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Anti-inflammatory effects of physical activity in relationship to improved cognitive status in humans and mouse models of Alzheimer's Disease

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Abstract

Physical activity has been correlated with a reduced incidence of cognitive decline and Alzheimer's disease in human populations. Although data from intervention-based randomized trials is scarce, there is some indication that exercise may confer protection against age-related deficits in cognitive function. Data from animal models suggests that exercise, in the form of voluntary wheel running, is associated with reduced amyloid deposition and enhanced clearance of amyloid beta, the major constituent of plaques in Alzheimer's disease. Treadmill exercise has also been shown to ameliorate the accumulation of phosphorylated tau, an essential component of neurofibrillary tangles in Alzheimer's models. A common therapeutic theme arising from studies of exercise-induced neuroprotection in human populations and in animal models involves reduced inflammation in the central nervous system. In this respect, physical activity may promote neuronal resilience by reducing inflammation.

Keywords

exercise; running; hippocampus; inflammation; Alzheimer's disease

Physical exercise is increasingly being recognized as an effective neuroprotective strategy. Both the human and experimental animal literature suggest that cardiovascular exercise maintains and can improve the structural integrity and the function of the central nervous system (CNS) [1–2]. In humans, cardiovascular fitness is associated with a reduced incidence of cognitive decline [3]. Specifically, higher levels of participation in recreational physical activity are associated with a reduced prevalence of Alzheimer's disease [4]. Cardiovascular exercise increases blood flow to areas of the CNS that are specifically vulnerable to Alzheimer's disease (AD), such as the hippocampus and entorhinal cortex [5].

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Moreover, cardiovascular fitness training alters the blood oxygen level dependent (BOLD) signal in areas implicated in cognition and executive function [6]. The extant human literature also supports an association between cardiovascular fitness and age-related cognitive decline.

Animal models of Alzheimer's disease are useful to identify potential therapeutic targets by allowing the investigation of the basic molecular mechanisms underlying neurodegeneration. In mice, cardiovascular fitness training is typically modeled using voluntary wheel running or involuntary treadmill training. Using these paradigms, several studies have now shown that physical exercise can arrest, or decelerate, the molecular mechanisms underlying neurodegeneration in Alzheimer's disease. The most prevalent hypotheses concerning AD etiology suggest that AD is characterized by the formation of amyloid- β (A β) plaques and neurofibrillary tangles composed of hyperphosphorylated forms of the microtubule protein, tau. In transgenic mice that carry familial mutations of the gene encoding amyloid precursor protein (APP), wheel running has been shown to reduce the expression of APP mRNA [7], and attenuate alterations in A β processing [8]. Transgenic mouse models of AD that present extensive neurofibrillary tau pathologies treadmill running was also shown to reduce tau phosphorylation [9]. While the results are somewhat mixed due to the use of different exercise protocols, and variant animal strains there is some indication that running may be neuroprotective at the molecular level in animal models of AD.

Epidemiological correlations between physical fitness and reduced incidence of dementia

Epidemiological studies have begun to assess the relationship between dementia and physical fitness. Laurin et al [4] explored this relationship in the Canadian Study of Health and Aging population study (www.csha.ca). Data analysis from the study has demonstrated that, even after adjusting for age, sex, and education, physically active individuals were less likely to exhibit cognitive impairment without dementia compared to more sedentary individuals in the study. In females, physical activity was associated with a reduced risk for cognitive impairment without dementia, and reduced risk of AD. This relationship, despite also being present, did not however reach statistical significance in men. This pattern corresponds with the more consistent findings of exercise-induced enhancement of cognitive function in female, relative to male rodents.

Exercise improves executive function: behavioral studies in humans

Increasing physical activity has been demonstrated to improve cognitive function in a population of adults that included individuals carrying the APOE ϵ 4 allele, a major risk factor for Alzheimer's disease [10]. This study also included individuals diagnosed with mild cognitive impairment (MCI), a mental state which may lead to Alzheimer's disease. Individuals with or without MCI both benefitted from exercise to a similar extent. Individuals in the treatment group participated in approximately 20 minutes of physical activity per day, and the positive effects of exercise treatment persisted for up to 12 months

after cessation of the treatment. This randomized trial strongly suggests that coordinated physical exercise can improve cognitive outcomes in individuals at risk for AD.

