Review

Exercise-Induced Modulation of Neuroinflammation in Models of Alzheimer's Disease

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Abstract. Alzheimer's disease (AD), a progressive, neurodegenerative condition characterised by accumulation of toxic βeta-amyloid (Aβ) plaques, is one of the leading causes of dementia globally. The cognitive impairment that is a hallmark of AD may be caused by inflammation in the brain triggered and maintained by the presence of Aβ protein, ultimately leading to neuronal dysfunction and loss. Since there is a significant inflammatory component to AD, it is postulated that anti-inflammatory strategies may be of prophylactic or therapeutic benefit in AD. One such strategy is that of regular physical activity, which has been shown in epidemiological studies to be protective against various forms of dementia including AD. Exercise induces an anti-inflammatory environment in peripheral organs and also increases expression of anti-inflammatory molecules within the brain. Here we review the evidence, mainly from animal models of AD, supporting the hypothesis that exercise can reduce or slow the cellular and cognitive impairments associated with AD by modulating neuroinflammation.

Keywords: Exercise, microglia, astrocytes, neuroinflammation, Alzheimer's disease

INTRODUCTION

The prevalence of sporadic Alzheimer's Disease (AD), the most common form of dementia, is increasing in proportion with life expectancy [1]. As yet, there is no effective treatment of AD; the cholinesterase inhibitors and N-Methyl-D-aspartate (NMDA) glutamate receptor antagonist drugs presently prescribed can only slow the worsening of symptoms of the disease [2], while efforts to develop effective and safe therapies targeted at clearing the amyloid β (Aβ) plaques that characterize AD have failed [3]. Discovery of effective treatments for AD will likely require a fuller understanding of the pathogenesis and progression of the disease than we now possess. While the question of how the disease is triggered remains unanswered, a collection of modifiable and non-modifiable risk factors for AD have been identified, including age, genetic factors, dietary factors, metabolic disease and cardiovascular disease [4]. Encouragingly, a number of modifiable lifestyle factors that may mitigate risk of development of AD have also been identified; these include diet [5], education and mental activity [6, 7] and social engagement [8]. However the most potent of these lifestyle factors appears to be exercise [9, 10], which will be the focus of this review.

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An acute neuroinflammatory response can be initiated by factors including infection, ischemia, and trauma that cause the activation of microglia. These 'resident macrophages of the brain' (Box 1) produce and secrete cytokines such as interleukin-1 (IL-1), interlekin-6 (IL-6), and tumour necrosis factor α (TNF-α), which can lead to recruitment of peripheral immune cells to the brain and elimination of infection-causing pathogens or repair of damage from an imposed trauma [11]. Astrocytes, the most numerous cell type in the brain, contribute to acute immune responses such as adjusting the permeability of the blood brain barrier (BBB) to allow immunologically active molecules into the central nervous system (CNS) from the periphery [12] and secretion of cytokines [13] (Box 1). However a chronic neuroinflammatory response is associated with a number of neurodegenerative diseases, including AD [14]. Although initially this inflammation was considered to be solely detrimental, more recently it has been proposed that inflammation has the potential to contribute positively to brain repair, including the regeneration and clearance of pathological aggregates [15]. As such, strategies to modify inflammation within the brain may be of preventive or therapeutic benefit in the context of AD.

One such strategy may be engagement in regular physical activity. Sedentary behavior has been associated with impaired cognitive function in old age [16, 17], while regular exercise appears to preserve cognitive function in later life [18, 19]. Although physical activity is inversely linked with risk of development of AD [9, 20, 21], the type, frequency, intensity and duration of exercise required to reduce risk has not as yet been identified [22]. The mechanisms underlying this exercise-induced protection may include preservation of brain volume [23] and the patency of the cerebral vasculature [24], with evidence from animal studies strongly linking exercise and maintenance of cognitive function with neurogenesis and expression

