

Amyloid Precursor Protein in Autism Spectrum Disorder

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Abstract

Amyloid precursor protein (APP) gets cleaved by α , β , and γ secretases in both amyloidogenic and non-amyloidogenic processing. In amyloidogenic processing, A β 40 and A β 42 peptides result, leading to amyloid plaques in the brain, associated with various dementias, especially Alzheimer's disease. Amyloid plaques also occur in the brains of children with autism spectrum disorder (ASD), while both elevated and diminished levels of soluble APP have been found in the serum of ASD patients. Treatment with mGluR5 inhibitors has successfully lowered APP and A β levels *in vitro* as well as ASD symptoms in a mouse model. Differences in ASD genotype and phenotype along with similarities to neurodegenerative dementias must be considered when investigating new biomarkers and treatments for ASD.

Keywords: Central nervous system; Brain; Autism spectrum disorder; *UBE3a* gene

Introduction

Amyloid precursor protein (APP) is an integral membrane protein expressed throughout the body, especially in the central nervous system [1]. There is evidence that the extracellular region of APP has trophic function: influencing synaptogenesis, neurite outgrowth and cell adhesion [2]. APP also assists with maintaining the integrity of brain development, memory formation, and neural plasticity [3-5]. During amyloidogenic processing, APP can be cleaved into amyloid beta peptides, A β 40 and A β 42, when β secretase frees sAPP β , and γ secretase subsequently cleaves the APP intracellular domain from the A β region of the peptide, generating A β 40 or A β 42 [6]. In non-amyloidogenic APP processing, α secretase catalyzes the proteolysis of APP to generate sAPP α , disrupting the central domain of APP. If this central domain is cleaved, APP cannot form pathogenic A β peptides. Gamma secretase is expressed throughout the brain and is also integral to embryonic and adult neurogenesis via undetermined mechanisms [7]. A β plaques develop in the brain as a result of the accumulation of insoluble proteins, A β 40 and A β 42, which interlace to form larger oligomeric fibrils and plaques. These lesions accumulate in the brain and cause the hallmark abnormalities used to diagnose Alzheimer's dementia [8]. There is a growing body of evidence that suggests these plaques may disrupt cognitive function in neurologic disorders other than AD as well [9]. However, much of the research previously conducted has focused on the involvement of APP in Alzheimer's disease alone.

Discussion

Autism spectrum disorder (ASD) is quite prevalent in the United States and is reported to be present in as many as 1 in 41 children [10]. Core symptoms include difficulties with communication, deficits in interpersonal interactions, and restricted patterns of stereotyped behavior or interests [11]. Early symptoms present as early as 18 months, but the majority of cases are not diagnosed prior to 3 years of

age [12]. It is ideal for ASD to be diagnosed as early as possible in order to intervene and minimize disability [13]. Unfortunately, lack of knowledge about the heterogeneous etiology of ASD complicates the discovery of an effective treatment for this disorder [14,15].

There are a wide variety of risk factors and etiologies that underlie the genesis of ASD. Environmental risk factors could include prenatal exposure to stress, teratogens, or inappropriate hormone levels [16-18]. Numerous genetic abnormalities have been identified as being associated with ASD [19]. One of the most prevalent causative genetic abnormalities leading to ASD is *UBE3a* overexpression caused by a maternal 15q11-13 duplication or triplication [20]. This accounts for 1-3% of all ASD cases and symptoms are gene dose-dependent [20]. The *UBE3a* gene encodes for E6-Associated protein (E6AP), a well-known E3 ubiquitin ligase and transcriptional coactivator for steroid hormone receptors [14]. How, exactly, overexpression of E6AP leads to ASD is still unknown.

Elevated levels of sAPP α can be detected early in life, and these levels were elevated in the blood of 60% of autistic children in a 2008 study [21]. However, these findings can be confusing since some ASD patients actually exhibit lower sAPP levels than neurotypical controls [22]. That study explained the differences with "mild" vs. "severe" ASD categorization, but we remain skeptical of this assertion [22]. Significantly greater intraneuronal A β deposits have been found in ASD patients exhibiting a 15q11-13 duplication compared to subjects with idiopathic autism [23]. This categorization of ASD patients into "15q11-13 copy number variation" vs. "other cause" makes much more sense and we posit this may also explain differences found in the plasma APP studies. Further investigation into this distinction may yield a more accurate early biomarker test for ASD. Additional investigation into the relationship between excess E6AP and APP may yield new avenues for ASD treatment. Other classically Alzheimer's-associated biomarkers being investigated for ASD diagnosis include A β 42, tau protein, and the ApoE4 allele [24].

Interestingly, one of the most common models used to study ASD is Fragile X Syndrome (FXS) mice. Cognitive and behavioral symptoms such as developmental delay, inattention, hyper-excitation, and social

anxiety, along with characteristic physical features such as low muscle tone and loose joints, long narrow face with prominent ears, and large testicles in males are the hallmarks of FXS [25]. Along with some symptoms, these two neurodevelopmental disorders share a link to APP. It has been found that APP mRNA serves as a ligand for fragile X mental retardation protein (FMRP), FMRP regulates expression levels of APP, and this excess APP is converted to A β in Fragile X rodent models [26]. Furthermore, treatment with mGluR5 inhibitor fenobam successfully reduced APP *in vitro* on FXS cells and reduced A β and seizures in wildtype and Alzheimer's rodent models [26]. The seizure reduction is not trivial since many neurodevelopmental disorders include seizures independent of an epilepsy diagnosis. Since this was a proof of principle study, there is still a lot of work to be done such as increasing sample size, including FXS mice, and even testing this treatment on the ASD mouse model overexpressing E6AP. Another mGluR5 negative modulator, GRN-529, improved sociability and repetitive behaviors in an inbred idiopathic ASD mouse model [27]. GRN-529 has yet to be tested in an E6AP overexpression ASD model.

Conclusion

Enlightening data like these mentioned should encourage further studies on the role that APP plays in the developing brain. This inquiry may shed light on possible treatments for ASD. It is clear that APP and A β may be implicated in multiple neurodevelopmental and neurodegenerative disorders, including Alzheimer's disease, FXS, and ASD. There may be shared risk factors, biochemical processes, and treatment options amongst these diseases due to their similarities. These similarities should be emphasized in future investigative research to fully utilize findings for the greatest clinical gain.

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