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Dopamine Infusion Does Not Alter LH Levels Before or After Chronic Cocaine Exposure in Female Rhesus Monkeys

NANCY K. MELLO,[1] JACK H. MENDELSON, MAUREEN KELLY, NICOLAS DIAZ-MIGOYO AND J. WALLIS SHOLAR

The Endocrine Unit, Alcohol and Drug Abuse Research Center, McLean Hospital, 115 Mill Street, Belmont, MA 02178

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MELLO, N. K., J. H. MENDELSON, M. KELLY, N. DIAZ-MIGOYO AND J. W. SHOLAR. *Dopamine infusion does not alter LH levels before or after chronic cocaine exposure in female rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **58**(3) 819–828, 1997.—Cocaine stimulates release of luteinizing hormone (LH) in preclinical and clinical studies but the contribution of the indirect dopamine agonist actions of cocaine to its effects on LH are unclear. In the present study, we examined the effects of exogenous dopamine infusions on LH release in drug-naive, normally cycling, female rhesus monkeys. All studies were conducted during the mid-follicular phase (cycle days 6–8). Three successive 80-min dopamine infusions (10 μg/kg/min, intravenous) were alternated with 20- or 40-min interruptions of dopamine infusions. There were no significant changes in LH during or following dopamine infusions. Predopamine baseline LH levels averaged 30 ± 5.4 ng/ml. LH averaged 31.7 ± 1.3 ng/ml during dopamine infusions and 31.4 ± 1.3 ng/ml after dopamine infusions stopped. To determine whether chronic cocaine exposure influenced the effect of dopamine on LH, rhesus females were studied after more than 2 years of cocaine self-administration at an average dose of 6.5 ± 0.2 mg/kg/day. LH averaged 27.3 ± 3.3 ng/ml during baseline and 26.9 ± 0.7 ng/ml and 26.1 ± 0.7 ng/ml during dopamine infusions and interruptions, respectively. Similarly, during withdrawal from cocaine, baseline LH levels averaged 32.1 ± 4.5 ng/ml, and LH did not change significantly during dopamine infusions (31.2 ± 1.1 ng/ml) and infusion interruptions (32.1 ± 1.1 ng/ml). Under the conditions of the present study, dopamine administration did not change LH levels in gonadally intact rhesus monkeys, and these findings are consistent with previous studies in ovariectomized rhesus females. However, these data are not consistent with clinical reports, and some possible implications of this species difference are discussed. Moreover, these data suggest that the stimulation of LH by cocaine may not be explained by its indirect dopamine agonist actions. © 1997 Elsevier Science Inc.

Luteinizing hormone Dopamine Cocaine Rhesus monkey

COCAINE acts as an indirect dopamine agonist because it binds to the dopamine transporter and blocks dopamine reuptake (19,20,49). Consistent with its dopamine agonist effects, acute cocaine administration suppresses prolactin levels in rhesus monkeys (32,33,35), and chronic cocaine abuse may impair inhibitory dopaminergic regulation of prolactin to result in hyperprolactinemia in humans (1,3,9,38) and in female rhesus monkeys (29,34). In contrast to prolactin, the acute and chronic effects of cocaine on luteinizing hormone (LH) are not well understood. Recent findings from both clinical and preclinical studies have indicated that acute cocaine administration stimulates LH release [for review, see (29)]. For example, an acute dose of cocaine [0.4 and 0.8 mg/kg intravenous (IV)] significantly increased LH within 10–20 min at doses that suppressed prolactin in rhesus males and in normally cycling early follicular and mid-luteal phase rhesus females (32,35). LH remained above baseline levels for 40–50 min after cocaine administration (32,35). Moreover, cocaine enhanced LH-releasing-hormone (LHRH)-stimulated increases in LH in rhesus females during the early follicular phase (33), and deconvolutional analysis has shown that the LH secretory bursts were significantly greater after cocaine than after placebo, but the half-life of LH

[1] To whom requests for reprints should be addressed.

was not significantly altered (29). An acute dose of cocaine (30 mg IV) also increased LH in human males who were dependent on cocaine and opiates (39). Cocaine, administered intranasally (2 mg/kg), also increased LH in men who were cocaine naive (11). The peak LH increase occurred 15 min after intravenous cocaine administration (39) and 60 min after intranasal cocaine administration (11).

The mechanisms by which cocaine stimulates LH in humans and in rhesus monkeys are unknown. These findings were surprising because cocaine is an indirect dopamine agonist, and clinical studies have consistently shown that dopamine decreases LH release in normal men and women (14,15,21–23, 25,46,50,56,64). Moreover, in pathologic conditions such as polycystic ovary syndrome, where basal levels of LH are elevated, an enhanced suppression of LH by dopamine agonists has been reported (47), but a dopamine antagonist (metoclopramide) had no effect on LH (2). Similarly, in Graves disease, dopamine infusion suppressed LH significantly more than in normal controls (55). Taken together, these clinical observations are consistent with the interpretation that reduced dopaminergic inhibition of LH may contribute to pathologic increases in basal LH levels (63), although there have been exceptions to these general findings.

