Neuroscience and Biobehavioral Reviews 75 (2017) 297–313

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review article

Energy and the Alzheimer brain

Mortimer Mamelak

Baycrest Centre, University of Toronto, Canada

ARTICLE INFO

Article history:
Received 3 November 2016
Received in revised form 30 January 2017
Accepted 1 February 2017
Available online 11 February 2017

Keywords:
Alzheimer's disease
Neurofibrillary tangles
Beta amyloid
Down's syndrome
Familial Alzheimer's disease
Brain glucose utilization
Oxidative stress
Cerebral vascular disease
Ketone bodies
Gammahydroxybutyrate

ABSTRACT

The high energy demands of the poorly myelinated long axon hippocampal and cortical neurons render these neurons selectively vulnerable to degeneration in Alzheimer's disease. However, pathology engages all of the major elements of the neurovascular unit of the mature Alzheimer brain, the neurons, glia and blood vessels. Neurons present with retrograde degeneration of the axodendritic tree, capillaries with string vessels and markedly reduced densities and glia with signs of inflammatory activation. The neurons, capillaries and astrocytes of the mature Alzheimer brain harbor structurally defective mitochondria. Clinically, reduced glucose utilization, decades before cognitive deterioration, betrays ongoing energy insufficiency. β-hydroxybutyrate and γ-hydroxybutyrate can both provide energy to the brain when glucose utilization is blocked. Early work in mouse models of Alzheimer's disease demonstrate their ability to reverse the pathological changes in the Alzheimer brain and initial clinical trials reveal their ability to improve cognition and every day function. Supplying the brain with energy holds great promise for delaying the onset of Alzheimer's disease and slowing its progress.

Contents

E-mail address: m.mamelak@utoronto.ca

http://dx.doi.org/10.1016/j.neubiorev.2017.02.001
0149-7634/

The mature Alzheimer brain presents with a daunting display of pathology highlighted by intracellular aggregations of hyperphosphorylated tau (p-tau) and extracellular deposits of aggregated β-amyloid (βA) peptide (Wang et al., 2014b). Although repeatedly referred to as the hallmarks of Alzheimer's disease (AD) neither of these aggregations is unique to the disease (McKee et al., 2009, 2015) and, even at this late date in the history of Alzheimer's, their true nature remains an enigma. Are they epiphenomena of the aging brain, found in man and other primates (Finch and Austad, 2015) and without pathological significance or do they play a role in the ongoing deterioration of the brain? Is it possible that they actually have a neuro-protective function? How do they relate to one another and to the other well recognised features of the Alzheimer brain such as its atrophy, synaptic pathology, autophagic vesicles, granulovacuolar degeneration, neuro- inflammation and amyloid angiopathy? What accounts for the striking deterioration of the micro-circulation in the Alzheimer brain and the reduction in capillary density, loss of vascular endothelium and breakdown of the blood brain barrier (Baloyannis and Baloyannis, 2012; Brown and Thore, 2011; Zlokovic, 2011)? What causes the structural damage of the mitochondria in vulnerable neurons, astrocytes, capillary endothelial cells and pericytes (Aliyev et al., 2005; Baloyannis, 2006; Baloyannis and Baloyannis, 2012; Hirai et al. ,2001)? How do all of these pathological changes come about? The most parsimonious answer may lie in the progressive failure of the Alzheimer brain to generate the energy it needs to maintain its integrity. And therein may also be found the basis for its treatment.

1. Neurofibrillary tangles

1.1. Development and evolution

If the earliest appearance of abnormally phosphorylated tau (p-tau) marks the microscopic beginning of AD, its natural history has been suggested to start in young adulthood or even before puberty when soluble phosphorylated tau (pre-tangles) can be immunologically identified in certain brainstem and subcortical non-thalamic nuclei such as the noradrenergic locus coeruleus in particular but also in the serotonergic upper raphe, the cholinergic magnocellular nuclei of the basal forebrain and the hypothalamic tuberomamillary nucleus (Braak and Del Tredici, 2011, 2012, 2015). All of these nuclei give rise to diffuse sparsely myelinated long axons which project to the cerebral cortex and other brain regions. Phosphorylated tau can first be identified immunologically in the proximal axon of these neurons and subsequently fills the somatodendritic compartment. The soluble p-tau of this pre-tangle state is said to gradually aggregate into non-soluble fibrillary inclusions within dendrites to form neuropil threads (NTs) and within nerve cell bodies to form neurofibrillary tangles (NFTs). These insoluble argylophilic aggregates usually first appear in the trans entorhinal region in early middle age and resist removal by autophagy and other cellular mechanisms (Braak et al., 2011; Knopman, 2014). It remains debatable, however, whether the immunologically identified pre-tangle p-tau identified in brainstem and subcortical nuclei in the young is a true forerunner of Alzheimer tau and Alzheimer's disease (Attems et al., 2012; Attems and Jellinger, 2013; Braak and Del Tredici, 2013; Duyckaerts et al., 2015; Jellinger et al., 2015; Mann and Hardy, 2013). Neurons appear to be able to tolerate the presence of pre-tangles, NTs and NFTs and to survive for many decades even though they may not be functioning optimally. They tend to die prematurely leaving extraneuronal 'ghost' tangles in the neuropil. Ghost tangles, however, are always found in the company of fresh NFTs and NTs which reveal that the pathological process was ongoing at the time of death (Braak and Braak, 1997). Brain atrophy correlates well with the burden of NFTs (Josephs et al., 2008; Whitwell et al., 2008).

The pace at which tau pathology develops and spreads varies from person to person but pre-tangles, NTs and NFTs can remain localized to subcortical regions (Braak stages I/II) in some individuals until late age and only become associated with cognitive impairment and the dementia of AD when they spread to the neocortex. Little is known about the pace of this advance (Braak and Tredeci, 2011). Only after pre-tangles develop in brainstem and subcortical neurons do pre-tangles appear in the trans-entorhinal cortical region from which they spread in a systematic and sequential manner to defined regions of the brain according to their anatomical relationship to other neurones and not according to cell type. Thus, only specific neuronal circuits are targeted in AD. Abnormal tau molecules may propagate from region to region in a prion-like manner through synaptic contacts although other routes have also been proposed (Liu et al., 2012; McKee et al., 2015; Wu et al., 2013). The first transfer occurs between the subcortical terminal axons and the pyramidal cells of the trans-entorhinal region where the first signs of degeneration may be seen (Frost and Diamond, 2010). Glutamatergic cells in this region project to the entorhinal cortex which is the next region to degenerate followed by lesions of the hippocampus, amygdala and neocortex. Cortical and hippocampal pyramidal neurons which contain high levels of neurofilament protein and have long projections are particularly vulnerable to NFT formation (Braak et al., 2006a,b; Morrison et al., 1998). Thus, the pyramidal neurons most prone to NFT formation are found in cortical layers III and V which send long projections to other cortical regions and in the efferent neurons of layers II and IV of the CA1 field and entorhinal cortex. Neurofilaments in these neurons appear to participate in NFT formation as their density declines as NFTs are assembled. On the other hand, calcium −binding-protein containing interneurons are remarkably resistant to degeneration in AD. Interestingly, these interneurons rarely exhibit neurofilament immunoreactivity (Morrison et al., 1998). As will be discussed again later in this review, AD appears to begin in the CA1 region in association with the very early loss of the