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Effects of Dopamine Agonists on Appetitive and Consummatory Male Sexual Behavior in Japanese Quail

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CASTAGNA, C., G. F. BALL AND J. BALTHAZART. *Effects of dopamine agonists on appetitive and consummatory male sexual behavior in Japanese quail.* PHARMACOL BIOCHEM BEHAV **58**(2) 403–414, 1997.—The effects of pharmacological manipulations of dopaminergic transmission on appetitive and consummatory aspects of male sexual behavior were investigated in castrated male Japanese quail treated with exogenous testosterone. Appetitive male sexual behavior was assessed by measuring a learned social proximity response and consummatory behavior was assessed by measuring copulatory behavior per se. The nonselective dopamine receptor agonist, apomorphine, inhibited in a dose-dependent manner both components of male sexual behavior. Two indirect dopamine agonists were also tested. Nomifensine, a dopamine re-uptake inhibitor, decreased appetitive sexual behavior but increased the frequency of mount attempts, a measure of consummatory sexual behavior. Amfonelic acid, a compound that enhances dopaminergic tone by a complex mechanism, increased aspects of both appetitive and consummatory behaviors. These data suggest that, in quail, as in rodents, increases in dopaminergic tone facilitate both appetitive and consummatory aspects of male sexual behavior. Apomorphine may be inhibitory in quail because it acts primarily on D2-like receptors, unlike in rats, where it stimulates sexual behavior and acts primarily on D1-like receptors at low doses but interacts with D2-like receptors at higher doses. This is supported by the observation that stereotyped pecking, a behavior stimulated selectively in quail by D2 agonists, was increased by apomorphine but not by the two indirect agonists. The observed partial dissociation between the effects of these dopaminergic agonists on appetitive and consummatory sexual behaviors suggests that these two components of male sexual behavior may be controlled by the action of dopamine through different neuronal systems. © 1997 Elsevier Science Inc.

Dopamine Re-uptake inhibitor General agonist Apomorphine Nomifensine Amfonelic acid Japanese quail *Coturnix japonica*

THE catecholamine, dopamine, is thought to be a key component of the neuroendocrine mechanism regulating the activation of male sexual behavior in mammalian species (15,29, 33,46). Neuropharmacological studies in rodent species have suggested that dopamine stimulates male sexual motivation and copulatory performance (29,33). The dopaminergic system of vertebrates consists of a number of independent cell groups that exhibit a complex pattern of projections to nuclei within the forebrain [e.g., (14,44)]. Different dopaminergic inputs appear to be involved in different aspects of male sexual behavior. For example, dopamine released in the medial preoptic area (mPOA) enhances the rate and efficiency of copulation and facilitates genital reflexes, whereas dopamine released in the nucleus accumbens (NAc) enhances general responsiveness to motivational stimuli associated with preparatory or appetitive aspects of male sexual behavior (15,29).

As part of a long-term research project on the neuroendocrine mechanisms mediating the activation of male sexual

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behavior in Japanese quail (*Coturnix japonica*), a series of neuroanatomical, neuroendocrine, and neuropharmacological studies have been initiated on the interrelations among dopamine, the sex steroid hormone testosterone, and male sexual behavior. Laboratory procedures have been developed for the testing of appetitive (anticipatory) and consummatory aspects of male sexual behavior (12,42). Appetitive behaviors include searching for and approaching a female, whereas consummatory behaviors refer to the actual sexual contact that includes the copulatory act. Dopaminergic projections have been described to steroid-sensitive brain nuclei such as the sexually dimorphic medial preoptic nucleus (POM) that is required for the activation of copulatory behavior (2,3,6,7,11, 37). Other hormone-sensitive sites that receive dopaminergic inputs and may be involved in motivational aspects of male sexual behavior have also been identified (9). Little is known concerning the functional significance of these dopaminergic projections to areas that potentially control male sexual behavior in quail, but a previous behavioral pharmacological study found, in contrast to what has been described in rodents, that the dopaminergic agonist apomorphine inhibited consummatory sexual behavior in this species (1).

Cloning studies of dopamine receptors in the mammalian central nervous system have identified five types of dopaminergic receptor subtypes (25) that can be divided into two major groups: the "D1-like" and the "D2-like" receptors. In general, D1-like receptors stimulate adenylyl cyclase (AC) and exhibit a high affinity for compounds in the benzazepine family and low affinity for compounds in the butyrophenone family, whereas D2-like receptors inhibit AC, but stimulate K^+ channels and have a high affinity for butyrophenones and certain bezemides and a low affinity for benzazepines (25). Apomorphine is a nonselective dopamine agonist that appears to act primarily on D1-like receptors at low doses, whereas, at higher doses, its effects result predominantly from an interaction with D2-like receptors. The discrepancy between the effects of apomorphine on sexual behavior in quail, compared with what has been found in mammals, could be explained by a higher ratio of D2 vs. D1 receptors in birds compared with mammals, as has been reported in one study (38,39). If this is generally true, the stimulatory action observed in mammals, with relatively low doses of apomorphine and mediated by the D1 receptor type, would be masked in birds by the inhibitory effects mediated by the D2 receptors.

A goal of the present study is to test this possibility by comparing the behavioral effects of apomorphine with the effects of two indirect agonists of dopamine, nomifensine and amfonelic acid. Nomifensin increases dopaminergic transmission by the inhibition of dopamine re-uptake. This compound exhibits a high affinity for the dopamine transporter, and peripheral injection of nomifensin in rats results in a marked increase in dopamine levels measured in striatal dialysates (36). The actions of amfonelic acid are more complex. Some studies have suggested that it acts by enhancing the release of vesicular dopamine (24,34,43). This compound also shows a high affinity for the dopamine transporter and appears to be able to act also as a dopamine re-uptake inhibitor (32,36,40). However, in vivo studies did not reveal as large an increase in the release of endogenous dihydroxyphenylacetic acid (27,28) or dopamine (36) as one would have predicted based on its affinity for the transporter even though marked behavioral responses (i.e., dopamine-dependent stereotypies) were observed (36). Therefore, it was suggested that amfonelic acid may enhance dopaminergic transmission through an increase in release, but also through the direct stimulation of dopamine receptors (36). In any case, because of their mechanism of action is very different from that of apomorphine, these two indirect agonists of dopamine would not be expected to display a dose-dependent differential effect on D1 and D2 receptors.

A second goal of the present study is to measure the effects of dopamine on male sexual behavior in more detail. Since the completion of the original apomorphine study (1), procedures for the measurement of appetitive aspects of male sexual behavior, in addition to consummatory aspects of sexual behavior, have been developed (12) based on methods first described by Domjan and colleagues (17,20–22). A learned social proximity response is used to measure appetitive sexual behavior. During this response, a male will stand continuously in front of a window providing a view of the female after he has been given an opportunity to copulate with her (12). Because appetitive and consummatory male sexual behavior may be differentially regulated by dopamine, a comparison of the effects of dopaminergic drugs on male sexual behavior as measured with both of these behavioral procedures was undertaken.

