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Does physical activity reduce risk for Alzheimer's disease through interaction with the stress neuroendocrine system?

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Abstract
Lack of physical activity (PA) is a risk factor for Alzheimer's disease (AD), and PA interventions are believed to provide an effective non-pharmacological approach for attenuating the symptoms of this disease. However, the mechanism of action of these positive effects is currently unknown. It is possible that the benefits may be at least partially mediated by the effects on the neuroendocrine stress system. Chronic stress can lead to dysfunction of the hypothalamic–pituitary–adrenal (HPA) axis, leading to aberrant basal and circadian patterns of cortisol secretion and a cascade of negative downstream events. These factors have been linked not only to reduced cognitive function but also increased levels of amyloid-β plaques and protein tau "tangles" (the neuropathological hallmarks of AD) in the non-demented mouse models of this disease. However, there is evidence that PA can have restorative effects on the stress neuroendocrine system and related risk factors relevant to AD. We explore the possibility that PA can positively impact upon AD by restoring normative HPA axis function, with consequent downstream effects upon underlying neuropathology and associated cognitive function. We conclude with suggestions for future research to test this hypothesis in patients with AD.

Keywords: *Alzheimer, cortisol, HPA axis, hippocampus, physical activity, stress*

Introduction

Alzheimer's disease (AD) is a neurodegenerative condition creating progressive deterioration of higher cognitive functioning in the areas of memory, problem solving, and thinking (Rimmer and Smith 2009). AD is the most common form of dementia and its pathological hallmarks in the brain are neuritic plaques (composed predominantly of amyloid-β peptides) and neurofibrillary tangles (formed by hyper-phosphorylated forms of tau protein; Cummings et al. 1998). AD is characterized by an inability to carry out everyday tasks or perform instrumental activities, and may be accompanied by behavioral disorders such as agitation, aggression, and wandering (Onor et al. 2007; Rimmer and Smith 2009). Mild cognitive impairment (MCI) often represents a prodromal form of dementia, conferring a 10–15% annual risk of converting to probable AD (Risacher et al. 2009). As the world's population ages the prevalence of this debilitating disease is increasing, which is becoming a social and economic concern important to families, caregivers, professionals, and others in public health systems (Haan and Wallace 2004). In 2006, the prevalence of AD worldwide was reported to be 26.6 million, and by 2050 this number is estimated to quadruple to 106.8 million (Brookmeyer et al. 2007). The estimated worldwide societal cost of AD in 2005 was US$315.4 billion (Wimo et al. 2007). Given the scale and impact of the problem, it is imperative that acceptable and inexpensive intervention strategies are identified in order to retard the onset or attenuate the progression of the disease. It has been estimated that if interventions could delay disease onset or progression of AD by as little as 1 year, nearly 9.2 million fewer patients would be expected by the year 2050 (Brookmeyer et al. 2007).

Risk factors for AD

Over 99% of AD cases are sporadic, not associated with any known genetic mutation, although the

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presence of one or two alleles of apolipoprotein (APOE) e4 as opposed to APOE e2 or APOE e3 increases disease risk by several fold (Corder et al. 1993). Aging is probably the biggest risk factor for non-AD-associated dementia and AD (Querfurth and LaFerla 2010). However, environmental, behavioral, and social factors can increase the risk of developing AD, indicating that disease progression is potentially modifiable. Such risk factors include head trauma (Rothman and Mattson 2010), alcohol abuse, addictive smoking, diet filled with high fat content (Gustaw-Rothenberg 2009), and lack of mental stimulation (Wilson et al. 2007) through the life span.

Chronic stress is a major risk factor for the development of AD, and there is evidence that it exacerbates the cognitive deficits and the accompanying brain pathological characteristics of the condition (see Rothman and Mattson 2010, for a review). People exposed to chronic stress have been estimated to be 2.7 times more likely to suffer from AD, and they are also more likely to experience more rapid disease progression (Wilson et al. 2006). Similarly, depression is considered a risk factor for AD (Green et al. 2003) since it may be strongly related to stress (Davidson et al. 2002). As effective social support is known to be a successful buffer to psychological stress (Cohen and Wills 1985), it is not surprising that a lack of social support and meaningful social networks may also contribute to the development of AD (Fratiglioni et al. 2004; Solfrizzi et al. 2008).

Chronic stress is related to increased risk of cardiovascular (CV) conditions (Björntorp 1997; Rosmond et al. 1998) which are also risk factors for AD, and play a role in the development of the disease (Gustafson et al. 2003; Arvanitakis et al. 2004; Kivipelto et al. 2005; Whitmer et al. 2005; Helzner et al. 2009). Furthermore, type 2 diabetes is associated with chronic stress (Nader et al. 2010) and a risk factor for AD (Ott et al. 1999; Messier 2003; Arvanitakis et al. 2004; Strachan et al. 2008; Maher and Schubert 2009). Indeed, type 2 diabetes and/or elevated fasting glucose are reported in up to 80% of patients with AD (Janson et al. 2004). A later systematic review of this literature found that individuals with diabetes had a higher incidence of AD in 8 of 13 studies (Biessels et al. 2006). Relevant to this review, lack of PA (along with other detrimental health behaviors such as smoking, poor diet, and sleep disruption) can be a behavioral product of chronic stress (Kyrou and Tsigos 2009), and is also consistently identified as a risk factor for AD (Laurin et al. 2001; Podewils et al. 2005; Rovio et al. 2005; Karp et al. 2006; Larson et al. 2006; Simons et al. 2006; Taaffe et al. 2008). See Figure 1 for a summary of the links between stress, risk factors for AD, and disease progression.

This wide range of risk factors is indicative of an underlying system (or systems) that interacts with the disease process to contribute to disease progression, and points to a role for the stress neuroendocrine system. We go on to explore the possible pathways by which psychological stress can affect cognitive function and the neuropathological bases of AD.

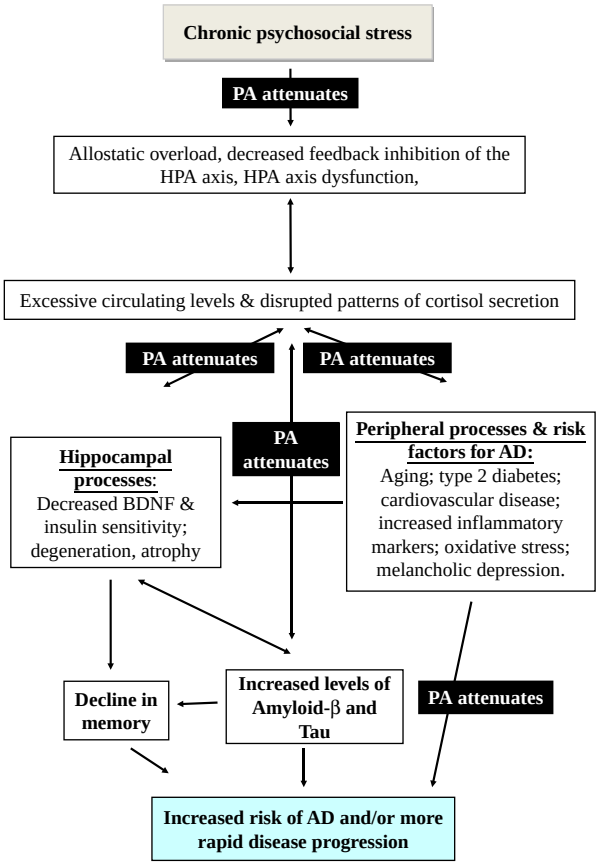

Figure 1. Summary diagram: arrows indicate pathways between psychosocial stress and AD (arrows indicate direction of causality). PA = physical activity and is located on arrows where it has been shown to attenuate that pathway (see text).

