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Filling the void: a role for exercise induced BDNF and brain amyloid precursor protein processing

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Running Head: Exercise induced BDNF and amyloid precursor protein

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Abstract

Inactivity, obesity, and insulin resistance are significant risk factors for the development of Alzheimer's disease (AD). Several studies have demonstrated that diet induced obesity, inactivity, and insulin resistance exacerbates neuropathological hallmarks of AD. The aggregation of beta-amyloid peptides is one of these hallmarks. Beta-site amyloid precursor protein cleaving enzyme 1 (BACE1) is the rate-limiting enzyme in amyloid precursor protein (APP) processing, leading to beta-amyloid peptide formation. Understanding how BACE1 content and activity is regulated is essential for establishing therapies aimed at reducing and/or slowing the progression of AD. Exercise training has proven to reduce the risk of AD as well as decrease beta-amyloid production and BACE1 content and/or activity. However, these long-term interventions also result in improvements in adiposity, circulating metabolites, glucose tolerance, and insulin sensitivity making it difficult to determine the direct effects of exercise on brain APP processing. This review highlights this large void in our knowledge and ~~aims~~ discusses our current understanding the direct of effect of exercise on beta-amyloid production. We have concentrated on the central role that brain-derived neurotrophic factor (BDNF) may play in mediating the direct effects of exercise on reducing brain BACE1 content and activity as well as beta-amyloid production. Future studies should aim to generate a greater understanding of how obesity and exercise can directly alter APP processing and AD related pathologies. This knowledge could provide evidence-based hypotheses for designing therapies to reduce the risk of AD and dementia.

Keywords: acute exercise, Alzheimer's disease, beta-amyloid, beta-secretase

Introduction

The world's population is aging at an alarming rate with projections that the number of Alzheimer's disease (AD) patients in the United States will reach 16 million by 2050 (8) and over 100 million people worldwide (11). In addition to this rapidly greying population, worldwide obesity has nearly doubled since 1980 (36). Both human and animal research has established that inactivity and a high caloric intake resulting in obesity is a significant risk factor for cognitive impairment and the development of sporadic AD (37, 60, 72, 83, 136). This is alarming and highlights the need for identifying and developing strategies for the prevention and treatment of AD.

Currently, therapies are limited to temporary relief of the symptoms of AD and few are targeted at the underlying disease mechanisms. Lifestyle factors, such as increased exercise or physical activity are known to reduce the risk of AD as well as slow the progression of the disease (30, 38, 64, 69, 109). However, the cellular and molecular mechanisms for such benefits have not yet been identified. Understanding these molecular mechanisms will have a significant impact on future therapeutic targets aimed at reducing AD.

The accumulation of senile plaques and neurofibrillary tangles are neuropathologic hallmarks of AD. Senile plaques are extracellular aggregates of small peptides known as beta-amyloid peptides and neurofibrillary tangles are intracellular aggregates of the hyper-phosphorylated microtubule-associated protein tau (49, 98). The excess accumulation and aggregation of beta-amyloid peptides are detrimental to neuronal networks (43) and play a pivotal role as an

upstream molecule in the process of neurodegeneration (47). Thus identifying beta-amyloid peptides as key players in the molecular mechanisms of early disease progression (42, 110). Previous work has shown that exercise training can reduce beta-amyloid production. However, long-term exercise interventions also result in improvements in whole body health making it difficult to determine the direct effects of exercise on brain amyloid precursor protein (APP) processing. This leaves us with a large void in understanding the exact mechanism(s) behind exercise-induced changes in APP processing in the brain. This review will discuss our current understanding of APP processing and how exercise can alter the production of beta-amyloid peptides. Further, this review will summarize published evidence for a role of exercise induced brain derived neurotrophic factor (BDNF) on reducing beta-amyloid peptide production.

