REVIEW

The impact of anorexigenic peptides in experimental models of Alzheimer’s disease pathology

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Abstract

Alzheimer’s disease (AD) is the most prevalent neurodegenerative disorder in the elderly population. Numerous epidemiological and experimental studies have demonstrated that patients who suffer from obesity or type 2 diabetes mellitus have a higher risk of cognitive dysfunction and AD. Several recent studies demonstrated that food intake-lowering (anorexigenic) peptides have the potential to improve metabolic disorders and that they may also potentially be useful in the treatment of neurodegenerative diseases. In this review, the neuroprotective effects of anorexigenic peptides of both peripheral and central origins are discussed. Moreover, the role of leptin as a key modulator of energy homeostasis is discussed in relation to its interaction with anorexigenic peptides and their analogs in AD-like pathology. Although there is no perfect experimental model of human AD pathology, animal studies have already proven that anorexigenic peptides exhibit neuroprotective properties. This phenomenon is extremely important for the potential development of new drugs in view of the aging of the human population and of the significantly increasing incidence of AD.

Introduction

A major problem in developed countries is that, although longevity has increased, the incidence of several so-called diseases of civilization is increasing simultaneously. Neurodegenerative diseases, obesity, type 2 diabetes mellitus (T2DM), hypertension and other diseases are profound examples of this tendency. Obesity, as well as Alzheimer’s disease (AD), directly affects millions of adults each year and results in health care costs in the billions of dollars range. It is estimated that care for AD patients costs USA $214 billion a year, and this will grow up approximately to $1.2 trillion in 2050 (Kim & Feldman 2015). Moreover, on the basis of WHO estimations for developed countries it is evident that the number of affected people by dementia including AD will double every 20 years to 81.1 million by 2040 (Ferri et al. 2005). Despite many advances in understanding of the etiology of all above-mentioned diseases, there is still no effective therapy for both these problems.

It has been suggested that some food intake-regulating peptides could be promising candidates for obesity and T2DM treatment (Maletinska et al. 2015, van der Klaauw 2018) and may also alleviate the cognitive deficits of neurodegenerative disorders (Giuliani et al. 2017, Holscher 2018, Mandal et al. 2018). Anorexigenic peptides lower food intake, while orexigenic peptides increase it. In the hypothalamus and hindbrain, these peptides act to
affect the feelings of hunger and satiety (Kunes et al. 2016, Andermann & Lowell 2017). These peptides are released not only in various parts of the central nervous system (CNS), mainly in the hypothalamus and brainstem (such as anorexigenic cocaine- and amphetamine-regulated transcript peptide, melanocortins or prolactin-releasing peptide and orexigenic neuropeptide Y or orexins), but also in the periphery (such as anorexigenic leptin, glucagon-like peptide and cholecystokinin and orexigenic ghrelin) (Fig. 1), and they all act centrally to regulate energy homeostasis (Spiegelman & Flier 2001, Frago & Chownen 2015, Prinz & Stengel 2017). Although many of these peptides have been known for a relatively long time, their mechanism of action and their interactions are still poorly understood. For example, in obese animals, the regulation of food intake and energy expenditure does not function properly; the levels of hormones responsible for the feeling of satiety are high, but their effect on the target tissue is compromised (Cui et al. 2017).

Moreover, a major problem associated with natural peptides is their low stability in the organism and their difficulty in crossing the blood–brain barrier (BBB) after peripheral application. Proposed solutions (e.g. lipidization) to these problems were summarized in several papers (Malavolta & Cabral 2011, Ahrens et al. 2012, Kunes et al. 2016).

AD is the most common cause of progressive dementia in the elderly population and is increasing in incidence (Nitrini et al. 2009, Curiati et al. 2014). AD is histologically characterized by the accumulation of amyloid-β protein (Aβ) as extracellular plaques and by the deposition of hyperphosphorylated tau protein in intracellular neurofibrillary tangles (NFT). Although several biomarkers for specific phases of AD have been described, a definitive diagnosis requires postmortem brain autopsy (Cummings 2011, Humpel 2011). It was demonstrated that lifestyle factors as well as the symptoms of metabolic syndrome (MetS), such as obesity, hypertension or glucose intolerance, play a critical role in the onset of dementia and AD as well as in their progression (Lara et al. 2013). To date, MetS has received relatively little attention as a risk factor for AD because epidemiological studies have not produced unambiguous results.

The objective of this review is to summarize current information on the potential neuroprotective properties of food intake-lowering (anorexigenic) peptides that have been tested in experimental models of AD-like pathology. We wish to speculate about the central integrative role of leptin, an adipose-derived anorexigenic protein that plays a key role in energy homeostasis, in these effects.

Accumulating evidence has indicated an association between higher serum leptin levels and lower frequency of dementia and/or mild cognitive impairment in women with normal body mass index (Zeki Al Hazzouri et al. 2013), suggesting that leptin might be a better predictor...
of dementia than traditional anthropometric measures such as height, weight and body mass index. Blood leptin levels were found to be negatively related to the incidence of dementia and AD (Lieb et al. 2009) and higher blood leptin level was suggested to be protective against cognitive decline and AD development (Holden et al. 2009). However, attenuated leptin concentrations were found in CSF and hippocampal tissue of AD patients (Bonda et al. 2014). Regarding brain leptin, leptin mRNA was undetectable in both neocortex and hippocampus of APP/PS1 mice and their WT controls until 18 months of age. It shows that leptin in both healthy and AD-like brain is not expressed in the brain areas connected with cognitive memory (King et al. 2018). However, age-dependent Aβ levels in the brain areas mentioned were linked to disturbed leptin signaling (King et al. 2018).

**MetS as a risk factor for AD**

Metabolic syndrome (MetS), also known as insulin resistance syndrome, was first described by Barker (Barker et al. 1993). In general, MetS is a cluster of common symptoms involving several vascular risk factors combining obesity, dyslipidemia, insulin resistance, glucose intolerance and arterial hypertension (Ricci et al. 2017). Together with obesity and insulin resistance, MetS increases the probability of development of AD and other neurodegenerative diseases in the elderly (Razay et al. 2007, Raffaitin et al. 2009).

Interestingly, a meta-analysis of the relationship between MetS and cognitive function clearly demonstrated the association between MetS and longitudinal changes in cognitive function (Siervo et al. 2014). The authors analyzed 13 studies, with a total sample size of 19,522 subjects. Although a small association of MetS with cognitive decline was observed, a marginal significant association was observed in the younger old group after age-stratification. These results emphasize the importance of age-stratified risk prediction models of dementia in subjects with chronic metabolic disorders.

**Type 2 diabetes mellitus (T2DM)**

It was demonstrated in epidemiological studies that patients with T2DM have a higher incidence of AD (Vagelatos & Eslick 2013, Ricci et al. 2017). T2DM is a serious metabolic and endocrine disorder that is characterized by resistance to the effects of insulin in the periphery, leading to increased glucose levels in the blood. One of the major risk factors for T2DM development is obesity that contributes to the development of insulin resistance through several mechanisms including increased plasma concentrations of free fatty acids leading to impaired β-cell function, increased levels of pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 6 (IL-6) and disturbances in hormone levels (increased levels of glucagon and leptin, decreased level of adiponectin) (Liu et al. 2016). Furthermore, it was discovered that T2DM and AD share several molecular processes that underlie the degenerative developments that occur in these two conditions. Disturbances in insulin signaling appear to be the main common impairment that affects cell growth and differentiation, cellular repair mechanisms, energy metabolism and glucose utilization. Insulin not only regulates blood glucose levels but also acts as a growth factor on all cells, including neurons in the CNS (Pomytkin et al. 2018).

Impairment of insulin signaling therefore not only affects blood glucose levels but also causes numerous degenerative processes. Other growth factors involved in signaling systems, such as insulin-like growth factors (IGFs) and transforming growth factors, are also impaired in both conditions (Li & Holscher 2007). Based on the similarity of these mechanisms, AD has been referred to as ‘type 3 diabetes’ (Steen et al. 2005, de la Monte 2014).

**Type 3 diabetes**

The concept that AD represents type 3 diabetes is supported by a number of findings. It was demonstrated that cerebral glucose utilization and energy metabolism worsen with the progression of cognitive impairment. This result could be related to impairment of insulin and IGF expression in AD because insulin/IGF receptor binding is reduced (de la Monte et al. 2006). The cited work demonstrates extensive impairment in insulin and IGF type I and II (IGF-I and IGF-II) signaling mechanisms in brains with AD.

In the CNS, insulin is required for neuronal synaptic and dendritic plasticity, for learning, and for memory formation triggered through the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) (Dineley et al. 2014). It was discovered that aging causes a significant decrease in insulin receptor (IR) number and in the concentration of insulin itself, thus leading to impaired insulin signaling and memory deficits in elderly people (Dineley et al. 2014, Velazquez et al. 2017).

As shown in Fig. 2, in physiological condition, insulin binds to the IR which cause autophosphorylation of the
tyrosine kinase domain of the IR which subsequently trigger activation of other kinases, such as insulin receptor substrate 1 (IRS-1), regulatory subunit of phosphoinositide 3 kinase (PI3K) p85 or Akt. Activated Akt phosphorylates glycogen synthase kinase 3β (GSK-3β) at Ser9, thereby inhibiting the kinase activity of GSK-3 (Liu et al. 2011). Besides insulin, leptin contributes to activation of Akt and reversely, leptin resistance results in a lowered Akt activation (Fig. 2). In old APP/PS1 mice, a decrease in Akt activation through an increase in suppressor of cytokine signaling (SOCS3) was linked to an inefficient leptin signaling (King et al. 2018).