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Box 1

Roles of glia in neuroinflammation

Microglia are considered the resident immune cell of the brain. Under resting conditions, they exist primarily in a state of surveillance in the CNS and their major role is the maintenance of homeostasis within the brain microenvironment [157]. Maintenance of microglia in a relatively quiescent state is attributed in part to astrocyte and neuronal activity [158]; for example, neurons can facilitate microglial quiescence by secreting signal factors including CD200, CX3CL1 and neurotrophins [159, 160]. Microglia share phenotypic characteristics with peripheral monocytes cells and, during injury to the CNS, are polarized towards a pro-inflammatory phenotype (M1 state), induced mainly by exposure to pro-inflammatory cytokines, such as IFN-γ, TNF-α and cellular or microbial debris. The M1 state is characterised by production of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6 and increased expression of inducible nitric oxide synthase (iNOS), inducing elevated production of NO and morphological change of microglia to an amoeboid shape [161]. However, in an effort at neuroprotection and repair, microglia can assume an 'alternative' activation, featured by an anti-inflammatory phenotype (M2 state). The M2 activation can be driven by anti-inflammatory cytokines, such as IL-4, IL-13 and IL-10 [162] and is characterised by increased production of anti-inflammatory cytokines, including IL-4, IL-10, IL-13, as well as upregulation of Arginase-1 (Arg1), Chitinase-3-like-3 (Ym1, in rodents) and Mannose receptor C (MRC-1) [163, 164]. Microglia activated towards the M2 state can also trigger inflammation resolution through the release of other anti-inflammatory factors, such as neurotrophins (eg BDNF) and growth factors (IGF-1 and transforming growth factor beta -TGF-β) [165, 166]. An involvement of microglial activation has been identified in the pathophysiology of several neurodegenerative diseases, such as AD and Parkinson's Disease (PD), mainly by increasing neurotoxicity and cellular damage, thereby contributing to the degenerative process [167, 168]. While polarisation toward an M1 or M2 state can be readily induced *in vitro*, the complex nature of the brain microenvironment and the multiple signals that glia are exposed to makes it likely that a spectrum of intermediate transitional activation states exists *in vivo* [169, 170]. Nevertheless, manipulation of microglial polarization is being actively investigated as a potential therapeutic strategy in a number of neurodegenerative conditions [171].

Astrocytes are the most populous cells in the CNS, where they provide structural and functional support to neurons, form part of the blood brain barrier (BBB) and participate in synaptic formation [172]. While their main role is in neuronal support and brain homeostasis [173], it is accepted that they play an important role in neuroinflammation [174]. Similar to microglia, astrocytes can be activated from the resting state in response to insults and pathologies and this reactive astrogliosis is characterised by increased expression of GFAP [175]. Activated astrocytes have been shown to be a significant source of pro-inflammatory cytokines, including TNF-α, IL-1β and IL-6 as well as other inflammatory mediators such as iNOS [176, 177]. Most recently, a harmful/helpful A1/A2 classification, analogous to the microglial M1/M2 phenotypes, has been suggested though it is proposed that, again similar to microglia, a continuum of activation states is likely, especially *in vivo* [178]. Accordingly, astrocytes exposed to IL-4 and IL-10 show typical "alternative" activation (A2 phenotype), increasing expression of Arg-1, Mrc-1 and Ym1 [176], while activated astrocytes can also help in tissue repair by releasing IL-10, which has been reported to supress neuronal apoptosis through TLR/NF-κB pathway activation [179]. In addition, astrocyte reactivity has been associated with several neurodegenerative diseases, including Huntingtons Disease, PD and AD [180–182] and most recently, it was suggested that the normal process of ageing induces astrocytes to present A1-like astrocyte reactivity, with pro-inflammatory features [183].

The ability of reactive astrocytes and microglia to influence each other's morphology and function is now being painstakingly investigated, for example it has recently been shown that the A1-type astrocyte phenotype can be induced by neuroinflammatory microglia [184]. It is hoped that investigation of the cross-talk between microglia, astrocytes and neurons will yield insights that may inform therapeutic interventions in diseases and disorders of the brain, including AD.

of brain-derived neurotrophic factor (BDNF) [25]. These data fit with the proposed theory of 'cognitive reserve' [26, 27], whereby lifestyle factors render individuals more resilient to insult, injury, age-related neurodegeneration or, with respect to AD, to the functional consequences of amyloid pathology [28].

