Exercise induces BDNF, improves learning and reduces β-amyloid

Carl W. Cotman
Institute for Brain Aging
University of California, Irvine
Behavioral Interventions: The New Direction

Exercise

Mental Activity

Diet
Outline

Part 1. Can exercise induce neurotrophic factors and improve learning?
Part 2. Can exercise reduce pathology in a AD transgenic mouse and improve learning?
BDNF (Brain Derived Neurotrophic Factor) is a Synaptic Modulator:
BDNF – Brain Derived Neurotrophic Factor

• Necessary for learning and long term synaptic change
• Stimulates synaptic growth and neurogenesis
• Protects neurons from injury

How to get more?
• Simple - exercise
Is BDNF increased by exercise in the brain?

- Where? And how fast and long lasting?

- How much exercise?
Exercise increases BDNF mRNA

HIPPOCAMPUS:

Rats: 1 week exercise (male sprague-dawley, 3 months)

Berchtold et al., 2002
Time course of BDNF Protein Induction

**DAILY EXERCISE**

**ALTERNATING DAYS**

Berchtold, et al., submitted
So..what is the functional significance?

• Learning?

• Stress Relief?
Exercise Enhances Learning in the Morris Water Maze

### Graph

- **Y-axis:** Time to reach platform (sec)
- **X-axis:** Days of training

**Legend:**
- Sedentary
- Exercising

**Significance:**
- *p* < 0.05

**Days of training:**
- Day 1
- Day 2
- Day 3
- Day 4
- Day 5
- Day 6

**Notes:**
- * indicates statistical significance.
Blocking BDNF action (anti-TrkB) during the exercise period on memory retention using the probe trial on the Morris Water Maze task (Vaynman, et al., 2004)
Can exercise prevent the stress induced reduction in BDNF?

- Animals given 3 wks. of voluntary running
- Subjected to acute immobilization stress
- Circulating corticosterone and brain BDNF measured

**Hypothesis:** Exercise will offset the effect of acute stress, possibly via a reduction in levels of circulating corticosterone.
At 10 hours post-stress, BDNF is decreased in stressed animals, but remains elevated in animals that had prior exercise.

* Significantly different (p<0.05) from control sedentary
Many plasticity genes are regulated by BDNF, e.g.,

- **Synapsin**: Regulates presynaptic vesicle availability
  Modulates neurotransmitter release into synapse
  - Block TrkB in vivo suppresses exercise-induction of synapsin mRNA (Gomez-Pinilla, 2003)
- **CREB**: Transcription factor, drives downstream gene expression
  Important in LTP, learning and memory
  - Block TrkB in vivo suppresses exercise-induction of CREB (Gomez-Pinilla, 2003)
- **NR2b**: Subunit of glutamate receptor (NMDA)
  Overexpression enhances LTP and improves learning
  - Slice culture: BDNF increases NR2b protein
- **NARP**: Trafficking/insertion of glutamate receptors in PSD, critical to LTP and learning
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- **COX-2**: Traditionally known for immune function
  Role in plasticity: localized to dendrites
  - Slice culture: BDNF increases COX-2 protein
Practical Questions

• How long lasting is the increase after stopping exercise?
• How frequent is necessary
• Can the increase be recovered rapidly if exercise is stopped for a period?
Is there a molecular memory for exercise?

- Many of the gene changes including CREB are linked to learning and memory
- Is the experience of exercise encoded so to allow the brain to learn to respond?

Thus, if so exercise may prime the brain to respond to experiences, and induce a “state of readiness”.
How Often to Exercise?: Is there a Molecular Memory Exercise

Paradigm:
- 14 days of exercise:
  - Daily (during 2 weeks)
  - Alternating (during 4 weeks)
- Wheels locked:
  - 1 week, 2 weeks
- Second short run period (2 days)
- Note: 2 days exercise alone is not sufficient to increase BDNF

- Prior Exercise Primes subsequent BDNF Responsiveness
- Priming effect endures at least 2 weeks
- Equivalent Secondary Responsiveness if prior exercise is Daily Regime or Alternating Days of Exercise
HIPPOCAMPUS

Genomic regulation
- Structural change
  - vascular
  - neuronal
  - neurogenesis
  - Increased neuronal health

EXERCISE

Peripheral Factors

Blood Brain Barrier

Estrogen
Glucocorticoids

IGF-1

BDNF

other plasticity genes

Locus coeruleus (NE)
Raphe (5-HT)

Medial Septum (ACh/GABA)

Cotman & Berchtold (2002)
Estrogen-deprivation reduces baseline BDNF gene expression (Berchtold, et al., E.J. of Neurosc., 2001)
Exercise-induced BDNF increase is lost after 7 weeks of estrogen deprivation