Thus, in central insulin resistance, activation of the insulin signaling cascade is impaired; this outcome is manifested by decreased phosphorylation of the implicated kinases and finally by decreased phosphorylation of GSK-3β at Ser9, its inhibitory site. This decreased phosphorylation leads to GSK-3β activation. GSK-3β is one of the most important kinases implicated in the hyperphosphorylation of tau (Dineley et al. 2014). GSK-3β kinase can be phosphorylated by AMP-activated protein kinase (AMPK) that is in the brain – unlike the periphery – inhibited though leptin signaling, which is as it was shown in neuronal cells (Greco et al. 2009). Insulin resistance could result from improper leptin signaling as shown in Fig. 2. In db/db mouse with non-functional leptin receptor, a model of spontaneous T2DM with obesity, hyperinsulinemia, hyperglycemia

Figure 2
Scheme of potential neuroprotective effects of anorexigenic peptides. Activation of leptin receptor (ObRb), insulin receptor (IR), prolactin-releasing peptide (PrRP) and glucagon-like peptide 1 (GLP-1) receptors by their natural or synthetic analogs activate the signaling pathways with potential neuroprotective effect including the IRS-1/PI3/Akt pathway which further resulted in inhibition of apoptosis and increased phosphorylation of glycogen synthase kinase 3β (GSK-3β). When GSK-3β is phosphorylated at Ser9, it decreases its kinase activity toward tau protein; hyperphosphorylated tau protein forms neurofibrillary tangles (NFT). Moreover, leptin activates Janus activated kinase 2 (JAK2) that phosphorylates signal transducer and activator of transcription 3 (STAT3) that can activate sirtuin 1 (SIRT1) and further blocks production of Aβ plaques by inhibiting nuclear factor-κB (NFκB) and beta-secretase 1 (BACE). Suppressor of cytokine signaling 3 (SOCS3) interfere with leptin receptor signal transduction. For memory formation, neuronal synaptic and dendritic plasticity, the activation of extracellular signal-regulated kinase 1/2 (ERK1/2) and cAMP response element-binding protein (CREB) is required. ERK1/2 can be activated by leptin, insulin and through G-protein coupled receptors that activates protein kinase A (PKA) through increased level of cAMP.
and hypothermia, neuronal Tau hyperphosphorylation was determined (El Khoury et al. 2016). Therefore, leptin was qualified as a potent AD therapeutics Tezapsidis et al. 2009).

Central insulin resistance could be partly caused by increased level of pro-inflammatory cytokines, e.g. TNF-α (Ferreira et al. 2014). TNF-α is produced in brain by microglia or can penetrate to brain through BBB from the periphery where it is produced by adipocytes, as described earlier. TNF-α triggers pro-apoptotic c-Jun N-terminal kinase (JNK), which further impairs activation of insulin signaling cascade by increased phosphorylation of IRS-1 at inhibitory Ser epitopes (Ferreira et al. 2014).

Because of the newly discovered link between T2DM and AD, a possible new strategy for the prevention and treatment of neurodegenerative diseases has emerged. It is hypothesized that agents that increase insulin sensitivity could ameliorate insulin function in the CNS and could thus be used as effective treatments for AD. The potential neuroprotective properties of many anorexigenic and/or insulin-sensitizing peptides are described later in this review, but here it should be mentioned that two anti-diabetic drugs that are analogs of the incretin hormone glucagon-like peptide 1 (GLP-1), liraglutide (Victoza, NovoNordisk) and exendin-4 (Byetta, AstraZeneca), were proven in several animal models of AD to significantly improve memory, decreased Aβ plaque load in hippocampus or reduce neuroinflammation; thus, these promising compounds were tested in clinical trials (https://clinicaltrials.gov/ct2/show/NCT01255163; Holscher 2018).

The relationship between insulin resistance and AD

Insulin resistance generally refers to a condition in which tissues do not respond properly to physiological concentrations of insulin, leading to hyperinsulinemia, hyperglycemia and hyperlipidemia (Turner & Heilbronn 2008). These symptoms drive MetS and diseases such as T2DM, obesity and chronic inflammation. In the brain, in addition to glucose utilization, insulin supports neuronal functions including synaptogenesis, synaptic remodeling and modulation of neurotransmitter function (Cholerton et al. 2011). Insulin resistance may induce metabolic stress and may cause mitochondrial dysfunction and chronic inflammation that further exacerbates Aβ clearance and metabolism (Farris et al. 2003). It was shown that at the subcellular level, oxidative damage caused by increased production of reactive oxygen species (ROS) leads to mitochondrial dysfunction in both preclinical AD models and in persons with the disease (Butterfield et al. 2014, Wang et al. 2014). Elevated oxidative stress is detectable by increases in the levels of lipid peroxides, 8-oxoguanine and oxidized proteins (Pugazhenthii et al. 2017, Reddy & Reddy 2017). Moreover, oxidative stress increases Aβ production in vitro and in vivo (Wang et al. 2014).

The molecular mechanisms of insulin activity in the brain include the PI3K/Akt pathway and the Ras/mitogen-activated protein kinase (MAPK) pathways, activation of both of them is decreased which is manifested by decreased phosphorylation of kinases implicated in the signaling cascades (Ghasemi et al. 2014, Guillot et al. 2016). Insulin signaling, which regulates glucose utilization in the brain, modulates acetylcholine levels and Aβ levels in the brain. Therefore, impaired activation of insulin signaling pathway can affect cognition in AD (Schioth et al. 2012, Li et al. 2018). In the brains of AD patients, a progressive neuronal dysfunction, a loss of neurons and synaptic connections, increased neuroinflammation, together with increased level of Aβ forming extracellular senile plaques, as well as vascular deposits and the hyperphosphorylated tau protein forming pathological intracellular NFT are observed (Cummings et al. 1998, Graham et al. 2017). Interestingly, Aβ accumulation in the brain has been shown to induce both brain and peripheral insulin resistance in animal studies (Doney et al. 2009, Bharadwaj et al. 2017). Thus, insulin resistance and impaired insulin signaling can contribute to the pathophysiological alterations observed in AD because insulin signaling is involved in tau phosphorylation and Aβ metabolism. However, it has also been demonstrated that Aβ oligomers can bind to insulin receptors, triggering their internalization, decreasing their neuronal responsiveness to insulin and promoting insulin resistance (Xie et al. 2002). Thus, it could be argued that Aβ is a convergent factor in the development of both pathologies.

Experimental models and methods used to study neurodegeneration

Animal models

To better understand the etiology of AD, appropriate experimental models are needed. The models most frequently used in the study of neurodegeneration are transgenic mouse models with Aβ and/or tau pathology. However, no animal model recapitulates the entirety of
AD in humans; therefore, it is important to understand both the utility and the limitations of particular animal models (Jankowsky & Zheng 2017). Most AD mouse models are representative of FAD, which accounts for only a small percentage of the total AD cases that are diagnosed each year. Each transgenic mouse model of AD provides different insights into aspects of AD pathogenesis and the cognitive deficits associated with the disease. The most frequently used mouse models contain APP and PS1 mutations or APP/PS1/tau mutations (also known as the 3xTg AD mouse model) (reviewed in Webster et al. 2014). The APP/PS1 model with the Swedish mutation of APP is the most widely used model; the first reported impairment in spatial working memory as well as Aβ pathology was observed using 6-month-old animals (Trinchese et al. 2004), and this model is most commonly used to test potential neuroprotective features of new compounds, including anorexigenic neuropeptides. In APP/PS1 mouse models, decreased neurogenesis has been repeatedly reported to be associated with further AD-typical pathological hallmarks such as extracellular Aβ plaque deposition, behavioral deficits and neuroinflammation. This model is a well-characterized AD model of amyloidosis, and for some of its neuropathological characteristics, this model most closely resembles the early stages of human AD (Price et al. 2000, Kreiner 2018).

Several transgenic mouse models of tau pathology have been created and characterized (reviewed Gotz et al. 2007, Hochgrafe et al. 2013, Dujardin et al. 2015). The tau models have been used to unravel the pathophysiology of AD, to search for disease modifiers and to develop novel treatment strategies. However, these models have very rarely been used to test new potential neuroprotective compounds, although such studies could be very valuable. Moreover, the existence of a number of neurodegenerative diseases featuring tau pathology in the absence of Aβ extracellular deposits underscores the relevance of research on tau (Gotz et al. 2007).

Rat and mouse models of obesity/diabetes develop neurodegeneration with age. Obesity can be caused by genetic mutations in the leptin receptor or by feeding animals a diet with a high percentage of fat, so-called models of diet-induced obesity (DIO). A research using animal models identified mechanisms that are shared by diabetes and AD (Crews et al. 2010, Park 2011, Cavanaugh et al. 2014). Some models exploit the exogenous application of streptozotocin (STZ), which disrupts insulin secretion, resulting in disrupted brain insulin signaling and increased tau pathology (Shi et al. 2017b).

Ablation of the nucleus arcuatus (Arc) by monosodium glutamate, resulting in dysregulation of energy homeostasis or non-functional leptin signaling with aging, also leads to increased tau pathology (Spolcova et al. 2014, 2015).