In view of the extensive clinical literature documenting the effects of dopamine on LH, it is surprising that there have been relatively few studies in rhesus monkeys, and these have used ovariectomized monkeys (16,45,53). We believe the present report is the first study to examine the effects of continuous dopamine infusions on LH in drug-naive, gonadally intact, rhesus females. In contrast to most clinical studies, administration of dopamine to ovariectomized monkeys did not decrease basal LH levels or LHRH-stimulated LH at doses that significantly suppressed prolactin (45,53). However, it is not clear whether these findings reflect a species difference or the absence of gonadal steroid hormones in the ovariectomized rhesus monkeys.

The potential importance of the gonadal steroid milieu in modulating the effects of cocaine on anterior pituitary hormones has been well documented. Cocaine did not change basal levels of LH in ovariectomized rhesus females (36) as it did in gonadally intact males and females (32,35). Moreover, LHRH-stimulated increases in LH were not enhanced by cocaine in ovariectomized rhesus females (36) as they were in follicular-phase females (33). The different effects of cocaine on LH in intact and ovariectomized females may be attributable to the influence of gonadal steroid hormones (36).

The present study was undertaken to determine whether dopamine mimicked the effects of cocaine on LH in normally cycling, drug-naive rhesus females. We hypothesized that if the stimulation of LH by cocaine in gonadally intact rhesus monkeys reflected an increase in dopamine levels through a cocaine-induced blockade of dopamine reuptake, then dopamine administration also might increase LH. Alternatively, because LH release is influenced by many neuromodulators in the brain, the stimulation of LH by cocaine could be due to its interactions with endogenous opioid peptides, norepinephrine, serotonin or multiple neurotransmitter systems. A second goal of this study was to determine whether the effects of dopamine on LH differed in drug-naive females and in females that were chronically exposed to cocaine. There is accumulating evidence that cocaine may produce long-term changes in neuroendocrine function [for review, see (29)] and in dopaminergic activity (4,12,59–61). Consequently, we also examined the effects of dopamine on LH during chronic cocaine self-administration and during cocaine withdrawal.

METHODS

Subjects

Nine adult female rhesus monkeys (*Macaca mulatta*) lived in individual cages, and a 12-h light–dark cycle (7 AM to 7 PM) was in effect. Monkeys weighed 5.0–7.5 kg and were maintained at ad libitum weight and given multiple vitamins, fresh fruit and vegetables, Purina monkey chow and nutritionally fortified banana pellets. Water was continuously available. Experimentally naive monkeys were adapted to the laboratory for 4–6 months before these experiments began. Monkeys lived in well-ventilated stainless steel chambers and had visual, auditory and olfactory contact with other monkeys. Menstrual cycle regularity was monitored daily with vaginal swabs to determine the onset and duration of vaginal bleeding throughout the study. All endocrine study days were scheduled during the mid-follicular phase of the menstrual cycle, 6–8 days after the onset of menstruation.

Baseline studies of LH responses to dopamine infusions were conducted in all monkeys before drug exposure. Six monkeys also were studied during chronic cocaine self-administration, and four monkeys were studied during cocaine withdrawal. During cocaine self-administration studies, each chamber was equipped with an operant panel, a pellet feeder and a water dispenser. After menstrual cycles were stable, four monkeys were trained to self-administer food (1-g banana pellets) and intravenous cocaine injections. Operant food and drug acquisition procedures provided an opportunity for environmental stimulation and enrichment (24).

Animal maintenance and research were conducted in accordance with the guidelines provided by the Committee on Laboratory Animal Resources. The facility is licensed by the U.S. Department of Agriculture, and protocols were approved by the Institutional Animal Care and Use Committee. The health of the monkeys was monitored periodically by consultant veterinarians expert in primatology.

Procedures to Examine the Effects of Cocaine on LH

Dopamine dose selection. Although exogenously administered dopamine does not cross the blood–brain barrier, it does act at the median eminence and the anterior pituitary (63). The dopamine system has cell bodies in TIDA neurons, which are located in the arcuate nucleus of the hypothalamus. TIDA axons terminate in the external layer of the median eminence, where dopamine is synthesized and released from the axon terminals into the portal vessels (63,65). The dose of dopamine used in the present study (10 μg/kg/min IV) produces plasma dopamine concentrations equivalent to those measured in hypophyseal stalk blood in rhesus monkey (41). This dopamine dose significantly suppressed prolactin in follicular-phase rhesus females and in estrogen-treated, stalk-sectioned rhesus females (41). This dose of dopamine also produced maximal suppression of prolactin in intact and stalk-sectioned female rhesus monkeys, whereas higher doses of dopamine (20–40 μg/kg/min) did not produce significantly greater decreases in prolactin and a lower dose (5 μg/kg/min) was not effective (43).

