Exercise for the prevention of Alzheimer's disease

Elsworthy, Richard; Dunleavy, Connor; Whitham, Martin; Aldred, Sarah

Link to publication on Research at Birmingham portal

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

Richard J. Elsworthy [a,b,*], Connor Dunleavy [a], Martin Whitham [a], Sarah Aldred [a,b]

[a] School of Sport, Exercise and Rehabilitation Sciences, College of Life and Environmental Sciences, University of Birmingham, Birmingham, UK, B15 2TT
[b] Centre for Human Brain Health (CHBH), University of Birmingham, Edgbaston, Birmingham, UK

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

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
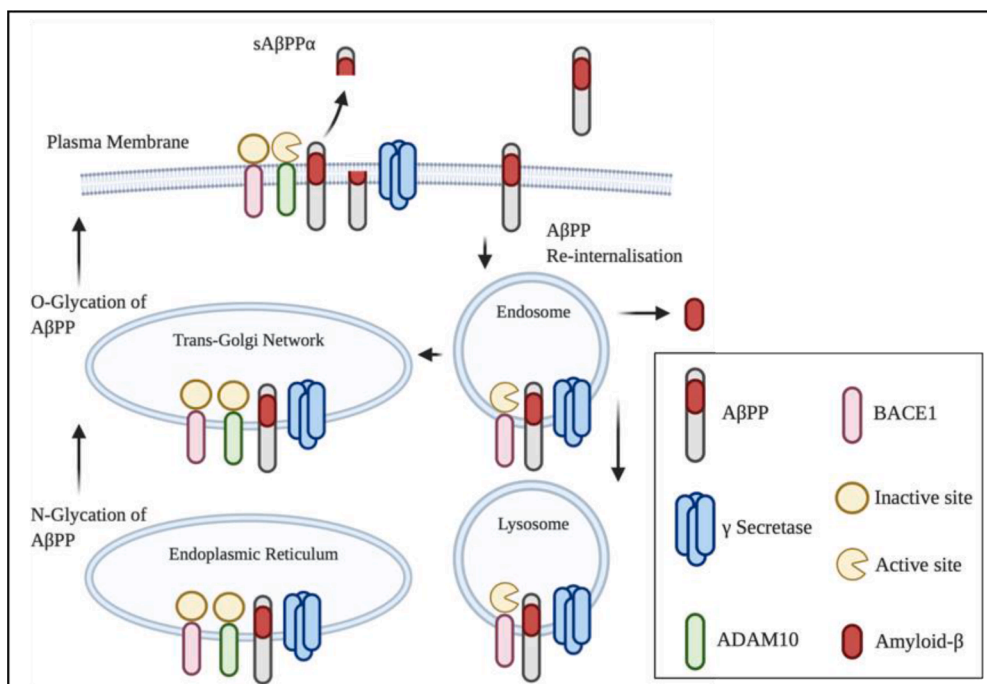
Fig. 1. Diagrammatic representation of the trafficking and processing of AβPP from intracellular compartments to the cell membrane. Movement of AβPP through the secretory pathway to the cell membrane is regulated by post-translational glycation. ADAM10 prodomain cleavage by proprotein convertase enzymes, 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	Treadmill running (exercise) or stationary	Acclimation: 5 days Protocol: 5 days per week for 12 weeks,	Increased ADAM10 levels and sAβPPα in exercise AD model
(Liu et al., 2013)	transgenic AD model (n = 8).	treadmill (control)	30–60mins/day.	compared to sedentary AD model in cortex.
	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
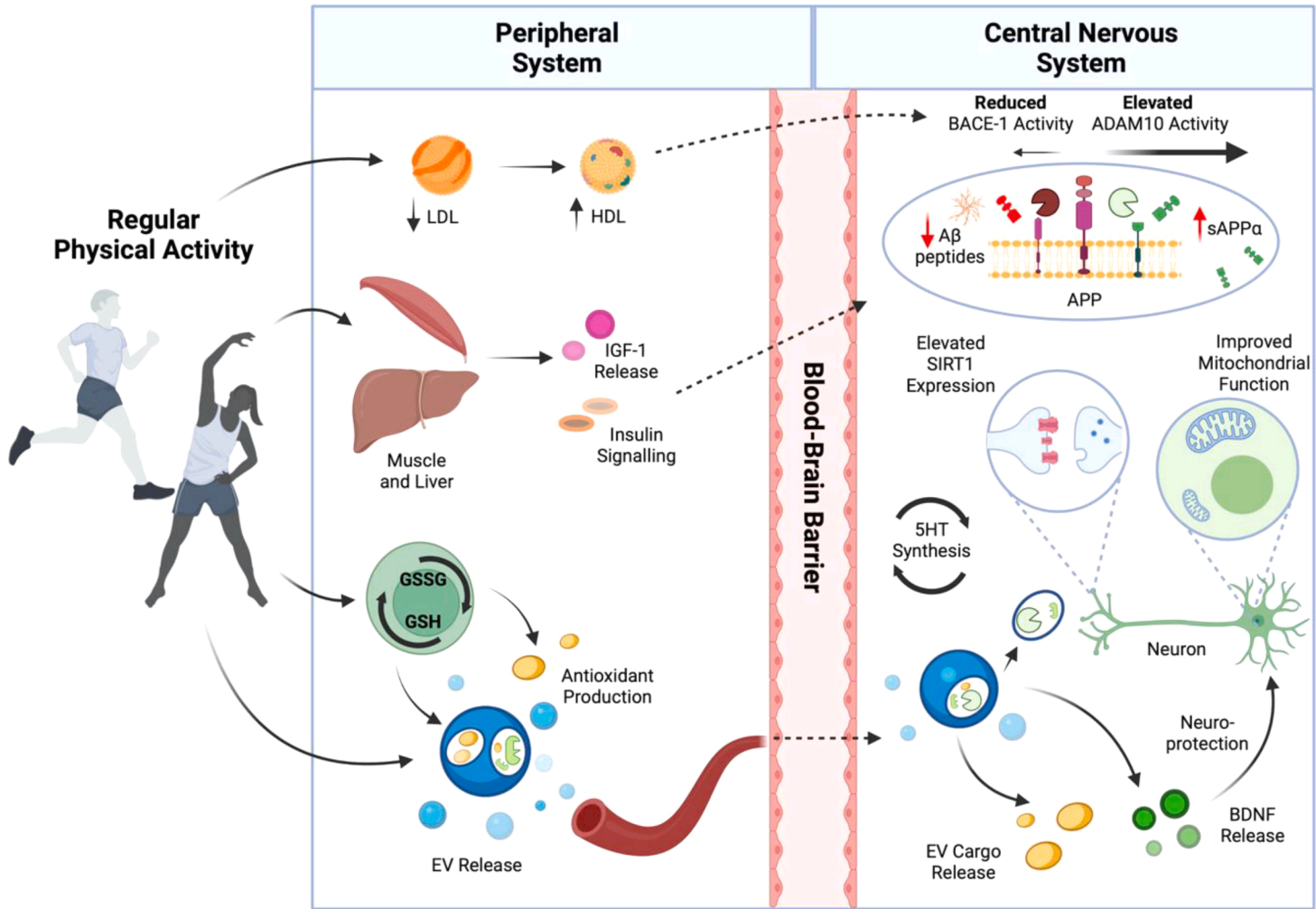
Fig. 2. Exercise can stimulate the release or upregulation of multiple pathways in both peripheral and central tissues. Peripherally secreted factors are able to cross the blood brain barrier and may influence AβPP processing. The effects of exercise on these systems are able to shift AβPP processing 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 Aβ$^+$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

