The Complex Role of Nociceptin Signaling in Stress: Clarity Through Neuroimaging?

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Shortly after it became the first orphan G protein–coupled receptor successfully cloned, the eponymously named nociceptin opioid peptide/orphaninFQ receptor (NOPR) and its endogenous ligand (N/OFQ) were speculated to mediate behaviors beyond nociception (1). Given the high levels of expression of N/OFQ and NOPR in hypothalamic, limbic, and monoaminergic structures across the mammalian brain (2,3), focus quickly turned toward the investigation of how this novel opioidergic system regulated stress and affective behaviors, such as anxiety and depression.

To date, much of what we know regarding the role of N/OFQ and NOPR in stress has come from experiments in laboratory rodents. Numerous studies have demonstrated that central administration of N/OFQ as well as small molecule agonists of NOPR produces an anxiolytic effect and reduces release of the primary stress hormone corticosterone (analogous to cortisol in humans). Further, global knockout of N/OFQ or antagonism of NOPR is sufficient to increase corticosterone and reduce adaptive responses to acute stressors. Finally, various acute stressors (e.g., social stress and restraint stress) increase the expression of both N/OFQ and NOPR across limbic regions. While these data are suggestive of an antistress effect of nociceptin signaling, it is worth noting that not all reports support this hypothesis [for a comprehensive review of stress/anxiety–related N/OFQ and NOPR findings, see (4)] and that antagonism of NOPR appears to elicit an antidepressant-like, pro-motivating effect (3), indicating a more complex relationship between nociceptin signaling and emotional behavior. Numerous potential explanations for these inconsistent findings exist, some methodological (differences in species, stress exposure, and timing of behavioral and neurochemical measurements) and others biological (differential effects of stress on nociceptin signaling in discrete brain circuits).

Given that preclinical research seeks to improve our understanding of how these systems are impacted in human disease and to harness this knowledge for therapeutic benefit, it is tempting to look for consistency in the human literature on the interplay between stress and N/OFQ signaling. Unfortunately, there is a dearth of studies in this area, mostly owing to the lack of sufficient tools to assess N/OFQ or NOPR in vivo in human subjects with high selectivity. Capitalizing on recent optimizations in the development of positron emission tomography (PET) radioligands with high affinity for NOPR (5), a single study has thus far examined this interaction. The authors demonstrate that NOPR radioligand binding is increased in women who recently experienced sexual trauma and that NOPR density was positively associated with posttraumatic stress disorder symptoms (6). However, it cannot be ascertained which aspect of stress (physiological vs. psychogenic) was responsible for the change in NOPR binding in this study.

In this issue of Biological Psychiatry, Flanigan et al. (7) attempt to bypass the aforementioned discrepant rodent findings and directly test how administration of a stress hormone alters NOPR availability in the brain of healthy human subjects. To answer this question, Flanigan et al. (7) conducted baseline stress and anxiety assessments prior to an initial PET scan using the radioligand \( [^{11}C] \text{NORP-1A} \) in 19 male and female subjects. Subjects were then injected intravenously with hydrocortisone (exogenously administered cortisol, the primary stress hormone in primates), and their heart rate and blood pressure were measured for 2 hours. Posthydrocortisone anxiety and depression assessments were made 1 hour after hydrocortisone injection. A second PET imaging session was performed 3.5 hours after injection, a time point at which there is significant elevation in NOPR in preclinical studies following an acute stressor (8).

Recognizing that NOPR expression is widespread throughout the central nervous system, the authors opted not to make region-specific hypotheses of how hydrocortisone would affect NOPR binding. Instead, they examined brain regions that have been previously linked to mediating stress effects on nociceptin signaling (amygdala, hippocampus, and ventral striatum) and several regions that have not been thoroughly characterized (e.g., caudate, putamen, cerebellum, and prefrontal cortex). Surprisingly, modest increases (10% to 15%) in radioligand binding to NOPR were observed across all brain regions following hydrocortisone administration, suggesting that after stress there may be brain-wide upregulation of NOPR expression and/or a decrease in endogenous nociception release, allowing for more PET ligand to bind. While the absolute value of change in total distribution volume in NOPR binding was small, almost all subjects exhibited an increase from baseline across regions following hydrocortisone injection. Intriguingly, these data appear to be in contrast to the authors’ previous report of a selective increase in NOPR binding selectively in the midbrain and cerebellum of women who recently experienced an extremely stressful sexual trauma (6).

One interpretation of these findings is that specific types of stressors may induce nociceptin release and/or modify NOPR expression in discrete brain regions, whereas global elevation of peripheral cortisol acts in a nonspecific manner to upregulate NOPR throughout the central nervous system. Preclinical studies also lend support to this idea (although these studies did not typically take an unbiased approach to region selection), with social and restraint stressors altering N/OFQ and...
In summary, while the precise role of N/OFQ and NOPR in stress and stress-induced behaviors remains unclear, the work presented here by Flanigan et al. (7) convincingly demonstrates a correlation between increased circulating stress hormones and increased brain NOPR expression and shows that this change in expression occurs in regions outside of those typically associated with stress and emotion processing. Basic science researchers should seek to translate these findings into rodents to better understand how NOPR expression in distinct brain regions, particularly those that have been less thoroughly studied, contributes to stress susceptibility and resilience.

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**Article Information**

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**References**

