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Exercise for the prevention of Alzheimer's disease: Multiple pathways to promote non-amyloidogenic AβPP processing

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ABSTRACT

With advancements in our ability to treat or manage more diseases than ever, people are able to live longer in greater health. However, for individuals who develop Alzheimer's disease (AD), therapeutic options are currently limited to symptom management or have minimal impact on underlying disease mechanisms. The effectiveness of available treatments also diminishes as the disease progresses. Therefore, it is critical that interventions are implemented in early stages of disease to prevent the establishment of pathological features and to delay or prevent cognitive decline that can severely lower quality of life. Regular exercise is known to reduce the risk of, and may slow the progression of AD. A significant portion of the known benefits of exercise are likely due to the modification of cardiometabolic risk factors, which are associated with AD. However, the mechanism by which exercise might confer neuroprotective benefits, specific to the pathology of AD, are not well understood. This review examines the effect of exercise on several biochemical pathways, focusing on their convergence at 'a disintegrin and metalloproteinase-10′ as a mediator capable of delaying the progression of Alzheimer's disease.

1. Introduction

Projections estimating the prevalence of Alzheimer's Disease (AD) suggest a looming epidemic of cases worldwide, in part explained by an ageing population [1]. Despite a declining trend in incidence rate, the number of years people are living with AD is increasing [2], which places a significant burden on health and economic cost. There is significant evidence to suggest that obesity, alongside associated metabolic and vascular comorbidities, is associated with AD and the link between obesity and AD is likely through direct mechanisms [3]. The combination of poor dietary intake and a lack of physical activity, which are major contributors to obesity, are both associated with an increased risk of AD [4]. This risk is thought to be particularly elevated for people with obesity in mid-life. Contrary to this, it has been suggested that obesity in later life may confer a lower risk of AD. However, it is highly possible that this is more representative of reverse causation, especially when considering the prodromal nature of AD. That is to say, older people who are in a prodromal phase of AD, are more likely to lose weight compared to individuals who remain cognitively healthy [5]. With advancements in our ability to treat more diseases than ever, it is understandable that people are able to live longer in greater health. However, for individuals who develop AD, therapeutic options are currently limited to symptom management and fail to address underlying disease mechanisms. Regular exercise is known to reduce the risk of AD and may slow the progression of the disease. A significant portion of the known benefits are likely due to modifying the cardiometabolic risk factors associated with AD. However, the mechanisms that confer the neuroprotective benefits specific to the pathology of AD are not well understood. This article aims to review the literature surrounding exercise as a preventative tool in the prevention of AD with particular focus on the effect of exercise on non-amyloidogenic Amyloid-β precursor protein processing.

2. Amyloid-β precursor protein processing in Alzheimer's disease

The hallmark neuropathological correlates of the AD brain are typically identified as extracellular plaques, primarily consisting of Amyloid-β (Aβ), and intracellular tangles of hyperphosphorylated Tau protein [6]. Synaptic degeneration, neuroinflammation and perturbed morphological features, such as, a reduction in hippocampal volume and cortical thinning are also common in the later stages of the neurodegenerative process [6]. Of these, Aβ has been extensively studied as one

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of, if not the major contributing feature to the progression of AD [7]. Identification of the mutations to *APP* and *PSEN1/2* genes that cause hereditary familial AD, alter the production and processing of the Aβ precursor protein (AβPP) [7]. The pathological features shared in both late-onset and familial AD brain added significant weight to the role of Aβ in AD. This has placed an importance on understanding how Aβ generation is regulated and how therapeutic options may be used to modify this process. The generation of Aβ occurs through the proteolytic shedding of AβPP by enzymatic 'scissors' that cut down the full-length protein in successive steps [8]. Post-translational modifications, such as glycosylation, are known to mediate AβPP trafficking through the secretory and endo-lysosomal pathways. N-glycosylated AβPP (Immature AβPP) is held in the endoplasmic reticulum, whereas the modification of O-glycosylation sites promotes AβPP (mature AβPP) movement to the cell membrane [9,10]. Mature O-glycosylated AβPP is also more likely to be held in the cell membrane [11]. AβPP is proteolytically cleaved in two distinct processing pathways which are highly dependant on the cellular trafficking of AβPP and the activity of three key enzymatic interactions (see Fig. 1). This consecutive shedding process is named 'regulated intramembrane proteolysis' and is typically associated with cell signalling pathways [12].

