Pituitary adenylate cyclase-activating polypeptide (PACAP) is a 38 amino acid neuropeptide highly conserved in mammals that stimulates cAMP formation in anterior pituitary cells. PACAP and the specific type 1 receptor (PAC1) mRNA are expressed at highest levels in extra-hypothalamic regions in cerebral cortex, hippocampus, thalamus, striatum, nucleus accumbens, substantia nigra, locus ceruleus, and pineal gland (Vaudry et al. 2009). PACAP is known to be neuroprotective and neurotropic (Vaudry et al. 2009). It also plays a central role in stress responses including the sympathoadrenomedullary and hypothalamic-pituitary-adrenal systems.

In animal studies, PACAP knockout mice (PACAP KO) exhibited depressive-like behavior (Hashimoto et al., 2009). In a community-based study in Japan, a single nucleotide polymorphism (SNP) in the intronic region of the PAC1 gene (rs1893154) was associated with MDD in adults. In a recent study, CC homozygotes of the PAC1 gene with the polymorphism rs267735 SNP were associated with increased PTSD symptoms in females (Ressler et al., 2011).

Extending from these studies, we hypothesized that childhood trauma and female gender would be associated with increased anxiety and depressive symptoms in adolescents homozygous for the C allele of SNP rs267735 in the PAC1 gene.

METHODS
Assessments: 332 adolescents (Male: Female – 159:163, White: Nonwhite Others – 99:186.46, Age 12-15 years) were recruited for a study assessing the development of depressive disorders and alcohol use disorders in adolescents.

In the initial visit, adolescents free of lifetime psychiatric disorders, completed the Mood and Feelings Questionnaire (MFQ), Childhood Trauma Questionnaire (CTQ) and Self-Report for Childhood Anxiety-Rated Disorders (SCARED) and provided blood samples for DNA extraction at baseline. Subjects were interviewed with K-10ADS.

Genotypes: rs267735 SNP located within the intron region of PAC1 (rs1893154) and tested for C and G alleles from DNA isolated from blood using real time PCR. Multivariate analysis of variance with MFQ score and SCARED score as the dependent variable with genotype, gender and childhood trauma as fixed factors and age as a covariate.

Statistical analysis: Multivariate analysis of variance with total MFQ and SCARED scores as the dependent variables with genotype, gender and childhood trauma (median split score) and additional covariates of age as fixed factors. Significance was set at p ≤ 0.05.

RESULTS

Genotype Frequencies

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC</td>
<td>0.5</td>
</tr>
<tr>
<td>CG</td>
<td>0.2</td>
</tr>
<tr>
<td>GG</td>
<td>0.3</td>
</tr>
</tbody>
</table>

In animal studies, PACAP knockout mice (PACAP KO) exhibited depressive-like behavior (Hashimoto et al., 2009). In a community-based study in Japan, a single nucleotide polymorphism (SNP) in the intronic region of the PAC1 gene (rs1893154) was associated with MDD in adults. In a recent study, CC homozygotes of the PAC1 gene with the polymorphism rs267735 SNP were associated with increased PTSD symptoms in females (Ressler et al., 2011).

Extending from these studies, we hypothesized that childhood trauma and female gender would be associated with increased anxiety and depressive symptoms in adolescents homozygous for the C allele of SNP rs267735 in the PAC1 gene.

In our study, there was a differential effect of CC and GG genotypes on anxiety and depressive symptoms of males and females. Additional analysis revealed that GG homozygotes with increased trauma had increased anxiety symptoms (F1,30 = 3.1, p ≤ 0.01) and depressive symptoms (F1,30 = 5.9, p ≤ 0.02) in males but not females.

DISCUSSION
Consistent with prior research, the PACAP-PAC1 signaling system appears to be involved in the early expression of anxiety and depressive symptoms during adolescence particularly among females with high levels of childhood stress – albeit mild.

Our results extend the findings of Ressler et al. (2011) to establish a gene-environment interaction for anxiety and depressive symptoms specific for adolescent females moderated by the PAC1 gene.

In our study, there was a differential effect of CC and GG genotypes on anxiety and depressive symptoms of males and females. Further studies by our group are underway to elucidate the neurobiological and signaling pathways underlying the PAC1 gene and its role in the future development of anxiety and depressive disorders during adolescence.

REFERENCES


CONTACT

Suman Baddam
Email: Suman.Baddam@uthscsa.edu

FUNDING

UTHealth San Antonio Office of Research;
National Institute on Alcohol Abuse and Alcoholism (NIAAA) Grant #R01AA023265;
National Institute on Drug Abuse (NIDA) Grant #R01DA007530;
Department of Veterans Affairs (VA) Merit Review Grant #I01I0109079;
National Institute on Drug Abuse (NIDA) Grant #R01DA041785;
National Institute on Drug Abuse (NIDA) Grant #R01DA041785-05;
National Institute on Drug Abuse (NIDA) Grant #R01DA041785-06;
Satterwhite Endowment;
Texas Veterans Commission Grant #10-1502.

CONFLICTS OF INTEREST

Suman Baddam: No conflicts; Rene Olvera: Research Support; Carolina Livi: No conflicts; Douglas Williamson: No conflicts.

ADDITIONAL INFORMATION

Adolescent Onset Alcohol Use Disorder - Williamson