METHODS

Animals and Endocrine Treatments

The two experiments reported in this paper were performed on a total of 40 male Japanese quail (*Coturnix japonica*) that were bought from a local dealer in Belgium (Dujardin, Liernu) at the age of about three weeks. Throughout their life at the breeding colony and in the laboratory, birds were maintained on a photoperiod simulating long summer days (16L:8D). The experimental subjects (males) and the stimulus females were housed throughout the experiment in individual home cages where they were provided with food and water ad lib.

Male subjects were castrated under complete anesthesia (Hypnodil, Janssen Pharmaceutica, Beerse, Belgium, 15 mg/kg) within one week after their arrival at the laboratory. The two testes were removed through a unilateral incision behind the last rib as described previously (13). Three weeks later, they received two Silastic implants (Dow Corning nbr 602–252; 1.57-mm i.d.; 2.41-mm o.d.; length = 2 × 20 mm) filled with testosterone. These capsules were implanted subcutaneously in the neck region. Throughout the experiment, birds were periodically weighed to the nearest gram and the size of their cloacal gland, an androgen-dependent structure (41) was measured with callipers (cloacal gland area = largest length × largest width in mm^2). These data confirmed the efficacy of the testosterone replacement as well as the absence of adverse effects of the experimental treatments on the general health condition of the subjects. All experimental procedures have been reviewed by the appropriate supervisory authorities and are in compliance with the relevant laws and regulations of both Belgium and the USA governing the treatment of experimental animals.

Test Cages

Behavioral observations were conducted in four similar test cages (90 × 90 × 50 cm) that were described previously in detail (12). The floor, ceiling, lateral, and back walls of each cage were made of 1-cm plywood. The front wall was made of Plexiglas to allow for the observation of the subjects. A vertically sliding door in the middle of the back wall permitted the introduction of birds and the cleaning of the cages. A smaller

cage for stimulus females (20 × 26 × 24 cm) was centered on the left lateral wall of the main cage and separated from it by a vertically sliding door, 20-cm wide × 20-cm high, that could be controlled remotely by strings and pulleys. A small vertical slit (1-cm wide × 15-cm high; the "window") cut in the plywood was located in the middle of this door and provided the male with limited visual access to the female. This window could be closed by an opaque swinging plywood panel attached by a hinge just above the door. That panel could be lifted remotely by strings and pulleys. A square area of the floor (30 × 30 cm), located in the middle of the lateral left wall (in front of the door/window) represented the test area for the bird position.

When the window was open, the male located in the main chamber could only see the female located in the lateral chamber if he stood in front of the window in the test area. This area was mounted on four springs. Four microswitches wired in parallel and powered by a 4.5-V battery were located under the test area (one in each corner) so that the depression of any of these switches generated a positive signal. The output signals were digitized and transmitted to a MacIntosh computer as implemented by commercially available hardware and software (MacADIOS 8ain A/D converter from GW Instruments, Somerville, MA). A specially designed program written in Basic recorded during the observations (5-min periods, see below), the total time spent by a bird in the test area, and the number of times that the birds entered in this area. Positions were sampled in each cage ($n = 4$) once every second.

Test Procedure

Four tests were always conducted in parallel in the four experimental cages. Each test lasted for a total of 25 min. In each cage, one male was first introduced into the main chamber and one stimulus female was placed into the adjacent smaller box. The "window" between the two compartments was closed at that time. Birds were given 5 min to habituate to the new environment. The position of the male was then recorded continuously during the next 5-min period with the window still closed. This provided a pretest control record. The window was then opened and the position of the male was again recorded for 5 min. The time spent by the experimental subject looking through the open window was also recorded during these 5 min. A beeper was activated and emitted a weak sound every 5 s. At each beep, the observer recorded whether the subject was actually looking through the window or not. Looking behavior was defined as a stereotyped positioning of the head that allows the subject to focus on the female through the window. This point sampling (31) therefore furnished a score for the looking behavior ranging from 0 (never observed) to 60 (behavior present at every beep). Data collected during this period provided measures of appetitive sexual behavior of the male.

At the end of this period, the door separating the two compartments was lifted and the two birds were allowed to freely interact for 5 min. During that time, the frequency and latency of the first occurrence of sexual behaviors exhibited by the male were recorded directly. The following behavior patterns were noted systematically: strut, neck grab (NG), mount attempt (MA), mount (M), and cloacal contact movements (CCM) [see (4,30) for a detailed description]. These data provide a measure of consummatory male sexual behavior in these birds. The female was then removed from the experimental chamber and the male remained for another 5 min before he was returned to his home cage. Birds were tested repeatedly by this procedure at the rate of four tests per week after being injected with the various drugs. The specific protocols of each experiment are described below.

Drugs Treatments and Specific Procedures

Experiment 1: Effects of apomorphine. This experiment was performed with a total of 18 castrated birds that had been implanted with testosterone-filled Silastic capsules as described above. Two weeks after implantation of testosterone, the birds were tested four times for consummatory sexual behavior in a small arena (50 × 60 cm) using behavioral procedures that were described previously (13). During these tests, 16 of 18 birds exhibited sexual behavior including CCM and were included in the study.

The birds were then tested for the acquisition of the learned social proximity response that is used to test appetitive behavior. Within a 14-day period, these 16 birds received in the two-chamber test cages eight associative learning trials (the opening of the window providing a view of the female is paired with the opening of door allowing an interaction between the male and the female). After an additional 20-day period, these quail were then assigned to one of two groups ([G1, $n = 8$; G2, $n = 8$] matched for the behavioral response they exhibited during their acquisition of the learned social proximity response (the mean of time at the window during the seventh and eighth acquisition tests). They were then alternatively injected with apomorphine at various doses (0.1, 0.5, or 1 mg/ml/kg) or with the vehicle as control. The dopaminergic agonist apomorphine HCl (APO; Sigma A-4393, Sigma Chemical Co, St. Louis, MO for the tests of the 0.1 mg/kg dose at a 15-min intervals or RBI D-004, Research Biochemicals International, Natick, MA for all other tests) was dissolved in distilled water containing 0.2% ascorbic acid at doses ranging from 0.1 to 1 mg/ml and injected (1 ml/kg) IP in the inguinal fold in front of the left leg. Similar volumes of solvent were injected as a control.

The behavioral effects of each of the three doses of APO (0.1, 0.5, and 1 mg/kg) were assessed at two different latencies from drug injection to behavioral testing: 15 and 30 min. These latencies refer to the interval between the injection of the drug and the beginning of the 25-min testing procedure so that appetitive behavior was actually tested 25 or 40 min after drug injection, and consummatory behavior was tested 30 or 45 min after injection (see the description of the testing procedure above for more detail). This combination of three drug doses and two time intervals therefore defined six separate experimental conditions. The three doses of APO were first studied in increasing order at the interval of 15 min. The three doses were tested subsequently at the 30-min interval in a random order (0.5, 1, and 0.1 mg/kg, respectively).