2.1. Amyloidogenic AβPP processing

The 'Amyloidogenic' pathway, termed based on the subsequent generation of Aβ, is initiated by β-Amyloid cleaving enzyme-1 (BACE-1). BACE-1 cleavage of AβPP predominately occurs in the trans-golgi network and endosomal pathways where BACE-1 possesses high activity releasing the N-terminal fragment, soluble AβPP-β, leaving the Aβ-containing C-terminal fragment C99 anchored to the membrane [13]. Subsequent cleavage by the γ-secretase enzyme, liberates the Aβ-peptide and the AβPP intracellular domain. Aβ peptides of differing lengths have been identified from Aβ1–37 to Aβ1–43. Most commonly, Aβ1–40 is produced and is considered the most physiologically normal Aβ peptide. In fact, the regulated release of Aβ1–40 may have benefits for the brain including aiding in fighting infection, maintaining the blood brain barrier integrity and regulating synaptic functions [14]. Conversely, the loss of regulated Aβ production leading to increased generation of longer Aβ peptides, in combination with poor clearance is deleterious in the brain. Crucially, longer Aβ peptides are able to more rapidly aggregate, forming soluble oligomeric Aβ species [15] which are more neurotoxic [16]. Intracellular Aβ oligomers have been implicated in elevating endoplasmic reticulum stress, calcium ion dyshomeostasis, mitochondrial damage and a loss of proteostasis leading to apoptosis [17–20] and thus are able to significantly disrupt cellular function. Further, Aβ oligomers can cause cellular damage by interacting directly in extracellular compartments. Such mechanisms include the direct binding to, and disruption of, the plasma membrane [21,22]; the formation of pores in the membrane that can lead to dysregulated permeability [23,24] and binding to receptors to influence cell signalling [25]. This multitude of interactions highlights the potential for Aβ oligomers to have widespread cytotoxic effects throughout the brain.

2.2. Non-Amyloidogenic AβPP processing

The non-amyloidogenic processing pathway is initiated by α-secretase enzymatic cleavage of AβPP through the Aβ region. This prevents the formation of Aβ peptides. The primary site of α-cleavage is at the cell membrane resulting in the release of the N-terminal fragment sAβPPα into extracellular compartments. The remaining intramembrane C-terminal fragment consisting of 83 amino acids can then be further cleaved by the γ-secretase enzyme to release a truncated Aβ peptide known as P3 and the AβPP intracellular domain [26].

Several zinc metalloproteinases are members of the 'a disintegrin and metalloproteinase' (ADAM) family and are known to possess α-secretase activity. This includes ADAM9, ADAM10, ADAM17 and ADAM19 [27,28]. Whilst the cleavage of AβPP can be shared between multiple ADAMs, in neurons, ADAM10 appears to be the major physiologically relevant α-secretase [29,30]. The ADAM10 zymogen (proADAM10) undergoes prodomain cleavage by proprotein convertase enzymes, PC7 and Furin [31]. This generates the catalytically active, mature ADAM10 (mADAM10) enzyme. Blocking this process can significantly reduce membrane expression of ADAM10 [32] and lower sAβPPα secretion [31]. The maturation of ADAM10 is regulated during trafficking to the cell membrane, where it is most active, by a series of Transmembrane-4 superfamily proteins known as Tetraspanins (TSPAN). In particular, a sub-group known as the C8-TSPANs have been of particular interest [33]. These partner proteins have been shown to direct the interaction of

