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Stimulation of β-Adrenoceptors Inhibits Lordosis Behavior in the Female Rat[1]

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MENDELSON, S. D. AND B. B. GORZALKA. *Stimulation of β-adrenoceptors inhibits lordosis behavior in the female rat.* PHARMACOL BIOCHEM BEHAV **29**(4) 717–723, 1988.—Existing reports on the effects of β-adrenergic antagonists on lordosis behavior appear contradictory, with (±) propranolol being reported to inhibit, and (±) pindolol to facilitate this behavior. In the present study, both the (−) and (+) optical isomers of propranolol were effective in inhibiting lordosis behavior in ovariectomized rats treated with estrogen and progesterone. This finding suggests that the lordosis-inhibiting effects of propranolol were not due to blockade of β-adrenergic activity, but rather to the membrane stabilizing effect of the drug. An observed inhibition of lordosis following the peripheral administration of the local anesthetic lidocaine is consistent with this possibility. (±) Propranolol had no effect 30 min after peripheral administration in estrogen-treated, ovariectomized rats with low baseline levels of lordosis behavior. (±) and (−) pindolol, but not (+) pindolol also inhibited lordosis 30 min after administration. However, in addition to its antagonist effects, pindolol acts as a partial agonist in some tissues. Centrally active doses of the pure β-antagonist (±) metoprolol produced no inhibitory effects. Indeed, metoprolol reversed the inhibitory effect of the β-agonist (±) salbutamol. This suggests that the lordosis-inhibiting effects of pindolol were due to its partial agonist effects. Taken together, the present data indicate that activity at central β-adrenoceptors inhibits rather than facilitates lordosis behavior.

Sexual behavior Lordosis β-Adrenoceptors Propranolol Pindolol Metoprolol Salbutamol Lidocaine Estrogen Progesterone

TWO selective β-adrenergic antagonists, propranolol and LB-46 (pindolol), have been evaluated for their effects on lordosis behavior in the female rat. The intrahypothalamic administration of propranolol was reported to inhibit lordosis in females treated with estrogen alone [10]. In females treated with estrogen and progesterone, the intrahypothalamic administration of propranolol appeared to be ineffective, as it neither attenuated nor enhanced the lordosis-inhibiting effects of norepinephrine [5]. When administered peripherally, propranolol inhibited lordosis in females treated with estrogen and progesterone but was ineffective in females made highly receptive by chronic treatment with estrogen [7]. In contrast with results obtained with propranolol, the intrahypothalamic administration of pindolol was reported to facilitate lordosis in females treated with estrogen [25].

Some of the apparent inconsistency in the reports on the effects of β-adrenergic antagonists may be accounted for by differences in the steroid treatments that were employed. Whereas pindolol facilitated lordosis in females treated with estrogen alone, it may well have been inhibitory in females treated with both estrogen and progesterone. Similar results have been observed with other drugs. For example, the serotonin type 1A (5-HT_{1A}) receptor agonist gepirone inhibits lordosis behavior in females primed with estrogen and progesterone, yet facilitates lordosis in females primed with estrogen alone [16]. Notwithstanding the inconsistency in the effects of centrally versus peripherally administered propranolol, it is possible that peripherally administered propranolol might have produced facilitation if low levels of receptivity had been obtained with acute estrogen treatment.

The apparent inconsistency in the effects of propranolol and pindolol may have been due at least partially to differences in the purity of the antagonist effects of the drugs. Whereas propranolol is a relatively pure antagonist, pindolol is known to act as a partial agonist in some tissues [21,24]. Differences in the abilities of these drugs to act as local anesthetics, that is, as agents that stabilize neural membrane activity, might also have contributed to this inconsistency. Whereas propranolol and several other β-adrenergic antagonists are known to produce stabilization of neural membrane activity, pindolol does not produce this effect to any significant degree [21].

