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A canine model of human aging and Alzheimer's disease☆

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Abstract

The aged dog naturally develops cognitive decline in many different domains (including learning and memory) but also exhibits human-like individual variability in the aging process. The neurobiological basis for cognitive dysfunction may be related to structural changes that reflect neurodegeneration. Molecular cascades that contribute to degeneration in the aging dog brain include the progressive accumulation of beta-amyloid (Aβ) in diffuse plaques and in the cerebral vasculature. In addition, neuronal dysfunction occurs as a consequence of mitochondrial dysfunction and cumulative oxidative damage. In combination, the aged dog captures key features of human aging, making them particularly useful for the development of preventive or therapeutic interventions to improve aged brain function. These interventions can then be translated into human clinical trials. This article is part of a Special Issue entitled: Animal Models of Disease.

Keywords

Beagle; Beta-amyloid; Cognition; Mild cognitive impairment; Oxidative damage

1. Introduction

In this review of the canine model of human aging and Alzheimer disease (AD), several key features of dog brain aging will be discussed including general aging characteristics, cognitive changes with age, and neuropathology that are consistent with the human brain. The dog model provides a complementary system in which to test various theories of aging and to develop therapeutics when used in combination with other models. However, the use of dogs in aging studies provides some unique advantages, as dogs are easy to handle and may share a common environment (including diet) with humans. Dogs also offer additional predictive validity when translating results to human clinical trials, as they absorb pharmaceuticals with similar if not identical pharmacokinetics. For example, due to similarities to humans in terms of responsiveness, drug tolerance and metabolism, the dog can be considered to be a useful model for chronic statin treatment [1,2]. Further, an interesting new study suggests that in the process of domestication in dogs, genes associated with digestion have been selected that allow dogs to thrive on a diet rich in starch unlike wolves and more similar to humans [3], suggesting similar dietary absorption of nutrients.

The median lifespan of dogs varies as a function of breed, with larger breeds typically having shorter lifespan than smaller breeds [4–6]. In our laboratory, we primarily work with beagles that have a median lifespan of 13.9 years and no significant differences between

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males and females [7]. Using a polynomial model, a young beagle under 5 years is similar to humans under 40 years [6]. Middle aged beagles between 5 and 9 years are similar to humans between 40 and 60 years and beagles over 9 years are similar to humans over 66 years. Interestingly, cognitive and neurobiological changes are observed in dogs beginning in middle age and become more pronounced as they progress to old age, consistent with humans. Further, dogs may also capture the phenotype of early AD neuropathology [8].

AD is accompanied by progressive dementia and the accumulation of senile plaques and neurofibrillary tangles [9]. Plaques contain a toxic peptide called beta-amyloid (Aβ),which is produced from the longer Aβ precursor protein (APP) by sequential proteolytic cleavage by beta-secretase and gamma-secretase [10]. Aβ forms either extracellular deposits or soluble assembly states (oligomers — see Section 4.1) [11–13]. Neurofibrillary tangles are composed of hyperphosphorylated tau protein that fills the cytoplasm of neurons, leading to degeneration [14]. As with most natural animal models of AD (with the exception of goats, sheep and chimpanzees, [15–17]), dogs develop Aβ pathology and some evidence for tau abnormalities but not full blown neurofibrillary tangles.

2. Cognition and aging

Cognitive aging in dogs has several key features including domain-specific vulnerabilities and individual variability in the extent of decline. Aged dogs show deficits in complex learning tasks including size concept learning [18,19], oddity discrimination learning [20,21], size discrimination learning [22,23], and spatial learning [24]. Tasks sensitive to prefrontal cortex function, including reversal learning and visuospatial working memory, also deteriorate with age [22,23,25]. Further, egocentric spatial learning and reversal (measuring the ability of animals to select the correct object based on their own body orientation) are also age-sensitive [24]. Spatial attention assessed using a landmark discrimination task originally developed in nonhuman primates is also vulnerable to aging [26,27]. Interestingly, on simple visual discrimination learning tasks and procedural learning measures, aged dogs perform as well as younger animals [28], suggesting that a subset of cognitive functions remains intact with age. Further, sensory deficits are likely not a significant contributor to increased error scores.