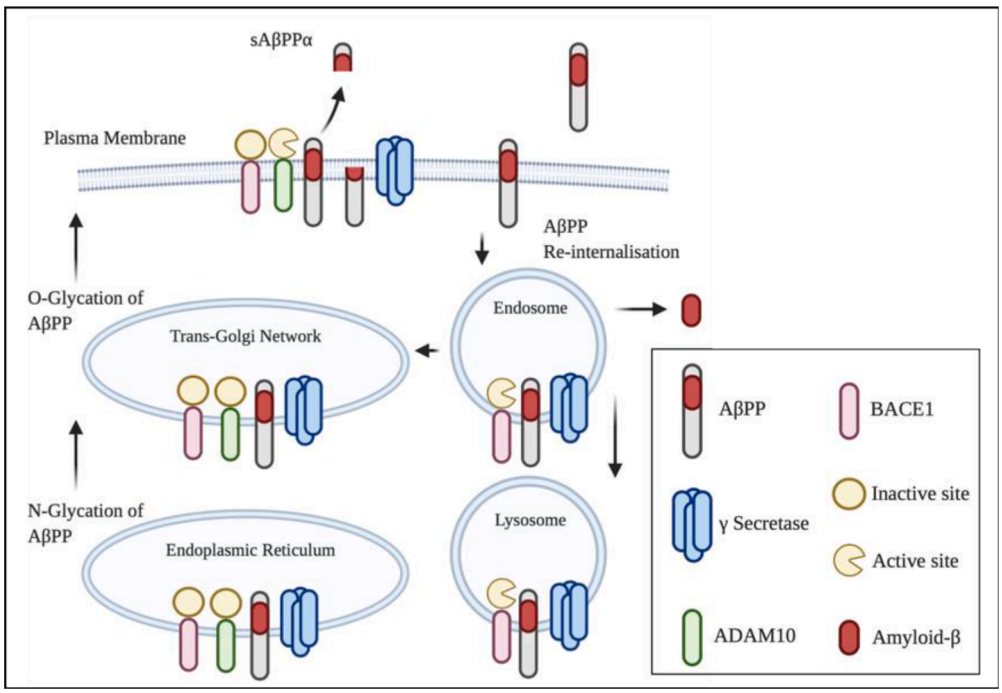

Fig. 1. Diagrammatic representation of the trafficking and processing of AβPP from intracellular compartments to the cell membrane. Movement of AβPP through the secretory pathway to the cell membrane is regulated by post-translational glycation. ADAM10 prodomain cleavage by proprotein convertase enzymes, PC7 and Furin, during trafficking, enables ADAM10 enzymatic activity at the cell membrane which is a major site for ADAM10 activity and non-amyloidogenic AβPP processing. ADAM10 cleavage of AβPP leads to the liberation of sAβPPα. The remaining intramembrane C-terminal fragment consisting of 83 amino acids can then be further cleaved by the γ-secretase enzyme to release a truncated Aβ peptide known as P3 and the AβPP intracellular domain (not shown). Internalisation of AβPP into the endo-lysosomal pathway is a major site of BACE-1 cleavage and Aβ generation. The N-terminal fragment, soluble AβPP-β is released, leaving the Aβ-containing C-terminal fragment C99 anchored to the lysosomal membrane. This is termed the amyloidogenic pathway.

ADAM10 with AβPP at the cell membrane and can either have inhibitory or promoting effects on non-amyloidogenic AβPP processing depending on the C8-TSPAN/ADAM10 pairing [33,34]. The upregulation of ADAM10 activity and therefore, non-amyloidogenic AβPP processing, significantly blunts the formation of Aβ peptides. This suggests that both pathways are able to compete for AβPP substrates [29]. In addition, the secretion of sAβPPα is associated with neuroprotective effects. These effects include neurogenesis, maintenance of synaptic function and supporting the formation of neuronal networks [35]. The generation of sAβPPα is thought to be protective in the adult brain, and even more so in the aged brain. This is supported by evidence that in AβPP deficient mice, the addition of exogenous sAβPPα can rescue long term potentiation and have beneficial effects on memory [36]. In both cell and animal models, treatment with sAβPPα has also been shown to reduce Aβ toxicity, tau hyperphosphorylation and inhibit BACE-1 activity [37,38]. Mutations to the ADAM10 gene that attenuate enzymatic activity are shown to associate with susceptibility to late-onset AD [39]. Therefore, the modulation of ADAM10 could be a target for therapeutic intervention in AD.

3. Exercise as a tool in the prevention of Alzheimer's disease

Regular exercise is widely regarded as an effective way to improve cerebrovascular and cardiometabolic health, maintain functional abilities and promote healthy ageing [40]. Exercise has also been investigated as a tool in the primary prevention of AD or as a disease slowing intervention [41]. From longitudinal epidemiological research, the effectiveness of exercise has been clearly shown to confer protection against the risk of cognitive decline, highlighting a role for exercise in delaying the onset of AD. Evidence for the ability of exercise engagement to slow the progression of severe stage of AD is less clear, however, it is evident that promoting exercise throughout the lifespan will convey some protective benefits for people with AD, whether this is by directly attenuating the core pathology or by reducing risk factors associated with AD [42,43]. Contrary to this, a lack of exercise engagement or prolonged sedentariness is linked with poor vascular function and an increase in the prevalence of risk factors associated with AD [44]. Although the optimal 'dose' of exercise required to elicit protective benefits for the brain is unknown, improved cognitive function is associated with increased physical activity in people with AD [43,45]. Overall, exercise is widely regarded as a non-pharmacological approach to preventing the progression of AD. The neuroprotective benefits of exercise are attributed to a number of mechanisms affected in the AD brain such as, improved energy metabolism, reduced oxidative stress, increased neurogenesis, synaptic plasticity, and reduced inflammation. One major area of interest is whether such improvements associated with engagement in exercise can reduce or prevent the establishment of Aβ pathology.

3.1. *Exercise and AβPP processing in Alzheimer's disease*

Investigating the effects of exercise on AβPP processing, and the subsequent generation and clearance of Aβ in animal models, suggests exercise can have positive effects. Despite large variance in the duration of exercise interventions, ranging from 3 weeks to over 12 months, both a reduction in the Aβ1–42:40 ratio [46–48] and Aβ plaque formation [49–51] have been evident. Interestingly, exercise interventions of shorter duration are most associated with lowering of Aβ peptide generation, which is a more transient marker of AβPP processing. In fact, even an acute bout of exercise offers protection against Aβ neurotoxicity [52]. The apparent interference of exercise in amyloidogenic AβPP processing has been linked to a lower amount of AβPP availability and reduced BACE-1 activity [46]. However, this effect was only apparent in Aβ-infused conditions and there was no effect of exercise in control conditions. This perhaps highlights a scenario whereby exercise is most effective at delaying or preventing Aβ accumulation under worsening pathology. High levels of cholesterol-rich membrane lipid rafts are a key site for BACE-1 – AβPP interaction. Following 12 weeks of treadmill running, *APP* and *PSEN1* transgenic mice had a lowered Hippocampal lipid raft content which coincided with lowered amyloidogenic AβPP processing [53]. This highlights one way in which exercise may indirectly modulate AβPP processing. Temporary suppression of Hippocampal BACE-1 content has also been shown following an acute exercise bout in high fat fed mice compared to sedentary controls [54]. Further to this, evidence of enhanced Aβ clearance suggests exercise is likely able to reduce Aβ pathology in multiple ways, not just by regulating Amyloidogenic AβPP processing [55]. Despite strong evidence of a reduction in Aβ-accumulation with exercise in animal models, the data generated from human participants is less convincing all be it relatively under investigated.