Aerobic training regulates brain structure and patterns of brain activation

Burns et al [11] observed that after accounting for confounding variables, individuals with AD exhibit lower peak oxygen consumption, a measure of physical fitness, relative to age-matched control subjects. This study provokes the question of whether an AD condition itself impairs physical fitness, or if physical fitness prevents AD. However, the observed relationships were significant even after controlling for physical frailty. Cardiorespiratory fitness, measured using peak oxygen consumption, was also associated with preservation of brain volume and white matter volume on structural magnetic resonance imaging scans. This study supports an association between objective measures of physical fitness and brain structure in humans. In an elegant approach to the question of how exercise influences the functioning of the human brain, Colcombe and colleagues [6] used both a longitudinal and a cross-sectional design to demonstrate that improved cardiovascular fitness is associated with improved executive function. In a sample of community-dwelling older adults, exercise intervention was associated with improved executive functioning, and increased activation of the middle frontal gyrus and superior parietal lobule. Conversely, exercise training reduced activity in the anterior cingulate cortex during an attentional control task. Overall, this study demonstrated that non-demented older adults exhibit alterations in brain activation following six months of aerobic exercise training. In another intervention study, Kramer and colleagues [12] observed that aerobic exercise training selectively improved performance on a task-switching paradigm that recruits frontal and prefrontal structures. Taken together with the extensive animal literature, these reports promote the question of whether extra-hippocampal regions might also be responsive to exercise in animal models.

Basic mechanisms of exercise-induced plasticity in the aging brain

The adult brain possesses an ability to generate new neurons throughout the lifespan via a mechanism termed adult neurogenesis. However, this process decreases dramatically with advancing age [13]. One month of running, beginning at nineteen months of age has been shown to increase adult neurogenesis in female mice [14]. The running-induced enhancement of adult neurogenesis in aged mice is apparently very rapid, as increased labeling for the DNA synthetic marker bromodeoxyuridine (BrdU) was reported following only ten days of running in 18-month-old female mice [15]. Increased neurogenesis occurred in concert with improved performance in a standard Morris water maze (MWM) acquisition protocol [14].

Lifelong running has also been shown to enhance hippocampal function in twenty month old male C57Bl6 mice [16]. Specifically, male mice exposed to lifelong running demonstrated reduced escape latencies and path lengths during acquisition training in the MWM. Moreover, lifelong running also increased the amount of time spent near the platform location during the probe trial, indicative of an improved recall of spatial memories. These behavioral improvements in learning and memory were accompanied by a number of targeted changes in CNS gene transcription. Habitually running animals activated genes

associated with inhibitory neurotransmission, including glutamic acid decarboxylase 1 (Gad1) and gamma-aminobutyric acid (GABA-A) receptor, subunit gamma 2 (Gabbr2), following learning tasks, whereas sedentary mice failed to upregulate these genes [16]. This suggests that one potential mechanism whereby running enhances and protects brain function involves the preservation of inhibitory neurotransmission.

Cellular protein markers associated with inhibition of neurotransmission decrease in the aged hippocampus, such that aged rats have fewer neuropeptide-Y positive interneurons in the dentate hilus [17]. Aged rats also exhibit reductions in the number of somatostatin- and calbindin-positive neurons sampled in the CA1 stratum oriens [18]. In contrast, habitual running promotes the expression of inhibitory neuronal markers in young rats [19] and in aged mice [16]. As Alzheimer's disease is thought to involve an imbalance in excitatory and inhibitory tone [20], an increase in inhibition may well contribute to the therapeutic enhancement of hippocampal function following lifelong habitual running.

Brain-derived neurotrophic factor (BDNF) is a secreted neurotrophic growth factor that is involved in neuronal differentiation and synaptic plasticity. A complex relationship between inhibitory neurotransmission and levels of brain-derived neurotrophic factor (BDNF) has been demonstrated. On one hand, application of exogenous BDNF can induce long-term potentiation (LTP), a stable, long-lasting increase in the strength of the synaptic response [21]. In agreement with this, abrogation of BDNF signaling can also lead to impairment of LTP [22]. LTP has traditionally been considered an excitatory phenomenon, dependent upon activation of N-methyl-D-aspartate (NMDA) receptors. However a role for inhibitory neurotransmission in BDNF signaling has not been considered until very recently. In the developing brain, activation of GABA-B receptors initiates the release of BDNF from neuronal dendrites [23]. In the aging brain, physical activity increases BDNF production [24] opening the possibility that one mechanism for the running-induced enhancement of cognition may involve BDNF as a mediator for the maintenance of inhibitory circuitry.

