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Impact of acamprosate on plasma amyloid-β precursor protein in youth: A pilot analysis in fragile X syndrome-associated and idiopathic autism spectrum disorder suggests a pharmacodynamic protein marker

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ABSTRACT

Background: Understanding of the pathophysiology of autism spectrum disorder (ASD) remains limited. Brain overgrowth has been hypothesized to be associated with the development of ASD. A derivative of amyloid-β precursor protein (APP), secreted APPα (sAPPα), has neuroproliferative effects and has been shown to be elevated in the plasma of persons with ASD compared to control subjects. Reduction in sAPPα holds promise as a novel molecular target of treatment in ASD. Research into the neurochemistry of ASD has repeatedly implicated excessive glutamatergic and deficient GABAergic neurotransmission in the disorder. With this in mind, acamprosate, a novel modulator of glutamate and GABA function, has been studied in ASD. No data is available on the impact of glutamate or GABA modulation on sAPPα function.

Methods: Plasma APP derivative levels pre- and post-treatment with acamprosate were determined in two pilot studies involving youth with idiopathic and fragile X syndrome (FXS)-associated ASD. We additionally compared baseline APP derivative levels between youth with FXS-associated or idiopathic ASD.

Results: Acamprosate use was associated with a significant reduction in plasma sAPP(total) and sAPPα levels but no change occurred in Aβ40 or Aβ42 levels in 15 youth with ASD (mean age: 11.1 years). Youth with FXS-associated ASD ($n = 12$) showed increased sAPPα processing compared to age-, gender- and IQ-match youth with idiopathic ASD ($n = 11$).

Conclusions: Plasma APP derivative analysis holds promise as a potential biomarker for use in ASD targeted treatment. Reduction in sAPP (total) and sAPPα may be a novel pharmacodynamic property of acamprosate. Future study is required to address limitations of the current study to determine if baseline APP derivative analysis may predict subgroups of persons with idiopathic or FXS-associated ASD who may respond best to acamprosate or to potentially other modulators of glutamate and/or GABA neurotransmission.

1. Introduction

Autistic disorder (autism) is a childhood-onset neurodevelopmental disorder characterized by social skills and communication deficits combined with interfering repetitive behavior. Autism is the classic type of pervasive developmental disorder (American_Psychiatric_Association, 2000), now termed autism spectrum disorder (ASD) (American_Psychiatric_Association, 2013). Despite many recent efforts focused on identifying factors

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contributing to the development of ASD, more than 75% of cases of ASD remain idiopathic (McGrew et al., 2012).

Among biological factors associated with ASD, macrocephaly is a consistently replicated finding affecting up to 20% of children with autism (Aylward et al. 1999, 2002; Davidovitch et al., 1996; McCaffery and Deutsch, 2005). Brain magnetic resonance imagery (MRI) studies in ASD have noted abnormal total brain volume enlargement in infants and toddlers (Courchesne et al. 2001, 2003; Courchesne and Pierce, 2005; Sparks et al., 2002). Furthermore, early brain enlargement marked by increased surface area overgrowth seen in youth with autism may be associated with a disruption in cell adhesion (Hazlett et al., 2011). Among factors contributing to the brain overgrowth theory of ASD pathophysiology, the potential contribution of dysregulation in amyloid-β precursor protein (APP) metabolism has been proposed (Lahiri et al., 2013; Ray et al., 2011; Sokol et al., 2006, 2011). APP has been associated with Alzheimer's disease (AD) where the amyloidgenic pathway of APP processing favors cleavage of APP by β-site APP cleaving enzyme or β-secretase (BACE1) resulting in neurotoxic amyloid-β (Aβ) peptides consisting 40 and 42 amino acids residues (Lahiri et al., 2003). Aβ40 and Aβ42 are the major components of senile plaques associated with brain atrophy in AD. BACE1, which plays a rate-limiting role in the production of potentially toxic Aβ within brain, is an important drug target for AD, and indeed, several BACE1 inhibitors are tested in clinical drug trials (Lahiri et al., 2014).

APP is predominantly located at the synapse (Mattson and Furukawa, 1998), produced in brain microglia, astrocytes, oligodendrocytes, and neurons (Mullan and Crawford, 1993), and released in an activity driven fashion (Jolly-Tornetta et al., 1998). Activation of metabotropic glutamate receptor type 1 and type 5 (mGluR1/5) increases APP secretion in cell culture (Jolly-Tornetta et al., 1998). The highest levels of APP occur early in synaptogenesis (Priller et al., 2006) and peak before 1 month of age in rodents (Lahiri et al., 2002). APP has been implicated in neurite outgrowth (Mattson and Furukawa, 1998; Mullan and Crawford, 1993) and promotes growth cone development working in opposition to (N-methyl-D-aspartate) NMDA and (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) AMPA glutamate receptors' pruning effects on growth cones (Mattson and Furukawa, 1998). As shown in cell culture studies, APP may block and reverse glutamatergic inhibition of dendrite outgrowth (Mattson, 1994). APP has been linked to suppression of neuronal cell adhesion (Schubert et al., 1989) and overexpression of APP accelerates migration of neuronal precursor cells into the cortex (Young-Pearse et al., 2007). The non-amyloidgenic APP processing pathway involving cleavage by the α-secretase family of enzymes (such as ADAM 9, 10 and 17) is the predominant APP processing pathway leading to release of non-amyloidgenic secreted APPα (sAPPα) (Mattson, 1994; Ray et al., 2011). Several reports have noted neurotrophic effects of sAPPα, including activity in inducing cellular proliferation including the proliferation of neural progenitor cells (Mattson, 1997; Stein and Johnson, 2003; Turner et al., 2003). Notably, sAPPα also activates microglia (Barger and Harmon, 1997). Overall, APP and specifically sAPPα are prime candidates to contribute to synaptic disruption and brain overgrowth in ASD given the proteins' enhancement of neural proliferation. APP modulation and Aβ have been shown to be a target of several drugs, including cholinesterase inhibitors and a partial NMDA receptor antagonist (memantine) (Alley et al., 2010; Greig et al., 2005; Lahiri et al. 1994, 1998).

