Pharmacology Biochemistry & Behavior, Vol. 26, pp. 393–400. Copyright © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Nicotinic Cholinergic Influences on Sexual Receptivity in Female Rats[1]

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Received 29 August 1986

WEAVER, D. R. AND L. G. CLEMENS. *Nicotinic cholinergic influences on sexual receptivity in female rats.* PHARMACOL BIOCHEM BEHAV 26(2) 393–400, 1987.—Drugs which alter nicotinic cholinergic transmission were administered to female rats to examine the neurochemical regulation of feminine sexual behavior. Nicotine (50, 100 or 200 μg/kg, IP) facilitated lordosis behavior 5 minutes after injection in estrogen-primed ovariectomized (OVX) rats. Pretreatment with the nicotinic antagonist, mecamylamine (MECA, 2.5 or 10 mg/kg) prevented this effect, while atropine pretreatment (30 mg/kg) reduced it. Mecamylamine pretreatment also reduced lordotic behavior induced by bilateral intracerebroventricular (ICV) injection of the cholinesterase inhibitor, eserine (5 μg/cannula). However, MECA treatment (5 or 10 μg/cannula, bilaterally, ICV, or 5 or 10 mg/kg, IP) did not reduce sexual receptivity in OVX rats made highly receptive with estrogen plus progesterone priming. By comparison with previously published results, MECA is apparently less effective than muscarinic antagonists in disrupting sexual receptivity in several paradigms. There appears to be a critical muscarinic link in the neural circuit for sexual receptivity, but there does not appear to be a comparable nicotinic link. In fact, the lordosis-facilitating effect of nicotine may be a pharmacological effect unrelated to the normal neurochemical regulation of sexual receptivity.

Lordosis Nicotine Sexual behavior Rats Psychopharmacology

IN gonadally intact female rodents, cyclicity in the level of ovarian hormones is responsible for the cyclic occurrence of sexual receptivity. Removal of the ovaries abolishes copulatory activity and administration of exogenous ovarian steroids will induce receptivity [28]. Receptivity can be assessed in rodents by the occurrence of the lordosis response, which consists of arching of the back, elevation of the head and perineum, and lateral deflection of the tail [17]. Lordosis occurs in sexually receptive females in response to mounting by the male and allows the male to achieve penile insertion (intromission).

Ovarian hormones are thought to induce sexual receptivity by altering neurotransmission within specific neural sites [15]. One approach to study this hormone-neurotransmitter-behavior relationship is to administer drugs which alter neurotransmission and determine their effect on sexual behavior. This psychopharmacological approach has been used to examine the effects of several known and putative neurotransmitters on sexual behavior [16].

Previous work from this laboratory has assessed the role of acetylcholine in the regulation of feminine sexual behavior. These studies [7–11, 19, 20] have demonstrated that pharmacological stimulation of central cholinergic receptors induces sexual receptivity in estrogen-primed ovariectomized (OVX) rats. This short-latency, transient effect is estrogen (E) dependent [8,9], progesterone (P) independent [1, 8, 9, 20], and independent of the adrenal glands [7].

In addition to the facilitative effect of cholinergic stimulation on lordosis, other studies have demonstrated that cholinergic transmission is required for hormone-induced sexual receptivity. Intracerebral infusion of hemicholinium-3, a compound which reduces endogenous acetylcholine formation, disrupted receptivity in E plus P primed OVX rats [6,8]. Furthermore, intracerebral infusion or application of a muscarinic cholinergic antagonist (atropine or scopolamine) also disrupted E plus P induced sexual receptivity [6, 9, 14]. Finally, systemic administration of muscarinic antagonists disrupted hormone-induced lordosis behavior [19,25]. These studies suggest that there is activation of cholinergic transmission in hormone induced receptivity.

Acetylcholine interacts with nicotinic as well as muscarinic receptors in the nervous system. Direct evidence for separate populations of muscarinic and nicotinic receptors in nervous tissue has been provided by receptor assays [2, 5,

[1]This research was supported by NIH grant HD-06760 to L.G.C. and an NSF predoctoral fellowship to D.R.W. The experiments reported here were included in a thesis submitted by D.R.W. to the Department of Zoology, Michigan State University, in partial fulfillment of requirements for the doctoral degree. Portions of this work have been presented elsewhere [26].

