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Locus coeruleus, norepinephrine and Aβ peptides in Alzheimer's disease

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ABSTRACT

Monoaminergic brainstem systems have widespread projections that participate in many central processes and, when dysregulated, contribute to a plethora of neuropsychiatric and neurodegenerative disorders. Synapses are the foundation of these neuronal circuits, and their local dysfunction results in global aberrations leading to pathophysiological disease states. This review focuses on the locus coeruleus (LC) norepinephrine (NE) brainstem system and its underappreciated role in Alzheimer's disease (AD). Amyloid beta (Aβ), a peptide that accumulates aberrantly in AD has recently been implicated as a modulator of neuronal excitability at the synapse. Evidence is presented showing that disruption of the LC-NE system at a synaptic and circuit level during early stages of AD, due to conditions such as chronic stress, can potentially lead to amyloid accumulation and contribute to the progression of this neurodegenerative disorder. Additional factors that impact neurodegeneration include neuroinflammation, and network de-synchronization. Consequently, targeting the LC-NE system may have significant therapeutic potential for AD, as it may facilitate modulation of Aβ production, curtail neuroinflammation, and prevent sleep and behavioral disturbances that often lead to negative patient outcomes.

1. Introduction

Alzheimer's disease (AD) affects over 5 million Americans and currently there is no effective treatment for this disorder. AD represents a multi-billion dollar cost to the health care system, a burden that will continue to grow as the population ages (Alzheimer's Association, 2015). It is a neurodegenerative disorder originally characterized by aggregates of the amyloid beta peptide (Aβ), and hyper-phosphorylated tau as symptoms of a disease state (Alzheimer, 1907). Today, the senile plaques composed of Aβ aggregates and neurofibrillary tangles (NFT) composed of hyperphosphorylated tau are regarded as hallmark features of AD, and together, are major histological components of AD observed in post mortem brain tissue.

Neurodegeneration is characterized by atrophy, synaptic and neuronal loss, and gliosis. In the clinic, AD is regarded as a continuum that is generally divided into three phases: the pre-symptomatic phase, mild cognitive impairment (MCI), and dementia. Individuals in the pre-symptomatic phase are cognitively normal but show some AD-related pathological changes including abnormalities in biomarkers of Aβ deposition (Jack et al., 2010). During this phase, Aβ is thought to gradually accumulate, creating functional and structural alterations leading to MCI (Sperling et al., 2011). Efforts by the Alzheimer's Disease Neuroimaging Initiative (ADNI) are currently underway to identify biomarkers and other diagnostic tools for the detection of AD-related abnormalities, including Aβ levels, during the pre-symptomatic phase (Lin and Doraiswamy, 2014; Duygu et al., 2015). Much of the impetus for such efforts are derived from the lack of efficacy of therapeutics targeting Aβ in clinical trials, whose failure has been attributed to the selection of participants whose amyloid burden is beyond intervention, having already progressed to MCI (Doody et al., 2014). MCI, is defined by the onset of cognitive symptoms that do not yet qualify as dementia, such as the inability to recall names, the location of valuable objects and increased difficulty planning and organizing (Alzheimer's Association, 2015). During this phase, individuals may also become moody or withdrawn, exhibit

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personality and behavioral changes, and alterations in sleeping patterns (Alzheimer's Association, 2015). Finally, dementia is defined as a loss of function produced by an array of impairments (Jack et al., 2010), some of which are cognitive, such as loss of awareness of recent experiences and difficulty communicating. Other symptoms manifest as physical impairments, such as loss of the ability to walk, sit, complete hygienic tasks and swallow, thus requiring full-time assistance with daily personal care (Alzheimer's Association, 2015). Importantly, during MCI and throughout the progression of dementia, there are non-cognitive behavioral and psychological symptoms of dementia (BPSD), which are important determinants in prescribing psychotropic drugs, and contribute significantly to quality of life of both patients and caregivers (McKeith and Cummings, 2005).

2. Locus coeruleus neuronal degeneration in AD

One of the earliest brain regions affected by AD is the locus coeruleus (LC), the dorsal pontine nucleus that provides the neurotransmitter norepinephrine (NE) throughout the entire neuraxis (Van Bockstaele and Valentino, 2008). Neuronal cell death in the LC and other brain stem nuclei is a well-defined characteristic of AD pathology (Bondareff et al., 1987; Zarow et al., 2003). The widespread projections of the LC terminate in areas important for learning and memory such as the hippocampus, as well as in regions important for the integration of the stress response such as the amygdala and the medial prefrontal cortex. Generally, the downstream consequences of LC degeneration are decreased levels of NE in terminal regions (Adolfsson et al., 1979; Iversen et al., 1983), and a compensatory upregulation of adrenergic receptors (Kalaria et al., 1989). In contrast to other major neurodegenerative disorders such as Parkinson's disease, patients with AD exhibited the greatest neuronal loss in the LC. Moreover, the duration of illness correlated significantly with neuronal loss in the LC of AD patients (Zarow et al., 2003). Analysis of post mortem AD brain tissue that have quantified the magnitude of LC degeneration indicate that cell loss reaches as high as 50% in the rostral region of the nucleus, and further, this is correlated with a 31% reduction of cortical NE levels (Matthews et al., 2002). Interestingly, this study also found a positive correlation between aggressive behavior and the magnitude of rostral LC loss, while the reduction of cortical NE levels correlated significantly with cognitive impairment (Matthews et al., 2002). Thus, LC-NE system dysregulation may contribute not only to cognitive symptoms, but also to the wide array of non-cognitive symptoms of dementia such as agitation and aggression (Lyketsos et al., 2000, 2002; Finkel, 2001; Mega et al., 1996; Sink et al., 2004), which have been linked to caregiver stress and depression (Nagaratnam et al., 1998). The neuronal cell loss in the rostral LC has additional significance, as this region of the LC is known to primarily project to the cortex, a region known to undergo highly detrimental changes during the progression of AD, and is the earliest region in which Aβ deposition is observed (Thal et al., 2002).

Clinical data suggesting that LC degeneration plays a significant role in AD pathogenesis is supported by preclinical studies showing that the degeneration of this nucleus has a significant impact on multiple facets of disease progression, including inflammation, synaptic function, neuronal metabolism and blood brain barrier permeability (Mravec et al., 2014). Importantly, the LC has been implicated in Aβ-induced neurotoxic insults, and studies of Aβ distribution in the clinic show the presence of Aβ in major projection regions of the LC during multiple phases of Aβ deposition (Thal et al., 2002). In the next section, aspects of AD pathology will be reviewed in the context of Aβ interactions with LC neurocircuitry, NE and the receptors through which NE exerts its effects.

3. Aβ production and the influence of NE

3.1. Amyloid precursor protein (APP) processing (Fig. 1)

The production of Aβ begins in the endoplasmic reticulum (ER), where the precursor to Aβ, amyloid precursor protein (APP) is synthesized. APP is subsequently transported through the Golgi and trans-golgi networks (TGN) where APP is post-translationally modified by N- and O-linked glycosylation, ectodomain and cytoplasmic phosphorylation and tyrosine sulfonation during the process of maturation (Haass et al., 2012). Mature APP is then delivered to the plasma membrane via TGN-derived secretory vesicles where it may be cleaved by α-secretase, precluding Aβ formation, to produce sAPPα (Sisodia, 1992a, 1992b). Alternatively, APP may be re-internalized from the cell surface via clathrin-mediated endocytosis. Generally, it is believed that internalization of APP, or its retention in acidic compartments of the cell favors amyloidogenic processing of Aβ (Hong et al., 2014).