Finally, a very specific model of accelerated aging, the senescence‐accelerated mouse prone 8 mouse (SAMP8), was developed in the Takeda laboratory (Takeda et al. 1981) and is now widely used as a model of spontaneously occurring aging. SAMP8 mice display several neurodegenerative features including Aβ pathology, tau pathology, impairment of memory and synaptic plasticity and disruption of BBB function (Morley et al. 2012, Akiguchi et al. 2017). This model is very complex because of polygenic character of neurodegenerative changes and is very useful for the testing of new potentially neuroprotective compounds.

Behavioral tests

The most frequently used behavioral tests include spatial memory tests that test long-term (MWM, radial arm water maze, Barnes maze) or short-term memory (Y-maze or T-maze), associative learning tasks (passive avoidance, fear conditioning) and recognition memory tasks (novel object recognition – NOR) (Webster et al. 2014). Although the MWM might appear to be the most robust of these tests (high motivation of animals to perform and low olfactory cue bias), high test-induced stress (Harrison et al. 2009) might influence the results of further biochemical and molecular analyses. It is even more important to consider this possibility in experiments with obese models because of changed mobility and motivation of obese animals (Friend et al. 2017). Other behavioral tests such as the Barnes maze can be less stressful for the mice, but they are not always easy to conduct due to lack of motivation. When testing different animal models, individual adjustments to the test protocols may be necessary.

All the animal studies that have been described in the literature have limitations. First, the investigation is sometimes not long enough, especially when the feeding of a high-fat diet is involved. Second, there are some problems associated with investigating potential cognitive deficits in working memory or measurement of anxiety (Walker & Harrison 2015). No animal model can mimic the entire range of symptoms that occur in human AD, and there is still a need to clearly define behavioral test/s for individual neurodegenerative diseases, including AD. Therefore, the results obtained from animal models with the intention of applying them to human AD should be drawn from several behavioral tests.
Cellular hallmarks of AD

Aβ senile plaques are formed by aggregated Aβ peptides that differ in length and contain 42–43 amino acids residues. Aβ originates from APP, a transmembrane protein. The main function of APP is not precisely known, but in the CNS, it has a positive effect on synapse formation and plasticity, neural activity and memory (Turner et al. 2003, Priller et al. 2006). However, under pathophysiological conditions, APP is processed in the amyloidogenic pathway; in this pathway, APP is cleaved by β- and γ-secretases resulting in the formation of Aβ chain 42–43 amino acids that form toxic oligomers. The Aβ chains polymerize into fibrils and are finally stored as senile plaques (Tabaton et al. 2010).

Tau belongs to the family of microtubule-associated proteins. This protein promotes the assembly of tubulin into microfilaments and helps stabilize the microtubules and thus stabilize the axons of neurons (Weingarten et al. 1975). For proper tau function, the phosphorylation state of tau is crucial; aberrant tau phosphorylation negatively influences its physiological function in microtubule assembly and stabilization (Lindwall & Cole 1984). Moreover, aberrant phosphorylation is responsible for tau aggregation into NFT, which are the hallmark of AD (Grundke-Iqbal et al. 1986). Thus, tau protein is under the control of kinases and phosphatases that together maintain its physiological phosphorylation. The most important kinases implicated in tau hyperphosphorylation are GSK-3β (Takashima 2006), cyclin-dependent kinase 5 (cdk5) (Jicha et al. 1999) and protein kinase A (PKA) (Lee & Leugers 2012). Recently, activated AMPK, which is important for maintaining cellular energy levels, was characterized as a tau kinase and shown to phosphorylate tau at several epitopes (Domise et al. 2016).

Another important component maintaining proper neuronal function are neurofilaments (NF) that form the neuronal cytoskeleton (Yuan et al. 2017). Damaged cytoskeleton observed in different neurodegenerative disorders is connected to accumulation of pathologic structures, such as NFT. It was discovered that some types of neurons, such as pyramidal neurons from neocortex or pyramidal neurons of cornu ammonis 1 (CA1), contain specific NF triplets which seem to make neurons more susceptible to neurodegeneration (Vickers et al. 2016). Cytoskeleton damage is also connected to formation of Aβ plaque-associated dystrophic neurites which contains increased amount of NF, such as NF triplets. It is not properly known if Aβ plaques precede or are the consequence of the dystrophic neurites (Vickers et al. 2016).

Apart from senile plaques and NFT, AD is characterized by decreased synaptic plasticity (Sheng et al. 2012, Skaper et al. 2017), increased oxidative stress (Zhao & Zhao 2013) and neuroinflammation (Heneka et al. 2015), decreased neurogenesis (Rodriguez & Verkhratsky 2011) and dysregulated calcium homeostasis (Bezprozvanny 2010).

Decreased synaptic plasticity is observed in the brains of AD patients long before the appearance of Aβ plaques or NFT and correlates well with the memory deficit (Terry et al. 1991). According to the amyloid hypothesis of AD, synapse failure is most likely caused by the presence of soluble toxic Aβ oligomers. The strength of synapses is measured by long-term potentiation (LTP). Decreased LTP was observed in animal models carrying mutations in APP or PS1 and in animals that had been intracerebroventricularly (ICV) injected with Aβ1–40 or Aβ1–42 (Rowan et al. 2003). However, this hypothesis also has its detractors. Decreased synaptic plasticity manifested by decreased LTP and memory decline was observed in rats with diet-induced insulin resistance (Stranahan et al. 2008). Decreased synaptic plasticity is manifested by reduced levels of presynaptic or postsynaptic density proteins. Synaptophysin, a presynaptic vesicle protein, is decreased in TG19959 mice carrying human APP with two mutations (Tampellini et al. 2010) and in APP/PS1 mice (McClean et al. 2011). Another presynaptic protein that is decreased in AD brains, mainly in the cortex, is GAP43 protein (de la Monte et al. 1995, Bogdanovic et al. 2000). The role of tau at synapses has been extensively studied (Pooler et al. 2014). Tau is found in presynaptic and postsynaptic components, where it forms part of the postsynaptic density (PSD) complex involving PSD95, a major scaffolding protein that is important for synaptic plasticity and transmission. Hyperphosphorylation of tau destabilizes this complex and results in impaired synaptic plasticity (Forner et al. 2017). Moreover, reduced expression of PSD95 has been found in mouse models of tauopathy as well as in a mouse model of amyloidopathy (Shao et al. 2011). Neurogranin, another postsynaptic protein, is a marker of early synaptic dysfunction, and decreased levels of neurogranin are observed in patients with AD (Casaletto et al. 2017).

To some extent, synaptic plasticity can be increased by neurogenesis, a physiological process that occurs especially in the dentate gyrus (DG) of the hippocampus. With aging, neurogenesis decreases; however, neurogenesis is much more impaired in AD brains (Mu & Gage 2011, Rodriguez & Verkhratsky 2011). The method most frequently used to measure neurogenesis is the labeling...
of newborn neurons with bromodeoxyuridine (BrdU), which is a marker of DNA synthesis. In this method, proper interpretation of data and the use of appropriate control samples are required to discriminate neurogenesis from DNA synthesis, e.g. in microglia or other cell types (Taupin 2007). Newborn neurons can be detected by immunohistochemical staining for doublecortin (DCX) whose level is decreased in the hippocampi of AD patients. The decline could also be connected to decreased levels of brain-derived neurotrophic factor (BDNF), a member of the neurotrophin family that is important in memory formation, neuronal development and neurogenesis, in AD brains (Numakawa et al. 2017). For instance, BDNF-infused to DG of adult rats for 2 weeks significantly ameliorated neurogenesis compared to vehicle-treated group (Scharfman et al. 2005). BDNF activates the TrkB receptor (tropomyosin receptor kinase B), which can further increase activation of Akt, ERK and cAMP response element-binding protein (CREB), kinases that have been implicated to play a role in memory formation (Numakawa et al. 2017).

Neuroinflammation was shown to be connected to AD pathology (Hauss-Wegnerziak et al. 1998). Neuroinflammation is mediated through increased activation of microglia and astrocytes, both of which are found to co-localize with Aβ plaques (Heneka et al. 2015). Activated microglia can be immunohistocemically detected by staining with ionized calcium-binding adapter molecule 1 (Iba-1), which is also known as allograft inflammatory factor 1 (AIF-1) (Heneka et al. 2015). Astrocytes are important in proper brain development and in the maintenance of brain energy homeostasis as well as for synaptic plasticity and LTP (Hol & Pekny 2015). In general, astrocytes can be stained using antibodies against glial fibrillary acidic protein (GFAP), the expression of which increases with age (Teter 2009). However, only reactive astrocytes that show changes in cellular morphology and increased levels of GFAP increase neuroinflammation and lead to AD progression (Hol & Pekny 2015, Osborn et al. 2016).

MRI and PET are established imaging techniques for diagnosis of AD (Scheltens et al. 2016) as is multimodal chemical imaging using matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS). This analytic approach shows great potential for comprehensive, high-resolution molecular analysis of histological features at cellular length scales with high chemical specificity (Kaya et al. 2017). Moreover, cerebrospinal fluid biomarkers in diagnosis of early Alzheimer’s disease might be very useful (Blennow et al. 2015). It was demonstrated that amyloid PET and CSF biomarkers identify early-stage AD equally accurately (Palmqvist et al. 2015).

**Leptin as a key player in food intake regulation: a role in neurodegeneration**

Leptin plays a key role not only in neurons that regulate energy homeostasis but also in neurons that are associated with learning and memory. Leptin, a satiety hormone that is produced in adipose tissue, is increased in the fed state and decreased during food restriction and fasting (Spiegelman & Flier 2001). The anorexigenic effect of leptin is mediated in the Arc of the hypothalamus, where the leptin receptor ObRb is highly expressed. Numerous leptin receptors have also been detected at hippocampal synapses (Shanley et al. 2002). Interestingly, hippocampal ObRb mRNA expression was also found to be enhanced by food restriction (Lin & Huang 1997), and the ObRb at hippocampal synapses was shown to be linked to hippocampal excitatory synaptic transmission (Shanley et al. 2001).

