Association Between Functional Polymorphism in Neuropeptide Y Gene Promoter rs16147 and Resilience to Traumatic Stress in US Military Veterans

To the Editor: Neuropeptide Y (NPY) is expressed in a number of brain regions and plays a key role in the regulation of fear, stress, anxiety, learning, and memory.[1] The functional single nucleotide polymorphism in the *NPY* gene promoter rs16147 accounts for more than half of the variation in the expression of plasma NPY,[2] and previous studies have found that *NPY* rs16147 genotype interacts with traumatic or stressful experiences to predict stress-related outcomes, with the T allele being protective under conditions of high stress.[3] To date, however, no known study has examined whether polymorphisms in this gene may be linked to resilience to traumatic stress.

Method. To address the research gap, we analyzed data from the National Health and Resilience in Veterans Study, which surveyed a nationally representative sample of 2,162 European American US military veterans from a survey panel of more than 50,000 US households maintained by GfK, Inc; 1,585 veterans were surveyed in 2011, and 557, in 2013.[4] Sample characteristics are shown in Table 1. *NPY* rs16147 genotype frequencies were as follows: C/C (n = 587; 27.2%), T/C (n = 1,095; 50.6%), and T/T (n = 480; 22.2%); they did not deviate from Hardy-Weinberg expectations ($\chi^2 = 0.51$, $P = .47$).

A univariate analysis of covariance (ANCOVA) and a multivariate ANCOVA (MANCOVA) were conducted to evaluate the relation between *NPY* rs16147 genotype, cumulative traumatic stress (ie, number of lifetime traumas assessed using the Trauma History Screen[5]; analyzed in quintiles due to positively skewed distribution), and the interaction of *NPY* rs16147 × cumulative traumatic stress in predicting both lifetime posttraumatic stress disorder (PTSD) symptoms (assessed using the PTSD Checklist for *DSM-IV*[6] in the 2011 sample and the PTSD Checklist for *DSM-5*[7] in the 2013 sample) and the 4 PTSD symptom clusters—intrusion symptoms, avoidance, alterations in negative cognitions and mood, and alterations in arousal and reactivity. Covariates are listed in the Table 2 footnote. The significance threshold was set to .05 in the ANCOVA, and to control for type I error in the MANCOVA, a Bonferroni correction was applied (0.00625 significance threshold for 8 main and interactive effects of NPY genotype).

Table 1. Sample Characteristics

Characteristic	Value	Range
Age, weighted mean (SD), y	62.7 (14.7)	21–93
Male sex, n (weighted %)	1,963 (92.2)	…
Combat veteran, n (weighted %)	758 (33.8)	…
No. of lifetime traumas, weighted mean (SD)	3.3 (2.6)	0–14
1st quintile (n = 259)	0 (0)	0–0
2nd quintile (n = 741)	1.5 (0.5)	1–2
3rd quintile (n = 325)	3.0 (0)	3–3
4th quintile (n = 443)	4.4 (0.5)	4–5
5th quintile (n = 386)	7.6 (1.7)	6–14
Index trauma, n (weighted %)		
Nonassaultive	1,733 (92.3)	…
Assaultive	157 (7.7)	…

Results. Results revealed a significant main effect of *NPY* rs16147 and *NPY* rs16147 × cumulative traumatic stress interaction in predicting overall severity of PTSD symptoms (Table 2). T allele carriers had lower severity and prevalence of PTSD (mean ± SD and prevalence for T/T homozygotes = 25.3 ± 0.8 and 3.1% [n = 17] vs 27.3 ± 0.7 and 6.7% [n = 64] in T/C heterozygotes vs 28.0 ± 0.8 and 7.2% [n = 17] in C/C homozygotes) and had lower severity and prevalence of PTSD under conditions of high (5th quintile) cumulative traumatic stress (mean and prevalence for T/T homozygotes = 29.9 ± 1.5 and 8.3% [n = 14] vs 35.8 ± 1.0 and 25.2% [n = 54] in T/C heterozygotes vs 37.8 ± 1.2 and 27.6% [n = 27] in C/C homozygotes).

Analyses of PTSD symptom clusters revealed a Bonferroni-corrected significant main effect of *NPY* rs16147 and *NPY* rs16147 × traumatic stress interaction in predicting reexperiencing/intrusive symptoms. None of the other effects were significant (Table 2).

Results of the current study suggest that the T allele of *NPY* promoter rs16147 is associated with resilience in the context of cumulative traumatic stress, particularly resilience to intrusion symptoms of PTSD. T allele carriers may be less physiologically reactive to trauma cues, because they produce greater levels of NPY during stress.[2] Greater NPY levels in plasma have been linked to lower stress reactivity,[1] which may in turn be linked to greater resilience to cumulative traumatic stress. Indeed, lower

Table 2. Results of Multivariable Analyses of Covariance Examining Association Between NPY rs16147 Genotype, Cumulative Traumatic Stress, and PTSD Symptoms[a]

	Total PTSD Symptoms		Intrusion Symptoms		Avoidance		Negative Alterations in Cognitions and Mood		Alterations in Arousal and Reactivity	
	F	*P*	*F*	*P*	*F*	*P*	*F*	*P*	*F*	*P*
NPY rs16147 T alleles	6.45	.002	12.02	<.0001	5.40	.005	2.72	.048	4.33	.013
Cumulative traumatic stress	78.93	<.0001	82.74	<.0001	43.40	<.0001	42.85	<.0001	71.56	<.0001
NPY rs16147 T alleles × cumulative traumatic stress	3.08	.005	4.94	<.0001	1.86	.084	2.26	.036	2.68	.014

[a]A univariate analysis of covariance was conducted to examine predictors of total PTSD symptoms; a multivariate analysis of covariance was conducted to examine predictors of PTSD symptom clusters. Results of both analyses are adjusted for age, sex, combat veteran status, nature of worst trauma (assaultive vs nonassaultive), and the 10 top principal components from genome-wide population stratification analyses. For main effect of *NPY* rs16147 T alleles, Cohen *d* effect size difference between T/T homozygotes and C/C homozygotes was 0.15 (95% confidence interval [CI], 0.02–0.27; $P = .000639$) and between T/T homozygotes and T/C heterozygotes was 0.10 (95% CI, 0.01–0.20; $P = .003039$). The difference between T/C heterozygotes and C/C homozygotes was not significant ($P = .322592$).

Abbreviations: NPY = neuropeptide Y, PTSD = posttraumatic stress disorder.

concentrations of cerebrospinal fluid NPY are associated with PTSD.[8] However, in light of prior studies showing heterogeneity in NPY expression with regard to NPY rs16147 genotype,[2,9] further research is needed to evaluate neurobiological mechanisms linking polymorphisms in the *NPY* promoter gene rs16147 to resilience and whether interventions designed to enhance NPY levels[1] may help promote stress resilience in trauma-affected populations.

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