There have been several reports on abnormalities in secreted APP and specifically sAPPα in the blood of youth with autism (Bailey et al., 2008; Ray et al., 2011; Sokol et al., 2006). Higher levels of plasma sAPP total and sAPPα were identified in a small sample of young children with autism and aggressive behavior compared to less impaired youth with autism without aggressive behavior and control subjects (Sokol et al., 2006). In a follow-up report involving 16 youth with autism and 18 control subjects, a similar increase in sAPPα was found in children with severe autism compared to youth with milder cases of autism and neurotypical control subjects (Ray et al., 2011). In the same study, reduced levels of Aβ40 and Aβ42 were detected in the youth with severe autism compared to control subjects. In a study involving 25 youth with autism aged 2–5 years and matched control subjects mean plasma sAPPα was significantly elevated in those with autism; 60% of those with autism had elevations in sAPPα (Bailey et al., 2008). Considering these results together, elevation in plasma sAPP (total) and specifically sAPPα could be a marker of molecular dysregulation contributing to the pathophysiology of autism.

Alterations in brain APP have also been reported in idiopathic ASD. Wegiel et al. (2012) have shown abnormal intracellular accumulation and extracellular Aβ deposition in the brain of persons with ASD. APP expression in brain has been demonstrated to be altered dependent on subject age and brain region in postmortem ASD specimens (Fatemi et al., 2013).

Monogenetic disorders associated with co-morbid ASD hold promise to provide insight in to the pathophysiology of idiopathic autism. Fragile X syndrome (FXS) is the most common single gene cause of ASD, responsible for approximately 3% of autism cases (Kosinovsky et al., 2005). The prevalence rate of ASD in FXS is estimated between 25% and 50%, depending on the criteria utilized (Clifford et al., 2007; Garcia-Nonell et al., 2008; Hatton et al., 2006; Kaufmann et al., 2004). FXS results from a CGG triplet repeat expansion in the promoter region of the Fragile X Mental Retardation gene (FMR1) on the long arm of the X chromosome. This expansion leads to gene methylation and silencing and subsequent deficiency in Fragile X Mental Retardation Protein (FMRP) production. FMRP is a known repressor of neuronal mRNA translation (Darnell et al., 2011; Lee et al., 2010; Veneri et al., 2004; Zalfa et al., 2003; Zou et al., 2008) and thus is important to synaptic plasticity and regulation of local protein synthesis at the synapse (Bagni and Greenough, 2005). Similar to reports in idiopathic ASD, children with FXS also exhibit early brain overgrowth (Hazlett et al., 2012). Additionally, FMRP has been demonstrated to regulate APP mRNA expression (De Rubeis and Bagni, 2010; Westmark and Malter, 2007). Specifically, FMRP mediates mGluR5-dependent translation of APP mRNA. In normal brain development, activation of mGluR5 neuroreceptors results in suppression of FMRP translational repression of APP, a phenomenon absent in FXS (Westmark and Malter, 2007). Baseline APP levels are elevated in *Fmr1* knockout (KO) mouse synaptoneurosomes and primary neurons, and APP levels do not increase following mGluR5 stimulation (Westmark and Malter, 2007). A preliminary study reported a relative elevation of sAPPα, Aβ40, and Aβ42 in 18 youth with FXS compared to age-matched control subjects (Lahiri et al., 2011). Additionally, Westmark et al. (2011) have demonstrated abnormal levels of Aβ42 in the plasma of persons with FXS. Findings from FXS point to enhanced translation of APP compared to potential specific enhancement of the sAPPα synthesis pathway noted in idiopathic ASD. Together, these data from monogenetic and idiopathic ASD converge to support the role of APP dysregulation, specifically excessive levels of sAPPα, in the pathophysiology of ASD. Given this, it is important to explore elevated sAPPα expression as a target of treatment in ASD. Conceptually, the three proteins APP, FMRP, and mGluR5 are proposed to serve as molecular links for ASD, AD, and FXS, and consequently any disruption in interaction of this “trinity” could lead to the disease phenotype (Lahiri et al., 2013). It may be that analyses of APP metabolites and APP processing enzymes hold promise as a target of treatment, pharmacodynamic marker of target engagement, and as a