More recently, the anti-inflammatory properties of physical activity have been increasingly investigated. Abundant research demonstrates the overall anti-inflammatory effects that exercise induces in peripheral body organs, and that these effects may contribute to the decreased risk of development of cardiovascular and metabolic disorders [29]. Increasing evidence indicates that these anti-inflammatory effects extend to the brain, reducing risk of development of neurodegenerative disorders that exhibit a significant inflammatory component, including AD [30, 31].

AD AND MODELS OF AD

The Bavarian psychiatrist and neuropathologist Alois Alzheimer first described the pathology of the disease that bears his name more than 100 years ago when he associated memory loss in a female patient with senile plaques identified in her brain post-mortem [32]. Memory loss is, of course, the major clinical symptom of AD [33] and the disease progression can be staged clinically according to the degree of cognitive impairment from normal age forgetfulness through mild cognitive impairment to mild, moderate and severe AD [34]. The classic pathological lesions that are a hallmark of AD are characterized by extracellular plaques, composed mainly of amyloid β (Aβ), and intracellular neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau protein, and progression of the disease results in neuronal loss and consequent brain shrinkage [35]. The severity of AD correlates more closely with the distribution of NFTs than the amyloid plaques [36–38] and activated astrocytes and microglia are found at the lesion sites, indicating an inflammatory component to the pathology [39, 40]. The generation of the neurotoxic amyloid species that constitute AD plaques by proteolysis of the amyloid precursor protein (APP) is well-described and has been extensively reviewed eg [41, 42]. Very briefly, the amyloidogenic pathway of APP processing involves cleavages at specific sites by β- and γ-secretases that generate Aβ fragments that can oligomerize and fibrillize, leading to AD pathology. While the presence of plaque pathology

is diagnostic of AD, advances in imaging technology have revealed that a cohort of the aged population have a high amyloid burden but no cognitive impairment [43], and that evidence of plaque pathology can precede symptoms of AD by as much as 20 years [44]. This is strong evidence to indicate that factors other than amyloid plaques, including NFTs and neuroinflammation, contribute to the loss of memory and other cognitive functions typical of AD.

Attempts to mimic in rodents the pathology of AD seen in the post-mortem human brain have been informed mainly by identification of the amyloid composition of AD plaques and by genetic information garnered from patients with familial Alzheimer's Disease (FAD), now commonly referred to as Early Onset Alzheimer's Disease (EOAD). EOAD, which usually becomes symptomatic in patients under the age of 65, is a rapidly progressing form of the disease and accounts for only 5–10% of all AD cases [45]. Mutations in three genes encoding APP, and the γ-secretase complex subunits presenilin 1 (PS1) and presenilin 2 (PS2), are causal in EOAD and are considered diagnostic [4], although these gene mutations account for only a small number of families with EOAD, indicating that additional AD-causing genes remain to be identified [45]. The sporadic form of AD, although influenced by environmental factors, is also impacted by genetics, the major gene investigated thus far being the ε4 allele of the apolipoprotein gene (APOE) [46–48]. However, genome-wide association studies are strongly suggesting a causative role for inflammation or immune dysfunction in AD [48, 49].

No transgenic mouse model can replicate pathology in the human brain precisely, but overexpression of mutated forms of APP, PS1 and/or Tau in the mouse brain has provided a means by which to assess the development and functional consequences of AD-like pathology [50–52]. While over 100 genetically engineered mouse lines have been developed with this goal in mind, there is a small number that has been widely used and in which pathology and cognition is well characterized [53] and will be focussed on here. With respect to APP, the Tg2576 model that overexpresses the 'Swedish' mutation [54] and the PDAPP that overexpresses the 'Indiana' mutation [55] show progressive AP deposition, loss of synapses, apoptosis, gliosis and hyperphosphorylated Tau, but no NFTs [50, 56]. Mutation of PS1 results in increased neurotoxic Aβ, but this mouse shows no plaque pathology [57]. Double and triple mutations have been employed in an attempt to model AD

