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Cholecystokinin-Octapeptide Produces Inhibition of Lordosis in the Female Rat[1]

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MENDELSON, S. D. AND B. B. GORZALKA. *Cholecystokinin-octapeptide produces inhibition of lordosis in the female rat*. PHARMACOL BIOCHEM BEHAV 21(5) 755–759, 1984.—The peripheral administration of 3 μg/kg CCK-8 produced inhibition of lordosis behavior in ovariectomized female rats primed with estradiol benzoate (EB) and progesterone (P). In Experiment 2, an interaction between CCK-8 and P was evident, with the inhibitory effects of CCK-8 being observed with P doses of 100 and 150 μg, but not 250 μg. No interaction between CCK-8 and EB was evident, as CCK-8 had no effect on lordosis behavior induced by chronic administration of EB alone. The ineffectiveness of CCK-8 in animals treated with high doses of P, or EB administered chronically, suggests that CCK-8 does not inhibit lordosis via a toxic or non-specific mechanism.

Cholecystokinin Sexual behavior Progesterone Estrogen Lordosis

THE gut peptide cholecystokinin (CCK) became of interest to behavioral scientists in the early 1970's when evidence first suggested that CCK could serve as a satiety factor in feeding [19]. Further interest in CCK was stimulated when the peptide was found to exist, primarily as the octapeptide (CCK-8), in the mammalian brain [46].

The neurobiology of CCK-8 remains largely unknown. However, existing evidence links the peptide with a variety of neuroregulator and hormonal systems. For example, CCK-8 has been found to co-exist with dopamine (DA) in some neurons of the ventral tegmentum and substantia nigra [23], and DA neurons in these areas have been shown to be sensitive to the intravenous or iontophoretic administration of CCK-8 [44]. Intraventricular administration of CCK-8 has been shown to alter both levels and turnover of brain DA, though the direction of change varies among areas of the brain, as well as with dosage and time [15,16]. Furthermore, CCK-8 has been shown to have neuroleptic-like activity in a number of behavioral paradigms [6,25], which suggests that it may act as a DA antagonist.

As with DA, levels and turnover of serotonin (5-HT) are altered by intraventricular administration of CCK-8 [15,16]; and, though the functional significance is unknown, interneurons containing CCK-8 have been described among the 5-HT neurons of the dorsal raphe [47].

CCK-8 is abundant in the hypothalamus [2,4], and has been shown to be a potent releaser of hypophysial hormones [38,48]. Furthermore, it has been reported that peripheral administration of CCK-8 stimulates the release of ACTH, with a concomitant rise in serum corticosterone [38].

Of relevance to the present investigation is the fact that those systems which have been shown to interact with CCK-8 have also been shown to modulate lordosis behavior in the female rat. The lordosis response has been shown to be inhibited by DA agonists, and facilitated by antagonists [1,14]. Increased levels of 5-HT activity have been associated with inhibition of lordosis behavior [18, 34, 35], while inhibition of 5-HT activity, by a variety of methods, has been associated with facilitation of lordosis [14, 34, 52]. Both ACTH and a variety of adrenal steroids are known to exert potent modulating effects on lordosis [22]. ACTH has been shown to inhibit lordosis when administered centrally, yet facilitate lordosis when administered peripherally in females with intact adrenals [11]. Adrenal steroids, such as deoxycorticosterone, are known to elicit a progesterone-like facilitation of lordosis in estrogen-primed, ovariectomized rats [21], whereas the facilitation of lordosis induced by adrenalectomy is attenuated by chronic corticosterone administration [10].

The following experiments were designed to determine if peripherally administered CCK-8 has a modulating effect on lordosis in the female rat, and whether the effect is estrogen or progesterone dependent. Furthermore, the possibility that CCK-8 alters receptivity via a non-specific or toxic mode of action was investigated.

