Disinhibition of female sexual behavior by a CRH receptor antagonist in Syrian hamsters

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Disinhibition of female sexual behavior by a CRH receptor antagonist in Syrian hamsters. Am J Physiol Regul Integr Comp Physiol 283: R591–R597, 2002. First published May 30, 2002; 10.1152/ajpregu.00233.2002.—Several conditions that inhibit female sexual behavior are thought to be associated with altered corticotropin-releasing hormone (CRH) activity in the brain. The present experiments examined the hypothesis that endogenous CRH receptor signaling mediates the inhibition of estrous behavior by undernutrition and in other instances of sexual dysfunction. Intracerebroventricular (ICV) infusion of CRH or urocortin inhibited estrous behavior in ovariectomized steroid-primed hamsters. Conversely, ICV infusion of the CRH receptor antagonist astressin prevented the suppression of estrous behavior by food deprivation or by ICV administration of neuropeptide Y. Astressin treatment also induced sexual receptivity in nonresponders, animals that do not normally come into heat when treated with hormones, and this effect persisted in subsequent weekly tests in the absence of any further astressin treatment. Activation of the hypothalamo-pituitary-adrenocortical axis was neither necessary nor sufficient to inhibit estrous behavior, indicating that this phenomenon is due to other central actions of CRH receptor agonists. This is the first direct evidence that CRH receptor signaling may be a final common pathway by which undernutrition and other conditions inhibit female sexual behavior.

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A NUMBER OF naturally occurring environmental challenges inhibits reproduction, including sexual behaviors, in female mammals. In women, conditions such as undernutrition, chronic stress, and depression have been reported to dampen sexual desire and satisfaction. These diverse conditions are associated with altered corticotropin-releasing hormone (CRH) activity in the brain (1, 12, 13), and work with experimental animals indicates that CRH suppresses estrous behavior. CRH infusion into the medial preoptic area, mesencephalic central gray (MCG), or lateral ventricle inhibits estrous behavior in ovariectomized, steroid-primed rats (33–35), and female transgenic mice that overexpress CRH do not mate (10). Furthermore, infusion of anti-CRH-gamma globulin into the MCG produces a long-lasting facilitation of lordosis in rats (33, 34). Strangely, this work has not been pursued to any degree in recent years.

Our work has focused on the behavioral aspects of nutritional infertility, the phenomenon where an insufficient supply of oxidizable metabolic fuels inhibits reproduction, particularly in female mammals. Indeed, of the various environmental factors influencing reproduction, food availability seems to play the most significant role (3). During nutritional challenges, information about metabolic fuel availability appears to be detected in the caudal hindbrain and then transmitted synaptically to the forebrain circuits that control female sexual behavior (6, 19, 23, 24, 39). Neuropeptide Y (NPY) is one neuromodulator that may play a significant role in this process. The visceral hindbrain sends NPY-containing projections to the forebrain, including the paraventricular nucleus of the hypothalamus (PVN) (31); NPY terminals are found in close proximity to CRH cell bodies in the forebrain (17, 20), and intracerebroventricular (ICV) administration of NPY inhibits estrous behavior in rats and hamsters (4, 5). Thus it is possible that underfeeding inhibits estrous behavior via NPY modulation of CRH signaling. To test this conjecture, we examined the effects of ICV treatment with CRH, urocortin, NPY, and the CRH receptor antagonist astressin (25) on female sexual behavior in Syrian hamsters.

