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Stress, exercise, and Alzheimer's disease: A neurovascular pathway

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Abstract

Genetic factors are known to play a role in Alzheimer's disease (AD) vulnerability, yet less than 1% of incident AD cases are directly linked to genetic causes, suggesting that environmental variables likely play a role in the majority of cases. Several recent human and animal studies have examined the effects of behavioral factors, specifically psychological stress and exercise, on AD vulnerability. Numerous animal studies have found that, while stress exacerbates neuropathological changes associated with AD, exercise reduces these changes. Some human studies suggest that psychological stress can increase the risk of developing AD, while other studies suggest that exercise can significantly reduce AD risk. Most animal studies investigating the mechanisms responsible for the effects of these behavioral factors have focused on neuronal processes, including the effects of stress hormones and neurotrophic factors on the neuropathological hallmarks of AD, namely amyloid-beta (Aβ) deposition and tau-phosphorylation. However, cumulative evidence indicates that, in humans, AD is associated with the presence of cerebrovascular disease, and cardiovascular risk factors are associated with increased risk of developing AD. There is an extensive literature demonstrating that behavioral factors, particularly stress and exercise, can powerfully modulate the pathophysiology of vascular disease. Thus, the following model proposes that the influence of stress and exercise on AD risk may be partially due to the effects of these behavioral factors on vascular homeostasis and pathology. These effects are likely due to both indirect modification of AD risk through alterations in vascular risk factors, such as hypertension, diabetes, and aortic stiffening, as well as direct influence on the cerebrovasculature, including changes in cerebral blood flow, angiogenesis, and vascular disease. Future studies examining the effects of behavioral factors on AD risk should incorporate measures of both peripheral and cerebral vascular function to further our understanding of the mechanisms by which behavior can modify AD susceptibility. Greater knowledge of the molecular mechanisms behind these behavioral effects would further our understanding of the disease and lead to innovative treatment and preventive approaches.

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Introduction

Exercise and Alzheimer's disease

Alzheimer's disease (AD) is a neurodegenerative disorder primarily characterized by the presence of intracellular neurofibrillary tangles, comprised of hyperphosphorylated tau protein, and extracellular senile plaques, made up of aggregated Aβ protein [1]. AD is the most common cause of dementia, accounting for more than half of all cases and affecting more than one third of individuals over 80 years of age [2]. With a worldwide aging population, an estimated 106.2 million people will be diagnosed with AD by 2050 [2]. The incredible financial and psychological costs of the disease for patients, their families, and society has led to intense investigation into its causes, correlates, and potential treatments.

Despite extensive investigation into potential therapies for AD, existing pharmacological measures are largely palliative and provide only modest, transient stabilizations in functioning [3]. Furthermore, no pharmacological measures have consistently demonstrated benefits in secondary prevention trials [4]. More recently, exciting findings within a few well-designed primary prevention trials have suggested that increased physical activity may reduce the risk of developing AD in older adults [5,6]. These trials were spurred by several large prospective studies indicating that increased physical activity levels are associated with a reduction in the risk of developing dementia [7-11].

Numerous pre-clinical studies utilizing animal models of AD have also demonstrated a protective effect of exercise on the disease. In these studies transgenic (tg) mice genetically modified to express one or more of the human genes responsible for the heritable forms of the disease, including human amyloid precursor protein (APP), presenilin-1, and presenilin-2, were placed in various exercise paradigms or kept in sedentary conditions. Findings indicated that exercise improves learning and memory, increases hippocampal neurogenesis, plasticity, and volume, and decreases Aβ load and plaque deposition in these animal models [12-17]. These findings are consistent with studies of exercise in normal and aged animals that demonstrate exercise improves learning and memory through increased hippocampal plasticity [18,19]. Thus, animal studies suggest that the benefits of exercise on AD risk may be due to direct effects on the neuropathological hallmarks of AD and neural mechanisms underlying learning and memory.

