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The Effects of Acute and Chronic Cocaine Administration on Paced Responding in Intact and Gonadectomized Male and Female Wistar Rats

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VAN HAAREN, F. *The effects of acute and chronic cocaine administration on paced responding in intact and gonadectomized male and female Wistar rats.* PHARMACOL BIOCHEM BEHAV **48**(1) 265–273, 1994. – Intact and gonadectomized male and female Wistar rats pressed a lever on a multiple (tandem Random-Interval 30-s, Differential Reinforcement of High Rate 0.5-s) (tandem Random-Interval 30-s, Differential Reinforcement of Low-Rate 5.0-s) schedule of reinforcement. The pacing requirements maintained high and low response rates under equal reinforcement frequencies. Low doses of cocaine (1 and 3 mg/kg) either did not affect or slightly increased high and low response rates of intact and gonadectomized female rats, while they did not affect or decrease high and low response rates of intact and castrated male rats. Higher doses of cocaine (up to 30 mg/kg) dose-dependently decreased both high and low response rates for all subjects. Intact male rats were less sensitive to the rate-decreasing effects of these doses of cocaine than castrated male rats or intact and ovariectomized female rats. Chronic cocaine administration consistently resulted in behavioral sensitization only in intact male subjects. The results of this experiment provide further support for the notion that the behavioral effects of psychomotor stimulant drugs are not necessarily rate dependent but may depend upon the extent to which schedule contingencies allow for behavioral variability without negatively affecting behavioral outcomes.

Gonadal hormones Ovariectomy Castration Schedule-controlled behavior Cocaine
Behavioral tolerance Behavioral sensitization Rats Lever press

DACKIS and Gold (10) and Kuhar and his colleagues (23) have previously argued that potentiation of dopaminergic (DA) neurotransmission in mesolimbocortical pathways is involved in the reinforcing and toxic properties of cocaine (COC) because: a) COC administration produces a dose-dependent increase in extracellular DA in limbic areas; b) selective DA receptor blockade attenuates the reinforcing properties of COC, while DA agonists substitute for COC; c) destruction of DA mesolimbic and mesocortical neurons by 6-hydroxydopamine disrupts COC self-administration; and d) prolonged use of COC causes paranoia and psychosis, symptoms associated with schizophrenia, a syndrome that is thought to involve DA limbic pathways. In addition, recent evidence suggests that the DA transporter acts as a COC receptor (6).

Gonadal steroids affect central neurotransmission, as has been most extensively studied by those interested in the neural mechanisms underlying the motivational and consummatory aspects of reproductive behavior (28). It has been shown that higher levels of DA are present in the limbic system, striatum, and the hypothalamus of intact male than in those of intact female rats (9). It has also been noted that fluctuations in ovarian hormones functionally affect striatal DA content and turnover: when plasma levels of estrogens are high, striatal DA levels are higher than when they are not (8). It has been argued that the nigrostriatal dopaminergic system is sexually dimorphic, based on the observation that ovariectomy but not castration affects amphetamine-stimulated DA release from striatal tissue in an in vitro superfusion system (3). Others have established that the concentrations of DA and dihydroxyphenylacetic acid (DOPAC, a DA metabolite) in the terminal field of the mesolimbic DA system (nucleus accumbens) decrease after castration. The decrease may be prevented by treatment with testosterone or its aromatized metabolites 5α-

dihydrotestosterone or estradiol. It has also been shown that castration increased DA concentrations in the medial preoptic area, but not in the substantia nigra or ventral tegmentum (1, 30).

It has previously been shown that the activity of gonadal hormones affects both reproductive and nonreproductive behavior in rodents (2,45). The role of gonadal hormones in modulating the behavioral effects of acute and chronic COC administration has not been studied in great detail, despite the fact that the evidence discussed above indicates that both interact with central dopaminergic systems. Some evidence has been presented to show that intact female Swiss-Webster mice were more susceptible to acute COC-induced lethality (75 mg/kg) than intact males (14). Sham-operated male Swiss-Webster mice and ovariectomized and sham-operated females who had additionally been treated with estradiol were also afforded protection against the lethal effects of 75 mg/kg COC (13). Other investigators observed that acute COC administration produced higher levels of locomotor activity and stereotypy in intact female rats than in intact male rats (32,44). It has also been shown that taste aversion conditioning requires a smaller dose of COC in female than in male Wistar rats (43). Evidence has recently been presented to support the contention that COC self-administration is functionally affected by the activity of the female's gonadal hormones (11, 33,34).