Dopamine administration procedures. The time course of dopamine infusions and interruptions was based on previous studies in rhesus monkeys which showed that dopamine suppresses prolactin within 80 min (34) and on studies in hyperprolactinemic monkeys which showed that prolactin usually returns to or exceeds baseline levels within 10–20 min after interruption of dopamine infusion (6). The sequence of dopa-

mine infusions and interruptions on each endocrine study day was as follows: after collection of two baseline samples at 20-min intervals, dopamine (10 μg/kg/min) was infused for 80 min followed by a 40-min dopamine infusion interruption. Dopamine was infused for three intervals of 80 min each. Samples for LH analysis were collected every 20 min throughout the sampling period. An additional sample was collected 10 min after each interruption of dopamine infusion. This sequence of dopamine infusions and interruptions was used in studies of three naive females and five females trained to self-administer cocaine. Two females also were studied in an earlier protocol in which successive dopamine infusions were separated by a shorter interval (20 min instead of 40 min) and samples were collected every 10 min except during the first and second interruptions of the dopamine infusion, when the first two samples were collected at 5-min intervals.

Dopamine was infused with a Harvard Apparatus Syringe Pump (Model 22) at the rate of 10 μg/kg/min into the saphenous vein of the leg opposite the blood sample collection catheter site. A total of 4.07 ml of solution was administered during each 80-min period of dopamine infusion. A fluid replacement volume of 12.2 ml of dopamine solution was infused over the course of the study. During interruptions of dopamine infusions, no fluid was infused through the catheter.

Venous catheterization and sample collection procedures during dopamine infusion studies. Monkeys were anesthetized with ketamine hydrochloride [5–10 mg/kg intramuscular (IM)], and a 10-gauge needle containing a 22-gauge Deseret radiopaque intracatheter (Deseret Medical, Parke Davis Co., Sandy, UT) was inserted into the saphenous vein using aseptic techniques. After removal of the needle internal stylet, the catheter was joined to heparin-impregnated sterile silicon tubing and secured with sutures. This saphenous vein catheter was used for blood collection, and a Surflo catheter (21-gauge needle in a 20-gauge catheter; Terumo Medical Corp., Elkton, MD) in the opposite leg was used for dopamine infusion. Ketamine has no effect on pituitary gonadotropin release (5,7).

Sample collection procedures. After venous catheterization, each monkey was placed in a standard primate chair for about 30 min before sample collection began. This adaptation period was to reduce any effects of stress associated with venous catheterization and to ensure that the sedative effects of ketamine were no longer evident. Each monkey was adapted to the restraining chair on at least three occasions before the first dopamine infusion study to minimize any possible effects of chair restraint on LH levels. It has been shown that habituation to chair restraint permits measurement of pulsatile release of LH (44) and pulsatile release of endogenous LHRH in cerebrospinal fluid (57,62). Some investigators have reported that LH pulsatile release patterns are identical in chair-adapted monkeys and in tethered monkeys (44), whereas others have found that a single episode of chair restraint inhibits LH secretion in rhesus females (42). Under the repeated chair adaptation procedures used in this laboratory, stress labile hormones such as ACTH (51) and prolactin (34) were at low basal levels at the initiation of endocrine perturbation studies. Moreover, cocaine stimulated a robust and sustained increase in LH in chair-adapted rhesus monkeys (32,33,35).

Bolus blood samples were collected in heparinized vacutainer tubes for analysis of LH. Each sample contained 2 ml of whole blood. Immediately after exfusion, samples were placed in chopped ice and then centrifuged, and aliquots of plasma were withdrawn and samples were frozen at −70°C.

All endocrine studies were conducted at the same time of day, and sample collection procedures were identical in monkeys studied before, during and after chronic cocaine exposure. During cocaine self-administration, monkeys continued to wear a protective vest while sitting in the primate chair during blood sample collection. The double-lumen cocaine infusion catheter was sealed with sterile stylets during the sample collection procedure. In monkeys studied during daily cocaine exposure, blood sample collection began approximately 1 h after the 8–9 AM cocaine session ended. Monkeys usually self-administered cocaine during the first 20–30 min of the session; thus, blood sample collection began about 90–100 min after the last cocaine injection.

Operant Behavioral Procedures and Apparatus

Operant behavioral procedures were used to maintain chronic cocaine and food self-administration. Monkeys controlled the number and frequency of cocaine injections delivered and controlled their total cocaine dose per day. Under these conditions of self-regulated cocaine access, monkeys remain healthy and may continue to self-administer cocaine for 2 or more years. The primate model of drug self-administration simulates human drug abuse insofar as monkeys self-administer cocaine at levels comparable to those often reported clinically. For example, in our previous studies, monkeys often self-administered 3–4 mg/kg/day of cocaine (26,28,31), which is equivalent to 1–2 g/week of cocaine in a 70-kg man (2.04–4.08 mg/kg/day) (37,38). One advantage of this primate model is that the contribution of cocaine alone to any changes in LH regulation can be examined without the confounding influence of polydrug abuse often seen in human cocaine abusers (8,17,18,52).

Food self-administration training. Monkeys were trained to self-administer food (1-g banana pellets) on gradually increasing response requirements until food-maintained responding was stable. The final schedule was a second-order schedule of reinforcement that required an average of 64 responses for each food pellet [FR4 (VR:16S)]. During food self-administration training, monkeys were adapted to placement in a standard restraining chair and to routine venipuncture procedures. Single blood samples were collected periodically under minimal sedation (ketamine, 3 mg/kg IM) for analysis of anterior pituitary hormones or blood chemistry profiles. Subsequently, monkeys were surgically implanted with an intravenous catheter and trained to self-administer intravenous cocaine (0.10 mg/kg/injection). We have used these operant procedures to maintain cocaine and food self-administration in a number of behavioral pharmacology studies (27,30,31).