Evidence that stress impacts on cognitive function and AD

Chronic stress, allostatic overload, aging, and memory function

Excessive and repeated responses to stress and/or the inability to turn off the response when it is no longer needed are associated with increased activity of the sympathetic nervous system and a dysfunction of the hypothalamic–pituitary–adrenal (HPA; McEwen 2008) axis. The latter causes, among other things, aberrant patterns of cortisol secretion (Meerlo et al. 2002; Nader et al. 2010) and typically excessive levels of basal circulating cortisol (Lupien and Lepage 2001), which over time produces accumulative wear and tear on the body and brain (McEwen 2008). Under these circumstances, the ability to achieve stability through change (allostasis) fails, producing

a condition of allostatic overload (Seeman et al. 1997; McEwen 1998; McEwen 2008).

Allostatic overload also has several behavioral sequelae known to be risk factors for AD, including disrupted sleep, unhealthy eating patterns, drinking too much alcohol, smoking, and lack of physical activity (PA; McEwen 2008; Kyrou and Tsigos 2009). Increasing age (the major risk factor for cognitive decline and AD) is associated with increases in the HPA axis response to the challenge in some studies [see Otte et al. (2005) for a meta-analysis of 45 stress challenge studies of young vs. old healthy participants]. However, only four of these studies involved psychosocial challenge, and thus the ability of acute psychological stress changes to change the sensitivity of the HPA axis which remains to be firmly established. Furthermore, the finding that females changed more in response to increasing age may be more closely related to their known greater sensitivity to pharmacological challenge than psychosocial-related threat (Uhart et al. 2006). Other studies have reported enhanced HPA responsivity to psychosocial stress in older males and not older females (Kudielka et al. 2004). Moreover, some studies have shown no age-related effects on HPA axis reactivity; see Kudielka et al. (2009) for a review of individual differences in salivary cortisol responses to challenge.

Increasing age in healthy participants is also associated with higher overall basal levels of cortisol secretion and flatter circadian profiles (van Cauter et al. 1996; Deuschle et al. 1997). However, some have suggested that an association is apparent only in depressed individuals (Kudielka et al. 2000). Other studies report aberrant cycles in sub-populations of the healthy old (Ice et al. 2004; Kumari et al. 2010). Interactions between increasing age, chronic stress exposure, and changing stress reactivity are a complex area recently reviewed and discussed by Gruenewald and Seeman (2010). They conclude that the biological changes typically observed with advancing age may render older adults more susceptible to negative biological and health consequences of chronic stress.

Allostatic overload is consistently associated with reduced memory function; for example, in a longitudinal study of 194 participants aged 70–79 years, increased urinary free cortisol excretion was correlated with a decline in memory performance (Seeman et al. 1997). This study showed significant differences in memory decline only for females, while males participating in the study did not present any significant associations. However, in a different longitudinal study of 154 healthy men and women aged between 70 and 79 years, urinary excretion of epinephrine predicted cognitive decline in men but not in women (Karlamangla et al. 2005). Interestingly enough, Seeman et al. (1997) found that the decline in women's memory was reversible: declines in cortisol were associated with improvements in memory. These data are consistent with evidence that elevated levels of cortisol are linked to impaired memory in healthy participants (Wolf et al. 2002a, 2009) and in patients with MCI (Wolf et al. 2002b; Arsenault-Lapierre et al. 2010).

Chronic stress and hippocampal function

Stress-associated decline in memory is attributed to hippocampal atrophy and degeneration caused by excessive levels of cortisol, as this area of the brain is characterized by high glucocorticoid sensitivity as a result of dense expression of glucocorticoid receptors (McEwen 1994; de Kloet et al. 2005). Furthermore, corticosteroids exert suppressive effects on cell proliferation (neurogenesis) in the dentate gyrus of the rat hippocampus (Cameron and Gould 1994). Thus, the inability to cope with stress may lead to a reduction in total hippocampal volume and loss of neurons in this region (Lupien et al. 1999; Warner-Schmidt and Duman 2006). The hippocampus is a key area for memory storage and processing, being one of the main areas affected by AD (Rothman and Mattson 2010). In fact, hippocampal atrophy is found in all stages of AD (Fox et al. 1996; Dickerson et al. 2001). Similar hippocampal atrophy is found in stressed patients and MCI (Lupien et al. 1999), and can be used as a predictor of conversion of MCI to AD (Apostolova et al. 2006). However, as noted in the recent review by Rothman and Mattson (2010), there are still no studies reporting changes in hippocampal plasticity in AD after chronic stress.

Cardiovascular factors

Chronic stress is related to increased risk of CV conditions (Björntorp 1997; Rosmond et al. 1998) that are implicated in cognitive decline (Gustafson et al. 2003; Arvanitakis et al. 2004; Kivipelto et al. 2005; Whitmer et al. 2005; Helzner et al. 2009). Indeed, cerebrovascular disease is the second most common cause of acquired cognitive impairment and dementia, and contributes to cognitive decline in the neurodegenerative dementias (O'Brien et al. 2003). For example, higher pre-diagnosis total cholesterol and low-density lipoprotein concentrations (and history of diabetes, see below) were associated with faster cognitive decline in patients with AD (Helzner et al. 2009). There is accumulating evidence that increased plasma homocysteine level (an amino acid linked to CV disease) may play a role in cognitive decline and the onset of AD (Seshadri et al. 2002; Zhuo et al. in press). A recent study has found a link between elevated levels of homocysteine in non-demented patients with type 2 diabetes and hippocampal atrophy (Shimomura et al. 2011). The mechanism by which elevated homocysteine may affect cognitive function is still under investigation,

but implicated pathways include increased oxidative stress, excitotoxic damage, and direct effects on amyloid-β and tau phosphorylation in the brain (see Zhuo et al. in press, for a summary).

