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Separate and Combined Effects of Dopamine D_1 and D_2 Receptor Agonists on Key Pecking in the Developing Chick

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DOSE, J. M. AND J. F. ZOLMAN. *Separate and combined effects of dopamine D_1 and D_2 receptor agonists on key pecking in the developing chick.* PHARMACOL BIOCHEM BEHAV **49**(1) 73-78, 1994.—The separate and combined effects of dopamine D_1 and D_2 agonists on key-peck responding of young chicks for heat reinforcement were determined. In the first experiment, 1- and 4-day-old chicks (n = 96) were injected SC with either distilled water or 5 mg/kg reserpine 18 h before testing. Twenty minutes before a 24-trial autoshaping session, chicks were injected IP with either distilled water or 10 mg/kg SKF 38393 and 2 mg/kg quinpirole. Chicks receiving both dopamine agonists had enhanced key-peck responding in both pretreatment conditions. In Experiment 2, 1- and 4-day-old chicks (n = 192) of two strains received 5 mg/kg reserpine SC 18 h before testing. Twenty minutes before their autoshaping session these chicks were injected IP with either distilled water, 10 mg/kg SKF 38393, 2 mg/kg quinpirole, or 10 mg/kg SKF 38393 and 2 mg/kg quinpirole. After reserpine pretreatment, chicks of both strains responded on more trials when given both dopamine agonists compared with controls given either distilled water or single agonist treatment. No age or strain differences in key pecking were produced by the combined administration of these dopamine agonists. Therefore, functional coupling of the dopamine $D_1$and D_2 receptors is found within 1 day after hatching in the domestic chick.

D_1, D_2 Receptors Dopamine Quinpirole SKF 38393 Reserpine Chick

THE dopamine superfamily of receptors includes five distinct receptor subtypes (30). The first two receptors in this family to be characterized and extensively studied both biochemically and behaviorally were the dopamine D_1 and D_2 receptors (1,2,17). At present, the dopamine D_1 and D_2 receptors seem to be functionally coupled in adults of most rodent species. The most widely accepted model of D_1 and D_2 interaction is that D_1 receptors are permissive and provide the necessary background tone for the induction of D_2-mediated behaviors (4,6,15,16,19,20,31). For example, stimulation of both receptor subtypes with the mixed dopamine agonist apomorphine elicits stereotypic behaviors in the adult rat (6,29). In contrast, partial D_1 agonists (e.g., SKF 38393) induce a dose-dependent increase in grooming and oral movements yet fail to induce stereotypy (1,11); whereas, D_2 agonists (e.g., quinpirole) produce low intensity stereotypy (1,2) as well as an increase in motility and a decrease in grooming (11). When these D_1 and D_2 agonists are given concurrently they produce intense stereotypic behavior and hyperactivity (1,2,6), an outcome that mimics the behavioral responses produced by apomorphine.

A similar model of dopamine receptor coupling in the altricial rat pup appears to be emerging from recent ontogenetic studies [for reviews see (22-24,26,27)]. In the rat pup, distinct ontogenetic differences do exist in the behavioral response profile induced by separate and combined administration of the D_1 agonist SKF 38393 and the D_2 agonist quinpirole (26). However, D_1 and D_2 receptor subtypes appear to be functionally coupled throughout the neonatal to weanling age period (24,27). For example, D_1 receptor activation is necessary for the expression of D_2-mediated behaviors in 11- and 17-day-old pups (22). In addition, coadministration of SKF 38393 and quinpirole produces several synergistic responses in 3-, 10- and 21-day-old pups, but only the 21-day-old pups show adult-like stereotypic oral movements during simultaneous receptor

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stimulation (26). Acute depletion of endogenous catecholamines using alpha-methyl-*p*-tyrosine (AMPT) and reserpine in 10- and 21-day-old pups produces an attenuation of SKF 38393- and quinpirole-induced behaviors found in normal animals; whereas, the combined administration of both dopamine agonists in similarly depleted pups reinstates some behaviors of the younger but not of the older pups (27). Although a complete adult-like functional coupling of D_1 and D_2 receptors is not found immediately after birth in normal pups and dopamine-depleted pups given agonist challenge do not show identical response patterns as adult rats (26,27), a synergism between D_1 and D_2 receptors is found in both young and adult rats (24).

Although brain D_1 and D_2 receptors seem to be functionally coupled in young and old rats, interactions between these receptor subtypes appear to be different in both adult guinea pigs (7) and normal common marmosets (21). Guinea pigs show responses to D_2 stimulation similar to those shown by altricial rats and mice, but do not respond in the same way as other rodent species to D_1 stimulation and blockade or to combinations of D_1 and D_2 agonists (7). In normal common marmosets, SKF 38393 does not produce increased motor activity, and D_1 receptor activation has no facilitating effect on D_2-mediated behaviors (21). Consequently, the synergistic effects of combinations of D_1 and D_2 agonists and, perhaps, the ontogeny of D_1 and D_2 receptor coupling may be species related. The chick, like the guinea pig, is precocial and provides another vertebrate model to evaluate species' similarities and differences in the ontogeny of functional D_1 and D_2 receptor coupling.