The notion that the subcellular localization of APP determines its participation in two divergent processing pathways has significant implications for AD and has become essential to our understanding of Aβ production. As such, understanding what drives APP to either pathway has become the subject of intense investigation and has highlighted the importance of synaptic activation in the etiology of Aβ production. For example, it has been demonstrated that increased synaptic activity results in increased production and secretion of Aβ into the extracellular space, as measured by levels of Aβ in interstitial fluid (Cirrito et al., 2003), and further, that this is an endocytosis-dependent process (Cirrito et al., 2008). The proposed model by which synaptic activity and endocytosis contribute to Aβ generation is predicated on the idea that intracellular calcium influx triggered by the depolarization of the cell results in synaptic vesicle release, and concomitant increases in synaptic membrane recycling via clathrin-mediated endocytosis. The increased recycling of membranous components results in greater internalization of APP which then serves as a substrate of β- and γ-secretases thereby enhancing Aβ production (Cirrito et al., 2008).

Investigation of the localization of APP, BACE-1 and γ-secretases at the synapse have revealed their presence in synaptic vesicles of hippocampal primary neuronal cultures (Groemer et al., 2011), and in catecholaminergic chromaffin cells in vitro (Toneff et al., 2013). Chromaffin cells have been utilized to investigate the regulated secretion of neurotransmitters from large dense core vesicles (LDCV) (Toneff et al., 2013), the primary site of neuropeptide synthesis and also a site of NE synthesis (Wang and ebrary Inc, 2008). Toneff and colleagues demonstrated that when chromaffin cells are stimulated by KCl depolarization, or forskolin, Aβ was co-secreted with other neuropeptides and catecholamine neurotransmitters, including NE. When LDCVS were isolated and examined using western blot analysis, BACE-1, γ-secretase, APP and Aβ are present, indicating that the LDCVs may be a site of Aβ synthesis and release (Fig. 1). Interestingly, a recent study of post mortem AD brain tissue revealed that the chromogranin peptides unique to LDCVs are dysregulated in AD. Particularly, Chromogranin A was shown to be elevated, within senile plaques, and highly associated with dystrophic neurites and activated glial cells (Lassmann et al., 1992; Lechner et al., 2004). Thus studying the mechanisms of LDCV release, and their synaptic components such as the chromogranin peptides within noradrenergic neurons in the brain may be an area of future research.

3.2. Adrenergic receptor influence on Aβ production

Extensive research on the involvement of GPCRs in APP processing and Aβ production have revealed that various GPCRs may

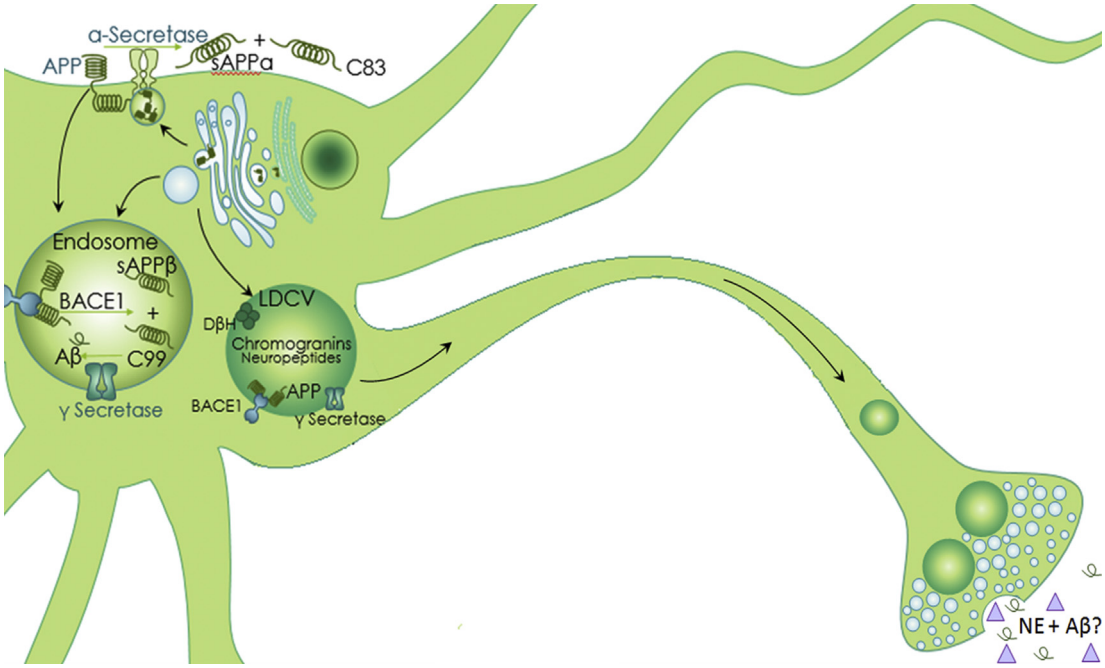

Fig. 1. Trafficking Route of APP, α-secretase, BACE1 and γ-secretase. Full length APP is synthesized in the endoplasmic reticulum and subsequently transported through the Golgi, and trans-Golgi network (TGN) where APP undergoes post-translational modifications such as glycosylation and phosphorylation during maturation. Full length APP can be transported to the cell surface in TGN-derived secretory vesicles, where APP may be cleaved by α-secretase present within the plasma membrane to produce sAPPα, or re-internalized via clathrin mediated endocytosis. Typically elevated retention within the endosome leads to increased production of the toxic amyloid beta by the β-secretase, BACE1, which is localized to and optimally cleaves in the acidic conditions of the endosome. BACE1 cleaves APP into the sAPPβ and C99 fragments, and the C99 fragment is then cleaved again by the gamma secretase also present in the endosome, to produce the amyloid beta peptide that is known to aggregate and become neurotoxic. Subsequently, Aβ may be degraded in the lysosome, or participate in the secretory pathway, where Aβ will be released into the extracellular space. Another potential site of Aβ production, still under investigation, are the large dense core vesicles (LDCVs). APP, β- and γ-secretases have been localized to LDCVs. Initial formation of LDCVs occurs at the TGN; following neuropeptide synthesis in the cell body, condensation of LDCV contents and maturation is facilitated by chromogranin peptides that reside within the LDCVs. LDCVs may be released at the soma, or undergo anterograde transport to terminal regions where they may be released away from active zones (Wang and ebrary Inc, 2008).

influence APP proteolytic cleavage by promoting or inhibiting the activity of the secretases that cleave APP or influence its subcellular localization. In the context of this review, we will specifically focus on the role of the β2 and α2 adrenergic receptors. Adrenergic receptors in the post mortem AD brain have been investigated; while α2AR density is unaltered (Matthews et al., 2002), β2AR density is elevated in the frontal cortex and hippocampus (Kalaria et al., 1989), and polymorphisms in the gene encoding the β2AR are associated with an increased risk of developing sporadic late onset AD (Yu et al., 2008). These findings have important implications for AD, as β2 and α2AR are localized to terminal regions of the LC and have a direct influence on synaptic transmission and the APP processing machinery residing at the synapse (Fig. 2). Moreover, these receptors have been implicated in the production and secretion of Aβ.

