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Review

A is for Autophagy and Alzheimer's

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Abstract

Improved understanding of the underlying cellular dysfunction and resultant neuropathology of sporadic Alzheimer's disease (AD) is needed to stem the anticipated public health crisis due to this increasingly common neurodegenerative disease. The four main risk factors for sporadic AD are age, female gender, genetic carriage of the APOE4 allele and type two diabetes mellitus (T2DM). Each of these four risk factors is associated with impaired and/or dysfunctional autophagy suggesting that perturbation of autophagy is a root contributor to AD. This article discusses normal cellular autophagy and how each of the named AD risk factors impacts autophagy; in addition currently existing interventions that favorably support the autophagic process are presented.

Keywords

Alzheimer's; autophagy; Kallikrein 8; APOE4; pre-diabetes; insulin resistance; T2DM; telomerase; mTOR; caloric restriction

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia having a worldwide prevalence of about 25 million in 2010; and according to the World Health Organization, that number is expected to double by 2030 due to increased life expectancy [1]. AD exacts a toll on families with affected love ones and on the health systems allocating resources to care for them. The burden of health care costs for patients with dementia in the last five years of life ($287,038) far outweigh those of heart disease ($175,136) and cancer ($173,383) [2]. Unfolding understanding of the pathology of AD and the long prodromal period that precedes clinical dementia has yet to result in effective therapies. This article discusses how disruption of the autophagic process is a unifying feature of the four main risk factors for late-onset AD. Those main risk factors are: age, female gender, genetic APOE4 carriage, and insulin resistance.

Derived from Greek auto (oneself) and phagy (eat), autophagy refers to a common and necessary lysosomal degradation pathway of cellular "housekeeping." Though this process has been studied for several decades, its broad role in biology has more recently increased understanding of molecular cellular processes; this includes recycling normal cellular molecules, protein quality control, pathogen elimination, regulation of immunity and inflammation, metabolism, and cell survival [3]. For his discovery of the mechanisms of autophagy, Yoshinori Ohsumi received the 2016 Nobel Prize in medicine.

The pathological proteins of AD are cerebral extracellular amyloid-β aggregation and intracellular tau tangles [4]. This pathology may be present decades before the onset of dementia [5, 6]. Autophagy mediated intracellular removal of metabolic debris is impaired in the brains of AD patients [7]. The ubiquitin proteasome system (UPS) and autophagy are complementary mechanisms that accomplish important cellular housekeeping functions: removal of protein aggregates, turnover of organelles, and elimination of intracellular pathogens [8,9]. Ubiquitin-tagged macromolecules - "cargo" - are delivered to the lysosome by various methods: endocytosis for extracellular elements [10], autophagy for intracellular cargo [11], and xenophagy for pathogens [12]. These various cellular processes, employing "taking out the trash" functions, are commonly referred to as autophagy.

The remainder of this article will discuss how the four main risk factors of late-onset AD: age [13-15], female gender [1, 16-19], APOE4 carriage [20-22], and insulin resistance [23-25] are associated with impaired and/or dysfunctional autophagy. Moreover, interventions that boost autophagy will be discussed. No human, animal, or plant subjects were a part of this article.

2. Age and Autophagy

The primary risk factor of AD is increasing age. The incidence of AD doubles every five years after the age of sixty-five [26, 27]. Characterized by a broad progressive decline in physiologic function, aging exacts a marked toll on the immune system. Aging causes an inadequate initiation and resolution of the immune response; this is frequently termed *immunosenescence* which coexists with a persistent low-grade inflammatory state – *inflammaging* [28]. These chronic, age-driven, altered states have been linked to metabolic syndrome, cancer, atherosclerosis, and neurodegenerative disease including AD [29]. Microglia are the innate immune cells of the central nervous system performing important physiological functions. Conversely, malfunction of