Amyloid Precursor Protein Processing

The accumulation of beta-amyloid peptides is central to the pathogenesis of AD (61, 79, 111) and can be observed almost a decade before cognitive impairment is seen in AD patients (12, 82, 115). This is known as preclinical AD where the pathological processes are active for several years prior to clinically detectable impairments (82). While the most reliable detection of beta-amyloid plaques is by post mortem analysis, advances in imaging techniques such as positron emission tomography (PET) and analysis of cerebral spinal fluid (CSF) can now detect beta-amyloid in vivo. Both PET and CSF beta-amyloid highly correlate with brain biopsy findings (112, 135). Previous work has reported that

preclinical AD, detected either by the CSF signature for AD (32, 51) or by PET, predicts symptomatic AD (82). Further, the two methods were directly compared with two different assays in a clinical cohort of consecutive patients with mild cognitive impairment who later developed AD dementia. The study concluded that both CSF analysis and amyloid PET perform equally well and that either method can be used in the clinical workup of AD for increased diagnostic accuracy (95). Given this information an understanding of the how beta-amyloid production is regulated is vital to developing strategies aimed at the prevention and treatment of AD.

Beta-amyloid peptides are proteolytic products of a type I transmembrane protein known as amyloid precursor protein (APP) (100, 120). APP is synthesized at the endoplasmic reticulum and enters intracellular transport along the secretory, endocytic, and recycling routes, in both the soma and neuronal processes (for review (86)). APP processing occurs via one of two pathways, the non-amyloidogenic pathway and amyloidogenic pathway; which is characteristic of AD (**Figure 1**). The non-amyloidogenic pathway is initiated by alpha-secretase, which cleaves APP releasing a large soluble fragment of APP (sAPPα) leaving the C-terminal fragment (APP-CTFα or C83) containing P3 and the APP intracellular domain (AICD) in the membrane. Subsequent cleavage of APP-CTFα by gamma-secretase releases the non-toxic P3 fragment as well as AICD (92).

The first step in the amyloidogenic pathway of APP processing is the cleavage of APP by the beta-secretase enzyme, also known as beta-site APP-

cleaving enzyme 1 (BACE1) (102). BACE1 is the rate-limiting enzyme in the production of beta-amyloid peptides and a significant increase in BACE1 activity has been reported in sporadic AD brains (123, 125, 138). Thus making BACE1 an important therapeutic and/or preventive target in AD research. BACE1 cleaves APP at the extra-membrane domain, producing a soluble fragment of APP (sAPPβ) and the C-terminal fragment (APP-CTFβ or C99). The sAPPβ peptide is released into the extracellular space through endosome recycling (48). Gamma-secretase subsequently cleaves APP-CTFβ at the intramembrane domain, producing beta-amyloid and the AICD (40, 45, 65). The exact site of the gamma-secretase cleavage of APP-CTFβ can vary, which results in the release of different beta-amyloid peptide lengths (65). The most common beta-amyloid peptide lengths are 40 and 42 amino acids, of which beta-amyloid 42 is considered to be the most pathogenic in the development of AD (27) (**Figure 1)**.

Due to its role in beta-amyloid peptide production, BACE1 is considered a biomarker for early detection, prediction, and progression of AD (46, 47, 124). Understanding how BACE1 content and activity is regulated holds potential for establishing therapies aimed at reducing and/or slowing the progression of AD. Although the level of BACE mRNA does not appear to be altered in human AD patients or transgenic mouse models of AD (57, 62, 140), BACE1 enzymatic activity is elevated in the aged brain (40) and in AD brains (39, 54, 139). In addition, humans with an APP mutation that effects the beta-cleavage site (59) and mice with a targeted deletion of BACE1 (73, 108) are protected from beta-amyloid peptide formation, thus providing strong evidence in support of the

concept that BACE1 reduction or inhibition could be efficacious for the treatment of AD. Given this, BACE1 has become a key therapeutic target with several BACE1 inhibitors undergoing clinical trials (as reviewed by (123, 137)). Currently there are four companies (Merck & Co., Biogen/Eisai, AstraZeneca/Eli Lilly, Johnson & Johnson, and Novartis) with BACE1 inhibitors in various phases (II-III) of clinical trials and various patient populations. With Eli Lilly having two BACE1 inhibitors fail in clinical trials (LY2811376 and LY2886721) and the recently halted clinical trial by Merck & CO of the BACE1 inhibitor verubecestat (MK-8931) (85), the results from other ongoing trials using BACE1 inhibitor drugs are highly anticipated.

