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Effects of Acute and Long-Term Domperidone Treatment on Prolactin and Gonadal Hormone Levels and Sexual Behavior of Male and Female Rats

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NASELLO, A. G., M. L. A. VANZELER, E. H. MADUREIRA AND L. F. FELICIO. *Effects of acute and long-term domperidone treatment on prolactin and gonadal hormone levels and sexual behavior of male and female rats.* PHARMACOL BIOCHEM BEHAV **58**(4) 1089–1094, 1997.—Domperidone (DOMP), a dopamine D_2 blocker that is unable to cross the blood–brain barrier, is an experimental tool used to induce hyperprolactinemia. Acute and long-term DOMP administration was tested in male and female rats for its effects on sexual behavior and plasma gonadal hormone levels. DOMP (4.0 mg/kg) was injected IP either acutely or daily for 30 days. Acute treatment failed to modify any behavioral parameter observed. The 5-day treatment stimulated and the 30-day treatment failed to inhibit sexual behavior of male rats. Serum testosterone levels were significantly reduced after 30 days of treatment in male rats. The 30-day treatment also inhibited sexual behavior and enhanced plasma progesterone levels in ovariectomized and intact female rats, respectively. The present results may be due to DOMP-induced long-term hyperprolactinemia. Alternatively, blockade of dopamine peripheral receptors induced by this treatment may also be responsible for the behavioral changes reported here. Moreover, these data suggest that female rats are more susceptible than males to the behavioral effects of long-term hyperprolactinemia. © 1997 Elsevier Science Inc.

Dopamine Prolactin Progesterone Estradiol Testosterone Sexual behavior

DOMPERIDONE (DOMP; 5-chlor-1-1-3-(2-oxo-1-bemzimidazolinyl)propyl-4-piperidyl-2-benzimidazoline), a D_2-dopamine receptor blocker, is a drug widely used in clinical gastroenterology to treat dyspepsia and vomiting (1,36). Although DOMP does not cross the blood–brain barrier (38), it is able to reach the hypothalamus, antagonizing the effect of apomorphine on body temperature (1) and to act on the hypophysis, increasing the secretion of prolactin (11,14,16). This last effect persists for at least 72 h (45). Prolactin, like all other hypophyseal hormones, is regulated by several releasing and inhibitory factors. Dopamine is the major prolactin inhibitory factor and acts through the D_2 receptor subtype [for review, (10)].

Most of the literature on the measurement of and hormonal correlates of sexual behavior in the rat focus on the central or peripheral influence of gonadal hormones (6,8,9). Nevertheless, the effects of protein hormones such as prolactin (PRL) are also important (4), particularly regarding its interaction with dopamine (7,12,31–33). PRL modifies dopaminergic activity in some brain nucleus (15,43). Earlier work has shown that PRL stimulates the in vitro release of dopamine from superfused corpus striatum from rats (15) and increases the in vivo output of DOPAC from the rat caudate nucleus when directly infused into the brain (43). High titers of circulating PRL are also associated with an increased number of tyrosine hydroxilase expressing neurons in the arcuate nuclei of mice (35). Several reports suggest that PRL activity in the brain can modify behavior. Dopamine-related behaviors, such as avoidance (21,48) and grooming (19,20,23) are in-

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fluenced by short as well as long-term exposure to PRL (21,22,48). Moreover, PRL has a major role in reproductive behaviors. PRL-induced stimulation of maternal care as well as inhibition of male and female sexual behavior have been described (3,13,49). The behavioral effects of dopaminergic blocking agents are predominantly a consequence of direct actions on the central nervous system but may also result from increased plasma PRL levels, which also have several effects (37,47). DOMP is an experimental tool for the study of these effects without the interference of the blockade of central dopamine receptors. The previously described PRL effects on sexual behavior were obtained injecting PRL into the brain or as a consequence of hyperprolactinemia induced by tumors, or the implantation of two or more ectopic pituitaries (3,18, 29). In DOMP-treated rats, there is only one hypophisis that is under all its physiological controls, except dopamine. This makes DOMP-induced hyperprolactinemia a unique and more realistic model for a dopamine blocker-induced hyperprolactinemia. In adult male rats acute or long-term DOMP treatment has no detectable effects on motor activity, active- and inhibitory-avoidance and apomorphine-induced stereotypy (38). However, in female rats, long-term treatment with this compound decreases the acquisition of an active avoidance task (48).