*** significantly different from sedentary  p<.005
Estrogen-replacement increases BDNF mRNA level

**Graph:**
- **Y-axis:** BDNF mRNA expression (% sedentary intact)
- **X-axis:** DG, hilus, CA3, CA1
- **Legend:**
  - O VX-7
  - O VX-7/E

Significance:
- *** p < .005
- T p = .08
Exercise Further Increases BDNF, Specifically in the DG

![Bar graph showing BDNF mRNA expression levels in different brain regions under sedentary (SED) and exercise (EX) conditions.](image)

- **BDNF mRNA expression (% sedentary intact)**
- **Regions:** DG, hilus, CA3, CA1
- **Legend:**
  - SED (white bars)
  - EX (black bars)

**Significance:**
- **T p = .06**
- **** p < .005

Notes:
- DG: Significant increase with exercise.
- Hilus: Highest expression with exercise.
- CA3: Moderate increase with exercise.
- CA1: No significant change with exercise.
Hormone replacement (17-beta Estradiol) Restores Running Behavior
Is exercise effective in AD transgenic models?

- Will voluntary running improve learning and memory?
- Stimulate neurogenesis?
- Reduce β-amyloid in the brain?
Animal model

Widespread plaque deposition, including the hippocampus and cortex

Voluntary Exercise Paradigm
(Adlard, et al., 2005)

• Utilized TgCRND8 mouse model

• Voluntary access to running wheels (animals run ~3 miles/day)

• Short-term running
  - start at 6 weeks of age
  - sacrifice four weeks later

• Long-term running
  - start at 6 weeks of age
  - sacrifice 5 months later
Exercise improves the performance of TgCRND8 animals in the Morris water maze

![Graph showing the average escape latency (seconds) ± standard error over days 1 to 6 for sedentary and exercise groups. The graph includes stars indicating significance at p<0.02.]

* p<0.02
Long-term running reduces β-amyloid load in TgCRND8 animals
(by immunohistochemistry)
Long-term running reduces β-amyloid load in TgCRND8 animals (by ELISA)
Long-term running enhances neurogenesis in TgCRND8 animals.
Mechanism: Long-term running had -

• no effect on steady-state levels of the amyloid precursor protein, APP

• no effect on secretase activity levels (α, β, γ)

Does short term running affect APP processing?
Short-term running mediates APP processing

- no effect on total APP
- no effect on secretase activity (α, β, γ)
- no effect on neprilysin or IDE
Summary

- BDNF increases with exercise in the hippocampus within a few days and lasts
- BDNF induction can be rapidly restored by a brief period of exercise even after exercise is stopped for weeks
- Exercise improves the rate of learning
- Exercise reduces β-amyloid in the hippocampus and cortex
- Exercise alters APP processing
Summary Part 2

• Exercise in a transgenic AD mouse improves learning
• Exercise reduces β-amyloid in the hippocampus and cortex
• Exercise alters APP processing
Diet? What effect does an antioxidant diet have on cognition?
Can antioxidants and/or Exercise/Environmental Enrichment Delay the Development of Age Dependent Cognitive Dysfunction and Neuropathology in Canines?
Canine Antioxidant Diet

- **Antioxidants**
  - dl-alpha tocopherol acetate - 1050 ppm (20 mg/kg - 800 IU)
  - Stay-C (ascorbyl monophosphate) - 100 ppm
  - Spinach, carrot granules, tomato pomace, citrus pulp, grape pomace - 1% each in exchange for corn (Increased ORAC by 50%)

- **Mitochondrial cofactors**
  - dl-Lipoic acid - 135 ppm (2.7 mg/kg)
  - l-carnitine, Acetyl-car - 300 ppm (6 mg/kg)
Enrichment Protocol

- Play toys
- kennelmate
- 3x20 min walks
- additional cognitive experience

Controls
6 months
Learning Is Impaired in Old Canines

Aged dogs make more mistakes as task complexity increases.
**Effect of diet on oddity discrimination in aged beagles**

Diet fortified animals make few mistakes as task difficulty increases.
Is the intervention able to “reverse” age related cognitive dysfunction?
What effect, if any, do the treatments have on brain pathology?
Effect of Antioxidant Diet on Total Amyloid Load (6E10)

By Brain Region

<table>
<thead>
<tr>
<th>Brain Region</th>
<th>Amyloid Load (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prefrontal</td>
<td>4.0 (Control)</td>
</tr>
<tr>
<td></td>
<td>5.0 (Antioxidant)</td>
</tr>
<tr>
<td>Entorhinal</td>
<td>2.0 (Control)</td>
</tr>
<tr>
<td></td>
<td>3.0 (Antioxidant)</td>
</tr>
<tr>
<td>Parietal</td>
<td>7.0 (Control)</td>
</tr>
<tr>
<td></td>
<td>8.0 (Antioxidant)</td>
</tr>
<tr>
<td>Occipital</td>
<td>1.0 (Control)</td>
</tr>
<tr>
<td></td>
<td>1.5 (Antioxidant)</td>
</tr>
</tbody>
</table>