GENERAL METHOD

Animals and Surgery

Female Sprague-Dawley rats were obtained from Charles River Canada Inc., Montreal, at 60 days of age. At approximately 70 days of age, these females were bilaterally ovariectomized, via bilateral lumbar incision. Surgery was performed while the animals were under ether anesthesia. Immediately following surgery, these females were housed in standard laboratory wire mesh single cages, in a room

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maintained under a reversed 12 hr dark/12 hr light cycle at 21±1°C. Animals had free access to food and water.

Drug Procedures

Estradiol benzoate (EB) and progesterone (P) (Steraloids) were dissolved in peanut oil. All injections of these steroids were via a 0.1 ml solvent vehicle administered subcutaneously. CCK-8 (Sigma) was dissolved in warm physiological saline to obtain a concentration of 1 μg CCK-8/0.1 ml solvent. This solution was administered intraperitoneally at a dose of 3 μg/kg. This dose has been demonstrated to elicit a variety of significant physiological and behavioral effects [7, 15, 19]. In the first two experiments, some animals received CCK-8 solutions which had been frozen for periods of up to 3 weeks. In the third experiment, CCK-8 solutions were prepared for immediate use from lyophilized 10 μg aliquots.

Lordosis Testing

Behavioral testing involved presentation of an experimental female to a stud male rat in a cylindrical pyrex testing arena measuring 45 cm in height, and 29 cm in diameter. Stud males were given brief access to fully receptive females (each given 10 μg EB 48 hr and 500 μg P 4 hr before presentation) immediately prior to sessions with experimental females. All sessions were conducted 4–6 hr after commencement of the dark cycle. Each experimental female was placed with a single male until 10 mounts with pelvic thrusting had occurred, or 15 min had elapsed. If a male would not mount, the female was placed in a different arena containing another male. If 10 mounts had not occurred in 15 min, the test was terminated, and the lordosis quotient was calculated from the mounts and responses which had occurred up until that time. This was necessary in only one instance. A female's response to a mount was considered a lordosis response if some degree of concavity of the back was observed. A lordosis quotient was calculated as the percentage of mounts with pelvic thrusting resulting in a lordosis response.

EXPERIMENT 1

The purpose of the initial experiment was to demonstrate the existence of a CCK-8 modulating effect on lordosis, and to establish the direction of such an effect. The steroid priming doses employed were chosen to produce sufficient lordosis to allow a CCK-8 inhibitory effect to appear, with the relatively low P dose still permitting a potential CCK-8 facilitatory effect to emerge.

Method

In this experiment, 8 sexually experienced females were primed with 10 μg EB, and 48 hr later received 150 μg P. CCK-8 or the saline vehicle was administered 4 hr after P, and the animals were placed with males for lordosis testing 10 min later. One week later, the animals were re-tested with the CCK-8 and saline treatments reversed.

Results and Discussion

The mean lordosis quotients with standard errors of females after CCK-8 and saline treatments were 54±13 and 80±8, respectively. A t-test for dependent samples indicated a significant inhibition of lordosis, $t(7)=3.54$, $p<0.01$. There was no evidence of a testing order effect.

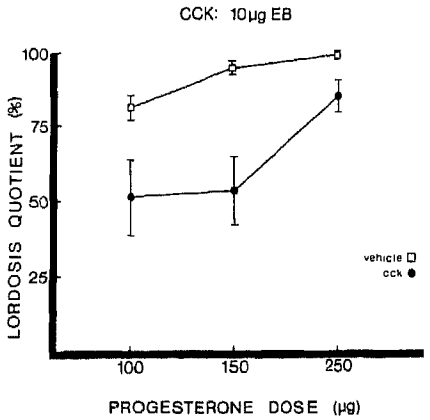

FIG. 1. Mean lordosis quotients ±S.E.M. of female rats primed with estradiol benzoate (EB) and varying doses of progesterone following the administration of CCK-8 (CCK) or the saline vehicle.

The results of this experiment demonstrate that CCK-8 significantly inhibits lordosis, but provide little information as to a possible mechanism of action. It is possible that CCK-8 merely acts as a toxic or noxious substance.