The present experiment was designed to investigate the effects of acute and chronic COC administration on schedule-controlled behavior in intact and gonadectomized male and female Wistar rats. The behavioral effects of psychomotor stimulant drugs, including COC, are a function of the parameters of the experimental environment in which they are investigated (38,41). High baseline rates of responding usually decrease, while low response rates tend to increase. The generality of this phenomenon (rate dependency or, as others have argued, rate constancy) has been established in a variety of experimental procedures that engendered high or low response rates even under similar reinforcement frequencies (5,12,17, 18,27,35). Evidence is available to support the suggestion that the rate-dependent drug effects of psychomotor stimulant drug administration may be affected by the activity of gonadal hormones (42,46).

Chronic COC administration may result in tolerance or sensitization to the behavioral effects of the drug, dependent upon the behavior under investigation and parameters of the experimental environment. Chronic COC administration most frequently results in sensitization to the increase in locomotor activity, (31,32), but tolerance has been observed to the disruptive effects on schedule-controlled behavior. The latter has been shown to depend on schedule parameters when behavior is maintained by fixed-ratio (FR) schedules of reinforcement (16,19). Limited evidence is available to support the notion that gonadal hormones may affect the development of tolerance or sensitization as sensitization to the increase in locomotor activity has been observed to occur after smaller doses of COC in females than in males ((32), and to be dependent upon or enhanced by the presence of female gonadal hormones (31,44).

In the present experiment, intact and gonadectomized male and female rats were exposed to a two-component multiple schedule in which high and low response rates were maintained under approximately equal reinforcement frequencies. It was the purpose of the experiment to investigate whether or not the presence or absence of gonadal hormones would differentially affect the acute effects of COC on different behavioral baselines and/or the development of behavioral tolerance or behavioral sensitization.

METHOD

Subjects

Twelve male and 12 female drug naive Wistar rats that had previously participated in another experiment (39) served as subjects. Half of the male rats had been castrated and half of the female rats had been ovariectomized, the remaining male and female rats had received sham surgery. The subjects were approximately 150 days old and weighed an average of 377 g (intact males), 350 g (castrated males), 252 g (intact females), and 248 g (ovariectomized females) at the start of experimentation. All were food-deprived for 22 h prior to each experimental session (20).

Apparatus

The experiments were conducted in six, identical, Coulbourn Instruments, two-lever rodent operant conditioning chambers that have been described in greater detail elsewhere (39). Each experimental chamber was enclosed in a sound-attenuating ventilated cabinet and connected to a PDP 11-23 microcomputer (Digital Equipment Corporation, Maynard, MA) located in the experimental room itself. Experimental contingencies and data acquisition procedures were programmed in SKED-11 (36).

Procedure

Multiple-schedule training. The houselight was illuminated and the first component of the multiple schedule was randomly determined at the beginning of each session. A Tandem Random-Interval (RI) 30 s, Differential Reinforcement of High Rate (DRH) X s was in effect on the left lever during one of the components of the multiple schedule. This schedule contingency insured that a 45 mg Bio-Serve food pellet was only presented immediately following a lever press that had been preceded by another lever press by less than X s which, in turn, had been emitted after the expiration of the RI 30 s schedule [e.g., (26)]. The stimulus lights above the left lever were illuminated and each lever press activated a clicker during this, the high rate component of the multiple schedule. A Tandem Random-Interval (RI) 30 s, Differential Reinforcement of Low Rate (DRL) Y s schedule was in effect on the right lever during the other component of the multiple schedule in which food was presented immediately following a lever press that had not been preceded by another lever press for at least Y s, but which lever press had been emitted after the expiration of the RI 30 s schedule. The stimulus lights above the right lever were illuminated and each lever press activated a Sonalert for 0.10 s during this, the low rate component of the multiple schedule. Each component of the multiple schedule remained in effect for 6 min or until 10 food pellets had been obtained, whichever came first. The components were separated by 30 s during which all stimuli were extinguished and responding did not have any scheduled consequences. The values of X and Y were systematically manipulated during training until all subjects responded reliably under the final schedule parameters [MULT (TAND RI 30 s, DRH 0.5 s) (TAND RI 30 s, DRL 5 s)]. Sessions were run 5 days a week (Monday through Friday) and were terminated once each component of the multiple schedule had been twice presented.

