

The Canine as a Model of Human Brain Aging

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Cognitive function declines with age

- Like humans, dogs naturally develop signs of cognitive decline (Milgram et al. 1994; Head 1995; Tapp et al. 2003), and with age brain atrophy in dogs often resembles that seen in the human Alzheimer's brain.
- The aged canine brain shows accumulation of human-type A β , but not tau (Cummings 1996; Head et al. 1998). In addition oxidative damage to proteins and lipids, caspase activation and other mitochondrial impairments are present.
- Over the past several years, we have used the aged canine as a model to evaluate the effect of "lifestyle changes" on these risk factors.
- This has led to identification of **diet** and **exercise** as two major contributors to improving cognitive decline with age.

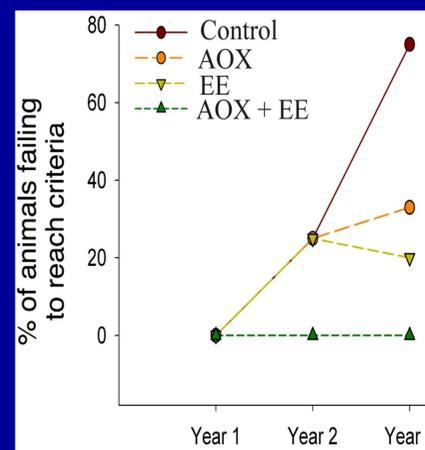
Enrichment for the aging brain

- Play toys
- Kennel-mate
- 3x/wk exercise
- Cognitive experience



Diet and enrichment improve brain aging – results from a 3-year study

Behavior results



Task: Object Size B/W discrimination

Molecular results

- Reduced amyloid pathology (Pop et al.)
- Reduced protein oxidation levels (Opie et al., 2008)
- Improved mitochondrial function (Head et al., 2009)
- Reduced caspase 3 production (Snigdha et al., 2012)

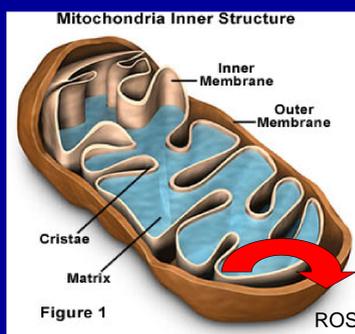
Diet for the aging brain

Antioxidants

- dl-alpha tocopherol acetate: 1050 ppm (20 mg/kg - 800 IU/day)
- Stay-C (ascorbyl monophosphate): 100 ppm (~100 mg/day)
- Spinach, carrot granules, tomato pomace, citrus pulp, grape pomace: 1% each in exchange for corn (Increased ORAC by 50%, equivalent to 4-5 servings of fruits and vegetables/day)

Mitochondrial cofactors

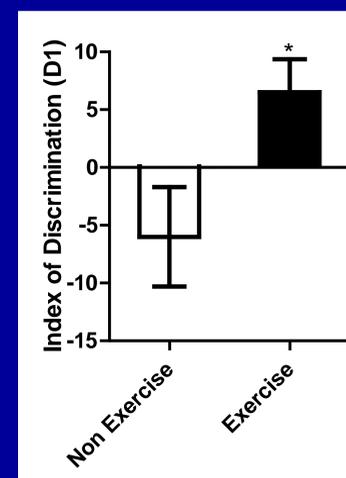
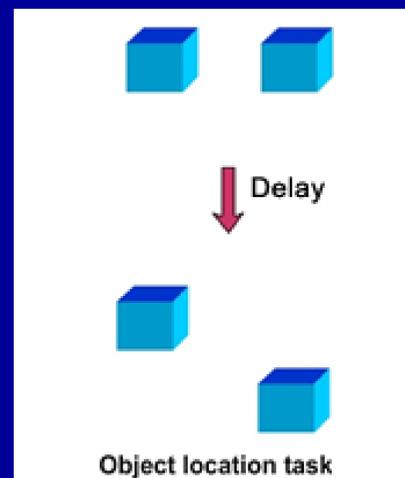
- dl-Lipoic acid: 135 ppm (2.7 mg/kg)
- l-carnitine: 300 ppm (6 mg/kg)



AOX: control environment/antioxidant diet; EE: behavioral enrichment/control diet; AOX+EE: behavioral enrichment/antioxidant diet, n=10/group

Exercise alone can facilitate cognition

Effect of acute post-trial exercise (10 minutes) on an object location memory (OLM) Task (24-hour inter trial interval)

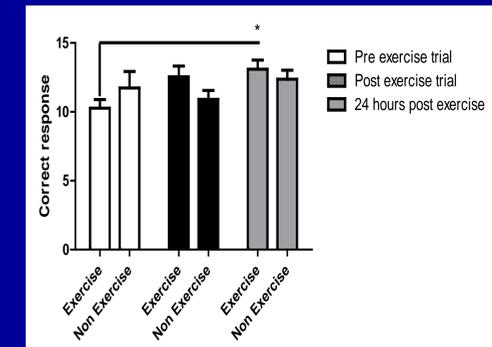


Discrimination index shows a significant difference between the two groups 24 h after the exercise. * $p < 0.05$. Significant difference between exercise and control group, with only the animals in the exercise group successfully discriminating novel location from familiar. $n = 6-8$ /group.

Exercise alone can facilitate cognition

Effect of Acute Exercise on a Concurrent Discrimination Task

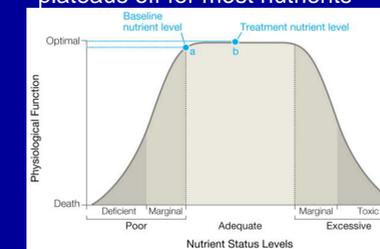
- Concurrent Discrimination Task measures ability of animals to remember object-object associations in the presence of active interference
- Day 1: preference testing, Day 2: baseline performance, followed by 10 min exercise and retesting Day 3: re-testing 24 h after the preceding day's exercise



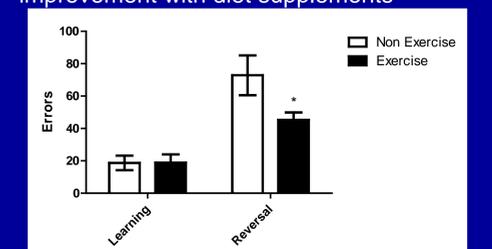
At 24 h post-exercise the animals in the exercise group were significantly improved compared to the pre exercise trial. * $p < 0.05$, $n = 11$ /group.

Exercise can facilitate cognition even when diet is already optimal

Physiological function improves with nutrient level and then plateaus off for most nutrients



Effect of exercise on a reversal learning task in animals that showed no additional improvement with diet supplements



Significant difference between exercise and control groups in the number of errors to reach criterion in the reversal phase of the task. * $p < 0.05$, $n = 11$ /group

Conclusions

- Exercise rather than further dietary supplements (when diet is optimal) would better serve brain health in aging.
- Exercise results in an increased number of synapses and higher protein levels, reflecting synapse growth.

Future Directions

- Extend investigations to human studies, in a new trial called EXERT
- Evaluate the molecular mechanisms that underlie the effects of exercise in the aging brain
- Investigate possible epigenetic mechanisms underlying synaptic changes observed with exercise

Acknowledgments

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