Association of In Vivo κ-Opioid Receptor Availability and the Transdiagnostic Dimensional Expression of Trauma-Related Psychopathology

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**IMPORTANCE** Exposure to trauma increases the risk for developing threat (ie, fear) symptoms, such as reexperiencing and hyperarousal symptoms, and loss (ie, dysphoria) symptoms, such as emotional numbing and depressive symptoms. While preclinical data have implicated the activated dynorphin/κ-opioid receptor (KOR) system in relation to these symptoms, the role of the KOR system in mediating these phenotypes in humans is unknown. Elucidation of molecular targets implicated in threat and loss symptoms is important because it can help inform the development of novel, mechanism-based treatments for trauma-related psychopathology.

**OBJECTIVE** To use the newly developed \[^{11}C\]LY2795050 radiotracer and high-resolution positron emission tomography to evaluate the relation between in vivo KOR availability in an amygdala-anterior cingulate cortex-ventral striatal neural circuit and the severity of threat and loss symptoms. We additionally evaluated the role of 24-hour urinary cortisol levels in mediating this association.

**DESIGN, SETTING, AND PARTICIPANTS** This cross-sectional positron emission tomography study under resting conditions was conducted at an academic medical center. Thirty-five individuals representing a broad transdiagnostic and dimensional spectrum of trauma-related psychopathology, ranging from nontrauma-exposed psychiatrically healthy adults to trauma-exposed adults with severe trauma-related psychopathology (ie, posttraumatic stress disorder, major depressive disorder, and/or generalized anxiety disorder).

**MAIN OUTCOMES AND MEASURES** \[^{11}C\]LY2795050 volume of distribution values in amygdala-anterior cingulate cortex-ventral striatal neural circuit; composite measures of threat (ie, reexperiencing, avoidance, and hyperarousal symptoms) and loss (ie, emotional numbing, major depressive disorder, and generalized anxiety disorder symptoms) symptoms as assessed using the Clinician-Administered PTSD Scale, Hamilton Depression Rating Scale, and Hamilton Rating Scale for Anxiety; and 24-hour urinary cortisol levels.

**RESULTS** \[^{11}C\]LY2795050 volume of distribution values in an amygdala-anterior cingulate cortex-ventral striatal neural circuit were negatively associated with severity of loss \((r = -0.39; 95\% \text{ CI, } -0.08 \text{ to } -0.66), \) but not threat \((r = -0.03; 95\% \text{ CI, } -0.30 \text{ to } 0.27), \) symptoms; this association was most pronounced for dysphoria symptoms \((r = -0.45; 95\% \text{ CI, } -0.10 \text{ to } -0.70).\) Path analysis revealed that lower \[^{11}C\]LY2795050 volume of distribution values in this circuit was directly associated with greater severity of loss symptoms and indirectly mediated by 24-hour urinary cortisol levels.

**CONCLUSIONS AND RELEVANCE** Results of this study suggest that KOR availability in an amygdala-anterior cingulate cortex-ventral striatal neural circuit mediates the phenotypic expression of trauma-related loss (ie, dysphoria) symptoms. They further suggest that an activated corticotropin-releasing factor/hypothalamic-pituitary-adrenal axis system, as assessed by 24-hour urinary cortisol levels, may indirectly mediate this association. These results may help inform the development of more targeted, mechanism-based transdiagnostic treatments for loss (ie, dysphoric) symptoms.


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A burgeoning body of studies has suggested that trauma-related psychopathology is characterized by heterogeneous clusters of symptoms that are transdiagnostic in nature, span the severity spectrum, and may be differentially linked to neurobiological systems. Using a framework proposed by the National Institute of Mental Health Research Domain Criteria project, these symptom clusters can manifest in the form of threat symptoms, which can be interpreted to include reexperiencing symptoms, such as intrusive memories and nightmares, avoidance of trauma-related reminders, and hyperarousal symptoms, as well as loss symptoms, which can be interpreted to include emotional numbing symptoms, such as diminished interest in activities, restricted range of affect, and detachment, as well as generalized dysphoric and anxiety symptoms. Thus, the expression of these 2 symptom clusters is best conceptualized as being transdiagnostic and dimensional in nature and spanning a broad spectrum of symptom severity, ranging from no to severe symptoms. However, to our knowledge, data are lacking regarding neurobiological abnormalities that underlie these core aspects of the trauma-related phenotype. Such data are essential to translating understanding of basic neurobiological processes that underlie transdiagnostic dimensions of psychopathology to the development of new, more targeted, mechanism-based prevention and treatment strategies.

