Introduction

Based on evidence to date, non-human animals do not spontaneously develop Alzheimer disease (AD) as they age. Furthermore, transgenic animal models of AD appear to only model some aspects of the earliest portion of the pre-clinical phase of AD. Transgenic models do not produce substantial neuron and synapse loss and consequently do not cause a clear memory/cognitive decline. It is possible that non-human animal brains have some "neuroprotective" factor that prevents the neuro pathological and neurobehavioral changes of AD. Alternatively, it may be that a long duration of time, in addition to cellular aging, is required for the preclinical biomarkers of AD to accumulate and reach the threshold for cognitive deficits to emerge. Transgenic animals don’t progress to dementia because they don’t live long enough to allow for sufficient accumulation of pathology to cause substantial neuron and synapse loss.

The following cascade of biomarker events were reported at different time intervals preceding the expected age of clinical onset based on the affected parent’s age of dementia onset. Twenty-five years prior, there was a decrease in concentration of amyloid beta 42 in CSF. Fifteen years prior, there was an increased amyloid beta deposition (PIB-PET) in the precuneus of carriers but not in non-carriers, increased protein tau levels in the CSF and brain atrophy measured by serial quantitative MRI. Ten years prior, there was cerebral hypo metabolism (FDG PET) and impaired episodic memory on neuropsychological testing. Five year prior, there were global cognitive changes as measured by MMSE and Clinical Dementia Rating Scale.

What implications does this human model have for the transgenic animal models of AD? Animal models of AD sometimes produce subtle cognitive deficits, but they do not produce anything approximating amnesic MCI or dementia. This is likely because existing animal models do not produce a substantial loss of neurons and synapses. Degree of cognitive impairment in human AD cases was found to highly correlate (correlation coefficient of 0.96) with synapse density in the mid frontal and inferior parietal regions of the brain [6]. Furthermore, the neurological threshold for amnesic MCI appears to be a 32-35% loss of neurons in the entorhinal cortex (EC) including a 50-64% loss of neurons in Layer 2 which gives rise to the perforant pathway (the major input into the hippocampus), 40% loss of neurons in Layer 4 (which receives the major output from the hippocampus) and 46% loss of neurons in the CA1 subfield of the hippocampus [7-9]. It appears that the threshold for amnestic MCI is ~50% loss of neurons in EC layer II, EC layer IV and the CA1 subfield of hippocampus, which are three critical links in the medial temporal lobe memory system. Therefore, transgenic...
animal models of AD do not produce amnestic MCI because they do not produce sufficient neuron and synapse loss.

Why do the transgenic mouse models of AD not produce substantial neuron/synapse loss? Do the non-human animal brains have some “neuroprotective” factor(s) that prevents them from developing the neuropathological and neurobehavioral changes of AD? An alternative explanation is that a long duration of “time,” in addition to cellular aging, appears to be required for the preclinical biomarkers of AD to accumulate and reach the threshold for cognitive deficits to emerge and progress.

The three major categories of risk factors for AD are age, genetics and environmental/lifestyle factors. The prevalence of AD doubles every five years after age 65 and 90% of people with ADs are age 75 and older. Age is the biggest risk factor AD. However, “duration of time” is confounded with age/aging. Accumulating neuropathology in the brain is likely a function of both biological aging and duration of time. For example, “aging” of brain cells may be necessary for starting and perpetuating the preclinical cascade of biomarkers leading to clinically expressed AD, but a long duration of time may also be necessary for Abeta plaques to accumulate and for p-tau to spread from neuron to neuron. In other words, a very long period of time might be necessary for the Alzheimer neuropathological changes to accumulate leading to a neurodegenerative and a progressive dementia.

Amyloid starts an abnormal rate of accumulation about 20-25 years before the clinical diagnosis of early Alzheimer dementia. Sometime later, tau starts to spread from neuron to neuron leading to progressive loss of neurons and synapses and to progressive memory/cognitive decline. Since 90% of people with ADs are age 75 and older, if we assume a symptom onset at age 75-80 and a 25-year preclinical phase, then the preclinical phase of AD does not begin for the vast majority of people who will develop Alzheimer dementia until age 50 or older. Most humans who go on to develop AD have no AD pathology for the first half century of their lives. It is likely that both cellular aging and the cumulative effects of lifestyle over time on brain cell metabolism interact with genetics to determine the onset and progression of accumulating Alzheimer pathology in the brain.