Obesity, insulin resistance, and APP processing

Inactivity, obesity, and insulin resistance are significant risk factors in the development of AD (16, 76-78, 83, 101, 133). It is known that diet-induced obesity results in impaired cognitive function in rodents (52, 87) and humans (29, 136). Moreover, a link between insulin resistance and type 2 diabetes and increased beta-amyloid deposition has been demonstrated in several transgenic mouse models of AD (16, 52, 60, 76-78, 105) as well as in humans (94). Together, this provides evidence that APP processing may be directly altered with obesity and insulin resistance. Several researchers have demonstrated that high fat feeding increases the expression of BACE1 (118, 131, 141). In agreement with this hypothesis, rodent models of type 2 diabetes (diet induced, streptozotocin (STZ) induced, and genetic models) result in increased BACE1,

APP, and beta-amyloid production in the brain (70, 141). However, this is not always the case. Others have demonstrated that high fat feeding increases the level of APP-CTFβ without changing APP or BACE1 content, indicating that a high fat diet may increase BACE1 activity, followed by promotion of APP cleavage (77). In agreement with this, we have demonstrated that high fat feeding of male wild type C57BL6/J mice results in an increase in BACE1 activity with no change in BACE1 protein content or mRNA expression (74). The exact mechanisms leading to the changes in BACE1 content and/or activity is likely multifaceted, however increased inflammation, cellular stress and impaired energy metabolism represent early abnormalities that precede or accompany the initial stages of neurodegeneration, all of which may be directly altered by exercise (74) (Figure 2a).

Exercise and APP Processing

Evidence from epidemiological and experimental studies clearly indicate that regular physical exercise not only combats obesity and obesity-related comorbidities, but that it also prevents cognitive decline due to aging and neurodegenerative diseases (25, 38, 50, 64, 69, 116, 129). Epidemiological studies have estimated that reduced physical activity (classified by total number of activities, hours per month, and percent intensity) was associated with a 250% increase in the risk of developing AD (38), while individuals who engage in physical activity (assessed from questionnaires and categorized as high (exercise 3 times/week or more and an intensity higher than walking), moderate

193 (exercise 3 times/week or more and an intensity equal to walking), and low) have
194 a significantly reduced risk of developing AD (69). Together, this provides
195 evidence that exercise is an effective strategy to improve brain health and reduce
196 and/or slow the progression of AD, however the mechanisms driving these
197 beneficial changes remain unknown. Several studies in animal models support
198 existing epidemiological studies demonstrating the benefit of exercise in
199 improving the pathology of AD (2, 21, 117, 121). The cognitive benefits of
200 exercise have been shown in rodents submitted to long-term voluntary exercise
201 in running wheels (90, 122), as well as after 3- to 12-week training periods on a
202 treadmill (5, 6, 13). Further work has demonstrated that endurance exercise
203 training is an effective strategy for improving high fat diet induced cognitive
204 impairment, which is more closely associated with the pathogenesis of AD in
205 todays society (20, 91). Treadmill training has been reported to improve spatial
206 memory in different animal models of AD, such as lesion induced (55) or STZ
207 induced (107). While long term physical activity has been shown to slow and
208 prevent high fat diet induced impairments in neurogenesis (26, 28, 66) and
209 memory (81).