This study was designed to evaluate and compare the endocrine- and sexual behavioral-effects of DOMP on male and female rats. In addition, the main question of how DOMP-induced hyperprolactinemia affects sexual behavior in male and female rats was also addressed. Adult animals of both sexes were submitted to two long-term (5 and 30 days) and one acute (a single injection) DOMP treatments. Serum PRL levels were measured after a single DOMP injection. Sexual behavior was observed in both sexes after acute and 5- and 30-day treatment with DOMP, while plasma levels of testosterone in males and of progesterone in females were measured on days 5 and 30 of DOMP treatment.

METHOD

Adult male and female Wistar rats derived from the same strain, born and raised under our laboratory conditions, about 90 days old at the beginning of the experiments and weighing 200–300 g were used. The animals were housed two per cage at a constant temperature (22–23°C). Three weeks before the beginning of DOMP treatments, female rats were ovariectomized and both male and female animals were submitted to reversed lighting conditions (lights off from 1000 to 2200 h). The animals were injected IP with 4.0 mg/kg DOMP, or its vehicle (Tween 80-saline), acutely (a single injection), or for 5 or 30 days, daily (injections at 0900 h), except for prolactin determination when doses ranging from 4 to 24 mg/kg DOMP IP were used to determine the minimal doses of DOMP necessary to mantain a high PRL level. Vaginal smears were taken daily before the injections. In all cases the last DOMP injection was administered 1 h before the behavioral test or decapitation for PRL measurement. Different groups of animals were used in each of the five treatment conditions. Each animal was tested only once and then discarded.

Female Sexual Behavior

Sexual receptivity was quantified using a previously reported system (25,26,28,42). Briefly, sexual behavior was induced in ovariectomized females. They were injected at the beginning of the dark period with 17β-estradiol benzoate 10.0 μg/kg. Forty-eight hours later, animals received 2.0 mg/kg of progesterone and after 6–8 h they were brought to an observation cage housing a sexually active male. Ten mounts were allowed and the number of lordotic responses was recorded. The lordosis quotient (LQ) was considered to be the number of lordoses divided by the number of mounts times 100.

Male Sexual Behavior

Male rats were allowed to acclimate to the behavioral arenas for 10 min before the introduction of a female rat to minimize the influence of the new environment. A separate group of ovariectomized females treated with estradiol and progesterone, as described above in the female sexual behavior experiment, was used as stimulus animals. The test lasted until the first intromission of the second ejaculatory series as described before (25,26). The male copulatory behavior recorded included mount latency, intromission latency, total number of mounts, i.e., number of incomplete mounts plus number of complete mounts or intromissions, ejaculation latency, two measurements of the postejaculatory interval, the postejaculatory mount latency, and the postejaculatory intromission latency. On day 30 both experienced (animals tested on day 5) and inexperienced rats were tested.

Hormone Measurements

For PRL measurements animals were handled daily for 5 days by the same person at the same time of day. On the day of sacrifice they were removed quietly and individually from the cage and transferred to a separate room for sacrifice by decapitation. During this time they were restrained by the hand of the same person. Trunk blood was collected into tubes and centrifuged, and the serum was frozen. PRL levels were measured by radioimmunoassay using materials supplied by the National Hormone and Pituitary Agency, NIADDK, Bethesda, MD. The concentrations were measured as ng/ml, based on RP-3 as standard. For progesterone and testosterone measurements 1 h after the last DOMP injection, intact animals were anesthetized with ether and arterial blood was collected from the aorta. EDTA (5%) was used to avoid blood clotting. Progesterone and estradiol in females and tes-