Memory also declines with age in dogs. To test memory, an object recognition task developed for nonhuman primates [29] and applied in the canine model also reveals age-related deficits in acquisition [28]. These age-dependent cognitive deficits are not linked to obvious sensory deficits or locomotor impairment [30]. Perhaps the most useful age-sensitive task in dogs is a spatial memory task in which dogs are required to recognize the location of a sample stimulus and then respond to a different location during the test trial. Spatial learning and memory are age-sensitive in dogs [31,32]. Interestingly, deterioration in spatial ability occurs early in the aging process, between 6 and 7 years of age in dogs [25]. Thus, cognitive decline in aged dogs is domain-specific and involves memory and executive function cortical systems.

Cognitive dysfunction is not an inevitable consequence of aging in humans [33]; research has focused on the distinction between those who retain function and those who show decline, including mild cognitive impairment [34,35]. As with human cognitive aging, increased individual variability in error scores in dogs is observed beginning in middle age [36]. Individual variability is largest in old animals. Using spatial learning and memory tasks, it is possible to distinguish three groups of old dogs: (1) successful agers, (2) impaired dogs whose scores fell 2 standard deviations above the mean of the young animals, and (3) severely impaired dogs who failed to learn the task [37]. This clustering of aged dogs on the basis of cognitive ability is consistent with cognitive aging in rats and non-human primates

[38–42] as well as in humans [43]. Individual variability with age in dogs provides a powerful approach to establish links between cognitive dysfunction and neurobiology. With this approach, animals with and without cognitive impairments at equivalent ages can be compared for differences in the extent of neuropathology.

Tasks used to assess cognition in dogs were developed such that they were conceptually analogous to those used in nonhuman primate aging research and to detect dementia in humans. Table 1 shows a comparison of the many tasks that have been modified or developed for use in aging canines.

3. Neurodegenerative changes in aged dog brain

Several structural and molecular changes occur with age in the dog brain and are linked to cognitive function. *In vivo* brain imaging studies show that cortical atrophy [44] and ventricular widening [44–46] are consistent features of canine brain aging. Further, MRI studies suggest differential vulnerabilities of specific brain areas to aging. For example, in aging dogs, the prefrontal cortex loses tissue volume at an earlier age (approximately 8–11 years) than does the hippocampus (after 11 years) [47]. The extent of cortical atrophy is significantly associated with cognition; animals with extensive atrophy perform more poorly on tests of learning and memory [48], similar to elderly humans with dementia [49,50]. Another similarity that has been reported between human brain aging and the canine is the spontaneous development of white matter hyperintensities seen with T2 imaging particularly in the white matter adjacent to the lateral ventricles [45]. Mechanistically this may be linked to changes in the capillaries of the white matter that have been reported to show a decrease in laminin immunoreactivity and iron deposits within astrocytes and macrophages, all of which suggest blood–brain barrier and white matter compromise [51].

White matter volume also declines with age in dogs and, interestingly, appears to show a different pattern in males and females [52]. Diffusion tensor imaging studies to measure changes in white matter function have not been assessed as a function of age in dogs but a recent report suggests that this may be a very useful tool in future studies [53,54]. Given that dogs show a loss of myelin with age, with the frontal cortex being particularly vulnerable, this may be critically involved with cognitive decline [55].

Atrophy may result from neuron loss or changes in neuronal density, as reported in normal human brain aging [56,57], although more extensive neuronal loss occurs in AD [58,59]. When neurons were counted using unbiased stereological methods within individual subfields of the hippocampus of young (3.4 to 4.5 years) and old (13.0 to 15.0 years) dogs, the aged dogs had significantly (~30%) fewer neurons in the hilus of the dentate gyrus [60]. The number of neurons was correlated with cognitive function; dogs with higher numbers of hippocampal neurons performed a visual discrimination task with fewer errors [60]. However, relatively speaking, the hilus accounts for a small number of neurons in the hippocampus overall.

Reduced neurogenesis in the mature brain may also contribute to age-associated cognitive decline, resulting in slower replacement of dying neurons. In the hippocampus of beagles, a 90–95% decline in neurogenesis was measured in aged dogs [61]. Further, the degree of neurogenesis was correlated with cognitive function; animals with fewer new neurons had higher error scores in measures of learning and memory, as well as poorer learning ability [61]. Similar reductions in neurogenesis in aged dogs have been reported in other laboratories [62,63].

4. Neurodegenerative mechanisms in aged dog brain

Neuron loss and cortical atrophy in vulnerable brain regions of the aged dog may be due to the accumulation of toxic proteins, including Aβ or oxidatively modified lipids, proteins, or DNA/RNA. Additionally, many up-or down-regulated pathways in canine brain aging could also lead to neurodegeneration [64].

