Biological Psychiatry: Celebrating 50 Years

# Commentary

# The Nociceptive Opioid Peptide Receptor System and Posttraumatic Stress Disorder: An Enigma Wrapped Around a Conundrum

William J. Martin and Tanya L. Wallace

At the dawn of receptor cloning 25 years ago, an opioid-like receptor had the distinction of being the first "orphan" G protein–coupled receptor cloned. Within a year of that discovery, two separate groups described the identification of the same peptide, nociceptin and orphanin FQ (N/OFQ), as an endogenous ligand for *OPRL1*. Deorphanizing a novel peptide neurotransmitter system catalyzed multiple parallel research efforts focused on understanding the biologic roles of N/OFQ peptide (NOP) and its receptor that continue today (1). From the outset, the enigmatic aspects of this neuropeptide system were apparent, beginning with nomenclature and expanding seemingly with each subsequent study. Though the receptor was termed "opioid-like," N/OFQ does not act directly on the classical μ, δ, or κ opioid receptors. Today, we know that the NOP receptor system modulates an array of biologic functions and behaviors beyond the initial description of pain. Its role now encompasses regulation of food intake, cognition, and perhaps critically anxiety as well as stress (2). The overlap between these behavioral domains and those associated with posttraumatic stress disorder (PTSD) presents an opportunity to characterize the possible therapeutic relevance of the NOP receptor system within the context of a debilitating neurobehavioral disorder.

PTSD is characterized by the persistence of fear and/or stress beyond the experience of a traumatic event, and it causes significant long-term mental and physical health consequences. Tragically, sexual violence is common in women, yet the prevalence of PTSD in women at any given time is much lower than lifetime prevalence. These data suggest that some victims of sexual violence recover from and/or exhibit resilience in response to the trauma and provide a rationale for examining the underlying neurobiological mechanisms involved with trauma-related recovery as a path toward treatment development. The complexity of PTSD itself has been a barrier to the development of effective treatments. Wide-ranging symptoms, including intrusive recollection, persistent avoidance, alterations in arousal and reactivity, and negative alterations in mood and cognition, are all part of the DSM-5 criteria for PTSD. As such, it is unlikely that a single intervention will effectively treat the full syndrome. That said, the core symptoms of PTSD converge around impaired memory consolidation and reconsolidation. Mapping new mechanisms that regulate this computation will directly inform the successes of novel therapeutic approaches.

As noted, the NOP receptor system regulates emotionally relevant behaviors, and its engagement of the hypothalamic-pituitary-adrenal axis is consistent yet complex, highlighting its dynamic modulatory role in stress and resiliency. A challenge with the NOP receptor has been the extent to which the methodology used to interrogate this system, and the species studied, have guided—or misguided—our understanding of its function. For example, N/OFQ neurotransmission has been implicated in the regulation of anxiety, but both increased anxiety-related behaviors and decreased anxiety-related behaviors have been demonstrated after stimulation of the NOP receptor in animal models (3). The literature is replete with such apparently contradictory findings across behavioral domains (e.g., fear, anxiety, and pain) informed by the use of NOP agonists or NOP antagonists in rodents, nonhuman primates, and humans (3–5). More often than not, consistency emerges along the following dimensions.

First, NOP signaling needs to be viewed through the lens of both regulation and dysregulation—that is, the physiological function of NOP may be reasonably different from the pathophysiological function of NOP, as one would expect from a tightly regulated system, wherein its core function may be in promoting adaptive responses. As such, state-dependency and/or inherent rapid desensitization of the NOP receptor after activation could influence the interpretation of "agonist" actions that might in fact reflect inactivation of the NOP receptor. Nonetheless, actions of N/OFQ on hypothalamic-pituitary-adrenal axis function consistently reveal markers of stress-induced activity, including elevated circulating adrenocorticotropic hormone and corticosterone levels and increased corticotropin-releasing factor concentrations within the brain after intracerebroventricular administration to laboratory animals. Second, the actions of NOP should be interpreted within the context of brain circuity rather than individual brain regions. Third, the surest way to advance our understanding of NOP in humans is to study the neuropeptide system in humans.

