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Mini Review

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Ambroxol hydrochloride, a chaperone therapy for Paget's disease of bone and other common autophagy-mediated aging diseases?

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Introduction

Paget's disease of bone (PDB) with or without frontotemporal dementia shares common pathogenic mechanisms with some neurodegenerative diseases such as Parkinson's disease, amyotrophic lateral sclerosis (ALS), Alzheimer's, disease, and inclusion body myopathy [1]. These disorders are known to be related to autophagy machinery impairment [1]. Recent studies have reported roles of Ambroxol hydrochloride in treatment of some oxidative stress induced and autophagy mediated diseases such as Parkinson's disease (PD), related synucleinopathies, Dementia, Alzheimer's, Huntington's, Creutzfeldt–Jakob/prion, and Gaucher (GD) diseases [2-8].

The hypothesis

We made the hypothesis that Ambroxol hydrochloride should be a therapeutic avenue for PDB.

Evaluation of the hypothesis and discussion

Why Autophagy is essential for the normal cell biology?

Autophagy is essential process for normal cell biology. It is responsible for eliminating non-functional or misfolded proteins [1,8,9], and plays an important role in cell proliferation and cell death regulation(1, 8-10); moreover it provides the energy needed for the cell and protect it against damaging by oxidative stress or starvation [1,11,12]. Autophagy can be initiated by some inducers such as excessive autophagic vacuoles, excessive aggregation of misfolded or unfolded proteins, accumulation of non-functional organelles, bacteria, virus, and by rapamycin (in vitro) [10,13]. The four main steps of autophagy are stimulation and initiation, nucleation, elongation, following by maturation and fusion between autophagosome and lysosome vacuoles initiators forming autolysosomes [1,10]. Autophagy machinery deficiency result in failure of elimination of misfolded/unfolded protein aggregates. Accumulation of non-functional misfolded proteins aggregates leads to symptoms of PDB, PD, related synucleinopathies, and other autophagy mediated aging diseases [1].

Mechanism of Autophagy impairment in PDB and in some autophagy mediated neurodegenerative disease:

SQSTM1/p62 gene mutations have been reported in some cases of ALS, PDB, and frontotemporal dementia [1,13-16]. Depriving the cell from full functional SQSTM1/p62 protein may lead to failing in autophagy functions; its role in eliminating misfolded/unfolded proteins aggregates and non-functional organelles [1,17]. In normal cells, Ubiquitin protein marks the non-functional proteins leading to its elimination by autophagosome. SQSTM1/p62 is able to bind ubiquitinated proteins. It induces the autophagic elimination of ubiquitinylated proteins by exporting them from the nucleus into the lysosomes [18]. Moreover, in nucleus, SQSTM1/p62 protein stimulates proteasomes to eliminate nuclear polyubiquitinylated protein aggregates [1,17]. On the other hand, SQSTM1/p62 has a protective effect on huntingtin-induced cell death. Dysfunctional mutant Huntingtin protein and impairment of autophagy machinery may lead to Huntington's disease [19].

Role of autophagy impairment in PD:

Formation of Lewy's bodies (intraneuronal inclusions mainly consists of α-synuclein protein) leads to Parkinson's disease [1,19,20]. Glucocerebrosidase (GBA) gene mutations are considered the most risk factor that predisposes to PD [3]. Furthermore, some familial forms of Parkinson's disease caused by point mutations and multiplications of the whole locus at α-synuclein gene [21]. α-synuclein overexpression suppresses macroautophagy in mammalian cells and in transgenic mice leading to mitochondrial dysfunction, induces cell susceptibility to proapoptotic assaults, accumulate p62 protein, and increase proteins aggregation [22]. Moreover the excessive secretion of α-synuclein protein may leads to suppression of Rab1a protein function, impairment of 26S proteasome function [22]. Other studies reported its role in inhibition of ubiquitin-proteasome activity in vitro [22-25]. Impairment of autophagy pathway suppress dopamine secretion, which is the main cause of PD [22]. Taken together, we can conclude that mutant α-synuclein protein is highly involved in autophagy impairment.

Role of Ambroxol Hydrochloride

Recent studies reported important roles of Ambroxol Hydrochloride in GD and PD with GBA mutations. It increases the lysosomal enzyme mass, reduces dihydroethidium oxidation stress rate, improves of glucosylceramidase activity in fibroblasts with GBA mutation. Moreover, it suppresses α-synuclein overexpression neuroblastoma cell lines [2]. Furthermore, it is suggested to be one of chaperone therapies for protein misfolding diseases such as Gaucher disease [4], and for impairment of autophagy–lysosome system occurred in many

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autophagy-mediated diseases [2]. Interestingly to mention that it's commercially available and widely used as a safe expectorant drug [4].

Consequently, we suggest a promised role for Ambroxol Hydrochloride in improving the autophagy process functions, decrease oxidative stress rate, and decrease the excessive osteoclasts activity, which is the main cause of sporadic and familial PDB.

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