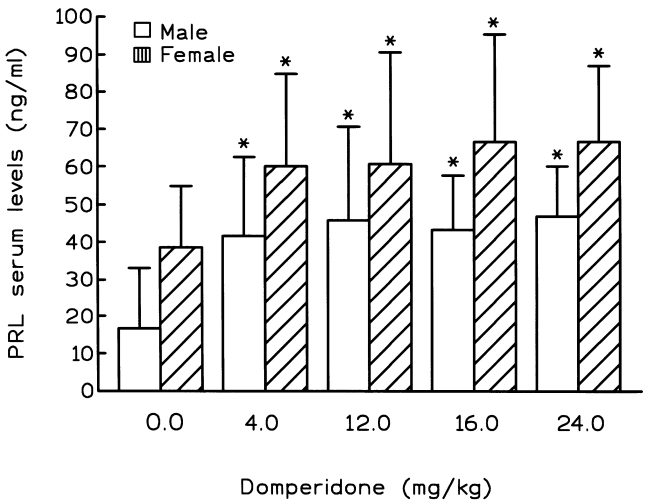

FIG. 1. Serum levels of prolactin (ng/ml) in rats treated with different doses of domperidone 1 h before decapitation (means ± SE). *Different from the respective control (0.0 mg/kg; $p < 0.05$). In all the cases males were significantly different from females ($p < 0.05$). ANOVA followed by Duncan test.

tosterone in males were measured in the plasma by radioimmunoassay using "Coat-a-count" kits (Diagnostic Products, LA, CA). Sensitivity and intraassay variation for PRL, testosterone and progesterone were 1.5 ng, 5.5%, 0.1 ng, 9.43%, 0.1 ng, and 16.3%, respectively. The animals used in this investigation were maintained in accordance with the guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council, USA.

Statistical Analysis

Data were analyzed statistically by analysis of variance followed by the Duncan test, with the level of significance set at $p < 0.05$. For the nonparametric data of female sexual behavior, results were analyzed by Kruskall–Wallis analysis followed by the Mann–Whitney *U*-test.

RESULTS

Acute DOMP treatment induced a significant increase in serum PRL levels in both male ($F = 7.59$, $p < 0.01$) and female ($F = 3.84$, $p < 0.05$) rats (Fig. 1). For all doses, PRL levels were higher in females than in males (Student's *t*-test; $p < 0.05$). No DOMP-induced dose-dependent change in PRL levels was observed in either male or female rats. These data are in accordance with previous results obtained with DOMP and other drugs (18,19). Although there were no significant differences in testosterone levels between control and experimental males on days 5 or 30, plasma testosterone levels were lower ($p < 0.025$) in rats treated for 30 days than in rats treated for 5 days with DOMP (Fig. 2). Plasma progesterone levels were increased both on days 5 ($p < 0.0001$) and 30 ($p < 0.025$; Fig. 3). Plasma estradiol levels were below the sensitivity of the assay in both 5- and 30-day DOMP-treated intact female rats.

Ovariectomized females with induced behavioral estrus showed no difference in sexual behavior when treated acutely or for 5 days with DOMP and a lower lordosis quotient on day 30 ($p < 0.05$; Table 1). In intact females permanent diestrus was observed starting on day 5 of treatment.

Male rats on day 5 of treatment showed shorter ejaculation latency ($p < 0.025$), a lower number of intromissions ($p < 0.05$), as well as shorter latencies for the first postejaculatory mount ($p < 0.05$), and postejaculatory intromission ($p < 0.005$). No differences were observed in the sexual behavior of males treated either acutely or for 30 days with DOMP (Table 2). Each experimental group was compared with its own control group, i.e., animals treated with the vehicle for the same time and in the same conditions them those of the groups treated with DOMP.