pathology more closely. For example the APP/PS-1 mouse shows an early and accelerated AP deposition with evidence of astrocytosis around Aβ deposits and loss of dendritic spines [50, 58, 59]. As with the APP point mutation models, there is no development of NFTs but hyperphosphorylation of Tau [60, 61] and neuronal loss [62] have been observed. The 3xTg, triple transgenic mouse model overexpresses mutated Tau in addition to APP and PS1; in these mice, hyperphosphorylation of tau and NFTs develop in middle-age, following development of plaque pathology, and astrocytosis is also present [63–65]. It is worth noting that, given the lack of NFTs in the majority of these models, it has been suggested that at least some represent models of amyloidosis rather than AD *per se*. It is also worth noting that evidence of inflammation is seen consistently in the region of plaques and lesions, which reflects the human pathology. Finally, not all approaches to modeling AD have been genetic; the disease has also been widely mimicked by direct infusion of aggregated amyloid into the brain ventricles [66, 67] or parenchyma [68], though these in general model acute responses to brief exposures to Aβ, in contrast to the chronic Aβ exposure characteristic of the disease process.

Cognitive deficits and impaired synaptic plasticity are consistently, and sometimes simultaneously, observed in mouse models of AD, as has been reviewed several times [52, 69], however these impairments do not always correlate temporally with AD-like pathology [50]. Aβ deposits are seen in PDAPP and Tg2576 from 6 months with deficits in spatial learning appearing prior to the pathology and increasing in severity with age in the case of PDAPP [70]; in Tg2576 mice the memory deficits reflect the timing of amyloid deposition more closely, but some learning impairments are noted prior to observation of significant pathology [71, 72]. Deficits in spatial working memory as assessed using the Y-maze appear in the APP/PS1 mouse as early as 3 months [73], at around the time amyloid deposition first appears, while deficits in the water maze task, and recognition memory appear from 6 and 12 months respectively [74, 75]. Memory deficits in the 3xTg mice as measured by Morris water maze and inhibitory avoidance tasks appear at 3 months [76, 77], coinciding with onset of Aβ deposition, with progressive impairment in a range of cognitive functions apparent from 6 months onward [78].

The characterization of these models behaviourally and pathologically has allowed spatiotemporal links between amyloid pathology and cognitive function

to be assessed and has revealed that these markers of AD do not necessarily correlate. However, consistent evidence of robust neuroinflammatory responses within the brain has been observed in each model, which has allowed this characteristic aspect of AD pathology to be explored.

AD AND NEUROINFLAMMATION

Neuroinflammation is a major feature of AD neuropathology, as has been recently and comprehensively reviewed [79–83]. There is evidence of increased proinflammatory cytokine expression in the AD brain [84, 85], which may increase the risk of progression from mild cognitive impairment to more severe stages of AD [86]. The presumed source of these cytokines is the reactive astrocytes and microglia that have been observed in the postmortem AD brain [39, 40]. Furthermore, genome-wide association studies have suggested that genes associated with increased risk of inflammatory disease also increase risk of AD [87]. Accordingly, there is some evidence that long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) may reduce risk of AD, although randomized control trials in the clinic have yet to prove successful [88].

These findings in the human brain have prompted assessments of the neuroinflammatory contribution to cognitive impairment and AD-like pathology observed in animal models. These studies, both *in vivo* and *in vitro*, have shown that Aβ can bind to pattern recognition receptors in both astrocytes and microglia, inducing an innate immune response [89]. With respect to astrocytes, AD-associated neuroinflammation is accompanied by reactive astrogliosis, the morphological and functional change seen in astrocytes in response to CNS injury or damage [90]. This has been repeatedly demonstrated in the APP/PS1 mouse [91, 92]. During this process, astrocytes are activated and undergo hypertrophy and/or proliferation [93] that can be identified by increased expression of glial fibrillary acidic protein (GFAP) [94], an intermediate filament protein of the astrocytic cytoskeleton. Reactive astrocytes are intimately associated with amyloid plaques in AD [95] and they can detect, take up and degrade Aβ, possibly via its high affinity for the nicotinic acetylcholine receptors expressed on astrocytes [39]. Astrocytes can become overburdened with Aβ, leading to their dysfunction and consequent lysis, contributing to formation of the amyloid plaque [96]. The debate as to whether