Type 2 diabetes and the role of brain insulin

Chronic stress and allostatic overload are associated with a group of related disorders, including type 2 diabetes (Chrousos 2009; Kyrou and Tsigos 2009). For example, the prevalence of newly diagnosed type 2 diabetes is related to a high number of relatively common major life events during the preceding 5-year period (Mooy et al. 2000). This is relevant here, as type 2 diabetes is associated with cognitive decline (Wrighten et al. 2009). These deficits are reported to be more selective for hippocampal-related memory performance (Gold et al. 2007), and in animal models these deficits are attributed to deficiencies in the regulation of insulin within the hippocampus (Moosavi et al. 2007). Insulin mediates several brain functions including cognition and memory (Craft et al. 1996; Craft and Watson 2004), which may be associated with a high concentration of insulin receptors in the hippocampus (Craft et al. 1996; Craft and Watson 2004; Craft 2009). In the hippocampus, insulin appears to have some neuroprotective effects against memory loss in animal and human studies (Moosavi et al. 2007; Reagan 2007).

Insulin and insulin receptors are reduced in animal models of AD, suggesting that insulin-signaling pathways might be impaired (Takeda et al. 2010; Wang et al. 2010). Increased plasma insulin administration through intravenous infusion improved memory in AD patients (Craft et al. 1996). Furthermore, Wang et al. (2010) demonstrated that diabetes induced by streptozotocin increased the amyloid load in a transgenic mouse model of AD. Another study using a mouse model of AD with diabetes indicates that the diabetic condition increases cognitive dysfunction, along with vascular inflammation and increased amyloid burden (Takeda et al. 2010). These changes were mediated by impaired brain insulin signaling. Furthermore, in this study, amyloid pathology seemed to negatively impact diabetes pathogenesis, once again pointing to the presence of deteriorating cycles of negatively interacting systems.

Brain-derived neurotrophic factor (BDNF)

Levels of BDNF are diminished in the hippocampus of patients with AD (Podewils et al. 2005; Querfurth and LaFerla 2010). There is compelling evidence from mice experiments on the negative impact of stress on BDNF production (reviewed in Duman and Monteggia 2006). Stress may play a key role in the growth factor's cascade due to altered levels of cortisol (Chao et al. 1998; Schaaf et al. 1998), serotonin (Vaidya et al. 1997), or interleukin-1β (Barrientos et al. 2003) in the hippocampus, interfering with growth factor signaling, reducing the BDNF availability in the hippocampus, and resulting in a decrease in neurogenesis and brain plasticity.

Inflammation

There is a strong correlation between inflammatory responses and the early stages of AD in humans (Parachikova et al. 2007). In rats, acute stress may facilitate innate immunity, and PA enhances this positive effect (Fleshner et al. 2002). However, chronic stress results in excessive levels of inflammatory markers (McEwen 2008). Furthermore, elevated levels of pro-inflammatory factors may be responsible for the decreased levels of growth factors, especially in the hippocampus [see Cotman et al. (2007) for a review of human and animal literature]. Inflammation increases peripheral and central risk factors driving cognitive decline and neurodegeneration in humans and rodents (Yaffe et al. 2003; Cotman et al. 2007).

Melancholic depression

Hippocampus atrophy, insulin resistance, decreased BNDF levels, and increased inflammation are also shown in patients with melancholic depression (Rothermundt and Arolt 2001; Duman 2005; Kyrou and Tsigos 2009). In parallel, serotonin expression is inhibited by depression and chronic stress (Cameron and Gould 1994; Lopez et al. 1998). High corticosterone levels decrease the density of 5HT fibers or 5HT1A receptors in rat brain (Cameron and Gould 1994). Data derived from studies on postmortem human brain tissue indicate that serotonin may play an important role in learning and memory formation (Elliot et al. 2009), possibly through enhancing neurogenesis in the dentate gyrus via activation of the 5HT1A receptor (Gould 1999).

Oxidative stress

Oxidative stress, the imbalance in production of reactive oxygen species (ROS) and antioxidative defense (Gella and Durani 2009), is associated with both psychological stress and experimental models of AD (Rothman and Mattson 2010). ROS are physiological products of aerobic metabolism involved in cellular repair and adaptation. However, ROS overproduction is strongly implicated as a causal factor in the aging process, and occurs in neurodegenerative diseases such as Parkinson's and AD (Radak et al. 2005, 2008) and correlated with cognitive decline (Gella and Durani 2009). In experimental animal models of AD, oxidative damage precedes pathological changes in AD (Querfurth and

LaFerla 2010), implicating ROS in disease onset. β-amyloid peptide (Aβ) is a potent generator of ROS, making it a prime generator of this damage and Aβ accumulation and a possible etiological factor in AD (Querfurth and LaFerla 2010; Wan et al. 2011). Experiments with male Wistar rats have shown that social stress (isolation) increases oxidative stress (Pajović et al. 2006). Moreover, other stressors (such as restraint or immobilization) increase the production of ROS (Kovács et al. 1996; Zaidi and Banu 2004). Not surprisingly, direct administration of corticosterone in rats promotes oxidative stress in the brain, suggesting that the stress neuroendocrine system plays a causal role in the oxidative stress process (Zafir and Banu 2009). At the same time, rats subjected to oxidative stress display serious damage to hippocampal pyramidal cells that is linked to impaired cognitive function (Sato et al. 2010).

Summary

Evidence from animal and human studies indicates that chronic psychological stress can impact upon a number of different interconnected routes relevant to cognition. It is also worth emphasizing that the hippocampus is involved in the regulation of the HPA axis (Jacobson and Sapolsky 1991; Lupien et al. 1998; Lupien and Lepage 2001). The hippocampus is rich in glucocorticoid receptors and many studies have demonstrated their role in HPA feedback regulation. In general, animal studies have shown that lesions to the hippocampus result in elevated corticosterone levels under basal and post-stress conditions (Wilson et al. 1980; Sapolsky et al. 1984). Stress-induced atrophy in this region can lead to further loss of the feedback inhibition of this system and a consequent reciprocal cycle of deterioration (Warner-Schmidt and Duman 2006).

The HPA axis in AD

HPA axis dysfunction is found in the early stages of patients with AD (Csernansky and Dong 2006), with reports of elevated basal levels of circulating cortisol (Swanwick et al. 1998; Wahbeh et al. 2008) and the inability to suppress cortisol after a dexamethasone (DEX) challenge (Hatzinger et al. 1995; Näsman et al. 1995). Furthermore, there is a relationship between hypercortisolemia and progression of the disease in humans (Weiner et al. 1993, 1997). In both of these studies, higher values of midday serum cortisol concentrations were associated with a more rapid cognitive decline. However, the sample size in these studies was small: just 12 patients followed up for 12 months in the first study, and 9 patients followed longitudinally for 2–3 years in the second study. Consistent with these findings, higher baseline morning cortisol levels are associated with a greater level of cognitive impairment in 27 patients diagnosed with AD (Miller et al. 1998). Similarly, higher morning levels of plasma cortisol are linked to rapid disease progression and decreased performance in neuropsychological tests in patients with mild or very mild AD (Csernansky and Dong 2006). This latter study was a longitudinal design, in which 33 community-dwelling participants with very mild and mild Alzheimer-type dementia [scores of 0.5 and 1 on the five-point Clinical Dementia Rating Scale (CDRS)] and 21 participants without dementia provided plasma for determination of morning cortisol concentration at the start of the study. Subsequently, they performed a battery of neuropsychological tests and the CDRS annually for up to 4 years. In both groups of dementia participants combined, but not in those without dementia; higher plasma cortisol levels were associated with more rapidly increasing symptoms and more rapidly decreasing performance on neuropsychological tests. The results support the idea of a negative impact of elevated cortisol levels on cognitive performance and thus on the progression of AD. However, this small study was not able to distinguish very mild from no dementia in terms of morning plasma cortisol levels at the start of the study.