Preclinical data have implicated the activated dynorphin/κ-opioid receptor (KOR) system in an amygdala–anterior cingulate cortex-ventral striatal neural circuit as a critical mediator of a chronic stress-induced phenotype that closely resembles trauma-related symptoms observed in humans. This work has revealed that while activation of the dynorphin/KOR system is implicated in behavioral models of anxiety, specifically learning-dependent fear- and anxiety-related behaviors, it has more consistently been implicated in behavioral models of the dysphoric component of stress such as the repeated forced swim and inescapable foot shock tests. However, to date, the specificity of association between KOR availability in this neural circuit and the phenotypic expression of trauma-related threat and loss symptoms has not been evaluated in humans.

Emerging evidence suggests a potential connection between the dynorphin/KOR and corticotropin-releasing factor (CRF) systems in the amygdala–anterior cingulate cortex-ventral striatal neural circuit in mediating the aversive psychological effects of stress. Specifically, trauma exposure has been linked to increased stress reactivity and dysregulation of the CRF-hypothalamic-pituitary-adrenal axis (HPA), which results in abnormal peripheral cortisol levels. Stress-related effects of CRF are mediated by KORs, suggesting that activation of the KOR by dynorphin results in reduced KOR availability via receptor internalization. In the human brain, the KOR, a 7-membrane-spanning G protein-coupled receptor, is widely distributed, with highest levels in an amygdala–anterior cingulate cortex-ventral striatal circuit that is implicated in threat and loss symptoms. Therefore, it is reasonable to expect that cortisol levels may influence the relation between KOR availability in this amygdala–anterior cingulate cortex-ventral striatal circuit and the phenotypic expression of threat and loss symptoms.

We developed a KOR-selective radioligand [11C]LY2795050 that provides an opportunity to study in vivo the role of the KOR system in relation to measures of psychopathology using high-resolution positron emission tomography (PET) To our knowledge, this is currently the sole method for providing an in vivo quantitative measurement of KOR availability in the brain.

Given the impetus of contemporary scientific efforts in the mental health field to identify links between neurobiological systems and transdiagnostic dimensional phenotypes, additional research is needed to (1) characterize common and unique dimensions of trauma-related psychopathology that cut across conventionally defined psychiatric disorders and (2) evaluate neurobiological factors linked to these dimensional and transdiagnostic phenotypes. To investigate these aims in a sample of individuals who represented a broad, dimensional spectrum of symptoms, ranging from no/minimal distress to severe distress, we used an inclusive sampling approach by recruiting a sample of healthy, nontrauma-exposed individuals from the community and a sample of trauma-exposed individuals from outpatient psychiatric settings who presented with a broad spectrum of mild-to-severe threat and loss symptoms.

Using the KOR-selective radioligand [11C]LY2795050 and high-resolution PET, we evaluated the relation between KOR availability in an amygdala–anterior cingulate cortex-ventral striatal neural circuit in relation to empirically derived, transdiagnostic and dimensional measures of threat and loss symptoms. On the basis of preclinical data suggesting that cortisol levels may mediate the relation between KOR availability in this circuit and the behavioral expression of threat and loss symptoms, we then examined the potential role of 24-hour urinary cortisol levels in mediating this association in humans. Given that PET imaging with the KOR-selective radioligand [11C]LY2795050 allows one to assess KOR availability brain-wide, we additionally examined how [11C]LY2795050 values in regions outside the amygdala–anterior cingulate cortex-ventral striatal neural circuit were related to threat and loss symptoms.