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18, 21, 23, 27] and psychopharmacology [4,22]. Considering the existence of two types of receptors for acetylcholine, it is reasonable to ask whether the effect of acetylcholine on receptivity is mediated by muscarinic or nicotinic receptors, or both. The facilitation of lordosis produced by cholinergic agonists can be blocked by the muscarinic antagonists, atropine and scopolamine, regardless of whether the agonist used is a mixed muscarinic-nicotinic agonist or whether it is a more purely muscarinic agonist [9, 11, 19]. This suggests that muscarinic receptor stimulation is responsible for the behavioral effects of these drugs. However, Fuxe, Everitt and Hokfelt [12] have reported that systemic injection of nicotine facilitated lordosis behavior in E-primed OVX rats 5 minutes after injection; pretreatment with the nicotinic receptor antagonist, mecamylamine, completely prevented the nicotine-induced facilitation of lordosis. The facilitation of lordosis by nicotine raises the possibility that nicotinic cholinergic transmission is also important in the regulation of sexual receptivity. The experiments reported here were performed to characterize the nicotinic contribution to the regulation of sexual receptivity in female rats.

GENERAL METHOD

Subjects

Female Sherman strain rats (Camm Research Industries, Inc., Wayne, NJ) were received at 60–70 days of age (190–215 grams) and allowed to acclimate to the laboratory for at least one week before any manipulations were performed. Animals were initially housed in pairs in stainless steel cages (30×23.8×23.8 cm); those that subsequently underwent stereotaxic surgery (Experiments 4 and 6) were singly housed at the time of surgery. Food (Tek-lad mouse/rat diet, Winfield, IA) and water were available at all times. The animals for Experiment 1 were given tetracycline solution (Professional Veterinary Laboratories, Minneapolis, MN; 1/2 teaspoon per 250 cc distilled water) in place of plain drinking water from the time of arrival until 3–5 days after ovariectomy (a total of 13 days). The colony room was maintained on a 14:10 reverse light-dark cycle, with lights off at 1100 local time (EST or EDT).

Seven to ten days after arriving in the laboratory, the animals were OVX under ketamine anesthesia (Vetalar, Parke-Davis, 60 mg/kg). Females were then screened to assess sexual receptivity in response to exogenous gonadal hormones seven to twelve days after OVX. Each female received 17β-estradiol 3-benzoate injections (EB, 0.5 μg/animal/day) 72, 48 and 24 hours before behavioral testing and a single injection of P (0.5 mg/animal) 4 to 6 hours before behavioral testing. This sequential treatment with EB and P normally induces high levels of sexual receptivity in females of this strain. This laboratory uses the criterion that an animal must achieve a lordosis quotient of 70 or more in order to be considered normally responsive; one animal (of 151) in the present series failed to meet this criterion and was excluded from subsequent experimentation.

Behavioral Testing

Tests for sexual receptivity were conducted before and after pharmacological treatments. Testing occurred under dim red illumination during the first half of the dark phase of the reversed 14:10 light-dark cycle, but never less than 1 hour after lights-out.

Lordosis behavior was assessed by placing the test female in a Plexiglas testing arena (45×50×58 cm) with a sexually vigorous Long-Evans strain stimulus male. The response of the female to each of 11 mounts by the male was scored on the lordosis intensity scale described by Hardy and DeBold [13] and responses scored as 1, 2, or 3 were considered lordosis responses. A lordosis quotient was calculated for each female after exclusion of the response to the first mount, so that LQ = No. lordoses/10 mounts × 100. Mean LQ's include all animals tested.

Hormone and Drug Solutions

Hormones (EB and P) were dissolved in sesame oil and injected intramuscularly. Injection volumes were 0.10 cc per animal except in Experiment 1, where the EB doses were administered on a μg/kg basis by adjusting the volume of injection at the rate of 0.4 cc/kg. Nicotine (free base), mecamylamine hydrochloride, and atropine sulfate were dissolved in saline and injected intraperitoneally (IP) at the rate of 0.8 cc/kg; control injections of the saline vehicle were also given. All drugs and hormones were obtained from Sigma Chemical Co. (St. Louis, MO).

Statistical Analysis

All data have been analyzed using non-parametric statistics [24] with the criterion for statistical significance set at $p<0.05$.