210 Evidence from animal studies suggest that exercise training could reduce
211 the development of neurodegenerative processes by preventing beta-amyloid
212 peptide production. Specifically, Adlard et al. (2) demonstrated that increased
213 physical activity decreases beta-amyloid peptide levels in the TgCRND8 mouse
214 model of AD. Using five months of voluntary exercise they found a reduction in
215 beta-amyloid 40 and beta-amyloid 42 in both cortical and hippocampal regions of

the brain (2). This reduction in beta-amyloid peptides was comparable to effects seen with beta-amyloid immunization interventions where there is a 50% reduction in beta-amyloid in this same transgenic line (58). In agreement with this work, Maesako et al. (77) demonstrated in APP transgenic mice that voluntary exercise inhibits high fat diet-induced beta-amyloid deposition and memory deficit. In a follow up study, they demonstrated the importance of voluntary exercise over diet control in reducing beta-amyloid accumulation and memory deficit (78). Studies utilizing controlled treadmill training have also demonstrated an exercise-induced reduction of beta-amyloid peptides (71, 142). The mechanisms linking exercise to a reduction in beta-amyloid peptides have not been elucidated, however studies indicate the exercise can alter APP processing. Adlard et al. (2) found no change in mRNA or protein levels of neprilyin or insulin degrading enzyme, both classic beta-amyloid degradation pathways (2). Interestingly, 10 weeks of voluntary exercise resulted in a down regulation of BACE1 activity in high fat fed APP transgenic mice (77).

It is clear that long-term exercise or physical activity has beneficial effects in improving cognition and in reducing beta-amyloid production. However, with exercise training and long-term physical activity there are changes external the brain that may result in indirect effects on brain health and signaling, such as reductions in adiposity as well as improved glucose homeostasis (74). This makes it difficult to determine if changes in the brain are due to direct effects of exercise, or are secondary to changes in adiposity and/or improved insulin sensitivity/metabolic health (74). It is important to determine if exercise has a

direct effect on the brain, without the long-term adaptations in other tissues, if we are to determine the mechanisms underlying the exercise-induced decreases in BACE1 content and/or activity and beta-amyloid peptides. Understanding the direct effects of exercise on the brain is key to our understanding of the long-term changes induced by exercise and in developing effective lifestyle interventions or therapies aimed at reducing AD.

The use of acute (one bout) exercise provides an ideal model to examine the direct effects of exercise on brain APP processing and BACE1. To address this question we recently examined the ability of one acute bout of exercise to reduce BACE1 content and activity in obese, insulin resistant mice. We made the novel finding that one bout of exercise reduced BACE1 content and activity and reversed high fat diet-induced markers of energetic stress in the cortex of obese male mice fed (74). These findings occurred in the absence of alterations in adiposity and circulating metabolites in the obese mice. This highlights the fact that exercise has a direct effect on brain BACE1 content and activity and provides further evidence in support of the therapeutic potential of exercise regardless of alterations in adiposity. However, the exercise induced signaling cascades leading to reduced BACE1 content and activity remain to be determined. This knowledge concerning the underlying mechanisms is needed in order to develop efficient exercise programs and pharmaceutical targets aimed at reducing beta-amyloid load.

Exercise and BDNF

A number of studies suggest that the synthesis and release of trophic factors particularly brain-derived neurotrophic factor (BDNF) plays a crucial role mediating the effects of exercise on the brain (88, 126). BDNF is a member of the neurotrophin family of growth factors and promotes neuronal survival, neurite outgrowth and synaptic plasticity through its interactions with its receptor, tyrosine kinase B (TrkB) (96, 99). Further, BDNF is vital for cognitive performance in the short-term and for adaptations in brain morphology in the long-term. (22, 84). Growing evidence suggests that a decrease in BDNF levels could be associated with the pathogenesis of AD (34, 41). Two cross-sectional studies examining plasma BDNF concentrations between older adults with AD and healthy controls found that concentrations of BDNF were significantly lower in those with AD compared to controls providing evidence in support of a link between BDNF and AD pathology (67, 68). In addition to circulating BDNF, in brains from AD patients, BDNF expression is decreased in the hippocampus and some cortical areas such as the temporal and frontal cortex (33, 113).