Electron microscopy studies have localized the β2 adrenergic receptor (β2AR) on dendritic spines of pyramidal neurons of the PFC and on GABAergic interneurons (Aoki et al., 1998), as well as on glia, where they may reduce the uptake of glutamate and regulate glucose availability (Fillenz and Lowry, 1998). Generally βARs are positively coupled to the Gs/cAMP second messenger system and are predominantly localized post-synaptically; however, reports have also identified pre-synaptic βARs that facilitate NE release (Berridge and Waterhouse, 2003). One proposed mechanism for the regulation of Aβ production by β2-AR is via the joint endocytosis of β2 and APP from the plasma membrane following stimulation, which increases the co-localization and availability of APP to act as a substrate for γ-secretase in the endosomal compartment (Ni et al., 2006). It has also been postulated that β2AR is able to modulate Aβ production via its association with β-arrestin2, which physically interacts with the α1A subunit of the γ-secretase complex, resulting in increased catalytic activity of the complex (Thathiah et al., 2013). Further support for β2AR regulation of Aβ production is derived from studies using β2 antagonists, which show diminished levels of Aβ40 and Aβ42 in a transgenic animal model after chronic treatment (Ni et al., 2006). Thus β2AR stimulation appears to promote Aβ production at noradrenergic synapses and transmission at these synapses is controlled by afferents from the LC, therefore dysregulation of the LC induced by stress may contribute to increased Aβ production during prodromal or early stages of the disease (Fig. 2). Following this logic, it may be hypothesized that subsequent upregulation of β2-ARs during the degeneration of the LC may contribute to Aβ deposition to a lesser extent due to decreased levels of NE. This is consistent with biomarkers of AD progression, which show that levels of Aβ gradually increase as early as 20 years prior to the onset of symptoms, and plateau during neurodegeneration (Jack et al., 2010).

The α2 adrenergic receptors (α2AR) are coupled to Gi/cAMP systems and are predominantly localized presynaptically, acting as autoreceptors that regulate NE synthesis and release (Berridge and Waterhouse, 2003). Early studies exploring catecholamine neurotransmitters and receptors in age-related cognitive disorders identified α2 adrenergic receptors as contributors to cognitive decline in the prefrontal cortex (Arnsten and Goldman-Rakic, 1985). More recently, the α2aAR has been implicated in the regulation of APP processing and subsequent Aβ production and secretion via the endocytic and secretory pathways (Chen et al., 2014). This study revealed that through an interaction with SorLA, a sorting-related protein known to retrogradely transport APP from the endosome to the Golgi, the α2AR promotes the

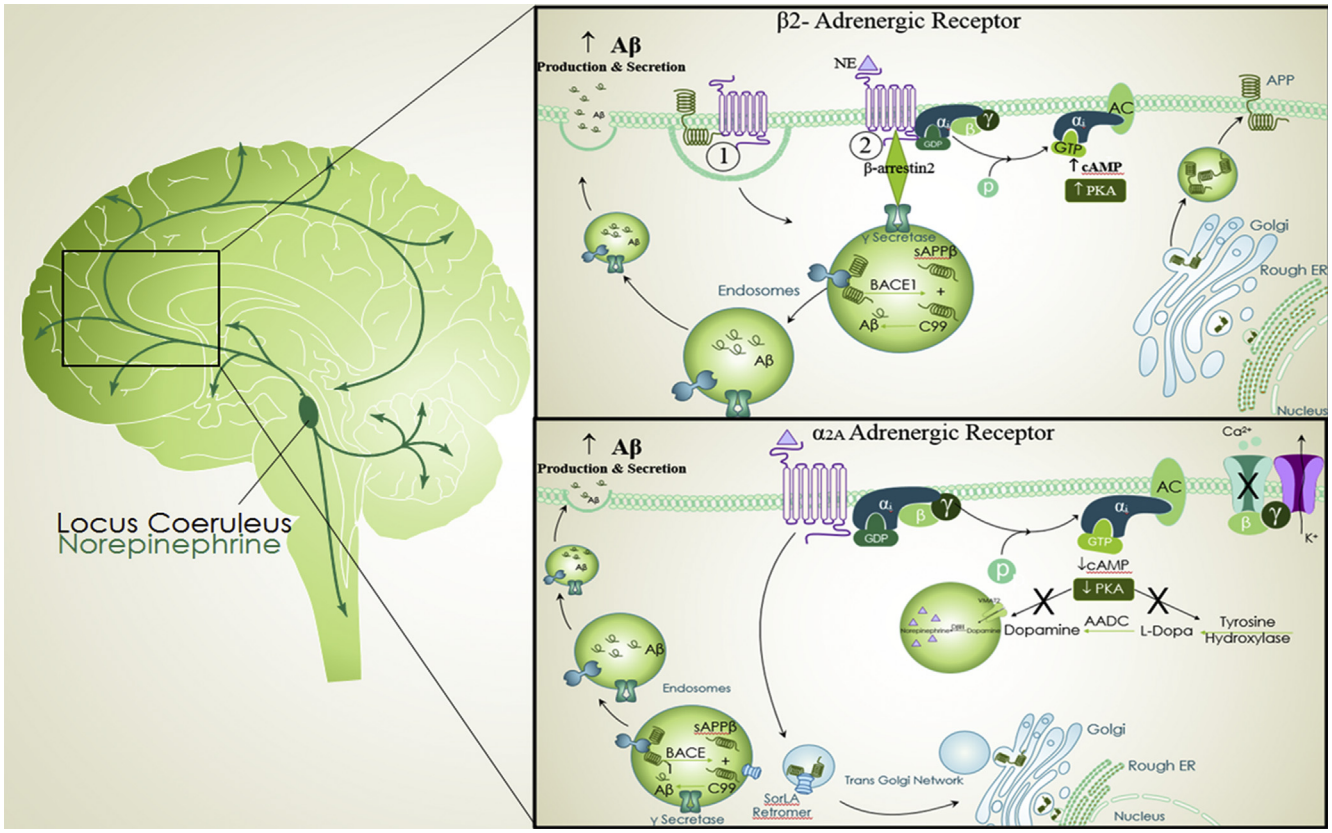

Fig. 2. Adrenergic Receptor Influence on Aβ production. The β2 adrenergic receptor is a Gs coupled receptor that may influence Aβ production in two ways. First, APP may be internalized with β2 following periods of prolonged stimulation, therefore allowing APP to act as a substrate for β- and γ-secretases in the endosome. Second, β2 may interact with the β-arrestin 2 protein that directly interacts with the α-1A subunit of γ-secretase, increasing its catalytic activity. The α-2A receptor is a Gi coupled receptor that influences Aβ production by disrupting the interaction of APP with SorLA, a retromer that protects APP from proteolytic cleavage.

production and secretion of Aβ in the cerebral cortex of AD transgenic mice. Based on this evidence it is clear that the β2 and α2aARs play a role in the modulation of Aβ production and secretion (Fig. 2). Importantly, this evidence may suggest that dysregulation of the LC-NE system in early stages of Alzheimer's contributes to increased Aβ accumulation in LC terminal regions. Thus, a pharmacological intervention aimed toward controlling adrenergic receptor influence on Aβ production and secretion in early stages of AD may delay subsequent degeneration. Such a therapeutic strategy may not be as effective in later stages of the disease when neurodegeneration of the LC results in decreased NE levels, and consequent decreased stimulation of adrenergic receptors.

