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# Separation of Dopaminergic and Serotonergic Inhibitory Mechanisms in the Mediation of Estrogen-Induced Lordosis Behaviour in the Rat

A. FERNÁNDEZ-GUASTI,*[1] S. AHLENIUS,† S. HJORTH‡ AND K. LARSSON§

**Sección de Terapéutica Experimental Departamento de Farmacología y Toxicología CINVESTAV-IPN, Apdo. Postal 22026, México 14000, D.F., México and División de Neurociencias, Instituto Mexicano de Psiquiatría, México 14370, D.F., México*
*†Astra Alab AB, Research and Development Laboratories, Pharmacology, S-151 85 Södertälje, Sweden*
*‡Department of Pharmacology, University of Göteborg, Box 33031, S-400 33 Göteborg, Sweden*
*§Unit of Psychobiology, Department of Psychology, University of Göteborg Box 14158, S-400 20 Göteborg, Sweden*

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FERNÁNDEZ-GUASTI, A., S. AHLENIUS, S. HJORTH AND K. LARSSON. *Separation of dopaminergic and serotonergic inhibitory mechanisms in the mediation of estrogen-induced lordosis behaviour in the rat.* PHARMACOL BIOCHEM BEHAV 27(1) 93–98, 1987.—The administration of the putative 5-hydroxytryptamine$_1$ (5-HT$_1$) agonist 8-hydroxy-2(di-n-propylamino) tetralin (8-OH-DPAT) (0.0625–1.0 mg·kg$^{-1}$) suppresses lordosis behaviour induced in ovariectomized female rats by daily treatment for 3–5 days with estradiol benzoate (1.25 μg/rat). A similar suppressive effect on the lordosis behaviour can be obtained by administration of the dopamine/serotonin agonist, lisuride (0.1–0.4 mg·kg$^{-1}$), or after the administration of the dopamine (DA) agonists, apomorphine (0.2–0.8 mg·kg$^{-1}$) or quinpirole (0.75–2.50 mg·kg$^{-1}$). The suppressive effects on the lordosis behaviour by 8-OH-DPAT cannot be antagonized by the DA receptor antagonist haloperidol (0.2 mg·kg$^{-1}$) neither with methiotepin (0.5 mg·kg$^{-1}$), which is assumed to be a non-selective 5-HT receptor blocking agent, nor with pirenperone (0.25 mg·kg$^{-1}$) which is assumed to be a 5-HT$_2$ receptor blocking agent. However, a partial blockade of the lordosis suppressive effects of 8-OH-DPAT was obtained by treatment with (−)-pindolol, which is thought to be a partial 5-HT$_1$ blocking agent, suggesting that 8-OH-DPAT exerts its suppressive effects on the lordosis behaviour through the 5-HT system. Haloperidol causes a complete blockade of the suppressive effects of apomorphine and quinpirole suggesting that these drugs exert their inhibitory effects on the lordosis behaviour by activating the DA system. We furthermore found that (−)-pindolol but not haloperidol antagonized the suppressive effect on the lordosis response induced by lisuride suggesting that the lisuride effect was mediated by the 5-HT system rather than by the DA system. It was concluded that 8-OH-DPAT suppresses lordosis behaviour by activating serotonergic 5-HT$_1$ receptors.

8-OH-DPAT Lisuride Apomorphine Quinpirole Haloperidol Methiotepin Pirenperone (−)-Pindolol Estrogen-induced lordosis behaviour

THE role of the monoaminergic system in the hormonal induction of lordosis behaviour in the female rat is not fully understood. Some evidence suggests that the stimulation of the serotonergic system induces a specific inhibition of the facilitatory action of progesterone on the lordosis behaviour [11, 14, 34]. The stimulation of the dopaminergic system results in an inhibition of the lordosis behaviour induced by estrogen plus progesterone as well as by estrogen alone [1, 2, 15–17, 35]. Recently we showed that the administration of the putative 5-HT$_1$ agonist 8-OH-DPAT [21] effectively inhibits the lordosis behaviour induced either by estrogen plus progesterone or by estrogen alone, and we concluded that the effects were due to stimulation of central 5-HT, presumably 5-HT$_{1A}$ receptors [5]. However, like dopaminergic agents, 8-OH-DPAT also inhibited the lordosis induced by estrogen alone. It thus became important to separate dopaminergic and serotonergic inhibitory mechanisms in the mediation of lordosis behaviour.