References

[1] Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther 2016;8(1):23. https://doi.org/10.1186/s13195-016-0188-8.

[2] Wolters FJ, Chibnik LB, Waziry R, Anderson R, Berr C, Beiser A, et al. Twenty-seven-year time trends in dementia incidence in Europe and the United States: the Alzheimer Cohorts Consortium. Neurology 2020;95(5):e519–ee31. https://doi.org/10.1212/WNL.0000000000010022.

[3] Alford S, Patel D, Perakakis N, Mantzoros CS. Obesity as a risk factor for Alzheimer's disease: weighing the evidence. Obes Rev 2018;19(2):269–80. https://doi.org/10.1111/obr.12629.

[4] Serrano-Pozo A, Growdon JH. Is Alzheimer's disease risk modifiable? J Alzheimer Dis 2019;67(3):795–819. https://doi.org/10.3233/JAD181028.

[5] Pegueroles J, Jiménez A, Vilaplana E, Montal V, Carmona-Iragui M, Pané A, et al. Obesity and Alzheimer's disease, does the obesity paradox really exist? A magnetic resonance imaging study. Oncotarget 2018;9(78):34691–8. https://doi.org/10.18632/oncotarget.26162.

[6] Trejo-Lopez JA, Yachnis AT, Prokop S. Neuropathology of Alzheimer's disease. Neurotherapeutics 2022;19(1):173–85. https://doi.org/10.1007/s13311-021-01146-y.

[7] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016;8(6):595–608. https://doi.org/10.15252/emmm.201606210.

[8] Zhang Y-w, Thompson R, Zhang H, Xu H. APP processing in Alzheimer's disease. Mol Brain 2011;4(1):3. https://doi.org/10.1186/1756-6606-4-3.

[9] Wang X, Zhou X, Li G, Zhang Y, Wu Y, Song W. Modifications and trafficking of APP in the pathogenesis of Alzheimer's disease. Front Mol Neurosci 2017;10:294. https://doi.org/10.3389/fnmol.2017.00294.

[10] Hoffmann J, Twiesselmann C, Kummer MP, Romagnoli P, Herzog V. A possible role for the Alzheimer amyloid precursor protein in the regulation of epidermal basal cell proliferation. Eur. J. Cell Biol. 2000;79(12):905–14. https://doi.org/10.1078/0171-9335-00117.

[11] Chun YS, Park Y, Oh HG, Kim TW, Yang HO, Park MK, et al. O-GlcNAcylation promotes non-amyloidogenic processing of amyloid-β protein precursor via inhibition of endocytosis from the plasma membrane. J Alzheimer Dis 2015;44(1):261–75. https://doi.org/10.3233/JAD-140096.

[12] Lichtenthaler SF, Haass C, Steiner H. Regulated intramembrane proteolysis–lessons from amyloid precursor protein processing. J Neurochem 2011;117(5):779–96. https://doi.org/10.1111/j.1471-4159.2011.07248.x.

