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Research report

Complex noradrenergic dysfunction in Alzheimer's disease: Low norepinephrine input is not always to blame

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ABSTRACT

The locus coeruleus-noradrenergic (LC-NA) system supplies the cerebral cortex with norepinephrine, a key modulator of cognition. Neurodegeneration of the LC is an early hallmark of Alzheimer's disease (AD). In this article, we analyze current literature to understand whether NA degeneration in AD simply leads to a loss of norepinephrine input to the cortex. With reported adaptive changes in the LC-NA system at the anatomical, cellular, and molecular levels in AD, existing evidence support a seemingly sustained level of extracellular NE in the cortex, at least at early stages of the long course of AD. We postulate that loss of the integrity of the NA system, rather than mere loss of NE input, is a key contributor to AD pathogenesis. A thorough understanding of NA dysfunction in AD has a large impact on both our comprehension and treatment of this devastating disease.

1. Introduction to the noradrenergic system and its degeneration in Alzheimer's disease

The brain noradrenergic (NA) system plays a critical role in supporting interactions with and responses to environmental stimuli, and serves as a major contributor to normal cognitive activities in the cortex including attention, perception, and memory retrieval (Chamberlain and Robbins, 2013; Gannon et al., 2015). The majority of NA neurons are located in the locus coeruleus (LC) and, with widespread efferent projections, these neurons supply norepinephrine (NE) to the cortex, hippocampus, striatum, basal forebrain, preoptic area, and hypothalamus (Oleskevich et al., 1989; Swanson and Hartman, 1975). NE is a catecholamine that is synthesized from the amino acid tyrosine through sequential reactions catalyzed by tyrosine hydroxylase, DOPA decarboxylase and dopamine β hydroxylase (DβH). NE released from presynaptic terminals binds to different subtypes of adrenergic receptors to elicit a variety of physiological and pharmacological responses (Hein, 2006). Extracellular NE can be enzymatically degraded by enzymes such as catechol-O-methyltransferases (COMT) or monoamine oxidases (MAO) (Golan et al., 2011), or be taken back up into the presynaptic terminal by the norepinephrine transporter (NET), a Na/K pump. The amount of extracellular NE at the synapse is largely dependent on how much NE is degraded and taken back to the presynaptic terminal.

Changes of the NA system in Alzheimer's disease (AD) have been long observed. As AD progresses, there is profound neuronal loss in the LC (Chan-Palay and Asan, 1989; Forstl et al., 1994; German et al., 1992; Iversen et al., 1983; Mann et al., 1980; Marcyniuk et al., 1986; Matthews et al., 2002; McMillan et al., 2011; Zarow et al., 2003). However, despite this well documented phenomenon, its impact on AD pathogenesis has not been adequately addressed to date. While a decrease in NE has often been observed in advanced AD, in some cases, NE levels in AD patients remain constant, or even elevated. In addition, alterations of different adrenergic receptors have been reported with both decreases and increases observed in the levels of receptor expression and density (Kalaria, 1989; Kalaria et al., 1989a; Ruiz et al., 1993; Shimohama et al., 1986; Szot et al., 2006, 2007). These changes at the receptor level directly influence the sensitivity and amplitude of the physiological responses elicited by NE, adding another level of complexity to the consequence of NA degeneration in AD. Furthermore, some subtypes of adrenergic receptors have been shown to regulate Aβ generation (Chen et al., 2014; Ni et al., 2006; Wang et al., 2013b; Yu et al., 2010) or mediate Aβ toxicity (Wang et al., 2013a), indicating an important role of these

Abbreviations: AR, adrenergic receptor; AD, Alzheimer's disease; APP, amyloid precursor protein; COMT, catechol-O-methyltransferases; CSF, cerebral spinal fluid; DβH, dopamine β hydroxylase; GPCR, G-protein coupled receptor; LC, locus coeruleus; MAO, monoamine oxidases; NET, norepinephrine transporter; DSP-4, N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine.