As an additional consideration it may be noted that, like most β-adrenergic drugs, propranolol and pindolol each exist in two pharmacologically distinct forms, the (−) and (+) isomers [9, 18, 24]. Whereas the (−) and (+) isomers of each

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drug are equally potent in producing some non-β-adrenergic effects, for example, the membrane stabilizing effect [9], it is the (−) isomer that has the higher affinity for β-adrenoceptors [18,24]. Thus, if an effect of one of these drugs is mediated by β-adrenoceptors then the (−) isomer of the drug can be expected to be far more potent than the (+) isomer in producing this effect. In the earlier evaluations of the effects of propranolol [5, 7, 10] and pindolol [25], animals were treated with mixtures of equal parts of both isomers, that is, with the (±) forms of these drugs.

The present study examined whether different steroid treatments or baseline levels of receptivity account for the reported effects of (±) propranolol and (±) pindolol. Moreover, the effects of the (−) and (+) forms of propranolol and pindolol on lordosis behavior were evaluated. The effects of propranolol and pindolol were then compared with those of metoprolol, a relatively pure β-adrenergic antagonist without significant membrane stabilizing effects [21], and lidocaine, a membrane stabilizing drug without significant β-adrenergic activity. Finally, the effects of the β-adrenergic agonist salbutamol on lordosis were determined, both alone and when coadministered with metoprolol.

GENERAL METHOD

Animals and Surgery

Female Sprague-Dawley rats were bred in our facilities from stock originally obtained from Charles River Canada Inc., Montreal. Animals were weaned at 21 days of age and housed in groups of six in standard laboratory wire mesh cages. At approximately 70 days of age the females were bilaterally ovariectomized through lumbar incisions. Surgery was performed while the animals were under ether anesthesia. Immediately following surgery, females were returned to group housing conditions in a room maintained under a reversed 12 hr dark/12 hr light cycle at 21±1°C and all were allowed free access to food and water.

Drug Procedures

Estradiol benzoate (EB, Steraloids) and progesterone (Steraloids) were dissolved in warm peanut oil and administered subcutaneously in 0.05 ml of the vehicle. (±) Propranolol HCl [(±) propranolol, Sigma], and (+) and (−) propranolol HCl [(+), (−) propranolol; ICI] were dissolved in warm saline, as were (±) metroprolol tartrate (metoprolol, Sigma) and (±) salbutamol hemisulfate (salbutamol, Sigma). (±) Pindolol (Sigma), and (−) and (+) pindolol (Sandoz) were brought into solution in saline by titration with tartaric acid, as was lidocaine (Sigma) with HCl. All drugs were administered intraperitoneally in approximately 0.3 ml of vehicle in a blind fashion.

Lordosis Testing

Behavioral testing involved presentation of an experimental female to a sexually vigorous male rat in the testing chamber. The narrow, bi-level testing chambers used in the present study have been fully described elsewhere [17]. 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. A female's response to a mount was considered a lordosis response if some degree of concavity of the back was noted. Lordosis quotients were calculated as the percentage of mounts with pelvic thrusting resulting in a lordosis response.

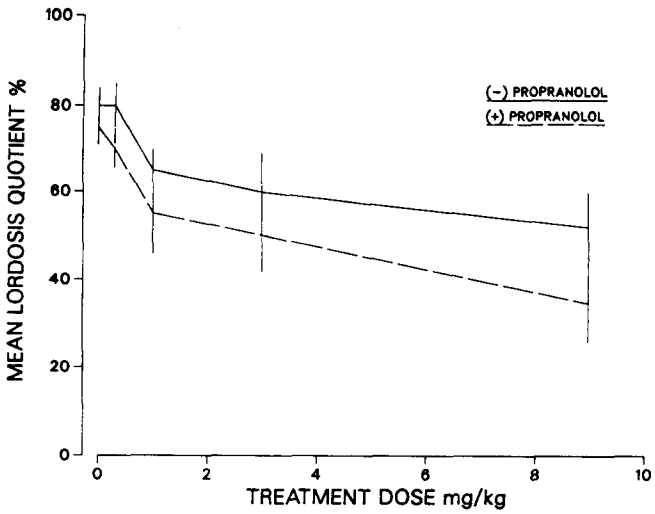

FIG. 1. Mean lordosis quotients ±S.E.M. of female rats primed with estradiol benzoate and progesterone following the peripheral administration of varying doses of (−) propranolol and (+) propranolol 30 min prior to behavioral testing.