[13] Zhang YW, Thompson R, Zhang H, Xu H. APP processing in Alzheimer's disease. Mol Brain 2011;4:3. https://doi.org/10.1186/1756-6606-4-3.

[14] Brothers HM, Gosztyla ML, Robinson SR. The physiological roles of amyloid-β peptide hint at new ways to treat Alzheimer's disease. Front Aging Neurosci 2018;10:118. https://doi.org/10.3389/fnagi.2018.00118.

[15] Zheng W, Tsai MY, Wolynes PG. Comparing the aggregation free energy landscapes of amyloid beta(1-42) and amyloid(1-40). J Am Chem Soc 2017;139(46):16666–76. https://doi.org/10.1021/jacs.7b08089.

[16] Huang YR, Liu RT. The toxicity and polymorphism of β-amyloid oligomers. Int J Molecul Sci 2020;21(12). https://doi.org/10.3390/ijms21124477.

[17] Umeda T, Tomiyama T, Sakama N, Tanaka S, Lambert MP, Klein WL, et al. Intraneuronal amyloid β oligomers cause cell death via endoplasmic reticulum stress, endosomal/lysosomal leakage, and mitochondrial dysfunction in vivo. J Neurosci Res 2011;89(7):1031–42. https://doi.org/10.1002/jnr.22640.

[18] Resende R, Ferreiro E, Pereira C, Resende de Oliveira C. Neurotoxic effect of oligomeric and fibrillar species of amyloid-beta peptide 1-42: involvement of endoplasmic reticulum calcium release in oligomer-induced cell death. Neuroscience 2008;155(3):725–37. https://doi.org/10.1016/j.neuroscience.2008.06.036.

[19] Poon WW, Carlos AJ, Aguilar BL, Berchtold NC, Kawano CK, Zograbyan V, et al. β-Amyloid (Aβ) oligomers impair brain-derived neurotrophic factor retrograde trafficking by down-regulating ubiquitin C-terminal hydrolase, UCH-L1. J Biolog Chem 2013;288(23):16937–48. https://doi.org/10.1074/jbc.M113.463711.

[20] Calvo-Rodriguez M, Hernando-Perez E, Nuñez L, Villalobos C. Amyloid β oligomers increase ER-mitochondria Ca. Front Cell Neurosci 2019;13:22. https://doi.org/10.3389/fncel.2019.00022.

[21] Sciacca MF, Kotler SA, Brender JR, Chen J, Lee DK, Ramamoorthy A. Two-step mechanism of membrane disruption by Aβ through membrane fragmentation and pore formation. Biophys J 2012;103(4):702–10. https://doi.org/10.1016/j.bpj.2012.06.045.

[22] Hong S, Ostaszewski BL, Yang T, O'Malley TT, Jin M, Yanagisawa K, et al. Soluble Aβ oligomers are rapidly sequestered from brain ISF in vivo and bind GM1

ganglioside on cellular membranes. Neuron 2014;82(2):308–19. https://doi.org/10.1016/j.neuron.2014.02.027.

[23] Drews A, Flint J, Shivji N, Jönsson P, Wirthensohn D, De Genst E, et al. Individual aggregates of amyloid beta induce temporary calcium influx through the cell membrane of neuronal cells. Sci Rep 2016;6:31910. https://doi.org/10.1038/srep31910.

[24] Peters C, Bascuñán D, Opazo C, Aguayo LG. Differential membrane toxicity of amyloid-β fragments by pore forming mechanisms. J Alzheimer Dis 2016;51(3):689–99. https://doi.org/10.3233/JAD-150896.

[25] Smith LM, Strittmatter SM. Binding sites for amyloid-β oligomers and synaptic toxicity. Cold Spring Harbour Perspect Med 2017;7(5). https://doi.org/10.1101/cshperspect.a024075.

[26] Haass C, Kaether C, Thinakaran G, Sisodia S. Trafficking and proteolytic processing of APP. Cold Spring Harbour Perspect Med 2012;2(5):a006270. https://doi.org/10.1101/cshperspect.a006270.

[27] Allinson TM, Parkin ET, Turner AJ, Hooper NM. ADAMs family members as amyloid precursor protein alpha-secretases. J Neurosci Res 2003;74(3):342–52. https://doi.org/10.1002/jnr.10737.

[28] Qian M, Shen X, Wang H. The distinct role of ADAM17 in APP proteolysis and microglial activation related to Alzheimer's disease. Cell Mol Neurobiol 2016;36(4):471–82. https://doi.org/10.1007/s10571-015-0232-4.

[29] Postina R, Schroeder A, Dewachter I, Bohl J, Schmitt U, Kojro E, et al. A disintegrin-metalloproteinase prevents amyloid plaque formation and hippocampal defects in an Alzheimer disease mouse model. J Clin Invest 2004;113(10):1456–64. https://doi.org/10.1172/jci20864.

[30] Kuhn PH, Wang H, Dislich B, Colombo A, Zeitschel U, Ellwart JW, et al. ADAM10 is the physiologically relevant, constitutive alpha-secretase of the amyloid precursor protein in primary neurons. EMBO J 2010;29(17):3020–32. https://doi.org/10.1038/emboj.2010.167.

