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Metabolic and non-cognitive manifestations of Alzheimer's disease: the hypothalamus as both culprit and target of pathology

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Abstract

Alzheimer's disease (AD) is increasingly recognized as a complex neurodegenerative disease beginning decades prior to the cognitive decline. While cognitive deficits remain the cardinal manifestation of AD, metabolic and non-cognitive abnormalities, such as alterations in body weight and neuroendocrine functions are also present, often preceding the cognitive decline. Furthermore, hypothalamic dysfunction can also be a driver of AD pathology. Here we offer a brief appraisal of hypothalamic dysfunction in AD, and provide insight into an underappreciated dual role of the hypothalamus as both a culprit and target of AD pathology, as well as into new opportunities for therapeutic interventions and biomarker development.

Introduction

Alzheimer's disease (AD), the most common cause of dementia in the elderly, is an incurable and devastating disease that has emerged as one of the major public health threats of our times (Alzheimer's Association, 2015). The pathogenesis of AD remains elusive, but the abnormal accumulation in the brain of amyloid-beta (Aβ), a peptide derived from the amyloid precursor protein (APP), and of the microtubule associated protein tau is believed to lead to the synaptic dysfunction and neurodegeneration underlying the dementia (Musiek and Holtzman, 2015). AD pathology develops decades prior to the initial cognitive symptoms in a preclinical or presymptomatic stage, in which Aβ and tau start to accumulate in brain, as amyloid plaques and neurofibrillary tangles (Sperling et al., 2011). Cerebrovascular function is also impaired in patients with early AD or at risk for AD, leading to a mismatch between the delivery of oxygen and glucose through blood flow and the energy demands of the active brain (Iadecola, 2013). In addition, cerebrovascular dysfunction may impair the vascular clearance of Aβ and promote AD pathology (Gupta and Iadecola, 2015). Therefore, AD is now believed to be a continuum with gradually worsening pathological changes in the brain that are the consequences of Aβ, tau, vascular

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dysfunctions, and other changes that take several years to decades before manifesting with clinical symptoms. Thus, an early preclinical stage is followed by mild cognitive symptoms (minimal cognitive impairment or MCI) before progressing to symptomatic AD and eventually terminal dementia (Albert et al., 2011; McKhann et al., 2011).

Since cognitive deficits are the most prominent feature of the disease, AD research has placed emphasis on brain regions associated with cognition and memory, such as the hippocampus and entorhinal cortex (Musiek and Holtzman, 2015). However, AD patients exhibit significant non-cognitive deficits such as weight loss, sleep-wake disorders and neuroendocrine alterations attributable to hypothalamic dysfunction (Csernansky et al., 2006; Prinz et al., 1982; White et al., 1996). These alterations can occur prior to the initial mental decline and progressively worsen as the disease advances (Johnson et al., 2006; Ju et al., 2013; White et al., 1996), suggesting that they are an intrinsic feature of AD pathophysiology. Although recent reviews have addressed selected features of AD attributable to hypothalamic dysfunction, such as systemic metabolic deficits or the sleep abnormalities (Kiliaan et al., 2014; Musiek et al., 2015), an appraisal of how AD affects the hypothalamus in light of recent advances in both hypothalamic physiology and AD pathobiology is conspicuously missing from the recent literature. Therefore, in the present Perspective we sought to provide an integrated view of the bidirectional relationships between hypothalamic dysfunction and AD, building a case for the hypothalamus as a contributor and a target of AD pathology and emphasizing its implications for the early diagnosis and treatment of the disease.

Alterations in the structure of the hypothalamus in AD

Despite occupying only 4 cm^3 of the brain, about the size of an almond, the hypothalamus is the master coordinator of a myriad of homeostatic functions essential for life such as growth, reproduction, sleep, metabolism, and autonomic homeostasis (Swaab, 1997). The hypothalamus is divided into different regions, each having specific nuclei or clustering of neurons with distinct behavioral and/or physiological roles (Figure 1) (Swaab, 1997). In the following sections, we will describe the evidence for alterations in the hypothalamus in AD from classical neuropathological to more recent neuroimaging studies.

Neuropathology

Several autopsy studies have reported amyloid plaques and neurofibrillary tangles in the hypothalamus of AD subjects (Table 1). One of the earliest studies (Stief, 1927), described a 70 year-old woman with dementia and a striking loss in body weight (from 34.5 kg on presentation to 28 kg at time of death). At autopsy, the body was noted to be completely devoid of fat tissue, and, in the brain, plaques and tangles were found not only in the cortex but also in the paraventricular nucleus of the hypothalamus and mammillary bodies (Stief, 1927). Since then, several other studies have reported plaques and tangles throughout the hypothalamus in patients with AD, including the landmark paper of Braak and Braak on staging of AD pathology (Braak and Braak, 1991) (Table 1). More recently, studies using immunohistochemistry in AD brains confirmed the presence of neuronal loss, amyloid and tau in the hypothalamus (Table 1). These studies also found reductions in various neuropeptides and neurotransmitters, e.g., vasopressin and neurotensin in the hypothalamus

(Table 1). Therefore, the hypothalamus is a target of AD pathology like the cortex and hippocampus.

Neuroimaging

Recent advances in neuroimaging have enabled the investigation of AD pathology in the living brain in a longitudinal fashion that was simply not possible with postmortem analyses. Volumetric analysis using magnetic resonance imaging (MRI) demonstrated that the brain atrophy well known to occur in cortex and hippocampus is also found in the hypothalamus and can be seen in the early stages of AD (Table 2). Perfusion studies using single-photon emission computed tomography (SPECT) showed a non-significant trend towards decreased perfusion in the hypothalamus (Table 2); however, limitations with the study including partial voluming and analysis of an overall small volume of brain may have resulted in the statistically negative result (Callen et al., 2002; 2004). Neuroimaging studies with positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (^{18}FDG) as a tracer have reported deficits in glucose metabolism in the hypothalamus of MCI or AD subjects (Table 2). Substantial reductions in hypothalamic glucose metabolisms have also been reported in "presymptomatic" transgenic mice overexpressing APP (Tg2576) (Niwa et al., 2002). More recently, PET imaging using amyloid or tau tracers has enabled investigators to study AD pathology *in vivo* (Fodero-Tavoletti et al., 2011; Klunk et al., 2004). However, to the best of our knowledge, no studies have thus far performed amyloid or tau imaging in the hypothalamus. Complicating factors include the limited spatial resolution of PET and off-target lipophilic binding of amyloid tracers, which may make it difficult to accurately assess a small brain region like the hypothalamus (Johnson et al., 2013; Su et al., 2015).

Alterations in hypothalamic function in AD

In addition to the structural abnormalities reviewed above, functional studies suggest that hypothalamic dysfunction is a common manifestation of AD, often early in the disease course. While the exact mechanisms underlying the various hypothalamic dysfunction remain to be elucidated, it is likely to include not only direct effects of Aβ and tau on the hypothalamus but also the vascular changes that are commonly seen in AD (Iadecola, 2013), since the release of many of the hormones and factors from the hypothalamus and the downstream pituitary gland are particularly sensitive to changes in the circulation (Fekete and Lechan, 2014; Hrabovszky and Liposits, 2013). In the following sections, we will discuss some of the common hypothalamic abnormalities associated with AD (Table 3) including dysfunction of the classic hypothalamic-pituitary pathways (Figure 2), body weight and systemic metabolism, bone metabolism, sleep-wake/circadian rhythm, and aggression/sundown syndrome and will review selected studies from animal models (Table S1) and AD subjects.