astrocytes are neuroprotective or detrimental in AD is still ongoing, and likely may depend on the phenotype of the activated astrocytes in the plaque region (Box 1). Similarly, the question of whether inflammatory changes mediated by astrocytes, and indeed microglia, contribute to pathogenesis of the disease or if they are secondary to deposition of amyloid-β or other pathological changes remains unanswered. While astrogliosis contributes to AD pathology by upregulating the expression of pro inflammatory cytokines and chemokines and regulating the generation and degradation of Aβ, the presence of Aβ has been shown to disrupt gliotransmission, neurotransmitter uptake, and alter calcium signaling in astrocytes, events that are linked with the cognitive dysfunction characteristic of AD [97]. Conversely, deletion of the genes encoding the filament proteins GFAP and Vimentin, that are required for astrocyte activation, in the APP/PS1 mouse model resulted in rapidly progressing neuropathology due to an increased plaque load and more abundant dystrophic neurites, furthering the hypothesis that astrocytes play a neuroprotective role within the CNS [98].

When microglial cells become activated they phagocytose target particles, release cytokines and, in some cases, free radicals [99]. In the case of neurodegenerative disorders, including AD, microglia can fail to carry out their normal functions, such as clearance of pathological protein aggregates and cell debris. They become chronically activated, continuously releasing neurotoxic substances, contributing to the pathogenesis of AD [100]. Activation of microglia can result in two opposing effects; beneficial anti-inflammatory effects leading to the clearance of Aβ and the release of neurotrophic factors or detrimental effects caused by the release of pro-inflammatory cytokines and free radicals [99]. In mouse models such as APP/PS-1, activated microglia accumulate in the vicinity of Aβ plaques [101]; upregulation of microglial markers has been reported in these mice as early as three months [102] and persists at 14 months and 24 months [103]. Unsurprisingly, microglial upregulation is coincident with expression of proinflammatory cytokines including IL-1β and TNFα [103, 104]. The use of *in vivo* multiphoton microscopy has demonstrated that when plaques begin to form in APP/PS-1 mice, microglial cells begin to aggregate around them within one to two days and that this aggregation is followed by dysmorphic changes in neurites [105]. Microglial activity can be modified by cytokine stimulation in these mice. Treating APP/PS-1 mice with macrophage colony-stimulating factor (M-CSF) leads to an increase in the number of microglia, their phagocytic activity towards Aβ and a consequent reduction in the number of Aβ plaques and improvement in cognitive function [106]. Treatment with the anti-inflammatory cytokine IL-4 in another model of AD, the Tg2576 mouse, reduced astrocytosis and microgliosis and decreased amyloid plaque number and load, changes that were accompanied by improvements in working memory [107]. However, experimental attenuation of neuroinflammation and impaired synaptic function in AD mouse models, in this case APP/PS-1 knock-in mice, is not always associated with alterations in amyloid pathology [108]. Finally, it has been proposed that microglia contribute to the progression of AD pathology via their senescence within the aged brain. The neuroprotective and phagocytic capabilities of these cells therefore reduce, rendering them less effective at combatting repeated insults in the aged or diseased brain and allowing pathology to worsen progressively [109].

A substantial volume of data demonstrates the significant contribution of inflammatory processes to AD pathology and the cognitive impairment associated with it. The search for appropriate drug targets and development of effective pharmaceuticals continues, with anti-inflammatory strategies likely to hold promise as prophylactics or therapeutics. However lifestyle interventions, especially exercise, can also generate anti-inflammatory stimuli that may prove effective in the prevention and treatment of AD.