The first series of experiments were made in order to compare the inhibitory effect of 8-OH-DPAT, on the

[1]Requests for reprints should be addressed to Dr. Alonso Fernández-Guasti, Sección de Terapéutica Experimental, Departamento de Farmacología, y Toxicología, CINVESTAV-IPN, Apdo. Postal 22026, México 14000, D.F., México.

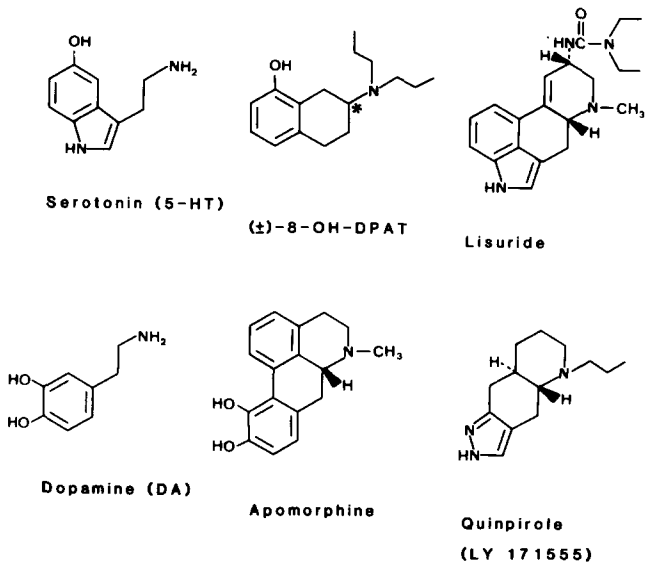


FIG. 1. Structure formulas of monoamine agents in comparison with those of 5-hydroxytryptamine and dopamine.

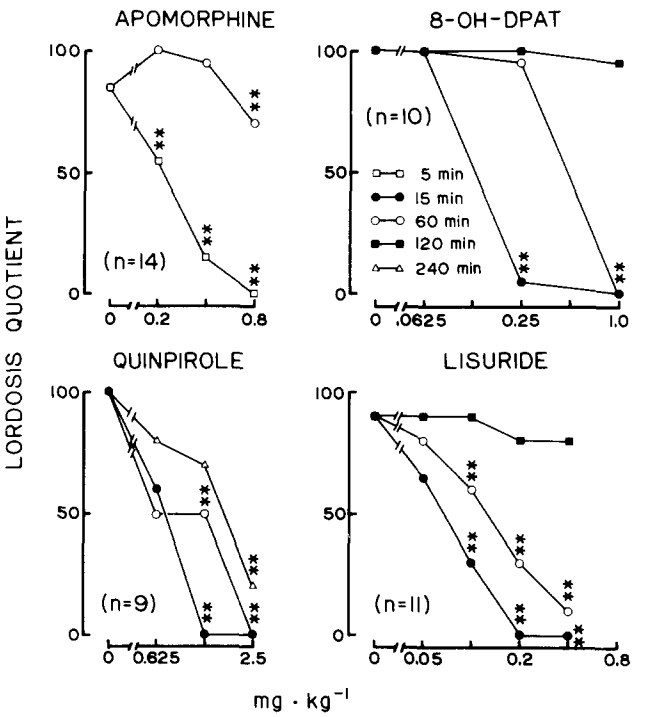


FIG. 2. Dose effect relationships and time course of action of 8-OH-DPAT, lisuride, apomorphine and quinpirole-induced effects on lordosis behaviour. Effects on the lordosis response were observed at different time-intervals in relation to an IP (8-OH-DPAT, lisuride, and quinpirole) or SC (apomorphine) drug injection (0 min) as indicated in the figure. Shown are the medians based on the performance of 9–14 animals/group. For each dose of the respective drug, repeated observations were made at specific time intervals, e.g., 5, 15, 60, 120 and 240 min in the same animals. Statistical evaluation was performed between pre-drug and post-drug LQ values by means of the Friedman two-way ANOVA followed by the Wilcoxon matched pairs signed ranks test. $^{**}p<0.02$, all other comparisons $p>0.05$ [42].

