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Interactions between stress and physical activity on Alzheimer's disease pathology

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ABSTRACT

Physical activity and stress are both environmental modifiers of Alzheimer's disease (AD) risk. Animal studies of physical activity in AD models have largely reported positive results, however benefits are not always observed in either cognitive or pathological outcomes and inconsistencies among findings remain. Studies using forced exercise may increase stress and mitigate some of the benefit of physical activity in AD models, while voluntary exercise regimens may not achieve optimal intensity to provide robust benefit. We evaluated the findings of studies of voluntary and forced exercise regimens in AD mouse models to determine the influence of stress, or the intensity of exercise needed to outweigh the negative effects of stress on AD measures. In addition, we show that chronic physical activity in a mouse model of AD can prevent the effects of acute restraint stress on Aβ levels in the hippocampus. Stress and physical activity have many overlapping and divergent effects on the body and some of the possible mechanisms through which physical activity may protect against stress-induced risk factors for AD are discussed. While the physiological effects of acute stress and acute exercise overlap, chronic effects of physical activity appear to directly oppose the effects of chronic stress on risk factors for AD. Further study is needed to identify optimal parameters for intensity, duration and frequency of physical activity to counterbalance effects of stress on the development and progression of AD.

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder for which there is currently no effective treatment. The increasing social, physical, and economic burden of AD for both patients and caregivers is becoming a major public health concern in many areas of the world. The complexity of the disease, involving multiple pathological changes, interactions with risk-associated genes, and effects of behavioral or environmental modifiers have made finding a successful treatment difficult. Multifactorial treatment strategies will likely be necessary to provide a significant benefit to both patients and caregivers.

It is generally accepted that physical activity decreases the risk of developing AD and many other disorders that occur with age (Adlard and Cotman, 2004; Kennedy et al., 2017; Paillard et al., 2015). Higher rates of reported exercise are correlated with improved AD biomarkers in cognitively normal older adults (Liang et al., 2010). However, some forms of physical activity can induce stress and the effects of intensity, duration, frequency, and mode of activity needed to maximize health benefits are not fully understood. Psychological stress is associated with increased risk of many disorders and has been repeatedly shown to exacerbate symptoms and accelerate disease onset in AD (Baglietto-Vargas et al., 2015; Csernansky et al., 2006; Dong et al., 2004; Selye, 1955). Conversely, mild stress can be beneficial, particularly for cognitive function (Bos et al., 2014). The circumstances under which stress or physical activity occur may determine its effects on AD pathology.

Acute stress activates the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), which increases the release of glucocorticoids (GCs) and catecholamines (Smith and Vale, 2006). These molecules then initiate a neuroendocrine response, mobilizing lipids, glucose, and other resources to facilitate cognitive and physical demands of a “fight or flight” challenge. In conditions of acute psychological stress, these neuroendocrine responses are not tied to an increased metabolic demand. In chronic stress, this prolonged activation of the stress system has been linked to a large number of comorbidities ranging from metabolic dysfunction and cardiovascular

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disorders, to cognitive dysfunction and psychological disorders, such as depression (McEwen, 2017). The effects of psychological stress are likely to be exaggerated in the presence of physical inactivity due to lack of use of the physiological and metabolic products produced in preparation for the body's anticipated physical response to a threat. For example, increasing pro-inflammatory cytokines to help repair tissue damage due to physical exertion is counterproductive in the absence of the tissue damage and may lead to aberrant responses in the system (Fleshner and Crane, 2017). Several of these physiological changes associated with chronic stress are also risk factors for AD (Mayeux and Stern, 2012).

Chronic physical activity may play a protective role in stress system dysregulation and increase resistance to stress-related disorders (Tsatsoulis and Fountoulakis, 2006). A recent review by Nation et al. (2011) carefully outlines the effects of stress and exercise specifically on the neurovascular system in AD, and highlights the importance of uncovering the mechanisms and interactions involved in the effects of exercise and stress on AD pathophysiology so that new behavioral and/or pharmacological strategies can be developed for effective treatment of the disease. Many studies have examined the effects of stress or exercise on AD neuropathology or cognitive function independently, but few have analyzed the interactions between stress and exercise on the pathophysiology and cognitive symptoms of the disease. The goal of this review is to evaluate the interaction between physical activity and stress on AD pathophysiology in the context of forced versus voluntary physical activity. Does physical activity promote stress resistance or resilience (or both) to AD pathology? Do parameters of physical activity such as intensity or duration matter such that there is a threshold to counteract the negative effects of psychological stress on AD pathology?

