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Exploring the Association Between a Cholecystokinin Promoter Polymorphism (rs1799923) and Posttraumatic Stress Disorder in Combat Veterans

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Abstract

Background: Cholecystokinin (CCK) is a neuropeptide that has been implicated in understanding the acquisition and extinction of fear. Research on CCK in anxiety has primarily focused on understanding panic attacks and panic disorder. Emerging data suggests that CCK may also hold promise in understanding the development and maintenance of posttraumatic stress disorder (PTSD).

Method: The present study examined whether a single nucleotide polymorphism in the promoter region of the CCK gene (C>T; rs1799923) was associated with an increased prevalence of PTSD as well as with severity of PTSD symptoms among a sample of 457 combat veterans.

Results: Results demonstrated that participants with either the heterozygous or homozygous T allele had an increased prevalence of PTSD relative to participants with the CC genotype (OR = 2.17; 95% CI [1.37 – 3.43]).

Limitations: The relatively small sample size precluded examination of racial/ethnic differences. Findings were also limited by the absence of a systematic assessment of comorbid anxiety psychopathology.

Conclusions: These data offer preliminary evidence supporting an association between the rs1799923 polymorphism in the CCK gene and PTSD. Additional research is needed to better understand the nature of this relationship.

Keywords

Cholecystokinin; CCK; Posttraumatic Stress; PTSD; Anxiety

Following exposure to a traumatic event, a significant percentage of individuals will develop posttraumatic stress disorder (PTSD). This condition is characterized by a pattern of symptoms including recurrent and intrusive memories of traumatic events, avoidance of cues associated with the trauma, emotional numbing, and hyperarousal. Epidemiological

estimates suggest that the lifetime prevalence of PTSD in the general population is approximately 7-8% (Kessler et al., 1995, 2005). However, the prevalence is higher among individuals exposed to certain types of traumatic events including military combat. Prevalence estimates of PTSD are as high as 30% among Vietnam era veterans (Kulka et al., 1990), with lower estimates of 11.1% and 13.8% emerging for veterans serving in the Gulf War and Operations Enduring Freedom/Iraqi Freedom; respectively (Kang et al., 2003; Tanielian and Jaycox, 2008). Symptoms of PTSD have been linked to significant impairment and disability among veteran samples (Magruder et al., 2004; Schnurr, Lunney, Bovin, & Marx, 2009; Zatzick et al., 1997).

Research suggests that genetic variation accounts for an estimated 30% (True et al., 1993; Stein et al., 2002) to 73% (Sartor et al., 2011) of vulnerability to PTSD. Although genetic influences on PTSD are likely polygenic (Pitman et al., 2012), candidate gene studies examining different classes of genes, including those involved in HPA-axis regulation, the locus coeruleus-noradrenergic system, neurotrophins, and the dopaminergic and 5-HT systems offer significant contributions to understanding PTSD risk (for reviews see Cornelis, Nugent, Amstadter, & Koenen, 2010; Pitman et al., 2012). For example, single nucleotide polymorphisms and variable number tandem repeat polymorphisms of the dopamine receptors *DRD2*, *DRD2*, *DRD4*, and the dopamine transporter *SLC6A3* have been shown to correlate with a higher prevalence of PTSD (Comings et al., 1996; Segman et al., 2002; Young et al., 2002; Dragan & Oniszczenko, 2009; Voisey et al., 2009; Valente et al., 2011). Furthermore, different single nucleotide polymorphisms, along with variable number tandem repeat polymorphisms in the serotonin transporter gene *SLC6A4* (also known as *SERT*, *HTT*, *5-HTT* and *5-HTTLPR*) have been associated with an increased prevalence of PTSD in both civilian and veteran populations (see Cornelis et al., 2010 for a review).

Cholecystokinin (CCK) may also offer promise in understanding the contribution of genetics to PTSD. CCK is a common neuropeptide hormone present in a variety of forms (e.g. CCK-58, CCK-39, CCK-33, CCK-22, and CCK-8) that is derived from a 115-amino acid precursor molecule (Dockray, 1978; Deschenes et al., 1984; Harro, 2006). As one of the most abundant neuropeptides in the brain (Crawley, 1985; Moran & Schwartz, 1994), CCK performs important regulatory functions in both cortical and limbic areas (Beinfeld & Palkovits, 1982; Beinfeld et al., 1981) including in the amygdala (Beinfeld, 2001; Sherrin et al., 2009). The role of CCK in anxiety is well established (Bradwejn et al., 1992; Harro, Vasar, & Bradwejn, 1993; Rotzinger & Vaccarino, 2003), and biological challenge paradigms utilize the panicogenic effects of exogenous cholecystokinin tetrapeptide (CCK-4; the bioactive C-terminus of CCK peptides) to study processes underlying acute anxiety and panic within the laboratory (Rehfeld, 1992; DeMotigny, 1989, Rehfeld, 2000). Infusions of CCK-4 have been shown to reliably induce panic attacks among individuals with panic disorder (Bradwejn, Koszycki, & Meterissian, 1990; Bradwejn, Koszycki, & Shriqui, 1991; Shlik et al., 1997) and PTSD (Kellner et al., 1998, 2000), as well as among non-clinical participants (Eser et al., 2009; Tőro et al., 2010). It appears that relative to healthy controls, those with panic disorder (Bradwejn et al., 1991) and PTSD (Kellner et al., 2000) are significantly more sensitive to the panicogenic effects of CCK-4.