The exact mechanism responsible for attenuating the patho-physiological changes associated with AD remains unclear. Studies using tg mice have variously shown that exercise leads to reduction of several markers of AD neuropathology, including Aβ load ($A\beta_{1–40}$ and $A\beta_{1–42}$), APP metabolism (α- and β-secretase), tau phosphorylation, and apoptotic signaling (cytochrome c, caspase-9, caspase-3, and Bax) [13-15,20-22]. Only one study found that exercise provided no benefit to tg mice [23]. Nonetheless, cumulative evidence suggests that exercise appears to slow the Alzheimer's process in tg mice and reduces the risk of AD in humans.

A series of studies point to a role for neurotrophic factors in exercise-induced improvements in cognitive functioning. For example, blockade of the brain-derived neurotrophic factor (BDNF) TrkB receptor abolished the effects of exercise on cognitive functioning in healthy rats [24], indicating a role for the TrkB receptor in the effects of exercise on learning and memory and in AD vulnerability. Hippocampal BDNF levels increase in response to exercise [25], and exercise training increases BDNF release from the brain in humans [26]. In addition, BDNF plays a critical role in promoting long-term potentiation (LTP) and synaptic plasticity that underlies learning and memory [27] through multiple intracellular pathways, including cAMP response element binding protein (CREB), calcium/calmodulin

protein kinase II (CaMK II), and mitogen-activated protein kinase (MAPK) [28]. Thus BDNF may promote neurogenesis and neuronal survival [29].

Taken together these findings indicate that exercise is capable of improving cognition and altering AD-like pathophysiology in animals and reducing the risk of dementia in humans. These findings have profound implications for the treatment of older adults at risk of AD since exercise is efficacious in primary prevention and may show potential in secondary prevention, unlike the pharmacological treatments more commonly employed in clinical practice [3-5]. Studies investigating the potential mechanisms behind the effects of exercise on AD risk have implicated hippocampal growth factors known to promote neurogenesis, neuronal survival, synaptic plasticity, and learning and memory. The following section will review the current evidence and theories regarding the role of psychological stress and stress hormones in increasing the risk of developing AD.

Stress, stress hormones, and Alzheimer's disease

There are considerably fewer human studies examining the effects of psychological stress on AD vulnerability. Epidemiological data suggests that proneness to psychological distress is associated with increased risk of dementia [30,31]. Additionally, self-reported stress is associated with more rapid cognitive decline in patients with mild cognitive impairment (MCI) [32], a major risk factor for AD, and a recent history of severe life stressors may be associated with the onset of dementia [33]. However, linkage of psychological traits to dementia risk does not necessarily indicate a causal role for psychological stress in AD vulnerability, and retrospective reports of life stressors may not be valid measures of stress burden in the general population. Nevertheless, these early studies suggest that psychological stress may play a role in increasing AD vulnerability, and future prospective studies will yield more insight into this possibility.

AD patients exhibit increased levels of stress hormones, including plasma and salivary cortisol, which correlates with disease progression, implicating hypothalamo-pituitary-adrenal (HPA)-axis dysfunction in AD [34]. In nondemented adults, cortisol elevations may improve cognition in the short-term, but long-term elevations have been associated with declines in cognitive functioning [35,36]. Thus, it has been hypothesized that chronic stress, associated with chronic elevations in stress hormones, may lead to accelerated cognitive decline with age. However, hippocampal glucocorticoid receptors provide negative feedback to regulate the HPA-axis activity, leading to speculation that HPA-axis dysregulation in AD may simply reflect hippocampal degeneration associated with the disease [37,38].

Animal studies have demonstrated links between stress, stress hormones, and AD-like pathology. Chronic stressors, including social isolation, are associated with decreased hippocampal neuro-genesis and volume, abnormalities in LTP and dendritic branching, decreased cued and contextual memory, and accelerated Aβ plaque deposition and tau-phosphorylation relative to those in nonstressed controls [39-42]. Only one study reported that social isolation stress produced no effect on neurodegeneration in tg mice [43]. Taken together, most studies suggest that chronic stress is capable of modulating the expression of AD pathophysiology in animals prone to develop the disease.

