Commentary

Biological Psychiatry

Hormone-Tuned Fear Circuits: Estrous Regulation of Corticotropin-Releasing Factor Neurons in the Bed Nucleus of the Stria Terminalis

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Fear-related disorders such as posttraumatic stress disorder, specific phobias, and panic disorder are marked by intense anxiety and changes in how fear is processed and remembered. These conditions affect between 4.7% and 12.5% of the global population, which translates to more than 380 million people (1). Women are nearly twice as likely as men to be diagnosed with one of these disorders. Despite well-documented sex differences, female participants have historically been underrepresented in both clinical and preclinical fear research. In recent years, however, there have been increasing efforts to better understand sex differences in fear processing, which may help find better treatments. Current treatments for fear-related disorders include psychotherapy, antidepressants, and anxiolytics. However, there are currently no pharmacological interventions specifically designed to target these fear-related disorders. A limited understanding of the mechanisms underlying fear processing prevents the development of more effective therapies (2). The bed nucleus of the stria terminalis (BNST) is one of the most sexually dimorphic structures involved in fear processing and is therefore an interesting target for studying sex differences in fear processing (3).

In the current issue of *Biological Psychiatry*, Chudoba and Dabrowska (4) present a tour de force in combining electrophysiology, behavior, neuropharmacology, and molecular biology for the study of sex differences in fear processing. The authors examine how sex and estrous cycle stage regulate corticotropin-releasing factor (CRF) neurons in the dorsolateral BNST ($BNST_{DL}$) in rats. The study reports that in females, $BNST_{DL}$ CRF neurons display greater excitability and distinct synaptic input patterns compared with neurons in males, with these properties fluctuating across the estrous cycle. Using chemogenetic approaches, Chudoba and Dabrowska show that $BNST_{DL}$ CRF neurons influence anxiety-potentiated startle in a sex-dependent manner, with sustained fear responses emerging during low-hormone phases in female rats. Importantly, after exposure to unpredictable fear conditioning, female rats demonstrated stronger contextual fear responses than male rats. Notably, this difference does not appear to be linked to CRF neuronal activity or the phase of the estrous cycle, pointing to a possible mechanistic separation between anxious arousal and contextual fear as assessed by anxiety-potentiated startle. These results link sex-specific cellular mechanisms to behaviors relevant to fear-related disorders, emphasizing the female hormonal modulation of fear circuits.

Chudoba and Dabrowska (4) acknowledge that hormonal modulation also occurs in males, which, in my view, represents an important direction for future investigation that currently lacks proper methods in neuroscience for both human studies and rodent studies. Hormonal modulation can be assessed in two ways: indirect methods that provide estimates of sex hormone levels (e.g., monitoring the menstrual or estrous cycle in females) and direct methods that allow precise quantification (e.g., measuring hormone concentrations in saliva or blood). These approaches are complementary, as the menstrual and estrous cycles reflect complex, coordinated physiological processes that encompass broader effects in the brain than the measurement of sex hormones such as estradiol, progesterone, or testosterone. Direct methods for obtaining blood samples in rodents are invasive and require training of the experimenter and habituation of the rodents to minimize the animals' stress during the procedure. Thus, indirect methods can be more easily implemented in many rodent laboratories and provide robust data about sex hormonal modulation, as shown in Chudoba and Dabrowska (4) using vaginal cytologies. However, unlike females, males do not have a stereotyped, repeatable cycle equivalent to the menstrual or estrous cycles, which makes longitudinal direct hormonal assessments necessary to capture male gonadal hormone dynamics. In males, monitoring of social dominance hierarchies (e.g., using the confrontation tube test or other dominance assays) serves as an indirect behavioral proxy for variations in anabolic-androgenic hormones like testosterone and its derivatives, which fluctuate with social and environmental contexts (5). Unfortunately, it is complicated to combine monitoring social dominance hierarchies with fear studies, as monitoring social dominance hierarchies requires many experimental days and can be stressful for the animals, potentially influencing subsequent fear procedures (6). Thus, it would be ideal to discover noninvasive indirect methods in male rodents that can also be applied in female rodents to monitor hormonal modulation in real time. A similar challenge exists for indirect hormonal estimations in men, as there are currently no well-established protocols. For now, such indirect methods are lacking in men and male rodents, representing a significant roadblock for neuroscience research that needs to be urgently addressed. Complementing the insights from hormonal modulation, sex-specific patterns of gene expression in distinct neuronal populations will provide additional information on the mechanisms of fear processing.