microglia is implicated in several pathological states [30, 31]. On a cellular level, the aged microglia enter a state of senescence wherein it adopts a senescent phenotype that is found in the aged and diseased brain [32]; and when responding to CNS damage, by way of dysregulated autophagy, have limited capacity to clear aggregated protein [33, 34]. The senescent state is due to telomere attrition. Telomeres are highly conserved repetitive DNA sequences that undergo shortening with each cell division (reflective of cellular replicative history) [35, 36]. Accelerated telomere shortening is associated with AD [37]. Telomere length in T-cells of AD patients is shown to correlate with disease state suggesting immune alterations in AD pathogenesis [38]. While the connection between telomere attrition and autophagy in AD is nascent, the telomere attrition/autophagy association is quite well established in idiopathic pulmonary fibrosis (IPF), dyskeratosis congenita, and chronic obstructive pulmonary disease (COPD) [39, 40].

Factors that accompany aging can confound the relative assignment of autophagic dysfunction to AD; e.g. age-related vascular disease and infection [41, 42]. Contrasting with early thoughts whereby AD was mostly regarded as a singular disease, it is now well established that vascular insufficiency also plays a real, yet variable role in AD. This is not limited to circulation itself but also to age-related changes in the blood brain barrier (BBB) [43]. Additionally, head injury is associated with AD [44]; and, trauma-induced vascular changes are linked to AD pathology [45].

Moreover, infectious burden is felt to play a role in AD [46]. In an age-dependent manner, most of the population harbours latent herpes virus infections acquired during their lifetimes. While infection rates in neonates are very low, in the case of herpes simplex virus type 1 (HSV1), by age 70 years 80–90% of the population is seropositive. The virus is present in the brain [47] of many elderly individuals and AD patients; it was proposed that sporadic reactivation of latent HSV1 in the brain, particularly in APOE 4 carriers, might confer an increased risk of later developing AD [47]. Strikingly, when patients were aggressively treated with anti-herpetic medications at the time of their initial infection, the relative risk of senile dementia (both vascular dementia and AD) was reduced by a factor of 10 [48]. Similarly, age-related infection by cytomegalovirus (CMV) plays a role in diverting the immune capacity [49, 50]. CMV is associated with an age-related prevalence ranging from 40% in twenty-year-olds to over 90% in eighty-year-olds [51]. It has been suggested that subclinical viral infection, exacting an exhaustive toll on immune function and attendant impaired autophagy, can lead to AD [52].

3. Gender and Autophagy

Women have a greater prevalence for AD than men accounting for two-thirds of all patients [53]. This is only partially explained by increased premature mortality of men (starting at 45 years); women aged 65 and older are twice as likely to develop AD compared to age-matched men [54]. Women have faster progression of mild cognitive impairment (MCI) [55]; and women have, after 80 years, a higher transition rate from MCI to AD [56]. Moreover, women display a greater severity in their clinical dementia [57-59]. The use of estrogen replacement for treatment of AD is controversial. However, there are observations that suggest that estradiol may decrease aggregates of amyloid by stimulating autophagy [60, 61]. Estrogen, as a therapeutic agent for neurodegenerative disease, has been investigated over the last decade. E2 (17β-estradiol) has been shown to be neuroprotective in a variety of neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease [62, 63]. Nascent evidence supports the concept that

activation of autophagy by E2 is protective in neurodegenerative diseases and acts by enhancing the removal of toxic protein aggregates [64]. Similarly, in animal studies sex differences in disease-related cognitive impairments and pathology burden are detected in various transgenic mouse models of AD. Female mice are more severely affected by cognitive deficits [65-67] and amyloid plaque pathology than males [68-71]; and estrogen is implicated in the sex differences in the AD mouse models [72]. Estrogen loss via ovary removal increases amyloid burden in female mice [73] while estrogen replacement reduces amyloid burden [74].

Recent studies searching for underlying female-specific risk for AD-related pathology identify kallikrein-8 (KLK8) protease as such a factor. Estradiol, but not testosterone, induces KLK8 synthesis in neuronal and microglial cells. The significant sex-specific difference in AD may be mediated by estrogen-induced overproduction of KLK8 in prodromal AD. Inhibition of KLK8 enhances autophagy. A higher level of KLK8 is detected in brains of female Alzheimer's disease patients at early disease stages compared with male counterparts. These studies conclude by suggesting that KLK8 overexpression and accompanying impaired autophagy in females is central to the preferential prevalence of AD in females [75].

