Brain Aging in the Dog

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Jeff Nichol and Elizabeth Head

Dogs develop behavioral and cognitive dysfunction with age. Interestingly, as with humans, not all aged dogs become impaired, and there can be significant individual variability. Studies of the brains of cognitively characterized aged dogs suggest several possible underlying neurobiological mechanisms for observed impairments. In this chapter, changes in canine brains associated with atrophy, neuron loss, accumulation of beta-amyloid (Aβ), mitochondrial dysfunction, and resulting accumulation of oxidative damage are described. There are many important features of brain aging in dogs that overlap significantly with human brain aging, suggesting they are a useful model system in which to test interventions that may lead to healthy aging.

5.1 Introduction

Several comprehensive reviews of the neuropathology of canine brain aging are available; this chapter will serve as an overview of key features that are relevant for cognitive decline (Bosch et al. 2012; Cotman and Head 2008; Head 2000, 2011, 2013; Schutt et al. 2016). The features include brain atrophy, neuron loss, and accumulation of Alzheimer's disease (AD) like neuropathology, vascular pathology, oxidative damage, and inflammation. Most of these neuropathologies increase with age in dogs and in several studies of cognitively characterized animals are also observed to be correlated with the extent of cognitive decline.

J. Nichol
Veterinary Emergency and Specialty Centers of New Mexico, Albuquerque, NM 87109, USA

E. Head (✉)
Sanders-Brown Center on Aging, Department of Pharmacology and Nutritional Sciences, University of Kentucky, Lexington, KY 40536, USA
e-mail: Elizabeth.Head@uky.edu

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5.2 Structural Brain Changes and Neuron Losses

A consistent feature of aging in humans is progressive brain atrophy, which is particularly striking in AD. Magnetic resonance imaging (MRI) studies have provided useful outcome measures reflecting changes in brain structure in vivo. Both generalized cortical atrophy (Su et al. 1998) and ventricular widening (Gonzalez-Soriano et al. 2001; Kimotsuki et al. 2005; Su et al. 1998) can be observed in older animals. However, as with various cognitive functions being differentially affected by the aging process, MRI studies suggest not all brain regions atrophy at the same rate.

Losses in tissue volume occur early with age in the prefrontal cortex around 8 – 11 years in beagles (this may differ with various breeds, given that larger breeds tend to have shorter life spans) (Tapp et al. 2004). The hippocampus atrophies in beagles after 11 years of age (Tapp et al. 2004). Paralleling correlations in cognition and frontal cortex volume in people with dementia (Du et al. 2006; Ezekiel et al. 2004), canine prefrontal cortex atrophy is also associated with impaired cognition (Rofina et al. 2006).

Changes in neuronal number or density are observed in normal human brain aging (Šimić et al. 1997; West 1993) and are more extensive in AD (Bobinski et al. 1997; West et al. 2000). In beagles, a selective loss of neurons is observed within the hilus of the hippocampus (up to 30% loss) when comparing young dogs (3 – 5 years) to older dogs (13 – 15 years) (Siwak-Tapp et al. 2008). In addition, hilar neuron number was correlated with cognition; higher numbers of neurons were associated with fewer errors on a visual discrimination task (Siwak-Tapp et al. 2008).

The reason for losses of neurons in the hippocampus may be due to slower replacement by neurogenesis. Interestingly, neurogenesis decreases by up to 90 – 95% in aging beagles (Hwang et al. 2007; Pekcec et al. 2008; Siwak-Tapp et al. 2007). Further, animals with fewer new neurons had higher error scores in measures of learning and memory, suggesting a link between neurogenesis and cognition with age (Siwak-Tapp et al. 2007). Neuron loss and cortical atrophy in vulnerable brain regions of the aged dog may be due to multiple neurodegenerative processes associated with the up- or downregulation of molecular pathways (Swanson et al. 2007). One of these pathways may be a decrease in growth factors such as brain-derived neurotrophic factor (Fahnestock et al. 2010).