Leptin-deficient ob/ob mice and db/db mice with non-functional leptin receptors displayed significantly decreased wet brains weight and decreased expression of synaptic and glial proteins, similar to immature brain (Ahima et al. 1999). It seems that functional leptin is necessary for a proper brain development.

In Zucker fa/fa rats and db/db mice, both of which have non-functional ObRb, LTP and LTD were not found during electrophysiological tests of hippocampal slices, and spatial memory in the MWM was decreased (Li et al. 2002). For activity-dependent synaptic plasticity in the brain, activation of N-methyl-d-aspartate glutamate receptors (NMDAR) is the most important. After NMDAR-mediated calcium influx to the cytoplasm, another glutamate receptor, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), is transported from the Golgi apparatus to the cell membrane (Moult et al. 2010). The transport of AMPAR exemplifies the principle of activity-dependent synaptic plasticity; LTP is mediated by AMPAR insertion into the membrane, whereas removal of AMPAR from the membrane mediates LDP (Collingridge et al. 2004, McGregor & Harvey 2017).

Leptin could contribute to AMPAR-mediated synaptic plasticity through Janus activated kinase 2 (JAK2), which phosphorylates ObRb (Harvey et al. 2006, Irving & Harvey 2014, McGregor & Harvey 2017). JAK2 directly activates/phosphorylates the signal transducer and activator of transcription 3 (STAT3). Phosphorylation of
STAT3 enables it to cross the nuclear membrane and act as a transcription factor for genes encoding key pro-survival proteins in neurons (Dziennis & Alkayed 2008). ObRb/JAK2 transphosphorylation is negatively regulated by the suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B). JAK/STAT signaling has been linked to NMDAR-dependent synaptic plasticity; it was shown in hippocampal slices that JAK2 activation contributes to NMDAR-induced LTD. The effect of leptin on synaptic plasticity (Harvey et al. 2006) and leptin-induced synaptic plasticity (Moul & Harvey 2011) have been investigated and established.

In addition to JAK2, ObRb/JAK2 transphosphorylation activates/phosphorylates two other signaling pathways/kinases, PI3K and MAPK. Because PI3K and MAPK inhibitors block the potentiating effect of leptin on NMDA-induced increases in intracellular Ca²⁺, leptin involvement in NMDA activation also seems possible (Shanley et al. 2001). All three leptin signaling pathways were suggested to affect synaptic plasticity in particular areas of the hippocampus (McGregor & Harvey 2017). Moreover, leptin was shown to affect the proliferation of DG hippocampal neurons through STAT3 and Akt activation (Garza et al. 2008).

Distorted neuronal leptin signaling is observed not only after improper brain development but also in old age and in neurodegenerative disorders such as AD. In the hypothalami of old rats, increased PTP1B (Morrison et al. 2007) and enhanced SOCS3 expression (Peralta et al. 2002) have been linked to leptin resistance. Therefore, one could expect that old age-induced leptin resistance also occurs in the hippocampus, as adult hippocampal neurogenesis in mice was shown to be mediated through STAT3 and Akt (Garza et al. 2008). In transgenic APP/PS1 mice, hippocampal ObR mRNA levels were decreased, indicating that Aβ toxicity could negatively affect leptin signaling (Pedros et al. 2015). This was confirmed in Tg2576 mice that carry only the APP Swedish mutation; in these animals, lower STAT3 phosphorylation was detected and was reversed by Aβ passive immunization (Chiba et al. 2009). Moreover, in crosses of APP23 mice bearing the APP Swedish mutation with ob/ob mice, the animals’ cognitive functions in the MWM were attenuated in comparison to those of mice of either of the parental genotypes. Interestingly, the progeny of this cross displayed exacerbated glucose intolerance, but Aβ was not affected (Takeda et al. 2010).

Distorted leptin signaling also affects neuronal tau protein phosphorylation. In db/db mice overexpressing human mutant tau protein (so-called Tau P301L mice), exacerbated hippocampal tau phosphorylation and NFT were detected (Platt et al. 2016). Activation of GSK-3β, the major tau protein kinase, was suspected to play a leading role in these changes.

A question arose regarding whether leptin can reverse already established changes resulting from old age or neurodegenerative disease. Leptin reversed the negative effect of Aβ on LTP and Aβ-induced LTD in hippocampal slices and increased the survival of Aβ-treated cortical neurons through ERK and Akt activation (Doherty et al. 2013). Treatment of CRND8 mice with the Swedish and Indiana (V717F) mutation with leptin for 2 months attenuated Aβ load in the blood and the brain, decreased tau protein phosphorylation and improved performance in object recognition and contextual fear tests (Greco et al. 2010). Leptin prevented spatial memory attenuation in both the Y-maze and MWM tests in healthy rats that received repeated ICV administration of Aβ and reversed the Aβ-induced decrease in late phase-LTP recorded as hippocampal field potentials (Tong et al. 2015). Treatment of APP/PS1 mice for 2 weeks with intranasally administered leptin combined with the peroxisome proliferator-activated receptor γ (PPARγ) agonist pioglitazone attenuated memory deficits recorded in the Y-maze and decreased brain Aβ levels (Fernandez-Martos et al. 2017). Acute intrahippocampal administration of leptin positively affected foot shock avoidance and step down inhibition avoidance in the T-maze in 12-month-old SAMP8 mice (Farr et al. 2006).

In conclusion, leptin is a potential cognitive enhancer; it improves hippocampus-dependent learning and memory and is probably involved in AMPAR trafficking, neuronal morphology and activity-induced synaptic plasticity. This ability declines with age (Scarpace et al. 2000), resulting in neurodegenerative changes such as AD.

Ghrelin, physiological antagonist of leptin with potential neuroprotective function

Ghrelin, the only known orexigenic gut hormone and endogenous ligand of GHS-R1α, is secreted primarily from the stomach. This 28-amino-acid peptide contains a serine esterified by n-octanoic acid, a unique modification necessary for its biological activity (Kojima et al. 1999). Ghrelin maintains the positive energy balance of the organism and has a key role in increasing appetite, food intake and body weight, facilitating adipose tissue accumulation and regulating energy metabolism (Delporte 2013). These effects, together with the anti-inflammatory

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effects mediated by peripherally distributed GHS-R1a, make ghrelin administration a promising anti-cachectic therapeutic strategy (Holubova et al. 2018).

Peripheral released and centrally acting leptin and ghrelin are both regulators of appetite/feeding and are physiological antagonists as shown for example on their opposite role in regulation of release of orexigenic (e.g. neuropeptide Y) or anorexigenic (e.g. melanocortins) peptides in nucleus arcuatus (Fig. 1). On the other hand, they play a positive role in neuroprotection and brain function (de Candia & Matarese 2018). Ghrelin has been shown to be involved in numerous higher brain functions such as memory, reward and mood, which are disrupted in neurodegenerative disorders, including AD (Procaccini et al. 2016, Shi et al. 2017a). Ghrelin-knockout mice showed decrease number of spine synapse and impaired memory tests compared to wild-type mice (Diano et al. 2006).

Neuroprotective effects of ghrelin have been shown in several models of AD-like pathology such as SAMP8 mice (Diano et al. 2006), 5xFAD mice with Aβ pathology (Jeong et al. 2018), mice (Santos et al. 2017) or rats (Eslami et al. 2018) with ICV injected Aβ1-40. In these studies, repeated administration of ghrelin or its agonists caused improved performance in memory tests and decreased markers of Aβ pathology.

Finally, orexigenic neuropeptides positively influenced by central action of ghrelin, such as neuropeptide Y, galanin or orexin were found to act also in hippocampus and are involved in learning and memory as well (Beck & Pourie 2013).

This is just very brief description of a role of orexigenic peptides in neuroprotection and further details are beyond the scope of this review, dedicated namely to anorexigenic peptides.

### The effect of anorexigenic peptides in AD-like pathology

The brain–gut axis affects neural function and controls eating behavior through biochemical signaling between the endocrine and nervous systems. This signaling is mediated by peptide hormones that are released both in the gastrointestinal tract and in the CNS (Wilson & Enniori 2015, Zanchi et al. 2017). Anorexigenic hormones involved in short-term regulation include the gut hormones GLP-1, peptide tyrosine tyrosine (PYY), cholecystokinin (CCK), amylin, oxyntomodulin that are controlled by the long-term satiety signal leptin (Frago & Chowen 2015, Prinz & Stengel 2017). These gut hormones are released into the digestive system and then act centrally as satiety signals that decrease food intake; their action occurs specifically in the hypothalamus and brainstem, which act as control centers for hunger and satiety. The Arc of the hypothalamus is considered the most important nucleus in the control of feeding behavior. Neurons in the hypothalamus receive information from the periphery; then, first-order neurons in the Arc and second-order neurons in the paraventricular nucleus (PVN) and the ventromedial nucleus (VMN) are activated, causing them to release neuropeptides that regulate food intake (Schwartz et al. 2000).

These neuropeptides include proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript (CART) peptide in the Arc and prolactin-releasing peptide (PrRP) and corticotropin-releasing peptide (CRH) in the PVN, all of which are positively influenced by leptin (Sohn 2015, Mandal et al. 2018), as shown in Fig. 1.

