Exercise and Brain Health

John A. Stanford, PhD
Molecular & Integrative Physiology
University of Kansas Medical Center

The scope of Alzheimer’s Disease
• 5.4 million Americans
• Age associated
  • 65 years: 1 in 9
  • 85 years: 1 in 3
• Health care burden

Effect of Medications on AD Course

Initiate Medications
Donepezil
Galantamine
Rivastigmine
Cholinesterase inhibitors
Namenda
Investigational Medicines

- Approved drugs alleviate symptoms but do not stop the underlying disease.
- Current investigational disease-modifying medications are primarily focused on amyloid:
  - Tricking the body into digesting amyloid by tagging it with an antibody (like when you have an infection)
  - Blocking the formation of amyloid

Results of Amyloid Therapeutics

- 2005: AN1792, active Abeta vaccination (Phase 2)
  - 480 participants - halted due to neuroanamnestic
  - Freeze-dried spray to brain despite intramuscular injection
- 2006: Piramost (Deserfin) reduces amyloid levels
  - 1486 total 40 participants no evidence of efficacy
- 2006: Alphamast (Transplant) inhibits Abeta formation and deposition
  - 1592 total 40 participants no evidence of efficacy
- 2006: Semagacestat: gamma secretase inhibitor
  - 350 total 50 participants halted early due to greater rates of progression
- 2012: Petocestat: antibody for amyloid
  - No efficacy in these patients with or without the familial genetic risk
- 2006: Solanezumab, antibody for amyloid
  - Minimal clinical benefit in 2008 patients with known elevated amyloid burden
- 2017: Verubecestat: BACE inhibitor blocks the first step in amyloid formation
  - Halted early due to no effect
- 2018: Azeliragon: RAGE inhibitor thought to block a key element of plaque formation
  - Halted early due to no effect
- 2018: Crenezumab: antibody for amyloid
  - Halted early due to no effect

Natural Selection – beneficial traits that are inheritable increase in frequency over time.
1) Physical activity/fitness/strength obligatory for survival
2) Thrifty Genes – highly efficient - store and conserve energy
Physical Activity: Then vs. Now

<table>
<thead>
<tr>
<th>Group</th>
<th>Steps/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paleolithic Stone Agers</td>
<td>24,000</td>
</tr>
<tr>
<td>Amish</td>
<td>18,000 (men) / 14,000 (women)</td>
</tr>
<tr>
<td>Colorado</td>
<td>6,733 (men) / 6,384 (women)</td>
</tr>
<tr>
<td>Total (26 studies) with 2767 subjects</td>
<td>7,473 (range, 2,140–12,371)</td>
</tr>
<tr>
<td>Drew (Pennington)</td>
<td>Mean = 5,000</td>
</tr>
<tr>
<td>11% of subjects</td>
<td>5,117</td>
</tr>
</tbody>
</table>

2. Hill et al. / Med Sci Sports 37, 1194, 2005
4. Katie Mikus and Tim Church (personal communication)

>90% of US citizens do not get enough exercise

What kind of exercise?

- Aerobic
- Resistance
- Stretching
- Balance Training
### Guidelines

- ≥150 minutes/week moderate aerobic activity or ≥75 minutes vigorous aerobic activity (HHS, ACSM, WHO)
- Resistance exercise at least 2 days/week (HHS, ACSM, WHO)
- Flexibility (e.g., yoga) 2-3 days/week (ACSM)
- “Neuromotor” (functional, balance) 2-3 days/week (ACSM, WHO)

---

### Evidence?

---

### Exercise

- Benefits patients with dementia

---

*Depts. Health & Human Services (2018)*

*American College of Sports Medicine (2011)*

*World Health Organization (2012)*
Exercise

- Decreases risk of cognitive decline

Exercise

- May prevent Alzheimer's disease!

Exercise, Hippocampal Volume, and Memory Performance in Older Adults


Improving Fitness -> Bigger Brain

Hyperinsulinemic-euglycemic clamp shows insulin resistance in AD

Impaired meal-stimulated metabolic response in AD
CNS insulin resistance in AD

Receptors widely distributed
Increasing plasma insulin increases insulin binding in hippocampus

Neurotransmission
Cell survival
Amyloid clearance
Tau phosphorylation
Energy production

Morris et al. 2012

Insulin resistance is negatively correlated with brain volume in aging and AD

Morris et al. 2014, Neuroscience

Cerebral glucose hypometabolism: a marker of AD

Impaired fasting glucose and progression of cognitive impairment

<table>
<thead>
<tr>
<th>Measure Timepoint</th>
<th>Normoglycemia</th>
<th>Impaired Glycemia</th>
<th>p-value (2yr D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCI to AD converters*</td>
<td>Baseline</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>CDR-SB*</td>
<td>Baseline</td>
<td>1.56 (0.86)</td>
<td>1.61 (0.84)</td>
</tr>
<tr>
<td>Global Cognition*</td>
<td>Baseline</td>
<td>−0.615 (0.55)</td>
<td>−0.761 (0.61)</td>
</tr>
<tr>
<td>Whole Brain Volume*</td>
<td>Baseline</td>
<td>0.677 (0.027)</td>
<td>0.672 (0.02)</td>
</tr>
<tr>
<td>Hippocampal Volume</td>
<td>Baseline</td>
<td>0.655 (0.90)</td>
<td>0.642 (0.08)</td>
</tr>
</tbody>
</table>