Cocaine and food availability. Each experimental day began at 9:00 AM and consisted of four alternating food and drug availability sessions and time-out periods when responses had no programmed consequence. Food sessions began at 11 AM, 3 PM, 7 PM and 7 AM each day, and drug sessions began 1 h later at 12 PM, 4 PM, 8 PM and 8 AM. Consecutive food and drug sessions were separated by time-out periods of 2 h (1–3 PM, 5–7 PM, 9–11 AM) or 10 h (9 PM–7 AM) duration. The response key was dark during time-out periods. Each food or drug session lasted 1 h or until 25 banana pellets (1 g) or 20 cocaine injections (0.10 mg/kg/injection) were delivered. Cocaine injections were limited to 20 per session or 80 per day (8 mg/kg/day) to minimize the possibility of adverse drug effects. During cocaine-withdrawal periods, the response key was dark during the times when cocaine was previously available, but the monkey continued to self-administer food during the four daily sessions.

Operant apparatus. Food and cocaine availability conditions each were associated with a different colored stimulus light (S+) projected on a translucent Plexiglas response key (2 in. in diameter) in the center of the operant panel. When a food pellet or drug injection was delivered, the appropriate stimulus light (S+) (red or green) was illuminated for 1 sec on one of the three circles (0.75 in. in diameter) located in a vertical column below the response key. Flashes of the 1-sec colored stimulus lights (S+) also signaled the completion of each successive VR component of the second-order schedule response requirement. Drug injections were delivered by a syringe pump in a single pulse that dispensed 0.1 ml of fluid over 0.9 sec. The operation of the syringe pump (Model 981210, Harvard Apparatus, South Natick, MA) was audible to the monkey. Schedules of reinforcement were programmed by custom-designed software and run on Apple II GS computers.

Surgical Procedures

After operant performance for food was stable on the final schedule of reinforcement, each monkey was surgically implanted with an intravenous double-lumen silicon catheter (inner diameter = 0.028 in., outer diameter = 0.080 in.) under aseptic conditions. Monkeys were sedated with ketamine (5 mg/kg subcutaneous), and anesthesia was induced with sodium thiopental (10 mg/kg IV). Atropine (0.05 mg/kg) was used to reduce salivation prior to insertion of a tracheal tube. Anesthesia was maintained with halothane (1–1.5% in oxygen). After surgery, monkeys were given aspirin PO for 3 days and 200,000 units of combiotic dihydrostreptomycin and penicillin G IM on alternate days, for a total of 5 injections. Catheters were implanted in the jugular or femoral vein and exited in the mid-scapular region. The intravenous catheter was protected by a tether system consisting of a custom-fitted nylon vest connected to a flexible stainless steel cable and fluid swivel (Spaulding Medical Products, Birmingham, AL) that permits monkeys to move freely. Catheter patency was maintained by IV cocaine administration and a saline flush. Catheter patency was checked manually each day. A short-acting barbiturate methohexital sodium (3 mg/kg IV) was used to evaluate catheter patency if necessary.

Drug Solution Preparation

Dopamine. Stock solutions of dopamine (3-hydroxytyramine, Sigma Chemical) were prepared by dissolving dopamine powder in sterile saline for injection U.S.P. The solution was filter sterilized using a 0.11-μg Millipore filter (Bedford, MA).

Cocaine. Cocaine hydrochloride was obtained in crystalline form from the National Institute on Drug Abuse (NIDA). The purity was certified by Research Triangle to be greater than 98%. Cocaine was dissolved in Sterile Saline U.S.P. for injection, to make a stock solution at a concentration of 50 mg/ml. The solution was then filter sterilized using a 0.22-μ Millipore filter and stored in sterile, pyrogen-free vials. Doses for cocaine self-administration were calculated on the basis of the weights of the monkeys, so that a final dilution of the stock solution (with sterile saline for injection U.S.P.) resulted in a unit dose of 0.10 mg/kg/injection in a volume of 0.1 ml/injection.

LH Radioimmunoassay

Plasma LH concentrations were determined in duplicate by a double-antibody radioimmunoassay procedure similar to that described by Midgley (40) by using materials prepared by Dr. W. Peckham and following his suggestions. Purified cercopithecus pituitary LH for radioiodination (WP-XV-117-3239), rabbit antiserum (WP-R13, pool D) to human choriogonadotropin and rhesus pituitary LH reference preparation (NICHD-rhLH, also known as WP-XV-20) were provided by the National Hormone and Pituitary Program, supported by the National Institute of Child Health and Human Development and the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases. Radioiodination was performed by using the chloramine-T reaction (10) with sodium iodide-125 purchased from DuPont New England Nuclear Products (Billerica, MA). Goat antirabbit gamma-globulin was obtained from Calbiochem-Novabiochem (San Diego, CA). Results are expressed in nanograms per milliliter in terms of the reference preparation. The LH assay sensitivity was 7.8 ng/ml. Intra- and interassay coefficients of variation were 6.1% and 8.7%, respectively.