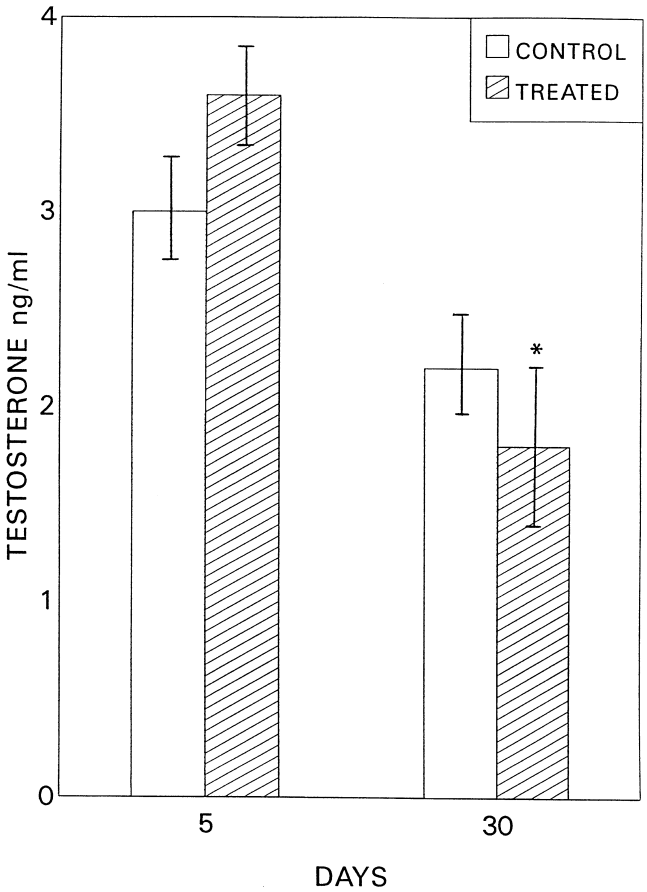

FIG. 2. Plasma levels of testosterone (ng/ml) in male rats treated with DOMP (4 mg/kg) or vehicle for 5 or 30 consecutive days, 1 h after the last injection (means ± SE), $n = 10$ in any case, $^*p < 0.05$, Student *t*-test as compared to 5-day DOMP-treated group.

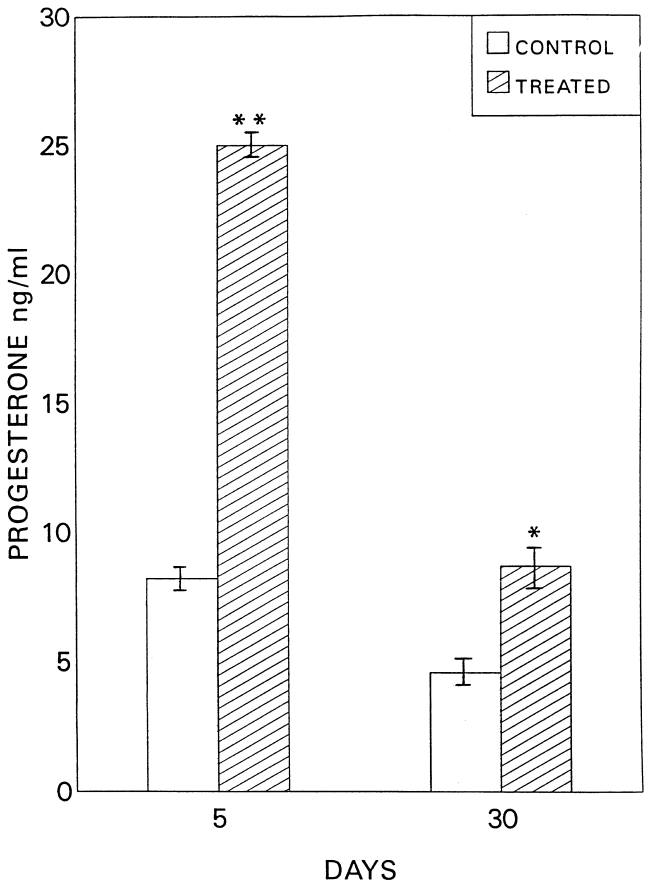

FIG. 3. Plasma levels of progesterone (ng/ml) in female rats treated with DOMP (4 mg/kg) or vehicle for 5 or 30 consecutive days, 1 h after the last injection (means ± SE), $n = 10$ in all cases, $^*p < 0.05$, $^{**}p < 0.001$, Student *t*-test compared to respective control.

TABLE 1

SEXUAL RECEPTIVITY, INDUCED BY ESTROGEN AND PROGESTERONE, OF FEMALE RATS TREATED WITH DOMPERIDONE (4 mg/kg) OR VEHICLE ACUTELY OR DURING 5 OR 30 CONSECUTIVE DAYS (MEANS ± SE)

	Lordosis Quotient		
Domperidone	Acutely	5 Days	30 Days
0.0 mg/kg	46.1 ± 5.6 (n = 13)	73.6 ± 4.9 (n = 14)	79.3 ± 6.2 (n = 14)
4.0 mg/kg	47.7 ± 7.8 (n = 13)	61.4 ± 7.9 (n = 14)	58.9 ± 8.2* (n = 14)

n, in parenthesis.