In addition to their role in the regulation of food intake, the above-mentioned peptide hormones, which are released both peripherally and centrally and act centrally, were recently proposed to function not only in the control of energy metabolism but also as growth factors that stimulate cell growth and cell repair in neurons (Holscher 2018). These hormones were also proposed to restore insulin signaling pathways in brain areas associated with learning and memory formation, such as the hippocampus, and thus to positively influence spatial and episodic memory (Mandal et al. 2018), as shown in several preclinical studies. Like insulin and leptin, they can also modulate the insulin/leptin signaling pathway, thereby acting as neuroprotective hormones (Yarchooan & Arnold 2014), improving hippocampal synaptic plasticity and enhancing cognitive performance (Fadel et al. 2013).

Table 1 describes the effects of pharmacological interventions involving anorexigenic peptides (leptin, melanocortins, CART peptide, PrRP, amylin and GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) analogs) on spatial memory and on the parameters of neurodegeneration in cortex and/or hippocampi in rodent models of AD-like pathology.

### Melanocortins in experimental models of AD-like pathology

The role of melanocortins and their receptors MC3 and MC4 in the CNS, especially in the hypothalamus, has been extensively investigated. Melanocortins are neuropeptides that are released in the Arc and act at specific receptors...
## Table 1 Pharmacological interventions of neuropeptides in rodent models of AD-like pathology.

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Intervention</th>
<th>Starting age</th>
<th>Compound/dose/injection/duration</th>
<th>Improvement of memory/behavioral test</th>
<th>Effect in hippocampus/cortex</th>
<th>Marker</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAMP8 mice</td>
<td>Leptin AC (0.05, 0.25 µg)</td>
<td>4 and 12 month old</td>
<td>Leptin 0.05, 0.25 µg Acute ICV</td>
<td>T-maze footshock avoidance test</td>
<td>Trace fear conditioning; NOR</td>
<td>Decreased Aβ pathology; Reduced Tau; Activated leptin signaling; Decreased Aβ pathology; Increased neurogenesis; Increased synaptic plasticity</td>
<td>Farr et al. (2006)</td>
</tr>
<tr>
<td>CRND8 mice</td>
<td>Leptin 20 µg daily</td>
<td>4 month old</td>
<td>SC Alzet minipumps, 8 weeks</td>
<td></td>
<td></td>
<td>Soluble Aβ ↓, Aβ plaques ↓, p-Ser396 ↓, AT8 ↓, PHF-1 ↓, Aβ plaques ↓</td>
<td>Greco et al. (2010)</td>
</tr>
<tr>
<td>APP/PS1 mice</td>
<td>Leptin 0.03 mg/kg i.n. + pioglitazone 10 mg/kg i.p., 14 days once daily</td>
<td>6 month old</td>
<td>Leptin viral vector ICV 3 months</td>
<td>Y-maze, MWM</td>
<td></td>
<td>Reduced Aβ plaques ↓, BrdU ↑, DCX ↑, LTP ↑</td>
<td>Pérez-Gonzalez et al. (2011)</td>
</tr>
<tr>
<td>S–D rats</td>
<td>Leptin 20 µg daily</td>
<td>4 month old</td>
<td>ICV 20 µg daily</td>
<td></td>
<td></td>
<td>Activated leptin signaling</td>
<td>Tong et al. (2015)</td>
</tr>
<tr>
<td>APP/PS1/P301L mice</td>
<td>NDP-α-MSH 340 µg/kg i.p. daily</td>
<td>12 weeks old</td>
<td>18 weeks ± inhibitor HS024</td>
<td>MWM</td>
<td></td>
<td>Increased synaptic plasticity; Soluble Aβ ↓, Aβ plaques ↓, PSD-95, SYP, GAD67↑, GFAP ↓, Iba1 ↓</td>
<td>Fernandez-Martos et al. (2017)</td>
</tr>
<tr>
<td>APP mice</td>
<td>NDP-α-MSH 340 µg/kg i.p. daily</td>
<td>24 weeks</td>
<td>300 µg/kg i.p. daily</td>
<td>MWM</td>
<td></td>
<td>Decreased Aβ pathology; Reduced Tau; Activated LTP; Increased synaptic plasticity</td>
<td>Giuliani et al. (2014a)</td>
</tr>
<tr>
<td>APP mice</td>
<td>α-MSH 0.5 mg/kg i.p. daily</td>
<td>5 month old</td>
<td>0.5 mg/kg i.p. daily</td>
<td>OF, Y-maze</td>
<td></td>
<td>Decreased Aβ plaques ↓, Aβ plaques ↓, p-APP Thr668 ↓, p-Ser396 ↓, p38 ↓, Caspase-3 ↓, IL-1↓, TNF-α↓</td>
<td>Giuliani et al. (2014b)</td>
</tr>
<tr>
<td>APP mice</td>
<td>NDP-α-MSH 340 µg/kg i.p. daily</td>
<td>24 weeks old</td>
<td>340 µg/kg i.p. daily</td>
<td>MWM</td>
<td></td>
<td>Decreased Aβ plaques ↓, Aβ plaques ↓, GAD67↑, Aβ plaques ↓, LTP ↑, GluC ↑</td>
<td>Ma &amp; McLaurin (2014)</td>
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<tr>
<td>APP/PS1 mice</td>
<td>D-TyrMTII ICV Alzet minipumps</td>
<td>5 month old</td>
<td>2.4 nmol/day 28 days</td>
<td>MWM</td>
<td></td>
<td>Increased synaptic plasticity; Soluble Aβ ↓, Aβ plaques ↓, PSD-95, SYP, GAD67↑, GFAP ↓, Iba1 ↓, LTP ↑</td>
<td>Giuliani et al. (2015)</td>
</tr>
<tr>
<td>S–D rats</td>
<td>CART antibody 25–100 ng/rat/day, 4 days</td>
<td>24 weeks old</td>
<td>CART antibody ICV daily</td>
<td>MWM</td>
<td></td>
<td>Decreased Aβ pathology; Reduced Tau; Synaptic plasticity; Reduced reactive oxygen species</td>
<td>Upadhy et al. (2011)</td>
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<tr>
<td>APP/PS1 mice</td>
<td>CART peptide 0.5 µg/kg 10 days + i.p. 0.5 µg/kg 20 days</td>
<td>8 month old</td>
<td>CART peptide i.v. 0.5 µg/kg 10 days + i.p. 0.5 µg/kg 20 days</td>
<td>MWM</td>
<td></td>
<td>Decreased Aβ plaques ↓, LTP ↑, SYP ↑, ROS ↓</td>
<td>Jin et al. (2015)</td>
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Table 1 Continued.