Methods

Participants

This study was approved by the New York University institutional review board, Yale University School of Medicine Human Investigation Committee, Yale University Magnetic Resonance Research Center, and Yale–New Haven Hospital Radiation Safety Committee. Thirty-five participants were recruited from the Molecular Imaging Program for Mood and Anxiety Disorders at New York University Langone Medical Center. Written informed consent was obtained from all study participants. Trauma-exposed participants were referred from New York University-affiliated outpatient psychiatry clinics (n = 30) and nontrauma-exposed participants were recruited...
Scores on clinician-administered measures of threat and loss symptoms (see Assessments section) in the sample represented a broad, transdiagnostic and dimensional spectrum of trauma-related psychopathology (Table 1). Thus, this sample is representative of the broader population of individuals in the community (ie, unaffected individuals) and those who present for treatment at an outpatient mood and anxiety disorders clinic (ie, mild-to-severe symptoms).

**Table 1.** Demographic, Trauma-Related, and Clinical Characteristics of the Sample

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
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</tr>
<tr>
<td>Age</td>
<td>28.9 (9.5)</td>
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<tr>
<td>Female, No. (%)</td>
<td>24 (68.6)</td>
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<tr>
<td>Race/ethnicity, No. (%)</td>
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<tr>
<td>White</td>
<td>16 (45.7)</td>
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<tr>
<td>African American</td>
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<tr>
<td>Hispanic</td>
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<tr>
<td>Other</td>
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<td>14.4 (2.3)</td>
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<tr>
<td>BMI</td>
<td>25.4 (6.8)</td>
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<td><strong>Trauma-related variables</strong></td>
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<tr>
<td>No. of traumas</td>
<td>4.1 (4.7)</td>
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<tr>
<td>Age at first trauma, y</td>
<td>10.9 (6.5)</td>
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<td>Nature of presenting trauma, No. (%)</td>
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<tr>
<td>Sexual abuse</td>
<td>18 (60.0)</td>
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<tr>
<td>Physical abuse/violence</td>
<td>6 (20.0)</td>
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<tr>
<td>Witnessed death of loved one</td>
<td>4 (13.3)</td>
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<tr>
<td>Motor vehicle crash</td>
<td>2 (6.7)</td>
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<tr>
<td><strong>[11C]LY2795050 V&lt;sub&gt;T&lt;/sub&gt; values</strong></td>
<td></td>
</tr>
<tr>
<td>Injection mass, μg/kg</td>
<td>0.14 (0.04)</td>
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<tr>
<td><strong>Neural circuit implicated in trauma-related psychopathology</strong></td>
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<tr>
<td>[11C]LY2795050 V&lt;sub&gt;T&lt;/sub&gt; value in</td>
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<tr>
<td>Amygdala</td>
<td>3.91 (0.50)</td>
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<td>Ventral striatum</td>
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<tr>
<td>Cingulate</td>
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<td><strong>Exploratory brain regions</strong></td>
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<td>[11C]LY2795050 V&lt;sub&gt;T&lt;/sub&gt; value in</td>
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<tr>
<td>Insula</td>
<td>3.34 (0.33)</td>
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<tr>
<td>Pallidum</td>
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<tr>
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<td>Hippocampus</td>
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<td>Posterior cingulate</td>
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<tr>
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<tr>
<td>Thalamus</td>
<td>2.22 (0.26)</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>1.92 (0.27)</td>
</tr>
</tbody>
</table>

*Only assessed among the 30 trauma-exposed participants.*

**Assessments**

Lifetime traumas were assessed using the Traumatic Life Events Questionnaire and psychiatric diagnoses were established using DSM-IV-TR criteria and the Structured Clinical Interview for DSM-IV, which was administered by an experienced psychiatric clinician. Only traumas that met criteria A1 and A2 for a DSM-IV-TR–based diagnosis of posttraumatic stress disorder (PTSD) were counted toward participants’ trauma histories. Nontrauma-exposed healthy adults did not report any trauma exposures on the Traumatic Life Events Questionnaire and did not have any lifetime psychiatric diagnosis including substance abuse or dependence or nicotine dependence. The severity of trauma-related psychopathology was assessed using the Clinician-Administered PTSD Scale for DSM-IV (CAPS), the Montgomery-Åsberg Depression Rating Scale (MADRS), and the Hamilton Rating Scale for Anxiety (HAM-A). Symptom dimensions assessed by the CAPS, MADRS, and HAM-A were derived from prior factor analytic studies of these scales, which have found that the CAPS yields 4 factors of reexperiencing (eg, intrusive thoughts of trauma), avoidance (eg, avoidance of trauma-related thoughts), emotional numbing (eg, detachment and restricted affect), and hyperarousal (eg, sleep disturbance and hypervigilance) symptoms; that the MADRS yields 3 factors of dysphoria (eg, sadness and the inability to feel), psychic anxiety (eg, inner tension and pessimistic thoughts), and vegetative (eg, reduced sleep and appetite) symptoms; and that the HAM-A yields 2 factors of cognitive (eg, anxious mood and depressed mood) and somatic (eg, cardiovascular symptoms and gastrointestinal symptoms) anxiety symptoms. For the current study, these symptom clusters were computed by summing the items that comprise each of the factors.