Despite well-established links between CCK and anxiety/panicogenesis, there is a relative dearth of research examining how CCK might be implicated in PTSD specifically. Early evidence from animal models found that a blockade of CCK_B receptors interfered with the development of anxiety-like behaviors following exposure to predator stress (Adamec et al., 1997). In the first human case study, Kellner and colleagues (1998) reported the induction of trauma-related flashbacks following a CCK-4 infusion in a male patient with PTSD. Although a study with eight PTSD patients failed to replicate the induction of flashbacks (Kellner et al., 2000), these authors found that as compared to healthy controls, patients with PTSD reported increased panic and anxiety symptoms, lower ACTH response (despite comparable baseline levels), and a faster decrease in stimulated cortisol following an infusion of CCK-4. Panic symptoms induced by CCK-4 were inversely related to dissociation among the patients with PTSD.

To our knowledge, there has been no investigation of potential links between polymorphisms of the CCK gene and PTSD. A polymorphism in the promoter region of the CCK gene (rs1799923) that disrupts a putative SP-1 transcription factor-binding site (GGGCGG; Kadonaga, Jones, & Tjian, 1986; Nielsen et al., 1996) has been linked to an increased prevalence of panic attacks and panic disorder (Maron et al., 2005; Wang et al., 1998), although other studies have failed to replicate this finding (Hamilton et al., 2001; Hösing et al., 2004; Koefoed et al., 2010; Wilson, Markie, & Fitches, 2012). Given that CCK is implicated in the etiology of both panic and PTSD, but inconsistent findings have emerged regarding the polymorphism rs1799923 in panic, the present study sought to examine whether this particular polymorphism was associated with an increased prevalence of PTSD among a sample of combat veterans.

Method

Participants

A total of 457 combat veterans were enrolled in this study. Of these, 65.2% ($n = 298$) met criteria for PTSD. The majority of participants were male (82.3%), and Caucasian (69.1%). Demographics and genotypes for the whole sample as well as for those diagnosed with PTSD versus control participants are presented in Tables 1-2. All participants were recruited through Veterans Affairs (VA) Medical Centers in Cincinnati, OH ($n = 188$) or Charleston, SC ($n = 269$). To be eligible for this study, participating veterans were required to have a history of combat exposure, as evidenced by a DD214, and report a history of combat exposure during the interview with a psychiatrist. Part way through the study an additional self-report measure was implemented to measure severity of combat exposure (Combat Exposure Scale [CES; Lund, Foy, Sippelle, & Strachan, 1984]) and therefore, for a subset of participants ($n = 420$ of the total 457) information on this measure was available.

For those with PTSD, 62.4% ($n = 186$) met criteria for comorbid major depressive disorder and 35.0% ($n = 100$) met criteria for a past substance use disorder. Individuals with a history of substance abuse and dependence were included if the last use of the substance was over 6 months prior to the enrollment. Participants with current or lifetime *DSM-IV* schizophrenia, other psychotic disorders, bipolar disorder, and active substance abuse or dependence in the

past six months were excluded. Control participants were free of Axis I psychiatric disorders.

Procedure

The Institutional Review Boards (IRB) of both the University of Cincinnati and Medical University of South Carolina approved the research protocol. Participants were recruited using similar methods at the two sites. A trained research assistant provided an overview of the brief description and voluntary nature of this study, and interested participants were screened to determine eligibility. Written informed consent was obtained from all of the participants before the formal interview. After collecting the demographic and deployment information, a board-certified psychiatrist (ZW) conducted a clinical interview with participants to obtain information regarding combat exposure history and PTSD status, as well as other major Axis I DSM-IV diagnoses that would be exclusionary (see inclusion/exclusion section above). Therefore, full diagnostic level data and demographic data are available for all 457 participants. All participants provided a peripheral blood sample via standard methods for isolation of genomic material.