5.3 Plaques and Aβ Accumulation

Plaques are extracellular deposits that contain the Aβ peptide, which is a 40–42 amino-acid-long cleavage product of the longer amyloid precursor protein (Selkoe 1994). Aβ accumulation can occur in different types of plaques (e.g., diffuse, neuritic), but also can form structures called oligomers, which are particularly toxic to synapses (Haass and Selkoe 2007; Lesné et al. 2006; Selkoe 2008; Walsh et al. 2002). A useful feature of the aged canine model is that the Aβ sequence is identical to that of humans (Johnstone et al. 1991; Selkoe et al. 1987). Indeed, it was this finding that led to interest in studying aging dogs as an approach to understand human aging and AD (Wisniewski et al. 1990).

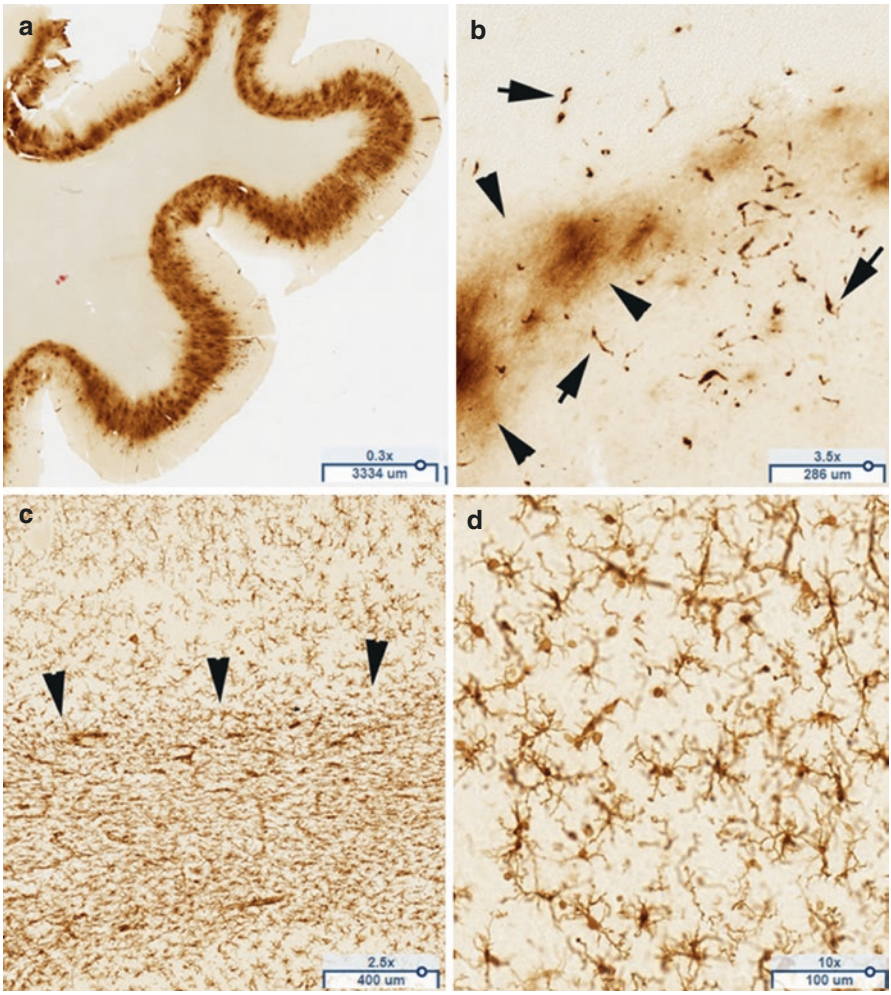

Fig. 5.1 Neuropathology in aging dogs. (**a**) Aβ immunostaining (6E10 antibody) in the parietal cortex of an aged pet dog (15-year-old Siberian Husky) shows extensive plaque deposition affecting deep cortical layers. (**b**) CAA (6E10 immunostaining—*arrows*) in the parietal cortex of an aged dog (14-year-old Sheltie) shows that vascular pathology can be extensive and tends to occur in clusters. Diffuse plaques are also identified by arrowheads. (**c**) Low-power photograph showing extensive microglial cell labeling (IBA-1 antibody) in gray matter along with intense labeling in the white matter (area below *arrows*) of a 15-year-old Shih Tzu. (**d**) Higher magnification photograph from (**c**) showing that individual microglia contain phagocytic vacuoles and have thickened processes suggesting that some have an activated morphology