Drug administration. Once responding had stabilized, subjects were intraperitoneally (IP) injected with different doses of COC hydrochloride (supplied by the National Institute on Drug Abuse, Research Triangle Park, NC) dissolved in physiological saline to obtain a constant injection volume (1 ml/kg). One of the following doses of COC was administered 10 min prior to the start of the experimental session on Tuesday and Friday of each week if response rates were stable during the preceding baseline control sessions: vehicle, 1, 3, 5.6, 10, 17, or 30 mg/kg. Each dose was administered at least twice, but not all doses were administered to each subject, as different doses completely eliminated responding in different subjects who were then not injected with the next highest dose.

The dose-effect function for COC was redetermined after subjects had been injected with a behaviorally active dose of COC prior to each experimental session for at least 30 sessions. This chronic dose of COC was equal to the acute dose that had greatly reduced but not completely eliminated responding maintained by one of the schedules of reinforcement. The chronic dose of COC was defined in terms of the acute behavioral effects to increase the likelihood of accepting a repeated level reflecting the relative presence of COC at the central and peripheral level in individual intact and gonadectomized male and female rats. Similar strategies have been used by other investigators to assess the behavioral effects of chronic COC administration (16,19). To determine whether or not chronic COC administration had resulted in behavioral tolerance or sensitization, all subjects were injected with different probe doses of COC on Tuesdays and Fridays, while the chronic dose of COC was injected prior to all other experimental sessions.

Estrus cycle. Vaginal smears were taken from intact female rats to determine the stage of the estrus cycle whenever they received an acute COC injection or a COC probe injection during chronic COC administration.

RESULTS

Figures 1, 2, 3, and 4 show the effects of acute (open symbols) and chronic (filled symbols) COC administration on high and low response rates (responses per minute) for individual intact female rats, ovariectomized female rats, intact male rats, and castrated male rats, respectively. Response rates during the high rate component are shown on the left, response rates during the low rate component are shown on the right in each individual panel.

Subjects always responded at higher rates during the high rate than during the low rate component of the schedule as is shown above C in each panel of the figures. These control response rates were obtained from sessions preceding those in which COC was administered. Reinforcement frequencies were approximately equal in both components of the schedule during control sessions (data not shown).

Acute COC administration did not produce different behavioral effects in the two components of the multiple schedule. COC dose dependently affected both high and low response rates in all groups of subjects. Low doses of COC (1 and 3 mg/kg) either did not affect or slightly increased response rates of intact and ovariectomized female rats (Figs. 1 and 2) and did not affect or slightly decreased both high and low response rates of intact and castrated male rats (Figs. 3 and 4). The increased high response rates for some of the intact and ovariectomized female rats were mainly observed in subjects who responded at relatively low rates in the absence of drug administration (subjects 102, 103, 201, and 205). Intermediate and high doses of COC (5.6, 10, 17, and 30 mg/kg) decreased response rates in both components of the multiple schedule, but less so for intact male rats than for subjects in the other groups. The highest doses of COC (17 and 30 mg/kg) eliminated responding in both components of the multiple schedule for most castrated male rats (5 of 6) and intact and ovariectomized female rats (4 of 6). Response rates of intact male rats only decreased after 17 mg/kg COC, while at least one intact male rat continued to respond under the control of schedule contingencies after 30 mg/kg of COC. The highest dose of COC sometimes produced behavioral effects with much variability (203, 102, 103, 503) when responding was sometimes totally eliminated, and sometimes greatly exceeded rates observed after any of the other doses of COC.