All participants were psychotropic medication free for at least 6 months before the scan. No participant had a lifetime...
exposure to psychotropic medications longer than 2 weeks. All participants were evaluated by physical examination, electrocardiogram, standard blood chemistry, hematology laboratory testing, toxicology testing, and urinalysis. Participants with significant medical or neurologic conditions, with substance abuse within 12 months of the scan, with lifetime history of intravenous substance dependence, or with history of head injury that involved loss of consciousness were excluded. The absence of substance use was determined by self-report and confirmed by the results of urine toxicology and breathalyzer tests at screening and on scanning days. The medical and psychiatric evaluation was followed by magnetic resonance imaging (MRI) and a resting-state PET scan on a high-resolution research tomographic PET scanner (Siemens/CTI) with the KOR-selective radioligand[^24]. ([11C]LY2795050) Peripheral measures of free urinary cortisol were ascertained over 24 hours. The collection started after the first urine void on the day prior to the PET scan and ended the morning of the scan. Processing of the samples followed established procedures (ARUP Laboratories).[38]

**PET and MRI Acquisition and Modeling**

In advance of the PET scan, MR anatomical images were acquired on a 3-T Trio (Siemens Medical Systems) using a MPRAGE pulse sequence. Positron emission tomographic imaging was performed using the high-resolution research tomograph, with spatial resolution of 2.5 to 3.5 mm. Participants wore a swim cap to which a rigid optical tracking tool was attached to record head motion with an infrared detector (Vicra; NDI Systems). Following a transmission scan, ([11C]LY2795050 was injected intravenously and PET data were acquired in list mode for 90 minutes. Dynamic list mode data were reconstructed and motion corrected as previously described.[39] To apply the regions of interest to the PET data, 2 transformations were estimated. First, a nonlinear coregistration (BioImage suite[^39]) was estimated between the template MRI and each participant’s MRI. Then, a summed image (0 to 10 minutes postinjection) was created from the motion-corrected PET dynamic image and registered to the participant’s MRI using a 6-parameter rigid coregistration. All coregistrations were estimated using a mutual information algorithm (FLIRT; FSL3.2; Analysis Group). The input function for tracer kinetic modeling was acquired by arterial blood sampling and high-performance liquid chromatography analysis for metabolites.[24] The MA1 analysis[^40] was applied to the regional time-activity curves (t = 30 minutes) to estimate total volume of distribution (V_T).