Wheel running alters the neuropathological phenotype in the TgCRND8 mouse model of Alzheimer's disease

The TgCRND8 murine model of AD possesses a human APP transgene containing two mutation sites associated with human AD etiology, *i.e.* the 'Swedish' and 'Indiana' mutations [25]. With regards to the effects of running upon the processing of APP in this model, in a pioneering study by Adlard and Cotman [8] (Table 1), five months of exercise improved hippocampus-dependent water maze performance in female TgCRND8 mice that were one month old at the start of training. Running also reduced concentrations of the major pathological isoforms of A β (A β 1–40 and A β 1–42) in the cortex, with a trend towards reduced A β accumulation in the hippocampus. Habitual running in this model reduced levels of both C-terminal fragments (α and β) of APP, without affecting total APP levels (Figure 1A). There were no reported alterations in beta or gamma secretase enzymes that cleave APP to generate multiple A β isoforms. There was also no change in levels of neprilysin or insulin-degrading enzyme, markers of A β degradation. This suggests that voluntary wheel running alters APP processing in female TgCRND8 mice. In contrast with the findings of

Adlard and Cotman [8], seventy days of running failed to influence A β plaque load in the hippocampus of male 3–4 month old TgCRND8 mice [26] (Table 1).

When the behavioral aspects of running were assessed in the TgCRND8 mice no significant effect of running or genotype on recognition memory in the novel object preference paradigm was observed [26]. Importantly, there was no effect of genotype on the amount of running. TgCRND8 mice were reported to exhibit higher levels of stereotypic behavior in the home cage, and this parameter was attenuated by wheel running [26]. However, running had no effect on the elevated fecal corticosterone concentrations observed in TgCRND8 mice. In the hippocampus-dependent Barnes maze task, running did not influence escape latency or path length, either in wild type mice or in TgCRND8 [26]. Overall, this study suggests that the time course or the efficacy of the effects of wheel running on cognitive function and A β deposition may differ between the female TgCRND8 mice used by Adlard and Cotman [8] and male mice employed by Richter et al [26]. These two studies used different genders of the same mouse lineage, and showed different results, therefore demonstrating that gender may be an important determinant of the brain's response to exercise in Alzheimer's models.

Regulation of neuropathology following running in the Tg2576 AD model

Using the Tg2576 AD model mice which possess a human APP transgene bearing the 'Swedish' mutation that predisposes preferential amyloido-genic proteolysis [27]. Extended periods of habitual running have been shown to attenuate soluble A β fibril accumulation in 16–18 month old Tg2576 mice [28] (Table 1). However, there was no effect of running upon total A β levels in the hippocampus. Sedentary Tg2576 mice exhibited increased expression of the pro-inflammatory interleukin-1 β and tumor necrosis factor- α (TNF- α) in the hippocampus, relative to wild type mice. Running reduced expression of interleukin-1 β and TNF- α to levels that were comparable to wild type mice. Conversely, sedentary Tg2576 exhibit reduced levels of interferon- γ and chemokine (C-C motif) ligand 3 (Ccl3, also termed MIP-1 α); this reduction was also reversed by physical activity. These data indicated that running can modulate the post-translational fates of A β in the Tg2576 model of Alzheimer's disease, possibly through alterations in the inflammatory response profile in the hippocampus.

Three weeks of running was shown to enhance hippocampus-dependent learning in 16–18 month old male and female mice [29] (Table 1). There were no genotype- or gender-dependent alterations in the amount of habitual running in the animals in this study. There was also no effect of running in aged wild type mice upon hippocampus-dependent memory tasks in the water-escape-motivated radial arm maze. Additionally, this study demonstrated improvement on some, but not all, parameters following housing with an immobilized running wheel. Two conclusions can be drawn from the study by Nichol et al [29]: first, that running ameliorates cognitive deficits even after the onset of pathology in Tg2576 mice, and second, that the reversal of age-related learning deficits reported using the water maze task in other studies [14] may be task-specific and not generalizable to other learning paradigms, such as the water-escape motivated radial arm maze.