4. Physiological and pathological role of Aβ in synaptic transmission and network synchronization

Multiple lines of evidence now support a physiological role for endogenous Aβ in the central nervous system. Previously unappreciated, it is now established that there are normal levels of endogenous Aβ in the low picomolar range in both human and animals CNS (Cirrito et al., 2003; Brody et al., 2008). Studies focusing on endogenous Aβ have demonstrated that its production and secretion is a tightly regulated process that occurs at the synapse following changes in synaptic activity (Cirrito et al., 2005) in a clathrin-mediated endocytosis-dependent manner (Cirrito et al., 2008). Using a specialized expression system to acutely deliver APP in organotypic hippocampal slices, Kamenetz et al. (Kamenetz et al., 2003) were able to determine the effects of APP overexpression on synaptic transmission and the reciprocal effects of synaptic transmission on APP processing. These studies demonstrated for the first time that increased neuronal activity increased Aβ production via increases in β-secretase activity, and that the resulting elevated levels of Aβ decreased synaptic function, suggesting a potential role for Aβ in a postsynaptic negative feedback loop mechanism (Kamenetz et al., 2003). The aberrant elevation of Aβ in conditions such as AD would be expected to overactivate the negative feedback arm of this mechanism, decreasing excitatory transmission (Palop and Mucke, 2010). Importantly, too high or too low concentrations of Aβ have been shown to impair synaptic transmission. Picomolar concentrations of Aβ significantly enhance synaptic transmission, whereas nanomolar concentrations cause synaptic depression. Thus Aβ may be part of a modulatory feedback mechanism that controls neuronal excitability (Palop and Mucke, 2010). While the details of Aβ interaction are a subject of intense ongoing investigation, some studies have proposed mechanisms by which Aβ may act pre- and post-synaptically to modulate neuronal activity. Evidence that Aβ acts as a positive regulator of synaptic activity at the presynaptic level has been demonstrated (Abramov et al., 2009); specifically, Aβ may act directly on presynaptic α7-nAChR to increase presynaptic Ca2+ and Aβ secretion (Palop and Mucke, 2010). At the post-synaptic level, Aβ has been shown to facilitate long term depression (LTD), and suppress long term potentiation (LTP) through the NMDA receptor signaling axis. A number of studies have investigated these effects, demonstrating that Aβ blocks the uptake of glutamate (Li et al., 2009), promoting spill-over of glutamate at the synapse, and engaging the perisynaptic NMDA receptors that have an important role in initiating LTD (Talantova et al., 2013; Liu et al., 2004). Other studies have suggested that these effects may be mediated by NMDA receptor desensitization, internalization, and subsequent collapse of

dendritic spines (Snyder et al., 2005). Importantly, evidence of Aβ-induced internalization and degradation of the β2-AR (Wang et al., 2011) suggests that mechanisms of Aβ interaction may be generalized to other signaling systems, and may be an important area for future research.

With mounting evidence for the role of Aβ in synaptic modulation, a new perspective on the downstream consequences of Aβ dysregulation has emerged. In this framework, the dysregulation of Aβ results in aberrant network synchronization that globally disrupts cognitive function and normal brain processes such as the balance between inhibitory and excitatory tone (Palop and Mucke, 2010). In particular, disruptions to the GABAergic and glutamatergic systems appear to contribute largely to the disruption of normal network synchronization. This hypothesis is supported by evidence that Aβ is predominantly distributed along networks with aberrant neuronal activity in AD patients (Buckner et al., 2005), and increases in Aβ may cause epilepsy and cognitive deficits (Palop and Mucke, 2009). Further, AD is associated with increased incidence of seizures independently of disease stage, a history of infrequent seizures is common in sporadic AD patients, and more discernible epilepsy is evident in familial early-onset AD [Reviewed in Palop and Mucke, 2009]. Importantly, increased neuronal activity and epilepsy can increase the production, release, and/or accumulation of Aβ (Mackenzie and Miller, 1994). In vivo models have also demonstrated abnormal EEG activity associated with spontaneous epileptiform activity in hAPP mice (Verret et al., 2012). Alteration in neurological functions in AD models, reflected in abnormal oscillatory rhythms or network synchronization are likely a result of changes in activity-regulated gene expression, complex signaling systems such as mitogen activated protein kinases (MAPK), cyclin-dependent kinase 5 (cdk-5), tyrosine kinases, and alterations in synaptic vesicle release and recycling (Palop et al., 2006). EEG studies in AD patients have revealed decreases in alpha, beta and gamma frequency bands (Koenig et al., 2005). Of particular interest are alterations to the gamma frequency band, which are thought to be important for attention, and memory storage and retrieval (Jensen et al., 2007). The activation of GABAA receptors is thought to contribute to underlying mechanisms promoting persistent gamma-frequency oscillations (Traub et al., 2003). Recent studies have demonstrated the ability of selective norepinephrine reuptake inhibitors (SNRIs), reboxetine and desipramine, to enhance gamma activity of the septo-hippocampal system (Hajos et al., 2003). In support of this, evidence in the literature suggests a role for NE stimulation of adrenoreceptors in modulating GABAergic inhibitory systems in the brain. These studies demonstrate the ability of NE to promote the induction of synaptic plasticity by GABAergic inhibition, as well as the ability of NE to enhance the frequency and amplitude of GABAergic inhibitory post synaptic currents and potentiate GABAergic processes (Waterhouse et al., 1980), effects which may be exerted differentially depending on the region of the brain and the receptor subtype activated (Tully and Bolshakov, 2010). Consequently, a reduction in LC-NE activity and NE levels could result in a decrease in GABAergic inhibitory activity leading to phenomenon such as spontaneous epileptiform activity, and abnormalities in gamma oscillations. Thus, multiple lines of evidence suggest that targeting the NE system via the utility of SNRIs in later stages of AD may provide support for GABAergic inhibitory systems while also potentially stabilizing gamma frequency activity.

5. Proposed contribution of stress and LC-NE system to Aβ modulation and AD pathology

The LC circuit has not yet been studied in the context of network de-synchronization resulting from aberrant Aβ deposition in the LC and its terminal regions. Thus, an outstanding question is whether aberrant LC activation and subsequent increased Aβ in projection areas of the LC provides impetus for global dysfunction of LC circuitry, initially in the form of aberrant, over-activation and subsequently in the retraction of dendritic spines, and degeneration of its widespread afferents. Fig. 3 illustrates our working model, and is based on the hypothesis that chronic exposure to stress may facilitate aberrant activity of the LC system (Fig. 3a). Consequently,