**Data Analysis**

To compute a weighted composite index of ([11C]LY2795050 V_T values in an amygdala–anterior cingulate cortex–ventral striatal neural circuit, we conducted a principal components analysis of ([11C]LY2795050 V_T values in these 3 brain regions. To generate composite indices of threat and loss symptoms, we computed standardized scores of the 2 core dimensions of trauma-related psychopathology that comprise each of these latent factors, with reexperiencing, avoidance, and hyperarousal symptoms of PTSD loading a latent factor of threat symptoms and PTSD-related emotional numbing. MADRS-assessed dysphoria, psychic anxiety, vegetative symptoms, and HAM-A-assessed cognitive and somatic anxiety symptom dimensions loading on a latent factor of loss symptoms. As appropriate, Pearson or Spearman correlations were then computed to evaluate associations between demographic and clinical variables, 24-hour urinary cortisol levels, and severity of threat and loss symptoms. Spearman correlations were computed to evaluate associations between composite ([11C]LY2795050 V_T value factor scores in the amygdala–anterior cingulate cortex–ventral striatal neural circuit and ([11C]LY2795050 V_T values in each of the regions that comprise this circuit, as well as the severity of threat and loss symptoms. If composite measures of threat or loss symptoms emerged as being significantly related to ([11C]LY2795050 V_T value factor scores, we conducted post hoc Spearman correlations to evaluate associations between each of the symptom clusters that comprised these measures and ([11C]LY2795050 V_T value factor scores; α was set to .01 for these analyses to reduce the likelihood of type I error. To evaluate an integrative model of the potential role of 24-hour urinary free cortisol levels in mediating the relation between ([11C]LY2795050 V_T value factor scores in an amygdala–anterior cingulate cortex–ventral striatal neural circuit and the severity of loss symptoms,[^27,^24] we conducted a bootstrapped mediation analysis.[^21] Finally, we computed Spearman correlations to explore whether ([11C]LY2795050 V_T values in regions outside the circuit of interest were related to the severity of threat and loss symptoms; because of the exploratory nature of these analyses, α was set to .05.

**Results**

**Sample Characteristics**

Table 1 shows the demographic, trauma-related, and clinical characteristics of the sample. On average, the sample was 28.9 years of age, predominantly female (68.6%), nonwhite (54.3%), and had a mean 14.4 years of education. Among trauma-exposed individuals, the mean number of lifetime traumas was 4.1, mean age at first trauma exposure was 10.9 years, and the most common index trauma was sexual abuse (60.0%).

**Principal Components Analyses of ([11C]LY2795050 V_T Values in a Neural Circuit Implicated in Trauma-Related Psychopathology**

As expected, a principal components analysis (PCA) of ([11C]LY2795050 V_T values in brain regions that compose an amygdala–anterior cingulate cortex–ventral striatal neural circuit implicated in trauma-related psychopathology revealed a 1-factor solution (eigenvalue = 2.59, 86.2% total variance explained). Factor loadings were very high for each of the brain regions that compose this circuit: 0.950 for the anterior cingulate cortex, 0.919 for the amygdala, and 0.916 for the ventral striatum. Factor scores of ([11C]LY2795050 V_T values in these 3 brain regions were computed to provide a composite summary measure of KOR availability in this neural circuit.
The second PCA of symptom clusters that reflect hyperarousal symptoms assessed by the CAPS (Cronbach α = .92). The second PCA of symptom clusters that reflect trauma-related psychopathology, as in most prior factor analytic studies,1,42,43 and the National Institute of Mental Health Research Domain Criteria project.4-6 The first PCA of threat symptoms—reexperiencing, avoidance, and hyperarousal symptoms—revealed a 1-factor solution (eigenvalue = 2.75, 91.5% total variance explained). Factor loadings were high for all component symptom dimensions: 0.949 for cognitive anxiety (HAM-A), 0.938 for psychic anxiety (MADRS), 0.920 for dysphoria (HAM-A), 0.781 for somatic anxiety (HAM-A), 0.766 for vegetative symptoms (MADRS), and 0.587 for emotional numbing (CAPS) symptoms (Cronbach α = .91). Scores on these composite measures of threat and loss symptoms were positively correlated (r = 0.42; 95% CI, 0.06-0.70; P = .01).