[31] Anders A, Gilbert S, Garten W, Postina R, Fahrenholz F. Regulation of the alpha-secretase ADAM10 by its prodomain and proprotein convertases. Faseb J 2001;15(10):1837–9. https://doi.org/10.1096/fj.01-0007fje.

[32] Seifert A, Düsterhöft S, Wozniak J, Koo CZ, Tomlinson MG, Nuti E, et al. The metalloproteinase ADAM10 requires its activity to sustain surface expression. Cell Molecul Life Sci 2020. https://doi.org/10.1007/s00018-020-03507-w.

[33] Matthews AL, Szyroka J, Collier R, Noy PJ, Tomlinson MG. Scissor sisters: regulation of ADAM10 by the TspanC8 tetraspanins. Biochem Soc Trans 2017;45(3):719–30. https://doi.org/10.1042/bst20160290.

[34] Seipold L, Saftig P. The emerging role of tetraspanins in the proteolytic processing of the amyloid precursor protein. Front Mol Neurosci 2016;9:149. https://doi.org/10.3389/fnmol.2016.00149.

[35] Yuan XZ, Sun S, Tan CC, Yu JT, Tan L. The role of ADAM10 in Alzheimer's disease. J Alzheimer Dis 2017;58(2):303–22. https://doi.org/10.3233/JAD-170061.

[36] Hick M, Herrmann U, Weyer SW, Mallm JP, Tschäpe JA, Borgers M, et al. Acute function of secreted amyloid precursor protein fragment APPsα in synaptic plasticity. Acta Neuropathol 2015;129(1):21–37. https://doi.org/10.1007/s00401-014-1368-x.

[37] Peters-Libeu C, Campagna J, Mitsumori M, Poksay KS, Spilman P, Sabogal A, et al. sAβPPα is a Potent Endogenous Inhibitor of BACE1. J Alzheimer Dis 2015;47(3):545–55. https://doi.org/10.3233/JAD-150282.

[38] Deng J, Habib A, Obregon DF, Barger SW, Giunta B, Wang YJ, et al. Soluble amyloid precursor protein alpha inhibits tau phosphorylation through modulation of GSK3β signaling pathway. J Neurochem 2015;135(3):630–7. https://doi.org/10.1111/jnc.13351.

[39] Kim M, Suh J, Romano D, Truong MH, Mullin K, Hooli B, et al. Potential late-onset Alzheimer's disease-associated mutations in the ADAM10 gene attenuate {alpha}-secretase activity. Hum Mol Genet 2009;18(20):3987–96. https://doi.org/10.1093/hmg/ddp323.

[40] Daskalopoulou C, Stubbs B, Kralj C, Koukounari A, Prince M, Prina AM. Physical activity and healthy ageing: a systematic review and meta-analysis of longitudinal cohort studies. Ageing Res Rev 2017;38:6–17. https://doi.org/10.1016/j.arr.2017.06.003.

[41] Morris JK, Vidoni ED, Johnson DK, Van Sciver A, Mahnken JD, Honea RA, et al. Aerobic exercise for Alzheimer's disease: a randomized controlled pilot trial. PLoS ONE 2017;12(2):e0170547. https://doi.org/10.1371/journal.pone.0170547.

[42] Hansson O, Svensson M, Gustavsson AM, Andersson E, Yang Y, Nägga K, et al. Midlife physical activity is associated with lower incidence of vascular dementia but not Alzheimer's disease. Alzheimers Res Ther 2019;11(1):87. https://doi.org/10.1186/s13195-019-0538-4.

[43] Jia RX, Liang JH, Xu Y, Wang YQ. Effects of physical activity and exercise on the cognitive function of patients with Alzheimer disease: a meta-analysis. BMC Geriatr 2019;19(1):181. https://doi.org/10.1186/s12877-019-1175-2.

[44] Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. Lancet Neurol 2014;13(8):788–94. https://doi.org/10.1016/S1474-4422(14)70136-X.

[45] Stephen R, Hongisto K, Solomon A, Lönnroos E. Physical activity and Alzheimer's disease: a systematic review. J Gerontol A Biol Sci Med Sci 2017;72(6):733–9. https://doi.org/10.1093/gerona/glw251.

[46] Alkadhi KA, Dao AT. Exercise decreases BACE and APP levels in the hippocampus of a rat model of Alzheimer's disease. Molecul Cell Neurosci 2018;86:25–9. https://doi.org/10.1016/j.mcn.2017.11.008.

[47] Zhao G, Liu HL, Zhang H, Tong XJ. Treadmill exercise enhances synaptic plasticity, but does not alter β-amyloid deposition in hippocampi of aged APP/PS1 transgenic mice. Neuroscience 2015;298:357–66. https://doi.org/10.1016/j.neuroscience.2015.04.038.

[48] Özbeyli D, Sarı G, Özkan N, Karademir B, Yüksel M, Kaya ÖÇ, et al. Protective effects of different exercise modalities in an Alzheimer's disease-like model. Behav Brain Res 2017;328:159–77. https://doi.org/10.1016/j.bbr.2017.03.044.

