Meta-analysis of expression and function of neprilysin in Alzheimer’s disease

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Introduction
As an age-related neurodegenerative disorder, Alzheimer’s disease (AD) shows progressive memory and cognition deficits and eventual disability. Although the exact pathogenesis of AD has not yet been fully elucidated, senile plaque containing aggregated β-amyloid (Aβ) and neurofibrillary tangles of hyperphosphorylated Tau are the major pathological features of AD [1]. The overproduction or abnormal degradation yields excessive Aβ, aggregating into the senile plaque which could induce neuronal damage [2]. Eliminating the redundant Aβ may be a potential strategy for AD therapy. Increasing evidence has indicated that Aβ-degrading enzymes, including neprilysin (NEP), insulin-degrading enzyme (IDE), and endothelin converting enzyme (ECE), play a key role in Aβ protein clearance [3].

NEP is a zinc-dependent metalloendopeptidase and is mainly located in presynaptic terminals of neurons especially in hippocampal and neocortical neurons. NEP, a membrane-bound peptide, has a long extracellular domain that constitutes its catalytically active domain [4]. Most Aβ-degrading enzymes are particularly involved in the degradation of monomeric Aβ species and are able to cleave both Aβ40 and Aβ42 peptides [5], while it is debatable whether NEP can hydrolyze oligomer forms of Aβ [6, 7].

Several animal experiments have verified the effect of NEP on brain Aβ balance [8]. The NEP- deficient mice have significantly elevated brain Aβ deposition and worsened behavioral phenotypes compared with wild type mice [9, 10]. In contrast, up-regulation of NEP protease reduced the Aβ level, retarded the plaque formation, and rescued the premature death in transgenic mice [11]. In addition, aged dogs with cognitive impairment showed 80% decreases in the level of NEP [12]. However, the expression and functional characteristics of NEP in AD post-mortem brains remain controversial among studies. Wang’s research suggested that NEP mRNA, protein level, and enzyme activity in AD were lower than in non-AD controls [14]. In contrast, Miners reported both unadjusted and adjusted NEP levels and activity were significantly increased in AD and positively associated with disease severity in AD patients [15]. Meanwhile, another AD subcellular analysis has shown that NEP protein level declined in cytoplasmic fractions and increased in membrane fractions compared with normal controls [16]. Thus, in this study, we performed a meta-analysis to assess the inconsistent results from published studies and concluded the potential association between NEP and AD pathogenesis.
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