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In studies of sex differences in fear processing and expression levels of neuropeptides, few studies have focused on whether different signaling molecules are expressed within the same neurons. The observation by Chudoba and Dabrowska (4) that striatal-enriched protein tyrosine phosphatase (STEP) is coexpressed with CRF 3 times less often in females than in males reveals a potential molecular basis for sex differences in fear processing. Because STEP influences synaptic plasticity and neuronal excitability, reduced coexpression in females suggests that CRF neurons in the $BNST_{DL}$ may function or adapt differently to fear processing. Concordantly, in vitro electrophysiological recordings showed that $BNST_{DL}$ CRF neurons exhibit greater excitability in females than in males, regardless of estrous cycle phase. Taken together, these findings may help illuminate neuronal mechanisms that contribute to the increased vulnerability of women to fear-related disorders. However, further research is needed to confirm and clarify this association. Building on these mechanistic insights, it is increasingly important to explore how sex-dependent differences in CRF signaling might translate to human physiology and inform the development of targeted therapeutic strategies.

The Chudoba and Dabrowska (4) study could have meaningful applications in humans, particularly through the future development of treatments that target CRF, either on its own or in combination with psychotherapy. The CRF signaling system includes two main receptors—CRF_1 receptor (CRF1R) and CRF_2 receptor (CRF2R)—both found in the central nervous system. CRF1R is mostly concentrated in the brain, while CRF2R also plays an important role in peripheral organs (7). These receptors differ significantly between species and show distinct patterns of distribution and function throughout the brain. Gaining a deeper understanding of these differences, including the sex and hormonal variations highlighted by Chudoba and Dabrowska, could help bridge the gap between preclinical CRF research and its clinical use. While large-scale clinical trials have not yet demonstrated the efficacy of CRF-targeting drugs in treating fear-related conditions in humans, existing research continues to offer encouraging insights, particularly in the context of acute stress responses. That said, it is important to note that Chudoba and Dabrowska did not incorporate CRF-targeting pharmacological agents into their experimental design, leaving open the question of whether the observed effects were directly mediated by CRF signaling. Consequently, it remains uncertain whether the observed effects were specifically mediated by CRF signaling. Furthermore, the possibility that DREADD (designer receptors exclusively activated by designer drugs)-induced neuronal activation influenced release of GABA (gamma-aminobutyric acid) cannot be excluded, particularly given that GABAergic neurotransmission is known to fluctuate across the estrous cycle. To better understand how these findings might inform future treatments, they can be viewed through broader theoretical models.

The current findings (4) can be interpreted through several theoretical lenses that connect stress and fear-related brain mechanisms to long-lasting anxiety. One useful framework is the dual-process model of fear and anxiety, which suggests that the BNST is responsible for sustained anxiety responses. Interestingly, $BNST_{DL}$ CRF neurons show an unexpected anxiolytic role, reducing anxious arousal in diestrus females. This effect suggests that their anxiolytic function becomes active when estrogen levels are low and progesterone levels are rising. This is apparently an interesting contradiction with previous research showing that the BNST is involved in responses to uncertain or prolonged threats, which differ from the rapid, short-term fear responses typically driven by the amygdala (8). Thus, further investigation will help clarify the mechanisms underlying the role of $BNST_{DL}$ CRF neurons across hormonal states in fear and anxiety. From an allostatic perspective, this hyperexcitability might reflect a long-term adaptation to hormonal fluctuations, potentially increasing the body's allostatic load and susceptibility to stress and fear-related disorders (9). When viewed through the lens of predictive coding, the hormonal changes described here could influence how threat predictions are updated in females, contributing to fear-related disorders (10). Taken together, these perspectives suggest that $BNST_{DL}$–CRF circuits may serve as a crucial link between hormonal regulation, neural activity, and the development of sex-specific vulnerability to fear-related disorders.

I anticipate that the fascinating findings of Chudoba and Dabrowska (4) will stimulate future research, especially on 1) how $BNST_{DL}$ CRF neurons interact with other circuits and brain areas, such as the central amygdala or the hypothalamus; 2) the dynamic modulation of STEP or other phosphatases by hormonal fluctuations across the estrous cycle; 3) real-time in vivo recording of $BNST_{DL}$ CRF neuronal activity during fear conditioning procedures; 4) how chronic generalization caused by the persistent effect on anxiety-potentiated startle shown in females resembles sustained anxiety in humans, suggesting that $BNST_{DL}$–CRF circuit may be a relevant mechanism in this process; and 5) further studying whether the sex differences uncovered in this study are organizational (developmental) or activational (hormone dependent).

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