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<tbody>
<tr>
<td>APP/PS1 mice</td>
<td>CART peptide i.v. 0.5 µg/kg 10 days + i.p. 0.5 µg/kg 20 days</td>
<td>MWM</td>
<td>Decreased Aβ pathology</td>
<td>Increased insulin signaling</td>
<td>Yin et al. (2017)</td>
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<td>Thy-Tau22 mice</td>
<td>Palm11-PrRP Alzet minipumps SC 5 mg/kg/day 2 months</td>
<td>Y-maze</td>
<td>Reduced Tau phosphorylation</td>
<td>Increased insulin signaling</td>
<td>Popelova et al. (2018)</td>
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<tr>
<td>Amylin</td>
<td>Pramlintide Alzet minipumps SC 0.24 mg/kg/day 5 weeks</td>
<td>NOR</td>
<td>Increased synaptic plasticity</td>
<td>Reduced reactive oxygen species</td>
<td>Adler et al. (2014)</td>
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<tr>
<td>APP/PS1 mice</td>
<td>Amylin, pramlintide 200 µg/kg i.p. or ICV once daily 10 weeks</td>
<td>Y-maze, MWM</td>
<td>Decreased Aβ pathology</td>
<td>Aβ plaques ↓, BACE 1 ↑</td>
<td>Zhu et al. (2015)</td>
</tr>
<tr>
<td>APP/PS1/P301L mice</td>
<td>Amylin 200 µg/kg i.p. or ICV once daily 10 weeks</td>
<td>Y-maze</td>
<td>Decreased Aβ pathology</td>
<td>Aβ plaques ↓, AT8 ↓, CD68 ↓, Iba1 ↓</td>
<td>Zhu et al. (2017)</td>
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<tr>
<td>APP mice</td>
<td>Amylin 200 µg/kg i.p. or ICV once daily 10 weeks</td>
<td>MWM</td>
<td>Decreased Aβ pathology</td>
<td>Aβ plaques ↓, p-Ser202 ↓, CD68 ↓, Iba1 ↓</td>
<td>Wang et al. (2017)</td>
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<tr>
<td>GLP-1</td>
<td>Exendin 4 SC Alzet minipumps 3.5 pmol/kg/min 16 weeks</td>
<td>MWM</td>
<td>Decreased Aβ pathology</td>
<td>Soluble Aβ ↓, APP ↓, Total Tau ↓</td>
<td>Li et al. (2010)</td>
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<td>Wistar rats + Aβ(1-40) ICV</td>
<td>Val16-GLP-[7-36] Acute ICV 0.05 pmol</td>
<td>MWM</td>
<td>Decreased Aβ pathology</td>
<td>Increased synaptic plasticity</td>
<td>Wang et al. (2010)</td>
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<tr>
<th>Animal model</th>
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<th>Effect in hippocampus/cortex</th>
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<tbody>
<tr>
<td>Wistar rats, 6 month old</td>
<td>Several GLP-1 agonists + exe(9–39) ICV acute 15 nmol</td>
<td>NOR, OF</td>
<td>Increased synaptic plasticity</td>
<td>LTP ↑</td>
<td>McClean et al. (2011)</td>
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<tr>
<td>Swiss TO mice HF diet 6 month old</td>
<td>Liraglutide 200 µg/kg SC bi-daily 28 days</td>
<td>NOR, MWM</td>
<td>Increased synaptic plasticity</td>
<td>LTP ↑</td>
<td>Porter et al. (2010)</td>
</tr>
<tr>
<td>APP/PS1 mice 7 month old</td>
<td>Liraglutide 25 nmol/kg i.p. daily 8 weeks</td>
<td></td>
<td>Decreased Aβ pathology Increased synaptic plasticity Reduced neuroinflammation</td>
<td>Aβ plaques ↓, Congophilic plaques ↓, APP ↓ LTP ↑, DCX ↑, SYP ↑ Iba1 ↓</td>
<td>McClean et al. (2011)</td>
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<tr>
<td>APP/PS1 mice, 9 and 18 month old</td>
<td>Val8-GLP-1 25 nmol/kg i.p. daily 3 weeks</td>
<td>MWM</td>
<td>Decreased Aβ pathology Increased synaptic plasticity Reduced neuroinflammation</td>
<td>Aβ plaques ↓, Soluble Aβ ↓ IRS-1, IRS-2 ↑</td>
<td>Gengler et al. (2012)</td>
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<tr>
<td>APP/PS1 mice, 9 and 13 month old</td>
<td>Exendin 4 25 nmol/kg i.p. daily/bi-daily 3 weeks</td>
<td>MWM, fear conditioning</td>
<td>Decreased Aβ pathology Increased insulin signaling</td>
<td>Aβ plaques ↓, APP ↓ p-GSK3β(Ser9) ↓ p-Akt (Ser473) ↑ ROS ↓</td>
<td>Ma et al. (2012)</td>
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<td>APP/PS1 mice, 10–12 month old</td>
<td>GLP-1(9–36) SC Alzet minipumps 500 µg/kg/day 2 weeks</td>
<td>MWM, fear conditioning</td>
<td>Decreased Aβ pathology Reduced neuroinflammation Increased insulin signaling</td>
<td>Aβ plaques ↓, Iba1 ↓, GFAP ↓ IRS1 (Ser616) ↓, IRβ ↓</td>
<td>Long-Smith et al. (2013)</td>
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<td>APP/PS1 mice, 7 month old</td>
<td>Liraglutide 25 nmol/kg i.p. daily 8 weeks</td>
<td></td>
<td>Increased synaptic plasticity Reduced neuroinflammation</td>
<td>LTP ↑, cAMP↑</td>
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<td>S–D rats Intra-hippocampus Aβ(25–35)</td>
<td>Liraglutide Acute ICV 0.05–5 pmol</td>
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<td>Increased neurogenesis Reduced neuroinflammation</td>
<td>BrdU↑↑, Ki67↑↑, NeuN↑↑, DCX↑↑ Iba1↑↑, GFAP↑↑ LTP↑↑, mRNA: SYP↑↑, BDNF↑↑, Mash↑↑, NTRK2↑↑</td>
<td>Parthasarathy &amp; Holscher (2013)</td>
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<td>APP/PS1 mice, 3, 6, 12, 15 month old</td>
<td>Liraglutide 25 nmol/kg i.p. daily 7 and 37 days</td>
<td>Locomotory activity</td>
<td>Increased synaptic plasticity</td>
<td>LTP ↑, mRNA: SYP, VEGF, GFAP ↓ ROS ↓ (8-oxoguanine) mRNA: IRS-1, Sirt1, NTRK-2, mTOR</td>
<td>Porter et al. (2013)</td>
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<td>Ob/ob mice, 14–16 weeks old</td>
<td>Liraglutide 50 nmol/kg SC bi-daily 28 days</td>
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<td>Increased synaptic plasticity</td>
<td>LTP ↑, mRNA: SYP, VEGF, GFAP ↓ ROS ↓ (8-oxoguanine) mRNA: IRS-1, Sirt1, NTRK-2, mTOR</td>
<td>Lennox et al. (2014)</td>
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<tr>
<td>APP/PS1 mice, 7 month old</td>
<td>Liraglutide 25 nmol/kg i.p. daily 8 weeks</td>
<td>NOR</td>
<td>Increased synaptic plasticity</td>
<td>LTP ↑, mRNA: SYP, VEGF, GFAP ↓ ROS ↓ (8-oxoguanine) mRNA: IRS-1, Sirt1, NTRK-2, mTOR</td>
<td>Lennox et al. (2014)</td>
</tr>
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<td>Swiss TO mice HF diet 6 month old</td>
<td>Val8-GLP-1 Glu Pal 30 nmol/kg i.p. bi-daily ± metformin 300 mg/kg PO 20 days</td>
<td></td>
<td>Increased synaptic plasticity Reduced reactive oxygen species Increased insulin signaling</td>
<td>LTP ↑, mRNA: SYP, VEGF, GFAP ↓ ROS ↓ (8-oxoguanine) mRNA: IRS-1, Sirt1, NTRK-2, mTOR</td>
<td>Lennox et al. (2014)</td>
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<th>Effect in hippocampus/cortex</th>
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<tbody>
<tr>
<td>APP/PS1 mice</td>
<td>Liraglutide 25 nmol/kg i.p. daily</td>
<td>NOR, MWM</td>
<td>Decreased Aβ pathology, increased synaptic plasticity, reduced neuroinflammation</td>
<td>Aβ plaques ↓, congophilic plaques ↓, soluble Aβ ↓, APP ↓, LTP ↑, DCX ↑, SYP ↑</td>
<td>McClean &amp; Holscher (2014a)</td>
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<tr>
<td>14 month old</td>
<td></td>
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<td>mRNA: BDNF, Iba1 ↓</td>
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<td>SAMP8 mice</td>
<td>Liraglutide 25 nmol/kg i.p. daily</td>
<td>NOR, MWM</td>
<td>Increased neurogenesis</td>
<td>Number of neurons ↑</td>
<td>Hansen et al. (2015)</td>
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<tr>
<td>6 month old</td>
<td></td>
<td></td>
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<tr>
<td>APP/PS1 mice</td>
<td></td>
<td>NOR, MWM</td>
<td>Decreased Aβ pathology, increased synaptic plasticity, reduced neuroinflammation</td>
<td>Aβ plaques ↓</td>
<td>McClean et al. (2015)</td>
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<td>APPsw/PS1 mice</td>
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<td>NOR, T-maze</td>
<td>Decreased Aβ pathology</td>
<td>Aβ plaques</td>
<td>Hansen et al. (2015)</td>
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<tr>
<td>7 month old</td>
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<tr>
<td>APPsw/PS1 mice</td>
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<td>NOR, T-maze</td>
<td>Decreased Aβ pathology</td>
<td>Aβ plaques</td>
<td>Hansen et al. (2015)</td>
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<td>5 month old</td>
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<tr>
<td>C57 mice + Aβ(1–42) ICV</td>
<td>Liraglutide 25 nmol/kg i.p. daily</td>
<td>Y-maze, MWM</td>
<td>Reduced Tau phosphorylation, increased insulin signaling</td>
<td>p-GSK3β(Ser9) ↑, p-Ser396 ↓, p-Ser202/199 ↓, p-Akt(Ser473) ↑, Akt-ERK signaling ↑</td>
<td>Qi et al. (2016)</td>
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<td>8 weeks</td>
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<td>C57 mice + methylglyoxal ICV</td>
<td>Liraglutide 25 nmol/kg SC daily</td>
<td>MWM</td>
<td>Reduced Tau phosphorylation, increased insulin signaling</td>
<td>p-GSK3β(Ser9) ↑, p-Ser202/199 ↓, p-Akt(Ser473) ↑, caspase ↓, cleaved caspase ↓ Aβ plaques ↓, p-Thr231 ↓, Iba1 ↓, pPKA-pCREB ↑, p-p38 ↓</td>
<td>Qi et al. (2017)</td>
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<td>8 weeks</td>
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<td>APP/PS1/P301L</td>
<td>Lixisenatide 10 nmol/kg i.p. daily</td>
<td>NOR</td>
<td>Decreased Aβ pathology, reduced Tau phosphorylation, reduced neuroinflammation</td>
<td>Aβ plaques ↓, decreased caspase ↓ Aβ plaques ↓</td>
<td>Cai et al. (2017)</td>
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<tr>
<td>12 month old</td>
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<tr>
<td>Swiss TO mice + Aβ ICV</td>
<td>Liraglutide 25 nmol/kg i.p. daily</td>
<td>NOR</td>
<td>Increased synaptic plasticity</td>
<td>LTP ↑</td>
<td>Porter et al. (2011)</td>
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<td>7 days</td>
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<tr>
<td>Swiss TO mice LF and HF diet</td>
<td>(α-Ala²)GIP 25 nmol/kg bi-daily SC</td>
<td>OF, NOR</td>
<td>Increased synaptic plasticity</td>
<td></td>
<td></td>
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<td>7 month old</td>
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<tr>
<td>Swiss TO mice LF and HF diet 6 month old</td>
<td>Inactive incretin metabolites: GLP(1–9–36) GIP(3–42), exe(9–39) 25 nmol/kg bi-daily SC 60 days</td>
<td>OF, NOR</td>
<td>Increased synaptic plasticity</td>
<td>LTP</td>
<td>Porter et al. (2012)</td>
</tr>
<tr>
<td>APP/PS1 mice 6 and 12 month old</td>
<td>(o-Ala)GIP 25 nmol/kg daily i.p. 34 days</td>
<td>ORT, MWM</td>
<td>Decreased Aβ patholgy</td>
<td>Aβ plaques ↓ Congophilic plaques ↓ LTP ↓ BrdU↑ DCX↑ Iba1↓</td>
<td>Faivre &amp; Holscher (2013c)</td>
</tr>
<tr>
<td>Dual/triple agonists</td>
<td>GLP-1 GIP glucagon</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICV/STZ rats</td>
<td>DA-JC4 = GLP/GIP agonist 10 nmol/kg daily i.p. 14 days</td>
<td>Y-maze, MWM</td>
<td>Reduced Tau phosphorylation</td>
<td></td>
<td>Shi et al. (2017b)</td>
</tr>
<tr>
<td>APP/PS1 9 month old</td>
<td>DA5-CH = GLP/GIP agonist 10 nmol/kg daily i.p. 28 days</td>
<td>OF, Y-maze, MWM</td>
<td>Reduced Tau phosphorylation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>APP/PS1 mice 6 month old</td>
<td>TA = GLP/GIP/glucagon triagonist 10 nmol/kg daily i.p. 2 months</td>
<td>MWM</td>
<td>Decreased Aβ patholgy</td>
<td></td>
<td>Tai et al. (2018)</td>
</tr>
<tr>
<td>APP/PS1/P301L mice 7 month old</td>
<td>GLP/GIP/glucagon triagonist 10 nmol/kg daily i.p. 30 days</td>
<td>OF, Y-maze, MWM</td>
<td>Decreased Aβ patholgy</td>
<td></td>
<td>Li et al. (2018)</td>
</tr>
</tbody>
</table>

