AGED BEAGLE DOGS DEMONSTRATE REDUCED BRAIN METABOLISM MEASURED BY FDG-PET-MR

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Novel models with greater translational value have been recognized as being necessary for evaluating Alzheimer's disease (AD) therapeutics. Here we describe several features of the aged dog that supports its value as a) a model of AD progression, and b) as a tool for either rapid or longitudinal screening of novel AD therapeutics. The aging dogs models aspects of both the pathophysiology and cognitive decline observed in Alzheimer's disease progression. The current study assessed the effects of age and task on brain-region specific uptake of ^{18}F-FDG in young and aged dogs.

PATHOLOGY

Aged dogs exhibit both early stage amyloid-β and tau pathologies

Canine amyloid-β (Aβ) protein precursor shows approximately 98% homology to the human sequence and the protein is processed into Aβ isoforms that are analogous in concentration and identical in sequence to that seen in humans (Fig. 1).

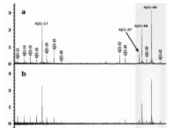

Fig. 1. Representative MOLDI-TOF mass spectra from (a) human and (b) canine CSF samples showing a similar pattern of Aβ isoforms (adapted from Portelius et al., 2010).

Endogenous Aβ is naturally deposited into plaques of the diffuse subtype in aged dogs, which are vulnerable to post translational modification and are fibrillar at the ultrastructural level - cerebral amyloid angiopathy (CAA) is also found in aged dogs. The pattern of Aβ deposition parallels that seen in humans and occurs over a 3- to 4- year window permitting the examination of interventions that may slow or halt deposition (Fig.2).

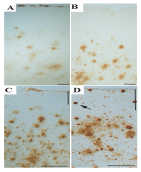

Fig. 2. Cortical Aβ deposition visualized using immunohistochemical staining in (A) cognitively normal aged human (B) cognitively normal aged Beagle, (C) cognitively impaired aged Beagle, and (D) Alzheimer's patient (Adapted from Head et al., 2000).

Oligomeric Aβ is also increased in the aged brain (Fig. 3).

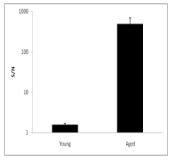

Fig. 3 Signal to noise (S/N) ratio for detecting oligomeric forms of Aβ in brains of young and aged Beagles. Oligomeric Aβ is exponentially higher in aged dogs, as is variability, compared to young dogs using the A4 assay developed by Amorfix (Toronto, Canada).

Intraneuronal hyperphosphoylated tau is also detected in aged dogs that is similar in some respects to the neurofibrillary tangle pathology seen in AD (Fig. 4).

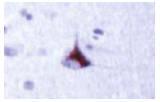

Fig. 4. Immunohistochemical stain with mAb tau AT-8 in aged dog brain in the cerebral cortex (adapted from Papaioannou et al., 2001).

Additional correlates of AD in aged dogs include:

1)Increases in oxidative stress;
2)Neuronal loss and reduced neurogenesis;
3)Reduced markers (e.g. N-acetyl aspartate) of neuronal health;
4) Cholinergic deficits; and
5)Cortical atrophy (Fig. 5).

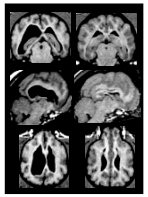

Fig. 5. Magnetic resonance imaging (MRI) of an aged (left panel) and young (right panel) Beagle. The aged (cognitively impaired) Beagle shows prefrontal and hippocampal atrophy as well as increased ventricular volume compared to the young, cognitively intact, Beagle (see Tapp et al., 2004).

COGNITION

Aged dogs show domain specific and progressive cognitive decline

Aged dogs show cognitive impairment that is correlated with pathology and is domain specific, such as on measures of selective attention (Fig. 6).

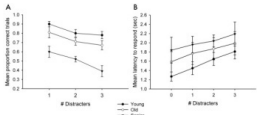

Fig. 6. A variable object discrimination task reveals both age related deficits in performance (A) and processing speed (B) in Beagles.

EFFECT OF AGE ON BRAIN METABOLISM

Methods

^{18}F-FDG PET-MR data were acquired on six young (mean age 2.3 years) and six aged (mean age 12.6 years) dogs. Repeatability was examined using two scans separated by 48 hours, and effect of cognitive load was assessed following simple object discrimination learning and more complex variable object discrimination (Fig. 7). An isotropic anatomical atlas of the canine brain was developed using six T_1-weighted anatomical MR scans (Mean age=6.66 years) registered to form an average MR brain template for region of interest analysis (Fig. 8). Effect of age and task on region specific uptake (% ID/g normalized to cerebellum) was evaluated using repeated-measures ANOVA.

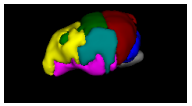

Fig. 7. Example of generated brain atlas used for region of interest analyses.

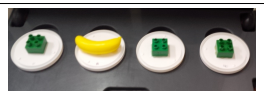

Fig. 8. Dogs were trained to respond to one (e.g, banana) of two objects in simple object discrimination learning. In the variable paradigm, the incorrect object distractor was also presented (0-3 times per trial).

Results

Repeatability at 48 hours

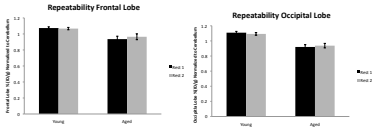

Fig. 9. FDG uptake in young and old dogs. Repeatability across 48 hours was excellent [p<0.002], especially in young dogs. Error bars represent SEM.

Effect of age on FDG uptake

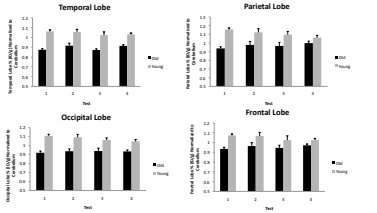

Fig. 10. FDG uptake in young and old dogs across brain regions. Uptake was significantly lower in aged compared to young dogs across several brain regions. Error bars represent SEM.

Effect of task on FDG uptake

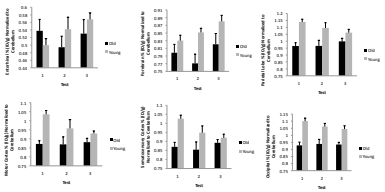

Fig. 11. FDG uptake varied by task condition primarily in young dogs. In entorhinal and forebrain, uptake increased with task difficulty. Reduced uptake was also evident in other brain regions. Error bars represent SEM.

CONCLUSIONS

1) **The aged dog is a unique natural model of AD progression.**
2) **Aβ pathology in aged dogs shows similar deposition, identical protein isoforms and oligomeric forms as those seen in humans.**
3) **Additional pathology includes the development of tau-like pathology, increases in oxidative stress, neuronal loss , decreased neurogenesis, reduced neuronal health, cholinergic deficits and brain atrophy.**
4) **The pattern and progression of cognitive decline in translational neuropsychological tests are consistent with that seen in AD conversion.**
5) **Here we examined the effects of age and task on uptake of FDG in young and aged dogs. FDG uptake measures were highly repeatable in scans separated by 48 hours.**
6) **FDG uptake was significantly lower in aged dogs compared to young dogs across several brain regions, indicating that brain metabolism declines with age.**
7) **There was evidence that FDG uptake varied by task, particularly in young dogs, which may reflect efficient recruitment of task-dependent brain regions. However, additional studies are warranted to confirm this.**
8) **Collectively, this supports the use of aging dogs for examining disease modifying AD therapeutics targeting early stages of the AD and suggests that FDG-PET may provide a useful biomarker in these endeavors.**

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