TABLE 1

SCHEMATIC ILLUSTRATION OF THE INJECTION SCHEDULE USED THROUGHOUT EXPERIMENT 1

Days	1	2	3	4
Group G1	APO	C	C	C
Group G2	C	C	APO	C

APO, injection of apomorphine; C, injection of the vehicle solution.

For each of these experimental conditions (the individual dose by latency combinations), all birds were tested four times on four different days within a one-week period (see Table 1). On the first day, half the birds (group G1) were injected with APO and the other half (group G2) received the vehicle. On the second day, both groups (G1 and G2) were injected with the vehicle. On the third day, group G1 received the control solution, and group G2 was injected with APO; and finally, on the fourth day, both groups received the control solution again. In this way, in each experimental condition, each bird was injected once with APO and three times with the vehicle, and each bird could be used as its own control. Controls for the recovery from the drug effect were also available for each group of subjects. For the first of these experimental conditions (0.1 mg/kg at 15 min), the entire test procedure was repeated twice (eight days of tests instead of four). Mean results of these two series of observations are used in the following analysis.

It was observed immediately during this experiment that birds injected with APO frequently exhibited a stereotyped behavior that consisted of frequent pecks directed at the floor or walls of the cage. This was not unexpected given previously published reports of such stereotypies after apomorphine administration (16,18,19,26). This behavior was recorded. It was impossible to measure the precise frequency of pecking because they were delivered at such a high rate that individual counts were unreliable. However, once the behavior was initiated, it was nearly continuous, therefore a more qualitative measure was taken (the presence or absence of stereotyped pecking during a given test).

Experiment 2: Effects of the indirect agonists. The second experiment testing the behavioral effects of the two indirect agonists was performed with a similar protocol. Only specific differences between these two experiments are described here. A total of 22 male quail were castrated and treated with testosterone as described above. When first screened for the presence of active copulatory behavior during four 5-min tests in the small arena, two subjects failed to show cloacal contact movements and were discarded from the experiment. The 20 remaining subjects then experienced eight associative learning trials during a 14-day period (opening of the window preceding opening of door) to establish the conditioned response to the female presentation. All birds were then included in an experiment testing the behavioral effects of a vasotocin receptor antagonist. This experiment lasted about two weeks and its results are not relevant to the present study. It should be stressed, however, that no effect of these treatments were observed on any aspect of the behavior of these birds, either in the short or in the long term.

Subsequently, the 20 subjects were assigned randomly to one of two groups (G1 and G2) that were matched for the conditioned response during the acquisition phase (mean of time at window during the seventh and eighth conditioning tests). The behavioral effects of two doses (1 and 5 mg/kg) of the re-uptake inhibitor nomifensine maleate and of one dose (1mg/kg) of the indirect agonist, amfonelic acid, were then tested in sequence. In these three sets of tests, a delay of 15 min between the injection and the beginning of the behavioral testing was always observed. For each testing sequence, a protocol similar to the one described in Table 1 was used. Testing took place during four consecutive days within a week, with the drug being injected to one half of the subjects on day 1 and to the other half of the subjects on day 3. Nomifensine maleate (RBI-N-123, Research Biochemicals International, Natick, MA) was dissolved in 0.01 N HCl (1–5 mg/ml) and amfonelic acid (RBI-D-044, Research Biochemicals International, Natick, MA) was dissolved in 0.5 N NaOH (1 mg/ml). The solvent was always injected as control. The drugs and the control solution were injected IP in the inguinal fold in front of the left leg.

Data Analysis

All data were analyzed by a combination of *t*-tests for independent and repeated samples and by one- or two-way analyses of variance (ANOVA) with repeated factors. Original screening of the data by *t*-tests for paired samples confirmed that injection of the three compounds tested here had no long-term effect on the behavior of the subjects. No difference was found between the scores of the birds before the injection and their behavior one day after the injection. The same conclusion had already been made in our study of the effects of APO on male copulatory behavior (1).

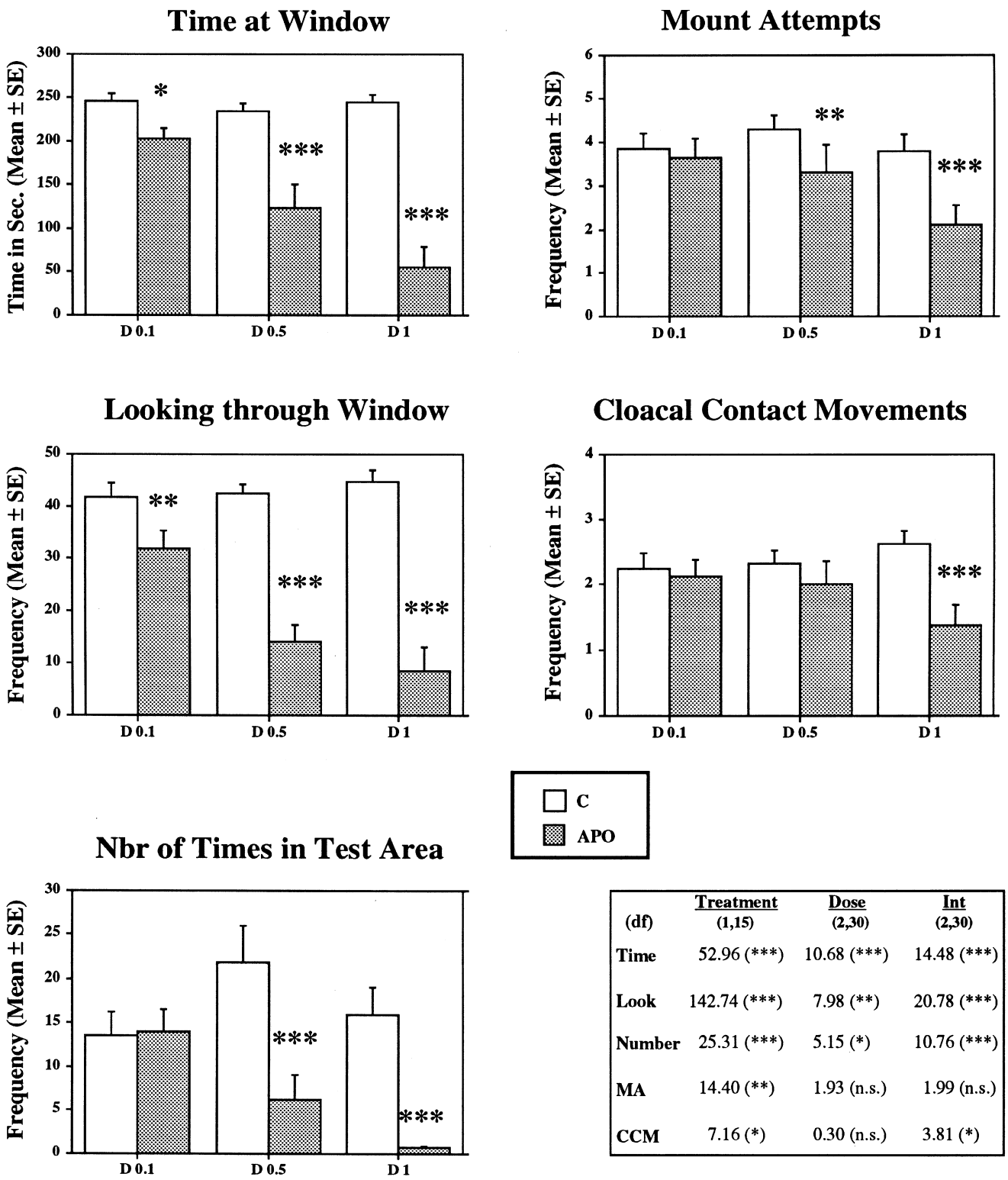
For each series of observations (four days of observations), each subject was tested once 15 min after the injection of the dopaminergic compound and three times in the control condition after injection of the vehicle. Inspection of the data confirmed the absence of significant differences between the three sets of scores obtained in the control condition. The means of these three sets of data were therefore calculated and used in the final statistical analyses that are presented here. Because the same birds were tested in all conditions and served as their own control, analyses were performed by two-way ANOVAs with two repeated factors; this analysis tested the effect of the treatment (drug or vehicle), of the dose of dopaminergic drug injected, and of the interaction between these two factors. When appropriate, post-hoc comparisons between pairs of groups were performed by Student's *t*-tests for matched samples using the relevant mean square of the ANOVA as the basis for comparisons. Data derived from the amfonelic acid experiment that only included one factor were analyzed by *t*-tests for matched samples.