INTRACEREBRAL STUDIES

In Experiments 4 and 6, intracerebral microinjections of drugs were performed. Bilateral cannulae assemblies constructed from 23-gauge thin walled stainless steel tubing (Small Parts Inc., Miami, FL) were stereotaxically implanted under ketamine anesthesia 1 to 12 days after the screening pretest. With the incisor bar at 0, cannulae were positioned 1 mm to each side of the sagittal suture at the anterior-posterior level of the coronal suture and lowered 2.7–2.8 mm from the level of dura. The cannulae assembly was secured to the skull with machine screws and dental acrylic, and each guide cannula was fitted with a removable occluding insert (HTX-27 tubing) that extended 1 mm past the end of the guide into the ventricle.

To perform an intracerebral injection, the subject was gently restrained, the occluding inserts were removed and replaced one at a time with an infusion insert (HTX-27 or HTX-28) attached to PE-20 tubing (Clay Adams, Parsippany, NJ) containing the solution for infusion. The infusion insert, like the occluding insert, extended 1 mm past the end of the guide into the ventricle. The solution was delivered using a reciprocal microinfusion pump (Harvard Apparatus, Millis, MA). On average, infusion of 0.5 microliters took 15–45 seconds at the pump settings used. Each occluding insert was replaced immediately after removal of the infusion insert from that side. Infusions were performed under dim white illumination.

Mecamylamine (Experiment 6) and eserine (Experiment 4) were dissolved in an artificial cerebrospinal fluid (CSF) vehicle immediately before ICV infusion; in Experiment 6 the CSF vehicle was also infused alone as a control. The CSF vehicle consisted of 130 mM NaCl, 25 mM $NaHCO_3$, 0.5 mM Na_2PO_4, 3.0 mM KCl, 0.8 mM $MgCl_2$, and 1.3 $CaCl_2$ in double distilled water, adjusted to pH 6.8. The CSF was allowed to warm to room temperature for approximately 1 hour prior to dissolving drugs in it.

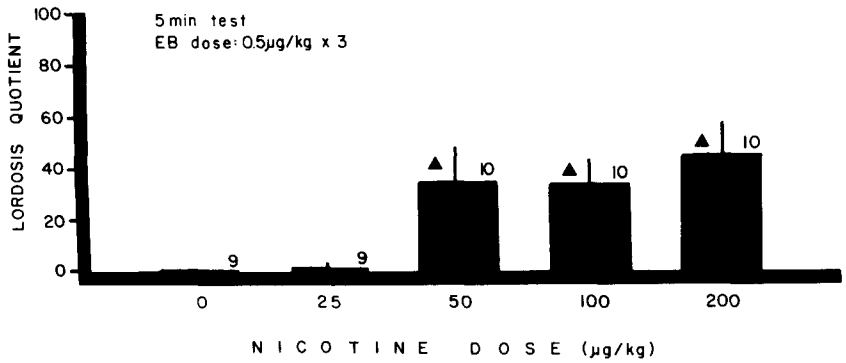

FIG. 1. Systemic nicotine treatment facilitated lordosis behavior. Mean lordosis quotients (± standard errors of the mean, or SEM) of EB-primed OVX rats 5 minutes after IP injection of nicotine. A significant increase in LQ compared to pretest level occurred for the 50, 100, and 200 μg/kg nicotine doses, as indicated by ▲. Number of tests in each is 9–10 as indicated.