The results reported by Narendran *et al.* (6) in the current issue of *Biological Psychiatry* provide evidence implicating the NOP receptor system as an emerging target of interest in stress-induced trauma. Narendran *et al.* (6) recognize that the individual differences observed in the development of PTSD and/or the resiliency or recovery from sexual violence highlight the need to better characterize the neurochemistry of stress-related neuropeptides to potentially inform therapeutic development. Narendran *et al.* (6) took advantage of the positron emission tomography radioligand for the NOP receptor to study whether NOP receptor density changes in the brains of 18 college women who had recently experienced sexual

SEE CORRESPONDING ARTICLE ON PAGE 1056

 
https://doi.org/10.1016/j.biopsych.2019.04.017
Biological Psychiatry June 15, 2019; 85:986–988 www.sobp.org/journal
ISSN: 0006-3223

trauma and a corresponding number of healthy control subjects. Higher NOP receptor density was associated with PTSD total symptom severity in the previous month. Moreover, the increased NOP receptor density was limited to the midbrain and cerebellum, with the positive correlation largely driven by the intrusion/re-experiencing and avoidance subscale. An intriguing finding was that midbrain NOP receptor density was reduced in women who had experienced sexual trauma yet did not meet the Clinician-Administered PTSD Scale for DSM-5 criteria for PTSD. Does a reduction of NOP receptors in brain regions positioned to regulate anxiety and emotional memory consolidation confer resilience in the setting of sexual trauma? If so, is this based on a regulatory or counter-regulatory action of NOP—that is, in which direction is the neuropeptide system dysregulated and over what time course?

A growing body of evidence links the NOP receptor system with stress and trauma-related signs. In a rat model of social defeat stress, which models aspects of PTSD, NOP messenger RNA was upregulated in limbic brain regions and was associated with impaired reward learning (7). Similarly, stress-induced disruptions in reward learning paradigms have been shown in humans, suggesting that dysregulation of the NOP system could be a shared mechanism across species that contributes to behavioral dysregulation after stress (3). In addition to its involvement in mediating stress responses, the NOP receptor system is an effective modulator of cognitive behaviors. Intracerebroventricular administration of NOP receptor agonists consistently impair memory; NOP receptor antagonists block this effect [see Andero (8) for review]. Considering that PTSD is characterized by altered fear learning and memory consolidation/reconsolidation processes, targeting therapeutic development toward systems that reduce stress-induced pathology could serve as an effective approach. A relevant example of altered memory processes after trauma was recently reported in women who had experienced sexual violence, independent of whether they were diagnosed with PTSD, and showed increased strength of stressful autobiographical memories as measured through the Autobiographical Memory Questionnaire (9).

The regulation of essential physiological and behavioral functions by NOP is unsurprising: neuropeptide systems are evolutionarily conserved across species precisely to buffer against sustained negative consequences. The canonical understanding of changes in receptor density is that up- or downregulation of receptor systems occurs in response to too little or too much exposure to the ligand. However, if the preclinical literature is a guide, then the regulatory elements of NOP signaling may be more nuanced. For example, Narendran *et al.* (6) speculate that an increase in NOP signaling could be accomplished by increased peptide release or upregulation of receptors. The question is: Which is the adaptive response? Do N/OFQ levels increase within discrete brain regions to reduce the glutamate and monoamine transmission that contribute to re-experiencing and consolidating the trauma? If so, then under these circumstances, downregulation of NOP receptors over a given time window would be an adaptive response to trauma to protect against the long-term influence of the trauma on emotional memory and PTSD symptoms. By contrast, what if the maladaptive response stems from increased NOP signaling, driven by higher receptor density? In one situation, appropriate pharmacologic therapeutic intervention would be selective augmentation of NOP signaling, and in the other, receptor blockade would provide benefit. If the NOP receptor system is tightly regulated, the directionality of the intervention might switch as a function of the timing of intervention. It will be difficult to resolve these open questions only by using positron emission tomography–based methods.