Exercise is known to increase both circulating BDNF as well as BDNF content in the brain, yet surprisingly no studies have assessed the mechanistic link between acute exercise-induced increases in BDNF and decreased BACE1 content or activity. In humans, acute exercise stimulates a peripheral increase of BDNF from sites including the liver, muscles, and blood cells [161, 162]. A recent review by Knaepen et al.(63) described the positive relationship between exercise intensity and plasma BDNF concentrations. The study suggested a dose-response relationship between acute exercise and plasma BDNF

concentrations, with high intensity and graded exercise tests eliciting the greatest exercise-induced increases in plasma BDNF concentration in healthy participants. In addition, there is also evidence that increases in plasma BDNF concentrations can be observed in response to a variety of different exercise protocols and modalities (e.g., step tests, VO_2max tests, sub-maximal endurance exercise, sub-maximal sprints) (35, 44, 103, 134). Importantly, BDNF can cross the blood brain barrier and then function to stimulate central neurotrophin increases, especially in the hippocampus (24).

Binding of BDNF to TrkB receptors leads to the autophosphorylation of the intracellular tyrosine kinase domain of these receptors. This results in the activation of several downstream signaling pathways (56, 106). The downstream pathways activated by TrkB signaling include mitogen-activated protein kinase (MAPK), phospholipaseCc (PLC-c), phosphatidylinositol-3-kinase (PI3K), protein kinase C (PKC) (56), and cAMP-response element binding (CREB) protein (127, 128). If or how these pathways may be related to APP processing remains elusive. In neuronal cultures, BDNF has specific and dose-dependent protective effect on neuronal toxicity induced by beta-amyloid 42. When treated with a selective inhibitor of the tyrosine protein kinase activity of the Trk family (K252a) this protective effect was inhibited (7). These results demonstrate a direct link between BDNF binding to its TrkB receptor and reduced beta-amyloid production. In an in-vivo model, Vayman et al. demonstrated that exercise induced BDNF promotes synaptic plasticity through downstream targets, cAMP-response element binding (CREB) protein, synapsin I, and synaptophysin, while

simultaneously increasing its own mRNA and its receptor TrkB (127, 128). Whether this exercise induced increase in BDNF and TrkB signaling is directly involved in beta-amyloid production in AD requires further study. Supporting evidence for a role of BDNF and TrkB in AD comes from a cell culture model where TrkB signaling can modulate APP content and processing. In SH-SY5Y cells, retinoic acid can increase expression of TrkB and concomitant treatment with BDNF can increase APP promoter transcription and promote accumulation of sAPP-alpha and AICD by shifting APP processing towards the alpha-secretase or non-amyloidogenic pathway (53). Further, recently published work from Nigam et al. (89) demonstrated the three weeks of voluntary wheel running reduced beta-amyloid levels and increased sAPPα in the hippocampus of a transgenic mouse model of AD. This was accompanied by a significant increased in hippocampal BDNF of the runner mice. These results lead the authors to hypothesize that exercise induced BDNF may alter alpha-secretase activity. To investigate this, SH-SY5Y cells were treated with an alpha-secretase inhibitor, BDNF, or the combination of BDNF and the inhibitor. From these experiments the authors concluded that BDNF reduces beta-amyloid levels through a mechanisms involving increased alpha-secretase activity (89). Interestingly cell lysates that were treated with the alpha-secretase inhibitor and BDNF displayed higher levels of sAPPα compared to cells that were treated only with the inhibitor. This indicates that BDNF may reduce beta-amyloid production through another pathway. If BDNF has a direct effect on BACE1 in response to an acute bout of exercise remains to be determined.