Clinical AD is the product of two decades of accumulation of beta-amyloid and spread of hyper-phosphorylated tau that eventuates in significant progressive loss of neurons and synapses (i.e., neurodegeneration) and only then is there measureable cognitive decline. It is not just “aging neurons” that contribute to the development of clinical AD; it is a long duration of time from the start of amyloid and tau accumulation/spread that eventually produces significant neuron and synapse loss and then progressive cognitive decline. The development of AD depends not only on cellular aging but also on the accumulation of pathological changes over a long period of time. During the long preclinical period, there is a slow accumulation of plaques, tangles and neuron/synapse loss that eventually reaches the threshold for memory/cognitive decline. A two-year old mouse may be the equivalent to a 64-year old human from a biological/cellular aging perspective, but a two-year lifespan falls way short of the seven to eight decades of accumulated time it typically takes for a human to become demented. Furthermore, the two-year life span of a mouse is a small fraction of the 20-25 years of time it takes for the incipient neuropathological changes in midlife to evolve to early Alzheimer dementia. A conceptual model of AD should consider two separate but interacting components of the variable “age:” a) the intrinsic biological neuronal aging component and b) the effects of duration of time. It takes a long time for amyloid and tau to accumulate and spread in the brain before the neurodegenerative phase begins in which cumulative neuron/synapse loss is accompanied by progressive memory /cognitive decline.

Although the thesis in this commentary is implicit in human models of AD, there is a value in explicitly recognizing that “time” and “aging” are dissociable factors. When talking about the effects of “age,” it is important to recognize that “aging” and “time” are confounded. “Aging” and “time” should be distinguished conceptually when talking about the effects of “age.” If a long-duration of time is necessary to produce clinical AD in both men and mice, then that may explain why non-human animal models don’t produce “clinical” AD. Neither mice nor even non-human primates live long enough for amyloid or tau to slowly accumulate over two decades in order to reach the threshold of brain damage needed for the emergence of clinical/cognitive decline. Even chimpanzees only live up to age 50 and very few humans have clinical AD or even neuropathological AD at age 50. One potentially useful application of transgenic mouse models of AD might be in studying factors that accelerate or decelerate the accumulation and spread of amyloid and tau.

The aging canine brain provides an alternative to the transgenic mouse model for Alzheimer’s disease in that some features of preclinical AD develop spontaneously in some very old dogs including cognitive decline. B-amyloid deposition in the form of diffuse senile plaques is a consistent feature of aging in dogs and cats, but aged dogs and cats do not develop neuritic plaques nor do they develop neurofibrillary tangles [12]. On the other hand, the goat, sheep, bear and wolverine are reported to develop neurofibrillary-like lesions but not senile plaques. However, only the dog has been extensively studied. In addition to B-amyloid deposition in the brain, aged dogs show evidence of neuron loss and dysfunction [12].

Memory tasks reveal frank differences in young versus old dogs, but like humans, dogs also show considerable individual variability with aging in learning and memory and in the degree of B-amyloid deposition in the brain [12]. The amount of accumulation varies across individual dogs with extensive plaques in some aged dogs that correlate with the development of significant memory impairment [12]. Specifically, performance on declarative-type memory tasks, but not procedural-type memory tasks were strongly correlated with B-amyloid deposition in both the prefrontal and entorhinal cortices (up to 68.9% of the variability on the memory test scores could be accounted for by the degree of B-amyloid deposition).

However, in humans, neocortical neurofibrillary tangle densities have been reported to be substantially correlated with dementia severity and to a greater degree than for senile plaque densities [13]. In another study in humans, neurofibrillary tangle density in the temporal lobe correlated with memory scores in normal aging and mild cognitive impairment, whereas density of
amyloid plaques did not [14]. Terry et al [6] reported that the density of neocortical synapses, but not plaques and tangles, correlated highly with global degree of cognitive impairment [6]. Thus, in the aging canine model, there is spontaneous substantial cognitive decline in some aged dogs associated with \( B\)-amyloid deposition (in the form of diffuse plaques) and associated with neuron loss, but there are no neuritic plaques nor neurofibrillary tangle formation.

In conclusion, when reporting research results from studies using animal models of AD, investigators ideally should indicate what specific stages of pre-clinical AD does the model being used simulate (e.g., early pre-clinical stage of beta-amyloid accumulation). Additionally, in behavioral studies using animal models, it would be helpful if investigators discuss how closely the magnitude, extent, and nature of behavioral effects approximate that seen in AD (e.g., subtle cognitive decline but not commensurate with human MCI, amnestic MCI, dementia).

REFERENCES


