

CREB and AKT Levels Higher in Attention Deficit Disorder (ADD) Individuals

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ABSTRACT

Attention-deficit hyperactivity disorder (ADHD) is a common psychiatric neurodevelopmental disorder in children and adolescents. CREB (cAMP response element-binding protein) is a cellular transcription factor, which plays a role in neuronal plasticity and long-term memory formation in the brain. Protein kinase B (PKB), also known as Akt, is the collective name of a set of three serine/threonine-specific protein kinases that play key roles in multiple cellular processes. In this study we used ELISAs to measure CREB and Akt levels in patients with ADD and found CREB levels to be significantly higher in the ADD group and the levels in individuals correlate significantly with significantly higher AKT levels we found in the same patients in a previous study.

Keywords

Attention-deficit hyperactivity disorder, Autism spectrum disorder, Attention deficit disorder.

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 Disorders, Fifth Edition (DSM-5), this condition is officially known as "attentional deficit/hyperactivity disorder, predominantly inattentive presentation" [1]. CREB (cAMP response element-binding protein) is a cellular transcription factor which plays a role in neuronal plasticity and long-term memory formation in the brain [3,4].

Protein kinase B (PKB), also known as Akt, is the collective name of a set of three serine/threonine-specific protein kinases that play key roles in multiple cellular processes such as glucose metabolism, apoptosis, cell proliferation, transcription, and cell migration [5,6].

In this study we used ELISAs to measure CREB and Akt levels in patients with ADD and found CREB levels to be significantly higher in the ADD group and the levels in individuals correlate significantly with significantly higher Akt levels we found in the same patients in a previous study. This suggests that Akt and CREB pathway may be involved in the etiology of ADD.

Materials and Methods

Subjects

Cellular phosphorylated Akt and CREB concentration 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.

ELISAs

ELISA's to measure cellular Akt and CREB (RayBiotech, Inc)) was previously described [7].

Cells and serum

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 a previous study we measured the concentration of phosphorylated Akt in 55 ADD patients and 32 neurotypical controls. We previously found that Akt levels were significantly higher in the ADD group ($p=0.0018$) [8]. In this study we measured CREB levels in the same ADD and control individuals and found that CREB levels were also significantly higher than in controls ($p=0.001$) (Figure 1), and the CREB levels correlated significantly with Akt levels (Figure 2).

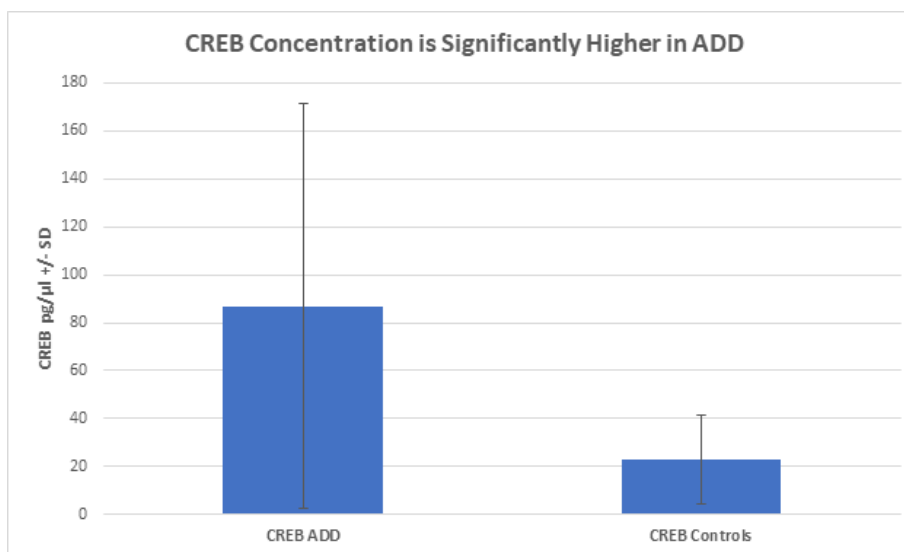


Figure 1: CREB levels are significantly higher in individuals with ADD ($p<0.001$).

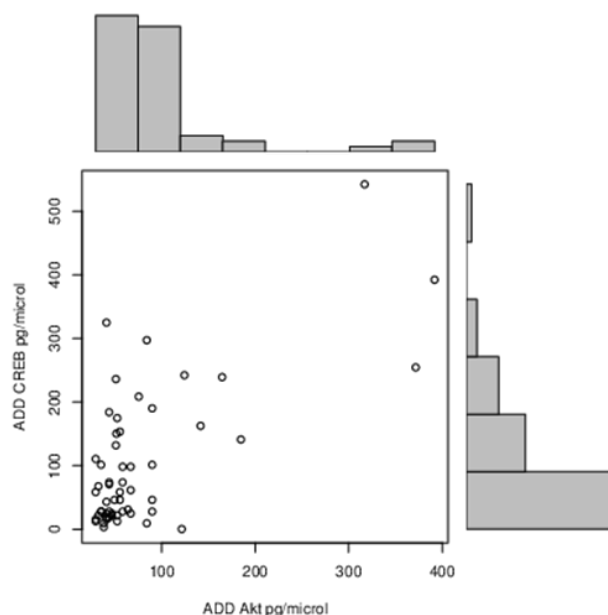


Figure 2: There is a significant positive correlation between the CREB and Akt levels in these ADD patients ($r=0.67$; $p= 0.0000000897$).

Discussion

Recently we reported that CREB and Akt levels were decreased in individuals with autism [9]. The fact that CREB and Akt levels are higher in ADD individuals suggests that their markers may play a role in the factors associated with the difference between the disorders. There is some evidence to suggest that low-functioning CREB is associated with major depressive disorder [10]. For instance, depressed rats, with an over expression of CREB in the dentate gyrus, behaved similarly to rats treated with antidepressants. Also, cortices of patients with untreated major depressive disorder contain reduced concentrations of CREB compared to both healthy controls and patients treated with antidepressants [11].

A review of studies in community samples has reported that the rate of MDD in youths with ADHD is 5.5 times higher than in youths without ADHD, with rates ranging from 12% to 50% [12]. Co-morbid depression in youths with ADHD occurs in clinical samples at even higher rates than in community samples [13,14]. Abnormal levels of CREB and Akt in ADD patients may therefore be associated with depression in these individuals.

This depression may have devastating effects on these patients. Depression or ADHD occurring alone in childhood is associated with substantial long-term impairment, morbidity, and an increased risk of suicide [15,16]. Lithium treatment for behavior modification in mood disorders may be associated with altering CREB levels. Chronic treatment with lithium significantly decreased CRE/CREB-directed gene expression in hippocampus, cortex, hypothalamus, and striatum to 60–70%, and likewise reduced CREB phosphorylation [17].

Curcuma longa is a major constituent of the traditional Chinese Xiaoyao-san, which has been used to effectively manage stress and depression-related disorders in China. Curcumin is the active component of curcuma longa, and its antidepressant effects have been described. These effects may be associated with its lowering of pCREB [18].

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