L., 2002. Inflammation in neurodegenerative disease—a double-edged sword. Neuron 35, 419–432.
Xiang, Y., Li, Q., Li, M., Wang, W., Cui, C., Zhang, J., 2011. Ghrelin inhibits AGEs-induced apoptosis in human endothelial cells involving ERK1/2 and PI3K/Akt pathways. Cell Biochem. Funct. 29, 149–155.
Yang, Y., Atasoy, D., Su, H.H., Sternson, S.M., 2011. Hunger states switch a flip-flop

memory circuit via a synaptic AMPK-dependent positive feedback loop. Cell 146, 992–1003.
Yeh, A.H., Jeffery, P.L., Duncan, R.P., Herington, A.C., Chopin, L.K., 2005. Ghrelin and a novel preproghrelin isoform are highly expressed in prostate cancer and ghrelin activates mitogen-activated protein kinase in prostate cancer. Clin. Cancer Res. 11, 8295–8303.
Yu, W.H., Cuervo, A.M., Kumar, A., Peterhoff, C.M., Schmidt, S.D., Lee, J.H., Mohan, P.S., Mercken, M., Farmery, M.R., Tjernberg, L.O., Jiang, Y., Duff, K., Uchiyama, Y., Naslund, J., Mathews, P.M., Cataldo, A.M., Nixon, R.A., 2005. Macroautophagy—a novel beta-amyloid peptide-generating pathway activated in Alzheimer's disease. J. Cell Biol. 171, 87–98.
Zhang, Y., Fang, F., Goldstein, J.L., Brown, M.S., Zhao, T.J., 2015. Reduced autophagy in livers of fasted, fat-depleted, ghrelin-deficient mice: reversal by growth hormone. Proc. Natl. Acad. Sci. U. S. A. 112, 1226–1231.
Zhao, T.J., Sakata, I., Li, R.L., Liang, G., Richardson, J.A., Brown, M.S., Goldstein, J.L., Zigman, J.M., 2010. Ghrelin secretion stimulated by {beta}1-adrenergic receptors in cultured ghrelinoma cells and in fasted mice. Proc. Natl. Acad. Sci. U. S. A. 107, 15868–15873.
Zhao, Z., Liu, H., Xiao, K., Yu, M., Cui, L., Zhu, Q., Zhao, R., Li, G.D., Zhou, Y., 2014. Ghrelin administration enhances neurogenesis but impairs spatial learning and memory in adult mice. Neuroscience 257, 175–185.
Zhou, X., Xue, C., 2009. Ghrelin inhibits the development of acute pancreatitis and nuclear factor kappaB activation in pancreas and liver. Pancreas 38, 752–757.
Zigman, J.M., Jones, J.E., Lee, C.E., Saper, C.B., Elmquist, J.K., 2006. Expression of ghrelin receptor mRNA in the rat and the mouse brain. J. Comp. Neurol. 494, 528–548.