**Correlates of Threat and Loss Symptoms**

Table 2 shows the correlations of independent variables and scores on composite measures of threat and loss symptoms. The results of these analyses revealed that a lifetime diagnosis of alcohol or drug use disorder was positively associated with the severity of both threat and loss symptoms and that current smoking status was positively associated with the severity of loss symptoms. Lifetime alcohol or drug use disorder was associated with loss, but not threat, symptoms. While lifetime alcohol or drug use disorder was positively associated with the severity of threat and loss symptoms, it was unrelated to composite [11C]LY2795050 VT value factor scores in an amygdala–anterior cingulate cortex–ventral striatal neural circuit significantly negatively related to the severity of loss (r = −0.39; 95% CI, −0.08 to −0.66), but not threat (r = −0.03; 95% CI, −0.30 to 0.27) symptoms; post hoc correlations with individual symptom clusters associated with composite [11C]LY2795050 VT value factor scores revealed that this association was significant for dysphoria (r = −0.45; 95% CI, −0.10 to −0.70; P = .006); other symptom clusters were not significant at the P < .01 level: psychic anxiety (r = −0.38; 95% CI, −0.04 to −0.65; P = .02); emotional numbing (r = −0.37; 95% CI, −0.03 to −0.67; P = .03); somatic anxiety (r = −0.37; 95% CI, −0.03 to −0.61; P = .03); cognitive anxiety (r = −0.35; 95% CI, −0.01 to −0.63; P = .04), and vegetative symptoms (r = −0.21; 95% CI, −0.51 to 0.12; P = .23). Urinary free cortisol levels were also significantly negatively associated with loss, but not threat, symptoms. While lifetime alcohol or drug use disorder was significantly associated with increased severity of threat and loss symptoms, it was unrelated to composite [11C]LY2795050 VT value factor scores (r = −0.06; 95% CI, −0.30 to 0.26; P = .74). None of the other correlations were significant.

**Mediation Analysis**

As shown in Figure 2, the results of a bootstrapped mediation analysis, which provides an integrative model of how KOR and HPA-CRF systems interact in predicting the severity of loss symptoms, revealed that [11C]LY2795050 VT values in an amygdala–anterior cingulate cortex–ventral striatal neural circuit were directly associated with the severity of loss symptoms and that this association was indirectly mediated by 24-hour urinary cortisol levels. Specifically, composite [11C]LY2795050 VT value factor scores in this circuit were significantly negatively related to the severity of loss symptoms, as well as 24-hour urinary cortisol levels, which were in turn significantly negatively related to the severity of loss symptoms.
Associations Between KOR Availability in Brain Regions Outside Amygdala–Anterior Cingulate Cortex–Ventral Striatal Neural Circuit and the Severity of Loss Symptoms

Exploratory Spearman correlation analyses revealed that $[^{11}C]LY2795050 V_t$ values in the insula ($r = -0.42; 95\% CI, -0.07$ to $-0.69; P = .01$), caudate ($r = -0.37; 95\% CI, -0.02$ to $-0.65; P = .03$), frontal cortex ($r = -0.37; 95\% CI, -0.02$ to $-0.67; P = .03$), thalamus ($r = -0.36; 95\% CI, -0.01$ to $-0.68; P = .03$), and hypothalamus ($r = -0.36; 95\% CI, -0.01$ to $-0.65; P = .04$) were also significantly negatively related to the severity of loss symptoms.

Discussion

This study had 2 main findings. First, using the KOR-selective radioligand $[^{11}C]LY2795050$ and high-resolution PET imaging, we found that lower in vivo KOR availability in an amygdala–anterior cingulate cortex–ventral striatal neural circuit, as well as related regions, such as the insula, caudate, and frontal cortex, was significantly associated with increased severity of loss, but not threat, symptoms in a cohort of individuals whose symptoms represented a broad transdiagnostic and dimensional spectrum of trauma-related psychopathology. Thus, results of the current study may be generalizable to the broader population of adults whose symptom levels represent a spectrum of trauma-related psychopathology, ranging from nontrauma-exposed healthy individuals to trauma-exposed individuals with severe trauma-related psychopathology. This finding, which is consistent with animal data implicating the dynorphin/KOR system in a chronic stress-induced phenotype, suggests that reduced KOR availability in an amygdala–anterior cingulate cortex–ventral striatal neural circuit is uniquely linked to the phenotypic expression of loss symptoms, most notably dysphoria, which is characterized by sadness, lassitude, and emotional numbing. This finding accords with preclinical work, which has implicated the activated dynorphin/KOR system as a key mediator of dysphoria-related symptoms, as evidenced by KOR agonist–induced antidepressantlike effects in the forced swim test. Taken together, these results may have important implications for clinical trials of KOR antagonists, which are currently entering the clinical arena, to be evaluated in several patient populations, including individuals with mood and anxiety disorders, as they suggest that such drugs may have particular effectiveness in mitigating loss (ie, dysphoric) symptoms.