In cognitively healthy individuals, lower levels of physical activity are associated with an elevation in Aβ-accumulation, suggesting exercise may be protective against pathological features of AD [56]. However, conflicting evidence from cognitively healthy individuals with elevated cerebral Aβ burden suggests that, despite strong cardiometabolic benefits, exercise doesn't modify Aβ pathology [57]. Further, there is evidence to suggest that exercise effects on Aβ become less pronounced in people with subjective memory complaints or mild cognitive impairment. This evidence has been comprehensively explored by Brown et al. [58]. This raises a challenging question. Why is exercise promoted as beneficial to protect against AD if human data often falls short of identifying significant improvements in pathology and symptoms? This may be answered by highlighting a number of limitations to the current literature surround exercise in people with AD.

Exercise interventions for AD are often conducted over a short time frame relative to the time-course of AD progression. Thus, aiming to detect changes in established amyloid pathology, which may have a long temporal development prior to clinically recognised symptoms [59] with interventions lasting a number of weeks/months, is likely too short. Further, exercise interventions are often in relatively small sample sizes. Instead, implementing exercise interventions much earlier, perhaps in mid-life may be more suited to uncovering the benefits of exercise for preventing AD [60]. This will be supported by the development of more sensitive methods of detecting changes linked to the progression of AD in the prodromal phase.

Exercise and increased physical activity are however, associated with a number of benefits that can impact brain health. Exercise is associated with improved cerebral blood flow, stimulation of neurotrophic factors, improved neurotransmission, reduced inflammation and improved cholesterol metabolism [61]. Investigating the mechanisms and pathways linked to the potential benefits of exercise for modulating AD is critical to improve and optimise physical activity recommendations. One such target is the non-amyloidogenic AβPP processing enzyme ADAM10. Although direct evidence of this is limited to animal models (see Table 1), there is strong suggestion that a number of factors that can enhance ADAM10 expression and activity are induced by both acute exercise bouts and adherence to greater physical activity [49,50,53,62]. This may also explain why limited beneficial effects are seen for reversing established AD pathology, instead working as a method to prevent the disease progression. Not only this, but ADAM10 may also be a useful marker for optimising exercise bouts for maximising the benefits in people with AD.

3.2. *ADAM10 as a target for exercise induced non-amyloidogenic AβPP processing*

As previously described, promoting non-amyloidogenic AβPP processing could be beneficial in AD by promoting ADAM10 activity and increasing the secretion of sAβPPα. Further, it is possible that elevated ADAM10 activity can decrease Aβ generation by reducing BACE-1 interaction with AβPP, however, evidence supporting this competing effect is mixed and limited to specific subcellular compartments [26].

Table 1
Effects of exercise on ADAM10 activity.