RESULTS

Experiment 1

Effects of apomorphine after a 15-min delay. When behavioral effects of apomorphine were studied in behavioral tests that were initiated 15 min after the injections, a strong and reliable inhibition of all appetitive aspects of male sexual behavior was observed. Analysis of the time spent in front of the window, of the time spent looking through the window, and of the number of times the subjects entered the test area by two-way ANOVA with two repeated factors identified for each dependent variable a significant ($p < 0.0001$) overall effect of the drug, a significant ($p < 0.05$ or better) effect of the dose injected, and a significant effect of the interaction between these two factors (see Fig. 1 for details).

The significant interactions resulted from the fact that higher doses of apomorphine induced more profound behavioral inhibitions and that the behavior of the birds was similar in the three series of controls matched to the three doses of APO. This conclusion was confirmed by one-way repeated ANOVAs that were computed for each dependent variable in order to compare these three sets of control data. No significant difference among the three control situations was detected except in the analysis of the number of times birds entered the test area: the high scores obtained during the second set of observations (control for the 0.5 mg dose) resulted in a significant overall change in the control scores [Time: $F(2,30) =$



(df)	Treatment (1,15)	Dose (2,30)	Int (2,30)
Time	52.96 (***)	10.68 (***)	14.48 (***)
Look	142.74 (***)	7.98 (**)	20.78 (***)
Number	25.31 (***)	5.15 (*)	10.76 (***)
MA	14.40 (**)	1.93 (n.s.)	1.99 (n.s.)
CCM	7.16 (*)	0.30 (n.s.)	3.81 (*)

FIG. 1. Effects of the general dopaminergic agonist, apomorphine (APO) on appetitive and consummatory aspects of male sexual behavior in castrated male quail treated with exogenous testosterone. Three doses of apomorphine, 0.1, 0.5, and 1mg/kg (D 0.1, D 0.5, and D 1, respectively) were tested with an interval of 15 min between the injection and the beginning of the behavioral observations. Data were analyzed by ANOVAs with two repeated factors, the treatment (control [C] and APO) and the three doses. Their results are summarized in the table located in the bottom right panel. For each main factor and for their interaction, the table provides the F value, the associated probability (in parentheses) and the number of degrees of freedom (df). At each dose level, the control and APO data were compared by post-hoc t-tests as described in the methods and the results of these tests are indicated by asterisks at the top of the bars. *$p < 0.05$; *$p < 0.01$; **$p < 0.001$.

0.935, $p = 0.4037$; Look: $F(2,30) = 1.379$, $p = 0.2674$; Number: $F(2,30) = 4.266$, $p = 0.0234$]. Post-hoc tests comparing the apomorphine data with their respective controls at each dose indicated that all doses of this dopaminergic agonist inhibited at least some aspects of the behavior significantly and that stronger inhibitions (associated with smaller p values) were detected at the higher doses (see Fig. 1 for details).

A similar pattern of results was observed in the analysis of the two measures of consummatory sexual behavior (MA and CCM) except that the magnitude of the behavioral inhibition was, in this case, smaller, so that the dose factor and the interaction between the drug and dose factors were often not significant and the post-hoc tests failed to identify significant differences between the control and drug situation in a larger number of cases (see Fig. 1 for details of statistical analyses). As was the case for the different aspects of the appetitive behavior, the consummatory sexual behavior observed in the three control situations was, however, stable and no significant difference could be detected between these three sets of data [MA: $F(2,30) = 1.111$, $p = 0.3423$; CCM: $F(2,30) = 1.525$, $p = 0.2339$].

Based on previous work in birds (16,18,19,26), it was suspected that apomorphine injection may induce stereotypies and, in particular, intense pecking responses. The occurrence of this behavior was recorded. No unusual stereotyped pecking was detected in birds when they were injected with the lowest dose of apomorphine (0.1 mg/kg). Such pecking did become apparent after the injection of 0.5 mg or 1 mg/kg of the drug. The behavior was nearly continuous after it was initiated by a given bird and its presence or absence was recorded in each subject during the 5 min when appetitive behavior was observed (window open, door closed) and during the 5 min when consummatory behavior was observed (door open). During the appetitive behavior testing phase, 9 or 11 birds of 16 pecked intensely when injected with the 0.5 mg or 1 mg dose, respectively, whereas only 1 or 0 birds pecked in the corresponding control conditions ($p < 0.002$ and $p < 0.0001$, respectively, by the two-tailed Fisher exact probability test). The corresponding numbers during the measure of consummatory behavior were 15 and 12 birds pecking in the drug condition (0.5 and 1 mg APO, respectively) and none pecking in the two control conditions ($p < 0.0001$ in both cases by the two-tailed Fisher exact probability test).

Effects of apomorphine after a 30 min delay. In order to analyze the duration of the behavioral effects of APO, the same three doses of this compound were tested a second time by similar methods except that a longer interval (30 min) was now observed between the injections and the beginning of the observations. Data obtained in this second part of the experiment were summarized and analyzed statistically by the methods described above. The means of all behavioral measures and the results of the statistical analyses are summarized in Fig. 2.