Both chronic voluntary wheel running and moderate to high intensity treadmill exercise training of rodents results in the up-regulation of BDNF mRNA and protein content in the hippocampus (3, 4, 14, 114, 126). Similar to the human studies described above, studies investigating the effects of acute exercise on brain BDNF levels in rodents have similar findings where brain BDNF expression is increased. A study comparing low and moderate intensity acute treadmill exercise (30 minutes at 15m/min vs 30 minutes at 25m/min) demonstrated that exercise resulted in elevations of BDNF mRNA in the hippocampus (specifically the CA1, CA3, and dentate gyrus regions) with the highest levels occurring ~1.5 hours post-exercise [179]. This evidence showing that exercise increases circulating and brain BDNF content as well as signaling is strong, however a direct link between BDNF signaling and BACE1 activity has yet to be determined.

Conclusions

There is a clear void in our understanding of the mechanisms underlying the direct effects of exercise on changes in BACE1 content and activity. This review has aimed to highlight a potential role for exercise induced BDNF on reducing beta-amyloid production through alterations in BACE1 content and/or activity. We suggest that BDNF signaling is directly involved in the exercise induced reduction in BACE1 activity and beta-amyloid production. However more evidence is needed to support this idea and to elucidate the underlying signaling cascades linking the two. Future studies need to assess the extent to which