estrogen-induced lordosis behaviour, to that of the dopaminergic agonists apomorphine [7,13] and quinpirole [41] and to that of the mixed dopaminergic/serotonergic agonist, lisuride [27,30]. The second series of experiments was undertaken in order to establish whether the dopaminergic or the serotonergic system mediate the inhibitory action of 8-OH-DPAT, lisuride, apomorphine and quinpirole on the lordosis behaviour. Thus, an attempt to block the inhibitory action of these drugs by using the dopaminegic antagonist haloperidol [8], or by administering the serotonergic blocking agents methiotepin, pirenperone or (−)-pindolol [24, 26, 29, 36] was made.

## METHOD

### *Animals*

Adult male and female Wistar rats (Mollegaard, Vejle, Denmark) were used in this study. All animals were maintained in a temperature controlled room (23°C), under reversed light-dark conditions (12 hr light:12 hr dark, lights on at 2200 hr). Animals were housed 3 per cage and fed with commercial rat chow and water ad lib. All females were bilaterally ovariectomized (OVX) under Brietal® anesthesia (50 mg/kg, IP) fifteen days before the steroid treatment.

### *Drugs and Steroid Hormones*

*Steroids.* Estradiol benzoate (EB, Sigma Chemical, St. Louis, MO) was injected subcutaneously in a volume of 0.1 ml of sesame oil.

*Drugs.* The drugs used in these experiments were: apomorphine·HCl (Sigma Chemicals, St. Louis, MO), 8-hydroxy-2(di-n-propylamino) tetralin·HBr (8-OH-DPAT·HBr, racemate) (Organic Chemistry Unit, Department of Pharmacology, University of Göteborg, Sweden*), quinpirole (LY-171555, Lilly, Minneapolis, MN*), lisuride (lisuride hydrogen maleate, Schering, Berlin, Germany*), methiotepin (Hoffman-La Roche, Basle, Switzerland*), pirenperone (R50656) (Janssen Pharmaceuticals, Beerse, Belgium*), (−)-pindolol (Sandoz, Basle, Switzerland*) and haloperidol (Janssen-Leo Pharma AB, Helsingborg, Sweden*).

All drugs, but apomorphine and (−)-pindolol were injected IP in a volume of 2.0 ml/kg. Apomorphine and (−)-pindolol were injected SC in the same volume. All drugs but haloperidol were dissolved in physiological saline. Haloperidol was dissolved in a few drops of glacial acetic acid and thereafter glucose 5.5% was added to the final volume.

### *Procedure*

The ovariectomized female rats received over 3 days a daily SC injection of 1.25 μg/animal EB. Twenty-four hours after the last injection, animals were tested for lordosis behaviour and only those animals showing a LQ of 70 or higher were selected for further experimentation. In the first series of experiments (experiments that compare the effect of the various serotonergic and dopaminegic agonists), this pre-drug LQ median value was considered as control for statistical comparisons. All drugs in these experiments were injected 10 minutes after the pre-drug test. The observations were made at 5, 15, 60, 120 and 250 minutes after the drug administration. The statistical comparisons in these experiments were made by help of the Friedman two-way ANOVA