A significant inhibition of the two main measures of appetitive sexual behavior was also observed in these conditions (effects of treatment, dose, and interaction are significant for both the time spent in the test area and the time spent looking through the window). There was also in this case an overall effect of the treatment on the number of times that the birds entered in the test area, but no dose effect and no interaction of dose by treatment was detected in this case. The effects on consummatory sexual behavior were, in contrast, reduced markedly. No significant effect of these treatments on the frequency of MA was present, although the interaction of treatment by doses was close to significance ($p = 0.065$). The frequency of CCM was decreased significantly by APO in these conditions, but no effect of the dose or of the interaction of the dose by treatment could be detected (see Fig. 2 for details).

The post-hoc t-tests for repeated samples indicated significant effects of the highest dose of APO (1 mg) on all behavioral dependent measures plus a few additional differences at the lower doses (see Fig. 2). However, it should be noted that the inhibitory effect on MA frequency detected by this statistical method is suspect because it is associated with a general ANOVA that falls short of statistical significance assuming $\alpha = 0.05$ (treatment effect: $p = 0.065$, no effect of dose and no effect of interaction).

As in the other set of observations performed after a shorter interval, the values observed in the control condition were stable over time; comparison of the three sets of controls values associated with the three doses of APO by a series of one-way ANOVA for repeated measures did not detect any significant variation ($p > 0.05$ for each of the five dependent variables).

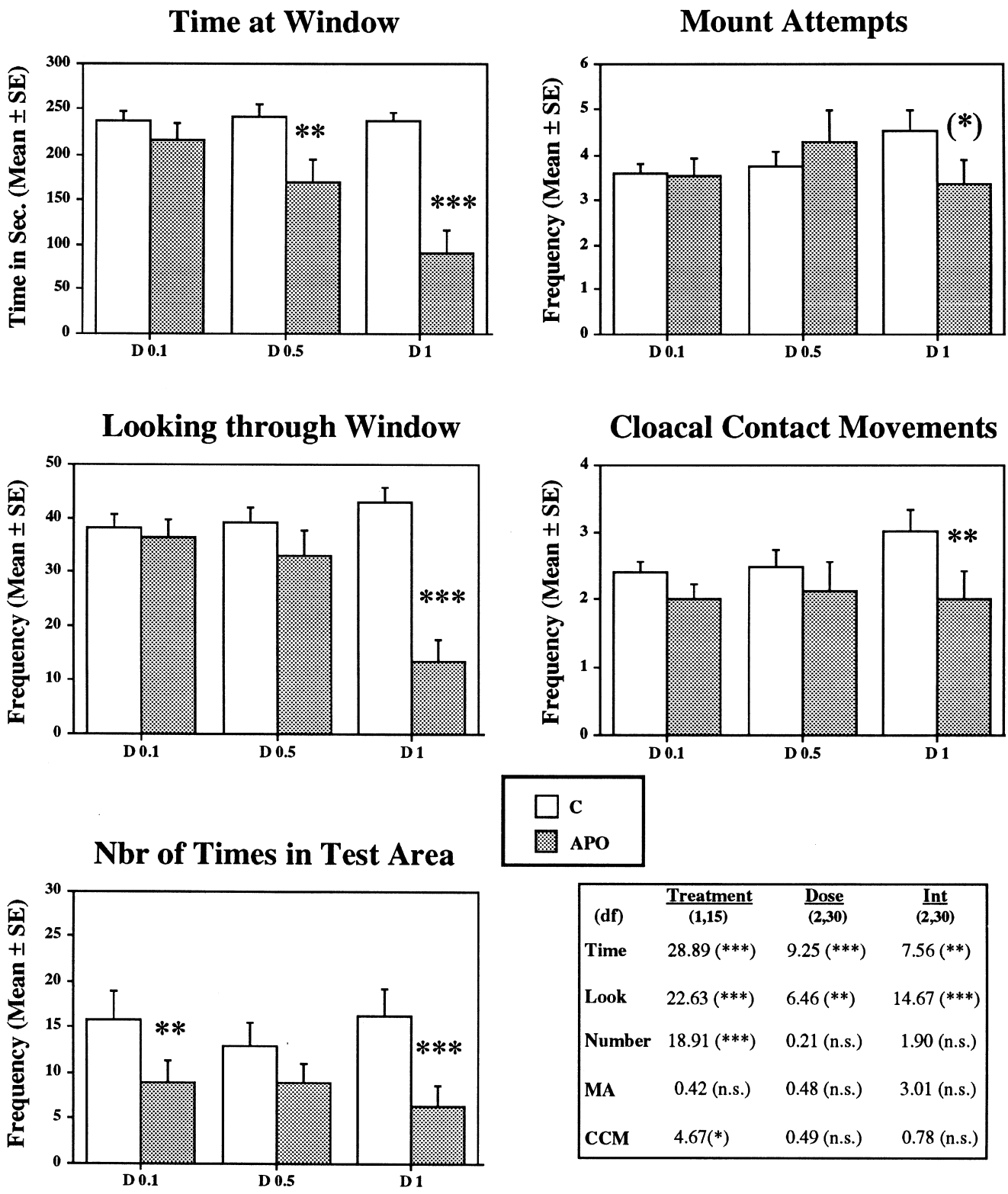
Stereotyped pecking was also observed in this case in birds treated with the dopaminergic agonist. During the observation period testing appetitive behavior, 9 of the 16 birds pecked after injection of 0.5 or 1 mg APO, whereas this behavior was never observed in the control conditions ($2p < 0.001$ by the Fisher exact probability test). Nine of 16 birds still pecked during the tests for consummatory behavior performed after injection of 0.5 mg APO, but only three did so after injection of the highest dose (1 mg) of the drug. This behavior was still completely absent in the corresponding control conditions ($2p < 0.001$ and $2p = 0.226$, respectively).

Experiment 2

The behavioral effects of the re-uptake inhibitor, nomifensine maleate, were studied with an experimental protocol similar to the one described above, except that only two doses of this compound were tested at a single time interval (15 min). Data were therefore analyzed by the same statistical methods (two-way ANOVA with two repeated factors) except that the dose factor was studied here at only two levels. The summary of the behavioral results and of their analysis is presented in Fig. 3.