The mechanism responsible for the effect of stress on AD-like pathology is uncertain. However, one study found that concomitant administration of the selective serotonin reuptake inhibitor (SSRI), fluoxetine, prevented the effects of social isolation stress on hippocampal cell proliferation and contextual memory. In a recent follow up study, increased plasma corticosterone, glucocorticoid, and CRF receptor (CRFR1) in the cortex and hippocampus were associated with social isolation and correlated with the accelerated neuropathological changes observed in these animals [44]. Additionally, CRF antagonism

was found to inhibit stress-induced Aβ deposition within the cortex of tg mice [45]. Thus, alterations in neurotransmitter and/or stress hormone activity may be responsible for the exacerbation of AD-like pathology in animals exposed to chronic stress.

Findings from studies utilizing animal models of AD are generally consistent with the extensive literature on the effects of stress on hippocampal structure and function in healthy animals [46]. For example, chronic stress or administration of corticosterone or CRF reduces dentate gyrus proliferation, causes simplification and retraction of dendrites in hippocampal cells, and increases phosphorylation of tau protein in rodents [46-49]. Additionally, a recent study in aged mice indicated that chronic treatment with dexamethasone led to impaired learning and memory, hippocampal and cortical apoptosis, and increased hippocampal expression of APP and pro-apoptotic enzymes [50]. Thus, converging evidence from normal, aged, and disease prone animals indicates that psychological stress can exacerbate pathophysiological processes known to play major roles in the development of AD.

The effects of exercise and chronic stress on Alzheimer's disease

Interestingly, the mechanisms involved in the beneficial effects of exercise on AD vulnerability may also be affected by psychological stress. For example, psychological stress reduces BDNF mRNA levels while antidepressants increase BDNF levels in animals [51,52]. Furthermore, BDNF+/− mice show less dendritic branching in the hippocampus and do not show further reductions in response to chronic stress, while antidepressants prevent the effects of stress on hippocampal volume and cell proliferation [46,53]. Other studies have found that chronically stressed animals exhibit increased corticosterone levels and do not show exercise-induced increases in hippocampal neurogenesis acutely [54]. Conversely, regular exercise can reduce HPA-axis activation to stressors, indicating that stress and exercise modulate neuroendocrine function at multiple levels [55,56]. Taken together these studies suggest that modulation of BDNF may be in part responsible for the effects of chronic stress on hippocampal structure and function and that the effects of stress and exercise may share common pathways. Interestingly, the one study that found no exercise benefit in tg mice utilized a forced exercise paradigm, in which mice were run on a treadmill and given shocks to keep them running forward, such a stressful exercise paradigm may have negated the exercise benefit [23].

Psychological stress and HPA-axis dysregulation are not only consequences of AD neuropathology, but may also play a causal role in accelerating disease progression or potentially increasing AD risk. The interaction between disease promoting stress hormones and protective growth hormones may be involved in processes underlying the effects of both stress and exercise on AD. The convergence of these pathways important in modulating disease progression and risk requires further study and could yield insights into novel treatments. For instance, the coupling of stress management therapy in conjunction with exercise training may provide additional benefit for AD risk through changes in growth and stress hormone signaling in the hippocampus. Fig. 1A displays a schematic model of the neural effects of psychological stress and exercise potentially impacting AD risk.

The hypothesis: a neurovascular pathway

Most prior studies examining the effects of exercise and stress on AD have focused on mechanisms involved in neuronal functioning, with direct connections being made among AD pathology, exercise, and stress physiology in the brain. One major limitation of animal studies examining the pathophysiological mechanisms involved in genetic forms of AD, is the lack of generalizability to the much more common sporadic form of the disease. In addition, recent research has led to increasing recognition that sporadic AD is associated with vascular disease. All major risk factors for cardiovascular disease (CVD) are also now