EXERCISE AND INFLAMMATION

Accumulating evidence strongly supports a general anti-inflammatory role of exercise [110], though the molecular mechanisms have not yet been fully elucidated. In part, this anti-inflammatory effect seems to be related to the direct action of exercise on immune adaptations that occur locally in the exercised skeletal muscle. Skeletal muscle produces and secretes several cytokines, termed myokines, which mediate many of the metabolic changes induced by exercise [111]. The best known myokine is IL-6, which is released from working muscle during exercise and whose increase is reported to upregulate systemic production of anti-inflammatory cytokines, mainly IL-10, and to downregulate systemic levels of pro-inflammatory cytokines, such as TNF-α and IL-1β [112, 113], suggesting that IL-6 produced by skeletal muscle is a primarily anti-inflammatory

effector. Regular exercise modulates the peripheral immune system, decreasing circulating inflammatory cytokines e.g. TNF-α, and IL-1β and increasing anti-inflammatory cytokines such as interleukin (IL)-10 [114]. Exercise can transform adipose resident macrophages from a pro-inflammatory (M1) state, to an anti-inflammatory (M2) state via a mechanism believed to involve the downregulation of toll-like receptor (TLR)-4 expression on several cell types including adipocytes, monocytes, and hepatocytes, leading to a substantial reduction in inflammation and an associated decrease in the risk of development of many non-communicable diseases [29, 115].

Exercise may also exert powerful anti-inflammatory effects in the brain. In animal studies, exercise upregulates IL-10 expression and attenuates the increase in pro-inflammatory cytokine expression in the brain associated with age [116], and lipopolysaccharide (LPS)-induced inflammation [117]. In addition, exercise has been shown to prime microglia and astrocyte activation by decreasing the number of ionized calcium binding adaptor molecule 1 (Iba-1)[+] and GFAP^{+} cells in hippocampus and cortex, in parallel with an enhancement in spatial memory [118], while it has also been shown to increase the number of microglial cells co-localized with BDNF and to protect against cognitive decline in aged mice [117]. Together, these data suggest that exercise-induced enhancement or protection of cognitive function might be associated with the modulatory effect of exercise on systemic and central inflammatory profiles.

Of course, the beneficial effects of exercise on the structure and function of the brain may be mediated by mechanisms other than modulation of inflammation; in particular, a link between exercise, adult hippocampal neurogenesis and preservation of cognitive function in old age has been researched extensively. However the importance, or even presence, of neurogenesis in the adult human brain is hotly debated. As outlined in a recent minireview [119], widely-cited reports of adult human neurogenesis as assessed by bromodeoxyuridine (BrdU) labeling [120] and radiocarbon dating [121] have recently been both supported [122] and contradicted [123] thus we are far from reaching a consensus on this point. Regardless of the outcome of this debate, it is clear that the rodent brain is very neurogenic throughout the lifespan [124, 125] and many investigations of the functional consequences of neuroinflammation, the AD-type phenotype and the effect of exercise on both, have assessed neurogenesis as an output.

Accordingly, experimentally-induced neuroinflammation that activates microglia impairs neurogenesis in a manner that can be reversed by microglial inhibition [126] or administration of NSAIDs [127]. Similarly, IL-1β has been shown to directly reduce neurogenesis [128–130].

EXERCISE, NEUROINFLAMMATION AND AD

The ability of short- or long-term exercise to induce changes in brain structure and function has been assessed in a variety of mouse models of AD, using either voluntary (wheel running) or forced (treadmill running) exercise paradigms. The use of different models and exercise regimes at different ages makes it difficult to directly compare study outcomes. Nevertheless, in general, exercise has been seen to improve cognitive function in AD models, in a manner that in some studies is coincident with decreased Aβ load, increased neurogenesis or decreased inflammation (Table 1). While studies in the APP/PS1 [131–134], Tg2576 [135, 136], Tg-NSE/hPS-2 [137, 138], 3xTg [138, 139] and Tg4-42 [140] models have shown a beneficial effect of exercise on AD pathology and cognitive function, here we place emphasis on the few studies to date that have assessed the impact of exercise on neuroinflammation.