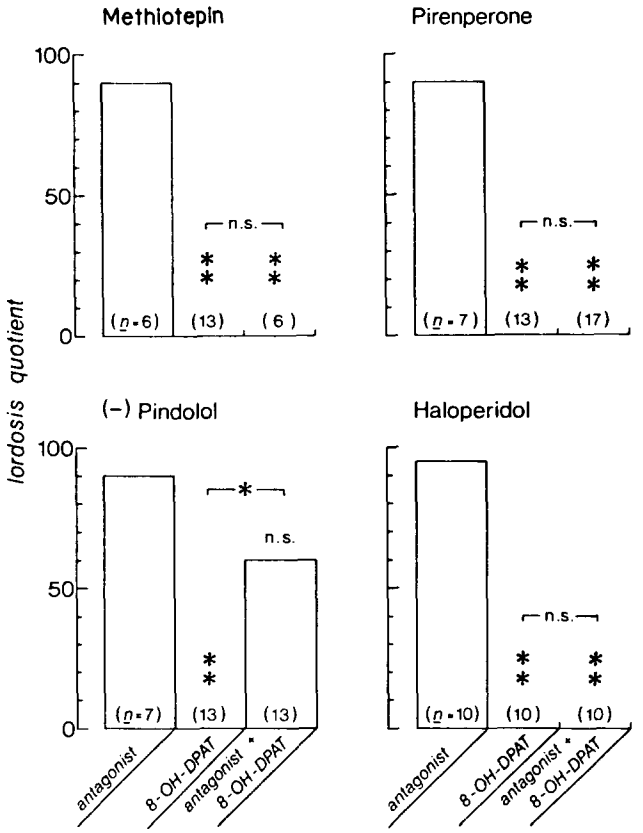


FIG. 3. Effects of some 5-HT and dopamine receptor blocking agents on the suppression of lordosis behaviour induced by 8-OH-DPAT. The various drugs were administered at doses and time intervals in relation to behavioural observations as follows: methiotepin, 0.5 mg·kg$^{-1}$ IP (−60 min); pirenperone, 0.25 mg·kg$^{-1}$ IP (−30 min); (−)-pindolol, 2 mg·kg$^{-1}$ SC (−30 min); haloperidol, 0.2 mg·kg$^{-1}$ IP (−30 min); 8-OH-DPAT, 0.25 mg·kg$^{-1}$ IP (−10 min). Shown is the median performance of 6–17 animals/group as indicated in the figure. Statistical evaluation was made by means of the Kruskal-Wallis one-way ANOVA followed by the Mann-Whitney U-test for comparisons with control animals receiving the antagonist, or as indicated by brackets in the figure. The pre-drug test lordosis quotient ranged between 85–100 in the various groups. $^{ns}p>0.05$, $*p<0.05$, $**p<0.02$ [42].

test followed by the Wilcoxon matched pairs signed ranks test [42]. In the next series of experiments receptive animals (with pre-drug test LQ values ranging between 85 and 100) were injected with the dopaminergic or serotonergic agonists and antagonists at the time intervals indicated in legends to Figs. 3–5. The statistical comparisons were made between the control groups (animals treated with either the agonist or the antagonist) and the experimental group (animals treated with the combination of agonist/antagonist) by means of the Kruskal-Wallis one-way ANOVA test followed by the Mann-Whitney U-test [42].

*Behavioural Observations*

Tests for lordosis behaviour consisted of the presentation of the female to a sexually active male. The number of lordosis in response to the mounts by the male was recorded. The measure for sexual receptivity used was the lordosis

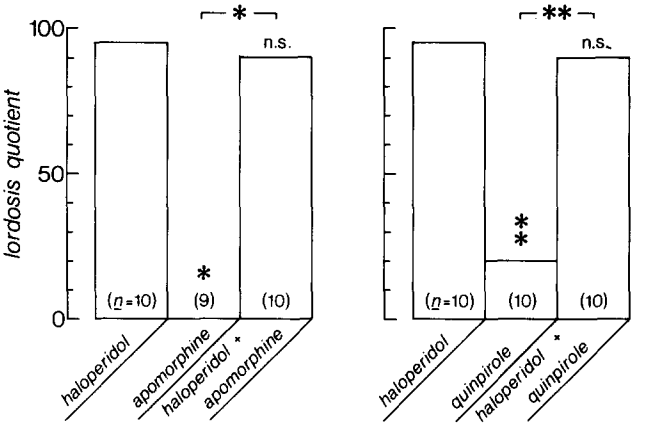


FIG. 4. Antagonism by haloperidol of the suppression of lordosis behaviour induced by apomorphine or quinpirole. Haloperidol, 0.2 mg·kg$^{-1}$ IP was administered 30 min before the observation. Apomorphine, 0.4 mg·kg$^{-1}$ SC and quinpirole, 1.25 mg·kg$^{-1}$ IP were injected 5 and 15 min before the observations respectively. Shown is the median performance of 9–10 animals as indicated in the figure. Statistical evaluation was made by means of the Kruskal-Wallis one-way ANOVA followed by the Mann-Whitney U-test for comparisons with haloperidol-treated controls or as indicated by brackets in the figure. The pre-drug test lordosis quotient ranged between 90–100 in the various groups. $^{ns}p>0.05$, $*p<0.05$, $**p<0.02$ [42].

quotient (LQ=number of lordosis/10 mounts × 100). (For details see [39].)