Taylor et al., Am J Clin Nutrition, 2017

Impaired fasting glucose is related to regional cerebral amyloid

Morris et al., 2016, NBA

Glycemic intake is related to regional cerebral amyloid

Taylor et al., Am J Clin Nutrition, 2017

Morris et al, NBA

NG vs. IFG cerebral amyloid
Potential therapies (metabolism)

- Intranasal insulin
- Insulin sensitizers
- Mediterranean diet
- Ketogenic diet
- Exercise

AD and ND subjects differ in fitness

- AD subjects have lower VO2 peak (Vidoni et al. 2012)
- Greater decline in VO2 over time
- Confounding effects of sex, genotype?

Exercise in Aging and AD

- BAP (Brain Aging Project: 2006-2008)
  - Longitudinal observational study, ND and AD
  - TEAM (Trial of Exercise on Aging and Memory: 2008-2015)
    - Exercise trial, cognitively healthy elderly
    - Exercise trial, probable AD
  - APEX (Alzheimer’s Prevention through Exercise: ongoing)
    - Exercise trial, cognitively healthy elderly “at risk” for AD
TEAM (Cognitively healthy elderly)

Over 6 months
- AEx group maintained (+1.5)
- ST group declined (−4.5)

Normal course of AD equates to loss of 1 point per month

Morris, Vidoni et al. 2017, Plos ONE

ADEPT (Alzheimer’s Disease)

Aerobic Exercise

ST control

Over 6 months
- AEx group maintained (+1.5)
- ST group declined (−4.5)

Normal course of AD equates to loss of 1 point per month

Morris, Vidoni et al. 2017, Plos ONE

Fitness change tracks with memory change in exercising AD subjects

Morris, Vidoni et al. 2017, PLOS One
Summary of past KU ADC trials

- Modest fitness gain overall in AD compared to ND elderly
  - Good compliance and benefit in functional fitness (6 min walk)
- Subjects with early AD may have a limited or more variable physiologic response to exercise
  - Disease severity
- Do inherent physiological differences limit cardiorespiratory fitness response?
  - Can these differences be overcome (and underlie benefit)?

ADMIT – Aging and Disease Mitochondria

Cross sectional study, 2 visits
- Visit 1: Cardiorespiratory fitness assessment (treadmill)
- Visit 2: Fasting blood draw & muscle biopsy

Goals:
- 1) Compare mitochondrial energy metabolism in cognitively normal elderly and mild cognitive impairment
- 2) Determine the relationship between muscle mitochondrial metabolism and whole-body cardiorespiratory fitness

MCI subjects exhibit impaired mitochondrial function in muscle
Mechanisms

- Increased blood flow/vascularization
- Neurotrophins (e.g., BDNF; IGF-1)
- Neurogenesis
- Reduce aggregation of pathogenic proteins

Rodent Exercise Protocols

Endurance/Aerobic

Resistance

Exercise in a Tau Pathology Mouse Model

Belardi et al., 2011
Strength training in rats?

Isometric Forelimb Press-While-Licking Task

Aged Sprague-Dawley Rats

From Fowler et al (1990)
Behav Neurosci 104:449-456
Isometric forelimb force training increases bone mineral density

Rat Groups: LCR and HCR

- Low Capacity Runners (LCR):
  - Greater body weight
  - Lower metabolism
  - Lower voluntary wheel running
  - Cognitive deficits and ↑pTau @ 22 months

LCR vs HCR Data
Task Engagement

Resistance Exercise Performance

Heat-Treatment, Exosomes & β-Amyloid Accumulation
HSP72 in Exosomes from Trained LCR Rats = HCR Rats

Value of Delaying AD Onset

Per capita annual cost of care of person 70+ years old (2010 dollars)

Value of Treatment

Per Capita Health Effects, Formal and Informal Costs of 70–74 Year Olds For Status Quo and Year(s) Delay In Onset Scenarios.
Conclusions

- Exercise should be prescribed for all adults
- Exercise may preserve brain health by improving central metabolic function
- Preclinical studies are essential to determine mechanistic effects of exercise
- Resistance training systemically upregulates HSPs; further research is needed to determine central effects
- Compliance with prescribed exercise protocols would lead to significant increases in quality of life and financial savings

Acknowledgements

- Stephen C. Fowler, PhD
- Jon Pinkston, PhD
- Paige Geiger, PhD
- John Thyfault, PhD
- Jill Morris, PhD
- Eric Vidoni, PhD
- Kim Stanford, MS
- James Odum
- Alex Rorie
- T.J. Murray
- Emma Renwick
- Fengyan Deng, PhD
- Mark Johnson, PhD
- Mark Dallas

NIH grants AG023549, GM103418, AG026491, HD57850, Kansas City Area Life Sciences Institute, KIDDRC, Lied Foundation

Thank you!