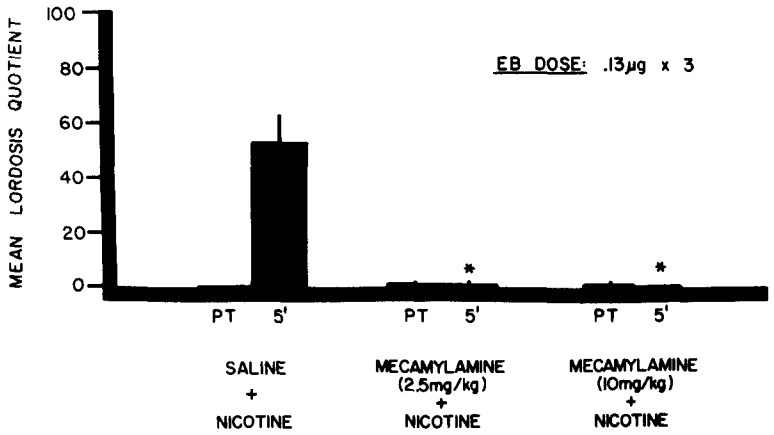

FIG. 2. MECA pretreatment prevented nicotine facilitation of lordosis. Injection of nicotine (150 μg/kg, IP) significantly increased LQ's in EB-primed OVX rats pretreated with saline. MECA pretreatment (2.5 or 10 mg/kg, 30 minutes before nicotine) completely prevented the nicotine-induced facilitation of lordosis. (*Indicates a significant reduction in LQ compared to the 5-minute test scores of the control group receiving saline + nicotine.)

Following completion of infusion studies, animals were anesthetized with pentobarbital (15 mg/animal, IP) and perfused transcardially with 0.9% saline followed by 10% phosphate buffered formalin. Frozen brains were sectioned at 50 microns, mounted on gel slides and stained with thionin; the site of termination of each cannula was determined independently by two observers. Only those animals for which both observers determined that both cannulae were in the ventricles have been included.

EXPERIMENT 1

As noted in the Introduction section, Fuxe *et al.* [12] reported that systemic injection of nicotine facilitates lordosis behavior in E-primed OVX rats. Experiments 1, 2, and 3 were performed to replicate those experiments with slight modifications in the methods and to extend the pharmacological characterization of this nicotine-induced effect.

Procedure

Beginning one week after their screening pretest, 24 OVX rats were tested at one week intervals for lordosis behavior. Each weekly test series was preceded by injections of EB (0.5 μg/kg) 72, 48, and 24 hours before behavioral testing. For each of the two weekly tests, the subjects were randomly assigned to one of five doses of nicotine (0, 25, 50, 100 and 200 μg/kg). Tests for lordosis behavior were conduced before (pretest, PT) and 5 and 20 minutes after nicotine injection. The results of the two weeks have been pooled.

Results

Nicotine facilitated lordosis behavior 5 minutes after injection (Fig. 1). An overall effect of nicotine dose was demonstrated, as the proportion of animals showing lordosis behavior 5 minutes after treatment varied between nicotine doses (Chi-square test, $\chi^2=17.9$, 4 degrees of freedom,

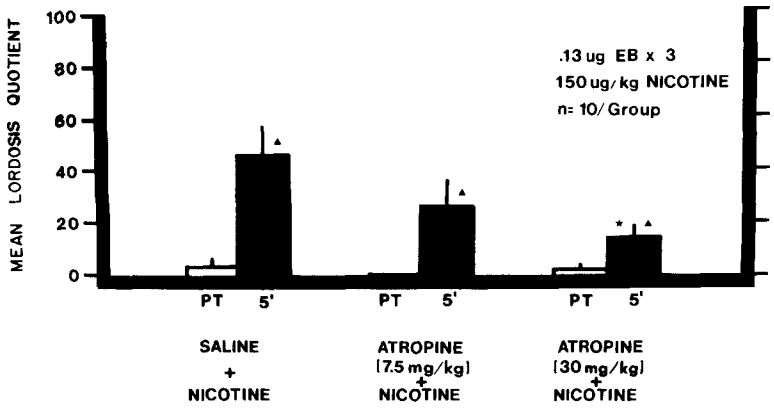

FIG. 3. Atropine pretreatment reduced but did not prevent facilitation of lordosis by nicotine. In all three pretreatment conditions, LQ's were significantly increased 5 minutes after nicotine injection (indicated by triangles). Pretreatment with atropine (30 mg/kg) reduced the magnitude of the nicotine-induced increase in LQ's.