Akt, insulin cascade kinases; APP, Aβ precursor protein; BACE 1, beta-secretase 1; Bax, pro-apoptotic protein; Bcl-2, anti-apoptotic protein; BDNF, brain-derived neurotrophic factor; BrdU+, bromoaurin positive neurons; CD68, microglial marker; CDK-5, cyclin-dependent kinase 5; DCX, doublecortin; exe, exenatide (GLP-1 agonist); lixisenatide (GLP-1 agonist); exe(9–39) GLP-1 antagonist; GAD67, glutamic acid decarboxylase; GFAP, anti-glial fibrillary acidic protein; GSK3β, glycogen synthase kinase 3β (Ser9 – inhibition, Tyr216 – activation); HF, high fat diet; Iba1, anti-ionized calcium-binding adaptor molecule 1; ICV, intracerebroventricular administration; i.n., intranasal; i.p., intraperitoneal; IRS-1, insulin receptor substrate-1; i.v., intravenous; Ki67, cell proliferation marker; LF, low fat; Lira, liraglutide (GLP-1 agonist); LTP, long-term potentiation; Mash 1, mammalian achaete-scute homologue 1 – neuronal differentiation; MG, monosodium glutamate; MWM, Morris water maze; NeuN, indicator of mature neurons; NOR, novel object recognition test; OF, open field; ORT, object recognition task; PD1K, 3-phosphoinositide-dependent kinase 1; PI3K, phosphoinositol 3 kinase; PP2A sub C, PP2A phosphoryase subunit C; PSD-95, post synaptic density; ROS, reactive oxygen species; SC, subcutaneous; STZ, streptozotocin – treated rats, mice; SYP, synaptophysin; T, maze; TRK2, neurotrophis tyrosine kinase receptor – type 2; Y, maze; Zif268, indicator of functionally integrated neurons.
within the brain (Giuliani et al. 2017). The neuroprotective properties of melanocortin agonists have been demonstrated in several models of neurodegeneration (Giuliani et al. 2017). In different mouse models of AD-like pathology, such as in Tg2576 mice (Giuliani et al. 2014b, 2015), TgCRND8 mice (Ma & McLaurin 2014) and in APP/PS1/P3011 mice (Giuliani et al. 2014a), intraperitoneal (i.p.) injection of the melanocortin analog NDP-α-MSH (Nleα, D-Pheβ)-α melanocyte-stimulating hormone) or α-MSH for several weeks improved synaptic plasticity and decreased neuronal loss, Aβ levels, tau phosphorylation in brain. Behavioral tests of these animals showed improved cognitive function (Table 1). Increased neurogenesis and decreased neuroinflammation were also described (Giuliani et al. 2015).

**CART peptide in experimental models of AD-like pathology**

CART peptides are widely distributed in the CNS and are involved in the regulation of food intake, reward and endocrine functions, and stress responses (reviewed in Rogge et al. 2008, Lau & Herzog 2014). Despite the large efforts that have been made in this area, CART peptide receptor(s) have not been identified to date, but specific binding and signaling in pheochromocytoma PC12 cells was described suggesting possible receptor in this cell line is present (Maletinska et al. 2007, Nagelova et al. 2014). Several studies report neuroprotective properties of natural CART peptide. In in Sprague-Dawley rats, icv administration of CART peptide improved performance in Morris water maze (Upadhya et al. 2011). In APP/PS1 mice after repeated peripheral administration (Jin et al. 2015, Yin et al. 2017) (Table 1), the number of Aβ plaques was decreased, and memory performance as well as synaptic plasticity improved in these studies. However, it was proven that the CART peptide does not have a central effect on food intake lowering after peripheral administration (Jensen et al. 1999); thus, neuroprotective effect of CART peptide after i.v. or i.p. administration is very surprising since central effect is needed for CART peptide effect.

**PrRP in experimental models of AD-like pathology**

PrRP is an anorexigenic neuropeptide belonging to the family of so-called RF amide peptides with a C-terminal arginine and phenylalanine amide sequence; both of these amino acid residues are essential for proper biological activity (Boyle et al. 2005, Maletinska et al. 2011).

The first described effect of PrRP, release of prolactin from the pituitary tumor cell line RC-4B/C (Hinuma et al. 1998), gave the name to the peptide. A direct prolactin-releasing effect of PrRP in mammals has, however, been questioned because no PrRP immunoreactive fibers were observed in the median eminence where classical hypophysiotropic hormones are released (Maruyama et al. 1999). This, together with the discovery that prolactin positive cells in the human pituitary do not co-localize with the PrRP receptor (Abe et al. 2003) and the finding that PrRP increases prolactin responses to TRH (Spuch et al. 2007), but itself does not significantly increase prolactin secretion in primary rat pituitary cells (Samson et al. 1998), has suggested that prolactin release is probably not a primary function of PrRP (Taylor & Samson 2001).

The presence of PrRP in hypothalamic nuclei implicated in maintaining energy balance suggested that it plays a role in food intake and weight regulation (Lawrence et al. 2000). However, because natural PrRP does not cross the BBB, new lipidized analogs that enable PrRP to act centrally after peripheral administration were designed (Maletinska et al. 2015, Praziennkova et al. 2017).

Two palmitoylated analogs of PrRP, palm1-PrRP (Spolcova et al. 2015) and palm11-PrRP (Popelova et al. 2018), were tested in two mouse models of neurodegeneration, as shown in Table 1. Palm1-PrRP was injected subcutaneously (sc) for two weeks into MSG-obese mice, in which obesity is caused by injection of newborn mice with monosodium glutamate (MSG), causing specific lesions in Arc (Spolcova et al. 2015). MSG-obese mice are leptin- and insulin-resistant, but they are normoglycemic (Matyskova et al. 2008). At the age of six months, increased activation of GSK-3β and hyperphosphorylation of tau at several epitopes was observed in the hippocampi of MSG mice. Treatment with palm1-PrRP ameliorated activation of the hippocampal insulin signaling cascade, decreased activation of GSK-3β manifested by increased phosphorylation at Ser9, and attenuated tau phosphorylation at epitopes Ser396, Thr231 and Thr212 (Spolcova et al. 2015).

The PrRP analog palm11-PrRP was administered to THY-Tau22 mice for two months using SC Alzet osmotic minipumps (Popelova et al. 2018). The THY-Tau22 mice are a model of AD-like tau pathology in which mutated human tau protein is overexpressed. The mice exhibited increased tau hyperphosphorylation and spatial memory impairment (Schindowski et al. 2006). Spatial memory in the Y-maze test was improved in mice treated with palm11-PrRP compared to mice treated with vehicle. In hippocampi, attenuated tau phosphorylation was...
observed at Thr231, Ser396 and Ser404. Moreover, increased phosphorylation of Akt at Ser473 was observed. Akt activation is important for further activation of PSD95, causing it to be consequently increased (Popelova et al. 2018).

**Amylin in experimental models of AD-like pathology**

Amylin is a metabolic peptide hormone that is co-secreted with insulin from beta cells in the pancreas; it activates many of the downstream targets of insulin. In addition to improvement of glycemic control, it also influences gastric emptying and satiety after peripheral administration (Zhu et al. 2015). Pramlintide, a synthetic analog of amylin, activates many metabolic pathways in the CNS; it positively influences memory and enhances the insulin signaling pathway in the brain. These effects were demonstrated in several mouse models (Table 1), including the SAMP8 mouse model (Adler et al. 2014) and APP/PS1 mice (Zhu et al. 2015). After peripheral or central injections of amylin or pramlintide for several weeks, Aβ and tau pathology in hippocampus was improved, and neuroinflammation decreased (Table 1; Soudy et al. 2017, Wang et al. 2017, Zhu et al. 2017).