In dogs, as shown in Fig. 5.1, Aβ accumulates in the cortex with a relatively well-described pattern that parallels observations in the human brain (Braak and Braak 1991; Braak et al. 1993; Giaccone et al. 1990; Head et al. 2000; Ishihara et al. 1991; Selkoe et al. 1987; Thal et al. 2002; Wisniewski et al. 1970, 1990). Aβ

deposition occurs earliest in the prefrontal cortex of the dog and later in the temporal and occipital cortex (Head et al. 2000), similar to previous reports in humans (Thal et al., 2002). Further, several groups have characterized the age-dependent maturation of Aβ deposits within the canine cortex into several phases (Satou et al. 1997; Schutt et al. 2016). Importantly, the extent of Aβ plaque deposition in the dog brain is linked to the severity of cognitive deficits (Colle et al. 2000; Cummings et al. 1996; Head et al. 1998; Rofina et al. 2006). Interestingly, not all studies show a correlation between Aβ and the presence of canine cognitive dysfunction (CCD) (Chambers et al. 2011; Ozawa et al. 2016). However, studies that show a link between the extent of Aβ and cognition also indicate that the location of the deposition is important. For example, dogs with reversal learning deficits indicative of executive dysfunction tend to show more extensive Aβ deposition in the prefrontal cortex (Cummings et al. 1996; Head et al. 1998). In contrast, poor size discrimination learning ability is associated with large amounts of Aβ in the entorhinal cortex (Head et al. 1998). Soluble Aβ can also be measured in the cerebrospinal fluid (CSF) of dogs, making it a useful marker for aging and cognition intervention studies (Head et al. 2010; Sarasa et al. 2013). The ratio of Aβ42/Aβ40 in the CSF is a good predictor of the extent of Aβ measured biochemically in the brain and also declines linearly with age (Head et al. 2010).

In studies characterizing Aβ deposits in plaques, the primary conformation is fibrillar, but Aβ not only exists in this or linear conformations but can also assemble into soluble states that are toxic to synapses and thus neuronal function. Aβ oligomers are small soluble assembly states that interfere with synaptic function and cognition (Kayed et al. 2003; Walsh et al. 2002). Interestingly, Aβ oligomers in the CSF of dogs are inversely related to the amount of total Aβ measured biochemically in the brain, suggesting that oligomers are sequestered into plaques (Head et al. 2010).

Posttranslationally modified Aβ has also been assessed in aging dog brains. These modified forms of Aβ are thought to represent deposits of Aβ that are chronobiologically older (Azizeh et al. 2000). Pyroglutamyl-modified Aβ increases with age in dogs (Frost et al. 2013; Schutt et al. 2016) as does the amount of racemized Aβ (Azizeh et al. 2000). In addition to modified Aβ, truncated Aβ that is observed in AD brain is also observed in the aged canine brain (Chambers et al. 2011).

5.4 Vascular Neuropathology

A frequent pathology detected in both normal human brain aging and particularly in AD is the presence of cerebral amyloid angiopathy (CAA), which is described as the accumulation of Aβ in the walls of cerebral vessels (Attems 2005; Attems et al. 2005; Herzig et al. 2006). Aged dogs are also vulnerable to vascular pathology with perivascular abnormalities; CAA is observed frequently in aged dogs (Giaccone et al. 1990; Ishihara et al. 1991; Shimada et al. 1992; Uchida et al. 1990, 1991, 1992, 1993, 1997; Yoshino et al. 1996). The consequences of CAA accumulating in

the brains of aging dogs may be a compromise to the function of the blood-brain barrier and impaired vascular function (Prior et al. 1996). In turn, vascular dysfunction and BBB disruptions may lead to microhemorrhages (Deane and Zlokovic 2007; Uchida et al. 1990, 1991). The distribution of CAA in dog brain is similar to humans, with particular vulnerability in the occipital cortex (Attems et al. 2005). However, in a systematic study of the extent of CAA in cognitively characterized pet dogs, CAA increased with age but did not correlate with cognition (Ozawa et al. 2016). Thus, aged dogs develop cerebrovascular abnormalities that may not contribute to cognitive decline but are otherwise consistent with those reported in humans.