EXPERIMENT 2

In the first experiment we demonstrated that CCK-8 inhibits lordosis. However, the question remained as to whether the peptide inhibits lordosis in a non-specific manner, or via an interaction with estrogen, progesterone, or both. As a step towards resolution, in the second experiment we examined the effect of CCK-8 upon lordosis behavior as a function of P dose in EB primed rats.

Method

In the second experiment, 9 sexually experienced females were primed with 10 μg EB, and 48 hr later received either 100, 150, or 250 μg P in a repeated measures design. CCK-8 or the saline vehicle was administered 4 hr later. Females were placed with males for testing 10 min later. Each female's sequence of treatments was randomly ordered, and the interval between successive tests was one week.

Results and Discussion

An examination of Fig. 1 suggests that CCK-8 inhibited sexual receptivity, and that the degree of inhibition varied with the P dose. An analysis of variance for a two factor repeated measures design confirmed a significant inhibition of lordosis by CCK-8, $F(1,8)=19.301$, $p<0.002$; and indicated a facilitation by P, $F(2,16)=6.530$, $p<0.008$; as well as an interaction between CCK-8 and P, $F(2,15)=4.53$, $p<0.028$. The Newman-Keuls post hoc comparison method was used to compare individual groups and revealed that CCK-8 significantly inhibited lordosis in animals receiving either 100 or 150 μg P ($p<0.05$), while the effect of CCK-8 was attenuated by a dose of 250 μg P ($p>0.05$).

This experiment confirmed the earlier observation of an inhibitory effect of CCK-8 upon lordosis. Because an interaction between CCK-8 and P was also observed, the results argue strongly against a non-specific, or simple toxic mode of CCK-8 action. Alternatively, if there were a non-specific effect of CCK-8, it could be attenuated by as little as

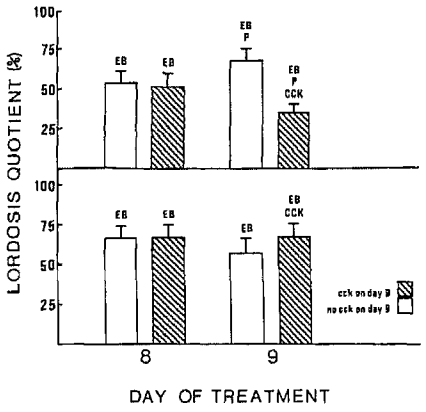

FIG. 2. Mean lordosis quotients ±S.E.M. of female rats that received daily injections of 0.8 μg estradiol benzoate (EB). The bottom panel displays the lordosis quotients from days 8 and 9 of animals that received daily EB only; the top panel displays the lordosis quotients from days 8 and 9 of animals that received daily EB, as well as 75 μg progesterone (P) prior to behavioral testing on day 9. Within each panel, animals were further divided according to whether they were treated with CCK-8 (CCK) or the saline vehicle prior to testing on day 9.

250 μg P. Further studies are necessary to determine the nature of the interaction between progesterone and CCK-8. Moreover, the possibility that other hormonal or neurotransmitter systems are involved remains to be determined.

EXPERIMENT 3

The first two experiments consistently indicated that CCK-8 inhibits lordosis, while the results of Experiment 2 suggested further that CCK-8 activity is dependent upon an interaction with progesterone. To strengthen evidence that CCK-8 acts via a specific interaction with progesterone, EB alone was chronically administered in the first phase of Experiment 3. Previous studies have shown that chronic administration of 0.8 μg EB can mimic acutely administered EB and P in maintaining lordosis behavior in ovariectomized rats [9,20]. The failure of CCK-8 to inhibit lordosis in females chronically treated with EB alone could be interpreted in at least two ways: CCK-8 interacts mainly with progesterone, or chronic EB treatment protects the organism against the inhibitory influence of CCK-8. Therefore, the second phase of Experiment 3 was designed to differentiate between these alternatives. Specifically, CCK-8 was administered to females treated chronically with EB, and acutely with P.