MATERIALS AND METHODS

Animals and surgery. Female Syrian hamsters (Mesocricetus auratus) weighing between 80 and 100 g were obtained from Charles River Breeding Laboratories. Animals were singly housed in wire-bottom, stainless steel cages (17.5 × 17.5 × 24.5 cm) in a room maintained at 20°C with a 14:10-h light-dark cycle (lights on at 0700) and fed PMI Laboratory Rodent Diet 5001 placed in hoppers mounted on the outside of the cages. Food and water were available ad libitum except where indicated. After a 1-wk period of adaptation to the laboratory, hamsters were anesthetized using pentobarbital sodium (80 mg/kg), supplemented when necessary with methoxyflurane (Metofane), and bilaterally ovariectomized. At the same time, each hamster was implanted with a unilateral...
stereotactically guided cannula aimed at the lateral ventricle. The cannula was placed 1.1 mm rostral to bregma, 1.7 mm lateral to the midline, and 1.2 mm ventral to the dura mater (5). The University of Massachusetts Institutional Animal Care and Use Committee approved all procedures.

Behavior testing. To determine whether experimental animals were responsive to hormones, they were given a screening test. One week following surgery, hamsters were administered a priming dose of 2.5 μg estradiol benzoate (EB; Sigma Chemical) dissolved in sesame oil, followed 42 h later with 500 μg progesterone (P; Sigma Chemical) dissolved in 5% benzyl alcohol, 15% benzyl benzoate in sesame oil, and administered subcutaneously. One week following the initial priming dose, hamsters were administered the same steroid regimen, but this time, hamsters were screened for the display of sexual receptivity, 6 h after P injection. Behavioral testing took place between 1200 and 1500. Testing was conducted as follows. Each hamster was placed alone in a Plexiglas arena (30 × 36 × 30 cm) for 5 min. After the 5-min habituation to the testing chamber, a sexually experienced male hamster was placed in the test chamber with the female for 3 min while the experimenter continually brushed the female’s flanks with a soft artist’s paintbrush to ensure that they received consistent tactile stimulation. The male was permitted to investigate and mount the female but not to intromit. During the test, the amount of time that the female spent in lordosis was recorded (27). The animals that displayed lordosis durations of <40 s in two consecutive weekly tests were classified as nonresponders and used in separate experiments. At least 1 wk elapsed between behavioral tests. In experiments in which food intake was measured, animals were deprived of food for 1 h before ICV drug infusions (to synchronize the onset of a meal), fresh pellets were placed in the animal’s home cage, and food intake was measured to the nearest 0.1 g and corrected for spillage.

Drug infusions. ICV injections were made 30 min before the start of lordosis testing. This procedure involved replacing the obturator with an injector that extended 1.0 mm beyond the tip of the guide cannula. Each injector was connected by saline-filled polyethylene (PE) tubing to a 50-μl syringe controlled by an infusion pump. A small air bubble separated saline in the PE tubing from ICV solutions. The volume of ICV infusions was 5 or 15 μl, delivered over a 1- or 3-min period (5). All peptides were obtained from the American Peptide and dissolved in artificial cerebrospinal fluid (aCSF; Harvard Apparatus) for infusion.

Restraint stress. Ovariectomized, steroid-primed animals were placed in Plexiglas cylinders (15-cm long, 3.8-cm inner diameter) for 3 h before testing. One group was tested immediately upon removal from the restraining tubes, and another group was returned to their home cages for 30 min before testing. Controls remained undisturbed in their home cages. All animals were deprived of food and water during the 3.5 h before testing. Immediately following testing, animals were decapitated and blood was collected.

Corticosteroid RIA. For serum corticosteroid measurements, animals were decapitated within 1 min of handling. Samples were taken between 1300 and 1500, the approximate time of behavioral testing. Trunk blood was allowed to clot for 24 h at 4°C and was separated by centrifugation at 3,000 g for 30 min. Serum was aspirated and immediately frozen at −20°C until the radioimmunoassays were performed. Serum cortisol and corticosterone levels were determined in duplicate using Coat-A-Count single-antibody radioimmunoassay kits (Diagnostic Products) previously shown to produce reliable results in hamsters (15). The standard curve was linearized (cortisol: \( R^2 = 0.995 \) and corticosterone: \( R^2 = 0.9989 \)). The cortisol assay detection limit was 2.0 ng/ml with a coefficient of variation of 1.7, and the corticosterone assay detection limit was 5.7 ng/ml with a coefficient of variation of 6.8.