Hypothalamic-pituitary-adrenal axis

Disruption of the hypothalamic-pituitary-adrenal axis (HPA, Figure 2) has been consistently demonstrated in AD. Increased basal cortisol levels and overall insensitivity to glucocorticoid feedback have been reported for all stages of AD even in early AD (Csernansky et al., 2006; Davis et al., 1986; Greenwald et al., 1986; Rasmuson et al., 2001),

and may be associated with a more rapid disease progression (Csernansky et al., 2006; Swanwick et al., 1996). Various transgenic mice with increased brain Aβ deposition, e.g., TgCRND8, Tg2576, exhibited evidence of increased HPA axis activation at an early age (Carroll et al., 2011; Touma et al., 2004). Additionally, acute intracerebroventricular administration of Aβ25–35 peptides in rats was reported to induce memory impairment, anxiety and HPA axis hyperactivity (Brureau et al., 2013), suggesting that HPA axis dysfunction is an early consequence of the amyloid presence in the brain.

A major regulator of the HPA axis is the paraventricular nucleus of the hypothalamus through the release of the neuropeptide corticotropin-releasing hormone (CRH), which in turn stimulates pituitary secretion of ACTH and subsequently adrenal secretion of glucocorticoids (Figure 2). CRH in the CSF has been found to be increased (Banki et al., 1992), decreased (May et al., 1987), or unchanged (Pomara et al., 1989) in AD subjects. Relatively small postmortem studies of AD brains have also yielded mixed results (Bissette et al., 1985; Nemeroff et al., 1989; Powers et al., 1987; Raadsheer et al., 1995), calling for new investigations that are appropriately powered. However, in a transgenic mouse model of AD chronic stress can induce tau pathology, neurodegeneration, and learning impairments, which can be blocked by CRH receptor 1 antagonists and enhanced by CRH overexpression (Carroll et al., 2011). These data suggest that the increases in CRH and the HPA axis could contribute to brain dysfunction in AD, but supportive evidence in humans is still missing.

Hypothalamic-pituitary-thyroid axis

Although both hypothyroidism or hyperthyroidism have long been associated with cognitive impairment and increased risk of AD (Tan and Vasan, 2009), the link between the hypothalamic-pituitary-thyroid (HPT) axis and AD remains not well understood. With an intact HPT axis, low circulating thyroid hormones stimulate production of thyrotropin releasing hormone (TRH) from the hypothalamus and thyroid stimulating hormone (TSH) from the pituitary to increase thyroid hormone production (Figure 2). Studies measuring TRH levels in the CSF have reported either increases (Banki et al., 1992) or decreases (Oram et al., 1981) in AD subjects, while a postmortem study found no differences in the hypothalamus and extrahypothalamic areas (Yates et al., 1983). Similarly, studies in which TSH and thyroid hormones were measured reported increases, decreases, or no differences in AD (Ganguli et al., 1996; Johansson et al., 2013; Parsaik et al., 2014; Quinlan et al., 2010; Tan et al., 2008; van Osch et al., 2004). More appropriately, one study evaluated the function of the entire HPT axis by measuring serum TRH, TSH, and thyroid hormones in AD subjects (Yong-Hong et al., 2013) and found levels lower than controls. Since no TRH or TSH increases were seen, the findings suggest a dysfunction at the hypothalamic and/or pituitary levels resulting in a hypothyroid state. Based on these results, AD pathology could lead to neuronal dysfunction in the hypothalamus causing a decrease in TRH, or insensitivity to low thyroid levels, which, in turn, would decrease TSH secretion from the pituitary, and ultimately reduce thyroid hormone causing hypothyroidism. On the other hand, the hypothyroid state could exacerbate AD pathology (Tan and Vasan, 2009). There is evidence that TRH and thyroid hormones are neuroprotective against AD pathology. For example, TRH administration to hippocampal neurons resulted in a decrease in GSK-3β and tau phosphorylation, while TRH knockdown increases both (Luo and Stopa, 2004). Analogs

of TRH were neuroprotective in glutamate and Aβ toxicity in neuronal cultures (Faden et al., 2005). Administration of L-thyroxine in mice in which Aβ was microinjected in the hippocampus prevented the resulting cognitive and memory impairment (Fu et al., 2010). Therefore, HPT dysfunction could be both a cause and a consequence of AD pathology.

Hypothalamic-pituitary-gonadal axis

The natural aging process results in alterations of the hypothalamic-pituitary-gonadal (HPG) axis (Figure 2) leading to a dramatic decline in estrogen in women and a gradual decline in testosterone in men (Vest and Pike, 2013). It has been hypothesized that these alterations of the HPG axis, particularly low estrogen in postmenopausal women, could precipitate AD or contribute to its progression (Vest and Pike, 2013). Both low estrogen in women (Manly et al., 2000) and low testosterone in men have been consistently associated with poor cognitive performance and increased risk of AD (Moffat et al., 2004; Yaffe et al., 2002). Conversely, several studies have supported a role of testosterone and estrogen in protecting against neurodegeneration and cognitive decline by improving synaptic function, preventing neuronal death, and inhibiting Aβ accumulation and/or tau hyperphosphorylation (Vest and Pike, 2013). Unfortunately, testosterone or estrogen supplementation trials have not demonstrated consistent improvements in cognitive function or delay in AD progression (Emmelot-Vonk et al., 2008; Espeland et al., 2013; Lu et al., 2006; Shumaker et al., 2003). One possible explanation for the failure particularly of estrogen replacement in early trials is that the estrogen treatment began too late. It has been suggested that there is a “critical period” or “window of opportunity," where estrogen replacement would have to occur in close temporal proximity to menopause to be beneficial (McCarrey and Resnick, 2015). Recently, two large clinical trials tested this “critical period” hypothesis, but these studies found that hormonal replacement neither harmed nor provided any benefit to cognition in women with early menopause (Espeland et al., 2013; Gleason et al., 2015). Additionally, the enthusiasm for testosterone or estrogen supplementation has waned as the potential harmful consequences of long term sex hormone therapy in older men and women have become increasingly recognized (Rossouw et al., 2002; Vigen et al., 2013).

While age-related changes in the HPG axis have focused on the sharp decline in estrogen and testosterone, loss of the hypothalamic negative feedback from the sex hormones has also been implicated in AD (Rossmanith et al., 1994). Furthermore, hypothalamic dysfunction leading to gonadotropin releasing factor (GnRH) signaling deficits could also play a role. Several reports have demonstrated cognitive improvement with modulation of GnRH signaling in animal models and AD subjects (Bowen et al., 2015; Zhang et al., 2013). In one study, CSF GnRH levels were found to be significantly reduced in AD (Oram et al., 1981). However, a study in transgenic mice with amyloid pathology found dramatic increases in GnRH expression in the hippocampus, which were attenuated by Lupron, a GnRH superagonist that downregulates GnRH receptors (Nuruddin et al., 2014). Unfortunately, the GnRH levels in the hypothalamus were not reported in this study. Therefore, it remains unclear if dysfunction of the feedback loop in the HPG axis contributes to AD pathophysiology.

A recent study in mice found that aging causes hypothalamic NF-κβ-driven inflammation leading to decrease in GnRH signaling and cognitive dysfunction, which was rescued by GnRH replacement therapy (Zhang et al., 2013). This important study highlights a potential role of reduced hypothalamic GnRH in aging and possibly AD, but the downstream effectors of its beneficial actions remain unclear. For example, luteinizing hormone (LH), a gonadotropin secreted by the pituitary in response to GnRH, may exacerbate AD pathology. Thus, several studies have suggested an association between increased LH levels and cognitive decline and AD (Rodrigues et al., 2008; Short et al., 2001). In animal studies, exogenous LH potentiates both amyloidosis and cognitive impairment (Berry et al., 2008; Bowen et al., 2004), while LH receptor deficiency in transgenic mice overexpressing APP significantly decreased amyloid load and tau hyperphosphorylation (Lin et al., 2010). Recently, a Phase 2 clinical trial found that high doses of Lupron, which decreases LH, in combination with an acetylcholinesterase inhibitor stabilized the cognitive decline in mild to moderate AD (Bowen et al., 2015). Thus, modulation of the HPG axis and in particular GnRH signaling are potential therapeutic targets in AD, but a better appreciations of the downstream effector mechanisms is needed, e.g., LH, since they may be harmful.