The reports of effects of running upon APP processing in the Tg2576 mice are mixed however, suggesting that the actual AD pathophysiology responsible for the disease process is more complex than previously appreciated [30]. For example, fifteen- to nineteen-month old Tg2576 mice failed to exhibit any change in A β 1–40 or A β 1–42 levels following three weeks of voluntary running [31] (Table 1). There was also no change in the number of thioflavin-S stained plaques in the hippocampus, nor were there any changes in total APP levels. However, despite the absence of changes in molecular markers of Alzheimer's disease, there was some amelioration of cognitive deficits in the water-escape motivated radial arm maze. The behavioral findings were interpreted in the context of increased expression of the inflammatory markers chemokine (C-X-C motif) ligand 1 (CXCL1) and chemokine (C-X-C motif) ligand 12 (CXCL12). CXCL1 is a chemokine that protects neurons against A β -induced toxicity [32]. Treatment with a CXCL12 antagonist impairs hippocampus-dependent learning in mice, suggestive of a role in plasticity [33]. These findings suggest that voluntary exercise improves hippocampal function in Tg2576, not by altering A β expression, but instead by modulating the expression of chemokines.

Additional studies provide further support for a complex and multifaceted effect of exercise upon AD pathology. A β 1–40 or A β 1–42 levels in the hippocampus and cortex of five-month-old male and female Tg2576 mice were not affected by four months of voluntary running [34] (Table 1). However, while sedentary and forced-exercise groups in this study failed to form a memory for the familiar object in the novel object preference test, voluntary runners did show recognition memory, indicated by a preference for the novel object. Voluntary running, but not forced running, reduced the number of thioflavin-S positive plaques in the hippocampus. Voluntary running was also associated with increased hippocampal volume.

By parallel examination of these studies and the studies by Nichol et al [28–29] and Parachnikova and Cotman [33], it is possible to form a time line for the events occurring in the brains of the Tg2576 mouse model of Alzheimer's disease. Early-onset running, beginning at five months of age as shown by Yuede and colleagues [34], lowers the threshold for object recognition memory and reduces plaque deposition in the hippocampus. In contrast, late-onset running, beginning at 15–19 months of age as shown by Nichol et al [28–29] and Parachnikova and Cotman [33], alters the accumulation of soluble A β fibrils and protects against neuroinflammation.

Running attenuates neuropathology in the NSE/APPswe AD model

The NSE/APPswe model of AD possesses a 'Swedish' mutated APP transgene under the control of a neuron specific enolase (NSE)-CAT promoter [35]. Treadmill training has been shown to ameliorate neuropathologies in APPswe mice [36] (NSE/APPswe mice; Table 1). Three months of treadmill training reduced A β 1–42 levels in whole brain homogenates. Exercise also reversed the increase in escape latency observed in the Morris water maze in these mice. However, this may have been attributable to an increase in swim speed, as noted by the authors. Running activity in this model also can increase levels of BDNF as well as the astroglial glucose transporter GLUT1. Exercise also attenuated pathological increases in mitochondrial stress proteins and caspases typically observed in NSE/APPswe mice. Lastly,

exercise reduced the hyperglycemia, hyperinsulinemia, and elevated cholesterol levels that were observed in NSE/APPswe mice. This study illustrates the concept that one mechanism whereby exercise, in addition to other therapeutic mechanisms, can improve CNS structure and functional integrity may involve an overall enhancement of the efficiency of somatic metabolism [30, 37, 38].