recognized risks for AD, including hypertension, diabetes, and hyperlipidemia [57]. There are also several important areas of overlap in the pathophysiology of CVD and AD, including chronic elevations in inflammation and oxidative stress, and recent neuropathological studies have found an association between cerebrovascular and AD pathology [58,59]. In fact, one of the key features of AD, recognized since Alois Alzheimer first described the disease, is the presence of cerebral amyloid angiopathy (CAA), a form of vascular disease associated with approximately 80% of sporadic cases [60]. Although tg mice prone to develop AD exhibit cerebrovascular dysfunction characteristic of CAA, they do not spontaneously develop atherosclerosis or vascular risk factors that are extremely common in human aging and are associated with increased AD risk. Behavioral factors, particularly exercise and psychological stress, are recognized as especially important in determining risk, progression, and outcomes of vascular disease, a notion that is supported by extensive basic and clinical research [61]. Taken together, these data suggest that in the human, sporadic form of AD, exercise and stress may modulate important aspects of AD pathophysiology through vascular mechanisms.

Evaluation of the hypothesis

Vascular mechanisms in Alzheimer's disease

The mechanisms underlying the link between CVD and AD are incompletely understood, but a number of hypotheses have been proposed. Frank stroke may lead to upregulation of APP and dys-regulation of Aβ metabolism in response to injury [62]. Additionally, reductions in cerebral blood flow (CBF) short of frank ischemia are associated with cerebrovascular disease may have similar effects [63]. Disruption of CBF may also impair the clearance of Aβ from the brain [64]. Furthermore, increased pulsatile forces resulting from both cerebrovascular and systemic arterial stiffening may disrupt Aβ clearance mechanisms and blood- brain-barrier function, causing a buildup of Aβ and other neurotoxic blood products within the brain parenchyma [65,66]. It has been hypothesized that subclinical cerebrovascular disease may lead to dysfunction of the neurovascular unit, disrupting the ability of cerebrovascular microvessels to dilate in response to increased neuronal activity [67]. This could lead to neuronal dysfunction and reduced activity, causing cognitive dysfunction and Aβ accumulation [67]. These hypotheses provide slightly different causal explanations for the connection between vascular disease and AD, but they are closely related in that each involves some disruption of neurovascular function and CBF. It is well established that AD is associated with reductions in resting CBF within specific brain regions and alterations in activity-induced regional CBF [68]. There is a strong literature supporting the potential contribution of both stress and exercise to the modulation of the core mechanisms involved neurovascular disease and dysfunction. Thus, although the importance of neuronal changes associated with stress and exercise are well supported and should not be overlooked, the potential contribution of neurovascular changes to these effects requires further investigation.

Atherosclerosis and vascular risk factors

Atherosclerosis of the large cerebral vessels, particularly within the Circle of Willis, has a known association with AD [69]. Additionally, peripheral atherosclerosis has also been associated with age-related cognitive decline and AD. Specifically, AD patients exhibit impaired brachial artery flow-mediated dilation, a measure of endothelial function and vascular disease, in comparison with non-demented controls [70]. Brachial artery endothelial and vascular smooth muscle dysfunction have also been associated with cognitive impairment in nondemented adults with vascular disease [71]. Consistent with these findings, other studies have found that peripheral pulse pressure (PP) and aortic pulse wave velocity (PWV), measures of arterial stiffness and subclinical atherosclerosis, are

associated with declines in cognitive domains known to be affected in early AD [72,73]. AD patients exhibit elevated PP relative to age-matched controls and PP elevation is associated with increased risk of developing AD [74,75]. Thus, in addition to the cerebrovasculature, the extent of vascular disease in the periphery is associated with increased risk of AD. Although the exact mechanism behind this association remains unclear, it has been hypothesized that increased PP and PWV secondary to aortic stiffening may place increased pulsatile strain on delicate cerebral microvessels, leading to elevated risk of microvascular disease [76]. In support of this hypothesis, PP has been associated with white matter lesions in patients with AD and hypertensive adults [74,77]. Thus, cumulative evidence suggests that systemic atherosclerosis is associated with AD and increased AD risk through mechanisms that are not completely understood, but may involve increased pulsatile strain on cerebral microvasculature.