The filled symbols in Figs. 1, 2, 3, and 4 represent the effects of different doses of COC on the tandem RI-DRH (left panel) and the tandem RI-DRL (right panel) performance after chronic administration of a behaviorally active dose of COC. One of the intact male (503) and one of the intact female rats (204) died during the 30 sessions of chronic treatment prior to the redetermination of the dose-effect curve; one other intact female rat (202) died during the redetermination of the dose-effect curve. Intact male rats received a higher chronic dose of COC prior to each daily experimental session than most subjects in any of the other groups. Chronic administration of a behaviorally active dose of COC resulted in sensitization to the behavioral effects of this dose in all but one of the intact male subjects (506). The chronic dose produced a decrease in response rates in both components of the multiple schedule for three of the castrated male (401, 402, and 403), one of the intact female (203), and two of the ovariectomized female rats (102, 103). Habituation to the chronic dose was only observed in one intact male (506), three castrated males (404, 405, and 406) and three ovariectomized female rats (101, 104, and 105). When subjects were tested with doses smaller than the chronic dose sensitization to the behavioral effects of COC was consistently observed in intact male rats. The behavioral effects of doses smaller than the chronic dose varied between and within the other groups of subjects, as subjects showed evidence of behavioral tolereance as well as behavioral sensitization. Finally, it should be noted that none of the behavioral effects of acute and chronic COC administration in intact female rats were in any way systematically related to the stage of the estrus cycle during which COC was administered.

DISCUSSION

The behavioral effects of acute COC administration reported above were unlike those observed in other experiments. Previously, it had been observed that the acute behavioral effects of psychomotor stimulant drugs, including COC, were very much dependent upon the response rates maintained in the absence of drug administration. High response rates usually decreased, while low response rates increased after low doses of COC (38,40). In the present experiment, high and low response rates were maintained by different pacing requirements in tandem with a RI schedule of reinforcement in different components of a multiple schedule. These pacing requirements maintained high and low response rates under approximately equal reinforcement frequencies in the absence of COC administration. Low to intermediate doses of COC did not increase low rates or decrease high rates, irrespective of the hormonal status of an individual subject. These results lend further support to the hypothesis that drug effects on