EXPERIMENT 1

(±) Propranolol (0.8–20 mg/kg) has been reported to inhibit lordosis behavior 2 hr after peripheral administration to female rats primed with estrogen and progesterone [7]. However, if the inhibitory effects of propranolol are due to the blockade of central β-adrenoceptors, then (−) propranolol, the isomer most active at β-adrenoceptors [9,18], should be far more potent than (+) propranolol in inhibiting lordosis.

In a preliminary study in this laboratory, (±), (−) and (+) propranolol (0.1–0.9 mg/kg) were all found to be ineffective 2 hr after peripheral administration to females primed with estrogen and progesterone. However, Sprague-Dawley rats were employed in this laboratory, whereas Long-Evans rats were used in the published report [7]. Strain differences in the time- or dose-response to propranolol may account for our failure to observe an inhibition after 2 hr. In experiment 1, animals treated with estrogen and progesterone received varying doses of (−) and (+) propranolol 30 min before testing. Moreover, to investigate the possibility that peripherally administered propranolol might facilitate lordosis behavior in females with low baseline levels of receptivity, the effects of (±) propranolol were evaluated in animals treated with estrogen alone.

Method

Females were divided into 2 sets of 40 animals, one set that received (+) propranolol and a second that received (−) propranolol. Each set was divided into 5 groups of 8 animals that received 10 μg EB 48 hr, 500 μg progesterone 4 hr, and either 0.3, 1, 3, or 9 mg/kg of drug or the saline vehicle 30 min prior to behavioral testing.

In the second part of Experiment 1, animals were divided into 5 groups of 9 animals that received 10 μg EB 48 hr, and either 0.3, 1, 3, or 9 mg/kg of (±) propranolol or the saline vehicle 30 min prior to behavioral testing.

Results and Discussion

From an examination of Fig. 1 it is apparent that both (+) and (−) propranolol inhibited lordosis responding. It also appears that (+) propranolol was somewhat more effective than (−) propranolol in inhibiting lordosis behavior. By an analysis of variance it was confirmed that there was a significant inhibition of lordosis behavior with increasing doses of (−) and (+) propranolol, $F(4,63)=7.958$, $p<0.0001$. In addition it was found that (+) propranolol was significantly more effective than (−) propranolol in producing the inhibition of lordosis, $F(1,63)=5.376$, $p<0.023$. Because there were significant main effects of dose and drug, data were partitioned and separate analyses were performed to evaluate the simple effects of dose for each isomer of propranolol. Significant dose effects were confirmed for both (+) propranolol, $F(4,35)=4.743$, $p<0.004$, and (−) propranolol, $F(4,35)=3.804$, $p<0.012$. It was determined by the Newman-Keuls method of multiple comparisons that each drug produced a significant inhibition of lordosis only at the 9 mg/kg dose ($p<0.05$), even though the overall inhibitory effect of (+) propranolol was significantly greater than that of (−) propranolol.

Although the baseline level of receptivity of females that received estrogen alone should have allowed a facilitatory effect of (±) propranolol to emerge, no significant facilitation was observed. Lordosis quotients of animals that received 9 mg/kg of (±) propranolol were slightly but not significantly lower than those of animals in the control group. Low baseline levels of receptivity in the control group may have prevented this inhibition from reaching statistical significance.

Although (−) propranolol is approximately 100 times more effective than (+) propranolol at β-adrenoceptors [9], (−) and (+) propranolol were found to be equally effective in inhibiting lordosis behavior in females treated with estrogen and progesterone. Moreover, these inhibitions occurred only at the 9 mg/kg dose of each drug, a dose well beyond that required to produce an effective blockade of β-adrenoceptors by either (−) or (±) propranolol [9]. Taken together, these data suggest that the lordosis-inhibiting effects of propranolol were mediated by a non-β-adrenergic mechanism (for review of the non-stereoselective, non-adrenergic effects of propranolol, see [2]).