A subsample of 420 participants completed the *Combat Exposure Scale (CES)* (Lund et al., 1984), a 7-item self-report measure, used to obtain information regarding exposure to wartime stressor events. The measure has total scores ranging from 1 to 41, with a higher number reflecting a higher severity of combat exposure.

Laboratory procedure.—Genomic DNA was extracted from peripheral blood using a Wizard Genomic DNA purification kit (Promega, Madison, WI) following the manufacturer's protocol. The CCK promoter polymorphism rs1799923 was investigated using a TaqMan probe-based single nucleotide polymorphism genotyping assay (Applied Biosystems, Foster City, CA). The TaqMan reaction was performed in a final volume of 10 μ L consisting of 1 μ L of 20 ng/ μ L genomic DNA and 5.0 μ L of TaqMan reaction mix, 0.5 μ L of Applied Biosystems assay, and 3.5 μ L of water. The ABI StepOnePlus™ Real-Time PCR System (Applied Biosystems) was used to perform the thermal cycling. After a pre-PCR read at 60 °C 30s, amplification of a holding stage of 10 min at 95 °C, 50 cycles of denaturing at 92 °C (15s) and annealing/extending at 60 °C (90s) were performed, followed by a post-PCR read stage at 60 °C (30s). Genotypes were read using the ABI StepOne software v 2.2.

Data Analytic Plan

Calculations for deviation from the Hardy-Weinberg equilibrium were performed using the χ^2 test. Descriptive and symptom data were then examined as a function of CCK C>T genotype via χ^2 tests for categorical variables (or Fisher's exact test for cell sizes of less than five) or one-way analyses of variance (ANOVAs) for continuous variables. Bivariate associations between the PTSD diagnosis and demographic and genotype data were then conducted via χ^2 tests for categorical variables (or Fisher's exact test for cell sizes of less than five) and via independent samples *t*-tests for continuous variables.

For the main outcome analysis, we examined the relation between CCK C>T genotype and PTSD diagnosis via the χ^2 test. To test whether the associations between genotype and PTSD status remained significant after controlling for demographic factors, a logistic regression analysis was conducted. Race and gender were included as covariates in step 1. Race was entered as two dummy coded variables (i.e., African American, Other) with White coded as 0. Step 2 included a dichotomously coded genotype variable with the homozygous C allele coded as 0 and the CT or TT alleles coded as 1. The CT and TT genotypes were combined for this analysis given the small number of participants without PTSD who had a TT genotype. This same model was run with CES and data collection sites (Cincinnati VA, Charleston VA) included as additional covariates in Step 1.

Finally, as the CCK C>T genotype distribution differs by racial/ethnic status in the population (Sherry et al., 2001), we also ran the primary analyses in the subset of participants who were White. Given the small sample of participants reporting their race as African American or Other, cell sizes were too small to adequately power regression models within these racial groups.

Results

Descriptive Statistics

The observed genotype distribution of the CCK promoter polymorphism rs1799923 in veterans with ($\chi^2 = .11, p = .74$) and without ($\chi^2 = .67, p = .41$) PTSD did not differ significantly from the expected Hardy-Weinberg equilibrium. Prevalence of PTSD was higher among participants recruited from the Charleston VA (72.9%) as compared to those recruited from the Cincinnati VA (54.3%; $\chi^2 = .16.89, p < .001$). There were no differences in distribution of genotype as a function of recruitment site ($\chi^2 = .246, p = .30$). Of the total sample, 30.0% were genotyped as CT and 3.1% as TT (Table 1). Within our sample, White participants were more likely to have a CC genotype as compared to either CT or TT. In contrast, African American participants were more likely to be heterozygous or homozygous for the T allele. Prevalence of PTSD was lower among those with a CC genotype as compared to those who were either heterozygous or homozygous for a T allele. Genotype was not associated with differences in age, gender, severity of combat exposure, MDD diagnosis, or past SUD diagnosis. Participants with PTSD were more likely than those without PTSD to be male, African American, and to have a history of more severe combat exposure. Age did not differ between those with and without PTSD in the present sample.

Primary Hypothesis Tests

Table 3 provides an overview of the results for the primary analyses. Specifically, step 1 of the model was significant, [$X^2(3, N = 457) = 22.63, p < .001$; Nagelkerke $R^2 = .07$], with African American race, and male gender predicting increased likelihood of PTSD. The inclusion of genotype in step 2 of the model resulted in a significant increase in model chi-square, [$X^2(1, N = 457) = 11.45, p = .001$; Nagelkerke $R^2 = .10$]. Specifically, relative to individuals with the CC genotype, those with the homozygous or heterozygous T allele were estimated to be 2.17 times more likely to have PTSD. This model remained significant when

controlling for combat exposure and recruitment site [$B = .68$, $SE = .24$, Wald = 7.18, OR = 1.97, $p = .006$, 95% CI: [1.21, 3.19]].

