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Review

Brain metabolism as a modulator of autophagy in neurodegeneration

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ABSTRACT

Emerging evidence that autophagy serves as a sweeper for toxic materials in the brain gives us new insight into the pathophysiology of neurodegenerative diseases. Autophagy is important for maintaining cellular homeostasis associated with metabolism. Some neurodegenerative diseases such as Alzheimer's and Parkinson's diseases are accompanied by altered metabolism and autophagy in the brain. In this review, we discuss how hormones and nutrients regulate autophagy in the brain and affect neurodegeneration.

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Contents

1. Introduction

As its name (from the Greek "*auto*" meaning "self" and "*phagy*" meaning "to eat") suggests, autophagy is a cellular process that leads to degradation of damaged organelles and aggregated proteins (Mizushima et al., 2008). Autophagy participates in a variety of cellular physiological processes such as lipid metabolism (Singh et al., 2009), glucose homeostasis (Kotoulas et al., 2006), and aging (Cuervo et al., 2005; Cuervo, 2008; Rubinsztein et al., 2011). Cellular dysfunctions are often caused by the failure of autophagy to remove defective proteins or damaged organelles. In *Caenorhabditis elegans*, premature aging occurs when autophagy is inhibited (Toth et al., 2008). In contrast, enhanced autophagy extends the lifespan of *Drosophila melanogaster* (Simonsen et al.,

Abbreviations: Atg, Autophagy-related gene; PD, Parkinson's disease; Aβ, Amyloid-β peptide; AD, Alzheimer's disease; HD, Huntington's disease; HFD, High-fat diet; ER, Endoplasmic reticulum; LC3, Microtubule-associated protein light chain 3; CNS, Central nervous system; APP, Amyloid precursor protein; T2D, Type 2 diabetes; mTOR, Mammalian target of rapamaycin; HCN, Hippocampal neural stem; AMPK, AMP-activated protein kinase; GHSR, Growth hormone secretagogue receptor; METH, Methamphetamine; KA, Kainic acid; LAMP-2, Lysosomal-associated membrane protein 2; PrP, Prion protein; PIP3, Phosphatidylinositol(3,4,5)-trisphosphate; NPC, Niemann-Pick type C; LD, Lafora disease

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2008). Deletion of the autophagy-related gene (Atg) family provokes an imbalance of body homeostasis, resulting in insulin resistance (Yang et al., 2010), obesity (Meng and Cai, 2011), diabetes (Jung and Lee, 2010), and neurodegeneration (Komatsu et al., 2006). As a sweeper necessary for degradation of aggregated proteins or damaged organelles (Mizushima et al., 2008), autophagy can be a therapeutic target for the treatment of neurodegenerative diseases. When aggregated proteins are not properly removed by autophagy, their toxicity causes neurodegenerative diseases; for example, accumulation of aggregated forms of α-synuclein (Pan et al., 2008; Webb et al., 2003) and tau protein (Rodriguez-Navarro et al., 2010) are involved in Parkinson's disease (PD), those of amyloid-β peptide (Aβ) (Spilman et al., 2010) and tau protein (Goedert et al., 1989) in Alzheimer's disease (AD), and that of huntingtin in Huntington's disease (HD) (Ravikumar et al., 2004).

Among all types of cells, neurons are easily damaged by impaired autophagy (Hara et al., 2006; Komatsu et al., 2006). Neurons that lack of autophagy have a problem to maintain axonal homeostasis (Komatsu et al., 2007) and synaptic activity (Hernandez et al., 2012). Neurodegenerative diseases are typically irreversible and prevalent in the aged population. However, some food types like high-fat diet (HFD) may cause memory deficit in young age (Alzoubi et al., 2009; Greenwood and Winocur, 2001). Some metabolic dysfunctions are linked to neurodegenerative diseases such as AD, PD, and HD. For example, PD is significantly correlated with diabetes (Sandyk, 1993) and increased iron deposition in neurons (Ayton et al., 2015).