EXPERIMENT 2

There is evidence to suggest that the 9 mg/kg doses of (+) and (−) propranolol found effective in Experiment 1 may have been sufficient to produce membrane stabilization in peripheral or even central neural tissues. For example, the intravenous administration of a 4.5 mg/kg dose of (+) propranolol was found to prolong the PR intervals in the electrocardiograms of intact cats. This effect, which is indicative of a decrease in the ability of the sinoatrial node of the heart to generate and conduct electrical impulses, was attributed to membrane stabilization [3].

The drug lidocaine is essentially inactive at β-adrenoceptors (although see [23]). However, being a local anesthetic, it produces membrane stabilization [19]. In Experiment 2 the effects on lordosis behavior of peripherally administered lidocaine were evaluated. If membrane stabilization is a plausible explanation for the non-stereoselective lordosis-inhibiting effect of propranolol, then lidocaine should inhibit lordosis.

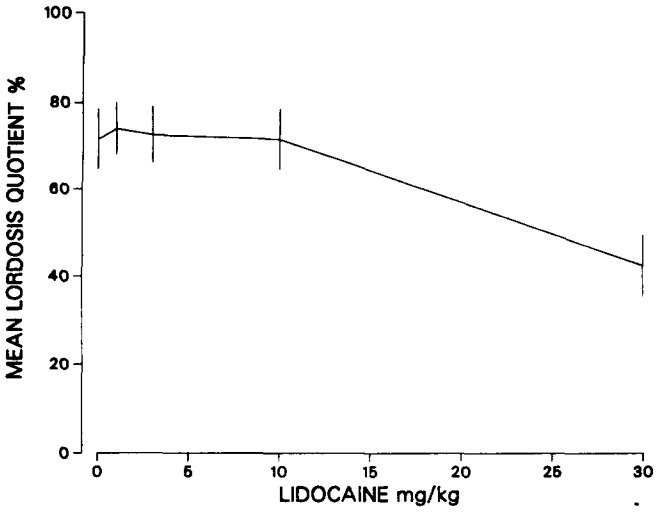

FIG. 2. Mean lordosis quotients ±S.E.M. of female rats primed with estradiol benzoate and progesterone following the peripheral administration of varying doses of lidocaine 30 min prior to behavioral testing.

Method

Females were divided into 5 groups of 13 animals, each of which received 10 μg EB 48 hr, 500 μg progesterone 4 hr, and either 1, 3, 10, or 30 mg/kg lidocaine or the vehicle 30 min prior to testing.

Results and Discussion

An examination of Fig. 2 suggests that the highest dose of lidocaine inhibited lordosis behavior. The inhibitory effect of the 30 mg/kg dose of lidocaine was confirmed by an analysis of variance, $F(4,60)=3.974$, $p<0.0064$, and, subsequently, the Newman-Keuls method ($p<0.05$). Although lidocaine is a local anesthetic, it should be noted that 30 mg/kg of the drug inhibited lordosis behavior without producing obvious sedation or motor impairment. Many animals with markedly inhibited lordosis responses were capable of displaying vigorous proceptive behavior, particularly, earwiggling, when approached by the male.

It is tempting to speculate that the membrane stabilizing effects of both lidocaine and propranolol contribute to their common effect on lordosis. However, one cannot rule out the possibility that lidocaine and propranolol inhibit lordosis by completely different mechanisms.

EXPERIMENT 3a

In contrast with propranolol, (±) pindolol has been reported to facilitate lordosis behavior when administered directly into the hypothalamus and medial forebrain bundle of estrogen-primed female rats [25]. However, it is conceivable that in females treated with estrogen and progesterone, pindolol might inhibit lordosis, as has been observed with propranolol ([7], Experiment 1 of the present study). In Experiment 3a, the effects of peripherally administered (±) pindolol were evaluated in females primed with estrogen, and with estrogen and progesterone.