*$p < 0.05$, Mann-Whitney U-test, compared with its control, i.e., 0.0 mg/kg for 30 days.

DISCUSSION

DOMP-induced hyperprolactinemia was detected in animals of both sexes (Fig. 1). Animals were considered to be hyperprolactinemic if the PRL values were significantly higher than their own control. This DOMP-induced increase in serum PRL levels observed in this study is considered as being hyperprolactinemia and similar to those previously described (24,45). The absence of a dose–response relationship in DOMP-induced increase in serum PRL levels confirms previous findings with DOMP (24) and another dopamine D_2 blocker, bromopride (25). This result shows that DOMP-induced hyperprolactinemia is not conditioned by dose in these experimental conditions. The lower DOMP dose tested was able to induce an increase in serum PRL levels and was selected for studding the effects of this mild hyperprolactinemia on behavioral and endocrine parameters. The DOMP-induced increase in serum PRL levels lasts at least 72 h (45) and the dopaminergic tuberoinfundibular system that controls PRL synthesis and release does not develop tolerance (44). These data suggest that DOMP-treated rats were kept continually hyprepreprolactinemic throughout the experimental period. This endocrine condition, i.e., moderate long-term hyperprolactinemia, is taken into account in the discussion that follows and for the interpretation of the endocrine and behavioral data reported here. Previous work has shown that PRL can access central areas beyond the blood–brain barrier and modulate neural activity and behavior (2,24,49).

The results show different effects of long-term DOMP treatment on male and female sexual behavior. In ovariectomized females with induced estrus, 30-day, but not 5-day DOMP treatment decreased sexual receptivity. In intact females, hyperprolactinemia induced a diestrous phase starting on day 5. The high progesterone levels observed on days 5 and 30 were due to the well-known luteotrophic action of PRL in rats (39,46, 50). As the behavioral tests were performed in ovariectomized females, one may suggest that PRL interference with female sexual behavior is not only a consequence of its effects on the gonads. It is known that long-term hyperprolactinemia can affect several aspects of the activity of central catecholaminergic neurons and influence dopamine binding in the striatum (17,27). However, some authors found no change in dopamine binding measurements when hyperprolactinemia was induced with domperidone (35,45). Moreover, this endocrine condition also reduces the release of LHRH, a peptide that facilitates sexual behavior (40,50). The decrease in sexual receptivity induced by the 30-day DOMP treatment in female rats may be due to a PRL-induced change in the activity of central catecholaminergic neurons associated with a decrease in LHRH release. Alternatively, the DOMP blockade of peripheral dopamine receptors and of receptors located in hypothalamic regions outside the blood–brain barrier may also interfere with this behavior.

In males, 5-day hyperprolactinemia improved sexual performance, but this improvement was no longer observed on day 30. The increase in sexual performance observed in 5-day DOMP-treated male rats agrees with data obtained by Drago et al. (22,23) who reported similar behavioral changes in 5-day hyperprolactinemic rats. There are several reports on the direct action of PRL on testicular function: hyperprolactinemia accelerates testis maturation and increases testosterone production in rats (41,47) and hamsters (5,11). The improvement in sexual behavior observed in 5-day DOMP-treated male rats may be due to a direct PRL-induced LH potentiation and an increase in plasma testosterone levels. Because plasma testosterone levels were not significantly changed after 5 days of DOMP treatment, the results suggest that the short-term (5-day) hyperpro-