Body weight and systemic metabolism

Weight loss is commonly seen in AD patients and correlates with disease severity and mortality (White et al., 1996; 1998). Furthermore, low body mass index (BMI) has been associated with worsening AD pathology in postmortem brains (Buchman et al., 2006; Vidoni et al., 2011) and worsening CSF biomarkers (tau and Aβ1–42) *in vivo* (Ewers et al., 2012). Importantly, there is substantial evidence that late life weight loss or low body weight can be seen prior to the cognitive decline (Barrett-Connor et al., 1996; Buchman et al., 2005; Gao et al., 2011; Johnson et al., 2006; Stewart et al., 2005). Furthermore, once cognitive impairment or dementia develops, low body weight or a further decrease in body weight is associated with worsening morbidity and mortality, while increased body weight may be protective (White et al., 1998). In contrast to late life weight loss, mid-life weight gain and obesity are associated with an increased risk of AD (Whitmer et al., 2005) independent of other cardiovascular risk factors (Whitmer et al., 2008; Xu et al., 2011). However, a recent large UK population study found that mid-life obesity decreases AD risk, while low body weight in mid-life is associated with an increased risk (Qizilbash et al., 2015), suggesting a complex interaction between body weight and AD. Clearly, a better understanding of the pathways by which systemic metabolism and body weight can influence AD risk is needed (Kiliaan et al., 2014). However, that late life weight loss can portend AD has been consistently reported in several different study populations (Barrett-Connor et al., 1996; Buchman et al., 2005; Gao et al., 2011; Johnson et al., 2006; Stewart et al., 2005) making it likely to be an early manifestation of AD linked to the pathophysiology of the disease.

The exact mechanisms underlying the body weight loss in AD are not known. Owing to its major role as integrator of peripheral metabolic signals, e.g., glucose, insulin, leptin, etc., and as regulator of body weight and systemic metabolism (Williams and Elmquist, 2012), the hypothalamus is likely to be a major driver of the weight loss in AD. Increasing evidence suggests that leptin, an adipocyte-derived hormone that acts on the hypothalamus as a negative afferent signal to maintain body weight and energy homeostasis (Friedman and

Mantzoros, 2015), is involved in AD. Low plasma leptin levels have been associated with increased risk of AD and cognitive decline (Holden et al., 2009; Lieb et al., 2009). Similar to the early weight loss seen in AD, transgenic mice overexpressing APP (Tg2576) exhibited low body weight, due to reduced fat mass, and low plasma leptin levels prior to amyloid plaque formation and cognitive deficits (Ishii et al., 2014). In hypothalamic slices from Tg2576 and or wild type slices exposed to Aβ1–42, the electrophysiological responses to leptin were abnormal in leptin-responsive NPY-expressing arcuate neurons, suggesting that Aβ-induced hypothalamic dysfunction may underlie the early body weight and systemic metabolic deficits (Ishii et al., 2014). Conversely, other studies found that leptin supplementation ameliorates, while leptin receptor deficiency exacerbates, the cognitive deficits and amyloid pathology in transgenic mice (Greco et al., 2010; Pérez-González et al., 2014; Takeda et al., 2010). Collectively, these studies suggest that early in AD, Aβ1–42 can potentially cause hypothalamic dysfunction in cells critical for leptin signaling resulting in low body weight and low adiposity. The hypothalamic dysfunction caused by Aβ1–42 could lead to an inability to sense the low plasma leptin levels resulting from low adiposity. This lack of response to the normal feedback signals would lead to the persistence of the low body weight and pathologically low leptin state. The low leptin levels may also contribute to cognitive deficits in AD, because leptin has beneficial effects on cognition by improving synaptic and hippocampal function, decreasing Aβ load, and reducing tau hyperphosphorylation in cell and animal models (Doherty et al., 2013; Greco et al., 2010). Beside leptin, other peripheral hormones involved in regulating systemic metabolism and body weight, e.g., adiponectin, ghrelin, and insulin (see below) have their main site of action in the hypothalamus and as such may also play a role (Kiliaan et al., 2014; Moon et al., 2011). Alternatively, since olfactory and taste deficits are common in AD (Doty et al., 1987; Velayudhan, 2015), the weight loss could be due to decreased appetite secondary to these deficits. However, at least in mouse models, the early body weight deficits were found to be from increased metabolism not reduced food intake (Ishii et al., 2014). Longitudinal study in humans investigating how the olfactory/taste changes in AD affects appetite and body weight, are clearly needed to evaluate the contribution of changes in olfaction and taste to the weight loss in AD.

In addition to changes in body weight, recent epidemiological studies have found that diabetes, particularly in mid-life, is associated with an increased risk of developing AD (Biessels et al., 2006; Kim and Feldman, 2015; Ott et al., 1999). There is also accumulating evidence to suggest that insulin resistance in the brain may have a significant role in AD pathobiology with some labeling sporadic AD as “type 3 diabetes” (la Monte, 2014). Insulin receptors are widely expressed in the brain including the olfactory bulb, cortex, hippocampus, amygdala and the hypothalamus (Ghasemi et al., 2013; Kim and Feldman, 2015; Unger et al., 1991), and insulin signaling has important roles in the regulation of body weight and systemic metabolism, reproduction, cognition and memory (Ghasemi et al., 2013). Importantly, there is significant evidence that insulin regulates Aβ and tau, while Aβ can disrupt insulin signaling (Kim and Feldman, 2015; la Monte, 2014). Based on these observations, insulin signaling has been proposed as a therapeutic target of AD, and treatment with insulin has been demonstrated to have beneficial effects on AD pathology and cognition in animal and human studies (Claxton et al., 2015; Kim and Feldman, 2015;

Vandal et al., 2014). Due to the widespread expression of insulin receptors in the hypothalamus and the critical importance of the hypothalamus in brain insulin signaling, the hypothalamus is well-positioned to serve as the critical link between diabetes/impaired insulin signaling and AD.