5.5 Oxidative Damage and Mitochondrial Dysfunction

There are several reviews of the potential role for oxidative damage and mitochondrial dysfunction on brain aging in dogs (Cotman et al. 2002; Dowling and Head 2012). The production of free radicals during the aging process can lead to damaged proteins, lipids, and nucleotides, which may cause neuronal dysfunction and degeneration. The aging dog brain accumulates carbonyl groups, a measure of oxidative damage to proteins (Head et al. 2002; Skoumalova et al. 2003). Typically, the activity of endogenous antioxidants balances the production of free radicals. However, several of these protective mechanisms decline with age. Carbonyl groups are associated with reduced endogenous antioxidant enzyme activity/protein levels, including those of glutamine synthetase and superoxide dismutase (SOD) (Head et al. 2002; Hwang et al. 2008; Kiatipattanasakul et al. 1997; Opii et al. 2008). The end products of lipid peroxidation (oxidative damage to lipids), including 4-hydroxynonenal (4HNE) (Hwang et al. 2008; Papaioannou et al. 2001; Rofina et al. 2004, 2006), lipofuscin (Rofina et al. 2006), lipofuscin-like pigments (Papaioannou et al. 2001; Rofina et al. 2004), or malondialdehyde (Head et al. 2002); all of these increase with age in the canine brain. In addition, there are several reports of increased oxidative damage to DNA or RNA in the aged dog brain (Cotman and Head 2008; Rofina et al. 2006).

The consequences of increasing oxidative damage with age in dogs may be compromised neuronal function leading to deficits in cognition. In aged pet dogs, higher levels of oxidative end products are correlated with more severe behavioral changes (Rofina et al. 2004, 2006; Skoumalova et al. 2003). Similarly, in studies of laboratory beagles, higher protein oxidative damage (3-nitrotyrosine) and lower endogenous antioxidant capacity (SOD and glutathione-S-transferase activities) in aging animals are associated with poorer prefrontal-dependent learning and spatial learning (Opii et al. 2008). The mitochondria are a critical contributor to oxidative damage, being a source of free radicals that damage proteins, lipids, and DNA/RNA (Shigenaga et al. 1994). Mitochondria isolated from young beagle brain have lower levels of reactive oxygen species production than those isolated from older beagles (Head et al. 2009). Due to the similarities in oxidative damage in dogs and humans,

several research groups have suggested that the canine is particularly well suited for studies focused on this mechanism of neurodegeneration (Dowling and Head 2012; Romanucci and Della Salda 2015).

5.6 Inflammation

Neuroinflammation in the aged human and AD brain may lead to the exacerbation of cognitive decline or potentially mediate other neuropathological events causing dementia (Heneka et al. 2015; Wilcock 2013). Although not as well characterized as neuroinflammation in the human brain, there are several small studies in aged pet dog brains. In a recent study, Schutt and colleagues (Schutt et al. 2016) measured canine cytokines in the prefrontal cortex of 15 aged dogs as compared with 2 young dogs. Pro-inflammatory cytokines were generally at low levels and were not associated with the extent of cognitive dysfunction. However, using measures of glial activation (microglial cells and astrocytes), increasing numbers of both types of cells were associated with more extensive CCD in a study of 37 dogs with various breeds included (Ozawa et al. 2016). Similarly, the level of S100β astrocytosis, a putative measure of inflammation, is also correlated with cognitive deficits in pet dogs (Pugliese et al. 2006).

5.7 White Matter Pathology

White matter degeneration can contribute to cognitive decline in humans (Bartzokis 2004; Gold et al. 2012). In a study of myelin protein levels as a function of age in dogs, Chambers et al. report a loss of prefrontal myelin protein (Chambers et al. 2012) that was also associated with some Aβ deposition in CAA. In another study, the extent of ubiquitin labeling in aging dog brains (n = 37) was associated with CCD and is thought to reflect failures in the protein homeostasis in the synapse or in myelin (Ozawa et al. 2016).

5.8 Summary

Identifying neurodegenerative mechanisms underlying cognitive dysfunction in aging dogs will provide novel targets for future intervention studies. These treatments may involve lifestyle changes (e.g., exercise can lead to enhanced neurogenesis and benefit cognition in dogs (Intlekofer and Cotman 2013; Snigdha et al. 2014)), diet changes (e.g., antioxidant diets (Cotman et al. 2002)), removal of Aβ by vaccines (Cotman and Head 2008), or pharmacological manipulations. As more of the gaps in our knowledge are filled, we may learn more of the role of vascular factors and inflammation in canine brain aging, which are also modifiable and may lead to cognitive benefits.

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