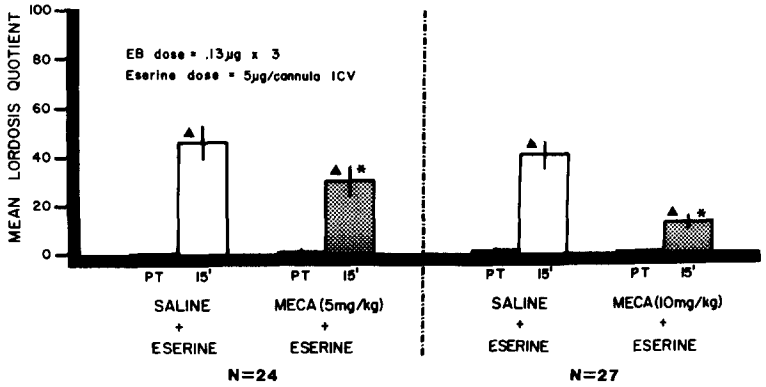

FIG. 4. MECA pretreatment reduced but did not prevent the facilitation of lordosis by bilateral ICV eserine infusion (5 µg/cannula). As indicated by triangles, eserine infusion produced a significant elevation in LQ's in all pretreatment groups. The 15 minute test LQ scores were lower when eserine infusion was preceded by MECA treatment (5 or 10 mg/kg), indicated by *.

$p<0.01$). Nicotine at doses of 50, 100 and 200 µg/kg produced a significant increase in LQ's 5 minutes after injection compared to pretest LQ's (sign tests, $p=0.031$, 0.004, and 0.016, respectively). By 20 minutes after injection, LQ's have returned to low levels.

EXPERIMENT 2

Experiment 2 was designed to replicate the experiment by Fuxe *et al.* [12] which showed that MECA pretreatment blocks the facilitation of lordosis induced by injection of nicotine.

Procedure

Twelve OVX screened rats underwent three test series at weekly intervals, with the first test series occurring one week after the screening pretest. Each animal was primed with EB (0.13 µg × 3) before each weekly test series. For each test series, the animals were pretested for lordosis (PT), injected with mecamylamine (MECA, 2.5 or 10 mg/kg, IP) or the saline vehicle, and 30 minutes later injected with nicotine (150 µg/kg). They were then retested for lordosis behavior 5 minutes after nicotine. In this way, the ability of MECA pretreatment to prevent the nicotine-induced facilitation of lordosis was assessed. Each animal received all three possible pretreatments; the order of pretreatments was counterbalanced.

Results

As expected, nicotine injection (150 µg/kg) produced a statistically significant facilitation of lordosis in the Saline + Nicotine group (Fig. 2; PT vs. 5-minute test, Wilcoxon matched-pairs signed-ranks test, $p<0.05$). MECA pretreatment (2.5 or 10 mg/kg) completely prevented the facilitation of lordosis by this dose of nicotine (Friedman two-way analysis of variance, $p<0.001$, followed by Wilcoxon matched-pairs signed-ranks test to compare saline vs. each MECA test, one-tailed, $p<0.005$).

EXPERIMENT 3

Experiment 3 was performed to extend the pharmacologi-

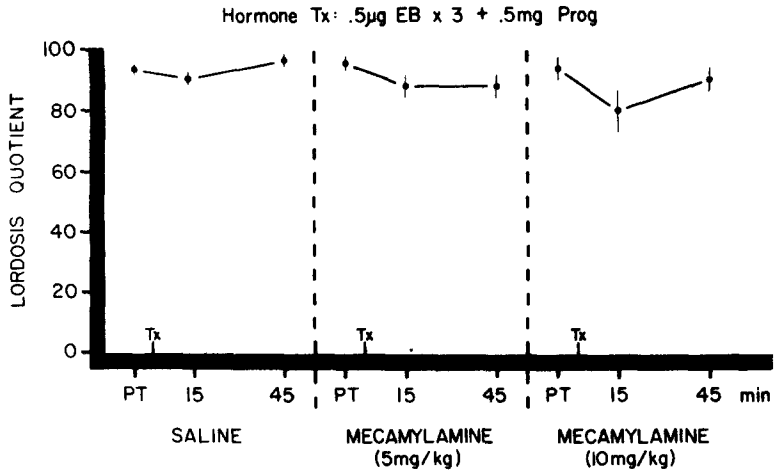

FIG. 5. Systemic treatment (Tx) with MECA did not inhibit receptivity in EB plus P primed OVX rats. There was no effect of MECA on lordosis at either dose. Ten animals received one of the three treatments each week for 3 weeks, so that each animal received all three treatments.

cal characterization of the nicotine-induced facilitation of lordosis. Specifically, Experiment 3 was designed to assess the ability of the muscarinic antagonist, atropine, to block the nicotine-induced facilitation of lordosis in EB-primed female rats.

