Corticotropin Releasing Factor Activates Different Circuits in Male and Female Rats
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Introduction
Stress-related psychiatric disorders, such as anxiety and depression, occur twice as frequently in women as in men. Corticotropin-releasing factor (CRF) orchestrates the stress response and is dysregulated in these disorders. Thus, sex differences in responses to CRF could contribute to the sex bias in disease prevalence. We previously identified sex differences in CRF, receptor signaling and trafficking in the locus coeruleus (LC) that render LC neurons of female rodents more sensitive to CRF. However, the extent of sex differences in CRF responses and their behavioral consequences remain unknown. Here we began to address these questions by examining how central CRF alters anxiety-related behavior and activates brain regions in male and female rats.

Methods

Design

Fig. 1. Schematic depicts the experimental design. CRF-evoked behaviors were scored by a rater blind to the condition as depicted below. Tissue was processed for cFOS immunohistochemistry and counts were conducted on four sections per brain region by a rater blind to the condition.

CRF-Evoked Behavior in Males and Females Across the Estrous Cycle

Burying  Headshakes  Grooming

Fig. 2. Depiction of CRF-evoked behaviors. Burying is a defensive coping strategy. Headshakes are related to high arousal. Grooming is an anxiety-related, displacement behavior associated with arousal reduction.

Fig. 3. Central infusions of CRF (0.5µg) evoked more behaviors than a vehicle (aCSF) infusion for all hormonal conditions. For grooming, females in the proestrus phase of the cycle groomed more than males and diestrus females treated with CRF. Asterisks indicate (p<0.05).

Table 1. Mean cFOS profiles ± SEM in regions where there was no effect of the p-values reflect the hormonal status by drug interaction.

<table>
<thead>
<tr>
<th>Region</th>
<th>Testosterone</th>
<th>Diestrus</th>
<th>Proestrus</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dorsal Raphe Lateral</td>
<td>97.9±</td>
<td>103.8±</td>
<td>104.5±</td>
<td>153.3±</td>
</tr>
<tr>
<td></td>
<td>103.8±</td>
<td>104.5±</td>
<td>153.3±</td>
<td>0.509</td>
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<td></td>
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</tbody>
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Fig. 4. CRF increased cFOS positive cells more than aCSF, regardless of sex or hormonal condition, for the paraventricular nucleus of the hypothalamus (PVN), medial prefrontal cortex (mPFC), and the septum. Asterisks indicate (p<0.05).

Fig. 5. Photomicrographs depict cFOS positive cells in the basal nucleus (LDTg), periaqueductal gray (PAG), and ventral medial dorsal raphe (vmDR) for CRF treated rats (left). CRF increased cFOS positive neurons only in the diestruis group for these regions. Asterisks indicate (p<0.05).

Fig. 6. Photomicrographs depict cFOS positive cells in the basal nucleus and nucleus accumbens shell in CRF treated rats (right). CRF significantly increased cFOS in these regions in males and proestrus females, but not in diestruis females. Asterisks indicate (p<0.05).

Fig. 7. Photomicrographs depict cFOS-positive neurons in the LC in CRF treated rats (above). CRF increased cFOS positive neurons in females, regardless of hormone condition, but not males. Asterisks indicate (p<0.01).

Conclusions

• CRF administered centrally significantly increased grooming in proestrus females compared to diestruis female and male rats. Because the proestrus is the estrous cycle phase when levels of progesterone and estrogen are higher, this result suggests that one or both of these hormones potentiate the effect of CRF.

• In contrast, when cFOS profiles were assessed following central CRF, it was often the diestruis, not proestrus, females that had a different activation than other groups. Given that the CRF-evoked behavior of diestruis females was more similar to males, this suggests that the circuits activated in this group may be in part compensatory, aimed at keeping female behavior similar to that of males.

• The differential effect of CRF on various circuits in males and females could be an important mechanism by which sex differences in stress responses, anxiety, and stress-related disorders are established.

Acknowledgements: The authors wish to thank Nina Duncan for the artwork, as well as, Sabina Khantsis and Hannah Simko for their technical assistance. Supported by PHS grant MH092438 to DAB.