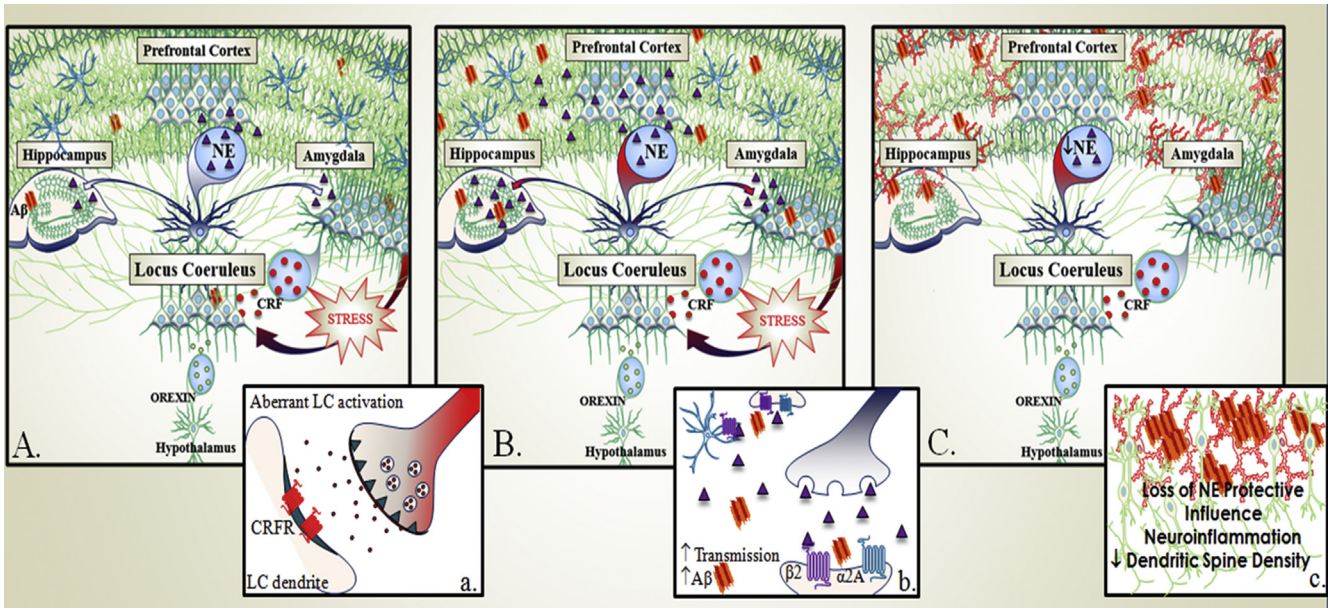

Fig. 3. Model of proposed contribution of LC-NE Dysregulation in Alzheimer's disease. Our current working model proposes that aberrant activation of the LC at the synaptic level (a), leads to global aberrant LC activity in its widespread projection areas (A). With increased synaptic activity, increased transmission of NE may occur concomitantly with increased Aβ production in synaptic vesicles such as the LDCVs (B). Increased Aβ production and secretion may result from the described mechanisms of adrenergic receptor influence on APP processing (b). Further, the ability of NE to undergo volume transmission, engaging extrasynaptic mechanisms of transmission on neighboring neuronal and glial cells, has significant implications for the microenvironment (B, C). Finally, following a prolonged period of Aβ accumulation, cortical thinning, decreased noradrenergic transmission, and downstream loss of inflammatory modulation results in the detrimental activation of glial cells, and decreased dendritic spine density, and potentially network de-synchronization.

we expect elevated levels of Aβ in the LC and its terminal regions, where adrenergic receptors are present and may contribute to the production of Aβ (Fig. 3b). It may be further hypothesized that Aβ dysregulation and resulting network desynchronization contribute to LC degeneration. Thus, the initial accumulation of Aβ resulting from stress would be evident prior to degeneration of the LC, and subsequent loss of noradrenergic tone in widespread terminal regions of the LC may exacerbate other aspects of AD pathology (Fig. 3c). While there is still much to be explored, there is substantial evidence that the dysregulation of this system may have detrimental effects in the AD brain. The LC-NE system is uniquely positioned, as it is involved in multiple processes involved in memory and cognition, may be stimulated by external factors such as stress, and targets global projection areas, allowing for large-scale changes in the brain environment. Of particular interest are the afferents expressing corticotropin releasing factor (CRF) from the central nucleus of the amygdala (CeA), which are thought to activate the LC in response to environmental stressors (Valentino et al., 1983, 1992a; Van Bockstaele et al., 1998), and the hypocretin afferents of the lateral hypothalamus to the LC, which have an important role in mediating transitions of sleep to wake and promoting overall wakefulness (Mignot, 2001; Peyron et al., 1998). The importance of these afferents is based on their ability to modulate LC function, thereby influencing the actions of NE on widespread terminal regions. Further, dysregulation of Aβ peptide synthesis and release at the synaptic intersection of these regions and the LC may contribute to aberrant LC activation and promote global network de-synchronization of its afferents.

6. LC-NE stress integrative circuitry and Aβ

A number of clinical studies have suggested an important role for stress and stress-related neurocircuitry in AD patients. The observations that led to this assertion include elevated baseline cortisol levels in AD patients that correlate with changes in performance on the ADAS-Cog exam (Weiner et al., 1997), more rapidly increasing symptoms of dementia and a more rapid decline in performance on neuropsychological tests when compared to non-demented controls (Csernansky et al., 2006). Clinical studies show that patients with a high level of distress are 2.7 times more likely to develop AD, and that this trait is also associated with accelerated progression of the disease (Wilson et al., 2003, 2005). Reports of abnormalities of several levels of the HPA axis in patients with AD have been reported, suggesting increased central drive of this critical physiological and neurological axis in responding to stressful stimuli (Rasmuson et al., 2001). For example, patients with AD have been reported to have increased production of glucocorticoids (GC) and decreased sensitivity to GC negative feedback, as well as downregulated ACTH responses to corticotropin releasing hormone (CRH) (Rasmuson et al., 2001). Clinical findings are supported by preclinical studies that have demonstrated increased central drive of the stress system and decreased GC feedback contribute to cognitive dysfunction in models of AD (Elgh et al., 2006; Hebda-Bauer et al., 2013). Interestingly, in the Tg2576 model of AD, cognitive decline was rescued following administration of the glucocorticoid receptor antagonist RU486, which may represent a novel therapeutic strategy (Lante et al., 2015).

The LC-NE system is often described as a stress integrative circuit based on the fact that the LC responds, in parallel with peripheral stress responses, to a vast array of stressful stimuli, both cognitive and physical (Van Bockstaele and Valentino, 2008). This has been demonstrated in microdialysis studies investigating the effects of restraint, tail shock, auditory and hypotensive stressors on extracellular levels of NE in terminal regions of the LC (Abercrombie et al., 1988; Britton et al., 1992). In agreement with these findings are studies investigating other endpoints of LC-NE system activation including expression of tyrosine hydroxylase mRNA and c-fos mRNA expression (Beck and Fibiger, 1995; Bonaz and Tache, 1994; Campeau and Watson, 1997; Chan and Sawchenko, 1995; Chang et al., 2000; Makino et al., 2002). Corticotropin releasing factor (CRF) is believed to mediate stress-induced LC activation, and this hypothesis is supported by anatomical evidence that CRF-immunoreactive fibers densely innervate the peri-coerulear regions into which the locus coeruleus dendrites extend (Valentino et al., 1992a). Further, high resolution electron microscopy analysis of this region identified asymmetrical (excitatory) synaptic specializations between CRF-immunoreactive axon terminals and LC dendrites, suggesting that CRF afferents to this region directly control LC neuronal excitability and activity (Van Bockstaele and Valentino, 2008). Importantly, the LC receives CRF input from multiple regions, including the central nucleus of the amygdala (CeA), bed nucleus stria terminalis, paraventricular nucleus of the hypothalamus (PVN), Barrington's nucleus, and the nucleus paragigantocellularis (Reyes et al., 2005; Valentino et al., 1992a). Under normal physiological conditions, following glucocorticoid synthesis and release from the adrenal cortex in response to a stressful stimulus, glucocorticoids participate in a negative feedback loop that suppresses the activity of the PVN, thus having downstream consequences for CRF release in the LC. Conditions such as AD, in which corticosteroid receptors, or other aspects of the corticosteroid regulatory feedback system are dysregulated, represent circumstances in which LC activity would be predicted to be tonically elevated (Van Bockstaele and Valentino, 2008). The significance of this response becomes more pronounced when downstream consequences of LC and stress related circuit dysregulation are considered in the context of Aβ deposition and Alzheimer's pathology. The following section will explore how amplification of the stress system disrupts normal neuronal processes on a circuit level and affects cellular and molecular processes at the synapse, promoting Aβ production and accumulation.

