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Light at the beginning of the tunnel? Investigating early mechanistic changes in Alzheimer's disease

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Modern medicine has been increasing life expectancy worldwide. However, longevity comes with a steep price tag; in industrialized countries, more than one-third of those over 85 years of age suffer from dementia, most of them owing to Alzheimer’s disease pathology. In this issue of Brain, Rorabaugh and co-workers address the lack of suitable experimental models with which to investigate mechanistic changes in early stages of Alzheimer’s disease, and add to knowledge about the deleterious effects of locus coeruleus degeneration in the disorder (Rorabaugh et al., 2017).

The hallmarks of Alzheimer’s disease pathology include extracellular amyloid-β positive plaques and intraneuronal hyperphosphorylated tau aggregates. These pathological deposits spread following a characteristic topographical sequence, and are directly correlated with, and probably play a role in, neuronal and synaptic loss in affected brain regions. As the majority of neurons are post-mitotic and neurogenesis in the adult human brain is limited, neuronal death marks the ‘point of no return’ in Alzheimer’s disease pathogenesis. Thus, it is reasonable to argue that effective treatment can only be achieved during early phases of the disease when neurons are still viable.

Until recently, Alzheimer’s disease was considered a cortical pathology characterized by a retrograde spread of tau pathology from limbic cortex (entorhinal region and hippocampus) through polymodal and primary association cortices to primary sensory cortical fields, a phenomenon captured by the Braak staging system (Braak and Braak, 1991). On the other hand, amyloid-β pathology spreads in an anterograde fashion from polymodal association cortices to allocortex. Involvement of subcortical structures in Alzheimer’s disease was deemed to be of secondary importance or occurring only at later disease stages, which indeed seems to be the case for amyloid-β pathology.

About a decade ago, we demonstrated that the serotonergic dorsal raphe nucleus develops Alzheimer-type tau aggregates before the entorhinal cortex does, challenging the concept of the entorhinal cortex as the first brain area to develop Alzheimer-type tau pathology (Grinberg et al., 2009). Around the same time, Braak and colleagues revisited their influential topographical study on the sequence of formation of Alzheimer-type tau aggregates in the human brain (1991), and described how yet another subcortical structure, the noradrenergic locus coeruleus (Fig. 1), also develops Alzheimer-type tau pathology before the entorhinal cortex: now known as Braak stages 0 a–c in their revised staging system (Braak et al., 2011).

Ageing per se may affect brain structure and function, to varying degrees, and the threshold between normal ageing and early manifestations of Alzheimer’s disease is yet to be defined. In theory, tau aggregates in subcortical nuclei could be harmless without clinical or pathological consequences. Thus, evidence of increasing tau burden and accompanying frank and progressive neurodegeneration are necessary to demonstrate that these subcortical tau aggregates are an integral part of the chain of events associated with early-stage Alzheimer’s disease. To clarify the matter, several recent, unbiased, quantitative stereological studies have investigated changes in the locus coeruleus of individuals spanning a broad range of age, cognitive and Braak stages. These studies suggest that accumulation of tau aggregates in the locus coeruleus has deleterious consequences even at early stages. In summary, an average of 8% locus coeruleus neurons show tau aggregates at Braak stage 0, and the tau burden in the locus coeruleus neurons increases linearly with the progression of Braak stages (Ehrenberg et al., 2017; Theofilas et al., 2017). Also, despite the fact that the onset of locus coeruleus...
neuron loss is protracted compared to the onset of tau aggregation—as is the case in other brain areas—the average neuronal diameter and locus coeruleus volume begin to decrease at Braak stage 1. Locus coeruleus neuronal loss starts at presymptomatic disease stages and correlates with cognitive decline (Arendt et al., 2015; Theofilas et al., 2017). Furthermore, three independent studies using unbiased stereology failed to identify any differences in locus coeruleus volume or neuronal numbers between young individuals and cognitively normal, old-aged controls, all with scarce or absent tau aggregates, suggesting that the structural