Effects of running wheel activity on neuropathology in the APP23 AD model

This mouse model contains the human APP695 transgene containing the double mutation Lys670-Asn, Met671-Leu, inserted into B6/SJL F2 mice using a hamster prion protein cosmid vector [27]. Eight and a half months of voluntary running in this model failed to influence plaque burden in the hippocampi of female APP23 mice [7] (Table 1). The mice in this study were ten weeks old at the onset of training. Physical activity in these mice also did not induce any identifiable neurogenic activity in the hippocampal dentate gyrus [7]. In correlation with these observations, running failed to improve hippocampal-dependent memory in the water maze, but however did improve motor coordination measured using time spent on a standard mechanized rotarod apparatus [7]. Interestingly, running decreased APP mRNA in the hippocampus, suggesting that, although long-term exercise reduced APP mRNA, there are limited behavioral improvements following running in the APP23 mouse model of Alzheimer's disease [7].

Ten days of voluntary running has been reported however to enhance adult neurogenesis in 18 month old but not in 8 month old female APP23 mice [15] (Table 1). Running failed to alter the area of Congo Red-positive plaques at 18 months of age, but did however reduce the A β 1–40/A β 1–42 ratio in the hippocampus (Figure 1A). In contrast to the previous reports [7] running did not influence expression of APP mRNA. Alongside the data of Wolf et al [7], this study suggests that short-term running, but not long-term running, promotes adult neurogenesis in APP23 mice. Conversely, long-term running protocols (eight and a half months; [7]) reduced APP mRNA, while short-term running (ten days; [15]) did not affect APP mRNA expression. Instead, late-onset short-term running reduced the A β 1–40/A β 1–42 ratio. This suggests that early-onset long-term running alters APP production, while late-onset short-term running regulates A β processing in the APP23 mouse model of Alzheimer's disease.

Effects of wheel running activity on neuropathological features of APOE ϵ 3/4 AD mice

APOE ϵ 3 and APOE ϵ 4 transgenic mice [39] possess the human alleles of APOE that are associated with an increased incidence of sporadic and late-onset AD [40–41]. Six weeks of voluntary running improves water-escape-motivated radial arm maze performance in 10–12 month old male and female APOE ϵ 3 and APOE ϵ 4 mice [42]. Running also increased hippocampal BDNF concentrations in both APOE ϵ 3 and APOE ϵ 4 mice as well as potentiating the expression of synaptophysin, specifically in APOE ϵ 4 mice. This study

indicates that running improves cognition, neurotrophic factor production, and synaptic marker expression in mice carrying a known genetic risk factor for Alzheimer's disease.

Modulation of tau pathology through physical training in TgNSE-htau23 AD mice

Tg-NSE/htau23 mice express the human tau23 isoform protein under the control of the neuron-specific enolase (NSE) promoter in the genetic background of C57BL/6 mice [43]. These mice express excessive tau hyperphosphorylation in a manner characteristic of the mature human AD condition. Three months of involuntary treadmill training attenuated this tau pathology in male and female TgNSE-htau23 mice [9] (Table 1). Training began at fifteen months of age and continued for three months. Treadmill training restored normal levels of copper-zinc superoxide dismutase, catalase, and manganese superoxide dismutase in both male and female TgNSE-htau23 mice. Running also restored normal catalase and superoxide dismutase activity. Running increased the phospho-PK α /PK α ratio, reduced the phospho-PKA/PKA ratio, and reversed the increased ratio of active phospho-p38 mitogen-activated protein kinase (MAPK) to total p38-MAPK. Running also reduced the active phospho-extracellular signal-regulated (ERK)/ERK ratio, and attenuated the increase in the active phospho-c Jun N-terminal kinase (JNK) to JNK ratio. In contrast, running increased the active phospho-Akt to total Akt ratio (Figure 1B), which was reduced in both male and female TgNSE-htau23 mice. Overall, this study indicated that running influences the activity status of serine-threonine kinases that may regulate the degree of tau phosphorylation as running effectively reduced tau phosphorylation at multiple sites (Figure 1B).

Conclusion and future directions

Physical activity improves multiple aspects of somatic physiological function, and the CNS is no exception to this. Cardiovascular fitness is associated with reduced incidence of cognitive decline, including dementia of the Alzheimer's type. Not only is lifelong physical activity a preventative strategy to reduce the likelihood of developing neurodegenerative disease, exercise has also been shown to be effective as an intervention in aged populations at risk for [10, 44] or suffering from [45] Alzheimer's disease.

