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High Protein Kinase B (Akt) Concentration in Attention Deficit Hyperactivity Disorder

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is characterized by inattentiveness, hyperactivity, and impulsivity. It has been suggested that the mTOR pathway, which downstream includes activation of Akt, is involved in ADHD. In this study we measured the concentration of phosphorylated Akt in 55 ADD patients and 32 neurotypical controls using an ELISA. We found that Akt levels were significantly higher in the ADD group and may be important to the etiology of ADD/ADHD.

Introduction

Attention-deficit hyperactivity disorder (ADHD) is one of the most common psychiatric neurodevelopmental disorders in children and adolescents. It is characterized by inattentiveness, hyperactivity, and impulsivity (1). It is often accompanied by other disorders such as autism spectrum disorder (ASD) (2).

Attention deficit disorder (ADD) is a term that is sometimes used for attention deficit presentation of Attention Deficit Hyperactivity Disorder (ADHD). In the Diagnostic and Statistical Manual of Mental Didorders, Fifth Edition (DSM-5), this condition is officially known as "attentional deficit/ hyperactivity disorder, predominantly inattentive presentation (1).

It has been suggested that the mTOR pathway, which downstream includes activation of Akt, is involved in ADHD (3). As an example ,psychological stress during pregnancy has been linked to ADHD (4), Maternal stress, such as that associated with anxiety, depression and trauma may be associated with increased cortisol levels (5). An increase in glucocorticoids has been shown to downregulate the PI3K/Akt-signaling pathway (6). This may, in turn be associated with dysregulation of Akt in ADHD children.

The mTOR/Akt pathway has been associated with the schizophrenia (7) and ASD (8,9).

In this study we measured the concentration of phosphorylated Akt in 55 ADD patients and 32 neurotypical controls using an ELISA.

Materials and Methods

Subjects

Cellular phosphorylated Akt and CREB concentra-

tion was measured in 55 Attention Deficit Disorder children and 32 age and gender similar neurotypical, controls the diagnostic criteria used in this study were defined by DSM-IV criteria.

Plasma and white blood cells from consecutive individuals were obtained from patients presenting at the Health Research Institute (HRI)* over a two-year period. All ADD individuals who presented to HRI were asked to participate, and patients who participated in this study were randomly chosen from all patients who volunteered. Neurotypical control plasma was obtained from HRI and the Autism Genetic Resource Exchange (AGRE)** and randomly chosen from a selection of about 200 samples.

Patient consent was obtained from all patients involved in this study and this study was approved by the IRB of the HRI.

ELISA's to measure cellular Akt and CREB (RayBiotech, Inc)) wasmpreviously described (9)

Buffy coat white blood cells

All experimental and control cells were separated from whole blood using centrifugation and were treated in an identical fashion- refrigerated (4C) immediately after collection and cell/serum separation. Frozen buffy coat was placed at -70C and used for ELISAs within 6 months of retrieval.

Serum/plasma

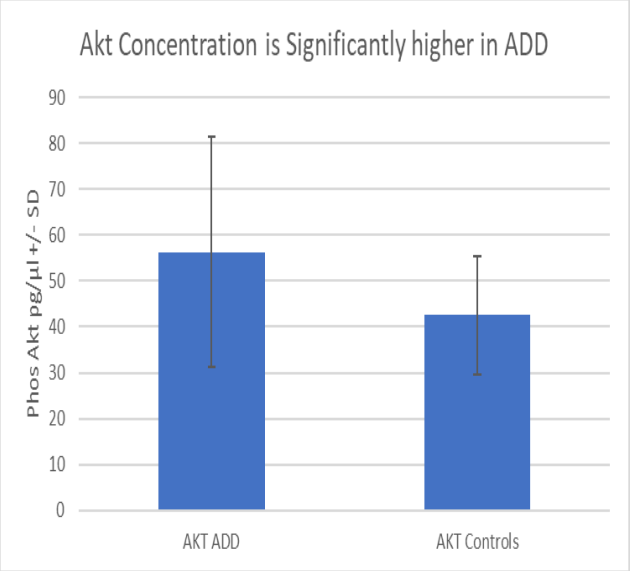
All experimental and control plasmas were treated in an identical fashion-refrigerated (4C) immediately after collection and cell/serum separation, then used to measure Akt.

Statistics

Inferential statistics were derived from t-test with 95% confidence intervals.

Results

In this study we measured the concentration of phosphorylated Akt in 55 ADD patients and 32 neurotypical controls. We found that Akt levels were significantly higher in the ADD group (p=0.0018).



Discussion

We previously reported that Akt levels are lower in autistic children (9,10) This data shows that Akt levels are higher in ADD individuals. Akt levels, therefore. may be an etiological factor that distinguishes ASD from ADD.

Akt phosphorylation has been associated with the etiology of autism, but to our knowledge not much is known about its relationship to inattentive ADHD (ADD). High functioning adult ASD individuals have lower levels of Epidermal Growth Factor (EGF) (11). Our lab has also found reduced EGF in children with ASD (12). These low plasma levels negatively correlate with the severity of hyperactivity, the deficit in gross motor skills, and the tendency for tip toeing (12). In addition, we

found that patients with ASD show decreased phosphorylated protein kinase B (Akt) associated with high epidermal growth factor receptor (EGFR) and low gamma-aminobutyric acid (GABA) (13) In an animal model of autism, high Akt phosphorylation has been found in prenatal exposure to valproate (14) where animals show abnormal growth of brain regions like what is seen in ASD. This data supports the notion that EGFR/ AKT pathway may play an important role in the pathophysiology of ASD. Our data suggests that it may also be important to the etiology of ADD/ ADHD.

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