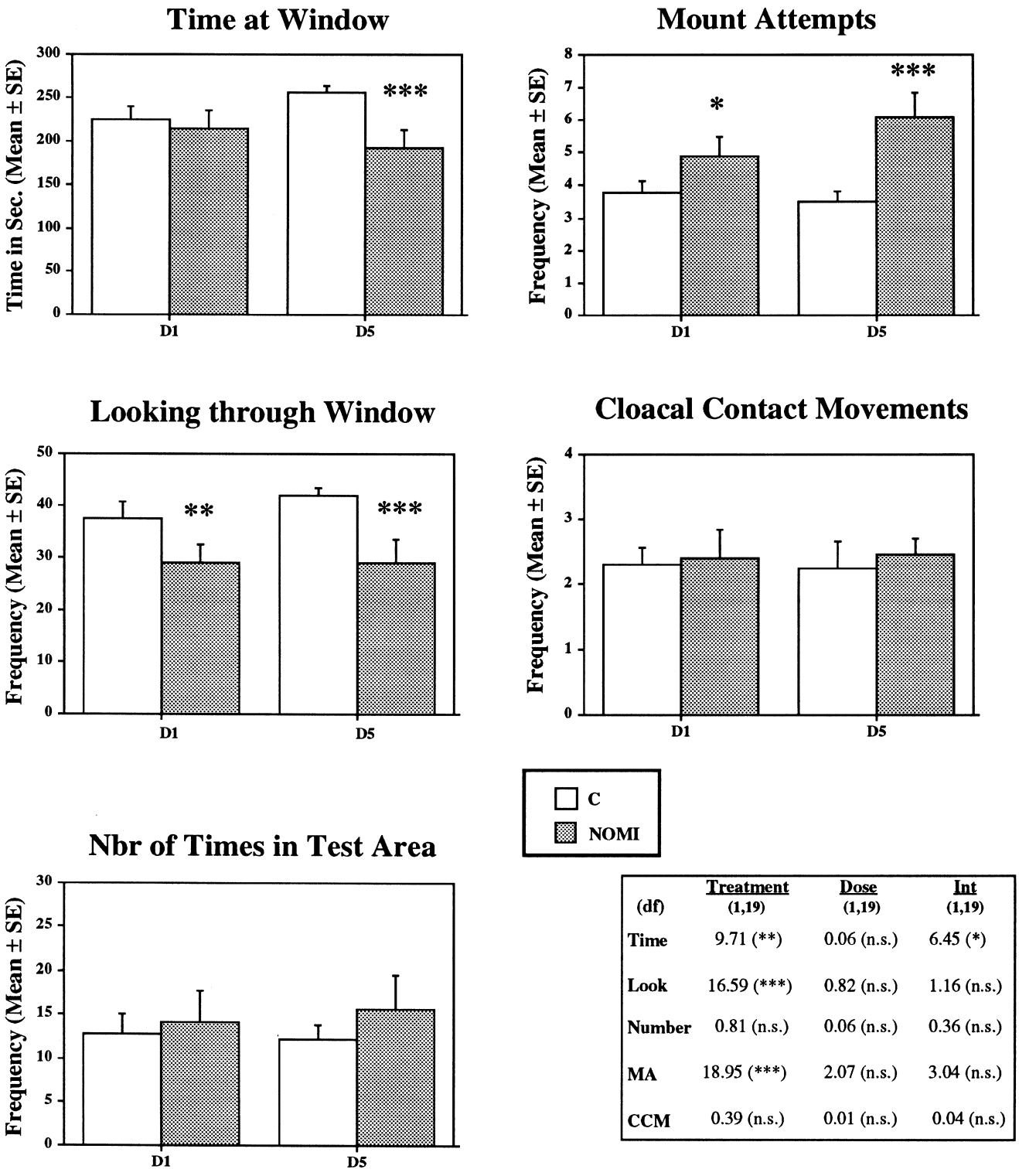
The increase of the general dopaminergic tone caused by nomifensine produced behavioral changes that were substantially different from those obtained by the injection of the receptor agonist, apomorphine. As was the case for APO, significant decreases in the two main measures of appetitive sexual behavior (time at the window and look through the window) were detected. This was reflected in significant overall treatment effects for both behaviors, significant interaction between treatment and dose (for time at the window only), and significant differences between the control and experimental situation at both doses of the compound for the frequency of looks, but only at the higher dose for the time spent in the test area. The number of times that birds entered the test area was not affected.

However, in contrast to APO, nomifensine increased the frequency of consummatory behaviors. This effect was minimal and far from significant for cloacal contact movements, but more pronounced and fully significant in the case of mount attempts (significant overall effect in the ANOVA and significant differences between the control and experimental situations at both doses). Nomifensine also differed from APO in that it did not activate pecking behavior. None of the subjects was observed to engage in stereotyped continuous



(df)	Treatment (1,15)	Dose (2,30)	Int (2,30)
Time	28.89 (***)	9.25 (***)	7.56 (**)
Look	22.63 (***)	6.46 (**)	14.67 (***)
Number	18.91 (***)	0.21 (n.s.)	1.90 (n.s.)
MA	0.42 (n.s.)	0.48 (n.s.)	3.01 (n.s.)
CCM	4.67(*)	0.49 (n.s.)	0.78 (n.s.)

FIG. 2. Effects of the general dopaminergic agonist, apomorphine (APO) on appetitive and consummatory aspects of male sexual behavior in castrated male quail treated with exogenous testosterone. Three doses of apomorphine, 0.1, 0.5, and 1 mg/kg (D 0.1, D 0.5, and D 1, respectively) were tested with an interval of 30 min between the injection and the beginning of the behavioral observations. See legend of Fig. 1 for additional explanations concerning statistical analyses. (*) = $p < 0.05$ by the post-hoc t-test after an ANOVA in which main effect was not fully significant (see text).



(df)	Treatment (1,19)	Dose (1,19)	Int (1,19)
Time	9.71 (**)	0.06 (n.s.)	6.45 (*)
Look	16.59 (***)	0.82 (n.s.)	1.16 (n.s.)
Number	0.81 (n.s.)	0.06 (n.s.)	0.36 (n.s.)
MA	18.95 (***)	2.07 (n.s.)	3.04 (n.s.)
CCM	0.39 (n.s.)	0.01 (n.s.)	0.04 (n.s.)

FIG. 3. Effects of the dopamine re-uptake inhibitor, nomifensine (NOMI) on appetitive and consummatory aspects of male sexual behavior in castrated male quail treated with exogenous testosterone. Two doses of nomifensine, 1 and 5mg/kg (D 1 and D 5, respectively) were tested with an interval of 15 min between the injection and the beginning of the behavioral observations. See legend of Fig. 1 for additional explanations concerning statistical analyses.

pecking after treatment with nomifensine. A few subjects (3 of 20) occasionally pecked at the floor during the phase of observation testing appetitive behavior after the injection of the lowest dose (1 mg), but a similar behavior was observed in the control situation (2 of 20 birds showing occasional pecks). Nomifensine also had no long-term effect on the behavior of the subjects, as indicated by the fact that behavioral measures obtained in the two control conditions associated with the low and high dose were not different when compared by *t*-tests for matched samples ($p > 0.10$ in each case), except for the time spent in the test area, which increased slightly but consistently from the first to the second series of measures ($t = 2.839$, df = 19, $p = 0.0105$).

Because effects of only one dose of amfonelic acid were tested, the behavioral data collected in this part of the experiment were analyzed directly by *t*-tests for matched samples. Data analyses and mean results are summarized in Fig. 4.

As can be seen immediately, the behavioral effects of this other indirect dopamine agonist were somewhat different from those observed previously. Increases were observed after administration of the drug in all behavioral measures that were collected to assess both appetitive and consummatory aspects of male sexual behavior. These increases were only statistically significant for the frequency of looks through the window and for the frequency of the two consummatory sexual behaviors, mount attempts and cloacal contact movements. Stereotyped pecking at the floor or walls of the cage was never observed during these tests. Two weeks after the injection of the amfonelic acid, many of the birds in this experiment appeared to be ill and the experiment was terminated. Because of their obvious discomfort, all the birds were euthanized. This toxicity appeared to be related to the solvent used for this drug, but this proved impossible to confirm because birds served as their own control and all subjects had therefore received the same injections. No sign of acute toxicity was detected, however, during behavioral observations. All other birds in the same animal facility were not affected.