Procedure

As in Experiment 2, OVX, screened rats (n=10) were tested for lordosis behavior in 3 test series spaced one week apart. The first test series was one week after the screening pretest. Each week, each female was primed (0.13 μg EB × 3), pretested for lordosis (PT), injected with a pretreatment, and 30 minutes later injected with nicotine (150 μg/kg, IP). Each animal was then retested for lordosis 5 minutes after the nicotine injection. The pretreatments were IP injections of atropine (7.5 or 30 mg/kg) or the saline vehicle; each animal received all three pretreatments and the order of pretreatments was counterbalanced.

Results

The results of Experiment 3 are presented in Fig. 3. Using within-animal comparison of the response over the three weeks (Friedman two-way analysis of variance), atropine pretreatment was found to be without effect on nicotine-induced lordosis behavior ($\chi^2=4.55$, 2 degrees of freedom, $p>0.05$). However, pre-planned comparisons between the 5-min tests of the saline week versus each of the two atropine pretreatment weeks revealed that the high pretreatment dose of atropine (30 mg/kg) significantly reduced lordosis responding (Wilcoxon matched-pairs signed-ranks test, $p<0.05$). Pretreatment with the lower dose of atropine (7.5 mg/kg) did not significantly reduce lordosis behavior in response to nicotine injection.

EXPERIMENT 4

The results of Experiments 1, 2, and 3 indicate that nicotinic receptor stimulation can facilitate lordosis. Previous work from this laboratory has shown that intracerebral infusion of agents which stimulate muscarinic receptors will facilitate lordosis in EB-primed OVX rats, and infusion of agents that disrupt muscarinic cholinergic transmission disrupts ongoing EB plus P-induced sexual receptivity [9,14]. Some of the agents which have been used to stimulate muscarinic receptors may also stimulate nicotinic receptors. The cholinesterase inhibitor eserine (physostigmine) is an example. By blocking the enzymatic degradation of acetylcholine, eserine produces an increase in synaptic acetylcholine which could potentially stimulate both muscarinic and nicotinic receptors. The present experiment was designed to assess the contribution of nicotinic receptors to the eserine-induced facilitation of lordosis.

Procedure

A total of 51 Sherman strain rats were OVX, screened, and implanted with cannulae which were later determined to terminate bilaterally in the lateral ventricles. Two lordosis test series were administered; the first test series was one week after stereotaxic implantation of the intracerebral cannulae, and the second test series was one week later. Prior to each weekly test series, each female was primed with EB (0.13 μg × 3). Animals were pretested for lordosis behavior (PT), injected with a pretreatment (MECA or saline), and infused with eserine (5 μg/0.5 μl/side, bilaterally) 30 minutes later. The animals were retested for lordosis behavior 15 minutes after ICV eserine infusion. Twenty-four animals received MECA pretreatment (5 mg/kg) one week and the saline vehicle the other. Another group of animals (n=27) received 10 mg/kg MECA (10 mg/kg) one week and the saline vehicle the other. Each animal thus received two eserine infusions spaced one week apart; one week the eserine was preceded by one of the two doses of MECA and the other week eserine was preceded by the saline vehicle. Order of the pretreatments was counterbalanced within each group of animals.

Results

In agreement with previous results, eserine infusion increased LQ's in animals receiving saline pretreatment (Fig. 4). Following MECA pretreatment (at either dose), eserine infusion still produced a statistically significant facilitation of

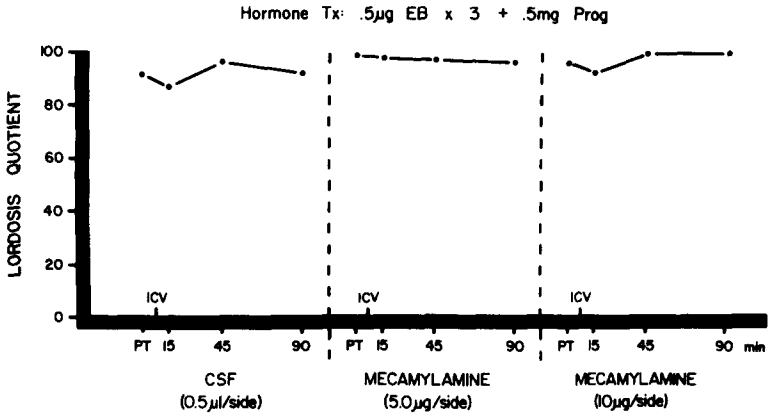

FIG. 6. ICV infusion of MECA did not inhibit receptivity in EB plus P primed OVX rats. There were no reductions in LQ's in tests 15, 45, and 90 minutes after infusion of MECA. For each MECA dose, seven animals received MECA infusion one week and the CSF vehicle the other week. The CSF tests (n=14) from the two groups have been combined for clarity.