Some of the most persuasive data linking psychological stress and AD are evidence of increased formation of amyloid-β plaques and protein tau "tangles," alongside a decrease in their degradation, following stress exposure in mice models of AD (Green et al. 2006; Jeong et al. 2006; Dong et al. 2008; Lee et al. 2009). These neuropathological features are considered the two main hallmarks of AD and implicate stress in the disease process, rather than just cognitive function. However, it is also possible that elevated levels of amyloid-β plaques in the hippocampus may precede elevations in basal levels of plasma corticosterone, which could imply that the observed alteration in the HPA axis in AD may be subsequent to neuropathology (Green et al. 2006; Nuntagij et al. 2009; Rothman and Mattson 2010). Further work is required to elucidate the extent to which these pathways are causally associated in AD.

Converging evidence from human and animal studies indicates that chronic stress and AD cause similar cognitive impairments and pathological hallmarks, specifically in the hippocampus, and that stress may both increase the risk of developing AD and cause a more rapid disease progression (Rothman and Mattson 2010; see Figure 1).

The stress–AD link implies that stress management could be a key component of AD prevention and treatment. Within non-pharmacological approaches, PA could be an inexpensive option for reducing the effects of stress, with many proven health benefits and very little or no side effects. However, to our knowledge, the mechanism of the effect of PA on

disease progression in AD patients has not been explored.

PA and stress: current evidence of interactions and mechanisms

In the UK, it is recommended that adults should participate in a minimum of 30 min of at least moderate intensity activity (such as brisk walking, cycling, or climbing the stairs) on 5 or more days of the week (Department of Health 2004) to maintain health and well-being. However, only 39% of men and 29% of women in England meet this recommended level (Craig et al. 2008). PA participation has remained low despite its benefits being widely publicized. Guidelines for older adults are provided by the World Health Organisation (2010). It is recommended that older adults (65 years plus) should do at least 150 min of moderate intensity, or 75 min of vigorous intensity, aerobic PA throughout a typical week or do an equivalent combination of moderate- and vigorous-intensity activity. Promoting PA for older adults is deemed especially important because this population is the least physically active of any age group.

Evidence of the effects of PA on stress response systems is complicated by the wide array of PA and stressors investigated. For ease of reference, relevant studies are summarized in Tables I (for evidence in humans) and II (for evidence from rodent studies).

The tables indicate that there is increasing evidence of the benefits of PA to cope with psychological/exercise stress from both human (for example, Sinyor et al. 1983; Holmes and McGilley 1987; Deuster et al. 1989; Brown 1991; Korkushko et al. 1995; Unger et al. 1997; Broocks et al. 2001; Salmon 2001; Traustadóttir et al. 2004; Rimmele et al. 2007; Rimmele et al. 2009) and animal studies (for example, Watanabe et al. 1991; Droste et al. 2003, 2006, 2007; Greenwood et al. 2007; Hill et al. 2010; Kannangara et al. 2011). However, there are significant inconsistencies in both literatures (humans: de Geus et al. 1993, see meta-analysis by Jackson and Dishman 2006; Heiden et al. 2007; rodents: Moraska et al. 2000; Fediuc et al. 2006).

There are several potential reasons for identified inconsistencies, including the use of different PA training protocols and different stressors (Rimmele et al. 2007). It seems that the effects of PA may vary depending on factors such as intensity, type, and the duration of the exercise. In human studies, population characteristics, such as age and gender, are also important, as these factors are associated with activity of the stress neuroendocrine system and may interact with the effects of PA. Another factor that needs to be taken into consideration, for both human and rodent studies, is whether the interaction being studied is between PA and a physical exercise stressor (which may or may not be novel) or psychological stressor, which is typically novel (see Dickerson and Kemeny 2004). Considering all these possibly interacting variables, it is not surprising that, alongside the controversy about the interaction of PA with psychological stress, the underlying mechanisms that mediate the claimed effects remain unclear.

The effects of PA on responses to physical exercise stress

It is clear that the effects of a single bout of PA are different than those seen with regular PA. Acute bursts of PA induce a strong neuroendocrine stress response in rodents (Timofeeva et al. 2003; Campbell et al. 2009). Similarly, short bursts of PA increase levels of adrenocorticotrophic hormone (ACTH) and glucocorticoids in humans (Kiive et al. 2004), especially if the exercise is of high intensity (Viru et al. 1992). In rodents, these changes are attenuated after long-term adaptation to exercise [Campbell et al. 2009; unless absolute intensity is gradually increased (Park et al. 2005)]. In humans, if the intensity of the exercise is moderate or light, acute exercise may not increase cortisol secretion (Nieman et al. 2005).

Long-term regular physical training in rodents may reduce or enhance the stress response, depending on whether exposure is to a familiar physical stressor, a novel physical stressor, or a psychological stressor (Droste et al. 2003, 2006, 2007). There is evidence from both human and rodent studies that exercise training produces adaptations in HPA axis reactivity to familiar acute exercise stress. This includes evidence from rodents of higher threshold of activation and attenuated ACTH and corticosterone responses (Watanabe et al. 1991; White-Welkley et al. 1995; Dishman et al. 2000). Greater maximal capacity of the adrenal glands is reported in both human (Luger et al. 1987; Kjær 1992; Deuster et al. 1998) and rodent studies (Watanabe et al. 1991). Similar adaptations are also reported in older humans (Korkushko et al. 1995). However, in rats, physical training increases HPA axis reactivity to a novel physical stressor (White-Welkley et al. 1996; Droste et al. 2007). The higher cortisol responses after a novel physical stress may be adaptive, as novel physical stressors can be seen as life-threatening challenges, requiring increased glucocorticoid levels to successfully respond to the physical challenge (Droste et al. 2007).

The effects of PA on responses to psychological stress

The interaction between PA training and psychological stress is called "cross-stress adaptation." Studies have reported inconsistent findings, especially in human populations, with most of them focusing on CV changes (Rimmele et al. 2007). Some studies focusing on HPA axis reactivity did not show lower levels of cortisol after a psychological stress for aerobically fit human participants (Sinyor et al. 1983;

Table I. Effects of PA on stress responding human studies.