[49] Koo JH, Kang EB, Oh YS, Yang DS, Cho JY. Treadmill exercise decreases amyloid-β burden possibly via activation of SIRT-1 signaling in a mouse model of Alzheimer's disease. Exp Neurol 2017;288:142–52. https://doi.org/10.1016/j.expneurol.2016.11.014.

[50] Zhang J, Guo Y, Wang Y, Song L, Zhang R, Du Y. Long-term treadmill exercise attenuates Aβ burdens and astrocyte activation in APP/PS1 mouse model of Alzheimer's disease. Neurosci Lett 2018;666:70–7. https://doi.org/10.1016/j.neulet.2017.12.025.

[51] Liu HL, Zhao G, Zhang H, Shi LD. Long-term treadmill exercise inhibits the progression of Alzheimer's disease-like neuropathology in the hippocampus of APP/PS1 transgenic mice. Behav Brain Res 2013;256:261–72. https://doi.org/10.1016/j.bbr.2013.08.008.

[52] Rossi Daré L, Garcia A, Neves BH, Mello-Carpes PB. One physical exercise session promotes recognition learning in rats with cognitive deficits related to amyloid beta neurotoxicity. Brain Res 2020;1744:146918. https://doi.org/10.1016/j.brainres.2020.146918.

[53] Zhang XL, Zhao N, Xu B, Chen XH, Li TJ. Treadmill exercise inhibits amyloid-β generation in the hippocampus of APP/PS1 transgenic mice by reducing cholesterol-mediated lipid raft formation. Neuroreport 2019;30(7):498–503. https://doi.org/10.1097/WNR.0000000000001230.

[54] Yang AJ, Hayward GC, MacPherson REK. Acute exercise and brain BACE1 protein content: a time course study. Physiol Rep 2019;7(8):e14084. https://doi.org/10.14814/phy2.14084.

[55] He XF, Liu DX, Zhang Q, Liang FY, Dai GY, Zeng JS, et al. Voluntary exercise promotes glymphatic clearance of amyloid beta and reduces the activation of astrocytes and microglia in aged mice. Front Mol Neurosci 2017;10:144. https://doi.org/10.3389/fnmol.2017.00144.

[56] Liang KY, Mintun MA, Fagan AM, Goate AM, Bugg JM, Holtzman DM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. Ann Neurol 2010;68(3):311–8. https://doi.org/10.1002/ana.22096.

[57] Vidoni ED, Morris JK, Watts A, Perry M, Clutton J, Van Sciver A, et al. Effect of aerobic exercise on amyloid accumulation in preclinical Alzheimer's: a 1-year randomized controlled trial. PLoS ONE 2021;16(1):e0244893. https://doi.org/10.1371/journal.pone.0244893.

[58] Brown BM, Peiffer J, Rainey-Smith SR. Exploring the relationship between physical activity, beta-amyloid and tau: a narrative review. Ageing Res Rev. 2019;50:9–18. https://doi.org/10.1016/j.arr.2019.01.003.

[59] Jack CR, Knopman DS, Jagust WJ, Petersen RC, Weiner MW, Aisen PS, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol 2013;12(2):207–16. https://doi.org/10.1016/S1474-4422(12)70291-0.

[60] Okonkwo OC, Schultz SA, Oh JM, Larson J, Edwards D, Cook D, et al. Physical activity attenuates age-related biomarker alterations in preclinical AD. Neurology 2014;83(19):1753–60. https://doi.org/10.1212/WNL.0000000000000964.

[61] Maliszewska-Cyna E, Lynch M, Oore JJ, Nagy PM, Aubert I. The benefits of exercise and metabolic interventions for the prevention and early treatment of Alzheimer's disease. Curr Alzheimer Res 2017;14(1):47–60. https://doi.org/10.2174/1567205013666160819125400.

[62] MacPherson REK. Filling the void: a role for exercise-induced BDNF and brain amyloid precursor protein processing. Am J Physiol 2017;313(5):R585–RR93. https://doi.org/10.1152/ajpregu.00255.2017.

[63] Clarke JR, Ribeiro FC, Frozza RL, De Felice FG, Lourenco MV. Metabolic dysfunction in Alzheimer's disease: from basic neurobiology to clinical approaches. J Alzheimer Dis 2018;64(s1):S405–SS26. https://doi.org/10.3233/JAD-179911.

[64] Bell SM, Barnes K, De Marco M, Shaw PJ, Ferraiuolo L, Blackburn DJ, et al. Mitochondrial dysfunction in Alzheimer's disease: a biomarker of the future? Biomedicines 2021;9(1). https://doi.org/10.3390/biomedicines9010063.

[65] Ferreira LSS, Fernandes CS, Vieira MNN, De Felice FG. Insulin resistance in Alzheimer's disease. Front Neurosci 2018;12:830. https://doi.org/10.3389/fnins.2018.00830.

[66] Pandini G, Pace V, Copani A, Squatrito S, Milardi D, Vigneri R. Insulin has multiple antiamyloidogenic effects on human neuronal cells. Endocrinology 2013;154(1):375–87. https://doi.org/10.1210/en.2012-1661.

[67] Jacobsen KT, Adlerz L, Multhaup G, Iverfeldt K. Insulin-like growth factor-1 (IGF-1)-induced processing of amyloid-beta precursor protein (APP) and APP-like protein 2 is mediated by different metalloproteinases. J Biolog Chem 2010;285(14):10223–31. https://doi.org/10.1074/jbc.M109.038224.