The majority of such studies have used the APP/PS1 model and usually the exercise protocols commence after the age at which plaques have begun to form. For example, a ten week intervention of voluntary wheel running begun in five month old mice, ie when plaque formation has begun but is not yet well advanced, led to a reduction in the number of GFAP[+] astrocytes in the hippocampus [141]. This was coincident with improved spatial learning in the water maze, increased hippocampal neurogenesis and decreased numbers of Aβ plaques and cells positive for phosphorylated tau when compared with sedentary controls. Similar results were observed in a group of APP/PS1 mice that also began exercise at five months, but with a regime of five months treadmill running [142]. Although cognitive function was not assessed, Aβ plaque number and size were reduced as were the number of GFAP^{+} cells, but not Iba-1^{+} cells, indicating modulation of astrocyte but not microglial activation. Exercise begun later in life has also yielded positive results. A five-week treadmill running protocol begun at the age of 7 months or 24 months old attenuated the activa-

Table 1
Exercise-induced effects on inflammation in mouse models of AD

Reference	Age	Exercise	AD pathology	Cognitive function	Inflammation
APP$_{SWE}$/PS-1$\triangle$E9 – Aβ plaques develop from 3–6 months [185]					
Zhang et al., (2018) [142]	5 months	5 months treadmill running	↓ Aβ and plaque number and size		↓ GFAP^{+} cells No reduction in Iba-1^{+} cells
Tapia-Rojas et al., (2015) [141]	5 months	Ten weeks voluntary wheel running	↓ Aβ oligomers and plaque deposits ↓ p-Tau^{+} cells	Improved performance in MWM	↓ GFAP^{+} cells
Xu et al., (2013) [144]	10 month	Six weeks wheel running, two hours per day	No effect on β & γ secretase expression and Aβ42 protein levels	↔ MWM	No reduction in GFAP[+] and Iba-1^{+} cells
Ke et al., (2011) [143]	7-8 & 24 month	Five week treadmill running protocol	↓ Aβ42 expression in adult mice ↔ Aβ plaque number in aged mice	↔ passive avoidance Improved performance in MWM in aged, not adult mice	↓ Microglial activation in adult and aged mice
Tg2576 – Aβ plaques develop from 9–12 months [54]					
Nichol et al., (2008) [146]	16–18 months	Three weeks voluntary wheel running	↓ soluble Aβ		↓ IL-1β and TNFα ↑CD40 and MHCII
Parachikova et al., (2008) [147]	15–19 months	Three weeks voluntary wheel running	No effect on amyloid pathology	Improved performance in radial arm water maze	↑ IL-11, CXCL1 & CXCL12 mRNA
Tg-NSE/hPS-2 – Aβ plaques develop from 12 months old [186]					
Koo et al., (2013) [149]	24 months	Three month treadmill running protocol		Improved performance in MWM	↓ COX2 protein ↓ Caspase-3 protein
Um et al., (2011) [150]	24 months	Three month treadmill running protocol	↓ Hippocampal Aβ42 protein ↓ Tau phosphorylation	Improved performance in MWM	↓ COX2 protein ↓ Caspase-3 protein
Leem et al., (2011) [148]	16 months	Three month treadmill running protocol	↓ Tau phosphorylation		↓ GFAP^{+} cells ↓ MAC-1^{+} cells ↓ TNF-α IL-1β and IL-6 mRNA ↓ COX-2 iNOS
Triple transgenic mice – Aβ plaques develop from 3-4 months [63]					
Do et al., (2018) [154]	8 weeks	Four weeks voluntary wheel running	No pathology in hypothalamus		↓ TNF-a and IL-6 in hypothalamus
Haskins et al., (2016) [187]	3 months	12 weeks treadmill running			↑ RANTES in blood ↓ RANTES in cortex ↓ MCP-1 in
THY-Tau22 – p-Tau^{+} cells develop from three months old [188]					
Belarbi et al., (2011) [151]	3 months	Nine months voluntary wheel running	↓ Abnormal p-Tau expression	Improvement in spontaneous alternation	No effect on GFAP^{+} cells and IL-1β, TNF-α and CD68 mRNA in the hippocampus

tion of microglia [143], although neither astrocyte number nor activation was assessed in this study. Performance of the older mice in the Morris water maze was improved, but no change in the Aβ plaque number was observed. Conversely, other studies have shown no effect of exercise on glial activation. Six weeks of wheel running begun at 10 months of age yielded no observable change in numbers of GFAP[+] astrocytes and Iba-1^{+} microglia, nor any effect on Aβ42 protein expression or spatial learning [144],