Author (year)	Study design	Participants	Type of PA	Type of stressor	Reported outcomes
Sinyor et al. (1983)	Case–control study	30 men, 20–30 years old (15 highly trained, 15 untrained control group)	Aerobic fitness level measured by fitness testing	Arithmetic task, quiz, color–word task	Trained individuals had a faster heart rate recovery and a lower state anxiety after psychosocial stress
Holmes and McGilley (1987)	Quasi-experimental clinical trial (no randomization)	67 healthy women aged 17–20 years (Training group: 18 low fit, 19 high fit; non-training group: 15 low fit, 15 high fit)	Aerobic exercise: 50 min per session, twice weekly, for 13 weeks	21-item questionnaire designed to assess subjective cognitive arousal Wechsler Adult Intelligence Scale Questionnaire measuring subjective cognitive and subject somatic arousal	Low-fit subjects showed greater heart rate and subjective responses to the stressor than did high-fit subjects at baseline Aerobic training reduced the heart rate response of low-fit subjects to a psychologic stressor Fitness training did not influence subjects' subjective responses to the psychologic stressor
de Geus et al. (1993)	Quasi-experimental clinical trial (no randomization)	62 participants aged 24–40 years	Aerobic training for 4 or 8 months with self-chosen duration of 1.5–2.5 h a week, except for participants of the 8 months group who exercised at a minimal frequency of 2.5 h per week	Tone avoidance task (four-choice reaction time task) Memory search task Cold pressor test	Fitness level at baseline was not associated with any psychological variables measured (heart rate and blood pressure reactivity, urinary catecholamine excretion) Aerobic training did not produce any effect on psychological make-up
Korkushko et al. (1995)	Case–control study	56 males in three groups: (1) healthy young untrained males 20–34 years ($n = 12$); (2) healthy elderly untrained males 60–74 years ($n = 32$); (3) healthy elderly trained male 60–74 years ($n = 32$)	Aerobic fitness level measured by total energy expenditure and running distance	Bicycle ergometer exercise test	Standard physical load resulted in greater increases in ACTH and cortisol in elderly untrained participants compared with young untrained and elderly trained participants There was an increase in the sympathetic control of the heart and a decrease in parasympathetic control associated with age. This increase was less pronounced in trained individuals
Unger et al. (1997)	Longitudinal study	2860 men and 4667 women, 70 years and older	PA scale based on self-report levels of PA	Widowhood	PA had a positive impact on functional decline and buffered the effects of widowhood on functional decline
Deuster et al. (1998)	Case–control study	5 healthy men and 5 healthy women, 27.3 ± 1.3	Participants reported an average running distance of 20–40 km per week	High-intensity exercise test after taking 4 mg of DEX. Two tests were performed, one at 90% and one at 100% of maximal aerobic capacity	Despite pituitary–adrenal suppression by DEX, plasma ACTH and cortisol increased with exercise testing and there were greater increases when the intensity was higher (100% of maximal aerobic capacity) Plasma cortisol responses, but not ACTH, were higher in women than in men
Broocks et al. (2001)	Clinical trial	12 untrained healthy volunteers, 33.5 ± 5.4 years	10 weeks of moderate aerobic exercise training	Three different challenge tests (m-CPP, ipsapirone, or placebo)	Cortisol response to m-CPP administration was attenuated after exercise training
Kiive et al. (2004)	Case–control study	46 males, mean age 43 years (24 depressed patients, 22 healthy volunteers)	No measures of fitness levels	Bicycle cardiopulmonary exercise testing	Acute bicycle exercise activated HPA axis, increasing cortisol levels in both groups Prolactin levels were only increased in depressed patients

TABLE I – *continued*

Author (year)	Study design	Participants	Type of PA	Type of stressor	Reported outcomes
Traustadóttir et al. (2004)	Case–control study	31 females: 9 young (19–36 years), 11 older unfit (59–81 years), 11 older fit (59–81 years)	Classified as unfit or fit based on their maximal oxygen consumption (VO_2 max.), their age, and the American Heart Association Classification Criteria	Short bout of treadmill exercise at submaximal intensity	Results indicate a prolonged ACTH recovery, but not cortisol, after high-intensity exercise associated with aging This prolonged recovery of ACTH was attenuated by fitness level
Traustadóttir et al. (2005)	Case–control study	36 females: 10 young unfit (19–36 years), 14 older unfit (59–81 years), 12 older fit (59–81 years)	Classified as unfit or fit based on their maximal oxygen consumption (VO_2 max.), their age, and the American Heart Association Classification Criteria	Matt Stress Reactivity Protocol which combines mental challenges, a physical challenge, and a psychosocial stressor	Older unfit women had greater cortisol responses to the challenge than the young-unfit and the older fit women Results suggest that aging is associated with greater reactivity of the HPA axis but PA attenuates this reactivity
Nieman et al. (2005)	Case–control study with no control group	15 healthy and non-obese females. Mean age: 37 years	People that reported to be accustomed to regular walking	Walking for 30 min at an intensity of 60% of VO_2 max. Walking using the BODY BAT Aerobic Exerciser	No significant increases in plasma cortisol were seen over time Walking produced modest positive changes in immune parameters
Heiden et al. (2007)	Randomized controlled trial	75 participants with stress-related illnesses (28 cognitive behavioral intervention; 23 PA intervention; 24 usual care control group Mean age: 44 years	Two sessions per week for 10 weeks	Autonomic regulation tests (mental arithmetic, handgrip, and deep breathing at a rate of 6 breaths/min) Algometric measurements (pressure pain thresholds) Questionnaires about physical and mental health and behavioral patterns	Neither PA nor cognitive behavior training produced significant improvements in autonomic activities and pressure pain thresholds compared with usual care
Rimmele et al. (2007)	Case–control study	22 trained elite sportsmen (21.50 ± 2.35 years) and 22 healthy untrained men (21.84 ± 2.24 years)	Trained men were mostly endurance athletes with a Swiss Olympic Card and/or members of the Swiss national teams. Untrained men reported to exercise for less than 2 h per week	Psychosocial laboratory stressor (Trier Social Stress Test)	Elite sportsmen showed significant lower cortisol secretion and lower heart rate reactivity to psychosocial stress than untrained men Trained men were also generally calmer and exhibited better mood and lower anxiety
Rimmele et al. (2009)	Case–control study	18 elite sportsmen (24.17 ± 0.89 years); 50 amateur sportsmen (24.82 ± 0.43 years); 24 untrained men (23.65 ± 0.61 years)	Participants were classified into three groups based on a physical fitness test and a self-report questionnaire	Psychosocial laboratory stressor (Trier Social Stress Test)	Elite sportsmen showed significant lower cortisol secretion, heart rate, and state anxiety responses than untrained men Amateur sportsmen showed a significant heart rate response reduction but no differences in cortisol responses than untrained men

Table II. Effects of PA on stress responding rodent studies.

