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Editorial

The Consequence of Noradrenergic Neuronal Loss in the CNS of Alzheimer's Disease - ∂

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The presence of plaques and neurofibrillary tangles (NFTs) are the hallmark neuropathology associated with Alzheimer's disease (AD); however AD is also characterized neuropathologically by neurodegeneration. My laboratory and many others have shown a substantial loss of noradrenergic cell bodies in postmortem brain tissue of AD subjects in the locus coeruleus (LC), the major source of noradrenergic projections to the whole brain (Marcyniuk et al. 1986; Chan-Palay and Asan, 1989; German et al. 1992; Szot, et al. 2006; McMillan et al. 2011). The degree of LC loss correlates with the degree of cognitive decline, indicating the importance of the noradrenergic nervous system to learning and memory (Bondareff et al. 1981; Matthews et al. 2002). Associated with this loss of LC neurons in postmortem AD subjects, my laboratory observed several compensatory changes at the cell body region and at terminal regions such as frontal cortex (FC) and hippocampus (HP). The surviving LC neurons demonstrate a compensatory increase in the mRNA expression in rate-limiting enzyme tyrosine hydroxylase (TH) (Szot et al. 2006). The increase in TH mRNA expression per cell corresponded to the loss of TH-positively labeled cells, i.e., the greater the degree of neuronal loss, the more TH mRNA expression per cell occurred. It is unclear if this increase in TH mRNA translates into increased protein and norepinephrine (NE) in the CNS. The other compensatory change in the surviving LC neurons is at the dendritic level. The NE transporter (NET), which is selective for noradrenergic neurons, localized over the cell bodies is correlated to the number of noradrenergic neurons in LC; but NET binding over the peri-LC dendritic region that surrounds the cell bodies isn't altered as compared to control subjects despite the loss of cell bodies (Szot et al. 2006), this suggests compensatory changes in dendritic innervation surrounding LC neurons. The autoreceptor (2-adrenoreceptor (AR)) localized to the dendrites in the LC also demonstrate a degree of compensatory (Szot et al. 2006). The autoreceptor localized on LC axon terminals in the HP and FC of postmortem AD subjects also indicate the surviving LC neurons in AD subjects are compensating for the loss (Szot et al. 2006, 2007). Changes in the noradrenergic system are also observed postsynaptic to the LC neurons;, an increase in postsynaptic 1-AR in the HP and FC of postmortem AD subjects. These changes documented in the noradrenergic nervous system in postmortem AD subjects suggest an increased activity. It is unclear is these changes late in the progression of AD are a direct consequence of LC noradrenergic neurons or due to other factors that are altered in AD.

Neuropathological markers associated with AD occur many years before the on set of cognitive impairment, with the LC being one of the earliest regions affected (Braak and Del Tredici, 2011a,b,2012; Braak et al. 2011, 2013). In the studies performed in postmortem human tissue the loss of LC neurons was approximately 80-90%, late in the progression of AD. Since AD is a progressive disorder, it can be hypothesized that LC neuronal loss will be gradual. To determine how changes in the noradrenergic nervous system affect the progression of AD, animal models of LC neuronal loss are required. My laboratory uses direct injection of the neurotoxin 6-hydroxydopamine (6-OHDA) into the LC bilaterally (Szot et al. 2012a,b) to reduce the number of LC neurons. Injection of 6-OHDA into the LC area affected only noradrenergic neurons in the LC and it did not affect dopaminergic neurons in the substantia nigra/ventral tegmental area (SB/VTA) (Szot 2012b). The reduction in LC neurons induced by 6-OHDA is not associated with compensatory response in TH mRNA in the surviving cells (Szot et al. 2012a,b); suggesting the compensatory response of TH in postmortem AD subjects may be due to some other factor associated with AD. The loss of LC neurons does result in a reduction in NET binding sites and tissue concentration of NE at axonal regions in the cortex, HP, amygdala and SN/VTA (Szot et al. 2012a,b). The reduction in NET and NE concentration in forebrain regions such as the cortex and HP correlates significantly to the loss of LC neurons (Szot et al. 2012a,b). However, the autoreceptor 2-AR demonstrates a reduction in specific areas of the forebrain (including the HP), but the loss does not correlate to the degree of LC neuronal loss. As observed in AD, when there is a loss of LC neurons there is an increase in postsynaptic 1-AR binding sites in many forebrain regions including the FC, bed nucleus of the stria terminalis, and thalamus (Szot et al. 2012a).