DISCUSSION

Male sexual behavior in mammals is regulated by several different components of the dopaminergic system (15,29,33, 46). There is a complex relationship between the actions of these different dopamine systems and the receptor subtypes they activate to modulate male sexual behavior. Dopamine receptors have been divided into at least two major categories: the D1-like receptor subtype, and the D2-like receptor subtype (25). Both of these receptor subtypes are involved in the control of male sexual behavior (15,29,33). Rodent studies have led to the hypothesis that there is a low-threshold D2 mechanism that disinhibits genital reflexes and a high-threshold D2 mechanism that facilitates ejaculation, but inhibits copulation per se. Working in accord with these D2-mediated mechanisms is a hypothesized moderate-threshold D1 mechanism that facilitates penile erections and speeds copulation (29).

The applicability of this positive relationship between dopaminergic transmission and male sexual behavior to other vertebrate taxa is not well known. The investigation of other animal groups is not of interest for purely comparative reasons; it also offers the potential to dissociate the various effects that different dopamine systems have on male sexual behavior. For example, certain actions of dopamine in mammals appear to be related directly to the generation of penile erections, whereas other actions influence sexual motivation as controlled by the central nervous system (29). In other vertebrate taxa, such as most avian species, males have no intromittent organ, so one can investigate dopamine's central effects independent of its actions on peripheral structures. The present study investigated the relationship between dopaminergic activity and male sexual behavior in Japanese quail. Male sexual behavior was measured with the use of procedures developed previously that allowed for the quantification of both appetitive as well consummatory aspects of the masculine sexual behavior (12). Three compounds were administered peripherally that are known to enhance dopaminergic activity. These are: the nonselective dopamine receptor agonist, apomorphine; the dopamine re-uptake inhibitor, nomifensine; and the indirect agonist with a complex mechanism of action, amfonelic acid. This suite of compounds was chosen because, although they all enhance dopaminergic tone, they accomplish this via different physiological mechanisms. The different but related effects that these three compounds had on male sexual behavior provide insight concerning the relationship between dopamine and the regulation of male sexual behavior in quail.

As reported previously in a study of consummatory sexual behavior (1), we found that APO, in addition to inhibiting consummatory sexual behavior, also inhibits appetitive male sexual behavior in quail as measured with the use of the learned social proximity response. The effects of APO were tested at two different latencies after the administration of the compound, 15 min or 30 min. After 15 min, appetitive behavior was inhibited in a dose-dependent manner, and it was completely blocked at the highest dose tested. Consummatory behavior was also inhibited significantly by the two highest doses. When the drug was administered at a latency of 30 min, there were still significant inhibitory effects on appetitive male sexual behavior but not on consummatory behavior (except for a decrease in CCM frequency after injection of the highest dose). The re-uptake inhibitor nomifensine also inhibited appetitive male sexual behavior in a dose-dependent manner when tested at 15 min latencies, but, somewhat surprisingly, it enhanced the frequency of mount attempts, one measure of consummatory male sexual behavior. Amfonelic acid was only tested at a single dose, and was found to enhance both appetitive as well as consummatory aspects of masculine sexual behavior.

These somewhat inconsistent findings can be interpreted in light of the different mechanism of action of these compounds. Apomorphine is a receptor agonist that acts on both D1 and D2 receptors. At higher doses especially, it appears to bind preferentially with the D2 receptor subtype. Nominfensin enhances the action of dopamine in the synapse by blocking the uptake action of the dopamine transporter, whereas amfonelic acid appears to both promote the release of dopamine and possibly act directly on dopamine receptors. Therefore, compounds that promote the presence of dopamine in the synapse either through blocking re-uptake or enhancing release tend to simulate consummatory and, in some cases, appetitive aspects of male sexual behavior. These data suggest that dopamine release facilitates male sexual behavior in quail, as has been reported in mammals (15,29,33,46).

However, this facilitation may be receptor-subtype specific. In particular, it appears that the activation of D1-like receptors facilitates male sexual behavior in quail, but that the activation of the D2-like subtype inhibits this behavior. What evidence supports this hypothesis? First, it seems highly likely that the inhibitory effect of the higher doses of APO results from its binding with D2-like receptors. For example, there is evidence that birds have higher densities of the D2 relative to

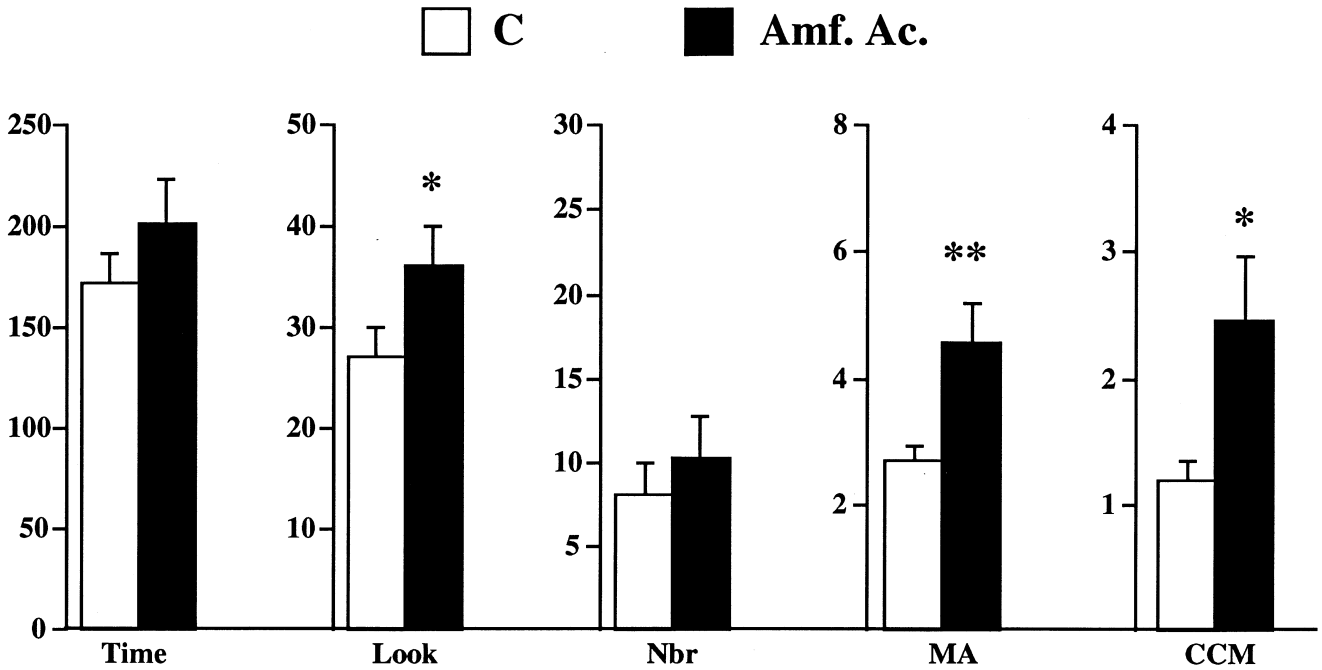


FIG. 4. Effects of the dopamine re-uptake inhibitor, amfonelic acid (Amf.Ac; 1 mg/kg tested 15 min after the injection) on appetitive and consummatory aspects of male sexual behavior in castrated male quail treated with exogenous testosterone. Data were analyzed by *t*-tests for matched samples and these results are indicated by asterisks at the top of the bars. $*p < 0.05$; $*p < 0.01$.