2. Physical activity terminology and characteristics

Physical activity refers to any movement of the body resulting from skeletal muscle contraction that elevates total body energy expenditure above that at rest (Caspersen et al., 1985). Physical activity encompasses a wide variety of endeavors, including walking around the block, gardening, mowing the lawn, or running several miles. Caspersen et al. (1985) suggest that physical activity can be categorized in multiple ways, for the purposes of this review we categorized physical activity as acute or chronic (Fig. 1). Acute physical activity refers to one bout or session, such as walking to the store or a long bicycle ride, and can be subdivided into normal daily physical activity and exercise. Chronic physical activity refers to a structured, repetitive regimen carried out over weeks, months, or years intended to improve psychological or physical health, and can be subdivided into exercise training and sub-exercise training. Exercise training refers to chronic physical activity with a goal of increasing physical fitness above that of a sedentary individual (e.g. improved cardiovascular or muscle endurance, muscle strength, or flexibility). Exercise training regimens must be of sufficient intensity (physically taxing), duration (length of time exercise is performed), and frequency (number of exercise bouts performed) to overload the body and increase function. For a chronic physical activity regimen to meet the criteria of exercise training an increase in a physiological function must be demonstrated (referred to as an exercise training effect). Examples of an exercise training effect would be an increase in maximum oxygen consumption, an increase in the activity of a skeletal muscle mitochondrial enzyme associated with the Krebs cycle or electron transport chain (e.g. citrate synthase), or an increase in muscle strength. Sub-exercise training chronic physical activity refers to a structured regimen where the intensity, duration, and frequency are not at a high enough level to change physical fitness above that of a sedentary individual, such as a casual daily walk.

3. Studies of the effects of physical activity in mouse models of AD: can we determine the effects of stress?

Environmental factors influence disease onset and progression in AD, and being able to uncover the experience-dependent mechanisms for modifying the course of the disease is important to provide treatment guidelines and predict the success of therapeutic interventions. Studies of the effects of physical activity in animal models of AD have primarily used two methods: voluntary running on a wheel (Table 1) or running at a fixed speed on a treadmill (Table 2). Forced exercise, typically in the form of treadmill running, has been shown to increase biomarkers of the stress response in rodents (Moraska et al., 2000; Svensson et al., 2016; Yanagita et al., 2007). Due to the findings by Dong et al. (2008, 2004) and others (Baglietto-Vargas et al., 2015; Carroll et al., 2011) that chronic stress exacerbates AD pathology in mouse models, it is important to determine the influence of stress in forced exercise studies. Treadmill running provides a measure of control over exercise intensity and duration not available in voluntary running conditions; however, the psychological stress component could possibly counteract some of the positive benefits of chronic physical activity. Presumably voluntary exercise results in less stress on the mouse than forced exercise and comparison of voluntary and forced exercise in exercise training and sub-exercise training regimens can provide insight into the opposing relationship that psychological stress and physical activity have on biomarkers of AD.

We directly evaluated the effects of intensity-matched forced and voluntary chronic physical activity regimens on the cognitive and pathological changes in a transgenic AD mouse model and found that both forms of chronic physical activity decreased plaque count and increased hippocampal volume, but only mice in the voluntary group performed better on a cognitive task (Yuede et al., 2009). Psychological stress in forced exercise bouts can be due to the physical discomfort of the shock stimulus at the back of the treadmill belt designed to motivate the mice to run, or by the emotional distress associated with having to run at a constant predetermined speed. To differentiate between those two forms of stress we included a group that received the foot shock only, but did not run. Interestingly, we did not find a significant impairment in our shock-only control group suggesting that the shock exposure the forced exercise group received during treadmill running was not a strong enough stressor to have an effect on AD pathology. However, the animals in the forced exercise group did not achieve all of the same benefits as the animals in the voluntary exercise group indicating a qualitative difference between the physical activity regimens. We concluded that it was more likely that the psychological stress associated with the forced exercise mitigated some of the beneficial effects,

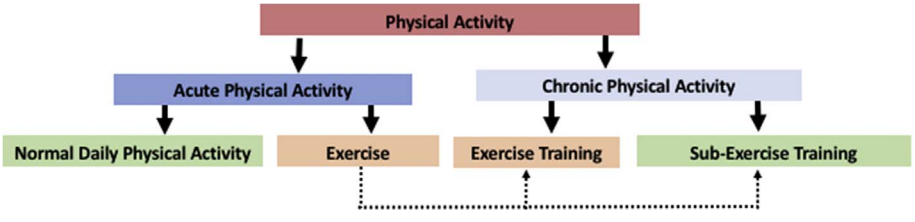

Fig. 1. Classification of Physical Activity. Acute physical activity refers to an individual bout of activity that can be part of the normal process of conducting daily business (normal daily physical activity) or it can be exercise which refers to a planned session of physical activity such as walking, jogging, bicycling, swimming, weight lifting or stretching intended to be part of a chronic physical activity program with the goal of improving health. Chronic physical activity is a regimen of exercise carried out over time with the goal of improving physical or psychological health. Exercise training is a chronic physical activity regimen of sufficient intensity, duration, and frequency to increases physical fitness. Sub-exercise training is a chronic physical activity regimen that is not of sufficient intensity, duration, or frequency to improve physical fitness, but may reduce psychological stress and improve psychological health.