By Brain Region

- **Control Diet**
- **Antioxidant Diet**
Conclusion

• A growing clinical literature suggests that exercise and diet can delay the onset of cognitive decline and AD
• Animal models show that exercise induces BDNF, a key plasticity and neuroprotective factor
• Animal models show that exercise and diet can reduce β-amyloid levels
Summary Part 3

- A diet enriched in mitochondrial antioxidants improves learning in aged dogs
- Reduces β-amyloid accumulation
- Diet plus environmental enrichment is better than either alone
Reduced reactive oxygen species (ROS) production by mitochondria in treated aged dogs

![Mitochondria diagram](image)

**Figure 1**

<table>
<thead>
<tr>
<th>Time</th>
<th>% Increase in Reactive Oxygen Species Production</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 min</td>
<td></td>
</tr>
<tr>
<td>10 min</td>
<td></td>
</tr>
<tr>
<td>15 min</td>
<td></td>
</tr>
</tbody>
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- **Young**
- **Old Control**
- **Old Antioxidant**
Long-term running enhances neurogenesis in TgCRND8 animals
Is there a molecular memory for exercise?

• Exercise may prime the brain for learning and induces a state of readiness?
Is there a molecular memory for exercise?
BDNF is a Synaptic Modulator

• Is BDNF induced by exercise and where in brain?
• How much exercise?
Exercise increases BDNF mRNA

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Rats: 1 week exercise (male sprague-dawley, 3 months)

Berchtold et al., 2002
Exercise increases BDNF protein
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Exercise “restores” some of the age-related losses in synaptic proteins
CNS and Peripheral Factors Interact with Exercise to Regulate BDNF

Exercise ➔ Hippocampus ➔ Downstream functional changes

Peripheral Factors ➔ BDNF ➔ Hippocampus

- Estrogen
- Glucocorticoids
- Blood-Brain Barrier
- IGF-1

Peripheral Factors

- Medial Septum (ACh/GABA)
- Locus Coeruleus (NE)
- Raphe (5-HT)

Cotman and Berchtold (2002), TINS
Practical Questions

• How long lasting is the increase after stopping exercise?
• How frequent is necessary
• Can the increase be recovered rapidly if exercise is stopped for a period?
BDNF Protein Stability After Exercise Ends

Paradigm:
- 4 weeks daily voluntary exercise
- Day 0 - end of exercise period, wheels locked
- Sacrifice on days 0, 1, 3, 7, 14 after end of exercise
- Protein levels assessed

Berchtold, et al., submitted
Time course of BDNF Protein Induction

Berchtold, et al., submitted
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Thus, if so exercise may prime the brain to respond to experiences, and induce a “state of readiness”.

Once exercise stops is the induction stored in molecular memory?!

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• Prior Exercise Primes subsequent BDNF Responsiveness
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So … What is the functional significance of brain changes induced by exercise?

• Learning?
• Stress relief?
Exercise Enhances Learning in the Morris Water Maze

![Graph showing time to reach platform for Sedentary and Exercising groups over days of training. Days 1, 2, 3, 4, 5, 6 are shown. * indicates p < 0.05.]

- Sedentary
- Exercising

*p < 0.05
Is exercise an effective intervention in AD transgenic models?

• Will voluntary running improve learning and memory?
• Reduce β-amyloid in the brain?
• Stimulate neurogenesis?
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Why is learning and memory improved?

• Hypothesis – Neurogenesis?
• Hypothesis – Aβ may impair CREB and Elk transcriptional activity essential for learning and memory, e.g., induced by BDNF
Long-term running enhances neurogenesis in TgCRND8 animals
Recent clinical/epidemiological findings

- Exercise and intellectual activities in mid life delay AD onset (Friedland, 2001)
- TV is associated with an increased risk of AD, 1.3X risk/hr of TV/day (Friedland, 2005)
- Exercise increases brain volume in select areas and larger brains are associated with those most fit (Kramer, 2004, 2005)
- Women who get the most exercise show less cognitive decline (Yaffe, 2005; Grodstein, 2004)
- Those engaged in 4 or more physical activities have half the risk for AD, but mainly for ApoE4 carriers (Lyketsos, 2005)
Exercise

Functional changes:

- Increase BDNF
- Synaptic plasticity
- Increased neuron number
- Improve learning