Method

Females were divided into 4 groups of 8 animals, each of

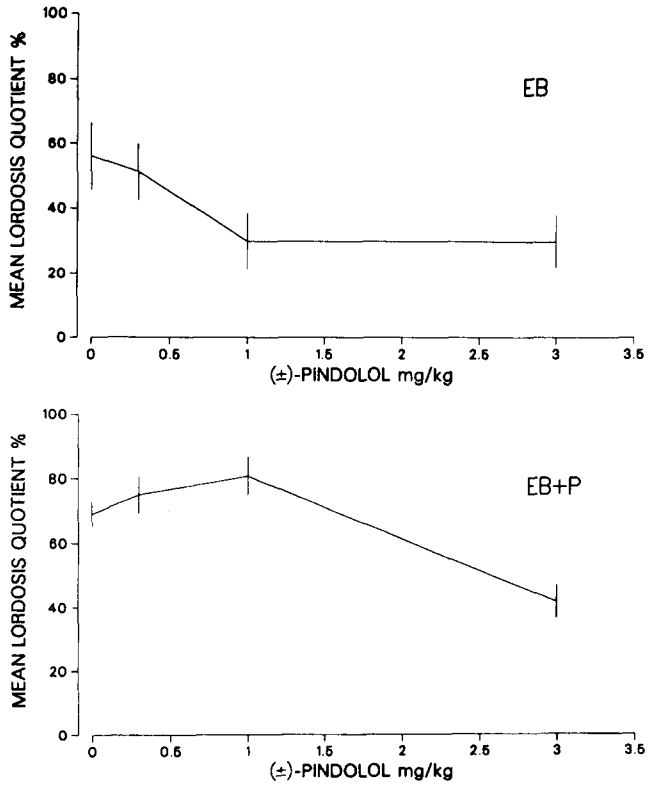

FIG. 3. Mean lordosis quotients ±S.E.M. of female rats primed with estradiol benzoate (EB; top panel), or estradiol benzoate and progesterone (EB+P; bottom panel) following the peripheral administration of varying doses of (±) pindolol 30 min prior to behavioral testing.

which received 10 μg EB 48 hr and either 0.3, 1, or 3 mg/kg (±) pindolol, or the vehicle 30 min prior to testing. The second part of Experiment 3a was performed one week later, and was identical to the first except that the 4 groups consisted of 10 animals and all animals received 500 μg progesterone 4–6 hr prior to testing.

Results and Discussion

From an examination of Fig. 3 it appears that peripheral administration of (±) pindolol inhibited rather than facilitated lordosis behavior in females primed either with estrogen or with estrogen and progesterone.

An analysis of variance failed to reveal a significant inhibitory effect of (±) pindolol in females treated with estrogen alone. However, significant inhibitory effects of (±) pindolol were confirmed in animals treated with estrogen and progesterone, $F(3,36)=10.676$, $p<0.0001$. By use of the Newman-Keuls method it was determined that the inhibitory effects of (±) pindolol occurred at the 3 mg/kg dose ($p<0.05$).

Although pindolol failed to produce a significant inhibition of lordosis in animals treated with estrogen alone, this failure may simply reflect lower baseline lordosis quotients and higher variability than was observed in animals treated with estrogen and progesterone.

EXPERIMENT 3b

As is the case with propranolol, the (−) isomer of pindolol is most active at β-adrenoceptors [24]. In Experiment 3b the effects of the (−) and (+) isomers of pindolol were evaluated in females primed with estrogen and progesterone. It was assumed that if the effects of (±) pindolol observed in Experiment 3a were indeed mediated by β-adrenoceptors, then (−) pindolol would be more effective than (+) pindolol in inhibiting lordosis behavior.

