Which synapses are affected in aging and what is the nature of their vulnerability? A commentary on “life span and synapses: will there be a primary senile dementia?”

John H. Morrison*

Kastor Neurobiology of Aging Laboratories, Fishberg Research Center for Neurobiology, and the Department of Geriatrics and Adult Development, Mount Sinai School of Medicine, New York, NY 10029, USA

Received 1 November 2000; accepted 1 November 2000

1. Introduction

In their provocative article “Life span and synapses: will there be a primary senile dementia?” [14], Terry and Katzman appropriately focus on the role of cortical disconnection as a critically important substrate for dementia. The focus in their article is on synapse loss as a mechanism for disconnection, however, degeneration of the cells of origin of key cortical circuits (e.g. corticocortical projections) has also been put forward as a major contributor to the cortical disconnection that occurs in Alzheimer’s disease (AD) [5]. Clearly, degeneration of such neurons would lead to a loss of synapses provided by those neurons as well as their afferent inputs, yet there may very well be terminal degeneration without overt loss of neurons as well. In fact, this is likely to be the case in normal aging where neuron loss is minimal in cerebral cortex [11], yet as pointed out by Terry and Katzman, normal aging is accompanied by a loss of synapses and this synaptic loss may impact function [4,9].

Whether or not synapse loss would continue at the pace proposed by Terry and Katzman as life expectancy increased and culminate in a primary non-AD dementia is an important question requiring additional analyses. I would like to encourage attention to three issues as we continue to refine studies on synapse loss in aging: 1) the importance of animal studies on normal aging; 2) the relevance of selective vulnerability to synapse loss; and 3) the importance of neurochemical alterations at the synapse in the absence of frank synaptic degeneration.

Studies of normal aging in animal models have turned out to be critically important in several respects. First, animal studies are not complicated by the presence of early AD and AD-related pathologies as are the human post-mortem specimens which are generally the objects of analysis in human studies, and thus offer an opportunity to study aging without the overlay of AD pathology. In addition, neuron loss does not appear to be an important contribution to age-related functional decline in animals [10,11,12], yet synapse loss remains an important potential correlate of functional decline [4,13]. Detailed neurochemical and morphologic analyses in animal subjects that have been characterized behaviorally will continue to be particularly important [2], since such studies allow for direct correlations to be drawn between neurobiological indices such as synaptic alterations and functional decline as measured by performance. Of course such structure/function correlations require that the neurobiological indices be quantified accurately, further reinforcing the need to apply the most rigorous quantitative neuroanatomic procedures to studies of the aging brain. Another important advantage of animal models with respect to synaptic alterations is that the morphologic and neurochemical data on aging can be considered in the context of an expansive literature on synaptic plasticity and synaptic physiology, which is not possible in the human studies.

With respect to selective vulnerability, just as all neurons are not equally prone to degeneration in a given neurodegenerative disorder [5], all circuits are unlikely to be equally vulnerable to synaptic alterations in normal aging. Thus, it will be critically important to determine which synapses are vulnerable in aging and which are not. For example, a recent study using synaptophysin as a synapse marker demonstrated that in aged-impaired rats as compared to aged-unimpaired or young rats, synaptic alterations occurred in the hippocampus, but only in key terminal zones of the perforant path, the circuit that interconnects entorhinal cor-

* Corresponding author. Tel.: +1-212-659-5985; fax: +1-212-849-2510.
E-mail address: John.Morrison@mssm.edu (J.H. Morrison).
I would encourage the neuroscience community to take full advantage of animal models, bear in mind the principles of selective vulnerability, and employ approaches that will reveal neurochemical compromise at the synapse in the absence of frank degeneration. Such approaches are likely to reveal a complex set of circuit-specific synaptic alterations that lead to age-related functional decline, and some of these alterations may be amenable to pharmaceutical, endocrine, and behavioral interventions aimed at functional restoration.

References