Data Analysis

Group data for predopamine baseline LH levels (samples 1 and 2) were compared across conditions with a two-factor analysis of variance (ANOVA) for repeated measures. A two-factor ANOVA for repeated measures was used to determine whether there were significant differences in LH across time during both dopamine infusion periods and periods when dopamine infusions were interrupted. Statistical significance of all ANOVAs was evaluated using the Huynh–Feldt epsilon factor for degrees of freedom adjustment of within-group means (SuperANOVA Software Manual, Abacus Concepts, Berkeley, CA).

RESULTS

Baseline LH Levels

Basal LH levels before dopamine administration averaged 30 ± 5.4 ng/ml in drug-naive females. These levels are consistent with basal LH levels during the follicular phase (days 6–8) previously measured in this laboratory (32,33,35). During chronic cocaine exposure, after an average of 798 ± 90 days (range = 519–1088 days) of cocaine self-administration, basal LH levels averaged 27.36 ± 13.3 ng/ml. During cocaine withdrawal, after an average of 825 ± 103 days of chronic cocaine exposure, baseline LH levels averaged 32.10 ± 4.4 ng/ml. Monkeys had been cocaine abstinent for at least 30 days at the time of the endocrine study conducted during cocaine withdrawal.

Effects of Dopamine on LH Levels

Figure 1 shows the effects of three successive dopamine infusions alternated with abrupt infusion interruptions on LH levels in three drug-naive female rhesus monkeys. Two monkeys were studied on two or three occasions. LH levels tended to remain quite stable across the period of observation. Dopamine infusions did not increase or decrease LH release under these conditions. LH levels during the three 80-min dopamine infusion periods averaged 31.7 ± 1.3 ng/ml. LH levels during the three intervals after dopamine infusions stopped averaged 31.5 ± 1.3 ng/ml.

Figure 2 shows LH levels during cocaine self-administration and after chronic cocaine exposure. Chronic cocaine exposure