Among the subsample of White participants, those with the homozygous or heterozygous T allele were 2.50 times more likely to meet criteria for a PTSD diagnosis [$B = .92$, $SE = .29$, Wald = 9.98, OR = 2.50, $p = .002$, 95% CI: [1.42, 4.40]] after accounting for gender. This analysis also remained significant when controlling for combat exposure and recruitment site [$B = .88$, $SE = .30$, Wald = 8.49, OR = 2.41, $p = .004$, 95% CI: [1.33, 4.36]].

Discussion

The neuropeptide cholecystokinin has been consistently implicated in anxiety and panicogenesis (Bradwejn et al., 1992; Harro et al., 1993; Rotzinger & Vaccarino, 2003). The present study examined whether the rs1799923 polymorphism in the promoter region of the CCK gene—a polymorphism previously linked to elevated prevalence of panic attacks and panic disorder (Maron et al., 2005; Wang et al., 1998)—is associated with a diagnosis of PTSD or PTSD symptom severity among combat veterans. As hypothesized, both the heterozygous and homozygous T alleles were associated with a significantly increased prevalence of PTSD, and this association remained significant even after accounting for variance in PTSD associated with gender, race, severity of combat exposure, and recruitment site.

Although preliminary, these data are the first to document an association between the rs1799923 polymorphism in the promoter region of the CCK gene and PTSD among combat veterans. These data are consistent with initial research demonstrating that an infusion of CCK-4 results in both panic-like symptoms and trauma-related intrusions among individuals with PTSD (Kellner et al., 1998, 2000). It is possible that this polymorphism confers specific risk for the development of PTSD following exposure to combat. However, given that the current study compared individuals with PTSD to healthy combat veterans, we are unable to rule out the possibility that the rs1799923 polymorphism is actually associated with anxiety more generally, as opposed to being PTSD-specific. This issue of specificity is particularly important to examine in future research, as PTSD is highly comorbid with other types of anxiety. Given this, it is possible that the effects found in this study are actually associated with elevated anxiety in the PTSD group compared to the control group that is not specific to the PTSD-related pathology. It is also possible that the particular single nucleotide polymorphism examined in the current study is not directly linked to anxiety, but is rather associated with one or more other variants that underlie the observed association.

Recombination occurs during meiosis, where regions of DNA are exchanged between chromosomes, and if two loci are sufficiently proximal to each other, they may be inherited together. Within this scenario, rs1799932 may be physically adjacent to a variant that confers risk for anxiety or PTSD, but the proximity between the two loci precludes any differentiation when utilizing a candidate SNP approach. It will thus be important for future studies to examine the link between the rs1799923 polymorphism and a range of anxiety disorders, as well as to examine associations with other variants that may confer risk for PTSD, in particular haplotypes that include the T allele of rs1799923 and other SNPs.

Emerging evidence does seem to support a role for CCK in fear acquisition as well as in inhibitory or extinction learning more generally, with recent data suggesting that the CCK neuropeptide pathway may work in coordination with other systems including endogenous cannabinoids to modulate fear extinction (Bowers, Choi, & Ressler, 2012). The specific mechanism through which the rs1799923 polymorphism may relate to anxiety is not entirely clear, although it has been proposed that this allele may decrease the transcription of the CCK gene, as the transcription is dependent on the coordinate activity of multiple transcription factors, including SP-1 (Nielsen et al., 1996). One study found that targeted disruption of the SP-1 transcription factor binding site (-36C>T) resulted in a two-fold reduction of SP-1 transcription factor binding in neuroblastoma cells, but there was no direct effect on CCK transcription (Hansen et al., 2000). Given this, additional research aimed at improving our understanding of the mechanisms underlying the link between the rs1799923 polymorphism and anxiety is needed.

