NEUROPROTECTIVE EFFECTS OF EXERCISE

СИНТИЯ РОБИНСОН, ДОКТОР НАУК,
СПЕЦИАЛИСТ ПО ФИЗИЧЕСКОЙ ТЕРАПИИ
ОТДЕЛЕНИЕ РЕАБИЛИТАЦИОННОЙ МЕДИЦИНЫ
УНИВЕРСИТЕТ ВАШИНГТОНА
Г. СИЭТЛ, ВАШИНГТОН
США

THE AGING BRAIN

- Human brain begins to atrophy in 3rd decade of life
  - Alterations in structure and function
    - Frontal
    - Parietal
    - Temporal regions

Jernigan et al, 2001

THE AGING BRAIN

- Alterations in activity of neurons
  - Hippocampus
  - Frontal cortex
- Alterations in synaptic morphology
- Chronic inflammatory changes of immune system
  - Microglia/monocytes
  - Astrocytes
- Neurovascular Unit
  - Provides structural and functional basis for blood brain barrier
  - Changes associated with cerebrovascular alterations

Laitman & John, 2015

THE AGING BRAIN

- Changes in cerebrovascular function
  - Cerebral microvascular pathology
  - Reductions in cerebral blood flow
  - Reductions in glucose metabolism
  - Reductions in oxygen metabolism
  - Vascular leakage per high-resolution MRI and electron microscopy
    - Begins in hippocampus

Laitman & John, 2015

NEURODEGENERATIVE DISEASES

- Disease processes affecting cognition
  - Mild cognitive impairment (MCI)
  - Dementia
  - Alzheimer's disease (AD)

- Alterations in brain structure and function exceed those expected for age and educational level
  - Frontal
  - Parietal
  - Temporal
  - Most profound atrophy of hippocampus

Kirk-Sanchez & McGough, 2014
Pedersen et al, 2014

EXERCISE EFFECTS ON BRAIN

- Exercise is essential to maintenance of
  - Physical function and physiologic health
  - Brain health and cognitive performance

- Human brain responds to moderate aerobic exercise
  - Regions vulnerable to age- and disease-related atrophy
  - Alterations in structure and function

- Epidemiological studies report reduced risk for MCI and dementia in older adults who maintain higher levels of physical activity

Kirk-Sanchez & McGough, 2014

EXERCISE EFFECTS ON BRAIN

- Strong association of physical exercise with age-related declines in
  - Cognitive function
  - Sensorimotor function

- Exercise is associated with
  - Improved cardiovascular function
  - Improved blood flow within the CNS
  - Angiogenesis
  - Neurogenesis

- Molecular events responsible for this protective effect are not completely understood.

Laitman & John, 2015

EXERCISE EFFECTS ON BRAIN

Animal Studies

- Exercise strongly protects against neurovascular decline in aged mice
  - Improved behavioral outcomes
  - Improved markers of neuroplasticity
  - Reduced inflammation
  - Reduced complement induction

- Potential molecular mechanisms
  - Astrocytic ApoE decreases in aged mice
    - Associated with age-related neurovascular decline
    - Risk factor for Alzheimer's disease
  - Exercise protects against this reduction in ApoE levels

Laitman & John, 2015

EXERCISE EFFECTS ON BRAIN

Animal studies

•Exercise preconditioning exhibits neuroprotective effects after cerebral ischemia in rats

- 3 groups with 7 rats each
  - Control, Ischemia, Exercise + ischemia
- Run on treadmill 10-15 minutes at 5-7m/min, 5 days per week for 4 weeks

- Induced transient global cerebral ischemia
- Exercise + ischemia group demonstrated
  - Reduced rate of apoptotic and necrotic cell death in hippocampal CA1 neurons
  - Amelioration of ischemia-induced memory loss

Shamsaei et al, 2015

EXERCISE EFFECTS ON BRAIN

- Potential mechanisms by which preconditioning protects neurons
  - Alleviate over-activation of glutamate, which aggravates neuronal damage
  - Improved anti-oxidant capacity by blocking free radical formation
  - Tumor necrosis factor (TNF)-α mediates inflammation
  - Up-regulation of heat shock protein (HSP)-70 exerts effects through over-expression of anti-apoptic (pro-survival) proteins
  - Up-regulation of neurtrophic factors
    - Brain-derived neurotrophic factor (BDNF)
    - Nerve growth factor (NGF)