lordosis (PT vs. 15 minute test, Wilcoxon signed-ranks matched-pairs test, $p<0.05$). A comparison within animals across the two weeks, however, indicated that MECA pretreatment reduced the eserine-induced facilitation of lordosis (15′ tests compared within animal for saline vs. MECA week, Wilcoxon matched-pairs signed-ranks test, $p<0.05$). Thus, MECA pretreatment reduced but did not prevent the induction of receptivity by ICV eserine treatment.

EXPERIMENT 5

To determine whether nicotinic receptor stimulation is necessary for hormone-induced sexual receptivity, MECA was injected into EB-plus-P primed females.

Procedure

Ten OVX, screened rats served as subjects. Three test series were administered one week apart, with the first test series occurring one week after the screening pretest. Prior to each weekly test series, each female was primed with EB (0.5 μg × 3) plus P (0.5 mg) in order to induce high levels of sexual receptivity on the day of testing. The animals were tested for lordosis behavior before (PT) and 15 and 45 minutes after IP injection of MECA (5 or 10 mg/kg) or the saline vehicle. Each female received all three treatments, with treatment order counterbalanced.

Results

Systemic injection of the nicotinic receptor antagonist MECA was ineffective in disrupting hormone-induced receptivity (Fig. 5; Friedman two-way analysis of variance of 15-minute test LQ's or of the change in LQ ($LQ_{15} - LQ_{PT}$) across treatments within animals, $p>0.05$).

EXPERIMENT 6

While systemically administered MECA should be capable of crossing the blood-brain barrier and influencing CNS sites, we also determined the effect of intracerebrally injected MECA on lordosis behavior.

Procedure

Fourteen OVX, screened rats with bilateral ICV cannulae were used as subjects. Each rat underwent two testing series spaced one week apart, with the first of these occurring one week after stereotaxic surgery for implantation of the intracerebral cannulae. As in Experiment 5, EB (0.5 μg/day × 3) plus P (0.5 mg) priming preceded each test series. Animals were tested before (PT) and 15, 45 and 90 minutes after infusion. The animals were randomly divided into two groups (n=7 each), one of which received an infusion of a high dose of MECA (10 μg/0.5 μl/side, bilaterally) one week and the CSF vehicle the other week; the other group received a lower dose of MECA (5 μg/0.5 μl/side) one week and CSF the other week. Within each group, the order of infusion treatments was counterbalanced.

Results

Bilateral infusion of MECA did not significantly affect LQ's in EB plus P primed female rats [Wilcoxon matched-pairs signed-ranks test on 15 minute scores or on the change in LQ ($LQ_{15} - LQ_{PT}$), comparing CSF and MECA weeks within animal, $p>0.05$]. The CSF tests from the two MECA dose groups have been pooled for clarity in Fig. 6, which shows the response over time following infusion.

GENERAL DISCUSSION

The nicotine-induced facilitation of lordosis observed in Experiments 1, 2 and 3 is in agreement with the results of Fuxe *et al.* [12] despite methodological differences. Specifically, these differences include the strain of animals used (Sprague-Dawley vs. Sherman) and the EB priming regimen (Fuxe: 1.0 μg/animal/day × at least 5 days, vs. our 0.5 μg/kg × 3 or 0.13 μg/animal × 3). Fuxe *et al.* [12] also did not pretest their animals before administration of nicotine, and they used the tartrate form of nicotine (vs. our use of free base). Both our results (Experiment 2) and those of Fuxe *et al.* [12] demonstrate that pretreatment with the nicotinic antagonist MECA completely blocks nicotine-induced lordosis behavior. This supports the notion that the behavioral effects of nicotine depend upon stimulation of nicotinic receptors.