7. Effects of stress and glucocorticoid production on Aβ deposition

The reported clinical findings regarding the involvement of the stress system in AD pathogenesis are supplemented by preclinical studies that have further investigated aspects of the stress response system that may be involved in this dysregulation. It has been demonstrated in transgenic mouse models of AD that stress exacerbates Aβ production (Green et al., 2006; Jeong et al., 2006). For example, isolation stress increases corticosterone and glucocorticoid receptor levels in the hippocampus and cortex of Tg2576 mice in conjunction with increased Aβ plaque deposition. A strong correlation was identified between plaque deposition and plasma corticosterone levels in the cortex of these transgenic mice (Dong et al., 2008). Earlier studies from this laboratory showed that Tg2576 mice have increased Aβ deposition, decreased capacity for neurogenesis in the hippocampus, and impaired contextual memory following isolation stress (Dong et al., 2004). Other groups have shown that stress and excessive GC promotes the production of Aβ by shifting APP processing towards the amyloidogenic pathway in normal, middle aged rats (Catania et al., 2009). This study utilized multiple techniques to augment the stress system, including a chronic stress paradigm, exogenous GC administration, and exogenous Aβ administration, to demonstrate that increased production of the C-terminal fragment (C99) that is cleaved to form Aβ results from activating the stress system, and further, exacerbates spatial memory deficits induced by Aβ.

The detrimental effects of stress-induced CRF activation in the context of AD have also been explored in preclinical models. While

direct infusion studies of CRF in the LC of APP transgenic mice have not been conducted, it has been demonstrated that when other regions densely populated with CRF receptors such as the hippocampus are directly infused with CRF there is a resultant increase in interstitial fluid Aβ levels in a dose- and neuronal activity dependent manner (Kang et al., 2007). CRF induced responses are mediated by G-protein coupled CRF receptor1 (CRFR1) and CRF receptor 2 (CRFR2) (Bale and Vale, 2004). The major stress receptor, CRFR1, modulates cellular activity in many AD-relevant brain areas and has been demonstrated to impact both tau phosphorylation and amyloid β pathways (Campbell et al., 2015a). It has been demonstrated that isolation stress increases CRFR1 expression in conjunction with increases in Aβ levels and Aβ plaque deposition in the Tg2576 model of AD (Dong et al., 2008). Meanwhile, studies using a transgenic mouse line null for CRFR1 with PSAPP double transgenic mutations show significantly reduced Aβ 40, 42 peptides and decreased APPβ-CTFs in multiple brain regions compared to PSAPP counterparts as measured by ELISA (Campbell et al., 2015a). While a complete discussion of the effect of stress and CRFR1 signaling on the phosphorylation of tau are beyond the scope of this review, there is substantial evidence to support the involvement of the CRF axis of the stress system in AD pathology, and in relation to the LC. Briefly, studies utilizing mice null for CRFR1 have found that CRFR1 deletion blocks the stress induced upregulation of GSK-3β and JNK, kinases responsible for phosphorylating tau at AD relevant sites. Consequently, CRFR1 deletion results in decreased phosphorylation of tau in the hippocampus compared to stressed wildtype controls (Rissman et al., 2007). Further studies by this group have established that conditions of chronic, repeated stress in wildtype animals result in increased phosphorylation of tau, a portion of which is observed in a detergent-soluble cellular fraction, reflecting a possible pre-pathogenic form. Importantly, these effects were blocked when CRFR1−/− mice were subjected to the same chronic stress paradigms (Rissman et al., 2012). Studies utilizing CRF overexpressing mice demonstrate increased phosphorylation of tau at the S202/204, and S296/404 AD relevant sites, effects which are blocked following administration of the CRFR1-antagonist R121919 (Campbell et al., 2015b). Interestingly, recent reclassification of staging by Braak and colleagues proposes that tau dysregulation begins in the LC, and subsequently spreads transynaptically to other regions of the brain (Braak and Del Tredici, 2011). Thus, this evidence elevates the LC as a pivotal point of intersection for stress-induced aberrant activation of the CRFR1 signaling axis, resulting in the dysregulation of tau-phosphorylation and Aβ production and accumulation. The LC is a critical integration center for the stress response and is heavily populated with CRFR1; however the consequences of stress on LC circuitry in the context of tau-P and Aβ primary components of AD have not been elucidated and represent a significant gap in our knowledge that merits further exploration.

Exposure to severe or chronic stress results in the loss of dendritic spines and by extension, synapses, and has been attributed to actin cytoskeleton collapse downstream of CRFR1 within hippocampal excitatory synapse spine heads (Chen et al., 2012). In line with these results, triple transgenic mice that overexpress CRF and human APPβ with a conditional promoter specific for forebrain expression show increases in soluble Aβ and Aβ plaques with consequent decreases in dendritic branching and dendritic spine density in pyramidal neurons in layer IV of the frontal cortex and CA1 of the hippocampus (Dong et al., 2012). Studies utilizing a hAPPSL/hTau transgenic mouse line have demonstrated a synergistic relationship of Aβ and dysregulation of tau phosphorylation. This synergy is evident in 50% increased tau accumulation, particularly of insoluble Tau, compared to transgenic models of hTau alone. Additionally, this model shows no further alterations in hAPP levels, compared to single transgenic models of hAPP alone (Chabrier et al., 2014). Investigators also observed an upregulation of the Fyn kinase, a protein tyrosine kinase associated with both Aβ and tau-P disruption (Roberson et al., 2011), in this mouse model (Chabrier et al., 2014). The upregulation of Fyn occurred concurrently with a significant decrease of the post synaptic marker PSD-95 and reduction in mushroom spines, which has been correlated with cognitive decline in several models of AD pathology (Dickstein et al., 2010; Perez-Cruz et al., 2011). Importantly, these alterations were not observed in either single transgenic mouse line alone. Thus, these studies have suggested that human wild-type tau alone becomes hyperphosphorylated with age, but the presence of Aβ facilitates accumulation of both soluble and insoluble tau (Chabrier et al., 2014). The cellular and molecular alterations summarized here indicate that increased central drive of stress systems promote the production of Aβ and the phosphorylation of tau, compromising the integrity of synaptic connections, and ultimately contribute to synaptic loss in an Aβ-dependent synergistic fashion.

