Corticotropin-Releasing Factor Activates Different Circuits in Male and Female Rats

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Abstract

Background: Stress-related psychiatric disorders, such as post-traumatic stress disorder and major depression, occur twice as frequently in women as men. Corticotropin-releasing factor (CRF) orchestrates the stress response and is hypersecreted 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_1 receptor signaling and trafficking in the locus coeruleus (LC) that render LC neuronal responses to CRF greater in female than male rodents. However, the extent of sex differences in CRF sensitivity has not been systematically explored. Here we begin to address this question by examining how the central administration of CRF differentially regulates behavior and activates stress-related brain regions in adult male and female rats.

Methods: See adjacent panels.

Results: See adjacent panels.

Discussion: See adjacent panels.

CRF-Evoked Grooming in Males and Cycling Females

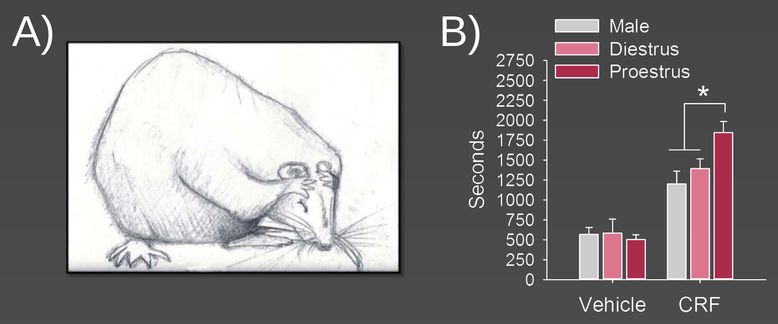

Fig. 1. Ovarian hormones regulate CRF-evoked grooming. A) Depiction of CRF-evoked grooming, which is thought to be a displacement behavior associated with anxiety reduction. B) Central ovine CRF (0.3 µg) increases grooming, an effect that is greatest in proestrus females. Asterisk indicates (p<0.05).

Analysis of CRF-Induced Neuronal Activation

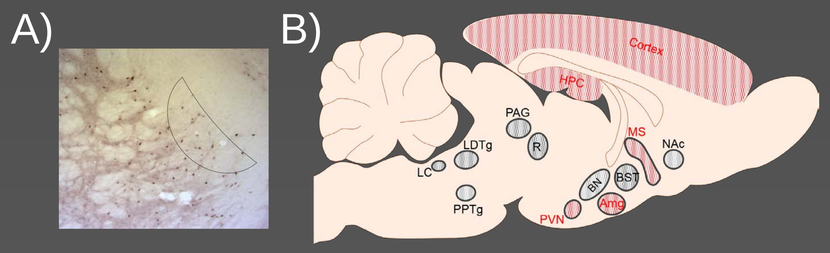

Fig. 2. CRF-induced neuronal activation was measured with the immediate early gene, cFOS. A) Example of cFOS labeling in the basal nucleus of Meynert. The line demarcates the region of interest where cFOS positive profiles were quantified. B) The schematic depicts the regions analyzed. Regions in red indicate where cFOS profiles were similarly increased by CRF in all groups.

Brain Regions Where CRF-Induced Neuronal Activation Differed Based on Hormonal Status

Region	Testosterone		Diestrus		Proestrus		p-value
	aCSF	CRF	aCSF	CRF	aCSF	CRF	Interaction
Nucleus Accumbens (NAc)	77.0 ± 14.6	157.0 ± 16.9	122.0 ± 18.5	126.3 ± 17.9	93.8 ± 21.1	201.9 ± 26.2	0.031
Basal Nucleus of Meynert (BN)	9.7 ± 2.2	28.8 ± 4.0	16.6 ± 3.0	17.5 ± 2.5	12.8 ± 2.0	36.3 ± 4.7	0.005
dorsomedial Periaqueductal Gray (dmPAG)	36.0 ± 6.4	23.6 ± 3.12	42.8 ± 8.1	80.4 ± 10.1	30.1 ± 6.1	36.6 ± 5.6	0.002
ventromedial Dorsal Raphe (vmDR)	49.1 ± 15.0	38.9 ± 3.7	34.9 ± 4.7	96.8 ± 13.8	67.3 ± 13.7	84.0 ± 17.0	0.017
laterodorsal Tegmental Nucleus (LDTg)	46.7 ± 7.2	40.9 ± 4.9	35.2 ± 5.4	64.8 ± 7.4	33.5 ± 5.8	47.9 ± 8.3	0.031
dorsomedial Periaqueductal Gray (dmPAG)	36.0 ± 6.4	23.6 ± 3.12	42.8 ± 8.1	80.4 ± 10.1	30.1 ± 6.1	36.6 ± 5.6	0.002
Locus Coeruleus (LC)	66.5 ± 10.9	105.7 ± 14.9	61.4 ± 10.8	235.7 ± 27.2	86.1 ± 10.9	163.8 ± 25.4	0.001

