GPCR Dysfunction in Alzheimer's Disease

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Alzheimer's disease (AD) is the most common neurodegenerative disorder afflicting the elderly. AD is clinically characterized by progressive neuronal loss and inflammation, memory impairment, cognitive deficits, and behavioral changes. Neuropathologically, the AD brain is characterized by two proteinaceous aggregates, amyloid plaques, mainly composed of the amyloid β-protein (Aβ), and neurofibrillary tangles (NFT), comprised of hyperphosphorylated aggregates of the tau protein. According to the amyloid hypothesis, the chronic excessive accumulation and deposition of Aβ in amyloid plaques, Aβ42 in particular, initiates a pathogenic cascade, which leads to the development of AD. More than 30 mutations in APP (the substrate) and 180 mutations in the two presenilin genes (the protease) have been identified; however, these missense mutations account for less than 0.5% of all AD cases. In contrast, sporadic AD is more common and is caused by a combination of environmental and genetic factors. Although significant progress has been made toward understanding the pathophysiology of AD, crucial questions remain unanswered. In this regard, several proteins have been demonstrated to influence the amyoid and tangle cascades in fundamental cell biological and transgenic animal studies. It is crucial to understand the role that these proteins play in the development of sporadic AD. Thus, we would like to expand our ongoing studies from cell culture and animal models to the most physiologically relevant context, i.e. the human brain, and to determine whether the effects observed in cell culture and animal models are valid in the human AD brain.

Recent evidence suggests that G protein-coupled receptors (GPCRs) might provide salient insight into a common underlying mechanism with regard to Aβ generation, and although these novel observations require further confirmation, they broaden our insight into an unanticipated spectrum of therapeutic targets for AD research and perhaps neurodegeneration in general. In this regard, we published an article (Thathiah et al. Science (2009)) in which we identified the orphan GPCR GPR3 as modulator of Aβ peptide generation in an AD transgenic mouse model. Most recently, we discovered a small family of GPCR regulatory proteins, the β-arrestins, are involved in modulation of Aβ generation via interaction with two GPCRs, GPR3 and the β2-adrenergic receptor (β2-AR) Thathiah et al. Nature Medicine (2013). We also discovered that GPR3 expression is elevated in a subset of sporadic AD patients and that β-arrestin 1 and 2 are differentially regulated in these patients. We would like to build on these initial observations to determine GPCR profile in the normal and AD brain to establish the repertoire of aberrantly regulated GPCRs in AD and to determine whether a true correlation exists between GPCR expression and the pathogenesis of AD. Most importantly, a systematic evaluation of the GPCR expression profile in the normal and AD brain has not been performed but could provide crucial insight into the normal and pathological GPCR network present in the human brain and facilitate assessment of the functionality of GPCRs in brain regions relevant in the pathogenesis of AD. Studies are currently underway to determine the mRNA GPCR and β-arrestin expression in AD and control brain samples and to determine whether the GPCR expression correlates with the degree of amyloidosis and tau pathology relative to Braak staging, ApoE expression, and patient age.