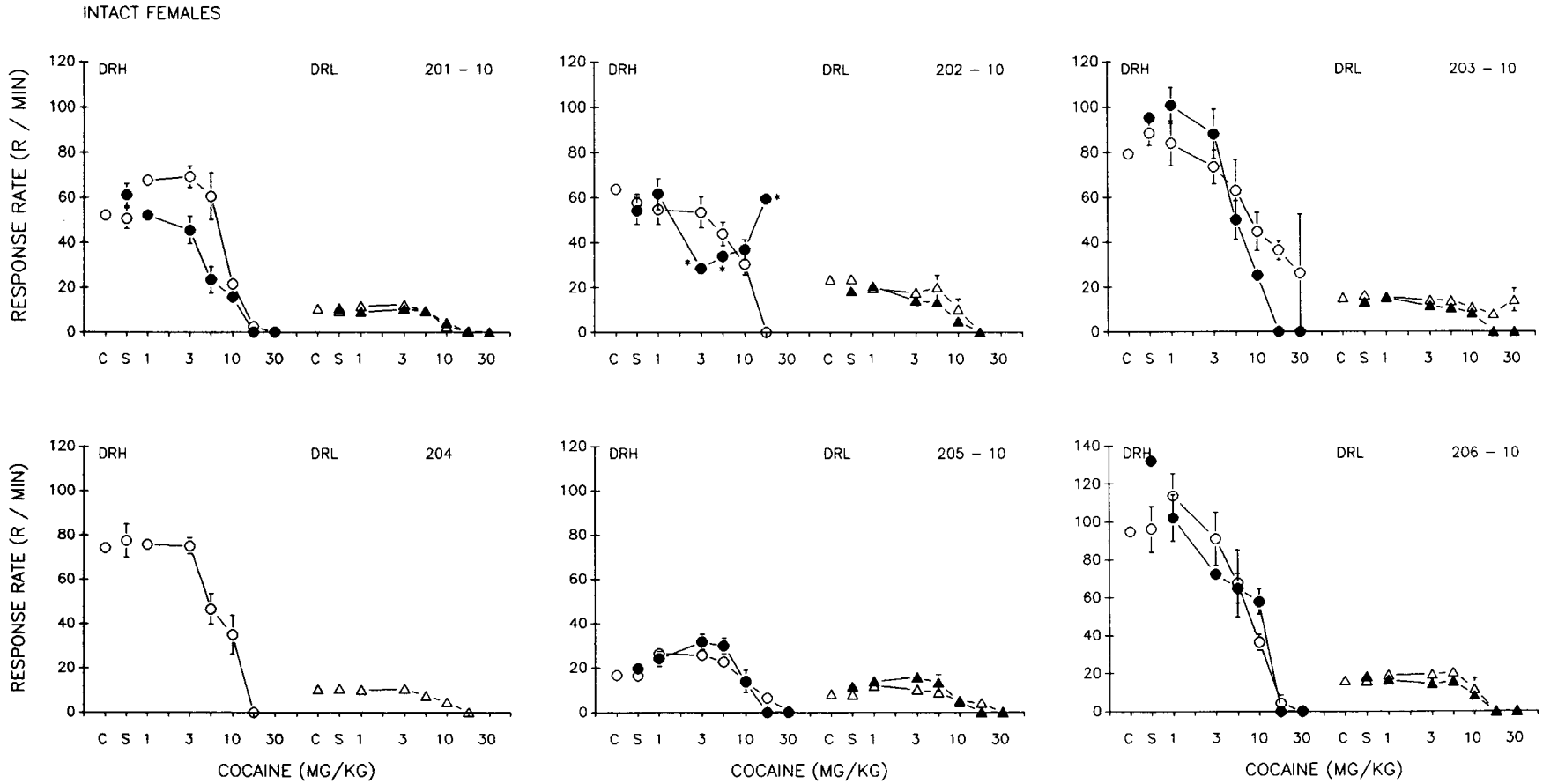

FIG. 1. Response rates (average number of responses per minute ± 1 SEM) as a function of the different doses of cocaine after acute administration (open symbols) and following chronic administration of a behaviorally active dose of cocaine (filled symbols) for individual intact female rats during the RI 30 s DRH 0.5 s component (left hand side of each individual panel) and the RI 30 s DRL 5 s (right hand side of each individual panel) of the multiple schedule.