Authors	Model	Mode of exercise and control	Exercise protocol	Main outcome on ADAM10
(Yu et al., 2021)	3-month-old C57BL/6 J WT ($n = 9$) and APP/PS1 ΔE9 CE model ($n = 9$).	Treadmill running (exercise) or stationary treadmill (control)	Acclimation: 3 days Protocol: 5 days per week for 12 weeks, 45mins/session.	Increased hippocampal levels of ADAM10 and sAβPPα in both control and AD model following exercise.
(You et al., 2021)	12-month-old C57BL/6 J WT ($n = 9$) and Adiponectin KO (APN) model ($n = 9$).	Treadmill running (Exercise)	Acclimation: 4 days Protocol: 7 days per week for 20 consecutive days, 60mins/session.	Increased ADAM10 levels in control. No change in APN model with exercise.
(Wang et al., 2021)	B6C3F1 (APPswe) APP/PS1 CE model. 9-week-old ($n = 7$), 24-week-old ($n = 7$).	Voluntary wheel running (Exercise) or no wheel access (control)	Acclimation: 7 days Protocol: 16 weeks, voluntary running.	Young AD mice showed significant elevation in hippocampal ADAM10 following exercise but not in cortex. ADAM10 decreased in the hippocampus of aged AD mice, no change in cortex.
(Choi et al., 2021)	24-month-old WT ($n = 9$) and APP-C105 CE model ($n = 9$).	Treadmill running (exercise) or stationary treadmill (control)	Acclimation: 7 days Protocol: 5 days per week for 8 weeks, 30mins/day.	ADAM10 levels not significantly increased following exercise, AD ADAM10 levels were not significantly different to healthy control levels following exercise.
(Zhang et al., 2019)	3-month-old WT ($n = 12$ and Tg2576/M145L (APP/PS1) transgenic AD model ($n = 12$).	Treadmill running (exercise) or stationary treadmill (control)	Acclimation: 6 days Protocol: 5 days per week for 12 weeks, 45mins/day.	Increased Hippocampal ADAM10 level following exercise in AD model, not control.
(Zhang et al., 2018)	5-month-old C57BL/6 WT ($n = 6$) and APP/PS1 transgenic AD model ($n = 6$).	Treadmill running (exercise)	Acclimation: 2 days Protocol: 6 days per week for 20 weeks, 30mins/day.	Increased brain homogenate ADAM10 level following exercise in AD model, not control.
(Nigam et al., 2017)	7/9-month-old B6C3-Tg (APPswe/PS1Δ9–85Dbo transgenic AD model ($n = 8$).	Voluntary wheel running (Exercise) or locked running wheel (control)	Acclimation: 2 days 3 weeks of voluntary running	Increased sAβPPα in hippocampus following exercise, this effect was blocked with α-secretase inhibitor.
(Koo et al., 2017)	12-month-old C57BL/6 x BDA/2 WT (sed, $n = 8$) and NSE/APPswe transgenic AD model ($n = 8$).	Treadmill running (exercise) or stationary treadmill (control)	Acclimation: 5 days Protocol: 5 days per week for 12 weeks, 30–60mins/day.	Increased ADAM10 levels and sAβPPα in exercise AD model compared to sedentary AD model in cortex.
(Liu et al., 2013)	3-month-old C57BL/6 J WT ($n = 12$) and APP/PS1 transgenic AD model ($n = 12$).	Treadmill running (exercise) or stationary treadmill (control)	Acclimation: 2 days Protocol: 5 days per week for 20 weeks, 30mins/day.	ADAM10 levels not significantly increased but restored to healthy control levels in AD model following exercise. No effect on sAβPPα.

Studies investigating the effects of exercise on ADAM10 levels/ activity in animal models. Sample size (n) is indicated as the number in the exercise group.

Whilst conflicting data between animal and human studies for the effect of exercise on AD pathology measured via Aβ and Tau has been found, ADAM10 may offer a more dynamic marker capable of detecting exercise effects on AβPP processing. Although there is only a limited amount of research into the potential effect of exercise on ADAM10, there are a number of specific mechanisms and pathways which make ADAM10 a plausible target (see Fig. 2 for overview).

3.2.1. Metabolism and redox balance

Significant evidence of both central and peripheral metabolic dysfunction in people with AD has been found with pathophysiological pathways beginning to be identified. These include cholesterol imbalance, impaired insulin signalling, mitochondrial dysfunction, redox imbalance and altered presence of key metabolites [63,64], each of which have been linked to the accumulation of Aβ and subsequent neurodegeneration. The beneficial effects of regular exercise for preventing or even reversing many metabolic diseases and for improving outcomes in people with AD is well characterised, however, whether exercise confers protection against AD through promoting ADAM10 activity is less well known. Impaired insulin signalling is widely recognised as a feature of the AD brain [65]. With exercise known as an intervention capable of restoring insulin sensitivity, it may be a possible pathway for restoring ADAM10 activity. Increased hormonal signalling by insulin and insulin-like growth factor-1 (IGF-1) has been demonstrated to increase non-amyloidogenic AβPP processing, perhaps through altering intracellular AβPP trafficking [66,67]. There is also evidence of a reduction in Aβ generation [68]. Although contrasting evidence of a reduction in both ADAM10 and BACE-1 processing has been shown in APP/PS1 mice following exposure to IGF-1 [69].

Evidence of impaired mitochondrial bioenergetics also points towards metabolic factors underlying AD pathogenesis. Damaged mitochondria cannot support neuronal activity and are unable to provide enough energy supply and other related mitochondrial functions to neurons [70], exposing neurons to mitochondrial related oxidative damage. Oxidative damage has been proposed as an early event in the development of AD [71]. In conditions where oxidative stress is evident, ADAM10 expression and activity is also lower [72,73]. Further, there is some evidence that oxidative insults may act to lower ADAM10 activity and sAβPPα secretion, whilst favouring amyloidogenic AβPP processing [74,75]. With the adaption to regular exercise leading to a better ability to tolerate oxidative stress [76], this may provide an avenue of preserving ADAM10 activity in AD.