Method

In phase 1 of the third experiment, 24 sexually experienced females received 0.8 μg EB daily for 8 days. On day 3, daily lordosis tests were initiated. EB injections were always given 2 hr after testing. By day 7, lordosis quotients had reached asymptotic levels, and animals were divided into matched groups. On day 8, both groups were again tested with EB only; however, on day 9, one group received 3 μg/kg CCK-8 10 min prior to the test, while the other group received the saline vehicle. After a ten day interval, phase 2 was initiated. The original matched groups were used, and the procedure was identical to the first phase except that on day 9 both groups received 75 μg P 4 hr prior to testing.

Results and Discussion

The results of tests on days 8 and 9 for each phase of the experiment are presented in Fig. 2. The data were subjected to an analysis of variance for a three factor mixed design. The factors were: phase, i.e., the presence or absence of progesterone on day 9; CCK-8 administration; and the day of treatment, i.e., day 8 or day 9. There were no significant main effects; however, a significant interaction of phase, CCK-8 administration, and day of treatment was indicated, $F(1,44)=7.746$, $p<0.007$. Because of the significant interaction, the Newman-Keuls post hoc comparison procedure was used to compare individual groups. This revealed that CCK-8 had no effect on the lordosis quotient of animals receiving chronic EB alone; however, the lordosis quotient of animals receiving CCK-8 with EB and P was significantly lower than the lordosis quotient of animals receiving just EB and P ($p<0.05$). There were no significant differences in phase 2 between treatment with EB alone versus treatment with EB, P, and CCK-8. Taken together with the results of phase 1, these findings are consistent with the idea that CCK-8 prevents the facilitatory effect of progesterone, rather than reducing the effectiveness of EB. However, a Newman-Keuls comparison across phases revealed that lordosis quotients were lower in animals receiving EB, P, and CCK-8 than those receiving EB and CCK-8 ($p<0.05$). Therefore, the possibility remains that CCK-8 not only eliminates the facilitatory effect of progesterone, but its interaction with progesterone may be antagonistic toward sexual receptivity.

The finding in phase 1 that CCK-8 does not inhibit lordosis in animals chronically treated with EB alone suggests that chronic EB administration *per se* is sufficient to block the CCK-8 effect. However, this interpretation now seems unlikely in view of the results of phase 2. When progesterone was administered subsequent to chronic EB treatment, CCK-8 effectively inhibited lordosis. These data support the conclusion that CCK-8 interacts with progesterone.

GENERAL DISCUSSION

This series of experiments has provided the first demonstration of potential CCK-8 involvement in sexual behavior. Specifically, the results have indicated an inhibition of lordosis by intraperitoneal (IP) administration of CCK-8 in ovariectomized rats primed with estrogen and progesterone. The inhibition by CCK-8 did not appear to involve a direct interaction with estrogen. However, a significant interaction between CCK-8 and progesterone was evident. At least two types of evidence argue against a possible toxic or nonspecific effect of CCK-8, as has been suggested in the literature for other results [12]. First, CCK-8 was ineffective in animals made receptive by chronic EB treatment. Second, the effectiveness of CCK-8 was a function of the progesterone dose. The nature of the apparent interaction between CCK-8 and progesterone is of prime importance to the present discussion. CCK-8 might interact directly with progesterone on the neural membrane, act upon neurons whose activities have been altered by progesterone, or interact with another neuroregulator system which mediates progesterone activity.

Progesterone is taken up in a variety of areas in the rat brain [50]. Moreover, studies employing central administration of progesterone in estrogen primed rodents have impli-

cated both hypothalamic and mesencephalic sites in the facilitation of lordosis [32, 39, 41]. Of particular relevance to the present results are data indicating that progesterone placed in or adjacent to the interpeduncular nucleus facilitates lordosis [31]. Dense networks of CCK-immunoreactive fibers are found in the interpeduncular nucleus [31], suggesting that CCK-8 is also active in this area.