Shamsaei et al, 2015

CARDIOVASCULAR RISK FACTORS

- Risk factors include
  - Hypertension (HTN)
  - Elevated cholesterol
  - Metabolic syndrome
    - Type 2 diabetes
    - Inflammation
  - Insulin resistance

- Cardiovascular risk factors are associated with
  - Cognitive decline
  - Brain atrophy

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS HYPERTENSION

- Hypertension (HTN) is associated with
  - Reduced cerebral blood flow and metabolism
    - Frontal, temporal and subcortical regions
  - White matter disease and atrophy

- HTN is associated with
  - Midlife reduction in cognitive performance
  - Later life mild cognitive impairment (MCI) and dementia

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS HYPERTENSION

- Pharmacologic management of HTN
  - Associated with neuroprotective effects
    - Less white matter disease
    - Elimination of increased risk for cognitive decline

- Prevention and management of HTN with exercise
  - Enhanced cerebral blood flow
  - Reduced brain tissue pathology
  - Protective effect
    - Brain health
    - Cognitive performance

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS METABOLIC SYNDROME

- Associated with significantly increased risk for cognitive impairment among older adults
  - 23% increased risk per unit increase in number of abnormal factors
    - Body mass index (BMI)
    - Elevated triglycerides
    - Low levels of high-density lipoprotein cholesterol (HDL)
    - Hypertension (HTN)
    - Hyperglycemia

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS METABOLIC SYNDROME

- High levels of inflammatory markers associated with cognitive decline
  - Interleukin-6
  - C-reactive protein

- Lower levels of inflammatory markers associated with exercise in older adults
  - Interleukin-6
  - C-reactive protein

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS INSULIN RESISTANCE

- Insulin resistance in older adults is associated with reduced
  - Brain health
  - Cognitive performance

- Elevated plasma insulin levels associated with
  - Increased inflammatory agents

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS INSULIN RESISTANCE

- **Aerobic exercise** associated with improvements in
  - Cardiorespiratory fitness
  - Glucose tolerance
  - Function within several cognitive domains

- Positive effects of exercise may be related to
  - Improved cardiovascular function
  - Improved cerebral vascular function
  - Reduced inflammation
  - Enhanced insulin-dependent energy metabolism

Kirk-Sanchez & McGough, 2014

CARDIOVASCULAR RISK FACTORS AND EXERCISE

- Well-established relationship
  - Exercise
  - Reduction of cardiovascular risk factors

- Unclear relationship
  - Exercise
  - Cognitive performance

  - Not clear which cardiovascular factors serve as mediators

Kirk-Sanchez & McGough, 2014

NEUROTROPHIC FACTORS AND EXERCISE

- Neuroprotective neurotrophins influence select regions of the brain, including the hippocampus
  - Facilitate plasticity
  - Enhance neurovasculature

Kirk-Sanchez & McGough, 2014

NEUROTROPHIC FACTORS AND EXERCISE

- Exercise associated with increased release of neuroprotective neurotrophins
  - Brain-derived neurotrophic factor (BDNF)
    - Regulate growth, maintenance, and survival of neurons in adult brain
    - Short-term and long-term aerobic exercise
    - 3 months aerobic endurance training → 4-fold increase in BDNF
  - Insulin-like growth factor (IGF-1)
    - Promotes neuronal growth, survival and differentiation
    - 6 months moderate to high level resistance training

- Majority of data comes from studies including young adults
  - Carry-over to older populations is not known

Kirk-Sanchez & McGough, 2014

SPECIFICITY OF TRAINING

- Animal models reveal that different types of training produce different changes in the brain
  - High-demand acrobatic training
    - Synaptogenesis – new circuits in response to novel learning experiences
  - Forced exercise
    - Increased angiogenesis in cerebellum
  - Voluntary exercise
    - Increased angiogenesis in cerebellum
  - Control group

Kirk-Sanchez & McGough, 2014

INTENSITY & VARIETY OF TRAINING

- Doetinchem Cohort Study, n=1,927, 6- and 11-year follow-ups
  - Intensity and variation, but not duration, of physical activities positively associated with cognitive function
    - Processing speed
    - Memory
    - Mental flexibility
    - Overall

Kirk-Sanchez & McGough, 2014

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

Cochran review of 11 randomized controlled trials (RCTs)

•Physical activity intended to improve cardiorespiratory fitness in order to improve cognitive function