Statistical analyses. Animals were randomly placed into treatment groups by body weight with the use of a Latin square design. The use of this design ensured that each group had a similar mean body weight and was used in all randomization procedures. Repeated testing of CRH and urocortin was analyzed with a two-way mixed ANOVA. All other experiments involved a single behavioral measure and were analyzed by a one-way ANOVA with treatment as the factor. Significant results at \( \alpha = 0.05 \) were followed up with a Fisher’s least significant difference post hoc analysis. For the restraint stress experiment, the cortisol data were not normally distributed, so they were analyzed using nonparametric Kruskal-Wallis ANOVAs on ranks, and the data are reported as medians.

RESULTS

CRH and urocortin infusions. In the first experiment, we examined the effects of ICV infusion of CRH and the CRH receptor agonist urocortin (38) on estrous behavior and food intake in Syrian hamsters. Thirty minutes before the first behavioral test, hormone-primed animals received ICV infusions of 5 μl of aCSF or one of three doses of CRH into the lateral ventricle. Females were given three tests for sexual receptivity at 2-h intervals with sexually active males. Hamsters that received 0.1, 0.2, or 0.6 nmol of CRH all showed a marked suppression of estrous behavior 30 min later \( F(3,19) = 10.63, P < 0.001 \); Fig. 1A). Animals that received CRH had fully recovered 4 h later, producing a significant effect of time \( F(2,38) = 62.16, P < 0.001 \). This experiment was then repeated in a separate group of animals using urocortin. Hamsters that received each of the three doses of urocortin also showed a marked suppression in estrous behavior \( F(3,31) = 5.97, P < 0.01 \), which also dissipated with time (Fig. 1B).

None of the doses of CRH had any effect on 2- or 24-h food intake \( F(3,19) < 1.0 \) \( F(3,19) < 1.0 \), and only the highest dose of urocortin significantly reduced 2- but not 24-h food intake \( F(3,39) = 4.59, P < 0.01 \) \( F(3,36) < 1.0 \) (Table 1).

Astrassin infusions. The fact that exogenous CRH and urocortin suppress estrous behavior does not necessarily mean that the endogenous peptides normally participate in the nutritional control of female sexual behavior. To investigate this question, we used the CRH receptor antagonist astrassin (25). The first experiment determined whether astrassin could prevent CRH-induced suppression of estrous behavior. CRH (1.0 nmol) infusion suppressed estrous behavior (lordosis duration = 7 ± 4 s) compared with aCSF-treated controls (93 ± 30 s), and concurrent ICV administration of astrassin (2.8 nmol) prevented the inhibitory effect of CRH (137 ± 17 s) \( F(2,14) = 13.17, P < 0.001 \). Furthermore, CRH treatment significantly decreased 2-h food intake \( 0.2 ± 0.1 \) g compared with vehicle \( 0.6 ± 0.1 \) g and CRH + astrassin-treated \( 0.6 ± 0.1 \) g animals \( F(2,14) = 3.81, P < 0.05 \).

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on food intake in female hamsters

Table 1. Effect of ICV infusion of CRH or urocortin on food intake in female hamsters

<table>
<thead>
<tr>
<th>Dose, nmol</th>
<th>2-h Intake, g</th>
<th>24-h Intake, g</th>
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<tbody>
<tr>
<td>CRH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>1.0 ± 0.1</td>
<td>14.7 ± 0.7</td>
</tr>
<tr>
<td>0.1</td>
<td>1.0 ± 0.1</td>
<td>13.9 ± 0.5</td>
</tr>
<tr>
<td>0.2</td>
<td>0.9 ± 0.1</td>
<td>14.9 ± 0.7</td>
</tr>
<tr>
<td>0.6</td>
<td>0.7 ± 0.2</td>
<td>15.3 ± 0.4</td>
</tr>
<tr>
<td>Urocortin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td>1.1 ± 0.1</td>
<td>10.9 ± 0.6</td>
</tr>
<tr>
<td>0.1</td>
<td>0.9 ± 0.1</td>
<td>10.9 ± 0.8</td>
</tr>
<tr>
<td>0.2</td>
<td>1.2 ± 0.7</td>
<td>9.9 ± 1.1</td>
</tr>
<tr>
<td>0.6</td>
<td>0.5 ± 0.1*</td>
<td>10.5 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SE. ICV, intracerebroventricular; CRH, corticotropin-releasing hormone. *P < 0.05 vs. vehicle-treated group.