Exercise also acts against the development and progression of AD via promoting mitochondrial fitness and regulation of mitophagy which is in part mediated by SIRT1 [77]. SIRT1 is a NAD^+-deacetylase and has been reported to be involved in the regulation of cellular senescence and

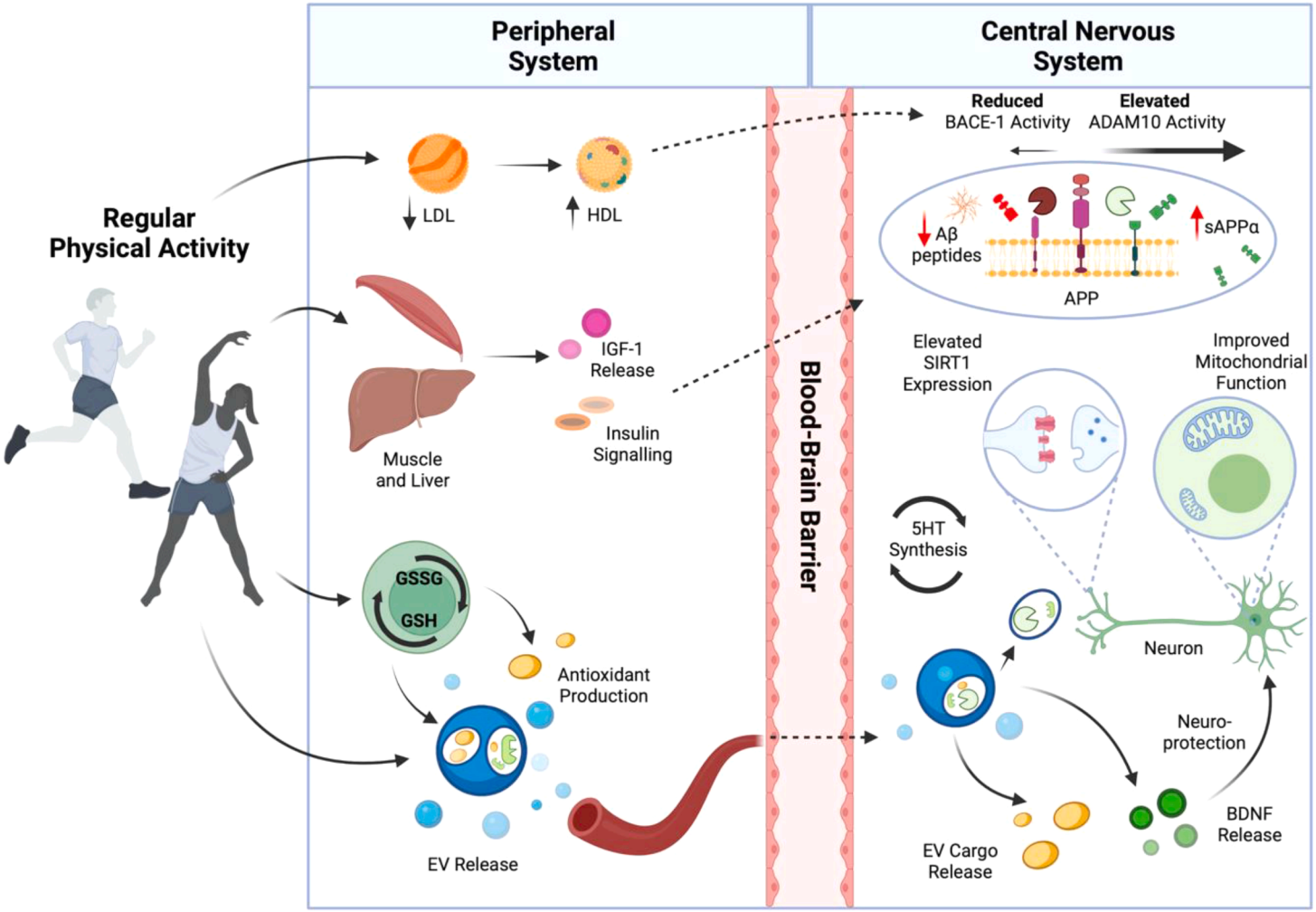

Fig. 2. Exercise can stimulate the release or upregulation of multiple pathways in both peripheral and central tissues. Peripherally secreted factors are able to cross the blood brain barrier and may influence AβPP processing. The effects of exercise on these systems are able to shift AβPP processing towards the non-amyloidogenic pathways by increasing ADAM10 activity and reduce Aβ production by limiting BACE-1 activity (Created with Biorender.com).

ageing, thus making it an interesting therapeutic target for AD [78]. Regular exercise has been shown to upregulate SIRT1 expression which plays a role in multiple interconnected regulatory networks that modulate dendritic and axonal growth, as well as survival against stress. SIRT1 is also involved in maintaining neuronal plasticity, cognitive functions, protection against ageing-associated neuronal degeneration and cognitive decline [79]. Interestingly, SIRT1 is also associated with ADAM10 and the upregulation of SIRT1 can boost ADAM10 activity [80, 81]. In fact, in a mouse model of AD, treadmill exercise inhibited Aβ production via upregulation of SIRT-1, which was proposed to bias amyloid precursor protein processing towards non-amyloidogenic processing [49]. From this, it is clear that exercise, by modulating cell metabolism and redox balance, may be able to upregulate ADAM10 activity, although this evidence is limited to a small number of studies, often from various cellular and animal models.