- Average 14% increase in maximal oxygen consumption (VO_2 max)
- Large effects on
  - Motor function
  - Auditory attention
- Moderate effects
  - Cognitive speed
  - Visual attention

Angevaren et al, 2008

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Cardiovascular fitness (VO_2 max) in individuals with early Alzheimer's disease compared to non-demented controls is associated with
  - MRI-measured whole brain volume (Burns et al, 2008)
  - Gray and white matter volume of medial temporal and parietal regions (Honea et al, 2009)

- Findings suggest that cardiorespiratory fitness may offer a protective effect by modifying Alzheimer's disease-related changes in brain structure

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Brain regions characterized by reduced gray matter and white matter volume with age
  - Closely mirror brain regions preserved with exercise (Colcombe et al, 2003)

- Higher cardiorespiratory fitness levels are associated with
  - Preservation of hippocampal volume
  - Better spatial memory task performance (Erickson et al, 2009)

- Higher estimated VO_2 max is associated with
  - Greater brain activation in regions associated with executive control
  - Less brain activation in areas believed to interfere with executive control (Colcombe et al, 2004)

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Optimal exercise dosage is not known
  - Positive relationship among older adults between
    - Higher dose
    - Cognitive health

- Higher exercise intensity (7.8±3.9MET versus 0.63± 7.4 MET hours per week) is associated with preservation of brain volume
  - Exercise volume seems to moderate brain volume, especially in the medial temporal lobe (key area for executive function and memory)

- Exercise volume found to be protective
  - Approximates recommendations for all older adults
  - 7.8 MET is roughly equivalent to moderate exercise for 30 minutes 5 days per week

Kirk-Sanchez & McGough, 2014

CARDIORESPIRATORY FITNESS AND BRAIN HEALTH

- Research findings from cross-sectional and prospective longitudinal studies (Kirk-Sanchez & McGough, 2014)
  - higher levels of physical activity
  - Provide protective benefit against cognitive decline

- Positive effects of aerobic exercise training have been demonstrated in diverse populations
  - Frail older adults (Hayes et al, 2014)
  - Post-stroke survivors (Hayes et al, 2014)

EXERCISE AND COGNITIVE PERFORMANCE

- Large **observational studies-** examine associations between midlife and late life activity and cognitive impairment
  - Lower risk for global cognitive decline
  - Lower risk for incident dementia

  - Honolulu-Asia Aging Study
    - 2,257 men followed for 3 decades
    - Men who walked <1 mile per day were at significantly greater risk (1.7-1.8) of dementia than men who walked >2 miles per day

  - Nurses' Health Study
    - 18,766 women followed for 10-15 years
    - Women ages 70-81 at time of follow-up who walked 90 minutes per week demonstrated higher cognitive scores than those who walked <40 minutes per week

Kirk-Sanchez & McGough, 2014

EXERCISE AND COGNITIVE PERFORMANCE

- **Randomized controlled trials** (RCTs) using **aerobic exercise** as an intervention demonstrate effects on cognitive performance in individuals with MCI
  - N=138, 24-week home **walking** program **versus educational** control (Lautenschlager et al, 2008)
    - Modest improvement in global cognition
      - Alzheimer's Disease Assessment Scale- Cognitive Subscale
  - N=29, 6 months **high intensity aerobic** exercise **versus stretching** control (Baker et al, 2010)
    - Improvements on tests of executive function
  - N=50, 12 month **aerobic** exercise program, 90 min per day, 2 times per week **versus education** control (Suzuki et al, 2012)
    - Better general cognitive function
    - Immediate memory
    - Language ability

EXERCISE AND COGNITIVE PERFORMANCE

- **Randomized controlled trials (RCTs)** using **aerobic exercise** as an intervention demonstrate effects on cognitive performance that can be related to
  - Changes in regional brain volume
    - White and gray matter in prefrontal and temporal cortices
    - Anterior hippocampal volume (2% ↑ vs 1.4% ↓)
  - Neurotrophin levels
    - Increased levels of brain-derived neurotrophic factor (BDNF)
  - Brain activation patterns
    - Increased activation in executive control regions
    - Decreased activation in other regions
    - Improved functional connectivity