Diet or nutritional intake can also significantly impact AD. High-fat diets, particularly those high in saturated fatty acids which are often associated with obesity and insulin-resistant diabetes, have been associated with increased AD risk and exacerbation of AD pathology in several animal and human studies (Julien et al., 2010; Morris and Tangney, 2014; Refolo et al., 2000). As high-fat diets, mid-life obesity, and diabetes have all been associated with an increased risk of developing AD, it is perhaps not surprising that caloric restriction particularly earlier in life has been shown to be protective against AD pathology and aging-related disorders in various animal models (Halagappa et al., 2007; Mattson, 2012; Patel et al., 2005). For example, reducing caloric intake to 60% of *ad libitum* fed mice in AD mouse models (APP+PS1 and J20) significantly decreased the accumulation of amyloid plaques and astrocytic inflammation (Patel et al., 2005). Similarly, reduction of caloric intake in the 3xTg triple-transgenic mouse model of AD significantly improved the performance in the water maze and had lower levels of Aβ1–42, Aβ1–40, and phospho-tau in the hippocampus (Halagappa et al., 2007). Interestingly, intermittent fasting by depriving food for 24 hours every other day in the 3xTg mice improved the performance of the mice in the water maze, but did not alter levels of Aβ1–42, Aβ1–40, and phospho-tau, suggesting that the beneficial effects of intermittent fasting may operate by a different mechanism than chronically reducing caloric intake (Halagappa et al., 2007). In addition to mouse models with increased amyloid deposition, caloric restriction in a mouse model of increased tau deposition (Tg4510) performed significantly better in the novel object recognition test and contextual fear conditioning compared to *ad libitum* fed mice; however, tau and phospho-tau levels were unchanged as were astrocyte and microglia activation markers (Brownlow et al., 2014). Collectively, these and other studies have consistently shown that caloric restriction can reduce AD-like pathology and improve cognitive behavior; however, the mechanisms underlying this beneficial effect are not known, but may include reducing cellular stress, altering systemic metabolism, and changing hormonal balance e.g., increased insulin sensitivity (Mattson, 2012). It has been proposed that the hypothalamus has a vital role in the benefits seen with caloric restriction (Dacks et al., 2013). Evidence to support a hypothalamic role include the loss of caloric restriction-mediated anti-tumor effects in NPY knockout mice and mice with lesions of the hypothalamic arcuate nuclei by monosodium glutamate, suggesting the importance of hypothalamic pathways that regulate appetite and systemic metabolism in mediating the beneficial effects of caloric restriction (Minor et al., 2011). Caloric restriction also upregulates the mammalian nicotinamide adenine dinucleotide (NAD)-dependent deacetylase SIRT1, a key mediator of metabolism and life span, in the dorsomedial and lateral hypothalamus, where it is hypothesized to play an important role in regulating aging and longevity (Satoh et al., 2010; 2013). The exact mechanisms underlying the beneficial effects of caloric restriction still remain to be elucidated, but the current evidence strongly suggests that the hypothalamus is likely to play a significant role.

Bone metabolism

Bone loss as measured by bone mineral density has been associated with both age-associated cognitive decline and increased risk of developing AD (Tan et al., 2005; Yaffe et al., 1999). Decreased bone density has also been found in the early stages of AD, and this decline was associated with brain atrophy and cognitive decline (Loskutova et al., 2009). A hypothalamic involvement has been suggested as the lower whole body bone mineral density found in early AD was positively associated with low grey matter volume of the hypothalamus (Loskutova et al., 2010). Therefore, hypothalamic regulation of bone metabolism is emerging as another key early feature of AD. The mechanisms underlying the bone metabolism deficits in AD are unclear but may involve the hypothalamic-gonadal pathways, leptin, NPY or other factors implicated in the hypothalamic regulation of bone metabolism (Sharan and Yadav, 2014).

Disruption of circadian rhythm

Circadian rhythm disorders are commonly reported in AD (Musiek et al., 2015). Although the underlying mechanisms remain to be elucidated, the suprachiasmatic nucleus (SCN) of the hypothalamus has long been recognized as the main biological regulator of circadian rhythms (Saper, 2013) and, as reviewed below, is likely to be involved in AD.

Early studies using rest-activity monitors found marked disruption of the normal circadian rest-activity rhythm in AD patients, which correlated with disease severity (van Someren et al., 1996). In addition, body temperature rhythms are also abnormal in AD (Harper et al., 2001). A prospective cohort study using wrist actigraphy found that a decreased circadian activity rhythm amplitude and delayed rhythms were associated with an increased risk of MCI and dementia (Tranah et al., 2011). In addition, detailed analysis of circadian motor activity in subjects with mild AD found that scale-invariance/fractal patterns of locomotor activity fluctuations, i.e., the temporal characteristics and properties of fluctuations that remain similar over time, were reduced in AD (Hu et al., 2009). The same group also found that the degree of scale-invariance or fractal activity disruption was strongly associated with the reduction of two major circadian neurotransmitters vasopressin and neurotensin in the SCN in postmortem AD brains (Hu et al., 2013), confirming previous results by others (Harper et al., 2008; Stopa et al., 1999). In addition, the amyloid plaque burden in SCN was significantly associated with decreasing density of neurotensin-expressing neurons (Hu et al., 2013). In contrast, another study found no changes in SCN vasopressin levels in AD brains (Wang et al., 2015). Irrespective of the neurotransmitters involved, these findings implicate the SCN in the circadian rhythm disruption in AD (Table 1).

As in humans, abnormal circadian rhythm patterns, i.e., increased daytime and decreased nocturnal activity levels, have been found in TgCRND8 mice (Ambrée et al., 2006) and exaggerated amplitude and alterations in core body temperature rhythms in 3xTg mice (Knight et al., 2013). However, there have been inconsistencies between animal models, which are likely due to the differences in the strains, genetic makeup, and testing conditions used in these studies (Coogan et al., 2013). Nevertheless, the functional and neuropathological studies in humans with AD have provided strong evidence that circadian rhythm abnormalities are commonly present in AD and linked to SCN dysfunction.

Sleep-wake cycle regulation

Closely related to the alterations in circadian rhythm are sleep disorders such as fragmented sleep and reduced sleep, which have been described at all stages of AD (Musiek et al., 2015; Prinz et al., 1982). EEG studies of the sleep architecture of AD subjects have found decreased rapid eye movement (REM) and slow wave (delta) sleep (Prinz et al., 1982). In a cross-sectional study of cognitively-intact community-dwelling older adults, self-reported shorter sleep duration and poorer sleep quality were associated with greater Aβ burden as measured by amyloid imaging (Spira et al., 2013). A similar longitudinal study found that self-reported reduced sleep was associated with an increased risk of developing dementia and AD (Hahn et al., 2014). Finally, a cross-sectional analysis of cognitively-intact normal individuals found that those who had CSF Aβ1–42 levels consistent with preclinical AD had worse sleep quality, compared to cognitively-intact CSF negative controls (Ju et al., 2013). In agreement with human studies, transgenic mice with increased amyloid deposition exhibited sleep disturbances including decreased total sleep time with fragmented sleep, decreased non-REM sleep, and altered nocturnal activity (Roh et al., 2012; Sethi et al., 2015; Wisor et al., 2005). Collectively, these studies highlight that sleep disturbances can occur prior to the cognitive decline in AD.

Recently, it was hypothesized that sleep disturbances could actually increase Aβ deposition and thereby potentiate AD progression. Kang et al., used *in vivo* cerebral microdialysis to measure Aβ levels from brain interstitial fluid (ISF) in awake, freely moving mice and found that ISF Aβ levels have a significant diurnal pattern with highest levels found during the dark (awake) phase (Kang et al., 2009). Studies of Aβ dynamics in humans found a similar diurnal pattern in CSF Aβ levels (Huang et al., 2012). Furthermore, sleep deprivation worsened Aβ pathology in transgenic mouse models, while administering an orexin antagonist to increase sleep reduced amyloid plaque burden (Kang et al., 2009). These studies established that Aβ levels are tightly associated with the sleep-wake cycle, but the exact mechanisms involved are not known. One possibility is that increased neuronal activity during the awake state increases Aβ levels and drive Aβ aggregation (Cirrito et al., 2005). Alternatively, sleep may be important in clearing Aβ from the brain, since the clearance of exogenously injected Aβ in the mouse brain was dependent on sleep (Xie et al., 2013). Collectively, these studies raise the intriguing possibility that the sleep disorders caused by the AD pathology in the early stages of the disease may potentiate amyloid deposition and accelerate AD progression.