## RESULTS

*Dose-Effect Relationships and Time-Course of Action of 8-OH-DPAT, Lisuride, Apomorphine and Quinpirole on the Estrogen-Induced Lordosis Behaviour*

The structural formula of the various compounds used in this experiment are shown in Fig. 1 together with formulas of 5-HT and DA. Figure 2 shows that maximal effects of 8-OH-DPAT were seen 15–60 min after its injection depending on dose, the lowest dose, 0.0625 mg/kg, being ineffective. The duration of the effect was less than 2 hr. The administration of apomorphine caused maximal effects on the lordosis behaviour within 5 min after its injection at all doses used. After 1 hr there was a reduction of the lordosis quotient only at the 0.8 mg/kg dose level. Lisuride had a maximal suppressive effect on the lordosis behaviour within 15 min and then the LQ values gradually returned to control levels within 2 hr. Quinpirole caused a statistically significant reduction of the lordosis behaviour within the first 15 min after its injection. At the highest dose level (2.5 mg/kg), this drug was relatively long acting causing a marked reduction of the lordosis response even 4 hr after its injection. The effects were clearly dose-related with all the drugs used in this experiment.

*Effects of Some 5-HT and Dopamine Receptor Blocking Agents on the Suppression of Lordosis Behaviour Induced by 8-OH-DPAT*

Figure 3 shows the effects of three 5-HT blocking agents, methiotepin, pirenperone and (−)-pindolol, and a DA blocking agent, haloperidol. All these blocking agents were given

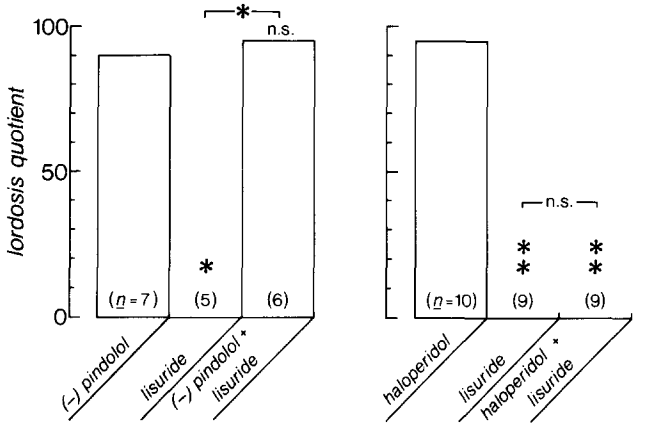


FIG. 5. Antagonism by (−)-pindolol but not by haloperidol of the suppression of lordosis induced by lisuride. Haloperidol, 0.2 mg·kg$^{-1}$ IP or (−)-pindolol, 2 mg·kg$^{-1}$ SC were administered 30 min before the observation. Lisuride 0.1 mg·kg$^{-1}$ was injected 15 min before the observation. Shown is the median performance of 5–10 animals, as indicated in the figure. Statistical evaluation was made by means of the Kruskal-Wallis one-way ANOVA followed by the Mann-Whitney U-test for comparisons with haloperidol or (−)-pindolol-treated controls or as indicated by brackets in the figure. The pre-drug test lordosis quotient ranged between 90–100 in the various groups. $^{ns}p>0.05$, $^{*}p<0.05$, $^{**}p<0.02$ [42].

in doses which had no suppressive effects on the lordosis behaviour by themselves, and all effects have been compared with controls receiving the antagonist only. As demonstrated by the figure, haloperidol was not able to block the suppressive effect of 8-OH-DPAT on the lordosis response, suggesting that this effect is not mediated by an action on the DA system.

By contrast, (−)-pindolol, which is supposed to be a selective 5-HT$_{1A}$ blocking agent, partially blocked the suppressive action of 8-OH-DPAT on the lordosis response, while methiotepin which is a mixed 5-HT$_1$ and 5-HT$_2$ blocking agent and pirenperone which is a selective 5-HT$_2$ antagonist did not have such effects. These findings suggest that the suppressive action of 8-OH-DPAT on the lordosis behaviour, at least partly, is mediated by the 5-HT system.