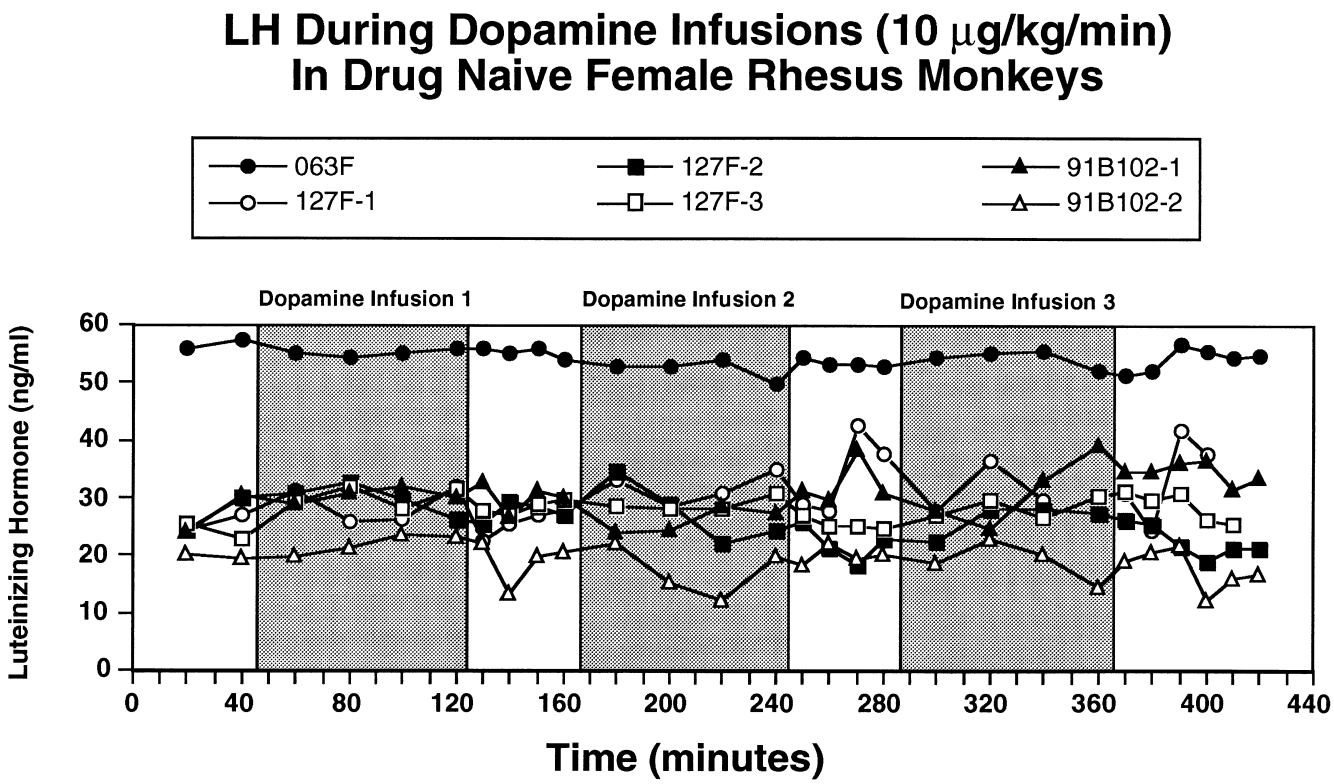

FIG. 1. Effects of dopamine infusions and interruptions on luteinizing hormone (LH; ng/ml) in drug-naive rhesus female monkeys. Data are shown for three individual monkeys during dopamine infusions and interruptions. A continuous intravenous infusion of dopamine (10 μg/kg/min) was started immediately after collection of samples 2, 10 and 18 and continued for 80 min. Dopamine infusions stopped abruptly after collection of samples 6, 14 and 22, and these infusion interruptions lasted for 40, 40 and 60 min. Bolus samples for LH analysis were collected at 20-min intervals. LH levels (ng/ml) are shown on the left ordinate. Time of sample collection is shown on the abscissa.

did not change the LH response to cocaine infusions and interruptions. During cocaine self-administration, LH averaged 26.9 ± 0.7 ng/ml during dopamine infusions and 26.1 ± 0.7 ng/ml after the interruptions of dopamine infusions. During cocaine withdrawal, LH averaged 31.2 ± 1.2 ng/ml during dopamine infusions and 32.1 ± 1.1 ng/ml after dopamine interruptions. The ANOVA confirmed that dopamine infusions and dopamine interruptions did not have significant effects on LH in drug-naive or cocaine-exposed female rhesus monkeys.

Figure 3 shows data for two individual monkeys before and on two occasions during cocaine self-administration. Monkey CH 548 had self-administered cocaine for 58 and 353 days at an average cocaine dose of 3.32 and 6.51 mg/kg/day during the 30 days immediately before the study. Monkey CH 712 had self-administered cocaine for 113 and 387 days at an average cocaine dose of 4.51 and 7.9 mg/kg/day during the 30 days immediately before the study. These data further illustrate that cocaine exposure did not change the LH response to dopamine infusions.

DISCUSSION

Dopamine and LH in Drug-Naive Monkeys

LH levels did not change significantly after dopamine infusions or interruptions in normally cycling drug-naive rhesus females (Fig. 1). These data are concordant with previous studies in ovariectomized rhesus monkeys, in which dopamine administration did not suppress basal LH levels or LHRH-stimulated LH (45,53). However, our findings in gonadally intact rhesus monkeys are not consistent with clinical reports that dopamine administration suppresses LH secretion in women (14,21,22,46,50,56,65) and men (15,23,25). The observed differences in the effects of dopamine on LH in humans and rhesus monkeys appears to be an unexplained species difference. These data suggest that the role of dopamine in LH regulation in rhesus monkeys is different from that in human females, but dopaminergic systems appear to influence LH release in rhesus monkeys under some conditions. For example, a dopamine antagonist, metaclopramide, inhibited hypothalamic LHRH pulse generator activity and LH pulsatile release in ovariectomized rhesus monkeys (16) but had no effect on LH in women (2). In rodents, unlike humans and rhesus monkeys, dopamine stimulated LH in both in vitro (13) and in vivo (13,58) studies.

Because dopamine did not stimulate LH release in the present study, cocaine-induced dopaminergic activity may not explain the increases in LH observed after acute cocaine administration. It is possible that the indirect dopamine agonist effects of cocaine are not related to its stimulation of LH in rhesus monkeys (32,33,35) and humans (11,39). Alternatively, the dose of dopamine selected may not have been adequate to stimulate LH. We consider this explanation unlikely because the dose of dopamine used in the present study was shown to be physiologically equivalent to dopamine levels measured in the hypophyseal stalk in rhesus monkeys (41). Moreover, this dose was sufficient to inhibit prolactin release in rhesus mon-