353 BDNF actually mediates the effects of acute exercise on BACE1 and beta-
354 amyloid production.
355
356 **Perspectives and Significance**
357 The importance of BACE1 as the rate-limiting enzyme involved in the
358 production of beta-amyloid peptides is clear. Novel information gained from
359 future studies exploring the direct effect of exercise induced BDNF on BACE1
360 content and activity will enhance our understand of the underlying mechanisms
361 regulating APP processing and will set the foundation for therapeutic targets and
362 drug development designed to improve approaches to prevent and treat AD. This
363 information is valuable in terms of both understanding the underlying cellular
364 mechanisms leading to declines in BACE1 but also in terms of designing
365 evidence based preventative or therapeutic interventions for individuals with an
366 elevated risk for AD.
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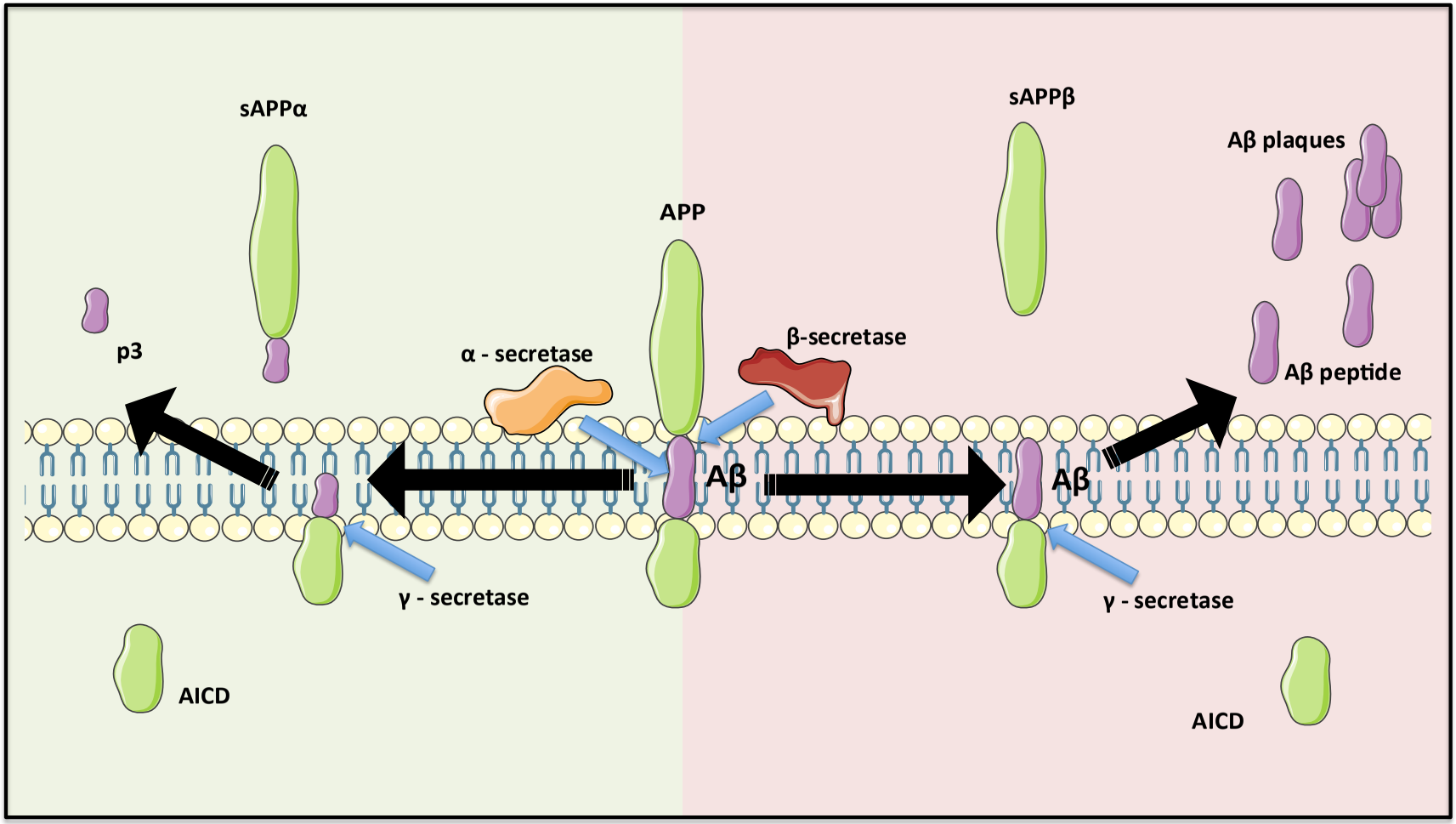
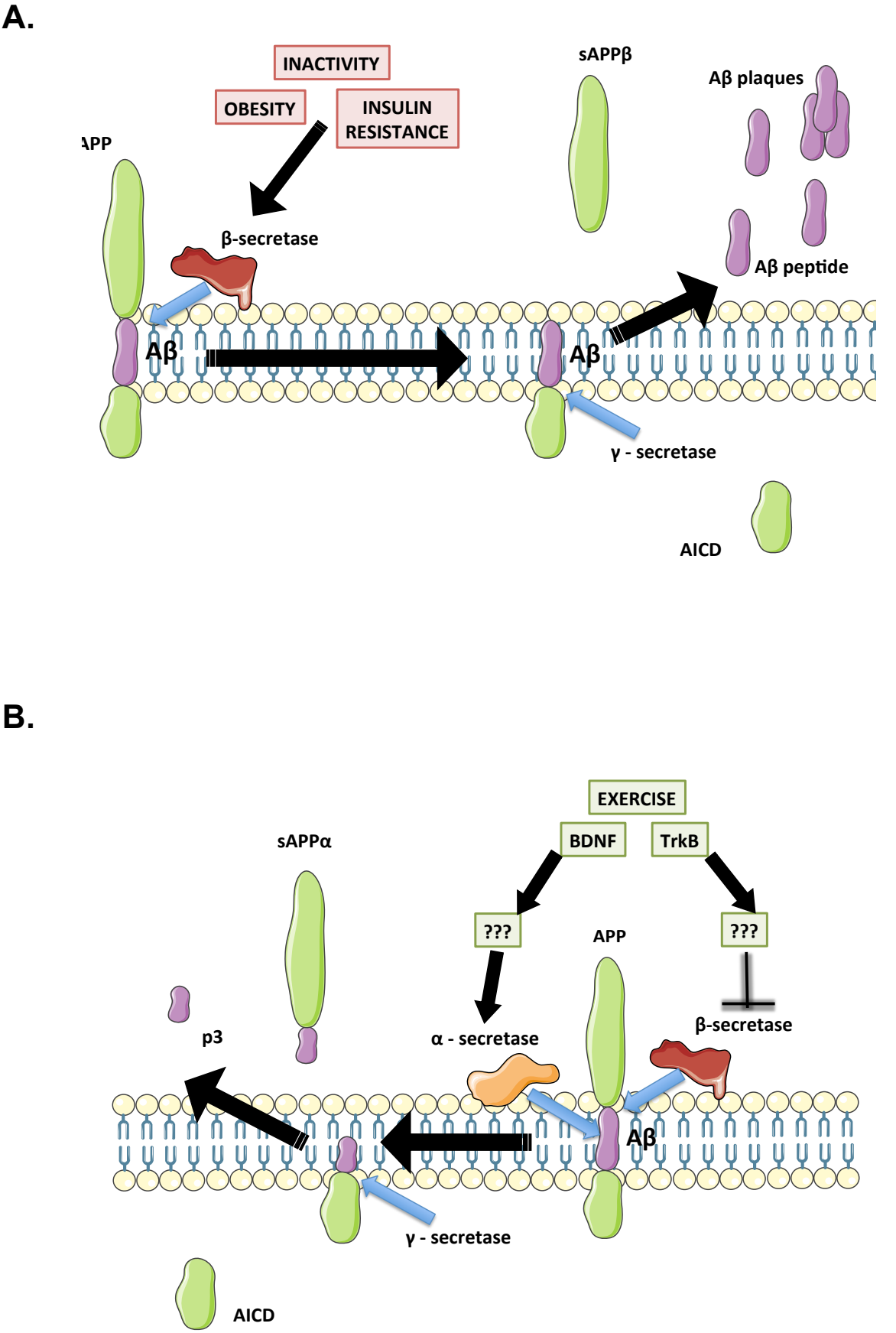
Figure Captions

