It Is All about (U)biquitin: Role of Altered Ubiquitin-Proteasome System and UCHL1 in Alzheimer Disease

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Free radical-mediated damage to macromolecules and the resulting oxidative modification of different cellular components are a common feature of aging, and this process becomes much more pronounced in age-associated pathologies, including Alzheimer disease (AD). In particular, proteins are particularly sensitive to oxidative stress-induced damage and these irreversible modifications lead to the alteration of protein structure and function. In order to maintain cell homeostasis, these oxidized/damaged proteins have to be removed in order to prevent their toxic accumulation. It is generally accepted that the age-related accumulation of "aberrant" proteins results from both the increased occurrence of damage and the decreased efficiency of degradative systems. One of the most important cellular proteolytic systems responsible for the removal of oxidized proteins in the cytosol and in the nucleus is the proteasomal system. Several studies have demonstrated the impairment of the proteasome in AD thus suggesting a direct link between accumulation of oxidized/misfolded proteins and reduction of this clearance system. In this review we discuss the impairment of the proteasome system as a consequence of oxidative stress and how this contributes to AD neuropathology. Further, we focus the attention on the oxidative modifications of a key component of the ubiquitin-proteasome pathway, UCHL1, which lead to the impairment of its activity.