[68] Wang X, Yu S, Gao SJ, Hu JP, Wang Y, Liu HX. Insulin inhibits Abeta production through modulation of APP processing in a cellular model of Alzheimer's disease. Neuro Endocrinol Lett 2014;35(3):224–9.

[69] Song F, Liu T, Meng S, Li F, Zhang Y, Jiang L. Insulin-like growth factor-1 alleviates expression of Aβ. J Molecul Neurosci 2018;66(4):595–603. https://doi.org/10.1007/s12031-018-1201-4.

[70] Wang W, Zhao F, Ma X, Perry G, Zhu X. Mitochondria dysfunction in the pathogenesis of Alzheimer's disease: recent advances. Mol Neurodegener 2020;15(1):30. https://doi.org/10.1186/s13024-020-00376-6.

[71] Nunomura A, Perry G, Aliev G, Hirai K, Takeda A, Balraj EK, et al. Oxidative damage is the earliest event in Alzheimer disease. J Neuropathol Exper Neurol 2001;60(8):759–67.

[72] Elsworthy RJ, Aldred S. The effect of age and obesity on platelet amyloid precursor protein processing and plasma markers of oxidative stress and

inflammation. Exp Gerontol 2020:110838. https://doi.org/10.1016/j.
exger.2020.110838.

[73] Elsworthy RJ, King MC, Grainger A, Fisher E, Crowe JA, Alqattan S, et al. Amyloid-β precursor protein processing and oxidative stress are altered in human iPSC-derived neuron and astrocyte co-cultures carrying presenillin-1 gene mutations following spontaneous differentiation. Molecul Cell Neurosci 2021; 114:103631. https://doi.org/10.1016/j.mcn.2021.103631.

[74] Quiroz-Baez R, Rojas E, Arias C. Oxidative stress promotes JNK-dependent amyloidogenic processing of normally expressed human APP by differential modification of alpha-, beta- and gamma-secretase expression. Neurochem Int 2009;55(7):662–70. https://doi.org/10.1016/j.neuint.2009.06.012.

[75] Muche A, Arendt T, Schliebs R. Oxidative stress affects processing of amyloid precursor protein in vascular endothelial cells. PLoS ONE 2017;12(6):e0178127. https://doi.org/10.1371/journal.pone.0178127.

[76] Powers SK, Deminice R, Ozdemir M, Yoshihara T, Bomkamp MP, Hyatt H. Exercise-induced oxidative stress: friend or foe? J Sport Health Sci 2020;9(5): 415–25. https://doi.org/10.1016/j.jshs.2020.04.001.

[77] Zhao N, Xia J, Xu B. Physical exercise may exert its therapeutic influence on Alzheimer's disease through the reversal of mitochondrial dysfunction via SIRT1-FOXO1/3-PINK1-Parkin-mediated mitophagy. J Sport Health Sci 2021;10(1):1–3. https://doi.org/10.1016/j.jshs.2020.08.009.

[78] Wong SY, Tang BL. SIRT1 as a therapeutic target for Alzheimer's disease. Rev Neurosci 2016;27(8):813–25. https://doi.org/10.1515/revneuro-2016-0023.

[79] Ng F, Wijaya L, Tang BL. SIRT1 in the brain-connections with aging-associated disorders and lifespan. Front Cell Neurosci 2015;9:64. https://doi.org/10.3389/fncel.2015.00064.

[80] Corpas R, Revilla S, Ursulet S, Castro-Freire M, Kaliman P, Petegnief V, et al. SIRT1 overexpression in mouse hippocampus induces cognitive enhancement through proteostatic and neurotrophic mechanisms. Mol Neurobiol 2017;54(7): 5604–19. https://doi.org/10.1007/s12035-016-0087-9.

[81] Lee HR, Shin HK, Park SY, Kim HY, Lee WS, Rhim BY, et al. Cilostazol suppresses β-amyloid production by activating a disintegrin and metalloproteinase 10 via the upregulation of SIRT1-coupled retinoic acid receptor-β. J Neurosci Res 2014;92 (11):1581–90. https://doi.org/10.1002/jnr.23421.

[82] Di Paolo G, Kim TW. Linking lipids to Alzheimer's disease: cholesterol and beyond. Nat Rev Neurosci 2011;12(5):284–96. https://doi.org/10.1038/nrn3012.

[83] Kivipelto M, Helkala EL, Laakso MP, Hänninen T, Hallikainen M, Alhainen K, et al. Midlife vascular risk factors and Alzheimer's disease in later life: longitudinal, population based study. The BMJ 2001;322(7300):1447–51. https://doi.org/10.1136/bmj.322.7300.1447.

[84] Gliozzi M, Musolino V, Bosco F, Scicchitano M, Scarano F, Nucera S, et al. Cholesterol homeostasis: researching a dialogue between the brain and peripheral tissues. Pharmacol Res 2021;163:105215. https://doi.org/10.1016/j.phrs.2020.105215.

[85] Wang Y, Xu D. Effects of aerobic exercise on lipids and lipoproteins. Lipid Health Dis 2017;16(1):132. https://doi.org/10.1186/s12944-017-0515-5.