8. LC-NE system and memory and learning circuitry

Given the evidence presented above from both clinical and preclinical studies, it is important to understand the neuroanatomical and pharmacological processes that may connect the stress system with Aβ production and memory impairment. The involvement of the noradrenergic system in learning and memory processes is a controversial topic, as various methods to interfere with adrenergic signaling, focusing on acquisition, consolidation, retrieval and reconsolidation of memory have yielded conflicting results (Murchison et al., 2004). This observation led Murchinson and colleagues to use a genetically modified mouse line null for the norepinephrine synthesizing enzyme, dopamine-β-hydroxylase (DβH) to explore multiple dimensions of learning in memory tasks. Further, the use of a synthetic norepinephrine precursor, L-threo-3,4-dihydroxyphenylserine (L-DOPS) injection at specific times during training and testing allowed for the examination of the role of NE during different phases of the learning and memory processes. The results of this study yielded the important finding that norepinephrine is critical for the retrieval of intermediate-term contextual and spatial memories in the hippocampus through β1-AR signaling (Murchison et al., 2004). Other regions implicated in noradrenergic mediation of memory processes include the amygdala and the prefrontal cortex, which are also heavily involved in the integration of the stress response. The basolateral amygdala (BLA) receives dense innervation from the LC and NE increases in the BLA in response to stress. Further, noradrenergic influence in the BLA has been shown to enhance memory consolidation induced by hippocampal (Roozendaal et al., 1999) and mPFC (Roozendaal et al., 2004) glucocorticoid receptor activation, an effect that is dependent on β2 adrenergic receptor activation in the BLA (O'Donnell et al., 2012). Moreover, noradrenergic influence of the BLA has been shown to have an important but not exclusive role in working memory processes of the PFC (Roozendaal et al., 2004). It has been demonstrated both in vitro and in vivo that Aβ42 induces the internalization and degradation of β2AR in prefrontal cortical neurons (Wang et al., 2011), an important finding considering the recent evidence that stimulation of β2ARs have beneficial effects on working memory in young and aging animals (Ramos and Arnsten, 2007). Further, this study shows that binding of Aβ to the β2AR leads to desensitization, and subsequent attenuation of cAMP, PKA signaling and phosphorylation of glutamate receptor subunits and subsequent mini EPSCs (Wang et al., 2011). This is particularly significant as studies have demonstrated that restoration of cAMP signaling using rolipram in mouse models of AD have demonstrated the ability to reverse long-term dendritic spine loss (Smith

et al., 2009). The role of β2AR in enhancing cognitive functions in the hippocampus, amygdala, and PFC (Ramos and Arnsten, 2007), and their participation in Aβ production, cAMP signaling, and potential modulation of dendritic spine density, represent additional mechanisms by which LC-NE dysregulation may contribute to AD pathogenesis.

9. Convergence of peptide interactions on the LC-NE system and influence on Aβ

The LC is known to play a physiological role in promoting wakefulness and attention. Afferents to the LC include the hypocretin (orexin) containing neurons of the hypothalamus, whose stimulation of hypocretin receptors present in the LC, results in increased discharge of LC neurons (Horvath et al., 1999). Under normal physiological conditions, orexin facilitates the transition from sleep to wakefulness at least in part, by exciting the LC, resulting in the synthesis and release of NE (Carter et al., 2012). Studies of AD post mortem brain tissue and ventricular cerebrospinal fluid indicate a loss of orexinergic signaling, reflected by a 40% decreased cell number, and 14% lower CSF hypocretin-1 levels (Fronczek et al., 2012). This is consistent with clinical reports of sleep disturbances in AD patients (Tractenberg et al., 2003), which correlate with severity of dementia (Mirmiran et al., 1992), and are often the primary reason for institutionalization (Pollak and Perlick, 1991; Vitiello et al., 1990; Vitiello and Borson, 2001). Interestingly, the hypocretin-orexin system has been implicated in Aβ generation and modulation. Studies of APP transgenic models show that periods of wakefulness initiated by the orexin system, are correlated with greater levels of Aβ in the interstitial fluid of the hippocampus than during sleep, an effect that is dependent on orexin signaling through orexinergic receptors (Kang et al., 2009). The mechanism by which orexin receptors promote Aβ synthesis was found to be independent of cAMP signaling, and requires further investigation (Kang et al., 2009). In line with these results, preclinical studies utilizing two different models of AD (APPswe and APPswe/Ps1dE9) demonstrate that sleep deprivation increased levels of Aβ and accelerated plaque formation compared to controls. Conversely, enhanced sleep, achieved via administration of an orexin receptor antagonist decreased Aβ plaque formation and deposition in these models (Ju et al., 2014; Roh et al., 2014). The orexin system has not been studied in the context of aberrant network activity due to Aβ dysregulation; however, this may be an important area for future research. Importantly, the LC is one of the regions most densely populated with orexinergic receptors (Horvath et al., 1999). Thus, the influence of orexin receptors on Aβ production and accumulation in the LC may contribute to its dysregulation. Further, it has been hypothesized that increased NE stimulation of β2AR in projection areas of the LC following orexinergic input result in increased Aβ production via mechanisms discussed above (Cheng et al., 2014). This concept supports the idea that dysregulation of LC functioning has significant consequences for the widespread projection areas in which adrenergic receptors reside and mediate the effects of noradrenergic transmission. The evidence presented here suggests a role for the orexin system in promoting the generation of Aβ, and while the precise mechanisms by which this occurs is not well understood, it has been suggested that the LC-NE system plays an important role in mediating these effects (Cheng et al., 2014). Thus restoration of normal noradrenergic transmission via the modulation of adrenergic receptors may provide additional benefit in treating the AD patient population by modulating responsivity to orexinergic input that promote wakefulness via NE transmission. Additionally, clinical studies have provided evidence for the link between stress-induced sleep disturbances and hyperarousal (Drake et al., 2004), a connection that is further validated by evidence that sleep deprivation increases CRF levels and CRF receptor binding (Fadda and Fratta, 1997). Thus, further research investigating peptidergic interactions influence on arousal, LC activation and Aβ production may provide insight on the convergence of these factors in AD pathology.

10. Female vulnerability in AD

In the clinic, multiple lines of evidence have suggested that men and women are affected by dementia differently. Of the 5.1 million Americans suffering from AD, approximately two-thirds are women (Alzheimer's Association, 2015). Longitudinal studies investigating the rate of cortical thinning in men and women with AD show that over a five year time period, women with AD display more rapid thinning in the left prefrontal cortex, bilateral medial frontal cortex, bilateral tempo-parietal associative cortex, and bilateral temporal lobe compared to men with AD. Importantly, there were no significant differences in baseline cortical thickness between the men and women examinees (Cho et al., 2013). Similar studies have shown significant gender differences in cognitive and functional decline (Lin and Doraiswamy, 2014), with some reporting that the memory impairment in women may progress at twice the rate of men (Seshadri et al., 1997). Recent studies by the ADNI have further demonstrated that the gender differences between men and women affected by AD are reflected in Aβ dysregulation; at every stage women had more amyloid plaques than men, and women were shown to have greater levels of amyloid load regardless of ApoE-ε4 carrier status. Interestingly, previous in vitro studies have demonstrated the ability of physiological levels of estrogen to modulate APP processing, promoting the production of sAPPα, precluding the production of Aβ in primary neuronal mouse and human cultures (Xu et al., 1998). In line with these results, postmenopausal estrogen replacement therapy has been associated with decreased risk of AD (Tang et al., 1996). While clinical trials examining the efficacy of estrogen replacement therapy in slowing AD progression in women proved to be unsuccessful, participants of the study had mild to moderate AD (Mulnard et al., 2000), conditions in which Aβ is expected to be elevated and beyond intervention. Given the recent evidence that the stress response plays a role in AD pathology, and that there are differences in stress responses between males and females (Goldstein et al., 2010; Bangasser et al., 2010), one study investigated the cortisol levels of women with AD. This study found that women with mild to moderate AD have significantly increased levels of cortisol production (Rasmuson et al., 2001).