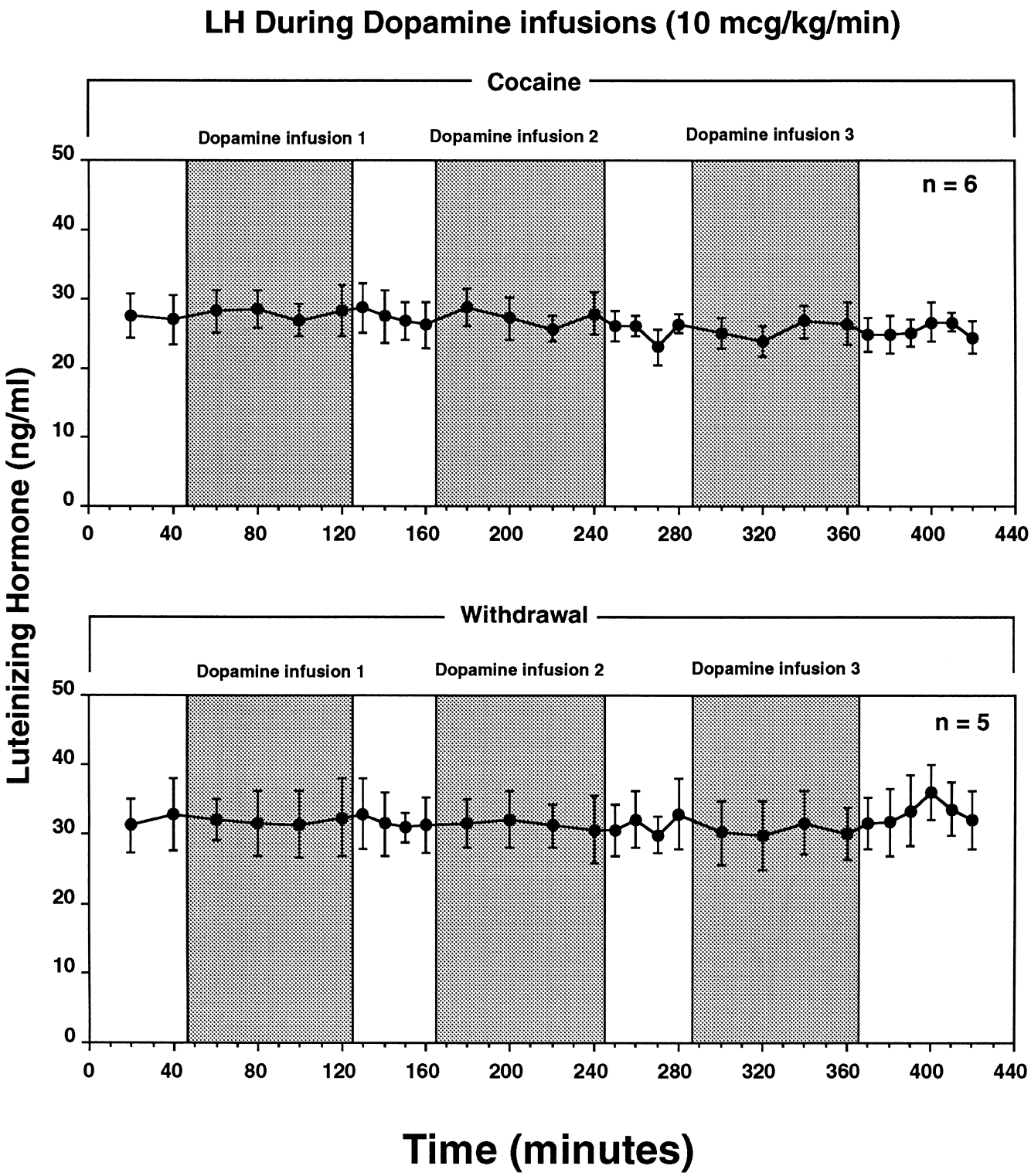

FIG. 2. Effects of dopamine infusions and interruptions on luteinizing hormone (LH; ng/ml) during cocaine self-administration and cocaine withdrawal. Top: Data are shown for a group of five monkeys after an average of 798 (±90) days of cocaine self-administration at an average dose of 6.5 (±0.2) mg/kg/day. Bottom: Data are shown for a group of three monkeys after withdrawal from cocaine, and two monkeys were studied on two occasions. Details of sample collection procedures are the same as those described in the caption to Fig. 1.