Although various brain areas and neurotransmitters/neuropeptides are involved in the sleep-wake cycle, the hypothalamic neuropeptide orexin (or hypocretin) plays a major role (Sakurai, 2013). APP/PS1 transgenic mice with the orexin gene knocked-out have marked decreases in Aβ pathology in the brain, while sleep deprivation or increasing wakefulness increased Aβ pathology (Roh et al., 2014). Therefore, alterations in hypothalamic orexin signaling can modulate Aβ pathology presumably by affecting sleep-wake cycles. However, recent studies in small cohorts of AD subjects gave conflicting results. A postmortem study found lower orexin levels in the CSF and hypothalamus in AD (Fronczek et al., 2012), while other studies found increased or no significant changes (Liguori et al., 2014; Schmidt et al., 2013). Interestingly, a recent case-control study investigating genetic variants in the orexin

or orexin receptor genes found that a polymorphism in the orexin receptor 2 gene increased the risk for AD (OR 2.53, 95%CI 1.10–5.80), suggesting that genetic variations in orexin signaling could contribute to AD susceptibility either through deficits in sleep regulation or another currently unknown mechanism (Gallone et al., 2014). One study interestingly found no significant difference in CSF orexin levels between AD and healthy control subjects, but CSF levels of melanin-concentrating hormone (MCH) were significantly elevated in AD subjects and correlated with CSF tau levels and severity of cognitive impairment (Schmidt et al., 2013). This is of particular interest because MCH is synthesized in the lateral hypothalamic area and may be a key regulator of sleep-wake states (Jego et al., 2013; Tsunematsu et al., 2014). In addition to orexin and MCH, galanin-expressing neurons are reduced in the intermediate nucleus or ventrolateral preoptic area of AD brains, a lower number of neurons correlating with worsening sleep fragmentation in both demented and non-demented older individuals (Lim et al., 2014). Therefore, loss of this neuropeptide may also be a factor in the sleep dysfunction. Finally, several studies have found elevated levels of CSF epinephrine and norepinephrine in AD, which may lead to increased arousal and agitation that is commonly seen in AD (Elrod et al., 1997; Peskind et al., 1998; Raskind et al., 1999).

Agitation/aggressive behaviors and sundown syndrome

Agitation and aggressive behaviors are common manifestations in AD affecting approximately 20% of those living in the community and 40–60% of those living in institutional care settings (Ballard and Corbett, 2013). They often lead to significant challenges in caretaking and are commonly a major factor in the decision to move a person with AD to an institutional care setting. While the exact etiology underlying the aggressive and agitation behaviors in AD are not known, they are likely to involve the hypothalamus. Since the early 20th century when electrical stimulation of the hypothalamus in cats were demonstrated to elicit aggressive behaviors, the hypothalamus has been long recognized as an integral brain region regulating aggressive behavior (Haller, 2013; Hess and Akert, 1955). Subsequent studies have found that the hypothalamic stimulation results in aggressive behaviors in nearly all animal species studied and have identified “hypothalamic attack areas” or specific regions of the hypothalamus including the lateral hypothalamic area and ventromedial hypothalamic nucleus that when stimulated leads to different aggressive behaviors (Haller, 2013). Furthermore, while there is supporting data in animal studies to suggest that serotonin, vasopressin, and other neurotransmitters such as norepinephrine and Substance P may have an etiological role in agitation and aggressive behaviors, human studies particularly in AD are unfortunately scarce (Haller, 2013).

Sundown syndrome or “sundowning” is a particular form of agitation found commonly in demented individuals where there is emergence or increase in neuropsychiatric symptoms such as agitation, confusion, anxiety, and aggression in the late afternoon, evening or at night (Khachiyants et al., 2011). The overall reported rate of sundowning among demented patients ranges from as low as 2.4% to as high as 66% depending on the study (Khachiyants et al., 2011). As sundowning has features of circadian, sleep, and agitation behavior disorders, the underlying neurobiological mechanism has been hypothesized to be due to dysfunction of the hypothalamus particularly the SCN (Bedrosian and Nelson, 2013;

Khachiyants et al., 2011). Thus, the sundowning seen in AD patients is likely a reflection of the neurodegeneration and pathological changes commonly seen in the SCN in AD (Table 2). In addition, one recent report found that AD subjects with sundowning had higher salivary cortisol levels than AD subjects without sundowning or healthy controls, suggesting that chronic exposure to high levels of glucocorticoids due to HPA axis dysregulation could play a role (Venturelli et al., 2013). Unfortunately, current clinical management strategies commonly rely on medications such as anti-psychotics, which may have detrimental consequences, and non-pharmacological treatments, which may not be effective in severe cases (Ballard and Corbett, 2013), and a better mechanistic understanding of these disturbances would help with the development of more rational management strategies.

Bench-to-bedside: challenges and opportunities

The evidence summarized in the previous sections indicates that hypothalamic dysfunction plays an important role in AD, and could ultimately lead to the identification of novel biomarkers and therapeutic targets. However, there are several issues that remain to be addressed.

There is controversy about the exact nature of the neuroendocrine dysfunction in AD. For example, although the age-related decline in estrogen and testosterone are consistently associated with cognitive decline and AD (Manly et al., 2000; Moffat et al., 2004; Yaffe et al., 2002), the role of the HPG axis, GnRH signaling in particular, remains controversial. This is not surprising since most human studies on neuroendocrine dysfunction in AD were underpowered and did not explore the entire hypothalamic endocrine axis, but only selected hormones. Another drawback of these studies is that the diagnosis for AD often relied exclusively on clinical criteria, which led to the possibility of misdiagnosing and misclassification particularly in subjects with milder symptoms (Sutphen et al., 2014). Appropriately powered studies using neuroimaging and/or CSF biomarkers for AD diagnosis should help address these problems. Studies in animals are also problematic, because there is no single animal model that recapitulates the full spectrum of pathological abnormalities seen in AD (Webster et al., 2014). Therefore, key findings in one model need to be verified in other models and ultimately in humans.

An important open question concerns whether the hypothalamic dysfunction in AD actually contributes to AD pathogenesis or is simply a consequence of the underlying disease process. The answer may be that it is both. One possibility is that, similar to the hippocampus and cortex, abnormal accumulation of Aβ and/or tau in the hypothalamus disrupts normal hypothalamic function leading to impairment in several downstream signals that are important for maintaining vital physiological processes, e.g., body weight regulation and neuroendocrine function (Figure 3). In this case the hypothalamic dysfunction would be a consequence of the underlying disease process of AD and manifests itself based on the hypothalamic pathways affected, e.g., neuroendocrine systems, body weight and systemic metabolism, circadian/sleep cycles, and bone metabolism. Another possibility is that hypothalamic dysfunction contributes to the pathogenesis of AD. Many of the hypothalamic signaling pathways that are affected in AD, such as thyroid hormones, sex hormones, leptin signaling, etc., have been shown to improve synaptic function, protect against neuronal

death, and inhibit Aβ accumulation and/or tau hyperphosphorylation (Fu et al., 2010; Greco et al., 2010; Tan and Vasan, 2009; Vest and Pike, 2013). Therefore, we propose that hypothalamic dysfunction could be both a target of AD pathology and a contributor to its underlying causes. Whereas the initial AD pathology may lead to hypothalamic dysfunction and its numerous disparate manifestations, the hypothalamic dysfunction, in turn, suppresses neuroendocrine hormones and brain signaling mechanisms that are important for maintaining cognitive function, and for protection against AD pathology (Figure 3). This model highlighting the importance of hypothalamic dysfunction in AD can therefore explain not only the progressive nature of the metabolic and non-cognitive manifestations seen in AD, but also suggests that the disruption of the underlying hypothalamic pathways leading to the metabolic and non-cognitive manifestations are important etiological factors of AD.