[86] Chang TY, Yamauchi Y, Hasan MT, Chang C. Cellular cholesterol homeostasis and Alzheimer's disease. J Lipid Res 2017;58(12):2239–54. https://doi.org/10.1194/jlr.R075630.

[87] Flowers SA, Rebeck GW. APOE in the normal brain. Neurobiol Dis 2020;136: 104724. https://doi.org/10.1016/j.nbd.2019.104724.

[88] Shackleton B, Crawford F, Bachmeier C. Apolipoprotein E-mediated modulation of ADAM10 in Alzheimer's disease. Curr Alzheimer Res 2017;14(6):578–85. https://doi.org/10.2174/1567205014666170203093219.

[89] Tokgöz S, Claassen JAHR. Exercise as potential therapeutic target to modulate Alzheimer's disease pathology in APOE ε4 carriers: a systematic review. Cardiol Ther 2021;10(1):67–88. https://doi.org/10.1007/s40119-020-00209-z.

[90] Sathya M, Moorthi P, Premkumar P, Kandasamy M, Jayachandran KS, Anusuyadevi M. Resveratrol intervenes cholesterol- and isoprenoid-mediated amyloidogenic processing of AβPP in familial Alzheimer's disease. J Alzheimer's Dis 2017;60(s1):S3–23. https://doi.org/10.3233/JAD-161034.

[91] Kojro E, Gimpl G, Lammich S, Marz W, Fahrenholz F. Low cholesterol stimulates the nonamyloidogenic pathway by its effect on the alpha -secretase ADAM 10. Procceed. Natl Acad Sci 2001;98(10):5815–20. https://doi.org/10.1073/pnas.081612998.

[92] Kojro E, Füger P, Prinzen C, Kanarek AM, Rat D, Endres K, et al. Statins and the squalene synthase inhibitor zaragozic acid stimulate the non-amyloidogenic pathway of amyloid-beta protein precursor processing by suppression of cholesterol synthesis. J Alzheimer Dis 2010;20(4):1215–31. https://doi.org/10.3233/JAD-2010-091621.

[93] Cole SL, Grudzien A, Manhart IO, Kelly BL, Oakley H, Vassar R. Statins cause intracellular accumulation of amyloid precursor protein, beta-secretase-cleaved fragments, and amyloid beta-peptide via an isoprenoid-dependent mechanism. J Biolog Chem 2005;280(19):18755–70. https://doi.org/10.1074/jbc.M413895200.

[94] Ostrowski SM, Wilkinson BL, Golde TE, Landreth G. Statins reduce amyloid-beta production through inhibition of protein isoprenylation. J Biolog Chem 2007;282 (37):26832–44. https://doi.org/10.1074/jbc.M702640200.

[95] Liu PZ, Nusslock R. Exercise-Mediated Neurogenesis in the Hippocampus via BDNF. Front Neurosci 2018;12:52. https://doi.org/10.3389/fnins.2018.00052.

[96] Vaynman S, Ying Z, Gomez-Pinilla F. Hippocampal BDNF mediates the efficacy of exercise on synaptic plasticity and cognition. Eur J Neurosci 2004;20(10): 2580–90. https://doi.org/10.1111/j.1460-9568.2004.03720.x.

[97] Phillips HS, Hains JM, Armanini M, Laramee GR, Johnson SA, Winslow JW. BDNF mRNA is decreased in the hippocampus of individuals with Alzheimer's disease. Neuron 1991;7(5):695–702. https://doi.org/10.1016/0896-6273(91)90273-3.

[98] Laske C, Stransky E, Leyhe T, Eschweiler GW, Wittorf A, Richartz E, et al. Stage-dependent BDNF serum concentrations in Alzheimer's disease. J Neural Transmiss 2006;113(9):1217–24. https://doi.org/10.1007/s00702-005-0397-y.

[99] Ng TKS, Ho CSH, Tam WWS, Kua EH, Ho RC. Decreased serum brain-derived neurotrophic factor (BDNF) levels in patients with Alzheimer's disease (AD): a systematic review and meta-analysis. Int J Mol Sci 2019;20(2). https://doi.org/10.3390/ijms20020257.

[100] Bharani KL, Ledreux A, Gilmore A, Carroll SL, Granholm AC. Serum pro-BDNF levels correlate with phospho-tau staining in Alzheimer's disease. Neurobiol Aging 2020;87:49–59. https://doi.org/10.1016/j.neurobiolaging.2019.11.010.

[101] Lim YY, Villemagne VL, Laws SM, Pietrzak RH, Snyder PJ, Ames D, et al. APOE and BDNF polymorphisms moderate amyloid β-related cognitive decline in preclinical Alzheimer's disease. Mol Psychiatry 2015;20(11):1322–8. https://doi.org/10.1038/mp.2014.123.

[102] Holback S, Adlerz L, Iverfeldt K. Increased processing of APLP2 and APP with concomitant formation of APP intracellular domains in BDNF and retinoic acid-differentiated human neuroblastoma cells. J Neurochem 2005;95(4):1059–68. https://doi.org/10.1111/j.1471-4159.2005.03440.x.