Autophagy occurs through distinct steps. When organelles are damaged or proteins are aggregated, those substrates are enclosed in autophagosomes and autophagosomes encounter lysosomes via a series of specific processes to produce autolysosomes. The formation of autophagosomes is initiated during the early stages of autophagy by the ULK1/Atg13/FIP200 kinase complex, which triggers the formation of a phagophore, the initial form of autophagosome (Hosokawa et al., 2009). Beclin 1, the mammalian orthologue of yeast Atg6, also participates in the formation of autophagosomes by forming a complex with hVps34 when the Bcl-2/Beclin 1 complex dissociates (Kihara et al., 2001; Pattingre et al., 2005). The origin of the autophagosomal membrane is still controversial, with the mitochondria (Cook et al., 2014; Hailey et al., 2010; Reggiori et al., 2005), endoplasmic reticulum (ER) (Axe et al., 2008; Ueno et al., 1991; Yla-Anttila et al., 2009), and Golgi (Geng et al., 2010; Guo et al., 2012; van der Vaart et al., 2010) being the main candidates. Microtubule-associated protein light chain 3 (LC3) is converted into LC3-I by Atg4 (Kabeya et al., 2000). Then LC3-I is conjugated with phosphatidylethanolamine, forming LC3-II by Atg7, an E1 enzyme and Atg3, an E2 protein (Ichimura et al., 2000). Adaptor proteins such as p62/sequestosome 1, NBR1 and NDP52 (Kirkin et al., 2009; Pankiv et al., 2007; Thurston et al., 2009) anchor substrates of autophagy to LC3-II. Subsequently, misfolded protein (Rabinowitz and White, 2010) or abnormal cellular organelles including mitochondria (Geisler et al., 2010), ER (Bernales et al., 2007), or peroxisome (Kim et al., 2008) are engulfed by double-membrane autophagosome. The autophagosomes are fused with a lysosome, forming an autolysosome where the entrapped substrates are degraded (Kirkin et al., 2009; Pankiv et al., 2007; Thurston et al., 2009). In some special conditions, autophagy is linked to cell death with autophagic features called autophagic cell death. Autophagic cell death requires *ATG7* and *beclin1* genes (Yu et al., 2004) and displays autophagic characteristics such as increased Beclin1 and LC3-II form (Yu et al., 2008). Autophagic cell death is different from apoptosis which is type I of programmed cell death. Apoptosis is also observed in neurodegenerative diseases such as hippocampal neurons in AD (Smale et al., 1995), dopaminergic neurons in PD (Duan et al., 1999), and striatal neurons in HD (Shehadeh et al., 2006).

Recent studies have shown a correlation between metabolic changes and autophagy (Li et al., 2012; Papackova et al., 2012; Shang et al., 2011; Yamahara et al., 2013; Yang et al., 2010) and between autophagy and neurodegeneration (Hara et al., 2006; Komatsu et al., 2006; Nixon, 2013; Pan et al., 2008). This review will discuss how metabolic changes affect autophagy, leading to neurodegenerative diseases. In particular, it will focus on the roles of hormones and nutrients in the specific autophagy and metabolism system in the brain, which provide the potential for targeted pharmacologic treatments in neurodegeneration.

2. Autophagy caused by metabolic changes in the brain affects neurodegeneration

Because the brain consumes the most oxygen and glucose, it generates large amounts of waste products. Many molecules such as hormones and nutrients modulate metabolism in the brain to maintain cellular energy homeostasis.

2.1. Hormones: insulin, ghrelin, and melatonin

Insulin is a hormone that participates in many functions in the brain, including cognition (Stranahan et al., 2008), memory (Zhao and Alkon, 2001), and energy homeostasis (Niswender et al., 2004). Insulin controls neuronal function in the central nervous system (CNS) (Plum et al., 2005) through a complex insulin/insulin receptor signaling pathway (Zhao and Alkon, 2001). Many brain areas such as the olfactory bulb, cerebral cortex, hippocampus, and hypothalamus express insulin receptors (Plum et al., 2005). The levels of insulin and insulin receptors decreased in the brain with aging (Frolich et al., 1998). Insulin inhibits autophagy via activating mammalian target of rapamycin (mTOR) (Kanazawa et al., 2004) that suppresses autophagy (Noda and Ohsumi, 1998; Schmelzle and Hall, 2000). In addition, from the neuropathological point of view, insulin has many important roles such as inhibition of phosphorylation of tau (Hong and Lee, 1997) and transport of Aβ from the Golgi apparatus to the plasma membrane (Gasparini et al., 2001).

The accumulation of extracellular Aβ and the twisted form of intracellular tau protein in neurons are considered to contribute to AD (Alzheimer's, 2014). Aβ is a major toxic peptide composed of 40 or 42 amino acids; its source is amyloid precursor protein (APP). Aβ is produced when APP is cleaved by β-and γ-secretases (Vassar and Citron, 2000). In the study of β-amyloidosis mouse model, autophagy generates Aβ, and autophagosomes are one of the Aβ generation sites (Yu et al., 2005). When autophagy was increased in AD model of mice, proliferation of autophagic vacuoles and Aβ production were also increased according to the level of autophagy. Thus, autophagy might be involved in Aβ-related neurodegeneration. Since insulin inhibits autophagy via activating mTOR signaling (Kanazawa et al., 2004), insulin may block Aβ production generated from autophagy.

Among neurodegenerative diseases, the etiology of AD is closely related to type 2 diabetes (T2D) (Craft, 2005; Watson and Craft, 2003). Impaired insulin signaling is one of the causes of AD (Steen et al., 2005). HFD induces T2D by impairing insulin signaling, which leads to insulin resistance (de Assis et al., 2009), in particular in the hypothalamus and hippocampus (De Souza et al., 2005; Stranahan et al., 2008). HFD also aggravates neurodegenerative diseases such as AD (Morris et al., 2003) and PD (Morris et al., 2010). The effect of HFD on neurodegenerative diseases and T2D suggests that metabolic changes affect neurodegenerative diseases.

When C57BL/6 mice were fed HFD for 22 months, they showed