the D1 receptor subtype in the brain compared with mammalian species (38,39). Thus, administering high doses of APO to quail may lead to an activation of a relatively larger number of D2 receptors than is the case in mammals. Second, the stimulation of D2 receptors by subtype specific agonists is known to induce stereotyped pecking in quail (Balthazart J., Castagna C., and Ball G. F., unpublished data) and, in the present study, administering APO at high doses, but not at low doses, resulted in such stereotyped pecking. This suggests that, as one activates a D2-dependent behavior (stereotyped pecking), one also inhibits male sexual behavior. Third, we have shown previously that injection of the D2-antagonist, spiperone, enhances male copulatory behavior in quail and in this way counteracts the inhibitory effects of APO (1). Finally, preliminary tests with D2-specific receptor agonists, such as quinpirole (LY171555) or PPHT (N-0434), confirm that these compounds inhibit male sexual behavior (10). If this hypothesis is correct, then we would predict that amfonelic acid facilitates dopamine release and/or acts as a receptor agonist in such a way that D1-like receptors are activated preferentially, whereas nomifensin inhibits dopamine re-uptake so that there is an activation of both the D1 and D2 receptor subtypes.

The high rate of stereotypical pecking observed in the APO group requires that the hypothesis be considered that the effects of APO on male sexual behavior may be nonspecific. If high rates of stereotypic behavior are observed, it is possible that other behaviors such as sex are not observed merely because the birds are induced to spend so much time engaging in the stereotypies that there is no time left for other activities. In other words, a simple time competition between pecking and sexual behavior could explain the behavioral inhibition. However, this appears to be unlikely because, at the lowest doses tested, APO inhibits sexual behavior and does not stimulate stereotyped pecking. Furthermore, the number of birds that pecked during the testing of consummatory behavior was almost as high as during the testing of appetitive behavior, especially at certain doses (e.g., 0.5 mg) and no significant inhibition of MA and CCM was detected (see, especially, data at the 30-min time interval). Therefore, even in the presence of high rates of stereotypic behavior, the birds can engage in certain components of sexual behavior. However, it cannot be completely precluded that there is some interaction between the effects of APO on the induction of stereotypic pecking and the inhibition of appetitive sexual behavior so that the stimulation of pecking would contribute to this inhibition of appetitive sexual behavior. Curiously, although both nomifensin and amfonelic acid are known to induce stereotypies in rodents [e.g., (35,36,45)], no such behavior was observed in quail in the present study. Overall, it appears that the inhibition of sexual behavior by APO cannot be attributed only to the activation by the drug of a stereotyped behavior competing for the general time-budget of the subjects. It is also possible that other nonspecific effects occurred (e.g., inhibition of locomotor activity), although this does not appear likely based on the qualitative observation of the birds during the behavioral testing sessions. It should also be mentioned that a substantial amount of data collected mostly in mammals (see Introduction) indicates that dopaminergic transmission plays a specific role in the activation of male sexual behavior, and the effects of APO described here are in general agreement with this argument.

Another interesting feature of the data presented in this study is that there were differential effects of the compounds in some cases on the appetitive behavioral measures of male sexual behavior compared with the consummatory behavioral measures. This was apparent in the APO experiment, where it was observed that both appetitive and consummatory sexual behavior was inhibited when behavior was tested with a 15-

min delay after the administration of APO, but, after a 30-min latency, only appetitive behavioral measures were inhibited. Similarly, nomifensin inhibited appetitive behavioral measures, but facilitated consummatory measures. These data suggest that these two aspects of male sexual behavior are controlled by different brain areas and/or dopaminergic mechanisms in the same area. This is consistent with studies on mammalian species that have argued that, although dopamine facilitates both appetitive and consummatory male sexual behavior, this may be mediated by different dopamine systems [e.g., (23)]. Further study will be required to identify the reasons for the differential effects of these compounds, but one possibility is that appetitive sexual behavior, as compared with consummatory sexual behavior, is more sensitive to the inhibitory effects of D2 receptor activation than to the stimulatory effects of D1 receptors. Preliminary data with D2-specific agonists are consistent with this idea. One needs to be cautious, however, when trying to separate differential effects of these dopaminergic compounds on appetitive vs. consummatory sexual behavior. For example, an increase in the frequency of mount attempts, as we observed in Experiment 2, could mean that there is an increase in sexual motivation. Alternatively, males could have a higher number of mount attempts because the drugs have harmed the males motor coordination abilities and they can no longer mount the females efficiently for physical reasons, requiring them to engage in more MA to attain a single CCM. Similar problems have been identified in rodent studies (29). Measures of appetitive behavior are also subject to difficulties of interpretation. For example, APO was found, in the present experiments, to decrease the number of times a male would enter the test area in front of the window providing a view of the female. Such a decrease in the movements around the test arena, especially those that include entering and leaving the area in front of the window that provides a view of the female, may be indicative of an diminished sexual motivation, i.e., a lowered motivation to seek out the female (a focused search) or a more general sexual search. Variation in such searching has been described in classical conditioning studies of sexual behavior in quail, where it was found that increases in the interval between a neutral conditional stimulus and an unconditional stimulus that consists of access to the female are associated with increases in general sexual search behavior (5,20). Alternatively, the decreases in movement observed here may result from nonspecific effects of the compound on activity levels in general. For this reason, it is important to observe consistent differences among several different measures of consummatory or appetitive sexual behavior before concluding that this behavioral system is affected by a particular compound.

In summary, the data presented here suggest that, as in mammals, stimulation of dopaminergic transmission enhances appetitive as well as consummatory aspects of male sexual behavior. However, this stimulation may be specific to dopamine acting via D1-like receptors rather than D2-like receptors. The pharmacological properties of dopamine receptors have been characterized partially in quail and they appear to exhibit a pattern similar to that described in mammals (8). Therefore, compounds that have been well characterized to act selectively at D1 or D2 receptors in mammals can be tested in quail. The dissociation between the effects of dopamine on appetitive compared with consummatory aspects of male sexual behavior will be explored further by intracranial injections targeting different dopamine systems of these subtype specific compounds.

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