Kirk-Sanchez & McGough, 2014

EXERCISE AND COGNITIVE PERFORMANCE

- **Resistance training** has also demonstrated positive effects on cognitive performance
  - N=63 men, 24-week, **moderate- and high-intensity** resistance exercise group (50% and 80% one repetition maximum for upper and lower body) **versus stretching** control (Cassilhas et al, 2007)
    - Improvements in several cognitive domains
    - Increased levels of insulin growth factor (IGF-1)
  - N=155 women, 12-month 1-2 times weekly **resistance** training **versus balance and toning** control (Lui-Ambrose et al, 2010)
    - Selective attention
    - Conflict resolution

EXERCISE AND COGNITIVE PERFORMANCE

- Few studies have investigated the effect of **multicomponent exercise** interventions on cognitive function
  - N=74, 6 months, home balance and strengthening program intended to reduce falls
    - Improved executive function, especially response inhibition
  - N=389, 1 year, Tai Chi versus stretching and toning control
    - Modest differences in memory and global cognition
    - High drop out rate
  - Tai Chi
    - Multiple physical components
    - Incorporates engagement across several cognitive domains
    - Older adults who performed Tai Chi and aerobic exercise demonstrated better memory performance than controls performing one or the other, or no exercise

Kirk-Sanchez & McGough, 2014

EXERCISE FOR PEOPLE WITH DEMENTIA

- Results of meta-analyses of exercise interventions for people with dementia
  - Do not consistently produce significant improvements in cognition
  - Do consistently produce improvements in
    - Physical performance
    - Behavior
    - Mood

- Dose may be a primary factor in effectiveness
  - Frequency
  - Intensity
  - Duration

Erickson et al, 2012

EXERCISE SUMMARY

- Results of observational studies support a dose-dependent neuroprotective relationship between physical exercise and cognitive performance in older adults.
- Longitudinal studies provide evidence that higher levels of physical exercise are protective against cognitive decline.
- Physical function likely improves prior to cognitive performance
  - Provides a stronger foundation for progression of exercise dose
    - Intensity
    - Frequency
    - Duration
- Duration of exercise programs
  - 16-20 weeks to improve cardiorespiratory fitness in older adults
  - 6-12 months may be necessary for cognitive changes to be measurable

Kirk-Sanchez & McGough, 2014

EXERCISE RECOMMENDATIONS

- **Aerobic exercise-** American College of Sports Medicine Guidelines (2009)
  - Frequency
    - Minimum 150 minutes moderate aerobic exercise per week (30 minutes, 5 days/week)
      OR
    - 60 minutes of vigorous exercise per week (20 minutes, 3 days per week)

    - Benefits can be achieved with 6-10 minute bouts of exercise, especially for individuals with limited capacity

  - Intensity
    - ≥60% of pretraining VO2 max

  - Duration
    - Minimum 16 weeks

Kirk-Sanchez & McGough, 2014

EXERCISE RECOMMENDATIONS

- **Resistance exercise-** American College of Sports Medicine Guidelines (2009)
  - Frequency
    - 2 days per week for major muscle groups
  - Intensity
    - Resistance equivalent to 60%-80% of one repetition maximum
      - Older, deconditioned, frail may begin at 40%-50%
    - Strengthening- adjusted to allow completion of 8-12 repetitions/set
      - 2-3 sets per exercise
      - 2-3 minutes rest between sets
      - Recovery period 48-72 hours
    - Endurance
      - Decrease intensity to 40%-50% one repetition maximum
      - Increase repetitions to 15-20 /set

Kirk-Sanchez & McGough, 2014

EXERCISE RECOMMENDATIONS

- **Neuromuscular fitness-** 2 days per week
  - Balance
  - Agility
  - Coordination

- **Flexibility-** 2 days per week

Kirk-Sanchez & McGough, 2014

EXERCISE RECOMMENDATIONS

- Structured training better than advice alone
- Individually designed program to accommodate physical and cognitive impairments
  - Promotes compliance and safety

Kirk-Sanchez & McGough, 2014

SUMMARY

- Human brain atrophies with age
  - Accelerated in presence of neurodegenerative diseases
  - Accelerated in presence of cardiovascular disease
- Exercise has been show to
  - Reduce symptoms of cardiovascular disease
  - Protect neural structures
  - Increase brain volume
- Effectiveness of exercise appear to be dependent
  - Dose- intensity, frequency and duration
  - Type- aerobic, resistance, high demand coordination
- Exercise can be safely prescribed in diverse populations
  - Frail, post stroke

THANK YOU

Questions?

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