Correlations Between Neuronal Activation and Grooming

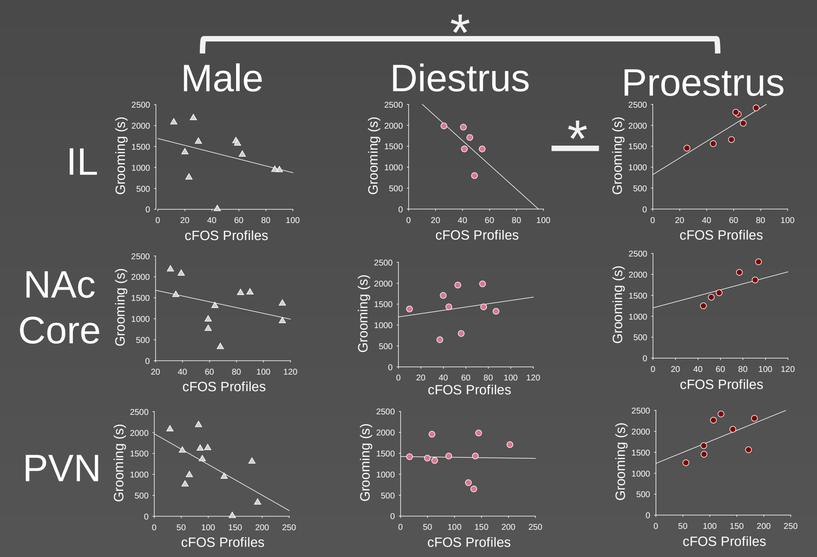

Fig. 3. The nature of the relationship between CRF-induced neuronal activation and grooming behavior differed across hormonal cycle for the infralimbic cortex (IL), NAc core, and paraventricular nucleus (PVN), Fisher's Z transformations revealed significant differences between the correlations for males and proestrus females in all three regions, as well as between diestrus and proestrus females in the IL.

Hormonal Status Alters the Functional Connectivity of CRF-Activated Networks

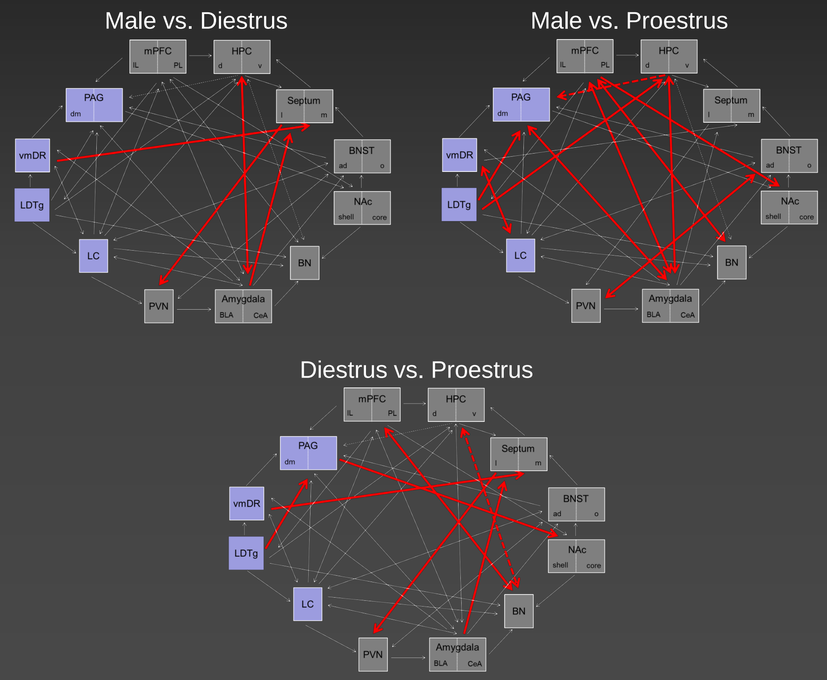

Fig. 4. CRF-activated functional connectivity networks. cFOS profiles were correlated between brain regions and Fisher's Z transformations revealed whether the nature of the correlations differed between the groups. Arrows indicate anatomical connections. Red arrows depict significant group differences between correlated brain regions.

Conclusions

- CRF evoked more grooming in proestrus female rats than diestrus female and male rats. Proestrus is the estrous cycle phase when levels of progesterone and estrogen are higher, so this result suggests that one or both of these hormones potentiate the effect of CRF on grooming.
- In some cases, CRF activation of brain regions differed depending on hormonal status. Additionally, for the IL, NAc core, and PVN, the nature of the relationship between CRF-induced neuronal activation and grooming was dependent on hormonal status.
- Patterns of network activation by CRF differed, in part, based on hormonal status. This analysis can inform future studies to determine whether hormonal status should be considered in the design.
- 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.

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