*Effect of Haloperidol on the Suppression of Lordosis Behaviour by Apomorphine or Quinpirole*

In this experiment the rats were injected with haloperidol (0.2 mg/kg) in a dose which does not facilitate the lordosis behaviour by itself in estrogen primed rats (data not shown). As demonstrated by Fig. 4, haloperidol completely blocked the suppressive effect of apomorphine and quinpirole on the lordosis behaviour suggesting that this effect was due to an activation of the dopaminergic system by either of these drugs.

*Effect of (−)-Pindolol and Haloperidol on the Suppression of Lordosis Behaviour Induced by Lisuride*

The administration of (−)-pindolol, in a dose which by itself did not affect the lordosis response, blocked the suppressive effect of lisuride on the lordosis response (Fig. 5). Haloperidol, by contrast, failed to have such an antagonizing effect on the behaviour. These findings support the conclusion that lisuride suppresses lordosis behaviour by activating a serotonergic rather than a dopaminergic mechanism.

## DISCUSSION

The results of the present study show that apomorphine and quinpirole, as well as 8-OH-DPAT and lisuride, inhibit the estrogen-induced lordosis behaviour. However, as suggested by the concomitant agonist-antagonist interaction studies, the drug-elicited inhibition of the lordosis response seems to involve different neurotransmitter receptors.

The dopaminergic agents apomorphine and quinpirole are considered as mixed D-1/D-2 and selective D-2 receptor agonists, respectively. A clear blockade of the inhibitory effect of these drugs was observed after the administration of the dopaminergic D-2 antagonist haloperidol [10], at a dose which *per se* did not affect lordosis behaviour. These findings indicate that the lordosis-reducing action of apomorphine and quinpirole results from a stimulation of dopaminergic, tentatively D-2 receptors, further supporting the idea that this neurotransmitter system plays an inhibitory role in the lordosis response [15,17].

Biochemical and behavioural investigations have shown that 8-OH-DPAT is a selective serotonergic agonist, essentially devoid of dopaminergic receptor activity [9, 21, 23]. Lisuride, by contrast, acts as an agonist both at serotonergic and dopaminergic receptors [21,27]. At least for the latter compound, it could therefore be suggested that the inhibition of lordosis behaviour is mediated via a dopaminergic mechanism. However, arguing against this interpretation, the present findings show that haloperidol does not prevent the lordosis-inhibitory action of either 8-OH-DPAT or lisuride. By inference, these data may instead indicate that these compounds inhibit lordosis behaviour by stimulating the serotonergic system.

8-OH-DPAT, and to a lesser extent also lisuride, can be considered 5-HT$_{1A}$ receptor-selective agonists [20, 31, 38]. In addition, the latter agent also displays potent 5-HT$_2$ antagonist properties [20]. Recently, it was proposed that 5-HT may serve a facilitatory or an inhibitory role in the regulation of lordosis behaviour, depending on the actual serotonergic receptor subtype engaged. Thus, it was proposed that stimulation of 5-HT$_1$ receptors results in an inhibition of lordosis; conversely, the stimulation of 5-HT$_2$ receptors would facilitate the response [25, 32, 33, 43]. During the preparation of this article, Mendelson and Gorzalka [33] reviewed and extended their previous "dual 5-HT role" hypothesis, suggesting that 5-HT$_{1A}$ receptors inhibit, while 5-HT$_{1B}$ and 5-HT$_2$ receptors facilitate lordosis. Our previous [5] as well as the present findings are consistent with this notion.

In general, the behavioural effects of 5-HT agonist have been difficult to antagonize due to the lack of selectivity of available serotonergic blocking agents. For example, in studies of the male sexual behaviour the use of several serotonergic antagonists such as methiotepin, metergoline and pirenperone have failed to prevent the action of 8-OH-DPAT and lisuride [3, 4, 6, 28]. Notwithstanding these results, we undertook experiments interacting 8-OH-DPAT and lisuride with various putative serotonergic antagonists in an attempt to consolidate the possible differential involvement of 5-HT receptor subtypes in lordosis behaviour. Interestingly, these studies showed that while methiotepin and pirenperone were ineffective, (−)-pindolol prevented both the 8-OH-DPAT- and the lisuride-induced inhibition of lordosis.