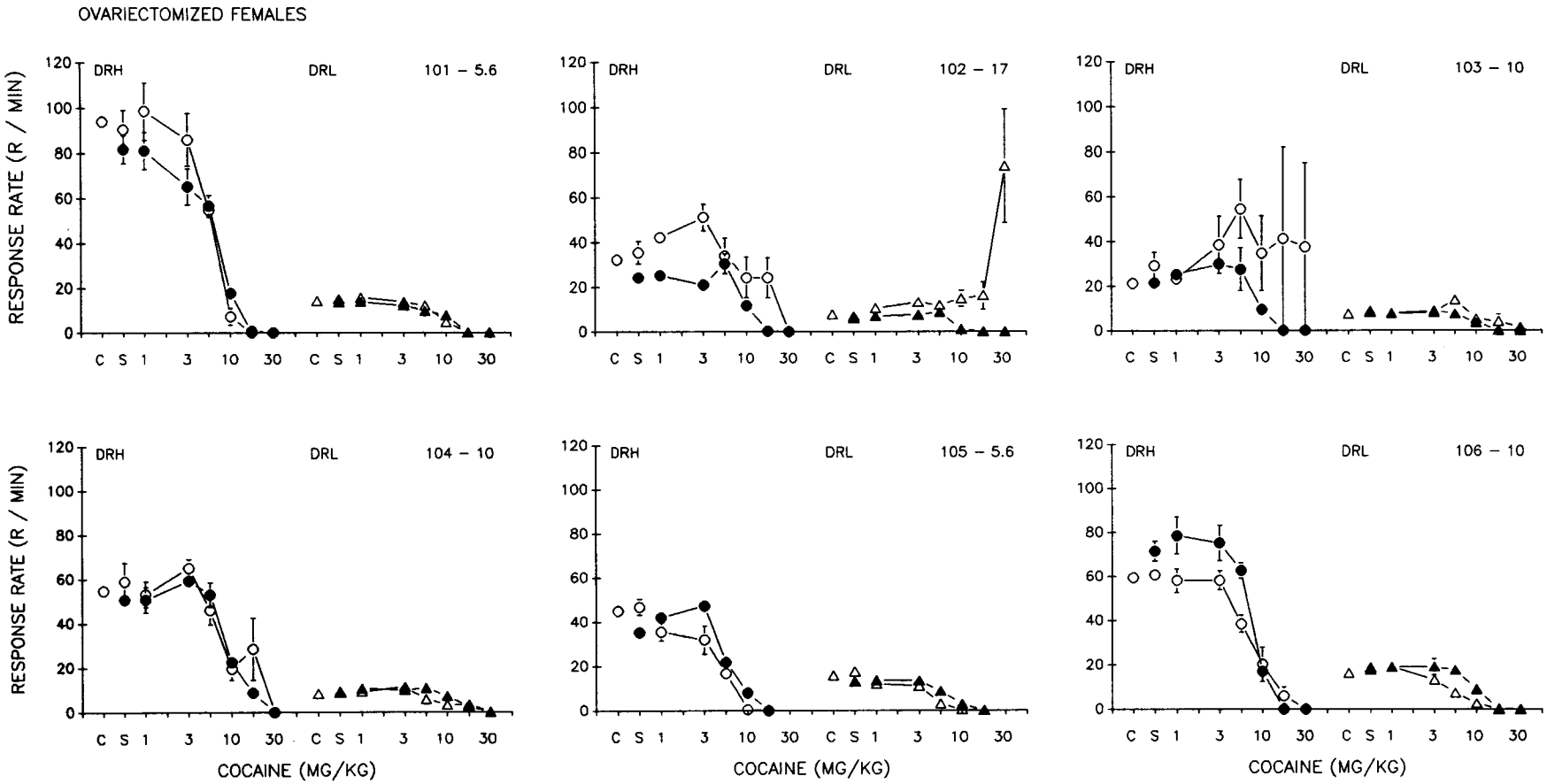

FIG. 2. Response rates (average number of responses per minute ± 1 SEM) as a function of the different doses of cocaine after acute administration (open symbols) and following chronic administration of a behaviorally active dose of cocaine (filled symbols) for individual ovariectomized female rats during the RI 30 s DRH 0.5 s component (left hand side of each individual panel) and the RI 30 s DRL 5 s (right hand side of each individual panel) of the multiple schedule.