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receptors in AD pathogenesis. In this review, we will analyze existing literature to discern, in the context of the long and progressive course of AD, NE input to the cerebral cortex and its potential effects through different adrenergic receptors. Although NE has been well appreciated as a neurotransmitter involved in cognition, it appears that NA system dysfunction in AD is much more complex than a simple loss of NE input to the cerebral cortex.

2. Compensatory mechanisms to counteract NA neuron loss occur during the long and progressive course of AD

Pathological changes in the LC, including tau accumulation in the neurons of LC, can occur as early as childhood or adolescence (Braak and Del Tredici, 2011a,b; Braak et al., 2011; Braak and Del Tredici, 2012; Braak et al., 2013). As AD progresses, degeneration of the LC neurons happens (Chan-Palay and Asan, 1989; Forstl et al., 1994; German et al., 1992; Iversen et al., 1983; Mann et al., 1980; Marcyniuk et al., 1986; Matthews et al., 2002; McMillan et al., 2011; Zarow et al., 2003). This, however, is not a rapid occurrence. Rather, the degeneration seems to be a gradual process, and there is evidence that compensatory mechanisms occur in an effort to counteract this change and maintain homeostasis.

First, at an anatomical level, NA degeneration in AD is accompanied by increased sprouting of the remaining LC neurons to different brain regions, including the prefrontal cortex (Szot et al., 2007) and hippocampus (Szot et al., 2006). NA sympathetic sprouting in the hippocampus has also been observed in late-onset AD subjects (Booze et al., 1993; Nelson et al., 2014). Secondly, changes in the enzymes responsible for NE generation have been reported in AD. Both tyrosine hydroxylase, which is the enzyme responsible for the rate limiting step in NE synthesis, (Iversen et al., 1983; Szot et al., 2006, 2007) and DβH (Giubilei et al., 2004; Miyata et al., 1984) levels are increased in AD patients compared to control subjects. Further, DβH levels are higher in middle and late stages of AD than in early stages (Mustapic et al., 2013). Elevated levels of these enzymes can lead to an increase in production of NE. Thirdly, decreased levels of NET have been found in AD patients using both autoradiograph (Gulyas et al., 2010) and radioligand binding studies (Tejani-Butt et al., 1993) of post-mortem tissues. As mentioned earlier, NE re-uptake is mediated by NET, a Na/K pump that returns NE to the presynaptic terminal and acts as a major determinant of the synaptic NE level. A decrease in the level of this transporter leaves more NE in the synapse. Taken together, enhancement in neuronal sprouting and NE production and reduction in NE reuptake could compensate LC neuronal loss to maintain the NE levels in AD. It is also possible that these mechanisms may overcompensate for the neuronal loss, especially at the early stages of the disease, leading to increased NE levels, as seen in some AD patients (Elrod et al., 1997; Tohgi et al., 1992), and thus creating another problem for AD patients. As AD continues to progress and LC degeneration becomes increasingly profound, these compensatory mechanisms may no longer be sufficient to counteract the neuronal loss. As a result, a decrease in the tissue levels of NE can be seen.

3. Is there really a loss of norepinephrine input in AD?

Given the well-documented loss of LC neurons, it is often assumed that there is a loss of norepinephrine input to the cerebral cortex in AD. Is this really the case?