As with the preclinical work on PTSD in rodents that preceded it, this study by Narendran *et al.* (6) should be seen as hypothesis generating, setting the stage for future research that incorporates additional methods to potentially address open questions. For example, there is an opportunity to deepen our understanding of the NOP receptor system within the context of PTSD by including functional magnetic resonance imaging neuroimaging methods to better understand the brain circuits that are dysregulated, and potentially protected, in response to sexual trauma. The relevance of functional magnetic resonance imaging–based approaches in PTSD has been highlighted by recent findings in which aberrant functional connectivity in specific brain networks defined the dissociative subtype of PTSD (10). In summary, it is worth noting that the obtained results would not have been possible if the study enrolled only individuals with the PTSD diagnosis. In this way, the study serves as a reminder of the value of exploring behavioral variation beyond strict categorical diagnoses.

## Acknowledgments and Disclosures

WJM and TLW are employees of and shareholders in BlackThorn Therapeutics, which is evaluating BTRX-246040, a nociceptive opioid peptide receptor antagonist, for the treatment of neurobehavioral disorders.

## Article Information

From BlackThorn Therapeutics, San Francisco, California.

Address correspondence to William J. Martin, Ph.D., BlackThorn Therapeutics, 780 Brannan Street, San Francisco, CA 94103; E-mail: bill@blackthornrx.com.

Received Apr 16, 2019; accepted Apr 17, 2019.

## References

1. Chiou LC, Liao YY, Fan PC, Kuo PH, Wang CH, Riemer C, *et al.* (2007): Nociceptin/orphanin FQ peptide receptors: Pharmacology and clinical implications. Curr Drug Targets 8:117–135.
2. Witkin JM, Statnick MA, Rorick-Kehn LM, Pintar JE, Ansonoff M, Chen Y, *et al.* (2014): The biology of nociceptin/orphanin FQ (N/OFQ) related to obesity, stress, anxiety, mood, and drug dependence. Pharmacol Ther 141:283–299.
3. Green MK, Barbieri EV, Brown BD, Chen KW, Devine DP (2007): Roles of the bed nucleus of stria terminalis and of the amygdala in N/OFQ-mediated anxiety and HPA axis activation. Neuropeptides 41:399–410.
4. Andero R, Brothers SP, Jovanovic T, Chen YT, Salah-Uddin H, Cameron M, *et al.* (2013): Amygdala-dependent fear is regulated by Oprl1 in mice and humans with PTSD. Sci Transl Med 5:188ra73.
5. Zhang Y, Gandhi PR, Standifer KM (2012): Increased nociceptive sensitivity and nociceptin/orphanin FQ levels in a rat model of PTSD. Mol Pain 8:76.
6. Narendran R, Tollefson S, Fasenmyer K, Paris J, Himes ML, Lopresti B, *et al.* (2019): Decreased nociceptin receptors are related to resilience and recovery in college women who have experienced sexual violence: Therapeutic implications for posttraumatic stress disorder. Biol Psychiatry 85:1056–1064.

7. Der-Avakian A, D'Souza MS, Potter DN, Chartoff EH, Carlezon WA Jr, Pizzagalli DA, Markou A (2017): Social defeat disrupts reward learning and potentiates striatal nociceptin/orphanin FQ mRNA in rats. Psychopharmacology 234:1603–1614.
8. Andero R (2015): Nociceptin and the nociceptin receptor in learning and memory. Prog Neuropsychopharmacol Biol Psychiatry 62:45–50.
9. Millon EM, Chang HYM, Shors TJ (2018): Stressful life memories relate to ruminative thoughts in women with sexual violence history, irrespective of PTSD. Front Psychiatry 9:311.
10. Rabellino D, Densmore M, Harricharan S, Jean T, McKinnon MC, Lanius RA (2018): Resting-state functional connectivity of the bed nucleus of the stria terminalis in post-traumatic stress disorder and its dissociative subtype. Hum Brain Mapp 39:1367–1379.