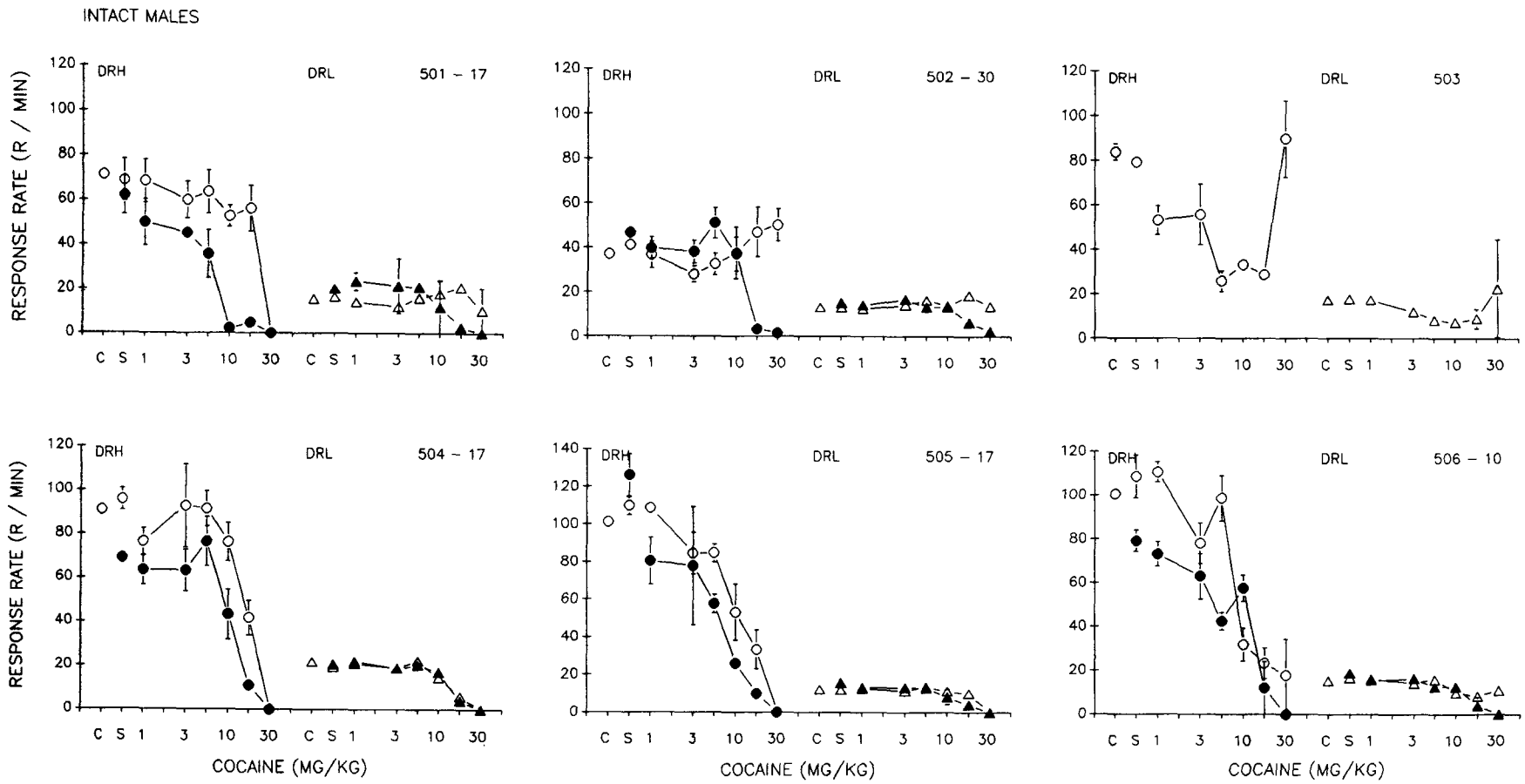

FIG. 3. Response rates (average number of responses per minute ± 1 SEM) as a function of the different doses of cocaine after acute administration (open symbols) and following chronic administration of a behaviorally active dose of cocaine (filled symbols) for individual intact male rats during the RI 30 s DRH 0.5 s component (left hand side of each individual panel) and the RI 30 s DRL 5 s (right hand side of each individual panel) of the multiple schedule.