The second main finding of this study was that urinary free cortisol levels indirectly mediated the association between reduced KOR availability and greater severity of loss symptoms. This finding, which builds on prior work linking reduced cortisol levels to greater severity of loss symptoms (eg, emotional numbing) in trauma survivors suggests that, in addition to having a direct influence on the severity of loss symptoms, reduced KOR availability may be linked to greater severity of such symptoms via lower cortisol levels. To our knowledge, these are the first in vivo data that extend to humans a well-known finding in animal models that CRF-induced activation of the dynorphin/KOR system in an amygdala–anterior cingulate cortex–ventral striatal neural circuit and cortisol levels play a central role in mediating the phenotypic expression of loss symptoms.

Taken together, the results of this study suggest that the dynorphin/KOR and CRF-HPA axis systems are both implicated in mediating the phenotypic expression of loss symptoms in humans. Specifically, they build on preclinical work to suggest that, in humans, lower KOR availability in an amygdala–anterior cingulate cortex–ventral striatal neural circuit, as well as lower cortisol levels, are associated with increased severity of loss (ie, dysphoric) symptoms; they fur-

Figure 1. Scatterplot of Composite $[^{11}C]LY2795050$ Volume of Distribution Value Factor Scores in the Amygdala–Anterior Cingulate Cortex–Ventral Striatal Circuit

Scatterplot of composite $[^{11}C]LY2795050$ volume of distribution value factor scores in an amygdala–anterior cingulate cortex–ventral striatal circuit implicated in trauma-related psychopathology and severity of loss symptoms. The axis values represent standardized units with zero equal to the mean of the full sample and each unit representing 1 SD from the mean. Error bars represent the 95\% CIs.

Figure 2. Bootstrapped Mediation Analysis

Results of a bootstrapped mediation analysis examining the role of 24-hour urinary cortisol levels in mediating the relation between composite $[^{11}C]LY2795050$ volume of distribution value factor scores in a neural circuit implicated in trauma-related psychopathology and severity of loss symptoms. The values represent standardized coefficients. Bootstrapped 95\% CIs:

- $[^{11}C]LY2795050$ volume of distribution value factor scores → loss symptoms: $-0.24$ to $-0.08$; $[^{11}C]LY2795050$ volume of distribution value factor scores → 24-hour urinary cortisol: $-0.10$ to $-0.73$; and 24-hour urinary cortisol → loss symptoms: $-0.01$ to $-0.59$.

$P < .05$.

$P < .01$. 

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ther suggest that cortisol levels indirectly mediate the relation between KOR availability in this circuit and the expression of this phenotype. While CRF and the HPA axis are well known to be dysregulated in mood and anxiety disorders,

accumulating evidence from animal studies further suggests an interaction of the dynorphin/KOR and CRF-HPA axis systems in mediating a dysphoric phenotype in animal models of human depression. Of particular interest are reports linking the mesocorticolimbic dopamine and activated dynorphin/KOR systems to dysphoric symptoms. Specifically, ventral tegmental area dopamine neurons receive inputs from dynorphinergic neurons and express KORs, and activation of these KORs depresses neuronal activity and dopamine release, which may consequently contribute to the development of loss symptoms. These data also suggest that severe stress exposure can trigger delayed but more sustained changes in KOR systems that increase vulnerability to loss symptoms at later times. This finding is especially relevant to interpretation of the data presented in this report because the mean age at first trauma exposure in our sample of trauma-exposed adults was during childhood (ie, 10.9 years of age). Given that hyperarousal symptoms tend to be most prominent early after trauma exposure and predict the subsequent development of loss symptoms (eg, dysphoria/emotional numbing), it is reasonable to speculate that changes in KOR systems and concomitant increases in loss symptoms observed in the current study reflect delayed but persistent changes in KOR systems that developed and are sustained over an extended period. Accordingly, it is possible that reduced KOR availability may be a result of compensatory changes associated with living with chronic loss symptoms, most notably dysphoria.