3.2.2. Cholesterol dysregulation

Dysregulation of cholesterol metabolism in the brain has been associated with the pathogenesis of AD [82]. Similarly, high blood cholesterol concentrations have been found in people with AD [82] which is associated with an increase in the risk of AD in later life [83]. An important consideration is that central and peripheral cholesterol levels are regulated independently, with dietary intake predominantly effecting blood cholesterol and *de novo* synthesis effecting the cholesterol content of the brain [84]. There is extensive literature published showing exercise as a method of improving blood cholesterol levels by increasing HDL, lowering LDL/VLDL and reducing triacyclglycerol content [85]. This may in turn negate the effects of poor cholesterol levels on cerebral vasculature function, promoting overall brain health. Yet less is known about how regular exercise may impact cholesterol synthesis and transport in the brain. This is important as one mechanism by which cholesterol increases the risk of AD is through effecting AβPP processing [82]. Strong evidence of the role of lipid transport in AD comes from the implications of carrying the ApoEε4 allele, which is a major risk factor for AD. ApoE is the main apolipoprotein class present in the central nervous system and is a major lipid transporter in the brain and in particular responsible for cholesterol transport. ApoE has three alleles, ε2, ε3 and ε4, of which ApoEε4 is the major risk factor for late-onset AD [86]. In AD, ApoE alleles are often studied for their effect on clearance of Aβ oligomers, activation of glial cells and to contribution to neuronal dysfunction [87]. In addition, there is some evidence that ApoE genotype may affect ADAM10 expression and activity, with ADAM10 levels reduced in ApoEε4 carriers compared to ApoEε2 and ApoEε3 isoforms. This is supported by evidence of reduced ADAM10 activity in both cell models exposed to ApoE and lower ADAM10 expression in solubilised fractions of human cortex [88]. In carriers of ApoEε4 exercise is still able to provide benefits against the pathology of AD through a number of pathways, one of which is through stabilising cholesterol levels [89]. This stabilising of cellular cholesterol may be a mechanism by which exercise modulates ADAM10 activity. Interestingly, elevated cholesterol is associated with decreased ADAM10 levels and elevated Aβ1–42 generation [90]. In contrast, depleting cellular cholesterol increases ADAM10 activity and improves membrane dynamics [91,92]. To support this data, treatment with statins, which act to limit cholesterol biosynthesis, is linked with increased ADAM10 activity [93]. Cholesterol reduction via statin treatment has been shown to increase sAβPPα generation and reduced Aβ production [92,94]. Further, a 12-week treadmill exercise programme in APP/PS1 mice was found to reduce total cholesterol, activity of 3-hydroxy-3-methylglutaryl-coenzyme A reductase, as well as reduce the number of lipid rafts in the hippocampus whilst increasing ADAM10 activity and limiting Aβ deposits [53]. Thus, the positive effects of exercise on cholesterol homoeostasis may act to regulate ADAM10 activity and thus, protect against AD.

3.2.3. Brain derived neurotrophic factor

Brain Derived Neurotrophic Factor (BDNF) can enhance neuroplasticity through regulation of several pathways relating to synaptogenesis, neurogenesis, and long-term potentiation [95]. BDNF may also be a crucial mediating factor between exercise and improved brain health [95,96]. For an extensive review see here [62]. Reduced BDNF has been long associated with AD, possibly linked to the progression of the disease [97,98]. In more severe cases of AD, lower BDNF can be detected peripherally in serum samples [99]. Further, alterations in hippocampal BDNF levels may be linked to the presentation of phosphorylated Tau pathology [100]. Polymorphisms linked to the BDNF gene have also been associated with a worse rate of cognitive decline in $A\beta^{+}$individuals defined as preclinical AD [101]. BDNF binds to Tropomyosin receptor kinase B (TrkB) and results in the autophosphorylation of the intracellular tyrosine kinase domain of the receptors. This affects a number of downstream signalling pathways such as, mitogen-activated protein kinase (MAPK), phospholipase C-c, phosphatidylinositol-3-kinase (PI3K), protein kinase C (PKC) and cAMP-response element biding (CREB) protein [62]. There is evidence that this BDNF signalling can modify ADAM10 activity. The differentiation of neuroblastoma into neuron-like cells through retinoic acid and BDNF is associated with a concomitant increase in α-secretase processing of AβPP [102]. Further, the disruption of BDNF signalling results in an increased secretion of Aβ, leading to neuronal death in primary hippocampal neurons [103]. Interestingly, a dose-dependant neuroprotective effect of BDNF against Aβ exposure has been shown in rats. Inhibiting TrkB signalling blocked this protection [104]. This is supported by evidence of an exercise-induced increase in α-secretase activity and a reduction of Aβ generation in transgenic mice. This was mediated by a redistribution of α-secretase within the cell and an inhibition of β-secretase activity [105]. Thus, it is possible that exercise may be of therapeutic value against AD through increasing BDNF, although the mechanisms merit further investigation.

3.2.4. Serotonin signalling

The effect of exercise on brain serotonin (5HT) levels has been of particular interest in understanding the potential for antidepressant action without need for pharmacological intervention. Neurogenesis and neuroplasticity are both associated with increased exercise which may be mediated by restored 5HT signalling [106]. A direct role for 5HT in exercise induced neurogenesis has been identified in Tryptophan hydroxylase-2 deficient mice [107]. Interestingly, these effects may act in shared pathways with BDNF [108]. Measuring peripheral tryptophan bioavailability, which is a precursor to 5HT, has also been seen to be elevated following both acute bouts and chronic exercise in older adults [109, 110].