**GLP-1 agonists, GIP agonists and dual and triple agonists in experimental models of AD-like pathology**

Incretins, namely, GLP-1 and GIP, represent one of the most studied groups of potentially neuroprotective compounds. Both are secreted by the small intestine when the glucose concentration is increased; they further stimulate the secretion of insulin, leading to lowering of blood glucose levels. In the periphery, incretin receptors are present in the pancreas; however, a large number of incretin receptors are found throughout the brain, mainly in the hippocampus (Vilsboll & Holst 2004, Drucker 2006).

The problem with naturally occurring incretins is their low stability due to the cleavage of their N-terminal sequence by dipeptidyl peptidase IV (DPP IV). Therefore, incretin analogs with prolonged stability have been designed (Drucker 2006).

One of the most studied GLP-1 analogs, liraglutide, has been approved as a treatment for T2DM (Victoza, NovoNordisk) and obesity (Saxenda, NovoNordisk) and is now undergoing phase II clinical trial testing in AD patients (NIH 2010, Holscher 2018). Many studies of liraglutide have been performed in different AD animal models. In APP/PS1 mice, treatment with liraglutide for two months reduced the level of soluble Aβ and Aβ plaques, prevented reduction in the number of synapses, and improved spatial memory in the MWM in 7-month-old (McClean et al. 2011) or 14-month-old mice (McClean & Holscher 2014a) (Table 1). Chronic liraglutide treatment increased neurogenesis, as shown by increased levels of doublecortin and BrdU labeling in APP/PS1 mice of different ages (Parthsarathy & Holscher 2013). Moreover, prophylactic administration of liraglutide to APP/PS1 mice for eight months prevented the formation of Aβ plaques, decreased neuroinflammation, improved spatial memory in the MWM and increased neurogenesis (McClean et al. 2015) compared to vehicle-treated APP/PS1 mice. Using SAMP8 mice, enhanced spatial memory and an augmented number of neurons in the CA1 region of the hippocampus were observed after liraglutide treatment (Hansen et al. 2015). Liraglutide has also been tested in mouse models of obesity and/or diabetes. It improved metabolic parameters, including body weight and glucose levels, and increased LTP in DIO mice (Porter et al. 2010) and in ob/ob mice (Porter et al. 2013). Liraglutide efficiently attenuates tau hyperphosphorylation. In DIO rats that developed T2DM, attenuation of the insulin signaling cascade and hyperphosphorylation of tau protein at different epitopes were observed; treatment of the animals with liraglutide for four weeks led to enhanced activation of kinases implicated in the insulin signaling cascade including increased phosphorylation of inhibitory Ser9 of GSK-3β and ultimately decreased phosphorylation of tau protein at Ser199, 202 and 396 (Yang et al. 2013). A similar mechanism of action of liraglutide was demonstrated in a model of tau pathology induced by administration of Aβ1–42 (Qi et al. 2016) or methylglyoxal (Qi et al. 2017); liraglutide treatment resulted in improved spatial memory as measured in the Y-maze and MWM tests, increased activation of Akt, decreased kinase activity of GSK-3β, and subsequent attenuation of tau hyperphosphorylation. The results of these studies are summarized in Table 1.

Another potent analog of GLP-1 is exenatide, a synthetic analog of exendin-4; it was tested as a treatment for AD in a pilot clinical trial. Its effect is mediated through activation of the PI3/Akt pathway (Wang et al. 2015). Its neuroprotective properties were manifested in APP/PS1 mice; in these animals, exenatide reduced the phosphorylation of IRS-1 at serine epitopes, a sign of insulin signaling impairment that resulted from Aβ-induced activation of JNK. Moreover, the treatment reduced the number of Aβ plaques and the level of soluble Aβ, and improved memory in the MWM (Bomfim et al. 2012). In 3xTg AD mice in which AD pathology was enhanced by...
injection of STZ to provoke diabetic conditions, treatment with exenatide resulted in reduced numbers of Aβ plaques (Li et al. 2010). In STZ rats, exenatide improved spatial memory in the MWM and increased activation of the insulin signaling pathway that resulted in increased phosphorylation at inhibitory Ser9 of GSK-3β, the main tau protein kinase, thereby decreasing phosphorylation of the tau protein at different epitopes (Chen et al. 2012).

Several other potent and long-lasting GLP-1 analogs, including lixisenatide (Cai et al. 2014, McClean & Holscher 2014b) and Val(8)GLP-1 (Gengler et al. 2012, Li et al. 2012, McGovern et al. 2012), which can also be palmitoylated (Lennox et al. 2013), were shown to display neuroprotective properties in in vivo experiments; the neuroprotective effects included beneficial effects on synaptic plasticity, spatial memory, and Aβ plaque reduction (Table 1).

Of the stable GIP analogs, the analog in which d-Ala² is substitute by L-Ala has been most studied in models of neurodegeneration. After acute or chronic administration, d-Ala²-GIP showed a beneficial effect on hippocampal synaptic plasticity in C57BL mice (Faivre et al. 2012), improved impaired neuronal synaptic plasticity and LTP in DIO mice (Porter et al. 2011); it also reduced blood glucose levels. d-Ala²-GIP was administered to APP/PS1 mice for 21 days when the animals were 6 and 12 months (Faivre & Holscher 2013b) or 19 months of age (Faivre & Holscher 2013a). At all ages, the treatment resulted in increased synaptic plasticity, reduced neuroinflammation and reduced numbers of Aβ plaques. At the age of 12 months, d-Ala²-GIP improved memory in the novel object recognition test and the MWM (Table 1).

Recently, drugs targeting additional receptors have been designed with increased anti-diabetic properties. These include dual agonists of GLP-1/GIP receptors and a triple agonist of GLP-1/GIP/glucagon receptors (Finan et al. 2015, Holscher 2018). One of the GLP-1/GIP analogs, DA-JC4 (Shi et al. 2017b), and the triple agonist (Tai et al. 2018) were also examined for potential neuroprotective properties. Both molecules improved spatial memory in the MWM and Y-maze tests and reduced neuroinflammation as manifested by decreased levels of reactive astrocytes and activated microglia using Iba-1 staining. Moreover, administration of DA-JC4 for two weeks to rats that had received ICV injection of STZ resulted in increased phosphorylation of tau protein, ameliorated the activation of kinases implicated in the insulin signaling pathway, including IRS1 and Akt, and attenuated tau hyperphosphorylation at several epitopes (Shi et al. 2017b). The triple agonist was administered to APP/PS1 mice for two months; it reduced the numbers of Aβ plaques and increased the level of the synaptic marker synaptophysin and of doublecortin, a marker of neurogenesis (Tai et al. 2018). Both analogs seem to be potent neuroprotective compounds (Shi et al. 2017b, Tai et al. 2018) (Table 1).

**Conclusion and future direction**

This review summarizes the findings about the possible role of anorexigenic peptides in experimental models of AD pathology. Undoubtedly, the pathogenesis of AD is a complicated process involving both genetic and environmental factors. Despite extensive studies and a lot of promising results, further studies are needed to understand the precise role of food intake regulating peptides in pathogenesis of AD. However, this is not simple because studies using highly selected clinical samples from patients with autosomal dominant AD suggest that the neuropathology of AD begins to develop decades before the onset of symptoms or detectable deficits (Fleisher et al. 2015). Moreover, conditions in utero may influence the risk of age-related diseases through epigenetic changes (Maloney & Lahiri 2016, Doehner et al. 2017). Because the preclinical phase of AD development has such a broad developmental window, it is very difficult to precisely specify the timeframe in which prevention must begin to be most effective. Other problem is that no experimental model precisely represents pathology of human AD; thus, comparison of several different animal models together could bring the light to the pathological processes of human AD.

If one accepts the hypothesis that AD is associated with impaired glucose metabolism and insulin and leptin resistance in the brain, it is reasonable to assume that improvement of these disorders can prevent AD. We and others have clearly demonstrated that peripherally administered anorexigenic peptides can improve systemic glucose resistance in obese animals (Maletinská et al. 2015, Holscher 2018, Mikulaskova et al. 2018) and that these compounds positively affect learning and memory (Fig. 2). The key role of insulin and leptin was demonstrated and neuropeptides positively regulated by insulin and leptin were shown to have neuroprotective effects with respect to AD pathology. In addition to their role in the regulation of food intake, also other food intake regulating hormones (e.g. melanocortins, CART peptide, PrRP, amylin or GLP-1 analogs), which are released both peripherally and centrally and act centrally, were recently
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Anorexigenic peptides in Alzheimer's disease proposed to function also as growth factors that stimulate cell growth and cell repair in neurons (Holscher 2018), to restore insulin signaling pathways in brain areas associated with learning and memory formation, and thus to positively influence spatial memory (Mandal et al. 2018) in animal studies. Like insulin and leptin, they can also modulate the insulin/leptin signaling pathway, thereby acting as neuroprotective hormones (Yarchoan & Arnold 2014), improving hippocampal synaptic plasticity and enhancing cognitive performance (Fadel et al. 2013). It was also shown especialmente that stable incretin GLP-1 analogs can be used to prevent neurodegenerative processes and improve neuronal and synaptic functionality in models of AD and PD and also in first clinical trials (Holscher 2014).

Thus, these studies support the idea that some neuropeptides might have the potential to improve neurodegeneration and thereby improve and/or slow down AD. However, many other studies are needed to understand the precise mechanisms of AD pathology, to find at least approximate developmental window for the onset of the disease and finally, to find potential drugs for the AD treatment.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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