As discussed above, AD is a long and progressive process, during which degeneration of LC neurons degeneration occurs gradually along with compensation events. When remaining LC neurons cannot sufficiently compensate the overall neuronal loss, a decrease in the tissue levels of NE is observed in the temporal lobe of advanced AD patients compared to healthy controls (Adolfsson et al., 1979; D'Amato et al., 1987; Gottfries et al., 1983; Herregodts et al., 1989; Hoogendijk et al., 1999; Matthews et al., 2002; Palmer et al., 1984, 1987; Reinikainen et al., 1988; Szot et al., 2006). Hoogendijk et al. (1999) found a NE reduction in frontal medial gyrus, temporal superior gyrus, hippocampus, amygdala, thalamus, and LC with AD NE levels ranging from 34% of healthy controls in the frontal medial gyrus to 65% of healthy controls in the hippocampus. Others have seen similar results, with 12–50% decreases seen in the gyrus frontalis, putamen, frontal and temporal cortex, hypothalamus, caudate nucleus, hippocampus, and gyrus cingula (Adolfsson et al., 1979; Gottfries et al., 1983; Matthews et al., 2002; Palmer et al., 1987; Reinikainen et al., 1988, 1990). Finally, the NE metabolite MHPG was found to be decreased in the temporal cortex of older AD patients (>70 years) compared to controls, but not in younger AD patients (<70 years) (Palmer et al., 1984). However, does a 12–66% decrease in the tissue levels of NE necessarily cause a change in the extracellular levels of NE, i.e. NE input, in the cerebral cortex?

Direct measurement of the extracellular levels of NE in vivo in LC-lesioned animals suggest that this may not be not the case. In one study, the noradrenergic specific toxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) treatment led to a 75% drop in noradrenergic content. However, in microdialysis experiments, the extracellular NE levels of the DSP-4 treated rats were almost 2x greater than sham controls (Hughes and Stanford, 1998). In other studies, 50% (Kask et al., 1997), 75% (Abercrombie and Zigmond, 1989) or even 90% (Ventura et al., 2003) depletion of the tissue levels of NE content, as measured by HPLC, does not lead to a significant change in the extracellular levels of NE in the frontal cortex measured by microdialysis. It is important to note that the varied levels of noradrenergic depletion can be due to inconsistencies in the methods of drug treatment such as drug doses, numbers of injections and treatment time. Nevertheless, these well-controlled studies suggest a clear disconnect between the tissue and the extracellular levels of NE.

Several lines of evidence from AD patients support that the extracellular levels of NE are likely maintained despite a decrease in the tissue levels of NE. First, in fresh cortical samples obtained during neurosurgery from AD patients who have an average 68% reduction in cortical NE levels, as measured by HPLC following tissue homogenization, the extracellular release of endogenous NE is not different from that in cortical samples of control subjects (Palmer et al., 1987). Additionally, NE reuptake in these AD samples is reduced to 47% of the control level. This unchanged release and reduced reuptake of NE would lead to sustained extracellular NE in the cerebral cortex of AD patients.

Secondly, when measured in the cerebrospinal fluid (CSF) of living AD patients, the levels of NE are unchanged or often increased compared to age-matched control subjects (Czech et al., 2012; Elrod et al., 1997; Kaddurah-Daouk et al., 2011; Oishi et al., 1996; Raskind et al., 1984, 1999; Tohgi et al., 1992; Watson et al., 2006). Furthermore, the increase in CSF NE has been shown to correlate with the severity of AD (Elrod et al., 1997; Oishi et al., 1996) and frontal temporal dementia (FTD) (Engelborghs et al., 2008), with higher NE levels in CSF correlating with more severe cognitive deficit. Additionally, the NE metabolite MHPG has been reported to negatively correlate with cognitive function in AD (Oishi et al., 1996). Even in healthy subjects, NE levels have been reported to increase with age, and are associated with poorer cognitive performance (Wang et al., 2013c). This evidence suggests that although important for cognitive functions, a higher level of NE could be detrimental. This is consistent with studies that have shown cognitive impairment in response to stress, under which conditions NE release is elevated (Finlay et al., 1995; Goldstein

et al., 1996). Exposure to uncontrollable stressors has been shown to cause rapid impairment of working memory in monkeys and rodents (Arnsten, 1998; Arnsten and Goldman-Rakic, 1998). Stress exposure in humans is also found to weaken working memory performance (Qin et al., 2009). Furthermore, blockade of α_1AR by antagonists, such as prazosin and urapidil, has been shown to protect cognitive functions from the detrimental effects of stress exposure (Arnsten and Jentsch, 1997).