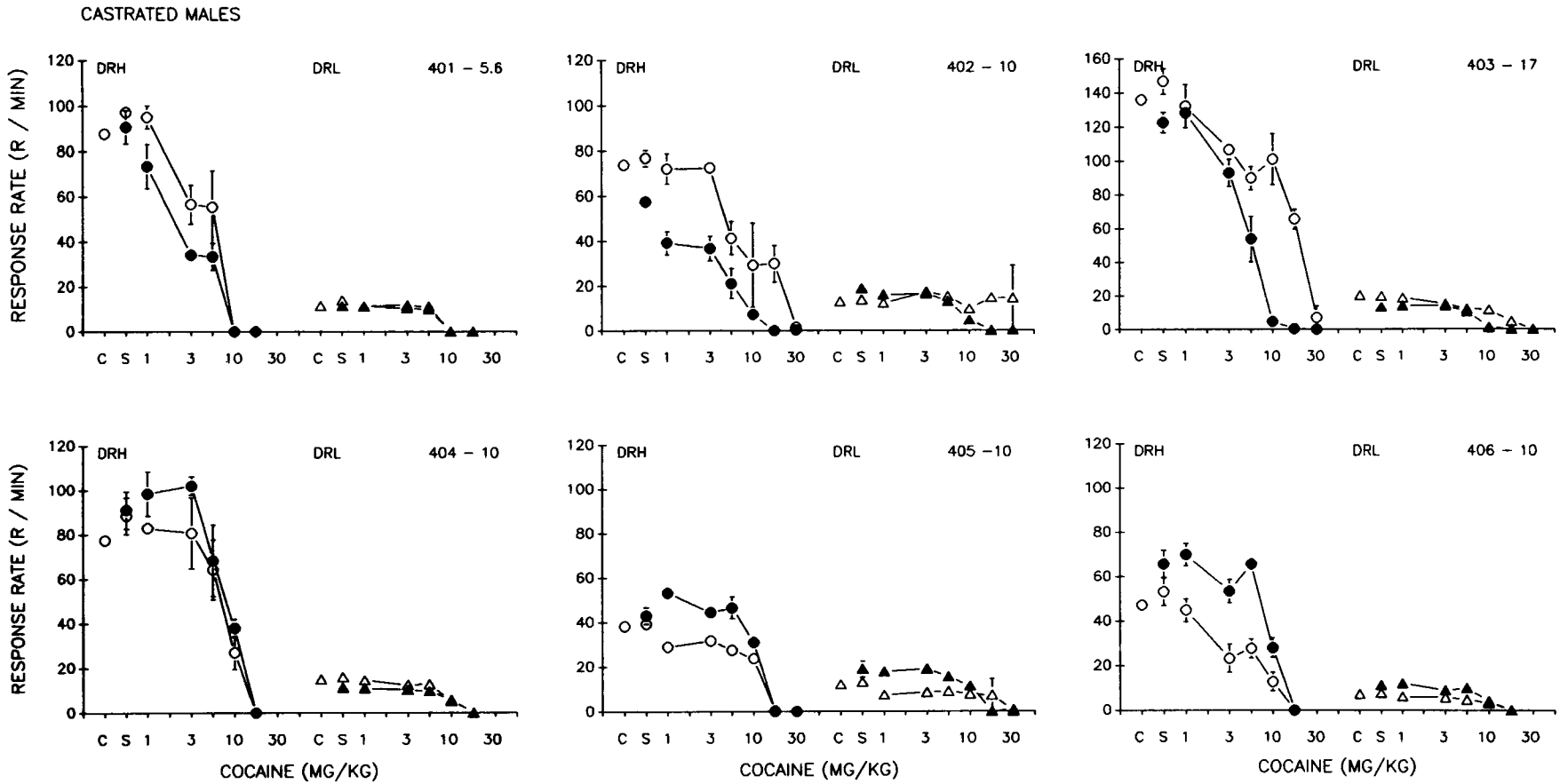

FIG. 4. Response rates (average number of responses per minute ± 1 SEM) as a function of the different doses of cocaine after acute administration (open symbols) and following chronic administration of a behaviorally active dose of cocaine (filled symbols) for individual castrated male rats during the RI 30 s DRH 0.5 s component (left hand side of each individual panel) and the RI 30 s DRL 5 s (right hand side of each individual panel) of the multiple schedule.

schedule-controlled behavior may be conjointly determined by unconditioned drug effects (on locomotor activity, for instance) and the extent to which direct schedule variables control behavior (37,40,47). It has been argued that behavior controlled by experimental contingencies that allow for little behavioral variability (in frequency and topography, for example) or which is under strong external stimulus control (21,24,25) may be less susceptible to drug-induced changes than behavior controlled by experimental contingencies that allow for greater behavioral variability. Some small differences were observed between intact and gonadectomized male and female rats after acute COC administration, as intact male rats were more resistant to the rate-decreasing effects of COC. These small behavioral differences between intact and gonadectomized male and female rats may also have been a function of the experimental contingencies arranged in the two components of the multiple schedule. Whether or not such was actually the case will have to be further explored in future studies. Even though the observation of sex differences may have been obscured by experimental contingencies, it remains important to note that the behavioral effects of pharmacological challenge may be determined by neuroendocrine function, and that neuroendocrine function may be altered by pharmacological challenge (4,7,22,29).

Chronic COC administration frequently results in tolerance to the behavioral effects of the drug on schedule-controlled behavior (16,19). Behavioral tolerance was not observed in the present experiment, which either may have been due to the dose of chronic COC administration or may have been a function of the prevalent experimental contingencies requiring subjects to emit a well-defined response sequence that had been thoroughly disrupted after acute administration of the same dose. These data suggest that the development of behavioral tolerance that requires adaptation to disruptions in behavior resulting from manipulations in environmental and/or pharmacological variables may also be dependent upon the extent of behavioral variability allowed by the contingencies of reinforcement.

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