This experiment demonstrates that astressin can prevent the effects of exogenously administered CRH on estrous behavior, but it does not address the issue of whether endogenous CRH plays a role in the nutritionally mediated inhibition of sexual receptivity. We next administered aCSF or astressin (4.2 nmol) to 48-h food-deprived animals (19, 23). Food-deprived hamsters showed a suppression in estrous behavior compared with ad libitum-fed animals, and ICV astressin infusion just before testing reversed this suppression [F(2,37) = 9.86, P < 0.001; Fig. 2A].

We then coadministered NPY (0.48 nmol) and astressin (4.0 nmol) to a new group of ad libitum-fed hamsters. NPY inhibited estrous behavior [F(3,34) = 8.28, P < 0.001] (5), and astressin treatment prevented this effect (Fig. 2B). NPY treatment significantly increased 2-h food intake [F(3,34) = 3.81, P < 0.001], but astressin treatment had no effect whether given alone or with NPY (Table 2).

Astellin in nonresponders. We then tested the effects of astressin in a model of sexual dysfunction in hamsters, nonresponders. A subset of the hamsters (~5–10%) bred in the laboratory or obtained from commercial suppliers does not display normal levels of estrous behavior following usualy adequate steroid priming. For this experiment, we used animals that exhibited lordosis durations of <40 s and actively rejected the males’ sexual overtures in two consecutive weekly tests. Repeated weekly testing detected little or no improvement in nonresponders over time (Fig. 3, ▼). On the other hand, females given an ICV infusion of astressin (4.2 nmol) 30 min before testing with a male on week 3 displayed high levels of sexual receptivity (Fig. 3, ●). Furthermore, these animals continued to

Table 2. Effect of ICV infusion of NPY (0.48 nmol) and astressin (4.0 nmol) on food intake in female hamsters

<table>
<thead>
<tr>
<th></th>
<th>First h, g</th>
<th>Second h, g</th>
<th>24 h, g</th>
</tr>
</thead>
<tbody>
<tr>
<td>aCSF</td>
<td>0.6 ± 0.1</td>
<td>0.3 ± 0.2</td>
<td>12.0 ± 0.8</td>
</tr>
<tr>
<td>Astressin</td>
<td>0.7 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>13.0 ± 0.7</td>
</tr>
<tr>
<td>NPY</td>
<td>0.7 ± 0.1</td>
<td>0.8 ± 0.1*</td>
<td>13.5 ± 0.4</td>
</tr>
<tr>
<td>NPY + astressin</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.1</td>
<td>12.0 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SE. NPY, neuropeptide Y; aCSF, artificial cerebrospinal fluid. *P < 0.05 vs. vehicle-treated group.
show high levels of sexual receptivity in subsequent weekly tests, despite the fact that they never again received astressin \[F(6, 90) = 11.40, P < 0.001\].

Administration of astressin on week 3 was concurrent with the females’ first positive mating experience with a male, raising the possibility that facilitation of sexual receptivity on subsequent tests was contingent on a positive mating experience. This conjecture was assessed by concurrently testing a third group of nonresponders infused with astressin (4.2 nmol) immediately after a negative mating test on \[F(3,22) = 3.06, P < 0.05\] and corticosterone \[F(3,21) = 11.28, P < 0.001\] levels compared with ad libitum-fed animals that received aCSF. Forty-eight hours of food deprivation did not increase either serum cortisol or corticosterone levels (Fig. 5, A and B). Nor did unmanipulated nonresponders exhibit elevated cortisol or corticosterone levels compared with unmanipulated responders (Fig. 5, C and D), indicating that their lack of sexual responsiveness is not due to chronic activation of the HPA axis.