4. APOE and Autophagy

Unlike early-onset familial AD, which accounts for less than one percent of AD cases and typically affects before the age of 65, the vast majority of AD cases occur at over 65 years of age and are most commonly referred to as late-onset AD (LOAD) [18]. LOAD is thought to have multiple genetic and environmental risk factors [76]. The inheritance of both APOE4 alleles (E4/E4) is the single greatest genetic risk for the development of AD [77-79]. The human APOE gene exists as three different alleles: E2, E3 and E4. They have a respective frequency of 8.4%, 77.9% and 13.7% (Figure 1) [20]. A single E4 allele increases AD risk by 2-3 folds. Having both alleles increases AD risk by about 12-fold [80, 81]. While APOE4 is strongly associated with AD, this allele is only found in half of LOAD cases [77-83]. APOE4 is associated with impaired memory and rapidity of memory decline as well as increased risk of progression from MCI (mild cognitive impairment) to AD dementia [84, 85].

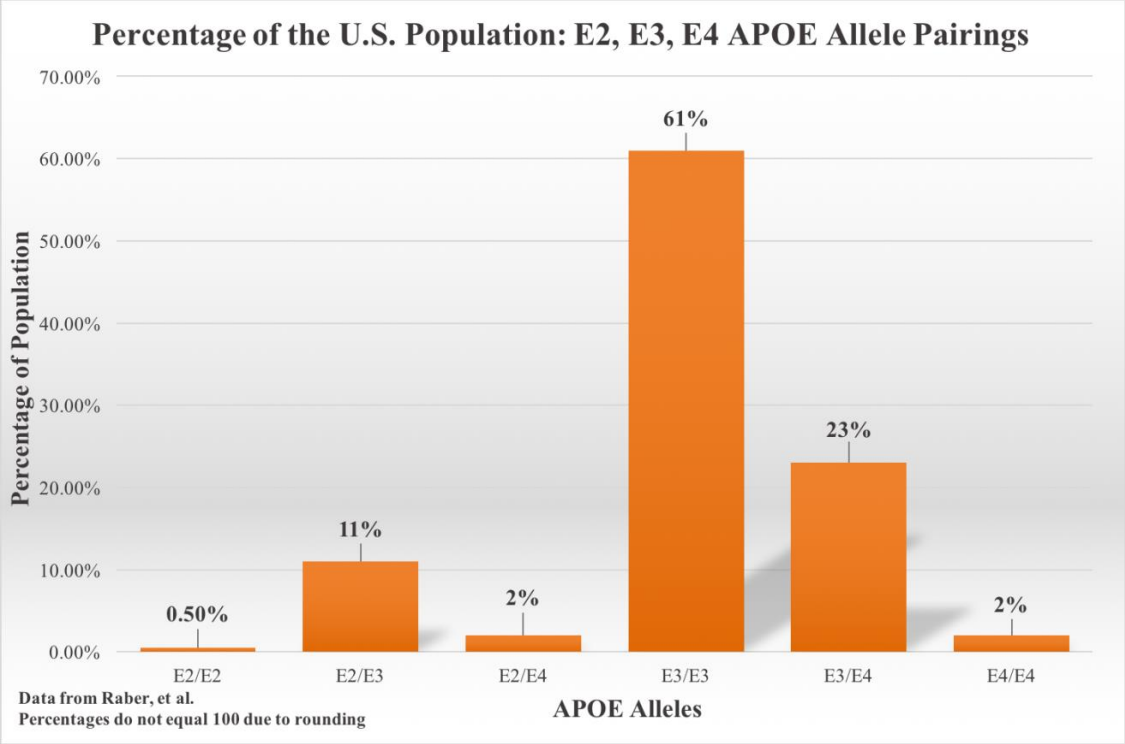

Figure 1 Percentage of the U.S. Population: E2, E3, E4 APOE Allele Pairings [86].