Apomorphine, given to young chicks, produces both intense, spontaneous (nondirected) pecking (12,32) and an increase in key pecking (25). Zarrindast and Amin (1992) have proposed that dopamine D_1 receptor stimulation is also necessary for the expression of D_2 induced pecking in 7-day and older chicks [also see (14)]. The functional involvement of D_1 and D_2 receptors in the pecking of younger chicks has not been determined. However, both nonselective and selective D_2 antagonists produce age-dependent responding between 4-day and younger chicks (35). In both an appetitive task requiring key pecks for heat reward and an aversive task in which key pecks for heat were punished, haloperidol (nonselective antagonist) depressed the responding of 4-day-old chicks yet enhanced the responding of 1-day-old chicks. Similarly, sulpiride (D_2 antagonist) enhanced punished key-peck responding in 1-day-old chicks, but not in 4-day-old chicks (35). Therefore, in the present study the separate and combined effects of SKF 38393 and quinpirole on the key-peck responding of 1- and 4-day-old chicks for heat reward were evaluated to determine if D_1 and D_2 receptors are functionally coupled at both ages.

EXPERIMENT 1: COMBINED EFFECTS OF DOPAMINE D_1 AND D_2 AGONISTS IN NORMAL AND RESERPINE-PRETREATED CHICKS

Method

Subjects and rearing procedures. Ninety-six Brown eggs (DEKALB-Warren Sex-Sal-Link, 1987) from the University of Kentucky poultry farm were incubated in a Petersime automatic incubator (Model 5) at 37–38°C and 68–70% relative humidity. Two days before hatching, the eggs were transferred to a dark hatching Petersime incubator. Chicks were removed from the hatching incubator within 4 h after hatching and reared socially in groups of 25–30 in white Plexiglas brooder compartments (56 × 33 × 23 cm) in a temperature-controlled room set at 35°C. Food and water were available ad lib until 15 h before testing, at which time food was removed. Brooder compartments were illuminated with fluorescent light from 0600 h until 2300 h. Early and late hatching chicks were not used, and all hatches were split so that chicks from the same hatch were represented equally in the 1-day and 4-day treatment conditions. Chicks were tested at posthatch day 1 (18–24 h) or posthatch day 4 (90–102 h).

Apparatus. Behavioral testing was performed in four conditioning chambers designed for testing young chicks with heat reinforcement [see (36)]. Each box was housed individually in a Forma Scientific incubator (Model 3665) in which the ambient temperature was set at 11°C (± 2°C). Another Forma Scientific incubator with an auxiliary 2,000-W heater was set at 37°C, and plastic ductwork connected each cold incubator with this heat source. Heat onset in each chamber was controlled by solenoids that when activated displaced two circular butterfly valves. One valve instantaneously diverted the warm 37°C air up through the conditioning chamber, whereas the other valve opened to replace in the airflow system the same amount of air that was diverted. A 28-V light bulb (GE 1820) located under each conditioning chamber was turned on so that the reinforcement consisted of both heat and light onset. A white masking noise of 76 dB(re 20 $\mu N/m^2$) was delivered through a 10-cm speaker on the back wall of each conditioning incubator and generated by a Grason-Stadler white noise generator (Model 901B).

The response keys were BRS/LVE Model PPK-002 and IEE 12 unit in-line projectors were used to present stimuli on the transparent keys. The stimulus–reinforcement contingencies were programmed and controlled by a BRS/LVE Interact computer control system, and response trials and response latencies were recorded.

Procedure. The chicks were removed from their home brooder 1 h before training, weighed, banded, and isolated in white Plexiglas cylinders (20 × 15 cm). Chicks were given one autoshaping session of 24 discrete trials. The autoshaping procedure used to train the chicks (8) to peck an illuminated key (a white 3.2 × 2.2 cm bar presented vertically on a red background) was: (a) key light onset for 16 s; (b) key light offset with 8-s reinforcement (37°C air and light); (c) 5-s intertrial interval (ITI) with house light on; (d) key light onset, and so forth. If a chick pecked the key at any time during the 16-s stimulus duration, reinforcement was given immediately and a new trial began after the 5-s ITI. The chicks were given a "free" reinforcer while being placed in the test chamber.