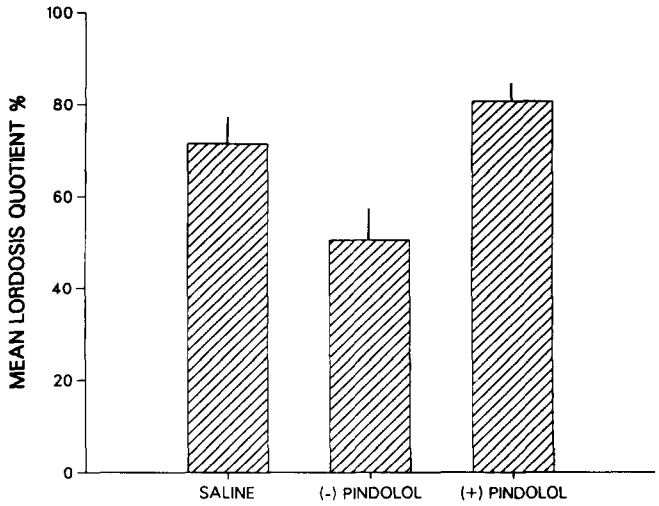

FIG. 4. Mean lordosis quotients ±S.E.M. of female rats primed with estradiol benzoate and progesterone following the peripheral administration of 3 mg/kg (−) pindolol, 3 mg/kg (+) pindolol, or the vehicle 30 min prior to behavioral testing.

Method

In Experiment 3b animals were divided into 3 groups of 13 animals. Animals in each group received 10 μg EB 48 hr, 500 μg progesterone 4–6 hr, and either 3 mg/kg (+) pindolol, 3 mg/kg (−) pindolol, or the vehicle 30 min prior to testing.

Results and Discussion

From an examination of Fig. 4 it is apparent that (−) pindolol inhibited lordosis whereas (+) pindolol was ineffective. A significant drug effect was confirmed by an analysis of variance, $F(2,36)=7.489$, $p<0.002$. By use of the Newman-Keuls method it was confirmed that (−) pindolol produced a significant inhibition of lordosis ($p<0.05$).

EXPERIMENT 4

In Experiment 4 the effects of the β-adrenergic antagonist metoprolol were evaluated. Unlike propranolol, metoprolol produces relatively little membrane stabilization [21]. Moreover, unlike pindolol, which appears to act as a partial agonist at β-adrenoceptors [24], metoprolol appears to be a relatively pure antagonist [21].

Method

Females were divided into 5 groups of 6 animals, each of which received 10 μg EB 48 hr and either 0.6, 2, 6, or 20 mg/kg metoprolol, or the saline vehicle 30 min prior to testing. The second part of Experiment 4 was identical to the first except that groups consisted of 7 animals and all animals received 500 μg progesterone 4–6 hr prior to testing. Doses

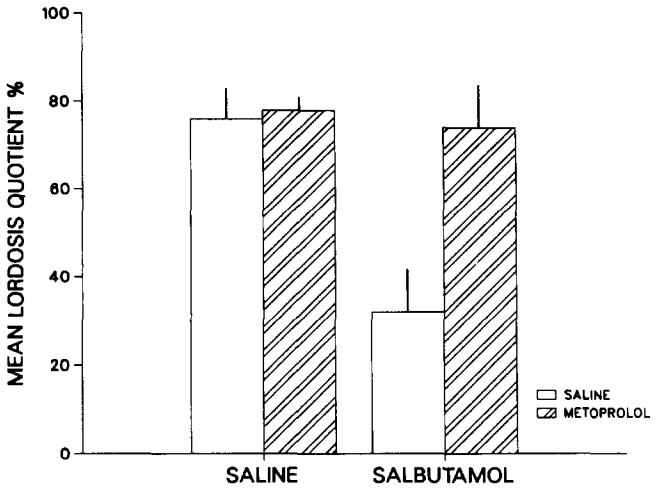

FIG. 5. Mean lordosis quotients ±S.E.M. of female rats primed with estradiol benzoate and progesterone following the peripheral administration of 20 mg/kg salbutamol, 20 mg/kg metoprolol, salbutamol and metoprolol, or the vehicle 30 min prior to behavioral testing.

of metoprolol were chosen on the basis of an earlier report of central effects after the peripheral administration of 5 mg/kg of the drug [6].