The dual significance of hypothalamic dysfunction in AD has important implications both for identifying additional biomarkers and for developing new therapies. As an early manifestation of AD, hypothalamic dysfunction could be an attractive area to improve AD diagnosis. First, hypothalamic deficits are often seen in the preclinical stages of AD. This could enable earlier diagnosis of AD and thereby increase the potential options for possible therapeutic intervention. Second, while neuroimaging and CSF biomarkers are rapidly increasing in sensitivity and specificity, these modalities are expensive, somewhat invasive, or simply not widely available. Therefore, examination of hypothalamic function by EEG sleep studies, or plasma neuroendocrine markers, may be a desirable alternative or an adjunct to other approaches for AD diagnosis. Finally, biomarkers based on hypothalamic function could potentially improve therapeutic trials in preclinical AD. Current trials rely on cognitive endpoints to assess therapeutic benefit, which are disrupted relatively later in AD (Kryscio, 2014; Sperling et al., 2011). Since the hypothalamic dysfunction seen in AD, such as body weight loss and sleep/circadian rhythm disturbances, occur early in the disease and worsen with disease progression, assessing hypothalamic function could provide additional information regarding the effectiveness of the drug early in the course of the trial.

If hypothalamic dysfunction promotes AD pathogenesis, then restoration of hypothalamic function should lead to improvements not only in the specific hypothalamic disorder but also in cognitive and memory deficits. Perhaps a striking example of how modulating hypothalamic function could help in AD was serendipitously provided by deep brain stimulation (DBS) studies of the fornix/lateral hypothalamus in humans for treatment of obesity. It was soon appreciated that the stimulation could evoke autobiographic memories by driving activity in mesial temporal lobe structures (Hamani et al., 2008). A phase I trial further supported that DBS of the hypothalamus could improve or at least slow down the cognitive decline in AD subjects without any significant adverse events (Laxton et al., 2010). These preliminary studies provide an important proof of concept that modulation of hypothalamic function could not only improve any neuroendocrine and non-cognitive deficits, but may also have direct therapeutic benefits on cognitive function and memory in AD. Future clinical studies are needed to determine if targeting select hypothalamic pathways affected in AD (e.g., HPG axis, sleep pathways, leptin etc.), by itself or in a combinatorial fashion, leads to similar results.

Conclusion

In this Perspective, we briefly reviewed several decades of AD research to evaluate the evidence for hypothalamic dysfunction in AD. These studies span from early pathological studies identifying the characteristic plaques and tangles in the hypothalamus of postmortem AD brains, to more recent investigations using genetic mouse models to elucidate the specific hypothalamic cell populations affected by amyloid toxicity. Although evidence pointing to hypothalamic dysfunction has long been provided, there has been a relative lack of attention to the hypothalamus in AD research. While the cognitive deficits are the cardinal manifestations of AD, it has become clear that metabolic and non-cognitive deficits are an integral part of the disease as well, and may contribute to its pathogenesis. Focusing on the hypothalamus has allowed us to tie together seemingly disparate manifestations of AD to a single brain region that has been demonstrated to be a pathological target of AD. Thus, exploring further the role of the hypothalamus in AD, may provide new directions in biomarker research and new therapeutic approaches. Since the non-cognitive deficits attributable to hypothalamic dysfunction involve a wide variety of organ systems traditionally associated with different disciplines, multidisciplinary approaches by basic scientists and clinicians with diverse interests and expertise would be required to move the field forward. Efforts in this direction promise to advance our understanding of an understudied but vitally important aspect of the pathobiology of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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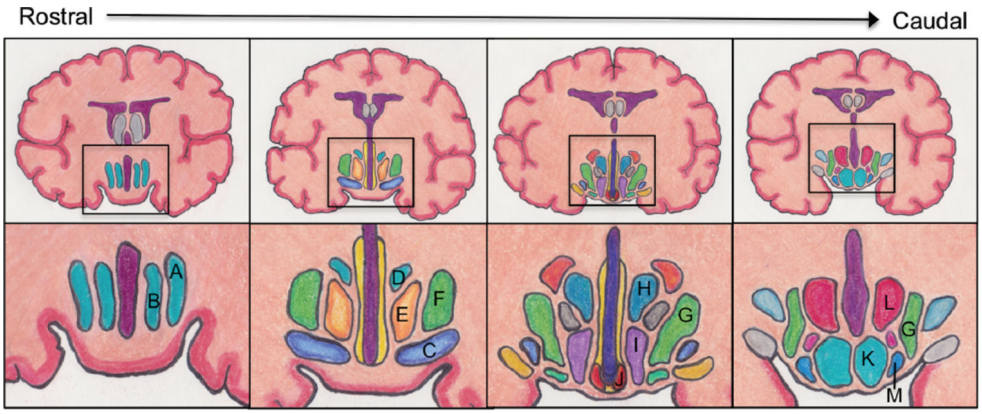

Nuclei (Figure Label)	Region	Function	Select Neuropeptides Neurotransmitters
Preoptic, lateral (A) and medial (B)	• Anterior • Preoptic • Medial	• Reproduction • Thermoregulation • Sexual behavior	• GnRH
Supraoptic (C)	• Anterior • Medial	• Neurosecretory	• Vasopressin • Oxytocin
Paraventricular (D)	• Anterior • Medial	• Hormonal regulation • Fluid balance • Gastrointestinal • Cardiovascular	• TRH • CRH • Oxytocin • Somatostatin
Anterior (E)	• Anterior • Medial	• Thermoregulation • Sweating	• ?
Suprachiasmatic (F)	• Anterior • Medial	• Circadian rhythm	• Vasopressin • VIP • Neurotensin
Lateral (G)	• Anterior • Tuberal • Lateral	• Thirst • Hunger • Arousal	• Orexin • MCH
Dorsomedial (H)	• Tuberal • Medial	• Cardiovascular • Gastrointestinal • Systemic metabolism	• NPY
Ventromedial (I)	• Tuberal • Medial	• Satiety • Sexual behavior	• BDNF
Arcuate (J)	• Tuberal • Medial	• Appetite control	• NPY • AgRP • POMC • CART
Mammillary (K)	• Posterior • Medial	• Memory	• Glutamate • Enkephalin • CCK
Posterior (L)	• Posterior • Medial	• Cardiovascular	• Dynorphin
Tuberomamillary (M)	• Posterior • Lateral	• Arousal • Systemic metabolism	• Histamine

Figure 1. Hypothalamic nuclei: structure and function

Coronal brain images illustrate the hypothalamus and the location of its nuclei (lettered) in order from most rostral (left) to caudal (right) with a description of key functions and neurotransmitters/neuropeptides associated with each hypothalamic nuclei. Abbreviations: AgRP – agouti related peptide; BDNF – brain-derived neurotrophic factor; CART – cocaine and amphetamine related transcript; CRH – corticotropin releasing hormone; GI: gastrointestinal; GnRH – gonadotropin releasing hormone; MCH – melanin concentrating

hormone; NPY – neuropeptide Y; POMC – proopiomelanocortin; TRH – thyrotropin releasing hormone; VIP – vasoactive intestinal peptide.