Author (year)	Animals	Type of PA	Type of stressor	Reported outcomes
Watanabe et al. (1990)	Male albino Wistar rats	Forced swimming 60 min a day 5 days a week during 4 weeks	Swimming	Plasma levels of ACTH and corticosterone after acute exercise are reduced with exercise training
White-Welkley et al. (1995)	Ovariectomized female Sprague-Dawley rats	Forced treadmill running for 6 weeks	Treadmill running Novel immobilization	Exercised rats showed an attenuated ACTH and prolactin response to running, but an increased ACTH response to immobilization compared with sedentary rats
White-Welkley et al. (1996)	Ovariectomized female Sprague-Dawley rats	Forced treadmill running for 6 weeks	Treadmill running Novel footshock Novel immobilization	Exercised rats showed increased HPA axis responses to novel footshock compared with sedentary rats
Dishman et al. (2000)	Female Sprague-Dawley rats	Forced treadmill running for 6 weeks	Familiar treadmill running Novel immobilization	Increased norepinephrine levels in hypothalamic and limbic brain regions with treadmill running and immobilization in exercised rats
Moraska et al. (2000)	Male Sprague-Dawley rats	Forced treadmill running for 8 weeks	Forced treadmill running with footshock	Forced running had similar effect as chronic stress with adrenal hypertrophy, thymic involution, decreased serum corticosteroid-binding globulin, increased lymphocyte nitrite concentrations, suppressed lymphocyte proliferation, and suppressed antigen-specific IgM
Fleshner et al. (2002)	Male Harlan Sprague-Dawley specific pathogen-free rats	Voluntary wheel running for 6–8 weeks	Tails shock and bacterial challenge	PA enhanced the benefits of acute stress on innate immunity
Droste et al. (2003)	Male C57BL/6N mice	Voluntary wheel running for 4 weeks	Forced swimming and restraint stress Novel environment	Exercising mice had higher corticosterone levels in response to forced swimming or restraint stress compared with sedentary mice, but ACTH levels remained similar Exercising mice presented lower ACTH responses to novel environment compared with sedentary mice
Timofeeva et al. (2003)	Male Wistar rats	Acute bout of 60 min of intense forced treadmill running	Treadmill running	Acute intense treadmill running leads to a strong expression of c-fos mRNA and activates the hypophysiotropic CRH system
Park et al. (2005)	Sprague-Dawley rats	Forced daily swimming 45 min/day, 5 days a week, during 2, 4, and 6 weeks	Swimming and sham exercise	HPA response to exercise training is not attenuated if exercise intensity is gradually increased Exercise training prevents increases in basal pituitary–adrenal activity
Droste et al. (2006)	Male C57BL/6N mice	Voluntary wheel running	Novel environment Restraint stress	Exercising mice had higher plasma corticosterone levels in response to restraint stress compared with sedentary rats Exercising rats presented lower plasma corticosterone response to a novel environment compared with sedentary rats
Fediuc et al. (2006)	Male Sprague-Dawley rats	Voluntary wheel running for 5 weeks	Restraint stress	Exercising rats showed normal circadian corticosteroid secretion, normal negative-feedback inhibition, and an attenuated increase in plasma ACTH levels after a novel stress compared with sedentary rats

TABLE II – *continued*

Author (year)	Animals	Type of PA	Type of stressor	Reported outcomes
Droste et al. (2007)	Male Sprague-Dawley rats	Voluntary wheel running for 4 weeks	Forced swimming Novel environment	Exercising rats had higher corticosterone levels in response to forced swimming or restraint stress compared with sedentary rats Exercising rats presented lower corticosterone response to a novel environment compared with sedentary rats ACTH levels remained similar for both groups in both types of stressors
Greenwood et al. (2007)	Adult male Fischer F344 rats	Voluntary wheel running for 2 and 6 weeks	Shuttle box escape after uncontrollable footshock	Voluntary wheel running for 6 weeks, initiated after stressor exposure, reduced the expression of conditioned freezing and reversed the escape deficit from the shuttle box. Two weeks of wheel running did not produce any effects
Campbell et al. (2009)	Male Sprague-Dawley rats	Voluntary short-term (2 weeks) and long-term (8 weeks) wheel running	Restraint stress and ACTH challenge	Two weeks of voluntary wheel running initially produces hyperactivity of HPA axis through increase in adrenal sensitivity to ACTH, but long-term training attenuates this effect
Droste et al. (2009)	Male Sprague-Dawley rats	Voluntary wheel running for 2 days, 1 week, and 4 weeks	Forced swimming Novel environment	Four weeks of voluntary wheel running produced no differences in hippocampal-free corticosterone responses to stress between exercised and sedentary rats
Hill et al. (2010)	Male Sprague-Dawley rats	Voluntary wheel running for 4 weeks	Wheel running	Regular exercise produces extensive changes in the GABAergic system that could explain some of the changes observed in stress sensitivity and emotionality with exercise
Kannangara et al. (2010)	Young and aged female mice	Voluntary wheel running for 11 days	Wheel running Isolated housing	Voluntary exercise reduces stress and increases hippocampal cell proliferation in aged female mice

Moyna et al. 1999). However, trained men and elite athletes are reported to have lower cortisol and heart rate responses to an acute psychological stressor than untrained men (Rimmele et al. 2007; Rimmele et al. 2009). More work is required to clarify the strength of these findings (for example, just how much exercise is required to generate an advantageous effect) and to examine the impact of potential interacting factors such as age and gender.

In studies using mice and rats, results are also inconsistent. However, in these studies, it is important to distinguish *forced* exercise from *voluntary* exercise (Droste et al. 2003; Dishman et al. 2006). Long-term forced exercise produces negative adaptations associated with chronic stress such as increased adrenal weight, thymic involution, and decreased serum corticosteroid-binding globulin (Moraska et al. 2000; Fediuc et al. 2006). However, long-term voluntary exercise may positively impact HPA axis regulation (Hill et al. 2010), contributing to a reversal of the effects of uncontrolled stress (Greenwood et al. 2007) and showing appropriate glucocorticoid responses to stress in mice (Droste et al. 2003, 2006, 2007; Kannangara et al. 2011).

Greenwood et al. (2007) demonstrated that 6 weeks of voluntary wheel running after stressor exposure can reverse the long-lasting behavioral consequences of uncontrolled stress (shuttle box escape) in rats (although 2 weeks of exercise was not sufficient to show positive results). Four weeks of voluntary running increases the glucocorticoid response to a novel physical stress (potentially life-threatening challenge, such as forced swimming), but decreases by 50% the glucocorticoid response to a mild psychological stressor such as a novel environment (Droste et al. 2007). In this study, plasma ACTH levels remained unchanged in both exercising and control mice, suggesting adaptive changes at the level of the adrenal cortex, for example, changes in sympathoadrenomedullary input (Droste et al. 2007).

