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Review

Obesity and sex interact in the regulation of Alzheimer's disease

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ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder, for which a number of genetic, environmental, and lifestyle risk factors have been identified. A significant modifiable risk factor is obesity in mid-life. Interestingly, both obesity and AD exhibit sex differences and are regulated by sex steroid hormones. Accumulating evidence suggests interactions between obesity and sex in regulation of AD risk, although the pathways underlying this relationship are unclear. Inflammation and the E4 allele of apolipoprotein E have been identified as independent risk factors for AD and both interact with obesity and sex steroid hormones. We review the individual and cooperative effects of obesity and sex on development of AD and examine the potential contributions of apolipoprotein E, inflammation, and their interactions to this relationship.

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1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia. The neuropathological hallmarks of AD include neuron loss, accumulation of amyloid-β (Aβ) plaques and hyperphosphorylated tau in the form of neurofibrillary tangles and neuropil threads, and gliosis (Cherry et al., 2014; Glass et al., 2010; LaFerla, 2010; Morris et al., 2014). There is compelling evidence that abnormal Aβ accumulation (Mucke and Selkoe, 2012; Tanzi, 2012) or hyperphosphorylated tau (Iqbal et al., 2010) or both (Zempel and Mandelkow, 2014) are the primary driving force(s) in the pathogenesis as well as strong support for key contributions by activated microglia and astrocytes (Cherry et al., 2014; Glass et al., 2010). Regardless of the proximal cause(s) of the neural injury in the AD brain, successful therapeutic intervention will require understanding of the factors that culminate in development of pathology.

The risk of AD is affected by numerous factors. Aging is the single greatest risk factor for AD, with the prevalence doubling every five years after the age of 65 (Hebert et al., 2003). However, the age-related physiological changes that contribute to this effect are uncertain. In addition to aging, AD risk is regulated by genetic factors. A small percentage of AD cases result from autosomal dominant mutations in the Aβ precursor protein, presenilin-1, and presenilin-2. The key consequences of these mutations appear to be increased production of Aβ and/or a change in the ratio of Aβ species, both of which foster Aβ accumulation (LaFerla, 2010; Tanzi, 2012). The most prevalent genetic risk factor for AD is the E4 allele (apoE4) of the cholesterol transporter apolipoprotein E (Saunders et al., 1993; Strittmatter et al., 1993), which also appears to regulate Aβ accumulation. In addition to apoE, there are a number of single nucleotide polymorphisms in genes that are associated with relatively subtle increases in AD risk. Among these are several genes associated with innate immunity (Tanzi, 2012), pointing to a role of the immune system, and microglia in particular, in AD pathogenesis. As with most diseases, AD risk is also significantly affected by several environmental and lifestyle factors, including education (Ferrari et al., 2014; Sharp and Gatz, 2011), head injury (Breunig et al., 2013), air pollution (Calderón-Garcidueñas et al., 2012), and physical exercise (Brown et al., 2013; Tolppanen et al., 2015). In recent years, an especially interesting risk factor has been obesity (Emmerzaal et al., 2015), which may contribute to links between cardiovascular diseases and AD (Hayden et al., 2006).

As with many disorders, significant sex differences exist in AD risk and development, with women being disproportionately affected by AD. These sex differences are likely to be mediated both via actions of sex steroid hormones, as well as by differences in neurophysiological substrates between men and women. Moreover, several normal age-related changes significantly increase AD risk including (i) estrogen depletion associated with menopause, (ii) age-related decreases in testosterone in men, and (iii) increasing adiposity in men and women. Since both estrogen and testosterone regulate adiposity, there are likely interactions between sex steroid hormones, adiposity, and AD risk that may be expected to exhibit sex differences.

In this review, we consider the individual and interactive effects of these AD risk factors as well as possible mechanisms that may be underlying these relationships. We begin by examining obesity as a risk factor for AD and sex differences in AD development. We then examine how sex differences and obesity interact in the context of AD, before exploring mechanisms underlying this relationship. Though there are likely to be a number of important mechanisms, our review will focus on inflammation, apoE4, and their interaction in the context of sex differences, obesity, and AD.

2. Obesity/metabolic syndrome as risk factors for AD

2.1. Epidemiological studies

Accumulating evidence over the past several years has identified obesity and related conditions as significant risk factors for the development of AD. Body mass index (BMI) is a commonly used measure of obesity, and though some studies show an association between BMI and AD, with an up to 40% increased risk for obese individuals (Fitzpatrick et al., 2009; Gustafson et al., 2003), others have found no association (Qizilbash et al., 2015; Yoshitake et al., 1995) (reviewed in Profenno et al., 2010). However, central adiposity may be a more important factor and better predictor of AD risk than BMI (Gustafson et al., 2009; Luchsinger et al., 2012; Whitmer et al., 2008), as visceral fat has been shown to be particularly harmful (Bloor and Symonds, 2014). Central adiposity has been shown to be a risk factor for AD as well as for cognitive impairment (Feng et al., 2013; Gustafson et al., 2009; Luchsinger et al., 2012; Whitmer et al., 2008), and visceral fat deposits are associated with lower brain volumes at middle age (Debette et al., 2010). Importantly, it appears that obesity at midlife is a particularly strong risk factor for onset of AD in late life (Emmerzaal et al., 2015; Fitzpatrick et al., 2009; Meng et al., 2014; Profenno et al., 2010; Xu et al., 2011). Intriguingly, the association between obesity and AD risk diminishes with age. Weight loss and low BMI are actually associated with increased risk of AD in older adults, whereas a higher BMI may be protective at advanced ages (Besser et al., 2014; Emmerzaal et al., 2015; Fitzpatrick et al., 2009; Hughe et al., 2009; Profenno et al., 2010). In fact, one study found that overweight and obese older adults were protected against AD, mild cognitive impairment (MCI), and vascular dementia (Doruk et al., 2010). One interpretation of these findings is that obesity at midlife may serve as a triggering factor for AD neuropathology, the effects of which do not become apparent until onset of clinical dementia later in life.

Obesity is associated with increased risk for the development of metabolic syndrome and type 2 diabetes (T2D), both of which are also independent risk factors for AD (Biessels et al., 2006; Samaras and Sachdev, 2012; Strachan et al., 2011). In addition, both obesity and T2D are risk factors for MCI (Samaras and Sachdev, 2012), and obesity is also linked with cognitive impairments in the absence of dementia (Benito-León et al., 2013; Gustafson et al., 2003; Mazzoccoli et al., 2014). In particular, central adiposity is a risk factor for cognitive decline, as increased visceral adipose tissue is associated with decreased performance on verbal memory and attention tasks, and with lower hippocampal volume (Isaac et al., 2011). Additionally, obesity can impair cognition even in children and young adults (Khan et al., 2014; Reinert et al., 2013; Schwartz et al., 2013; Yau et al., 2012). Thus, there are likely to be two independent pathways; one by which obesity impairs cognition and another pathway by which it promotes AD pathogenesis, that in turn impairs cognition in late life. Interestingly, while the relationship