Although evidence suggests that both CCK-8 and progesterone are active in the interpeduncular nucleus, the mechanism by which peripherally introduced CCK-8 could contribute to an interaction with progesterone in this area is not obvious. Being a peptide, CCK-8 would not be expected to passively cross the blood brain barrier. Although several peptides have been reported to cross the blood brain barrier [26,42], no labeled CCK-8 could be found in rabbit CSF after IP administration of the labeled peptide in one study [36]. The possibility remains that active transport, or paucity of the lipid barrier could allow CCK-8 access to specific central neural sites. However, there are no experimental data to indicate that the peptide does indeed pass specifically into sites where progesterone is active. Therefore, a direct interaction between CCK-8 and progesterone can neither be ruled out nor substantiated at this time. A study of patterns of uptake of peripherally administered, labeled CCK-8 would provide the critical information.

An argument has been made that progesterone facilitates lordosis by decreasing 5-HT activity [29,37]; indeed, a number of substances that in some way antagonize 5-HT can mimic progesterone by facilitating lordosis in the EB primed female [13, 43, 52]. Thus 5-HT may mediate an interaction between CCK-8 and progesterone.

The interaction of CCK-8 with 5-HT has not been firmly established, although the presence of neurons containing CCK-8 in the serotonergic dorsal raphe is consistent with such an interaction [47]. Existing behavioral and physiological evidence also supports this possibility. CCK-8 and a variety of 5-HT agonists have been reported to attenuate feeding [5, 19, 30]. CCK-8 also elicits prolactin release [48], an effect produced by increased 5-HT activity [40]. Furthermore, the states of inactivity and sleep produced by CCK-8 closely resemble those produced by electrical stimulation of the serotonergic midbrain raphe nuclei [28,33]. Another effect of the stimulation of the dorsal raphe, the suppression of the release of luteinizing hormone [3], is also found after intravenous (IV) administration of CCK-8 [48]. Despite these similarities, assays of 5-HT activity following CCK-8 treatment have produced inconsistent results [15, 16, 27, 51].

It remains to be determined whether the behavioral effects of systemically administered CCK-8 are centrally or peripherally mediated. Evidence suggests that in a number of areas of the brain densely populated with monoaminergic neurons, a small percentage of these neurons lie with perikarya and dendrites abutted directly against vascular structures, with no intervening lipid layer [17]. This arrangement would allow circulating peptides access to neural sites, which leads us to speculate that CCK-8 might in this way interact directly with central neuroregulatory processes. There is support for this idea in the results of a study concerning the substantia nigra, an area known to contain a percentage of neurons having direct contact with vascular structures [17]. Recent evidence demonstrates central activity of peripherally administered CCK-8 by revealing that the capacity of an acute, systemic administration of CCK-8 to excite, and subsequently induce DA autoreceptor supersensitivity in nigral A9 DA neurons is undiminished in animals with vagotomies, solitary nucleus lesions, and C1 transections [24].

In addition, evidence suggests that CCK-8 may affect lordosis via a peripheral mechanism. A number of behavioral effects of CCK-8 have been shown to be abolished by vagotomy, including the satiety effect [7,45] and the inhibition of exploratory behavior [7]. Furthermore, lesions of the solitary nucleus also abolish these CCK-8 effects [8]. Thus the possibility exists that CCK-8 inhibition of lordosis is a product of peripheral vagal stimulation, and central mediation by the solitary nucleus. The observation of CCK-8 inhibition of lordosis in vagotomized animals would resolve this question.

The question remains as to what role, if any, CCK-8 might play in the normal physiological modulation of lordosis behavior. It could be, as has been suggested in the literature, that CCK-8 elicits a general satiety effect [7], thereby attenuating both sexual and feeding behavior through the same mechanism. Sufficient quantities of progesterone may antagonize the general satiety and concomitant inhibition of lordosis behavior observed following CCK-8 administration in the female rat. Therefore, we would anticipate a potential interaction between progesterone and CCK-8 in the control of food intake in the female rat. This would be consistent with the results of Experiment 2, as well as with earlier findings that progesterone increases food intake in EB-primed, ovariectomized female rats [49]. Furthermore, if the observed inhibition of lordosis behavior following CCK-8 administration is indeed specific and progesterone dependent, then we would not expect CCK-8 to produce an inhibition of sexual behavior in the male rat.

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