While the majority of studies have found an increase in CSF NE levels in AD patients, one study did find reduced NE levels in the CSF of AD patients with moderate cognitive decline as compared to controls (Martignoni et al., 1992). As Martignoni noted in his publication, all of his AD patients and controls were hospitalized, while only the most severe AD patients were hospitalized in some of the other published studies. It is possible that institutionalization itself or other sickness that caused hospitalization in these patients could have affected the study. Another study found decreased NE levels in ventricular CSF of postmortem AD patients (Kaddurah-Daouk et al., 2011), though postmortem CSF measurement can be confounded by the cause of death, postmortem delay and storage period and pH of the CSF samples.

In addition to the direct measures of NE levels in CSF, studies with adrenergic antagonists point to NE levels remaining high enough in AD to exert effects through adrenergic receptors. Treatment with prazosin (Wang et al., 2009), an α_1AR antagonist, or propranolol (Pauszek, 1991; Peskind et al., 2005; Shankle et al., 1995), a βAR antagonist, significantly improved the agitation symptoms in AD patients compared to placebo. These results indicate that NE acting on the α_1AR or βAR is contributing to the agitation and aggressive behaviors seen in the AD patients. In addition, α_2AR responsiveness to a yohimbine blockade is enhanced in AD, as indicated by a higher increase in CSF NE levels by yohimbine treatment in AD patients compared to that in control subjects (Peskind et al., 1995; Raskind et al., 1999). These results suggest a higher level of α_2AR activation by the endogenous NE in AD.

Taken together, existing literature points to 12%-65% reduction in the tissue levels of NE in most AD cases, and yet, the extracellular levels of NE (i.e. NE input to the cortex) in these AD patients may very likely maintain at a level close to the normal condition. Thus, although NA degeneration occurs frequently, there may actually be a sustained NA tone in AD.

4. NE effects through the adrenergic receptors on cognition in the context of AD

NE elicits its effects through activating the adrenergic receptors, which are members of the G-protein coupled receptor (GPCR) superfamily. The α_1 subfamily of adrenergic receptors (α_{1A}, α_{1B} and α_{1D}) signals through the G_q signaling pathway and, upon activation, increase both IP3 and calcium levels (Chen and Minneman, 2005; Perez, 2007). The βARs (β1, β2 and β3) mainly signal though the G_s protein and increase cAMP generation upon activation (Hall, 2004). The α_2ARs (α_{2A}, α_{2B} and α_{2C}) signal though the $G_{i/o}$ signaling pathway, and activation of these receptors inhibits cAMP production and calcium influx (Knaus et al., 2007). The α_2 receptors also serve as auto-receptors on presynaptic NA terminals where they inhibit NE release. All three receptor subfamilies play important roles in normal cognitive function, which has been reviewed extensively (Chamberlain and Robbins, 2013; Gannon et al., 2015). Here we primarily focus on the effects of activation or inhibition of these receptors on cognitive functions in AD animal models or human patients.

In the non-disease state, inhibition of the β_1 and β_2ARs with propranolol, which blocks the β_1 and β_2ARs with equal affinity (Summers, 2006), leads to cognitive impairments, including impaired memory retrieval (Ouyang and Thomas, 2005), fear conditioning (Taherian et al., 2014), taste memory consolidation (Ruetti et al., 2014), scent recall (Veyrac et al., 2007) and spatial learning (Decker et al., 1990; Kenton et al., 2008; Saber and Cain, 2003). One might therefore assume that activating these receptors in AD patients would lead to positive outcomes. However, for the most part, blockade of the βARs seems to be cognitively beneficial, as demonstrated in AD animal models. This may be related to the role of βAR in Aβ generation. Activation of β_2AR promotes Aβ production through enhancing γ secretase activity (Ni et al., 2006). Thus, a β_2 antagonist, ICI 118,551, reduces Aβ plaque load in AD mouse models, whereas β_2 agonists increase the Aβ plaque load (Ni et al., 2006). Additionally, treatment of Tg2576 mice with a β_1 antagonist, nebivolol, reduces Aβ generation (Wang et al., 2013b). Consistently, in both Tg2576 AD model mice and a mouse model of age-related cognitive decline (SAMP8), treatment with a non-subtype selective β blocker, propranolol, leads to an improvement in cognitive function (Dobarro et al., 2013a,b). However, in a 3xTg mouse model, ICI 118,551 actually increased Aβ levels and impaired cognitive function (Branca et al., 2014). This discrepancy has yet to be fully addressed, though may be related to the different models used.