These studies suggest that in young animals, the response to psychological stress is different after voluntary, as opposed to forced, physical training, and is dependent on the duration of the training regime. The benefits of PA for stress in aged animals and humans have received less attention. Traustadóttir et al. (2004) found that older women had a higher HPA axis reactivity to a psychological stressor than younger women, but this age-related change was attenuated by physical fitness. Consistent with this finding, 11 days of voluntary running significantly lowered plasma corticosterone levels in socially housed aged mice, when measured at the onset of the mouse active cycle (Kannangara et al. 2011). However, more research is required to establish the benefits of PA upon the aging HPA axis and its responses to psychological stress. These studies are needed to inform the development of intervention strategies relevant to the aging population, as well as enhance the theoretical understanding of "cross-stress adaptation."

PA and corticosterone levels in the hippocampus

Rodent studies have shown that peripheral corticosterone levels do not necessarily predict corticosterone levels in the hippocampus (Droste et al. 2007, 2009), the brain area of interest for this review. Indeed, corticosteroid levels were not attenuated in the hippocampus after 4 weeks of voluntary running (Droste et al. 2009). The results need to be replicated and extended in healthy and AD mouse models and also in human populations to explore whether longer periods of exercise are needed to reduce corticosteroid levels in the hippocampus. Furthermore, due to the many pathways and interconnections existing between PA, stress, and AD, it is important to determine whether hippocampal amyloid load, BDNF, oxidative stress, CV factors, depression, and inflammatory processes (as described below) are beneficially affected by PA.

PA, AD, and stress: pathways and interconnections

PA and cognitive function

There is compelling evidence from longitudinal studies in humans to show that PA is protective against MCI, dementia, and AD (Laurin et al. 2001; Abbott et al. 2004; Podewils et al. 2004; Rovio et al. 2005; Karp et al. 2006; Larson et al. 2006; Simons et al. 2006; Taaffe et al. 2008; Rovio et al. 2010). Exercise seems to improve cognitive function, especially in older adults (Colcombe and Kramer 2003; Heyn et al. 2004; Weuve et al. 2004), and enhance learning and memory in mice (van Praag et al. 1999, 2005).

Voluntary exercise enhances memory in transgenic mouse models of AD (Adlard et al. 2005; Parachikova et al. 2008; Nichol et al. 2009), suggesting that PA may inhibit the normal progression of the disease. Equivalent evidence is currently scarce in humans, although studies show that AD patients' health and functioning are positively influenced by participating in a variety of physical activities (Palleschi et al. 1996; Arkin 2003; Teri et al. 2003; Rolland et al. 2007; Williams and Tappen 2007). However, the mechanisms of the benefits of PA on cognition in healthy and AD populations remain unclear. Interestingly enough, most accepted theories such as reduction in amyloid load (Adlard et al. 2005), reduction in peripheral risk factors (Kramer and Erickson 2007), increased neurotrophic factors (Cotman and Berchtold 2002; Cotman and Engesser-Cesar 2002; Garza et al. 2004; Berchtold et al. 2005; Vaynman et al. 2006;

Kramer and Erickson 2007), reduction in the negative effects of inflammation (Cotman et al. 2007), improved depression symptoms (Blumenthal et al. 1999; De Moor et al. 2006; Zheng et al. 2006; Blumenthal et al. 2007), increased serotonin expression (Ivy et al. 2003; Greenwood et al. 2005), and a protective effect against oxidative stress (Vaynman et al. 2006; Radak et al. 2008) may be linked to stress reduction (Cameron and Gould 1994; Björntorp 1997; Lopez et al. 1998; Traustadóttir et al. 2005; Duman and Monteggia 2006; Green et al. 2006; Jeong et al. 2006; Dong et al. 2008; McEwen 2008; Chrousos 2009; Kyrou and Tsigos 2009; Lee et al. 2009; Zafir and Banu 2009), suggesting that stress reduction could mediate some of the benefits attributed to PA for AD.

PA and amyloid-β plaques

PA has direct effects on the neuropathological signs of AD in animal models. Voluntary wheel running for 5 months, in the TgCRND8 mouse model of AD, produced an improvement in cognition and a reduction in the amyloid load in both cortical and hippocampal regions of the brain (Adlard et al. 2005). The mechanisms involved may be related to a change in the processing of the amyloid precursor protein (APP) seen after 1 month of exercise, with a decrease in the proteolytic fragments of APP. The reduction in the amyloid load was considered to be responsible for the improvement in learning and memory shown in Morris water maze.

Again, duration of the exercise appears to be a key factor. In another study, a short-term voluntary wheel running intervention (3 weeks, as opposed to 5 months) was not able to reduce the amyloid load, although it did improve cognition, of a Tg2576 mouse model of AD (Parachikova et al. 2008). Again, more studies into the links between PA and the neuropathological underpinnings of AD, exploring the causal mechanisms, are warranted.

PA and CV factors

There is compelling evidence that PA attenuates CV risk factors and vascular chronic diseases in humans (Blair and Connelly 1996; Dela et al. 1999; Ivy et al. 1999; Thomas et al. 2006; Mora et al. 2007; Mueller 2007), especially if we substitute sedentary time by light PA (Healy et al. 2008). This evidence could partially explain the preventive effects of PA on cognitive dysfunction, as cerebral CV events can be one cause of dementia. Another possible mechanism underlying this protective effect could be increased cerebral flow with exercise, resulting in the development of new capillaries (angiogenesis) in the hippocampus (see Kramer and Erickson 2007). In addition, the reduction in sympathetic outflow shown with exercise training may be important, as stress and CV diseases are both associated with overactivity of the sympathetic nervous system (Dishman et al. 2002; Mueller 2007). Increased activity of the SNS might also increase glucocorticoid secretion (Droste et al. 2007). However, it seems that the positive effects of PA on CV disease are not mediated through reductions in plasma homocysteine levels in humans (Mora et al. 2007). Thus, PA has direct effects on a key AD risk factor, one that is exacerbated by chronic psychological stress, providing the opportunity for interacting loops and pathways and a rationale for the development and testing of PA intervention strategies.

PA and type 2 diabetes

Another possible mechanism that deserves further attention is the role of PA in attenuating the onset of yet another stress-related condition in humans: type 2 diabetes (Blair and Connelly 1996; Dela et al. 1999; Ivy et al. 1999; Thomas et al. 2006). It is clear that regular PA reduces dyslipidemia and insulin resistance (Blair and Connelly 1996; Thomas et al. 2006) enhancing glucose uptake into cells (Dela et al. 1999; Ivy et al. 1999). Since insulin therapy slows cognitive decline in patients with AD (Plastino et al. 2010), it is predicted that PA may have a positive impact on AD through reducing insulin resistance. Yet again, more work in this area is warranted.