In AD, increasing 5HT concentrations in the synaptic cleft is thought to be of therapeutic value to slow the progression of pathological features [111]. This has also resulted in the development and trialling of small molecules to modulate 5HT receptor action as well as the potential utility of selective serotonin reuptake inhibitors (SSRI) for delaying AD [112]. Modulation of the 5HT receptors (5HTr), 5HT4r and 5HT6r, have been of particular interest for their regulation of AβPP. Agonist stimulation of 5HT4r is associated with a shift in AβPP processing towards sAβPP-α liberation by increasing ADAM10 activity [113,114]. A similar effect has been observed for 5HT6r [115]. In addition, treatment with SSRIs have been found to act on ADAM10 activity, increasing sAβPPα secretion [112,115-117]. Thus, it is possible that engaging in exercise may increase ADAM10 activity through modulation of 5HT signalling, although a better understanding of the mechanisms of underpinning this action is crucial and likely interlinks with BDNF signalling.

3.2.5. Small extracellular vesicles as a vehicle for ADAM10 and stimulating co-factors

Whilst the beneficial effects of exercise on brain health are widely accepted, the route of communication from periphery to central systems

and back again is less clear. The possibility of tissue-cross talk between systemic factors secreted from cells during exercise and central systems is a novel area of ongoing research. Extracellular vesicles are membranous structures known to be released from all cells and contain active biomolecules including proteins, RNA and DNA. Healthy cells shed microvesicles from the plasma membrane and exosomes are also formed from multivesicular bodies of endosomal origin. Since current technologies encounter difficulties in distinguishing these vesicle types, they will herein be collectively referred to as small extracellular vesicles (sEVs). First thought to simply represent debris of degenerated cells, it is now theorised that sEVs represent a means of intercellular communication. sEVs can transfer their cargo to recipient cells through membrane receptor interaction or by uptake into the recipient cell, eliciting a functional response. Importantly, evidence suggests that following in particular exhaustive endurance exercise, there is a significant increase in the level of EVs in circulation compared to the resting state [118]. Intriguingly, high coverage quantitative proteomic analyses of sEV lysates from human blood indicates the protein diversity carried in circulation is vast (>5000) [118,119], highlighting the potential for significant intercellular communication via sEVs during both physiological and pathological stimuli. Indeed, similar, cutting edge, mass spectrometry analyses of sEVs in the context of exercise confirms sEV released into circulation is significant and importantly, can identify, in an unbiased manner, the proteins carried within the sEVs [118]. One of the markers highly enriched in sEVs in response to both endurance (1hr) [118] and high intensity interval cycling (4 × 4 min at 90% VO2max, [119]) was ADAM10. ADAM10 positive sEVs were significantly elevated in an acute response post exercise, before returning to baseline between 1 and 3 h. Whether this transient elevation is affected by repeated bouts or in altered in response to chronic exercise interventions is not known. Interestingly, EVs are also site of AβPP processing and have been considered as a source of biomarkers for AD [120]. Thus, delivery of post exercise sEVs which are enriched with proteolytically active ADAM10, antioxidant enzymes and BDNF, to the brain may provide a mechanism to promote non-amyloidogenic AβPP processing and stimulate neurogenesis [118], particularly in light of the observation that sEVs can pass the blood brain barrier [121].

4. Conclusion

In this review we have focused upon the possible mechanisms by which exercise may promote non-amyloidogenic AβPP processing in the context of prevention of AD. Whilst the benefits of engaging in regular exercise for improving brain health reducing the risk of AD is widely acknowledged, the specific pathways for which this protection is provided is not known. The potential for ADAM10 to be a therapeutic target in AD is of interest due to opposing the amyloidogenic AβPP pathway and liberating sAβPPα which is neuroprotective. Further, ADAM10 has emerged as a key player in several developmental processes, including synaptic pruning and cell signalling events. The pleiotropic nature of ADAM10 interaction with partnering proteins and cleavage sites highlights a number of routes by which its proteolytic activity may be increased. This is of importance in AD as lower ADAM10 expression is typically seen. The pathways highlighted in this review showcase a number of ways by which exercise may lead to increased ADAM10 activity, however, it is clear that further investigation of these areas is warranted. Ultimately, further investigation of the link between ADAM10 activity and exercise may provide a novel biomarker for the effectiveness of exercise bouts and inform future therapeutic intervention for AD.

CRediT authorship contribution statement

Richard J. Elsworthy: Conceptualization, Writing – original draft, Writing – review & editing. **Connor Dunleavy:** Writing – original draft. **Martin Whitham:** Writing – review & editing. **Sarah Aldred:** Supervision, Writing – review & editing.

Declaration of Competing Interest

Declarations of interest: none

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