Results

Peripheral administration of centrally active doses of metoprolol appeared to have no effect on the lordosis behavior of animals primed either with estrogen, or with estrogen and progesterone. This was confirmed in separate analyses of variance. Indeed, it was observed in subsequent experiments that doses of metoprolol as high as 75 mg/kg were completely ineffective in females primed with both estrogen and progesterone.

EXPERIMENT 5

In preliminary studies, the β-adrenergic agonist salbutamol [6,18] appeared to inhibit lordosis behavior. If the apparent inhibitory effects of salbutamol were due to the stimulation of β-adrenergic receptors, then this effect should be blocked by the coadministration of a β-adrenergic antagonist. Doses of metoprolol comparable to those found ineffective in Experiment 4 have been found to block the central effects of the β-adrenergic agonist clenbuterol [6]. In Experiment 5, the effect of salbutamol on lordosis was evaluated in the absence or presence of metoprolol.

Method

Females were divided into 4 groups of 6 animals that each received 10 μg EB 48 hr, and 500 μg progesterone 4–6 hr prior to testing. A 2×2 design was employed such that each of the 4 groups received either saline or 20 mg/kg salbutamol 30 min, and either saline or 20 mg/kg metoprolol 30 min prior to testing. Both salbutamol and metoprolol have been reported to be centrally active at these doses [6,20].

Results

The data displayed in Fig. 5 suggest that salbutamol inhibited lordosis behavior. Metoprolol alone was ineffective, however, the drug appeared to reverse the inhibitory effect of salbutamol.

An analysis of variance revealed significant main effects of both metoprolol, $F(1,16)=7.45$, $p<0.0143$, and salbutamol, $F(1,16)=8.86$, $p<0.009$. Moreover, the analysis revealed a significant interaction between metoprolol and salbutamol, $F(1,16)=6.154$, $p<0.024$. Subsequent use of the Newman-Keuls method confirmed that metoprolol reversed the inhibitory effect of salbutamol. Lordosis quotients of animals that received salbutamol were significantly lower than those of control animals ($p<0.05$), of animals that received metoprolol ($p<0.05$), and of animals that received both metoprolol and salbutamol ($p<0.05$). The lordosis quotients of animals that received both metoprolol and salbutamol did not differ from those of control animals or of animals that received metoprolol alone.

GENERAL DISCUSSION

In the present study (−) and (+) propranolol were equivalent in their ability to inhibit lordosis behavior 30 min after peripheral administration. Because (−) propranolol is far more active at β-adrenergic receptors, the lordosis-inhibiting effects of propranolol were most likely due to a non-β-adrenergic mechanism. The inhibition of lordosis by lidocaine is consistent with the possibility that the membrane stabilizing properties of propranolol account for its inhibition of lordosis. (±) and (−), but not (+) pindolol also inhibited lordosis 30 min after administration. However, centrally active doses of the pure β-antagonist (±) metoprolol produced no inhibitory effects. Indeed, metoprolol reversed the inhibitory effect of the β-agonist (±) salbutamol. This suggests that the lordosis-inhibiting effects of pindolol are due to its action as a partial agonist at β-adrenoceptors [24]. In other words, it is plausible that the lordosis-inhibiting effect of pindolol is due to stimulation rather than blockade of β-adrenoceptors. Taken together, the present data indicate that activity at central β-adrenoceptors inhibits rather than facilitates lordosis behavior. Of course, it is possible that the effects observed in the present study were at least partially mediated by peripheral mechanisms.

Because metoprolol alone proved ineffective in the present study, it appears unlikely that β-adrenoceptors play a major role in the modulation of lordosis behavior. However, it might be that stimulation of β-adrenoceptors enhances the effect of a more primary lordosis-inhibiting system in the rat. In view of evidence that β-adrenergic agonists enhance the effect of serotonergic drugs [6,20], and that activity at 5-HT_{1A} receptors inhibits lordosis [15], it is reasonable to suggest that the lordosis-inhibiting effect of β-adrenergic stimulation is mediated indirectly by increased serotonergic activity at 5-HT_{1A} receptors.