Impaired autophagy is known to be both an early and a persistent finding of AD pathogenesis. APOE is abundantly produced in the brain and serves as the main lipid transport, and its messenger RNA is found in the regions of the brain that demonstrate AD pathology: the hippocampus, cerebral cortex, cerebellum, and medulla [87]. Autophagy reduces protein aggregation and studies show APOE4 competes with a transcription factor that controls autophagic gene expression. There is decreased autophagic activity in AD carriers of APOE4 relative to those with allele E2 and E3 which correlates with increased aggregated amyloid and tau proteins in the E4 carriers [88, 89].

5. Insulin Resistance and Autophagy

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia resulting from deficient insulin production and/or deficient insulin action. The International Diabetes Federation reports that type 2 diabetes (T2DM), the so-called noninsulin-dependent diabetes, accounts for approximately 90% of all cases of diabetes and affects nearly 415 million people worldwide [90]. In contrast to type 1 diabetes (T1DM), where little or no insulin is produced by the pancreas due to an autoimmune-mediated destruction of β -cells, T2DM arises as a result of hyperinsulinemia accompanied by impaired glucose tolerance, which is believed to be a result of compensatory insulin signaling impairment in peripheral tissues [91,92]. According to the CDC, more than 1 in 3 Americans have prediabetes and the majority are unaware of it [93]. Approximately 70% of individuals with prediabetes develop T2DM [94] and an estimated 35% of Americans over the age of 20 are pre-diabetic, while approximately half of the individuals over the age of 65 are affected by diabetes [95]. Peripheral insulin resistance is associated with compensatory insulin hypersecretion and decreased hepatic insulin clearance, rendering to a pathologic cycle of both

high blood glucose and high insulin levels [96, 97]. Autophagy plays an important role in pancreatic cell dysfunction of T2DM and insulin resistance [98, 99].

Though the brain holds about 2% of total body mass, it consumes about 20% of total body energy; this disproportionate energy demand is due to constant brain action even when at rest [99]. Brain levels of insulin and insulin receptors (IR) are lower in AD, and insulin signaling impairments have been documented in both AD post-mortem analysis and in animal models of AD. Accumulating evidence suggests that insulin resistance also develops in AD brains [100-103]. In the light of the epidemiological data supporting the link between T2D and AD, the increasing incidence of AD is likely a consequence not only of ageing alone, but of the diabetes epidemic itself [28]. It has been hypothesized that glucose transportation abnormalities may be related to insulin resistance and intracellular metabolic alterations to mitochondrial dysfunction observed in AD patients [104]. These changes happen decades prior to clinical symptoms. Cross-sectional positron emission tomography (PET) studies find that cognitively normal carriers of the APOE4 allele have abnormally low measurements of the cerebral metabolic rate for glucose (CMRgl) in the same regions as patients with Alzheimer's dementia [105].

The impaired signaling of insulin and insulin-like growth factor (IGF) that accompanies diabetes also disrupts autophagy. This imparts the core pathological features of AD: amyloid plaque and a modification of the tau protein producing the neurofibrillary tangle [23].

6. Discussion: Upregulating Autophagy

While there is no avoiding "the ravages of time," there is a rationale to consider strategies offering molecular support that increases autophagy in the aging brain. The mammalian target of rapamycin (mTOR) signaling pathway is a well described controller of autophagy. Neurons are small, polarized, and post-mitotic making them sensitive to the accumulation of aggregated and damaged cellular proteins. Neurons are thus dependent upon autophagy for survival [106].

mTOR responds to cellular levels of available glucose. Under normal conditions where there is no cell starvation, mTORC1 suppresses autophagy [107]. Under starvation conditions or rapamycin treatment, mTOR activity is inhibited, leading to autophagy initiation [108].

Rapamycin and rapalogs are protein kinases that inhibit mTOR [109]. Rapamycin has been shown to slow age-dependent changes in animal models [110]. mTOR signaling pathway is a master regulator of cell growth and metabolism [111]. Mounting evidence suggests that AD as well as Parkinson's, Huntington's, and spinocerebellar ataxia may all be related to mTOR protein synthesis and impaired autophagy [112]. Another autophagy inhibitor that acts by inhibiting mTOR is the antidepressant indatraline [113].

