Axonal and synaptic pathology in Alzheimer’s disease

by

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Summary

The cause of the initial synaptic disconnection and eventual widespread neuronal degeneration that underlies the onset and progressive development of dementia in sufferers of Alzheimer’s disease (AD) remains elusive. The pathognomonic features of AD, extracellular accumulations of soluble and fibrillar β-amyloid (Aβ) as well as intracellular neurofibrillary tangles comprised of hyperphosphorylated tau, that give rise to characteristic dystrophic neurites and neuropil threads, respectively, have been studied extensively in human AD cases and a variety of transgenic mouse models. Nonetheless, the degree to which these malformations affect different populations of neurons and their synaptic connections in the cortex remains to be defined. Furthermore, although white matter degeneration has previously been implicated in AD, not much is known about the extent of myelin loss in AD. This thesis, therefore, sought to address four aims analyzing the relationship between AD pathology and the mechanisms underlying AD. Firstly, to investigate the extent to which interneuron subpopulations are susceptible to Aβ plaque-mediated cytoskeletal alterations compared to a neurofilament-rich pyramidal neuron population. Secondly, to examine the relationship between Aβ plaque deposition and inhibitory and excitatory synaptic connections. Thirdly, to assess if the activity of glutamate decarboxylase, the enzyme catalysing the formation of the inhibitory neurotransmitter GABA, is altered in a transgenic mouse model of AD. Finally, to determine if AD pathology is associated with cortical demyelination and oligodendrocyte cell loss in human and transgenic mice.

The major conclusions drawn from these investigations were that inhibitory interneuron neurites were not as susceptible to Aβ plaque-mediated dystrophy as
neurofilament-rich neurites. Moreover, GABAergic synaptic density was not significantly decreased in proximity to Aβ plaques unlike excitatory glutamatergic synapse density. These decreases were accompanied by potentially compensatory changes in presynaptic bouton size, perisomatic innervation, as well as increased gliotransmission of GABA in Aβ plaque-rich neuropil. Neuritic plaque deposition was also associated with focal demyelination and concomitant decreases in several integral myelin-associated proteins. Interestingly, although mature oligodendrocyte loss was also present, there were significant increases in the number of immature oligodendrocytes and precursor cells, indicative of a reactive remyelinating response.

In summary, this thesis further clarified the pathological role of Aβ plaques in mediating cytoskeletal dystrophic changes and specific synaptic loss. It also identified the novel finding of focal demyelination associated with Aβ deposits. A better understanding of these early pathological alterations in the progression of AD is necessary for the development of effective therapeutic strategies. In particular, the compensatory changes in response to ongoing AD pathology could offer promising endogenous targets for slowing or repairing neuronal dysfunction.
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# TABLE OF CONTENTS

1. Introduction 1
   1.1 Pathological hallmarks of AD 2
   1.2 Genetics of AD 7
      1.2.1 Amyloid precursor protein 8
      1.2.2 Presenilins 9
      1.2.3 ApoE and other genetic risk factors 10
      1.2.4 Mouse models of AD 11
   1.3 The ‘Aβ hypothesis’ of AD 15
   1.4 Cytoskeletal pathology in AD 19
      1.4.1 Cortico-cortical projection neurons are vulnerable in AD 19
      1.4.2 Basal cholinergic neurons are vulnerable in AD 23
      1.4.3 Neurons expressing neurofilament triplets are vulnerable in AD 29
      1.4.4 Interneuron vulnerability in AD 32
   1.5 Synaptic pathology in AD 42
      1.5.1 Synapse loss in AD 43
      1.5.2 Presynaptic effects of Aβ 44
      1.5.3 Postsynaptic effects of Aβ 58
      1.5.4 Loss of dendritic spines is accentuated near Aβ plaques 72
      1.5.5 Network-wide effects of Aβ 73
   1.6 Myelin pathology in AD 75
      1.6.1 Basic function and composition of myelin 75
      1.6.2 Oligodendrogenesis and myelination 79
      1.6.3 Consequences of myelination 81
      1.6.4 Demyelination: an early feature of AD? 82
      1.6.5 Mechanisms of demyelination in AD 85
   1.7 Project aims 88

2. Materials and Methods 92

3. Neurites containing the neurofilament-triplet proteins are selectively vulnerable to cytoskeletal pathology in AD and transgenic mouse models 101
4. Synaptic remodelling in AD and transgenic mouse models 114

5. Increased GAD activity in aged APP/PS1 animals is due to increased astrocyte GABA production 131

6. Focal demyelination, oligodendrocyte loss and myelin protein alterations in AD cases and transgenic mouse models 141

7. Discussion 160
   
    7.1 Conclusions 168
    
    7.2 Experimental limitations 169
    
    7.3 Future directions 170

9. References 172

10. Appendix A 259