The results of the current study provide initial support for a model of candidate neurobiological systems—KOR and CRF-HPA axes—that underlie the transdiagnostic and dimensional phenotypic expression of trauma-related loss symptoms. They may ultimately help to inform the development of new, more targeted, and transdiagnostic treatments for this core and often most disabling aspect of the trauma-related phenotype. The development of treatments that target the loss-related symptoms that characterize the trauma-related phenotype is critical in light of data suggesting that trauma-related loss (ie, dysphoric/emotional numbing) symptoms are strongly linked to both the chronicity of trauma-related symptoms, as well as functional impairment in a variety of trauma-exposed populations. The data presented herein further substantiate findings in animal models, which suggest that the KOR system may be a promising target for novel treatment development particularly for trauma-exposed individuals with elevated loss symptoms. Preclinical data suggest that KOR agonists reproduce end points of depressive behavior and that KOR antagonists have antidepressant effects and can also block CRF-induced loss symptoms. These data have important translational implications for the development of novel, mechanism-based pharmacotherapies, especially in light of negative results from clinical trials with CRF hormone receptor 1 antagonists in humans with mood and anxiety disorders.

Despite the growing body of evidence proposing KOR antagonists as a promising target for treatment development, additional research is needed to better elucidate their mechanism of action and to evaluate the efficacy of these compounds in treating humans with elevated loss symptoms. Specifically, studies of how stress-induced increases in cyclic adenosine monophosphate response element binding protein (CREB) function in the amygdala–anterior cingulate cortex–ventral striatal neural circuit to produce threat and loss symptoms—as well as how cyclic adenosine monophosphate response element binding protein–induced activation of KOR via dynorphin specifically elicits loss symptoms—may provide insight into the putative mechanism of action or KOR antagonists and identify potential targets for treatment development.

Method limitations of this study must be noted. First, given that no prior factor analytic studies have evaluated the transdiagnostic factor structure of the CAPS, MADRS, and HAM-A, it is not clear whether a 2-factor model of threat and loss symptoms—which was inferred from prior factor analytic studies—to operationalize relevant constructs of threat and loss symptoms from the National Institute of Mental Health Research Domain Criteria project matrix—provides the optimal structural representation of the phenotypic expression of trauma-related psychopathology. Factor analytic studies in larger samples are needed to evaluate this question. Nevertheless, when examining individual symptom clusters associated with KOR availability in the amygdala–anterior cingulate cortex–ventral striatal circuit, the strongest association was with dysphoria, as assessed by the MADRS. This finding suggests that evaluation of component symptom clusters from transdiagnostic composite measures of loss symptoms may provide greater specificity regarding how KOR availability is linked to the phenotypic expression of these symptoms. Second, although results of exploratory analyses revealed that [11C]LY2795050 Vₚ values in the insula, caudate, frontal cortex, thalamus, and hypothalamus were negatively associated with the severity of loss symptoms, these findings should be interpreted with caution owing to lower relative [11C]LY2795050 Vₚ values in most of these regions compared with [11C]LY2795050 Vₚ values in the amygdala–anterior cingulate cortex–ventral striatal circuit. Nevertheless, molecular brain imaging techniques, such as PET, allow brain-wide assessments of KOR availability and thus the findings presented herein suggest a broader, more modulatory function of the KOR system in mediating the phenotypic expression of trauma-related loss symptoms in humans. Third, the sample size recruited for this study, while typical for PET studies, was relatively small and the trauma-exposed group comprised predominantly sexual/physical assault survivors. Thus, additional research is needed to evaluate the generalizability of these results in larger, more diverse samples of trauma survivors.

Conclusions

The results of this study suggest that KOR availability in the amygdala–anterior cingulate cortex–ventral striatal neural circuit mediates the phenotypic expression of trauma-related loss (ie, dysphoria) symptoms. They further suggest that an acti-


vated CRF/HPA axis system, as assessed by 24-hour urinary cortisol levels, may indirectly mediate this association. These results may help inform the development of more targeted, mechanism-based transdiagnostic treatments for loss (ie, dysphoric) symptoms.

Further research is needed to assess the generalizability of these findings, elucidate the neural mechanisms and temporal course that underlie the observed associations, and evaluate the efficacy of KOR antagonists in mitigating loss (ie, dysphoria) symptoms.

REFERENCES