The final experiment determined whether acute activation of the HPA axis by restraint stress would affect estrous behavior. Three hours of restraint stress significantly increased circulating cortisol levels, and steroid levels dropped over the next 30 min \[F(2) = 6.45, P < 0.05\]. On the other hand, restraint stress had no effect on lordosis duration (Fig. 6).

**DISCUSSION**

The effects of stress and CRH on gonadotropin secretion have been studied extensively (29, 30), but less attention has been paid to the effects of CRH receptor signaling on reproductive behaviors. This work reveals that endogenous CRH receptor ligands are likely to play a significant role in the control of female sexual behavior in a number of circumstances.

Astressin treatment reversed the effects of food deprivation and prevented the suppression of estrous behavior in food-deprived hamsters as well as ad libitum-fed or CRH/urocortin-treated hamsters. ICV administration of behaviorally effective doses of urocortin (0.1 nmol), but not CRH (0.1 nmol), 30 min before sampling increased serum cortisol \[F(3,22) = 3.06, P < 0.05\] and corticosterone \[F(3,21) = 11.28, P < 0.001\] levels compared with ad libitum-fed animals that received aCSF. Forty-eight hours of food deprivation did not increase either serum cortisol or corticosterone levels (Fig. 5, A and B). Nor did unmanipulated nonresponders exhibit elevated cortisol or corticosterone levels compared with unmanipulated responders (Fig. 5, C and D), indicating that their lack of sexual responsiveness is not due to chronic activation of the HPA axis.

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behavior by NPY. These findings provide the first direct evidence that endogenous CRH receptor signaling plays a pivotal role in the inhibition of female sexual behavior by undernutrition and fit nicely with what is already known about this phenomenon. During nutritional suppression of estrous behavior, information about metabolic fuel availability is detected in the caudal hindbrain (6, 19, 23, 24, 39), which sends NPY projections to the forebrain, including the PVN (31). NPY release into the PVN is increased when rats are food deprived (11), and NPY treatment increases ACTH secretion (40) and neural CRH immunoreactivity (8) and mRNA (36). Furthermore, cells containing CRH or urocortins send projections to forebrain sites including the ventromedial hypothalamus, medial preoptic area, and lateral septum (18, 37), all of which contain CRH receptors (37) and are involved in the control of estrous behavior (14, 22, 26).

CRH or the urocortins also appear to inhibit estrous behavior in situations unrelated to the level of nutrition. A single infusion of astressin just before behavioral testing permanently restored normal behavioral responsiveness in the animals that had failed to respond to exogenous hormone treatments previously. However, to be effective, astressin had to be infused just before a positive mating test with a male, as astressin infusion immediately after a negative mating test was without effect. This suggests that there is a learned component to this phenomenon. This lasting effect of astressin treatment does not appear to extend to other conditions. For example, ad libitum-fed animals given infusions of astressin as controls (e.g., Fig. 2B) were subsequently used in other experiments where they showed perfectly normal suppression of lordosis following food deprivation (Jones, unpublished data).

It is not clear why some hamsters do not come into heat when given hormone treatments that are effective in the vast majority of animals. Nonresponders are found in both the animals that we purchase from Charles River and those bred in our lab from the same stock. Whatever the ultimate cause, disordered CRH receptor signaling could contribute to this disorder.