Since AD is a progressive neurodegenerative disorder and the LC noradrenergic nervous system appears to be affected early in the progression of AD, my laboratory wanted to determine if an early loss of LC could mediate some of the early symptoms of AD. The CNS noradrenergic system has been implicated in the pathobiology of depression (Chandley and Ordway, 2012), though it is unclear if a loss of LC neurons results in depression. Depression is a common co-morbid condition most often observed in subjects with mild cognitive impairment (MCI), or very early in the progression of AD (Bhalla et al. 2009; Benoit et al. 2012; Lebedev et al. 2014). Again, LC neuronal numbers were reduced with the bilateral administration of 6-OHDA in a dose-dependent manner (5, 10 and 14 g/l) (Szot et al. 2016). To assess depressive-like behavior three weeks after 6-OHDA induced LC neuronal loss, a modified version of the forced swim test (FST) (Porsolt et al. 1978) was performed. Interestingly, only the lowest dose of 6-OHDA (5 g/l), with a minimal reduction in LC neurons, resulted in a significant increase in the FST immobility time (i.e., depressive-like behavior); even though the 10 and 14 g/l dose of 6-OHDA significantly reduced the number of LC noradrenergic neurons (Szot et al. 2016). In animals that received 6-OHDA (all doses), a significant positive correlation was observed between the number of surviving LC neurons and the amount of time spent in the immobile phase in the FST. This data indicates that animals with a minimal loss of LC neurons due to LC 6-OHDA (or had a greater number of surviving LC neurons) had longer FST immobile times, while animals with a greater loss of loss LC neurons (or less surviving neurons) spent less time in the immobile phase. This depressive-like behavior of a low dose of 6-OHDA was also observed with the sucrose consumption test, another behavior model of depressive-like behavior (Szot et al. 2016). Electrophysiological characteristics of the surviving LC neurons at the time this depressive-like behavior is observed demonstrated increased activity (increased firing frequency, more irregular firing pattern, and higher percentage of cells firing in burst) (Szot et al. 2016). The clinical implication of these findings

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is that the depression observed mainly in the early stages of AD can be attributed to a minimal loss of LC neurons, may also explain why depression appears to remit in AD (Lee et al. 2007; Lyketsos et al. 2011; Wang et al. 2012; Lebedev et al. 2014; Van der Mussele et al. 2014).

FUTURE FOCUS

The data presented indicates that the loss of LC neurons early (animal studies) and late (postmortem AD subjects) in the progression of AD may display compensatory changes. When LC neuronal loss is minimal as observed in MCI or early AD, there is enhanced activity of the surviving LC neurons, which is associated with depressive-like behavior. Future work would be to determine if these changes are translated into an increase in synaptic release. An enhanced noradrenergic system could also affect the clearance of the main pathological markers of AD, plaques and tangles. A newly described central nervous system clearance system called the glymphatic could affect the progression of AD. The glymphatic system plays an integral part in the clearance of amyloid and tau from the brain (Iliff et al. 2012; Jessen et al. 2015; Simon and Iliff, 2015; Tarasoff-Conway et al. 2015). The glymphatic system is "turned on" during normal sleep and substantially decreases during the awake state. The neurotransmitter norepinephrine (NE) is a key regulator of the switch between sleep and wakefulness, with low CNS noradrenergic activity facilitating normal sleep and high CNS noradrenergic activity driving aroused wakefulness. If the noradrenergic system is enhanced early in the progression of AD, this enhance noradrenergic system could affect the clearance of the early, future work would be to determine how an altered noradrenergic system affects plaques and NFT.

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