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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 (GPCR) 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 anti-stress 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).

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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 NOPR radioligand binding is increased in women who recently experienced sexual trauma, and that NOPR receptor density was positively associated with post-traumatic 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. In order to answer this question, Flanigan and colleagues (7) conducted baseline stress and anxiety assessments prior to an initial PET scan using the radioligand [^{11}C]NOP-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 two hours. Post-hydrocortisone anxiety and depression assessments were made one 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 pre-clinical studies following an acute stressor (8).

Recognizing that NOPR expression is widespread throughout the CNS, 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 the ventral striatum), and several regions that have not been thoroughly characterized (e.g., caudate, putamen, cerebellum, and prefrontal cortex). Surprisingly, modest increases (10–15%) in radioligand binding to NOPR was observed across all brain regions following hydrocortisone, 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 ΔV_T in NOPR binding was small, almost all subjects exhibited an increase from baseline across regions following hydrocortisone. 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 non-specific manner to upregulate NOPR throughout the CNS. 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 NOPR expression in specific limbic regions such as the hippocampus and subregions of the amygdala, as well as hypothalamic regions that release corticotropin releasing factor (CRF) (4). Further evidence for this interpretation comes from a negative finding emerging from the study by Flanigan and colleagues (7) that hydrocortisone treatment did not increase stress or anxiety in their subjects an hour after injection (in fact, subjects were significantly less anxious and stressed relative to baseline). Combined with their PET findings, this suggests that the subjective experience of stress may recruit precise circuits that cause nociceptin peptide release and NOPR regulation, while increases in brain CRF via peripheral cortisol administration are sufficient to globally alter NOPR expression even in the absence of stress and anxiety. Future experiments should seek to determine whether stressors of various modalities affect NOPR binding in discrete brain regions, and whether blockade of glucocorticoid signaling could prevent these changes.

An antagonistic relationship between stress hormones such as CRF and nociceptin signaling has been speculated for over a decade. Pre-clinical data suggest that a key locus for this functional antagonism is the amygdala and its extended nuclei, and that this regulation occurs at the level of NOPR and not N/OFQ. Reports indicate that acute stress upregulates NOPR expression in the central and basolateral amygdala without altering N/OFQ peptide levels (8) and that central administration of CRF upregulates NOPR expression in the bed nucleus of the stria terminalis (BNST) (9). The work reported by Flanigan and colleagues (7) is the first evidence that this functional antagonism may be present in humans, and that a compensatory upregulation in NOPR in response to elevations in circulating stress hormones may be more widespread across the brain than previously thought.

An intriguing sub-analysis performed by the authors demonstrated negative correlations between NOPR binding before and after hydrocortisone administration across all regions of interest (though only significantly in the amygdala and striatal subregions following multiple comparison correction). The authors postulate that this is potential evidence that subjects with more internalized NOPR at baseline have more receptors available to be upregulated following stress hormone exposure. This prediction would also suggest that subjects with low baseline V_T (and thus more internalized receptors) may have elevated levels of N/OFQ release across the brain, as receptor internalization of G-protein coupled receptors (GPCRs) occurs after extended agonist binding. Consistent with this, stress has been shown to reduce N/OFQ in the basal forebrain (10), which includes the ventral aspects of the striatum and is densely connected to the amygdala, both identified here as regions where baseline NOPR binding predicted post-hydrocortisone activity. In order to evaluate whether this relationship is in some way causal, future studies must determine whether [^{11}C]NOP-1A binds to internalized NOPR and the precise time-frame during which receptor upregulation occurs. Furthermore, the authors should consider nociceptin peptide release dynamics across brain regions and not simply as a total measure brain-wide, as local nociception release has been demonstrated, particularly in states of demanding motivation (3). Only then can firm conclusions be drawn regarding whether baseline NOPR expression might confer any stress resilience or susceptibility.

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 and colleagues (7) convincingly demonstrates a correlation between increased circulating stress hormones and increased brain NOPR expression, and 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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