Methiotepin can be regarded as a non-selective antagonist, albeit with a somewhat higher affinity for 5-HT$_2$

as compared to 5-$HT_1$ (A, B and C) binding sites [12], whereas pirenperone is claimed to be a selective 5-$HT_2$ receptor blocker (cf. [23]). On the other hand, (−)-pindolol—a non-selective beta-adrenergic agent—possesses higher affinity for 5-$HT_1$ vs. 5-$HT_2$ binding, and is 3–10 times more potent at the 1A vs. the 1B subtype (e.g., [12, 36, 37]). A common denominator for 8-OH-DPAT, lisuride and (−)-pindolol thus appears to be the ability of these compounds to interact with 5-$HT_{1A}$ receptors in a more or less selective manner. Indeed, there is much evidence supporting that (−)-pindolol can act as an antagonist of alleged 5-$HT_{1A}$-elicited biological responses [37,40]. The present results, showing that (−)-pindolol administration blocks the inhibitory action of 8-OH-DPAT and lisuride on the lordosis behaviour, are consistent with the idea that these effects are mediated through the stimulation of the 5-$HT_{1A}$ receptor subtype. However, (−)-pindolol can also act as an agonist at 5-HT receptors controlling the synthesis and release of this transmitter in vivo [22,24]. Both 5-$HT_{1A}$ and 5-$HT_{1B}$ receptors may be involved in these actions. Within the context of the hypothesis of Mendelson and Gorzalka [32,33], a possible alternative interpretation would therefore be that (−)-pindolol *per se* facilitates lordosis by stimulating 5-HT receptors of the 1B subtype, thereby counteracting the 8-OH-DPAT and lisuride-induced inhibition of lordosis. Analogously, the lack of effect of methiotepin and pirenperone could be related to the ability of these drugs to block 5-$HT_2$ receptors, thereby inhibiting lordosis [32]. It should however be pointed out that in preliminary experiments neither of the antagonists appreciably suppressed or enhanced the lordosis behaviour at the doses used in the subsequent interaction studies. Needless to say, until efficient antagonists that are selective for the putative 5-HT receptor subtypes (e.g., 1A and 1B) become available, a full pharmacological analysis of the serotonergic mechanisms involved in lordosis behaviour cannot be adequately performed.

It could be argued that (−)-pindolol effect on the 8-OH-DPAT- and lisuride-induced inhibition of lordosis behaviour involves the beta-blocking actions of the former agent. Against this suggestion we have recently shown that the administration of beta-blockers do not affect the estrogen-induced lordosis behaviour [18]. These findings, however, do not entirely exclude the possible interaction between both neurotransmitter systems, serotonergic and noradrenergic, in the neural control of the lordosis behaviour display. Indeed, recently we have shown that with regard to male sexual behaviour the action of lisuride can be effectively antagonized by noradrenergic lesions induced by the neurotoxin DSP4, thereby suggesting an interaction between these systems in the effect of some serotonergic agonists [19]. The possibility of a similar noradrenergic-serotonergic interplay in the regulation of the female sexual behaviour, however, remains to be established.

Available data indicate that either the stimulation of 5-$HT_{1A}$ receptors ([5]; present findings) or the blockade of $5HT_2$ receptors [32] results in an inhibition of the lordosis behaviour independently of the steroid priming (estrogen alone vs. estrogen plus progesterone) used for the elicitation of sexual behaviour. These findings suggest that the serotonergic system, rather than participating specifically in the mechanism of action of progesterone [34], is a neurotransmitter system involved in the arc reflex underlying the lordosis display. Further research, however, is required to test this hypothesis.

In summary the present results demonstrate that apomorphine and quinpirole inhibit the lordosis response in a haloperidol-sensitive manner, tentatively via a DA D-2 receptor mechanism. On the other hand, the lordosis-inhibitory actions of 8-OH-DPAT and lisuride do not appear to involve dopaminergic receptors. Instead, the results indicate that the lordosis effects of these latter compounds may be mediated through the stimulation of 5-$HT_{1A}$ receptors, thus strengthening the concept that this serotonergic receptor subtype plays an inhibitory role in the neural control of lordosis behaviour [5,36].

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