An extensive literature supports the notion that psychological stress accelerates the development of atherosclerosis, while exercise slows lesion progression in organisms at risk for the disease [61]. For example, either an unstable, stressful social environment or social isolation can accelerate atherosclerosis in hyperlipidemic monkeys, rabbits, and mice [78-80]. Conversely, physically active animals exhibit reduced atherosclerosis relative to sedentary controls [81]. Additionally, socially isolated humans display increased carotid atherosclerosis [82] and elevated ankle-brachial pressure index [83], a noninvasive measure of peripheral atherosclerosis, but exercise can improve these measures of subclinical atherosclerosis [84]. These findings suggest that stress and exercise can powerfully modulate the underlying systemic vascular disease that is known to be associated with increased risk of AD. Thus, stress and exercise may alter AD risk indirectly through effects on peripheral vascular functioning. Additionally, the effects of these behavioral factors on other vascular risk factors associated with AD, such as hypertension and diabetes, may further reduce the risk of developing AD [57].

Oxidative stress

Beyond these indirect effects, behavioral factors may have more direct effects on vascular functioning within cerebral vessels that could ultimately impact AD risk. Vascular oxidative stress may play an important role in the connection between cerebrovascular disease and AD [59,67]. Specifically, AD is associated with increased vascular and neural oxidative stress, possibly due to the toxic effects of soluble Aβ [59]. The most important enzymatic source of reactive oxygen species within the vasculature, NADPH-oxidase, has also been shown to powerfully modulate the pathophysiology of AD. Studies in tg mice have found that blockade of the gp91phox subunit necessary for activation of vascular NADPH-oxidase prevents the cerebrovascular dysfunction typically observed in these animals [85]. Furthermore, deletion of the NOX2 catalytic subunit of NADPH-oxidase prevented the development of oxidative stress, cerebrovascular dysfunction, and behavioral deficits in tg mice prone to develop AD-like pathology [86]. Thus, increased oxidative stress, largely due to increased activity of both neural and vascular NADPH-oxidase, is known to play a substantial role in the patho-physiological and behavioral presentation of AD-prone animals.

In hyperlipidemic animals prone to develop atherosclerosis, sedentary behavior has been shown to increase the activity of vascular NADPH-oxidase [87], while exercise reduces the activity of this enzyme [81]. A recent study in tg mice found that acceleration of AD-like pathology in chronically stressed animals was associated with increased markers of oxidative stress [45]. In normal rats, social isolation stress has also been shown to increase brain oxidative stress associated with NOX2 activity [88]. Furthermore, administration of the NADPH-oxidase inhibitor, apocynin, inhibits stress-induced elevations in markers of oxidative stress [88]. Thus, the direct effects of stress and exercise on both vascular and

neural NADPH-oxidase activity may be partially responsible for the modulation of AD pathology by these behavioral factors.

Inflammation

Another important characteristic of AD pathology is increased markers of chronic inflammation, including expression of the proinflammatory cytokines IL-1β, IL-6, and TNF-α [58]. These inflammatory mediators are primarily produced by microglia, the main effector cells involved in neuroinflammation, in response to Aβ aggregates and cellular debris [58]. While these inflammatory responses are secondary to the hallmarks of AD neuropathology, namely tau phosphorylation and Aβ accumulation, apoptotic signals produced by transcription factors downstream of pro-inflammatory cytokines, such as nuclear factor κB (NFκB), may constitute an overlying mechanism of cell death [58]. Additionally, proinflammatory cytokine signaling has been shown to upregulate expression of APP and both γ- and β-secretase through NFκB activation, further suggesting that they may play a role in accelerating AD pathology [89]. Thus, excessive inflammatory signaling may be responsible for the acceleration of neurodegeneration in the context of ongoing AD neuropathology through multiple mechanisms.