In animal models, physical activity regulates basic mechanisms underlying neurodegeneration. Exercise, in the form of wheel running, reduces plaque accumulation in some [8, 34] but not all studies [7, 26, 31]. Running also reduces the ratio of A β 1–40 to A β 1–42, indicative of changes in the processing of the amyloid- β protein [8, 15]. Treadmill training also reverses the increase in tau phosphorylation observed in mouse models of tauopathy [9]. Physical activity ameliorates learning deficits in animal models of Alzheimer's disease, again in some [8, 28, 29, 31, 36] but not all studies [7, 26, 34]. These diverse and mixed results are indicative of variations in the effects of late-onset versus early-onset exercise, as well as differences in the efficacy of short- and long-term activity. More studies are clearly necessary to resolve the following questions: First, what is the role of gender in determining the neuroprotective effects of exercise in Alzheimer's models? Second, what is the dose-response relationship between exercise and neuroprotection? And

third, what is the duration for the neuroprotective effects of exercise following cessation of activity? Understanding the answers to these questions will help to close the gap between the literature in humans and in non-human animal models and therefore aid the scientific community as whole to fully appreciate the growing field of activity-based interventions.

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Figure 1. Changes in amyloid precursor protein processing, plaque accumulation, and tau phosphorylation with increased physical activity

(A), Voluntary wheel running reduces amyloid precursor protein mRNA [7], and reduces levels of the alpha and beta C-terminal fragments [8]. Physical activity also reduces the ratio of Aβ₁₋₄₀ to Aβ₁₋₄₂ [8, 15, 36]. Lastly, running has been associated with reduced plaque burden in some [8, 34], but not all [7, 26, 31] studies. (B), Transgenic mice expressing human tau exhibit reduced phosphorylation of phosphoinositol-3 kinase (PI3K); physical activity reverses this effect [9]. Similarly, transgenic mice expressing human tau show reduced phosphorylation of Akt, and exercise reinstates Akt phosphorylation [9]. Phosphorylation of PI3K/Akt inhibits phosphorylation of glycogen synthase kinase-3β (GSK3β), which in turn phosphorylates tau. In keeping with this relationship, transgenic mice exhibit increased phosphorylation of GSK3β and tau. Treadmill running reversed the increase in phosphorylation of GSK3β and tau [9].

Table 1

Effects of exercise in animal models relevant to Alzheimer's disease.

Study	Model	Duration	Distance	Age at onset	Gender	Behavioral result	Molecular phenotype
[42]	APOE3 and APOEε4 mice	6 weeks	1.96 km/day	10–12 months	male and female	Improved water-escape motivated radial arm maze performance	↑ BDNF
[7]	APP23 mice	34 weeks	not reported	2.5 months	female	No change in water maze performance	No change in plaque load
[15]	APP23 mice	10 days	not reported	8 months or 18 months	female	not assessed	↓ Aβ1–40/Aβ1–42 ratio
[36]	Tg NSE-APP _{sw} mice	16 weeks	0.79 km/day	13 months	not reported	Improved water maze escape latency	↓ accumulation of Aβ1–42
[9]	Tg-NSEhtau mice	12 weeks	0.72–1.14 km/day	16 months	male and female	not assessed	↓ accumulation of phospho- tau
[34]	Tg2576 mice	16 weeks	0.65 km/day	5 months	male and female	No change in spontaneous alternation or object recognition	↓ thioflavin-S positive plaques
[31]	Tg2576 mice	3 weeks	not reported	15–19 months	not reported	Improved water-escape motivated radial arm maze performance	No change in thioflavin-S positive plaques, Aβ1–40, Aβ1–42, or total APP levels
[28]	Tg2576 mice	3 weeks	1.51 km/day	16–18 months	not reported	not assessed	↓ soluble Aβ, no change in total Aβ
[29]	Tg2576 mice	3 weeks	1.65 km/day	16–18 months	male and female	Improved water-escape motivated radial arm maze performance	not assessed
[26]	TgCRND8 mice	2.3 weeks	1.375 km/day	3 months	male	No effect of running on Barnes maze performance	No change in plaque load
[8]	TgCRND8 mice	5 months or 1 month	4.29 km/day	1–1.5 months	female	Improved water maze escape latency	↓ Aβ1–40, ↓ Aβ1–42, ↓ α- and β-C-terminal fragments