PA and neurotrophic factors

Rodent studies indicate that exercise increases (as opposed to stress, which decreases) neurotrophic factors in the hippocampus, which is associated with neurogenesis and neuroprotection (Cotman and Berchtold 2002; Cotman and Engesser-Cesar 2002; Garza et al. 2004; Berchtold et al. 2005; Vaynman et al. 2006; Kramer and Erickson 2007). Berchtold et al. (2005) showed voluntary daily, and also intermittent, exercise increased the expression of BDNF, enhancing brain health and function in Sprague-Dawley rats. Furthermore, BDNF levels remained elevated for several days after cessation of exercise, and a brief re-exposure to exercise rapidly re-induced BDNF expression to levels that would normally take weeks of exercise to achieve. Consistent with these findings, Nichol et al. (2009) found that exercise increased BDNF levels in the hippocampus of APOE3 and APOE4 transgenic mice. Cognitive function was particularly improved in APOE4 carriers. Interestingly, a 10-week strength training program (as opposed to the aerobic exercise regimes used in the rodent studies described above) in untrained human participants did not induce any changes in serum BDNF (Goekint et al. 2010). Thus, the relationship between different types and duration of exercise in human

studies and availability of neurotropic factors is another relevant candidate for the examination of the interactive effects of stress and PA.

PA and inflammatory processes

Another possible mechanism underlying the effects of PA on the brain and cognition is attenuation of the negative effects of inflammation (see Cotman et al. 2007 for a review). Although exercise can produce a short-term inflammatory response, moderate regular exercise causes more sustained anti-inflammatory effect (Kasapis and Thompson 2005). For example, in a longitudinal study of 870 human participants aged 70–79 years, high levels of recreational PA were related to lower levels of pro-inflammatory markers, such as interleukin-6 (Il-6) and C-reactive protein (Reuben et al. 2003). Voluntary PA for 6 weeks attenuated the stress-induced suppression of natural killer cell cytotoxicity in rats produced by a foot-shock stress in rats (Dishman et al. 2000). Similarly, 4 weeks of voluntary wheel running prevented the stress-induced suppression of the antibody response in rats (Moraska and Fleshner 2001).

It is proposed (Parachikova et al. 2008) that the benefits of exercise on cognition in the Tg2576 mouse model of AD were partially mediated by the alteration of the expression of inflammatory molecules, including increased levels of the chemokines CXCL1 (Groα) and CXCL12 (SDF1), which are involved in cognitive restoration (Watson and Fan 2005; Parachikova and Cotman 2007; Parachikova et al. 2008).

PA and depression

Anti-depressant drug treatment may block or reverse the effects of stress and depression on BDNF levels, neurogenesis, and brain volume (see Warner-Schmidt and Duman 2006 for a review). PA may have similar effects as anti-depressive treatment, improving depressive symptoms in humans (Blumenthal et al. 1999; De Moor et al. 2006; Zheng et al. 2006; Blumenthal et al. 2007) and a range of indicators in rats [for example, increasing expression of BDNF (Russo-Neustadt et al. 1999), IGF-1 (Trejo et al. 2001), and serotonin expression (Ivy et al. 2003; Greenwood et al. 2005)]. Furthermore, aerobic exercise (of relatively low intensity and which depends primarily on the aerobic energy system) in untrained healthy participants is associated with an attenuated cortisol response to the serotonergic agonist meta-chlorophenylpiperazine (m-CPP), possibly reflecting a downregulation of central 5-HT2C receptors (Broocks et al. 2001). Animal studies implicate serotonin in the mechanisms by which PA attenuates memory loss (Ivy et al. 2003) and the consequences of uncontrollable stress (Greenwood et al. 2005). 5-HT1A receptor activation seems to be especially influential for PA-induced effects on cognition in one region of the hippocampus, CA4 (Ivy et al. 2003).

PA and oxidative stress

In addition to the pathways described above, PA may also have positive effects on oxidative stress. While low concentrations of ROS are beneficial, excessive concentrations cause apoptosis and necrosis (see Radak et al. 2008 for a review). PA induces an increase in adenosine-5′-triphosphate demands (indicating increased intracellular energy transport) and increased aerobic and/or anaerobic metabolic activity, resulting in more ROS. However, regular PA is believed to enhance the resistance to oxidative stress, providing increased protection in rodent studies (Vaynman et al. 2006; Radak et al. 2008) by enhancing the antioxidant defense mechanisms, including enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (Ji 1999). This paradox could be explained by the hormesis theory, which basically states that small doses of toxic substances can enhance the body and brain protection against larger doses of those same substances (Radak et al. 2001, 2005, 2008). Animal studies indicate that this adaptation may be due to increased proteosome activity with PA (Ogonovsky et al. 2005). The proteosome is primarily responsible for disposing of oxidatively modified proteins (Grune et al. 1997) and increasing protein breakdown (Ogonovsky et al. 2005), both of which may contribute to reduced amyloid load (Celsi et al. 2004; Adlard et al. 2005). Another possible explanation is the increase in PA of the uncoupling protein 2 (UCP2), which is abundantly expressed in the hippocampus and is related to calcium homeostasis, ATP synthesis, and free radical management. UCP2 may also modulate BDNF production in the hippocampus, improving memory and learning (Dishman et al. 2006). The effects of exercise on oxidative stress depend on the intensity of the exercise, as moderate intensity increases oxidative stress protection while high-intensity exercise possibly increases oxidative stress (Goto et al. 2003). The duration of the exercise program is also a factor that needs to be considered, as an 8-week program of aerobic exercise did not reduce oxidative stress in patients with type 2 diabetes (Mori et al. 1999), whereas 12 months of endurance exercise was able to decrease oxidative stress markers in another sample of type 2 diabetes patients (Nojima and Watanabe 2008; Figure 1).

Conclusions

A range of physiological systems are activated by both psychological stress and AD, and evidence suggests their effects can be synergistic. The cascade of shared events includes HPA axis dysfunction, hippocampal atrophy, impaired memory, accumulation of amyloid

load, increased inflammatory markers, increased insulin resistance, decreased BDNF availability, decreased serotonin expression, and excessive levels of free radicals causing oxidative stress.

Evidence from animal and human studies suggests that PA might play an important moderating role in this cascade, as voluntary regular PA decreases HPA axis responses to psychological stress, promotes angiogenesis and neurogenesis within the hippocampus, improves cognitive function, reduces amyloid load, inflammatory markers, insulin resistance, and oxidative stress while increasing BDNF and serotonin function (see Figure 1).

Although the evidence reviewed here suggests that PA interventions might be a potentially useful strategy to reduce risk factors for AD and even retard disease progression, the evidence of the effects of PA on AD itself is patchy. More research needs to be performed to explore the multiple interacting factors. For example, to our knowledge, the hypotheses that PA influences HPA axis reactivity, reduces oxidative stress, and/or reduces insulin resistance in AD patients or mouse models of AD have yet to be directly tested. Further work is required to tease apart the specific and interacting effects of PA and psychological stress on a range of biological pathways relevant to cognitive function and AD (Iqbal and Grundke-Iqbal 2010). Research is also urgently required to establish the appropriate type, intensity, frequency, and duration of PA that will be acceptable to, and achievable, by AD patients. These preliminary studies should be followed by clinical trials to evaluate their efficacy in terms of disease progression so that policy guidelines can be established and implemented. Given the scale of the problem and the relative weight of the evidence described here, we would propose that such investigations are clearly justified.

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