These inflammatory signals are also known to play a role in cerebrovascular disease associated with AD, possibly through activation of vascular oxidative stress [90,91]. This suggests that excessive inflammation and reactive oxygen species formation may form a positive feedback loop, leading to an acceleration of both cerebrovascular disease and AD specific neuronal pathology. It is fairly well established that chronic stress can exacerbate chronic inflammation through changes in pro-inflammatory cytokine expression, while regular exercise leads to a long-term down-regulation of these inflammatory signaling molecules [87,92]. Higher physical activity levels [93] or physical fitness [94] leads to attenuated inflammation-like cellular responses by immune cells in circulation during psychological or physical stress tasks. These effects have been demonstrated in both vascular and neuronal tissues, suggesting that behavioral factors may inhibit patho-physiological mediators associated with AD through actions in both the cerebrovasculature and brain parenchyma [95,96]. Thus, in addition to the effects of stress and exercise on hemodynamic strain and oxidative enzyme activity, the effects of these behavioral factors on inflammatory mediators may be another mechanism involved in their modulation of AD risk.

Cerebral blood flow

Other vascular pathways potentially involved in the direct effects of behavioral factors on AD risk include alterations in CBF and angiogenesis. AD is associated with reduced CBF within a variety of brain regions, an observation that has been shown to be independent of simple cerebral atrophy [97]. Although the exact mechanism responsible for these alterations is unclear, there are likely several causative factors. Cholinergic neurons within the basal forebrain play a role in the autonomic regulation of vasodilation and are frequently damaged in AD, potentially leading to excessive vasoconstriction [97]. Additionally, endothelial dysfunction caused by cerebrovascular atherosclerosis or vascular Aβ deposition may lead to dysregulation of endothelial nitric oxide synthase (eNOS) and nitric oxide bioavailability, favoring increased vasoconstriction [97]. It has also been hypothesized that these alterations in CBF may further exacerbate neurodegeneration and cognitive decline in AD through impaired neurovascular coupling and energy metabolism [98]. Thus, reduced CBF may represent both an associated feature of AD and a mechanism contributing to ongoing neurode-generation and cognitive dysfunction.

Psychological stress has been shown to reduce CBF in both humans and animals, suggesting that stress may partially impact AD through effects on CBF [99,100]. Conversely, exercise has been shown to improve CBF and cognitive functioning in older humans and in both primate and rodent models [101-103]. The acute effects of exercise on CBF and cognition may be due to autonomic modulation of endothelial function, but chronic changes may also be due to angiogenesis, as exercise has been found to increase cerebral angiogenesis [103,104]. Exercise-induced angiogenesis has also been directly linked to exercise-induced neurogenesis within the hippocampus in both animals and humans [103,104]. Thus, the observed changes in CBF related to stress and exercise may be directly tied to the effects of these behavioral factors on angio-genesis and neurogenesis.

The interplay between angiogenesis and neurogenesis points to the significant overlap between vascular and neural growth signaling pathways. Key regulators of both processes have recently been termed “angioneurins”, underscoring the bidirectional communication between vascular and neural tissues, particularly in the context of tissue growth [105]. Multiple studies have suggested that increased expression of angioneurins, such as insulin-like growth factor I (IGF-1) and endothelial-derived vascular endothelial growth factor (VEGF), may be critical mediators of exercise-induced angiogenesis and improved CBF through local effects on both vascular and neural tissue [24,105,106]. Interestingly, VEGF has also been shown to upregulate BDNF expression in neurons and endothelial cells [107], further suggesting that signaling between vascular and neuronal tissues may play an important role in exercise-induced coordination of angiogenesis and neurogenesis [108].