4.1. Aβ and aging in dogs

Canines and humans have Aβ-containing lesions with identical amino acid sequence [65,66]. This observation first stimulated interest in the use of the dog to model human aging and disease [67]. Specific brain regions show differential accumulation of Aβ in the aging dog brain, paralleling reports in the aged human brain [66,68–75]. When cortical regions are sampled for Aβ deposition, each region shows a different age of Aβ onset [72]. Aβ deposition occurs earliest in the prefrontal cortex of the dog and later in temporal and occipital cortex, similar to previous reports in humans [75]. Canine plaques are typically diffuse and thioflavin S-negative but can form into more compact deposits [76] — thus, although the brain regions affected by senile plaques are similar in dogs and humans, they appear to mimic an earlier phase of Aβ deposition [8]. Importantly, the extent of Aβ plaque deposition in the dog brain is linked to the severity of cognitive deficits [22,48,77,78] and also in the prefrontal cortex to cortical atrophy observed by MRI [47].

Age and cognitive status can predict Aβ accumulation in discrete brain structures. For example, dogs with prefrontal cortex-dependent reversal learning deficits show significantly higher amounts of Aβ in this brain region [22,79]. On the other hand, dogs that did poorly in a size discrimination learning task show large amounts of Aβ deposition in the entorhinal cortex [22]. Aβ can also be measured in the cerebrospinal fluid (CSF) of dogs. The ratio of Aβ42/40 in the CSF is a good predictor of the extent of Aβ measured biochemically in the brain and also declines linearly with age [80].

Aβ not only exists in fibrillar or linear conformations, but can also adopt other assembly states that make it particularly toxic to synaptic and neuronal function. Specifically, Aβ oligomers are small soluble forms of Aβ that interfere with synaptic function and cognition [11,81]. Interestingly, Aβ oligomers can be detected in the CSF of dogs, but are inversely related to the amount of total Aβ measured biochemically in the brain, suggesting that oligomers are sequestered into plaques [80].

A common type of pathology observed in both normal human brain aging and particularly in AD is the presence of cerebral amyloid angiopathy (CAA), which is characterized by the accumulation of Aβ in the walls of cerebral vessels [82–84]. Vascular and perivascular abnormalities and CAA pathology are frequently found in aged dogs [68,69,85–92]. CAA may compromise the blood–brain barrier, impair vascular function [93], and cause microhemorrhages [90,91,94]. The distribution of CAA in dog brain is similar to humans, with particular vulnerability in the occipital cortex [83]. Thus, aged dogs develop cerebrovascular abnormalities that may contribute to cognitive decline and are consistent with those reported in humans.

4.2. Oxidative damage and mitochondrial dysfunction

Aging and the production of free radicals can lead to oxidative damage to proteins, lipids, and nucleotides that, in turn, may cause neuronal dysfunction and ultimately neuronal death. Normally, the activity of endogenous antioxidants balances the production of free radicals. However, a number of these protective mechanisms begin to fail with age. In the aging dog, the brain accumulates carbonyl groups, a measure of oxidative damage to proteins [95,96]. Carbonyl groups are associated with reduced endogenous antioxidant enzyme activity or

protein levels, including those of glutamine synthetase and superoxide dismutase (SOD) [95,97–99]. In addition, increased oxidative damage to proteins can be measured by the end products of lipid peroxidation (oxidative damage to lipids), including 4-hydroxynonenal (4HNE) [48,99–101], lipofuscin [48], lipofuscin-like pigments [100,101] or malondialdehyde [95]. Additionally, oxidative damage to DNA or RNA may be increased in aged dog brain [8,48]. Oxidative damage may also be associated with behavioral decline in dogs. Increased oxidative end products in aged companion dog brain are correlated with more severe behavioral changes [48,96,101,102]. Similarly, in laboratory studies of aging beagles, higher protein oxidative damage (3-nitrotyrosine) and lower endogenous antioxidant capacity (SOD and glutathione-S-transferase activities) are associated with poorer prefrontal-dependent and spatial learning [98]. Mitochondria are a source of free radicals that damage proteins, lipids and DNA/RNA [103]. In a study of aged beagles, isolated mitochondria show increased reactive oxygen species production in aged animals relative to young animals [104]. Thus, aged dogs exhibit mitochondrial dysfunction and oxidative damage, consistent with humans with age-related neurological dysfunction.