TABLE 2

SEXUAL BEHAVIOR OF MALE RATS TREATED WITH DOMPERIDONE (4 mg/kg) OR VEHICLE ACUTELY OR DURING 5 OR 30 CONSECUTIVE DAYS

	Groups					
	Acutely		5 Days		30 Days	
	Control	Treated	Control	Treated	Control	Treated
ML	11.0 ± 2.3	7.0 ± 1.3	15.6 ± 4.1	24.5 ± 5.2	12.4 ± 2.0	10.5 ± 4.0
IL	20.0 ± 6.7	9.0 ± 1.3	26.3 ± 12.1	30.2 ± 7.0	15.5 ± 2.7	16.4 ± 2.5
EL	357.0 ± 42.1	386.0 ± 44.5	1069.2 ± 136.3	687.4 ± 73.8*	832.0 ± 73.8	970.7 ± 138.4
IM	3.0 ± 0.5	4.0 ± 1.0	8.3 ± 1.3	6.6 ± 1.1	7.7 ± 1.4	8.4 ± 1.8
I	13.0 ± 1.1	14.0 ± 0.9	35.2 ± 3.2	26.7 ± 3.5*	31.2 ± 2.0	32.1 ± 3.4
TM	16.0 ± 1.3	18.0 ± 2.0	43.5 ± 4.1	33.4 ± 4.0	38.9 ± 3.1	40.3 ± 4.3
MLPE	338.0 ± 15.8	333.0 ± 18.1	358.5 ± 21.2	279.6 ± 22.0*	304.0 ± 16.8	301.3 ± 19.3
ILPE	338.0 ± 15.8	333.0 ± 18.1	364.2 ± 17.5	279.6 ± 22.0*	333.0 ± 16.8	301.3 ± 19.3

ML, mount latency; IL, intromission latency; EL, ejaculation latency; IM, number of incomplete mounts; I, number of intromissions; TM, total number of mounts; MLPE, postejaculatory mount latency; ILPE, postejaculatory intromission latency. Latencies are reported in seconds (means ± SE); n = 14, *$p <$ 0.05, compared with the respective control group. ANOVA followed by Duncan test.

lactinemia-induced increase in male sexual behavior is not related to changes in plasma testosterone levels. Nevertheless, according to Drago et al. (23), the facilitation of sexual performance observed in 5-day DOMP-treated male rats may be related to this PRL-induced testosterone potentiation. On the other hand, long-term hyperprolactinemia reduces LHRH release, and consequently, also LH and FSH release (29,32). The apparent lack of effect of 30-day DOMP treatment on male sexual behavior may be due to these two PRL-induced antagonistic actions, i.e., potentiation of LH and reduction of gonadotropin release. The long-term hyperprolactinemia induced by implantation of two or three ectopic hypophyses in the adrenal capsule, or by systemic PRL injection has been related to several behavioral changes, such as facilitation of maternal behavior (13,34), modulation of feeding behavior (6), improvement in the acquisition of an active avoidance task (5), increase in the expression of dopamine agonist-induced stereotyped behavior (23), induction of yawning (30), and decreased male sexual arousal, erectile function, and copulatory behavior (3,18). These behavioral data suggest that this endocrine state has central effects. The fact that there was no difference in male sexual behavior in 30-day DOMP-treated rats apparently disagrees with literature data. However, the tool we used to induce hyperprolactinemia was the dopamine D_2 receptor blocker DOMP which acted on a single and nonectopic hypophysis, while the above-mentioned authors used at least two ectopic hypophyses or injections of exogenous PRL. Those procedures probably induced higher plasma PRL levels, allowing a larger amount of PRL to enter the central nervous system, and consequently, facilitating behavioral changes. Other authors report a decrease in sexual performance in long-term hyperprolactinemic rats (3,18,47). This contradiction may be related to the method used by those authors to induce hyperprolactinemia, i.e., implantation of at least two ectopic hypophyses. In rats treated with DOMP, there is only one hypophysis under all its physiological controls, except dopamine. In this condition it may take longer for PRL to reduce male sexual behavior.

In summary our conclusions are: 1) male and female rat sexual behaviors are affected differently by long-term hyperprolactinemia induced by DOMP treatment. 2) Short-term (5-day) DOMP treatment stimulates male sexual behavior while long-term (30-day) DOMP-induced hyperprolactinemia inhibits lordosis in females. 3) The behavioral differences observed in 5-day DOMP treated male rats are not due to changes in plasma testosterone levels. 4) The DOMP-induced inhibition of lordosis is not only due to the PRL-induced increase in plasma progesterone levels.

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