Although astressin overcomes the suppression of estrous behavior in a variety of situations, it does not appear to be a universal facilitator of female sexual behavior. We have seen no evidence of facilitation in otherwise untreated animals, and astressin treatment did not overcome the effects of subthreshold hormone priming (Fig. 4). However, this finding seems to stand in contrast with that of Sirinathsinghji (34), who found that infusion of anti-CRH-gamma globulin into the MCG stimulated sexual receptivity in weakly receptive rats given estradiol alone. It is not clear whether this difference is due to species, the site of infusion, the nature of the antagonist, or to some other factors.

Although sexual dysfunction may often be associated with a general activation of the HPA axis, such an activation is neither necessary nor sufficient to inhibit estrous behavior in hamsters. ICV infusion of urocortin, which inhibited estrous behavior, also raised cir-

![Fig. 5. A-B: circulating cortisol and corticosterone in hamsters given the following treatments: fed ad libitum and infused with 5 μl aCSF (n = 7), food deprived for 48 h and infused with 5 μl aCSF (n = 7), fed ad libitum and infused with 0.1 nmol CRH (n = 6), and fed ad libitum and infused with 0.1 nmol urocortin (n = 6). Thirty minutes after infusion, animals were rapidly decapitated, and trunk blood was collected. C-D: circulating cortisol and corticosterone in untreated responders (n = 6) and nonresponders (n = 8). Different letters indicate P < 0.05 vs. one another.](image)

![Fig. 6. Effect of 3-h restraint stress before testing on estrous behavior and plasma cortisol levels in Syrian hamsters. Animals were tested immediately after being removed from the restraint apparatus (restraint, no break, n = 10) or else 30 min later (restraint + break, n = 10). Control animals were left undisturbed in their home cages before testing (n = 10). *P < 0.05 vs. controls.](image)
culating corticosteroid concentrations, but neither food-deprived animals nor ad libitum-fed nonresponders exhibited any increase in hormone levels. Furthermore, acute activation of the HPA axis by restraint stress elevated circulating cortisol levels without having any effect on estrous behavior. Therefore, inhibition of sexual receptivity by CRH or the urocortins is separate and distinct from an activation of the HPA axis.

In these experiments, only the highest doses of CRH (1.0 nmol) and urocortin (0.6 nmol) inhibited food intake, and astressin had no effect at all. Thus changes in estrous behavior need not be accompanied by disruptions of energy balance. These findings stand in contrast to what has been observed in rats, where CRH produces marked suppression in food intake and estrous behavior (2, 7, 33–35). However, only a limited range of doses of CRH has been used in studies of rat estrous behavior. The use of lower doses may make it possible to dissociate the two behavioral responses in rats, too.

Although CRH receptor ligands inhibit female sexual behavior in rats (33–35), hamsters, and white-crowned sparrows (21), this is not the case in all species. For example, ICV administration of CRH facilitates sexual receptivity in female muscle shrews (32), a species in which the HPA axis plays a major role in the control of female sexual behavior. We are aware of only one report that noted a possible role for CRH in male sexual behavior. Oral administration of the CRH type 1 receptor antagonist antalarmin increased masturbation in socially stressed rhesus macaques (9).

This work does not speak to the identity of the endogenous ligand(s), which inhibit female sexual behavior via CRH receptors, nor does it provide any information about the receptor subtype(s) involved. CRH, urocortin, and astressin all bind to both receptor subtypes (25). Furthermore, in addition to CRH, there are at least three urocortins to be found in the brain (16, 28, 38). Identification of the endogenous ligand(s), the receptor subtype(s), and the neural loci mediating their effects on female sexual behavior awaits further investigation. It may be noteworthy that the distribution of urocortin III and the CRH type 2 receptor overlaps with a number of sites involved in the control of estrous behavior (14, 18, 22, 26, 37).

In conclusion, CRH receptor signaling could represent a final common pathway by which undernutrition interferes with female sexual behavior. It will be interesting to determine whether other instances of female sexual dysfunction (e.g., as a consequence, social or physical stressors, depression, and short photoperiods) can be reversed or prevented by CRH receptor antagonists.

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