5. Therapeutics

Aging dogs have been used to test a number of different therapeutics that has also been tested in human clinical trials [8]. A diet rich in a broad spectrum of antioxidants and mitochondrial co-factors improved cognition [21,26,105] and reduced neuropathology in aging dogs over a 2.8 year period of time [98,106]. There was also strong evidence for maintenance of function over the duration of this study. Behavioral enrichment, which includes physical exercise, environmental enrichment, social enrichment and cognitive training also leads to significant cognitive [21,26,105] and neurobiological [98,106–108] benefits. Statins have been associated with reduced risk of AD [109–111]. Statins reduce cholesterol levels by inhibiting the enzyme, 3-hydroxy-3-methylglutaryl coenzyme reductase (HMG-CoA) to reduce cholesterol production. Rodent models may have limited utility when testing the effects of statins on the aging process as rats and mice upregulate HMG-CoA to compensate after statin administration [112]. Aging dogs treated with human dose atorvastatin showed both evidence of improved and impaired cognition with decreased BACE protein levels [113], increased haem oxygenase-1, and reduced oxidative damage [3,45]. No effects were observed on Aβ pathology, which was the original hypothesis given data from transgenic mice. However, a vaccine against Aβ, initially developed in transgenic mice [114], leads to maintenance of frontal function in aging dogs after 2 years of treatment along with a reduction in Aβ plaques [115]. However, there was no improvement in learning and memory while being vaccinated, which was similar to reports in human clinical trials [116,117]. Recent reports suggest that passive vaccination with solanezumab in patients with AD also did not report benefits but rather a delay in progression observed as a maintenance of function. These studies suggest that the dog is a useful and complementary model system to transgenic mice to help develop therapeutics or approaches that may slow or halt AD in clinical trials. A more thorough discussion of possible therapeutics development using the canine model has been provided in additional reviews [8,118].

5.1. Summary

The aged dog naturally develops decline in many different cognitive domains and exhibits human-like individual variability in the aging process. Some aged dogs develop significant cognitive decline more closely resembling persons with mild cognitive impairment. The neurobiological basis for cognitive dysfunction may be related to structural changes that reflect degeneration. Molecular cascades that may contribute to neurodegeneration in the dog brain may include the progressive accumulation of Aβ in diffuse plaques and in the cerebral vasculature. In addition, neuronal dysfunction may occur as a consequence of mitochondrial dysfunction and cumulative oxidative damage (although other pathological

processes have been observed in the canine brain and this review provides a few examples of these). Taken together, the aged dog may capture key features of human aging, making them particularly useful for studies of therapeutics that can be translated into human clinical trials.

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Table 1

Cognitive domains assessed in dog aging and comparison with nonhuman primate tasks and analogous tasks used in human neuropsychological testing.

Cognitive domain	Dog task	Localization in dog brain	Nonhuman primate tasks	Examples of human neuropsychological tasks[a]
Learning	Visual discrimination learning	Medial temporal lobe/parietal lobe[b]	Visual discrimination learning [112,113]	Digit copy, rotary pursuit, face discrimination [114], object discrimination [115,116]
	Reward and object approach learning	Nigrostriatal and motor cortex[b]	Food pickup task, fine motor learning [117,118]	
Memory	Delayed nonmatching to sample acquisition	Rhinal cortex [23]	Object recognition memory task [28]	Delayed recognition and recall, digit span [119]
	Delayed nonmatching to sample memory	Rhinal cortex [23]	Object recognition memory task [28]	
	Spatial delayed nonmatch to sample acquisition	Dorsolateral prefrontal cortex [23]	Delayed response task [120, 121]	
	spatial delayed nonmatch to sample memory	Hippocampus [122]	Delayed response task [120, 121]	
Executive function	Visual reversal learning	Prefrontal cortex/medial temporal lobe [123]	Visual reversal learning [112,113]	Card or object sorting tasks, set shifting, response inhibition [124]
	Oddity discrimination	Prefrontal cortex/medial temporal lobe[b]	N/A	
	Egocentric spatial reversal learning	Hippocampal/prefrontal cortex[b]	Spatial reversal [112]	
	Size concept learning	Prefrontal cortex/medial temporal lobe[b]	Hierarchical/relational learning [125]	
Visuospatial function	Landmark discrimination	Prefrontal cortex/parietal cortex[b]	Landmark discrimination [126]	Visual construction, block design, spatial learning [115,116]
	Egocentric spatial learning	Hippocampus/medial temporal lobe[b]	Spatial learning [112]	

[a] Neuropsychological tasks for humans that assess function in similar cognitive domains reproduced from [127].

[b] Proposed localization — not confirmed in lesion studies in dogs.