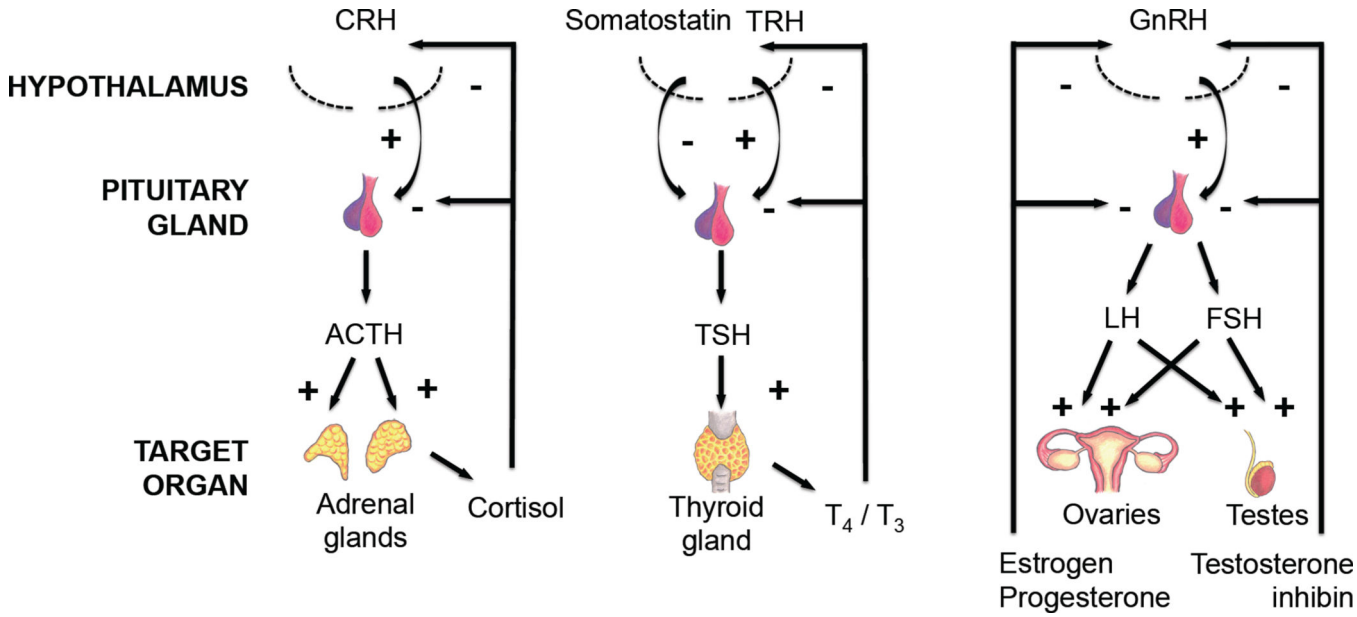

Figure 2. Hypothalamic-pituitary pathways affected in Alzheimer's disease

The normal homeostatic regulation of the hypothalamic-pituitary pathways due to stimulatory (+) and inhibitory (−) signals is shown. i.e., for the hypothalamic-pituitary-adrenal pathway, the hypothalamus releases CRH, which stimulates (+) the secretion of ACTH from the pituitary gland. The ACTH then stimulates (+) release of cortisol from the adrenal glands. The cortisol would then send negative feedback signals (−) to both the hypothalamus and pituitary gland to inhibit the any further release of CRH and ACTH respectively. Similar homeostastic regulation occurs with the hypothalamic-pituitary-thyroid and hypothalamic-pituitary-gonadal axes. Abbreviations: ACTH - adrenocorticotroic hormone, CRH - corticotropin-releasing hormone, FSH – follicle-stimulating hormone, LH - luteinizing hormone, TSH - thyroid-stimulating hormone, T_3 - triiodothyronine, T_4 - thyroxine. Figure was adapted and modified from original (Ishii, 2014).

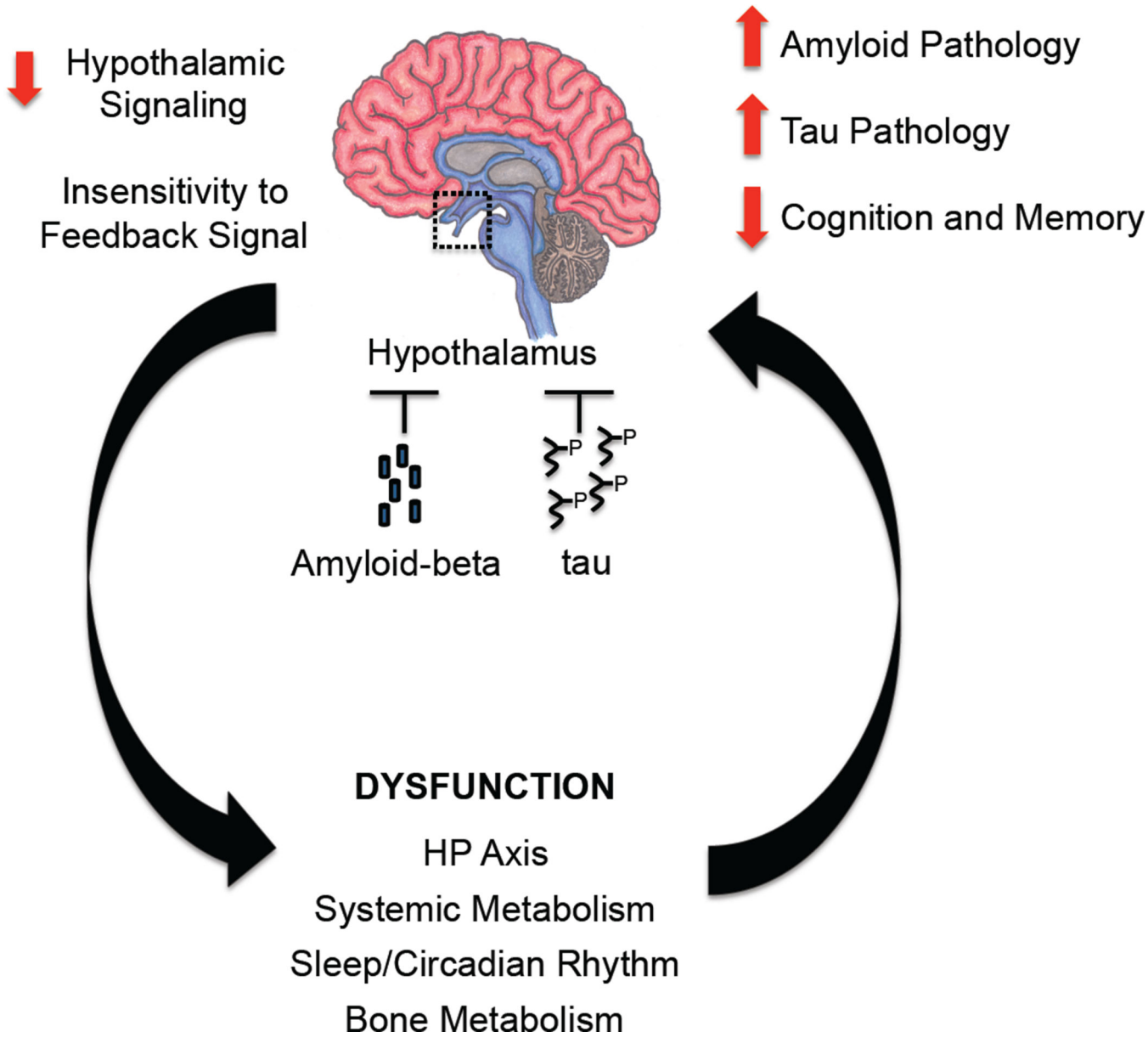

Figure 3. The hypothalamus: target and culprit of AD pathology?

Proposed mechanism depicting how abnormal accumulation of amyloid-beta and tau in the hypothalamus can result in decreased hypothalamic signaling and insensitivity to the normal hormonal feedback signals. Reduced hypothalamic signaling in turn leads to alterations in critical physiological functions including neuroendocrine axis, systemic metabolism, and sleep/circadian rhythm, which can potentially contribute to worsening amyloid and tau pathology and cognitive/mental decline.