In addition to β_2AR, a number of other G protein-coupled receptors have been linked to AD by altering APP processing, and this topic is reviewed well elsewhere (Thathiah and De Strooper, 2011).Within the adrenergic receptor family, α_{2A}AR also promotes amyloidogenic processing of APP (Chen et al., 2014). An α_2AR agonist, clonidine, increases Aβ plaque load, whereas an α_2AR antagonist, idazoxan, decreases it and rescues the cognitive deficit observed in APP/PS1 transgenic mice (Chen et al., 2014).

Although activation of the α_1ARs has been shown to improve spatial learning, fear learning, and working memory and attention in WT animals (Do Monte et al., 2013; Doze et al., 2011; Mishima et al., 2004; Nalepa et al., 2013; Veyrac et al., 2007), in an AD transgenic model, APP23 mice, blockade of these receptors by an antagonist, prazosin, improves the cognitive deficits (Katsouri et al., 2013). In AD patients, α_1AR activation is thought to contribute to the observed agitation symptom (Raskind and Peskind, 1994; Sharp et al., 2007), and prazosin is effective in alleviating such symptoms (Wang et al., 2009).

Taken together, the above evidence suggest dysfunction of adrenergic receptors in regulating cognitive functions under the pathological conditions of AD. This is not totally surprising given the substantial alterations in neuroanatamy including the primary and compensatory changes in the NA system in AD. At the molecular and cellular levels, aberant receptor densities (Kalaria et al., 1989a,b; Lemmer et al., 1993; Leverenz et al., 2001; Pascual et al., 1992; Ruiz et al., 1993; Shimohama et al., 1986; Szot et al., 2006, 2007), functional changes in G proteins (Cowburn et al., 2001; Hashimoto et al., 2004), changes in the levels of regulators, such as GRKs (Suo and Li, 2010; Suo, 2013) and β-arrestin 2 (Thathiah et al., 2013), and changes in levels and activity of downstream effectors, such as adynylyl cyclase and cAMP (Dierssen et al., 1996; Dierssen et al., 1997; Ohm et al., 1989; Ross et al., 1993; Yamamoto-Sasaki et al., 1999; Yamamoto et al., 1996, 1997), in AD brains could all lead to dysregulation of adrenergic receptors and their malfunction in cognition.

5. Conclusions and perspectives

Pathological changes to the NA system occur early in AD. However, the underlying mechanisms driving these changes and their contributions to AD pathogenesis remain to be determined. Nonetheless, existing evidence tends to paint a more complex picture of NA dysfunction in AD than a simple, straight-forward loss of

NE input to the cerebral cortex. Despite the well-documented loss of NE producing NA neurons, the extracellular levels of NE, especially at the early stages of disease, are likely unchanged or even increased due to a number of compensatory mechanisms. Moreover, the endogenous NE target, adrenergic receptors, are dysregulated at multiple levels in AD so that activation of these receptors seem to elicit a number of deteriorating effects rather than promoting cognition. Overall, the integrity of the NA system appears to be very integral in maintaining a balance that allows for the proper operation of a variety of physiological processes that are dysregulated in AD. Alterations at the anatomical, cellular, and molecular levels of NA components in AD support that loss of the integrity of the NA system, not merely loss of the NE input, is a key contributor to AD development.

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