Figure 1 Pontine tegmentum with locus coeruleus in humans and rat. (A) Unstained 350-μm thick horizontal section through the left hemi-brainstem of a 78-year-old female with darkfield illumination. Single locus coeruleus cells appear as small light-brown dots due to their rich neuromelanin content. The neurons form a cluster close to the ventromedial border of the trigeminal mesencephalic tract. Neuromelanin is a special feature of the human locus coeruleus, and it originates from metabolized noradrenaline. The functional importance of neuromelanin is a matter of debate. It has been proposed to be a simple waste product indicating high metabolism and interfering with physiological intraneuronal processes particularly in older age, or a buffer of toxic metabolites, or both. (B) Gallocyanin (Nissl) stained 110-μm thick coronal section through the right locus coeruleus of a 25-month-old female Han-SPRD rat. To give an idea of the true proportions of human and rat brainstems at nearly equivalent planes of section, an inset of B was mounted in scale into the fourth ventricle of A. Concerning form and internal architecture, human and rat brainstems are quite similar. Myelinated fibre bundles are more numerous in human brainstems, and the outlines of the human fibre bundles show a considerable increase in size. In the floor of the fourth ventricle, a dense fibre plexus consisting of small fibres can be detected in the human brain. The neurons of the medial part of the locus coeruleus are embedded in this fibre plexus, known as the bundle of Schütz or dorsal tegmental tract. The bundle of Schütz carries, most likely, fibres from the central amygdaloid nucleus, hypothalamus and periaqueductal grey and illustrates the intimate relationship of locus coeruleus neurons with these supraspinal nuclei. (C) Gallocyanin stained neurons of the right locus coeruleus of a 60-year-old female (section thickness = 400 μm). (D) Higher magnification of the locus coeruleus of B. Neurons in corresponding tegmental nuclei are bigger in humans, and the density of neurons (average distance between single neurons) is lower compared with rats. This may give a false impression that total locus coeruleus neuronal number is lower in humans than in rats. However, the volume of human brainstem nuclei exceeds that of rats by far. Whereas the total locus coeruleus neuronal number in rats is ~3000–4000, in humans it can go beyond 100,000. The shape of locus coeruleus neurons in humans and rats is similar after Nissl staining and Golgi impregnations, as is their dendritic arborization and likely the efferent noradrenergic connections. Interestingly, neurons of the locus coeruleus, but also the ventral tegmental area, substantia nigra, dorsal raphe and the basal nucleus of Meynert display widespread thin collateralized axons. These neurons are known for their selective disease-specific vulnerability in Alzheimer’s disease and Parkinson’s disease. In humans, the exponential increase in telencephalic cortical volume, the dense cortical noradrenergic innervation and a relatively low number of noradrenergic locus coeruleus neurons may represent an evolutionary bottleneck (Sharma et al., 2010) that plays an important or decisive role in Alzheimer’s disease, a neurodegenerative disorder exclusively manifesting in humans and, perhaps, senile apes. Arrows = locus coeruleus; Me5 = mesencephalic trigeminal nucleus; me5 = mesencephalic trigeminal tract; ttd = dorsal tegmental tract or bundle of Schütz (1891).
even at early stages. Mounting evi-
tau aggregates were detected at 16
control rats is 30 months, a 6-month
(tgF344-AD) overexpressing amyl-
celules total and neuronal volume
onset of locus coeruleus changes and
(TgF344-AD) overexpressing amyl-
tons; perifornical and lateral regions
of the hypothalamus; peri-peduncular
nucleus; substantia nigra and ventral
tegmental area; periaqueductal grey;
dorsal raphe; and parabrachial
nuclei—appear to accrue Alzheimer-
type tau aggregates prior to the
entorhinal cortex (stratmann et al.,
2016). All of these project to the
entorhinal region in a number of
mammalian species, including mon-
keys. Studies in humans and in
animal models exploring the biolo-
gical and clinical consequences of
Alzheimer-related degeneration of
these nuclei may prove as informative
as the studies on the locus coeruleus,
and may help to refine understanding
of the mechanisms involved in early
Alzheimer’s disease pathology.

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