Consequences of the hypothesis

Although the effects of exercise and stress on neural mechanisms may play an important role in modulating AD risk, findings suggest that upstream effects on vascular functioning and neurovascular signaling may underlie many of these observations. Furthermore, the importance of vascular disease in the highly prevalent, sporadic form of AD is not accounted for by animal models of the genetic forms of AD. The well established effects of exercise and stress on vascular disease are likely to play a large, multifaceted role in modulating AD risk. This is true both in terms of indirect systemic effects on vascular risk factors and direct cerebrovascular effects on neurovascular signaling, CBF, oxidative stress, and inflammation. Fig. 1B displays a schematic model of the neurovascular pathways potentially involved in the effects of exercise and stress on AD risk. In light of these observations, future studies examining the effects of stress and exercise on AD risk, or employing behavior-based treatment strategies for risk reduction, should include assessments of both systemic and cerebrovascular function in order to account for these potentially important mechanisms. Furthermore, future animal studies examining the effects of behavioral factors on AD pathology may be more relevant to human disease if they utilize double-knockout models prone to develop vascular risk factors (e.g., diabetes-prone ob/ob mice) or atherosclerosis (e.g., apoE$^{-/-}$ mice) in addition to AD-like pathology [91,109], allowing for interrogation of the relationship between vascular and AD pathology within different behavioral contexts.

The modulation of important pathophysiological mechanisms involved in AD risk by behavioral factors has major treatment implications. While no current pharmacological treatment has shown consistent benefit in secondary preventions trials, multiple clinical trials have found that exercise training reduces the risk of dementia in older adults [4,5,110]. Preclinical studies have indicated that psychosocial stress may be a risk factor for AD, suggesting that behavioral therapies focusing on stress management may be beneficial for individuals at increased risk of the disease. Few clinical trials have examined mechanisms thought to be involved in the effects of stress and exercise on AD pathophysiology. Studies investigating mechanisms responsible for the effects of behavioral factors on

neurodegenerative disease may reveal novel biochemical pathways capable of modulating AD pathophysiology, indicating new behavioral and pharmacological approaches to treatment and prevention.

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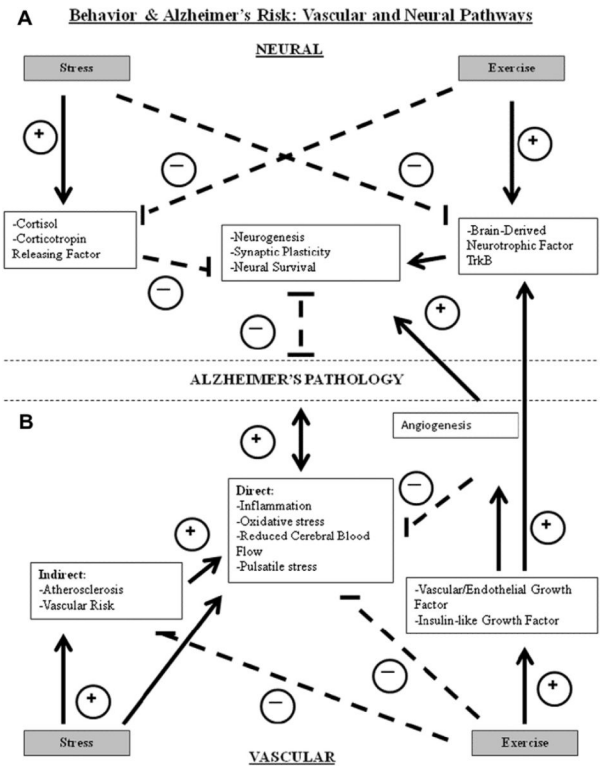

Fig. 1.

Schematic models are displayed for both the neural (A; above) and vascular (B; below) pathways involved in the effects of stress and exercise on Alzheimer's pathology. Solid lines indicate promotion (+) and dotted lines (- - -) indicate inhibition. (A) Stress and exercise differentially impact hormones that modulate neural proliferation, plasticity, and survival in the hippocampus, functions also impacted by Alzheimer's pathology. (B) Stress and exercise have direct effects on CBF, pulsatile strain, inflammation, and reactive oxygen species, as well as indirect effects through systemic atherosclerosis and vascular risk factors. These vascular functions play a role in modulating AD risk and Alzheimer's pathology may exacerbate cerebrovascular disease. The effect of exercise on angiogenesis and vascular hormones may impact both cerebrovascular and neural functions.