The findings of lordosis-inhibiting effects of peripherally administered pindolol in Experiments 3a and 3b appear inconsistent with the report that pindolol administered into the hypothalamus facilitates lordosis [25]. Because peripherally administered pindolol would have reached both hypothalamic and non-hypothalamic areas of the brain, these apparent inconsistencies may reflect regional differences in the effects of activity at β-adrenoceptors. However, recent evidence indicates that pindolol binds with a significantly high affinity to 5-HT_{1A} receptors as well as to β-adrenoceptors [12]. Indeed, during the preparation of this manuscript it was learned that (−) pindolol attenuates the inhibition of

lordosis by the potent and selective 5-HT_{1A} agonist 8-hydroxy-2-(di-n-propylamino) tetralin [8]. Although the affinity of pindolol for β-adrenoceptors appears to be roughly 100 times greater than its affinity for 5-HT_{1A} receptors [12,17], if the lordosis-inhibiting effects of β-adrenergic stimulation are mediated by an enhancement of activity at 5-HT_{1A} receptors, then under some conditions the lordosis-facilitating anti-serotonergic effects of pindolol might override the lordosis-inhibiting effects of the drug caused by its action as a partial agonist at β-adrenoceptors.

It should be emphasized that the β-adrenergic subtype of receptor can itself be classified into β_1- and β_2-subtypes [14]. Although salbutamol and pindolol bind non-selectively to β_1- and β_2-adrenoceptors [18], the agonist effects of both drugs appear to be limited almost entirely to the β_2-subtype [18,24]. Furthermore, although metoprolol, which reverses the inhibitory effect of salbutamol, is usually considered to be β_1-selective, the affinity of the drug for β_2-adrenoceptors is nearly equal to that of salbutamol [18]. Thus it is distinctly possible that the inhibitions of lordosis produced by pindolol and salbutamol in the present study were due to stimulation of central β_2-adrenergic sites.

The β-adrenergic agonist isoproterenol has been found to facilitate lordosis when administered directly into the medial preoptic and arcuate-ventromedial nuclei of estrogen-primed female rats [10], and to be ineffective when administered into the medial preoptic nuclei of females treated with estrogen and progesterone [5]. These reports appear inconsistent with the present results, which indicate that β-adrenergic activity inhibits lordosis behavior. Because drugs administered peripherally in the present study would have reached both hypothalamic and non-hypothalamic areas of the brain, these apparent inconsistencies might represent regional differences in the effects of β-adrenergic stimulation on lordosis behavior. In addition, because isoproterenol is a potent agonist at both β_1- and β_2-subtypes of receptors [14], it is tempting to suggest that activity at β_1-adrenoceptors might attenuate the apparent lordosis-inhibiting effects of β_2-adrenoceptor stimulation.

Isoproterenol also binds, albeit with low affinity, to α-adrenoceptors [22]. In some tissues, isoproterenol may act as an agonist at α-adrenergic sites [13]. In the evaluations of the effects of isoproterenol on lordosis, high (millimolar) concentrations of the drug were infused directly into the hypothalamus [5,10], an area where the α-subtype of adrenoceptors appears predominant [4]. In view of the controversy over the role of α-adrenoceptors in the modulation of lordosis [5, 7, 10, 11], it is conceivable that the effects produced by the activation of certain α-adrenoceptors may have masked any β-adrenergically mediated lordosis-inhibiting effects of isoproterenol.

In closing it must be mentioned that pindolol also binds with low affinity to α-adrenoceptors [1]. Although we believe it unlikely, we cannot rule out the possibility that activity at central or peripheral α-adrenoceptors contributed to the effects of pindolol in the present study. However, whereas propranolol binds with low affinity to α-adrenoceptors, the equal effectiveness of (−) and (+) propranolol suggests that the lordosis-inhibiting effects of propranolol are not mediated by α-adrenoceptors [22]. Moreover, it can be said with some certainty that the effects of salbutamol are not mediated by α-adrenoceptors. Salbutamol has an extremely low affinity for α-adrenoceptors [1], and therefore is not likely to be active at these sites.

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