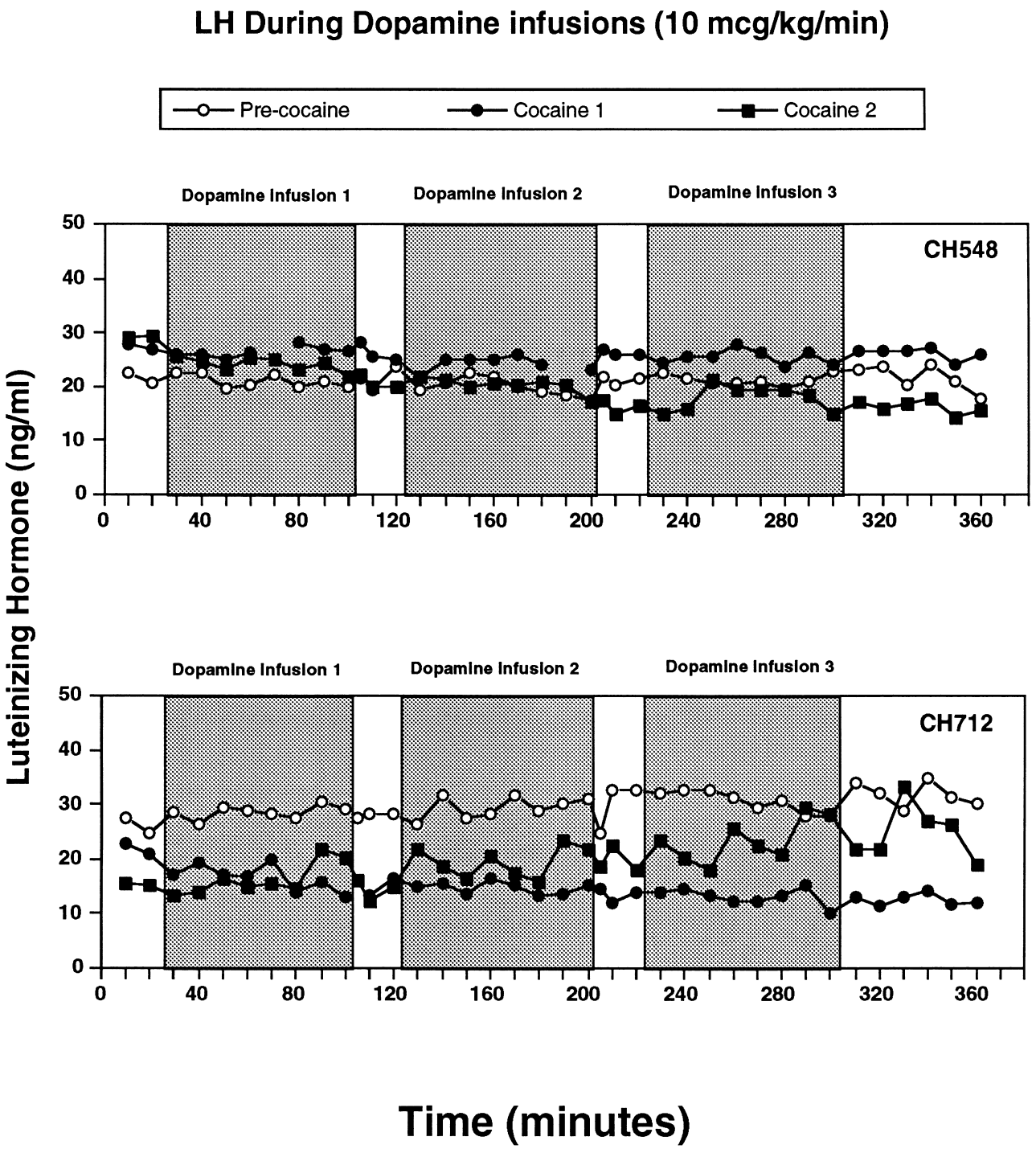

FIG. 3. Effects of dopamine infusions and interruptions on luteinizing hormone (LH; ng/ml) in rhesus females after chronic exposure to cocaine. Data are shown for two individual monkeys during dopamine infusions and interruptions before (open circles) and after chronic exposure to cocaine for an average of 74 days (cocaine 1) (closed circles) and an average of 300 days (cocaine 2) (closed squares). A continuous intravenous infusion of dopamine (10 μg/kg/min) was started immediately after collection of samples 2, 13 and 24. Each dopamine infusion continued for 80 min and stopped abruptly after collection of samples 10, 21 and 32. Consecutive interruptions of dopamine infusions lasted 20, 20 and 60 min. Bolus samples for LH analysis were collected at 10-min intervals except during the first two interruptions of the dopamine infusion, when the first two samples were collected at 5-min intervals. LH levels (ng/ml) are shown on the left ordinate. Time of sample collection is shown on the abscissa.

keys (41). However, the extent to which 10 μg/kg/min of exogenous dopamine is comparable to cocaine-induced increases in endogenous dopamine levels is unknown. Interestingly, cocaine was less effective than this dose of dopamine in reducing prolactin levels in rhesus monkeys. For example, infusion of dopamine (10 μg/kg/min) suppressed prolactin by 69% (34), whereas cocaine (0.4 and 0.8 mg/kg IV) suppressed prolactin by 18% and 36% (32). However, the time course of prolactin suppression was similar after dopamine infusion and IV cocaine administration. Prolactin reached a nadir within 80 min after the beginning of dopamine infusion and within 70 min after cocaine administration (32,34).

In conclusion, although dopamine administration did not mimic the effects of cocaine on LH, this does not mean that the indirect dopamine agonist effects of cocaine had no role in the LH stimulation generally observed. Rather, the effects of cocaine on LH may reflect an interaction between dopamine and other neuromodulatory systems that affect LHRH activity. For example, cocaine blocks reuptake of serotonin, norepinephrine and dopamine (48), and norepinephrine stimulates pulsatile release of LHRH in rhesus monkeys (54). The contribution of dopamine to LHRH regulation has long been controversial (63,66), and analysis of the effects of cocaine on the neuroendocrine system is in an early stage of development (29).

Dopamine and LH in Cocaine-Exposed Monkeys

There is evidence that chronic cocaine exposure may downregulate dopamine neurons, resulting in a decrease in D_1 binding sites and dopamine transporter binding sites in the rhesus monkey caudate nucleus (4,61). Dopamine D_2 receptor availability is decreased in the frontal lobes of human cocaine abusers as measured by positron emission tomography (59,60). If chronic cocaine exposure is associated with decreased dopamine synthesis and release, a different response to exogenous dopamine might be expected if the endpoint measured was under dopaminergic control. However, dopamine also did not alter LH levels in rhesus monkeys during chronic cocaine self-administration or during cocaine withdrawal (Figs. 2, 3). The lack of effect of dopamine on LH during cocaine self-administration and cocaine withdrawal further suggests that dopamine is not an important modulator of LH in rhesus monkeys as it is in humans. Thus, these data are one exception to the similarities between rhesus monkeys and women in neuroendocrine control of the menstrual cycle. The implications of this unanticipated species difference for our understanding of the neuroendocrine regulation of gonadotropins remain to be determined.

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