though in this study exercise was combined with antioxidant treatment. Mixed results have also been observed in other AD models. In the Tg2576 model, three weeks of wheel running begun at 16-18 months, which has been shown to improve performance in the radial arm water maze [145] decreases soluble $A\beta$ and reduces IL-1β and TNFα in the hippocampus to wild-type levels. In parallel, it increases expression of Cluster of differentiation 40 (CD40) and major histocompatibility complex class II (MHCII), found on antigen-presenting cells, in the hippocampus, indicating a shift from an innate to adaptive immune response [146]. A similar study assessing the effects of three weeks of wheel running in Tg2576 mice begun at 15–19 months showed identical cognitive improvements concomitant with increased expression of the neuroprotection-associated chemokines C-X-C motif ligand 1 (CXCL1) and C-X-C motif 12 (CXCL12) [147]. When 16 month old Tg-NSE/hPS-2 mice undergo three months of treadmill running, decreased tau phosphorylation is observed in parallel with decreased expression of cytokines and inflammatory markers and decreased numbers of GFAP$^+$ astrocytes and macrophage 1 antigen (MAC-1)$^+$ microglia [148]. When exercise is begun even later, at 24 months, improved spatial learning in runners is observed coincident with decreased expression of cyclooxygenase-2 (COX2) and caspase-3 in the cortex and decreased apoptosis in the hippocampus [149, 150]. Other studies have assessed the possible protective effects of exercise begun before plaque formation or hyperphosphorylation of tau begins. While 12 weeks treadmill running in three month old triple transgenic mice revealed a dose-dependent reduction in chemokine expression in blood and cortex, nine months of voluntary wheel running begun at three months failed to alter the number of GFAP$^+$ astrocytes or affect mRNA expression of IL-1β, TNF-α and cluster of differentiation 68 (CD68) in the hippocampus of THY-Tau22 mice [151], although tau pathology was reduced and cognitive impairment in the Y-maze task was prevented. The question of how efficacious exercise may be at different phases of the lifespan is key. Independent of AD pathology, age itself is a major risk factor for development of AD and is also associated with inflammation, leading to the coining of the term 'inflammaging'. Age-related increases in inflammatory markers are linked with decreased neurogenesis [152] and cognitive impairment [153], meaning that studies of the effects of exercise on models of AD must consider age as an independent factor. Finally, while most research has

focussed on the impact of exercise on cells of the hippocampus and cortex in these models, a recent study showed that voluntary exercise in the triple transgenic mouse model decreased phenotype-associated apoptosis and expression of inflammatory markers in the hypothalamus, suggesting metabolic dysregulation in this model that may be improved by exercise [154]. This is an intriguing result, given evidence of the increased risk of AD associated with metabolic disorders including type 2 diabetes mellitus [155, 156].

It is evident from these studies and others that crosstalk between the immune and nervous systems allows inflammation to affect neurogenesis and cognition both in wild type and AD mouse models and that exercise provides a potential mechanism to direct and tune the inflammatory response. Few studies to date have examined the effects of exercise on hippocampal neurogenesis, cognitive performance and inflammation in AD models simultaneously; such data could provide new insights into the mechanisms of disease progression and reveal novel therapeutic directions.

CONCLUSION

A growing body of evidence confirms the pivotal role of inflammation in the genesis and progression of AD pathology. Our understanding of the profound influence that regular exercise can have on the function of the immune system has grown in parallel. The merging of these bodies of knowledge and their reciprocal influence on the AD field is only beginning. However, we are now beginning to tease out the cellular mechanisms involved in the anti-inflammatory effects of exercise, for example the ability of exercise to modulate macrophage phenotype or 'polarization' in the peripheral tissues. Since exercise can also influence the activation of microglia and astrocytes, cells that play key roles in AD pathology, the field is ripe for specific assessments of how exercise may influence the phenotype and function of glia in the AD brain. Such studies will provide data leading to refinement of exercise regimes to more effectively regulate the neuroinflammatory response and hence cognitive function in these AD models. As such, it is hoped that a consensus will be reached on the appropriate timing and duration of effective exercise protocols, knowledge that may be of relevance to the human population. In the absence of effective

pharmaceutical treatment of AD, such information is of even greater importance to the individual and to society.

CONFLICT OF INTEREST

The author have no conflict of interest to report.

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