[103] Matrone C, Ciotti MT, Mercanti D, Marolda R, Calissano P. NGF and BDNF signaling control amyloidogenic route and Abeta production in hippocampal neurons. Proceed Natl Acad Sci 2008;105(35):13139–44. https://doi.org/10.1073/pnas.0806133105.

[104] Arancibia S, Silhol M, Moulière F, Meffre J, Höllinger I, Maurice T, et al. Protective effect of BDNF against beta-amyloid induced neurotoxicity in vitro and in vivo in rats. Neurobiol Dis 2008;31(3):316–26. https://doi.org/10.1016/j.nbd.2008.05.012.

[105] Nigam SM, Xu S, Kritikou JS, Marosi K, Brodin L, Mattson MP. Exercise and BDNF reduce Aβ production by enhancing α-secretase processing of APP. J Neurochem 2017;142(2):286–96. https://doi.org/10.1111/jnc.14034.

[106] Young SN. How to increase serotonin in the human brain without drugs. J Psychiatry Neurosci 2007;32(6):394–9.

[107] Klempin F, Beis D, Mosienko V, Kempermann G, Bader M, Alenina N. Serotonin is required for exercise-induced adult hippocampal neurogenesis. J Neurosci 2013; 33(19):8270–5. https://doi.org/10.1523/JNEUROSCI.5855-12.2013.

[108] Pietrelli A, Matković L, Vacotto M, Lopez-Costa JJ, Basso N, Brusco A. Aerobic exercise upregulates the BDNF-Serotonin systems and improves the cognitive function in rats. Neurobiol Learn Mem 2018;155:528–42. https://doi.org/10.1016/j.nlm.2018.05.007.

[109] Melancon MO, Lorrain D, Dionne IJ. Exercise increases tryptophan availability to the brain in older men age 57-70 years. Med Sci Sport Exerc 2012;44(5):881–7. https://doi.org/10.1249/MSS.0b013e31823ede8e.

[110] Melancon MO, Lorrain D, Dionne IJ. Changes in markers of brain serotonin activity in response to chronic exercise in senior men. Appl Physiol Nutr Metabol 2014;39(11):1250–6. https://doi.org/10.1139/apnm-2014-0092.

[111] Claeysen S, Bockaert J, Giannoni P. Serotonin: a new hope in Alzheimer's disease? ACS Chem Neurosci 2015;6(7):940–3. https://doi.org/10.1021/acschemneuro.5b00135.

[112] Elsworthy RJ, Aldred S. Depression in Alzheimer's disease: an alternative role for selective serotonin reuptake inhibitors? J Alzheimer Dis 2019;69(3):651–61. https://doi.org/10.3233/JAD-180780.

[113] Cochet M, Donneger R, Cassier E, Gaven F, Lichtenthaler SF, Marin P, et al. 5-HT4 receptors constitutively promote the non-amyloidogenic pathway of APP cleavage and interact with ADAM10. ACS Chem Neurosci 2013;4(1):130–40. https://doi.org/10.1021/cn300095t.

[114] Cho S, Hu Y. Activation of 5-HT4 receptors inhibits secretion of beta-amyloid peptides and increases neuronal survival. Exp Neurol 2007;203(1):274–8. https://doi.org/10.1016/j.expneurol.2006.07.021.

[115] Fisher JR, Wallace CE, Tripoli DL, Sheline YI, Cirrito JR. Redundant Gs-coupled serotonin receptors regulate amyloid-β metabolism in vivo. Mol Neurodegener 2016;11(1):45. https://doi.org/10.1186/s13024-016-0112-5.

[116] Bianco F, Bonora E, Natarajan D, Vargiolu M, Thapar N, Torresan F, et al. Prucalopride exerts neuroprotection in human enteric neurons. Am J Physiol Gastroint Liver Physiol 2016;310(10):G768–75. https://doi.org/10.1152/ajpgi.00036.2016.

[117] Bianco OA, Manzine PR, Nascimento CM, Vale FA, Pavarini SC, Cominetti MR. Serotoninergic antidepressants positively affect platelet ADAM10 expression in patients with Alzheimer's disease. Int Psychogeriatr 2016;28(6):939–44. https://doi.org/10.1017/S1041610215001842.

[118] Whitham M, Parker BL, Friedrichsen M, Hingst JR, Hjorth M, Hughes WE, et al. Extracellular vesicles provide a means for tissue crosstalk during exercise. Cell Metab 2018;27(1). https://doi.org/10.1016/j.cmet.2017.12.001. p. 237-51.e4.

[119] Vanderboom PM, Dasari S, Ruegsegger GN, Pataky MW, Lucien F, Heppelmann CJ, et al. A size-exclusion-based approach for purifying extracellular vesicles from human plasma. Cell Rep Method 2021;1(3). https://doi.org/10.1016/j.crmeth.2021.100055.

[120] Lee S, Mankhong S, Kang JH. Extracellular vesicle as a source of Alzheimer's biomarkers: opportunities and challenges. Int J Mol Sci 2019;20(7). https://doi.org/10.3390/ijms20071204.

[121] Banks WA, Sharma P, Bullock KM, Hansen KM, Ludwig N, Whiteside TL. Transport of extracellular vesicles across the blood-brain barrier: brain pharmacokinetics and effects of inflammation. Int J Mol Sci 2020;21(12). https://doi.org/10.3390/ijms21124407.