Preclinical data in mouse models of AD support the notion that the disease affects males and females differently. For example, a study utilizing a double mutant APP/PS1 transgenic mouse line reported that female mice had significantly greater Aβ load than males at all ages (Howlett et al., 2004). Other lines of preclinical research have suggested a model of sex-biased stress signaling, in which neurochemical (Curtis et al., 2006), morphological (Bangasser et al., 2011) and molecular (Bangasser et al., 2010) differences between males and females in CRF innervation and signaling to the LC render females more susceptible to stress-related psychiatric disorders [reviewed in Valentino et al., 2013]. The consequences of such differences between sexes have not been explored explicitly in AD, thus presenting an extensive gap in our current understanding of the clinical application of drugs used to treat non-cognitive symptoms of AD, and how these differences may inform future therapeutic approaches. It is possible that mood altering drugs such as anti-depressants could have protective effects on the progression of AD (Aboukhatwa et al., 2010). While CRFR1 antagonists have, so far, been unsuccessful in treating mood and anxiety disorders (Aubry, 2013), it would be of

interest to examine therapeutics targeting CRFR1 for the potential benefit in preclinical or early stage AD patients, particularly females.

11. NE as a modulator of neuroinflammation in AD

AD exhibits an inflammatory component, which is evidenced in both post mortem brain tissue, as well as a vast array of preclinical studies in the literature. Several chemokines and chemokine receptors known to play a role in communicating signals during inflammatory responses have been found to be up-regulated in the AD brain (Heneka, 2006). Cultured astrocytes and microglia from rapid autopsy of AD patients show increased levels of IL-8, MCP-1, CCR3 and CCR5 (Heneka, 2006). AD post mortem brain tissue analysis reveals an abundance of activated microglia that are IL-1β immunopositive and almost exclusively associated with amyloid deposits in the AD brain (Akiyama et al., 1993; Griffin et al., 1995). Further, the expression of the inducible form of nitric oxide synthase (NOS2) has been described in neurons and astrocytes of the AD brain (Heneka and Feinstein, 2001). These results have served as the basis for numerous preclinical studies to further explore and provide a mechanistic basis for the role of inflammation in AD. One factor that may contribute to these inflammatory alterations in the AD brain is oxidative stress, reflected in the oxidation of brain lipids, carbohydrates, proteins and DNA (Markesbery, 1999). Reactive oxygen species may then stimulate the activation of transcription factors such as NF-κB, which initiate the inflammatory cascade (Morgan and Liu, 2011). Of particular importance, is the finding that the LC-NE system is a critical player in mediating these inflammatory responses, and that the degeneration of the LC exacerbates inflammatory and cytotoxic insults induced by Aβ. The diversity among- NE receptors allows for an extensive influence over the cellular environment. For example, the presence of β2AR on astrocytes and microglia in addition to their presence on neurons, enables the modulation inflammatory gene expression (Feinstein et al., 2002). Importantly, βARs are present, and functionally relevant, on both astrocytes and microglia in the brain (O'Donnell et al., 2012) and are thought to play a role in modulating Aβ induced inflammation.

Studies of selective lesions of the LC utilizing the neurotoxin DSP-4 have helped to establish this brain region as a potentially important component of the inflammatory component of AD and as a protective force against Aβ induced cytotoxic insults that, when depleted, leaves the central nervous system more vulnerable to AD pathogenesis. One of the first major studies to suggest this relationship showed that injection of Aβ into the cortex of adult rats potentiated the induction of iNOS, IL-1β, and IL-6 expression following DSP-4 induced cell death in the LC. Further, when Aβ was co-injected with NE or the β-AR agonist isoproterenol in the cortex, the effects on cytokine expression were attenuated (Heneka et al., 2002). Other studies have demonstrated the ability of NE to block the expression of MHCII, TNF-α, IL-1β and iNOS, supporting the notion that NE acts as an anti-inflammatory agent (Feinstein et al., 2002; Frohman et al., 1988). Further investigation into the role of NE in inflammatory environments reveals that NE may have dual effects on the production of cytokines and proinflammatory mediators (Hinojosa et al., 2013). For example, it has been demonstrated that NE, through the activation of β2 AR, induces the production of CCL2 (MCP-1), which acts to protect against excitotoxicity by decreasing the synthesis and release of glutamate (Madrigal et al., 2009). This is highly relevant to AD, as it has been shown that high levels of glutamate occur in chronic degeneration conditions, including AD (Lipton, 2005). Additionally, results from studies using pro-inflammatory stimuli such as LPS, as well as Aβ, have demonstrated that the presence of such stimuli causes a large production of CX3CL1, CCL2 (MCP-1), CCL7, CCL12, and CXCL16, while NE has opposing effects, inhibiting the production of those cytokines (Hinojosa et al., 2013). Thus, NE may be classified as a modulator of neuroinflammation, having important consequences for the pathogenesis of AD. As described above, the progressive deterioration of the LC and concomitant decreases in NE suggest the possibility that one of the driving forces exacerbating the effects of Aβ is the loss of LC-NE influence.

12. Conclusions

Examining specific neuroanatomical structures such as the LC and the neuronal pathways that connect them provide a context for better understanding complex pathological processes associated with disorders such as AD. Perhaps one of the greatest challenges to modern medicine is the complex pathology of Alzheimer's disease, which has been the topic of intense investigation for over 100 years and still has no effective treatment. The synthesis and release of Aβ peptide is dysregulated in early stages of AD, prior to neurodegeneration. Recent studies implicating Aβ as a modulator of neuronal excitability have significant implications not only at the synaptic, but also circuit levels of brain processes. The LC is the brainstem nucleus characterized by its unique role as the sole source of NE for the neuraxis, as well as its ability to receive and integrate information from multiple brain regions to orchestrate widespread changes in arousal, wakefulness, and the stress response. A growing body of literature supports the clinical relevance of the LC, NE and noradrenergic receptors in AD, particularly in the dysregulation of Aβ production. A synthesis of evidence suggests that disruptions of LC excitability, likely associated with an aberrant response to stressful stimuli, lead to significant increases in Aβ deposition. Given the recently established physiological role of Aβ as a modulator of neuronal excitability, and the finding that Aβ function is a concentration-dependent process, there is the potential that abnormal levels of Aβ result in network de-synchronization and disrupt cognition on a global scale. Further, the presence of adrenergic receptors on neurons in projection regions of the LC provides a cellular mechanism by which NE may contribute to Aβ production, and whose presence on glial cells may contribute to decreased clearance of Aβ following reduction of NE levels, thus exacerbating neuroinflammatory conditions in later stages of AD. This underappreciated role of the LC-NE system in AD has important implications for potential therapeutic intervention as well as future studies. While early or preclinical stages of AD may benefit from treatments aimed at reducing LC aberrant activation, possibly via targeted gene therapy, later stage treatment may involve the use of SNRIs which have the potential to promote GABAergic signaling and stabilize the gamma frequency oscillations important for attention and memory functions. There are already numerous marketed compounds that directly modulate the NE system that could be evaluated for their ability to slow the progression of AD. There is also the possibility that retrospective analysis of AD patients treated with these compounds could provide valuable insight and influence the direction of future clinical trials. In addition, treatments specifically designed to stop or slow the accumulation of Aβ and degeneration of neurons in the LC could prove to be very promising.

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