Figure 1. Amyloid precursor processing (APP).
The non-amyloidogenic pathway (left side) is initiated by alpha secretase, which cleaves APP releasing a large soluble fragment of APP (sAPPα) leaving the C-terminal fragment (APP-CTFα or C83) containing P3 and the APP intracellular domain (AICD) in the membrane. Subsequent cleavage of APP-CTFα by γ-secretase releases the non-toxic P3 fragment as well as AICD. The first step in the amyloidogenic pathway of APP processing (right side) is the cleavage of APP by the beta-secretase enzyme, also known as beta-site APP-cleaving enzyme 1 (BACE1). BACE1 cleaves APP at the extra-membrane domain, producing a soluble fragment of APP (sAPPβ) and the C-terminal fragment (APP-CTFβ or C99). The sAPPβ peptide is released into the extracellular space. γ-secretase subsequently cleaves APP-CTFβ at the intramembrane domain, producing beta-amyloid and the AICD(40, 45, 65). The beta-amyloid peptides then accumulate and aggregate forming beta-amyloid plaques.

Figure 2. Potential effects of obesity and exercise on amyloid precursor processing. A. Inactivity, obesity, and insulin resistance can result in increased beta-site APP-cleaving enzyme 1 (BACE1) activity resulting in increased production of the soluble fragment of APP (sAPPβ), the C-terminal fragment (APP-CTFβ or C99) and beta-amyloid peptides. B. Potential role for exercise induced BDNF signaling through TrKB on reducing beta-amyloid production through increased alpha-secretase activity and reduced BACE1 content and/or activity.


sAPPα
p3
α - secretase
APP
β-secretase
sAPPβ
Aβ plaques
Aβ peptide
Aβ
Aβ
γ - secretase
γ - secretase
AICD
AICD


A.
INACTIVITY
OBESITY
INSULIN RESISTANCE
APP
β-secretase
sAPPβ
Aβ plaques
Aβ peptide
Aβ
Aβ
γ - secretase
AICD
B.
EXERCISE
BDNF
TrkB
sAPPα
???
???
APP
p3
α - secretase
β-secretase
Aβ
γ - secretase
AICD