As described earlier, age-related telomere shortening is a recognized factor in the pathogenesis of AD [38]. Telomere length in T-cells of AD patients is shown to correlate with disease state suggesting immune alterations in AD pathogenesis [39]. A cellular ribonucleoprotein enzyme complex, telomerase, "rescues" the cell from the senescent state (and senescent phenotype) by adding telomeres [114,115]. In a small study an oral telomerase activator has been used to benefit early age-related macular degeneration (AMD) [116] as a health supplement and may find its way into treatment of AD [117]. Attempts are also underway to develop a method to upregulate telomerase via an injectable telomerase activator [118].

The use of estrogen as a therapeutic agent for neurodegenerative diseases has been investigated over the last decade. E2 (17β-estradiol) has been shown to be beneficial in a number of neurodegenerative disorders, such as stroke, Parkinson's disease, and Alzheimer's disease [62, 63]. Estrogen may also exert undesirable stimulatory effects on the breast and uterus, potentially increasing the risk of developing breast and uterine cancers or stroke [62]. These limitations have prompted development and trials of selective estrogen receptor modulators (SERMs), a treatment that mimics the beneficial yet minimizes the adverse effects of estrogen. One widely used SERM drug is raloxifene (Ral). In vitro and in vivo studies have shown Ral demonstrates neuroprotection in animal models of neurodegenerative disease [119]. As described earlier, the significant sex-specific differences in AD are related to estrogen-induced overproduction of KLK8 in prodromal AD. KLK8 is manifest in AD affected areas: the hippocampus, frontal cortex and cerebellum [75]. Inhibition of KLK8 enhances autophagy and, in animal models, reduces amyloid and tau pathology [120].

We cannot change our genetics yet “knowledge is power” [121]. An individual’s knowing that they carry one or both alleles of the APOE4 gene may make them adopt lifestyle changes to their long term cognitive benefit. APOE4 regulates pathways that link aging and AD; APOE4 expression reduces the activity of Sirtuin1 (SirT1), a protein that suppresses AD related pathology. Most of the cellular abnormalities associated with APOE4 and AD could be prevented by increasing SirT1 [122]. While we cannot change our genetics there is reason to believe that we can influence our epigenetics, via telomerase activation [123]; not only has this been proposed, but human FDA trials are planned [124]. Caloric restriction (30-60% below *ad libitum* in animal studies) can increase lifespan by 20-50% [125] and does so by activating SirT1 [126,127]. There is active research looking for caloric restriction mimetics [128]. Knowledge of APOE4 carriage would allow individuals to fully explore the lifestyle changes to mitigate AD; those include sleep, diet and cortisol regulations [129]. Moreover, regular exercise has been shown to benefit AD risk [130] as well as the symptoms and pathology of AD [131].

AD is occasionally termed “type 3 diabetes” due to insulin deficiency and/or insulin resistance that is specific to the brain. As insulin is the primary treatment for diabetes, it is understandable that small clinical trials in patients with mild cognitive impairment/AD, nasal application of insulin or long-lasting insulin analogues, showed improvements in memory tasks, cerebrospinal fluid biomarkers, and in a fluorodeoxyglucose positron (PET) emission tomographic study [132]. However, in further studies, responses varied by APOE genotype and gender [133].

What is available today then for an elderly, female, APOE4 positive, and insulin resistant individual? Certainly, there are lifestyle recommendations regarding diet, sleep, exercise and stress reduction that may deter and defer the cognitive changes of AD. For tomorrow perhaps there will be telomerase activators, mTOR inhibitors, caloric restriction mimetics, KLK8 inhibitors, SirT1 activators, intranasal insulin, and antiviral treatments that may benefit those who are risk of developing AD dementia.

Author Contributions

CTD chose the topic for this article. CTD and JS contributed equally to the research and writing of this article.

Competing Interests

The authors have declared that no competing interests exist.

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