Several limitations to this study warrant discussion. First, the relatively small sample size limited conclusions regarding associations between PTSD and the CCK rs1799923 polymorphism among minority individuals. It is possible that different patterns may emerge across racial/ethnic groups as a result of genotype stratification as well as differences in PTSD prevalence. While the ancestral informative markers were not available in our genotyping panel, we controlled for population stratification based on self-reported racial/ethnic status. We attempted to lessen this effect by covarying for self-reported race/ethnicity in all analyses and repeated the analyses in the subsample of White participants. While assessment of MDD and past SUD was considered a strength of this study because it allowed for an examination of whether the prevalence of the polymorphism differed among PTSD positive individuals with and without these comorbid conditions, participants were not assessed for panic disorder or other comorbid anxiety disorders that may also be associated with the CCK polymorphism. Participants were also recruited from a population of veterans seeking healthcare at one of two VA Medical Centers and diagnoses were established via standard clinical interview rather than via a structured or semi-structured interview. Replication of these findings among a representative community sample of veterans as well as among a civilian sample exposed to trauma using standardized instruments would be ideal as associations may not generalize to PTSD following other types of traumatic events. Moreover, given that the C>T genotype distribution does differ as a function of racial/ethnic status (Sherry et al., 2001), it will be important to replicate these findings among larger samples of minority individuals with and without PTSD. Finally, the present study examined associations between the CCK rs1799923 polymorphism and PTSD diagnostic status only. Future studies should examine associations with continuous measures of symptom severity including measures of individual clusters of PTSD symptoms.

These limitations notwithstanding, this study adds to a mounting body of literature documenting the importance of CCK in understanding anxiety and anxiety disorders. This was the first study to demonstrate a link between the rs1799923 polymorphism in the promoter region of the CCK gene and PTSD. This gene may have important implications for understanding the development and maintenance of fear acquisition and extinction in PTSD as well as in other anxiety disorders.

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Table 1:*Descriptive and Clinical Information as a Function of CCK rs1799923 C>T Allele*

	CC n = 306	CT n = 137	TT n = 14	χ^2 or F	p
Male	254 (83.0%)	113 (82.5%)	9 (64.3%)	Fisher's exact = 3.14	.21
Race				Fisher's exact = 24.51	<.001
White	232 (75.8%) ^a	79 (57.7%) ^b	5 (35.7%) ^b		
African American	57 (18.6%) ^a	45 (32.8%) ^b	9 (64.3%) ^b		
Other	17 (5.6%) ^a	13 (9.5%) ^a	0 (0.0%) ^a		
Age	44.11 (15.10)	44.27 (13.67)	49.36 (17.20)	F = .85	.43
PTSD	182 (59.5%) ^a	103 (75.2%) ^b	13 (92.9%) ^b	Fisher's exact = 15.51	<.001
MDD	117 (38.2%)	61 (44.5%)	8 (57.1%)	$\chi^2 = 3.17$.21
SUD	70 (22.9%)	29 (21.2%)	1 (7.1%)	Fisher's exact = 1.71	.43
CES	21.78 (8.16)	21.28 (7.89)	19.71 (8.99)	F = .54	.58

Note: Unique superscripts denote significant differences after correcting for multiple comparisons via the Bonferroni method; CES = Combat Exposure Scale; MDD = Major depressive disorder; PTSD = Posttraumatic stress disorder; SUD = Substance use disorder.

Table 2: Descriptive, Genotype, and Clinical Information as a Function of PTSD Diagnostic Status

	PTSD + <i>n</i> = 298 <i>n</i> (%) or <i>M</i> (<i>SD</i>)	PTSD – <i>n</i> = 159 <i>n</i> (%) or <i>M</i> (<i>SD</i>)	χ^2 or <i>t</i>	<i>p</i>
Male	254 (85.2%)	122 (76.7%)	$\chi^2 = 5.14$.02
Race			$\chi^2 = 17.22$	< .001
White	195 (65.4%) ^a	121 (76.1%) ^b		
African American	89 (29.9%) ^a	22 (13.8%) ^b		
Other	14 (4.7%) ^a	16 (10.1%) ^a		
Age	44.52 (14.75)	43.95 (14.78)	<i>t</i> = –.39	.70
Genotype			$\chi^2 = 18.97$	< .001
CC	182 (61.1%)	124 (78.0%)		
CT	103 (34.6%)	34 (21.4%)		
TT	13 (4.4%)	1 (0.6%)		
CES	22.45 (7.86)	19.90 (8.30)	<i>t</i> = –3.10	.002

Unique superscripts denote significant differences after correcting for multiple comparisons via the Bonferroni method; CES = Combat Exposure Scale; PTSD = Posttraumatic stress disorder.

Table 3:

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	<i>B</i>	<i>SE</i>	Wald	OR	95% CI
<i>Step 1</i>					
Race					
African American	.90	.27	11.47	2.46**	1.46 – 4.14
Other	-.65	.39	2.84	.52	.25 – 1.11
Gender	.55	.25	4.67	1.73*	1.05 – 2.85
<i>Step 2</i>					
Genotype	.77	.24	10.85	2.17**	1.37 – 3.43

Note:

* $p < .05$,** $p < .01$