Table 1

Hypothalamus and Alzheimer's disease: select pathological studies

Study Subjects (n)	Pathological Studies	Hypothalamic Findings	Key References
70 year-old woman with AD	• Plaques • NFT	• AD pathology in mammillary body and PVN	(Stief, 1927)
AD (28)	• Plaques • NFT	• Posterior hypothalamus, lateral hypothalamus and mammillary body had worst AD pathology • NFT more common than plaques	(McDuff and Sumi, 1985)
AD (4) Controls (28)	• Neuronal counts	• Decrease in total SCN cell number	(Swaab et al., 1985)
AD (3) Controls (3)	• NFT • AChE histochemistry	• NFT in anterior, tuberal, and posterior regions of the hypothalamus • Vast majority of NFT AChE+	(Saper and German, 1987)
AD (17) Down syndrome (4)	• Plaques • NFT	• Plaques in all nuclei in late stages • NFT appreciable by Braak and Braak stage 3 in TMN	(Braak and Braak, 1991)
AD (5) Down syndrome (7) Controls (4)	• Plaques (Aβ42, Aβ40)	• Moderate amount of plaques that are Aβ42+ but Aβ40−	(Iwatsubo et al., 1996)
AD (11) AD with LBD (3) FTD (4) Controls (8)	• glial/neuron ratio • Vasopressin • Neurotensin	• SCN degeneration • Decrease in vasopressin and neurotensin in SCN	(Harper et al., 2008)
AD (12) Controls (12)	• Silver impregnation • EM analysis	• Neuronal loss, loss of dendritic branches and spines, and mitochondrial alterations in SCN, SON and PVN • Alterations in morphology of the mitochondria and Golgi apparatus in SCN	(Baloyannis et al., 2014)

Abbreviations: DLB – dementia with Lewy bodies; DMH – dorsomedial nucleus; EM – electron microscopy; NFT – neurofibrillary tangles; LH – lateral hypothalamic area; PVN – paraventricular nucleus; SCN – suprachiasmatic nucleus; SON – supraoptic nucleus; TMN – tuberomammillary nucleus; VIP – vasoactive intenstinal peptide; VMN – ventromedial nucleus.

Table 2

Hypothalamus and Alzheimer's disease: select neuroimaging studies

MRI(volume)			
Study Subjects (n)	**Degree of cognitive dysfunction**	**Findings**	**Key References**
Mild AD (19) Controls (16)	MMSE • Mild AD: 22.4±2.5	• Decrease in gray matter of anterior hypothalamus	(Baron et al., 2001)
AD (40) Controls (40)	MMSE • AD: 19.5±6.9	• Decrease in hypothalamic volume	(Callen et al., 2001)
Male AD (20) Female AD (20) Male controls (20) Female controls (20)	MMSE • Male AD: 20.4±6.2 • Female AD: 18.6±5.7	• Decrease in hypothalamicvolume (mammillary bodies and fornix) in males • Females less affected	(Callen et al., 2004)
Cognitive symptoms (20) MCI (20) AD (16) Controls (20)	MMSE • Cognitive symptoms: 28.7 • MCI: 27.2 • AD: 24.6 • Controls: 29.1	• Atrophy or decreased volume in fornix and mammillary bodies in AD>MCI	(Copenhaver et al., 2006)
AD (73) DLB (73) Controls (73)	MMSE • AD: 21 • DLB: 22 • Controls: 29	• Grey matter loss in hypothalamus	(Whitwell et al., 2007)
AD (26) Normal to AD (21)Controls (127)	3MS • AD: 76.7 • Normal to AD: 94.9 • Controls: 96.9	• Atrophy of medial basal forebrain including hypothalamus precedes dementia by 4–5 years	(Hall et al., 2008)
Mild AD (63) Controls (55)	MMSE • Mild AD: 26.1±3.7 • Controls: 29.5±0.7	• Decrease in hypothalamic volume correlated with BMD loss	(Loskutova et al., 2010)
SPECT (perfusion)			
Study Subjects (n)	**Degree of cognitive dysfunction**	**Findings**	**Key References**
AD (40) Controls (18)	MMSE • AD: 19.5+/−6.9 • Controls: 28.5+/−1.7	• Non-significant trend towards decreased perfusion in hypothalamus in AD	(Callen et al., 2002)
Male AD (20) Female AD (20) Male controls (20) Female controls (20)	MMSE • Male AD: 20.4±6.2 • Female AD: 18.6±5.7	• Non-significant trend towards decreased perfusion in hypothalamus in male AD	(Callen et al., 2004)
^{18}**FDG-PET (glucose metabolism)**			

Study Subjects (n)	Degree of cognitive dysfunction	Findings	Key References
AD (10) MCI (10) Controls (15)	MMSE • AD: 22.8+/−1.8 • MCI: 28.4+/−1.5 • Controls: 29.7+/−0.5	• Reduced in mammillary bodies in MCI and AD	(Nestor et al., 2003)
MCI (12) Controls (23)	MMSE • MCI: not reported Controls: 26−30	• Reduced in the hypothalamus in MCI	(Cross et al., 2013)

Abbreviations: MCI – mild cognitive impairment, BMD – bone mineral density; DLB – dementia with Lewy bodies; MMSE – mini mental state examination (scale: 0 to 30 with normal range: 27 to 30); 3MS – modified mini-mental state (scale: 0 to 100 with dementia/cognitive impairment < 79).

Table 3

Representative non-cognitive deficits suggesting hypothalamic dysfunction in Alzheimer's disease

Physiological parameter	Abnormality	Hypothalamic nuclei	Neuropeptides/ neurotransmitters	Key References
HPA – Cortisol	• Increases cortisol level • Insensitivity to glucocorticoid feedback • Altered CRH levels	• Paraventricular	• CRH	(Csernansky et al., 2006; Davis et al., 1986; Swanwick et al., 1996)
HPT – Thyroid	• Possible decrease in serum TRH, TSH, thyroid hormone levels but remains controversial	• Paraventricular	• TRH	(Tan and Vasan, 2009; Yong-Hong et al., 2013)
HPG – Estrogen and Testosterone	• Low estrogen or testosterone • Insensitivity to gonadal hormone feedback • Increase in LH	• Supraoptic • Paraventricular	• GnRH	(Manly et al., 2000; Moffat et al., 2004; Rodrigues et al., 2008; Short et al., 2001)
Body weight	• Decrease in late-life prior to cognitive decline • Decrease correlates with disease progression morbidity and mortality • Mid-life obesity associated with increased risk for AD	• Arcuate • Ventromedial • Lateral Area • Dorsomedial	• Leptin • Leptin receptor • NPY / AgRP • POMC • αMSH	(Barrett-Connor et al., 1996; Ewers et al., 2012; Johnson et al., 2006; Vidoni et al., 2011; White et al., 1998; Whitmer et al., 2008)
Circadian rhythm	• Abnormal circadian locomotor and core-body temperature rhythms	• Suprachiasmatic	• Vasopressin • Neurotensin • VIP	(Harper et al., 2001; 2008; Hu et al., 2013; van Someren et al., 1996)
Sleep	• Fragmented sleep pattern and reduced sleep time • EEG changes	• Intermediate nucleus (ventrolateralpreoptic area) • Lateral area	• Galanin • Orexin • MCH	(Ju et al., 2013; Liguori et al., 2014; Lim et al., 2014; Prinz et al., 1982; Schmidt et al., 2013)
Bone metabolism	• Decreased bone density	• Paraventricular • Dorsomedial • Arcuate	• HPG – Estrogen and Testosterone • Leptin (?) • NPY (?)	(Loskutova et al., 2010; Yaffe et al., 1999)

Abbreviations: HPA – hypothalamic-pituitary-adrenal axis; HPT – hypothalamic-pituitary-thyroid axis; HPG – hypothalamic-pituitary-gonadal axis; αMSH – alpha melanocyte stimulating hormone; AgRP – agouti related peptide; NPY – neuropeptide Y; POMC – proopiomelanocortin; CRH – corticotropin releasing hormone; MCH – melanin concentrating hormone; TRH – thyrotropin releasing hormone; GnRH – gonadotropin releasing hormone; VIP – vasoactive intestinal peptide.