The antagonism of nicotine by a high dose of atropine (30 mg/kg), a muscarinic antagonist, was unexpected. It is unlikely that atropine acted directly as a nicotinic antagonist since atropine does not displace nicotine from nicotinic binding sites *in vitro* [23]. It appears more likely that atropine antagonized the behavioral effect of nicotine in a nonspecific manner. While the lower dose of atropine (7.5 mg/kg) was ineffective in disrupting nicotine-induced receptivity, a similar dose of atropine was effective in preventing the induction of receptivity by ICV infusion of eserine, carbachol, or oxotremorine [9,11]. If nicotine stimulated lordosis by activating muscarinic receptors (either directly or indirectly), this lower dose of atropine should have prevented nicotine-induced lordosis. Therefore, the apparent antagonism of nicotine-induced receptivity by the higher dose of atropine may be a pharmacological artifact unrelated to specific blockade of either nicotinic or muscarinic receptors.

The finding that ICV eserine facilitated lordosis behavior in EB-primed female rats agrees with previously published results from this laboratory [9]. While MECA treatment was found to reduce this effect in Experiment 4, it did not completely prevent it. However, atropine pretreatment completely prevented the facilitation of lordosis by eserine or eserine plus acetylcholine infusion [9]. We interpret this to mean that nicotinic receptor stimulation is relatively less important than stimulation of muscarinic receptors in producing the facilitation of lordosis by ICV eserine.

Experiments 5 and 6 demonstrated that systemic or intracerebral treatment with MECA did not disrupt sexual receptivity in EB plus P primed females. The doses of MECA administered systemically had earlier been found to prevent nicotine-induced lordosis and to reduce eserine-induced lordosis behavior (Experiments 2 and 4). While we have no behavioral data of our own regarding the doses of MECA administered intracerebrally, Brezenoff and Jenden [3] showed that MECA (5 μg) completely blocked a delayed pressor response produced by carbachol when both drugs were infused (sequentially) into the floor of the fourth ventricle. Based on these data, the doses of MECA used in the present study should have been effective in disrupting nicotinic transmission. If an endogenous nicotinic mechanism relevant to hormone-activated sexual receptivity exists, then MECA should have disrupted receptivity; this was not observed.

If nicotinic transmission is not involved in the normal neurochemical regulation of sexual receptivity, then it is unclear how this drug facilitates lordosis behavior. Nicotine may act via nicotinic receptors to alter the function of a number of transmitter systems, and this may result in stimulation of lordosis. These transmitters and sites may or may not be the same as those which are normally involved in the hormonal regulation of feminine sexual behavior. Alterations in nicotinic receptor stimulation do not appear very important in the hormonal activation of sexual receptivity, which implies that nicotine facilitates lordosis by a mechanism unrelated to the pathways involved in activation of receptivity by gonadal hormones. In contrast, activation of muscarinic receptors appears critical for hormone-activated lordosis behavior. This suggests the involvement of a "muscarinic mechanism" in the regulation of sexual receptivity. Muscarinic cholinergic transmission may be important for activation of lordosis behavior by a wide variety of hormonal or pharmacological methods. Only those agents that facilitate lordosis via simultaneously activating several parallel routes should facilitate lordosis in the presence of muscarinic receptor antagonists. Nicotine may be one such agent. Gonadal steroids clearly alter the neurochemistry of a number of transmitters simultaneously; the effectiveness of muscarinic antagonists in reducing hormone-activated receptivity emphasizes the importance of muscarinic transmission in the regulation of lordosis behavior.

In summary, pharmacological stimulation of nicotinic receptors can facilitate lordosis, but stimulation of nicotinic receptors is not essential for hormone-induced sexual receptivity. Pharmacological stimulation of central muscarinic receptors also facilitates lordosis behavior. However, stimulation of muscarinic receptors appears critical for hormone-induced sexual receptivity [6, 9, 15, 19, 25]. Muscarinic cholinergic transmission therefore appears to be more important than nicotinic transmission in the regulation of lordosis behavior. The behavioral effects of nicotine may represent a receptor-mediated pharmacological effect unrelated to the normal neurochemical regulation of sexual receptivity in female rats.

ACKNOWLEDGEMENT

The authors would like to thank Mr. David Brigham for preparing the figures.

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