Experimental groups. All drug doses used in the present studies were derived from preliminary studies (13) and are similar to the doses used in previous reports (32). Eighteen hours before the autoshaping session, one-half of the chicks were injected subcutaneously (SC) in a skin fold along the ventral side of the rib cage with distilled water, and the rest of the chicks were injected SC with 5 mg/kg reserpine (10 ml/kg). Reserpine-treated chicks were placed in a separate brooder compartment to isolate them from nonreserpinized chicks during the 18-h pretreatment interval. Twenty minutes before the autoshaping session: (a) one-half of the chicks pretreated with distilled water were injected intraperitoneally (IP) with distilled water (DW/DW), and the rest of the chicks were injected IP with 10 mg/kg SKF 38393 and 2 mg/kg quinpirole (DW/CO), and (b) one-half of the chicks from the reserpine-pretreated group were injected IP with distilled water (RS/DW), and the rest of the chicks were injected IP with 10 mg/kg SKF 38393 and 2 mg/kg quinpirole (RS/CO). Hence, for each age chicks were randomly assigned to the four treatment

groups. All drugs were adjusted in volume equal to 1% of body weight (10 ml/kg) and obtained from Research Biochemicals Incorporated (Natick, MA).

A three-factor analysis of variance (ANOVA) was used to determine statistical significance levels for both response latencies and percentage of trials on which the chicks responded (response trials). These ANOVAs were supplemented, when appropriate, by Bonferroni t-tests, and simple effects analyses were performed on any significant interaction (33). Because latency and response trial data led to similar conclusions, only the analysis of percentage of response trials is presented.

Results

The mean percentages of response trials during the autoshaping session for the 1- and 4-day-olds are presented in Fig. 1. Chicks given both SKF 38393 and quinpirole responded on significantly more trials compared with control chicks given distilled water [drug effect, $F(1, 88) = 38.72$, $p < 0.001$]. In both pretreatment conditions the codrug chicks responded on more trials than controls. Reserpine pretreatment tended to produce a greater difference in responding between the codrug and control chicks, although this effect was not statistically significant [drug × pretreatment interaction, $F(1, 88) = 3.20$, $p < 0.08$]. The main effects of age and pretreatment and the age × drug, age × pretreatment, and age × drug × pretreatment interactions were not significant.

These data clearly show that the coadministration of relatively specific D_1 and D_2 agonists significantly increases key pecking in both 1- and 4-day-old chicks. However, in this first experiment appropriate controls were not included to assess the effects of either SKF 38393 or quinpirole alone on the chicks' key pecking. At some doses, quinpirole itself produces slightly enhanced key-peck responding in both reserpine-pretreated and normal chicks [see (14)]. Hence, the enhanced key-peck responding in this first experiment may have been caused solely by the D_2 agonist quinpirole.

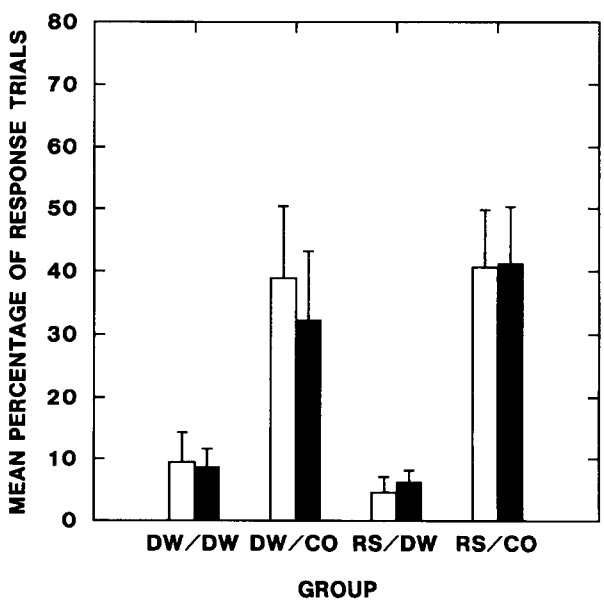

FIG. 1. Mean percentage of key-peck responses (±SEM) for 1- and 4-day-old Brown chicks during a 24-trial autoshape session. Chicks of each age were pretreated with either distilled water (DW) or 5 mg/kg reserpine (RS) 18 h before testing and then injected 20 min before testing with either DW or 10 mg/kg SKF 38393 and 2 mg/kg quinpirole (CO). One-day-old chicks, open bars; 4-day-old chicks, black bars.

EXPERIMENT 2: SEPARATE AND COMBINED EFFECTS OF DOPAMINE D_1 AND D_2 AGONISTS IN RESERPINE-PRETREATED CHICKS OF TWO STRAINS

This experiment assessed key-peck responding in 1- and 4-day-old chicks injected with either SKF 38393 or quinpirole alone or both agonists together. Because there was a trend for reserpine treatment to increase key pecking compared with distilled water pretreatment (Fig. 1), all chicks were reserpinized before their appropriate agonist treatment. Chicks given both D_1 and D_2 agonists were expected to show a marked increase in key pecking when compared to all other groups. Also, 1- and 4-day-old chicks were expected to show similar drug effects (see Experiment 1). In addition, quinpirole-injected chicks were expected to have enhanced key-pecking when compared with chicks in the distilled water and SKF 38393 groups. To evaluate the generality of any drug and age effects, two strains of domestic chicks were tested.

Method

Subjects and rearing procedures. Ninety-six DEKALB-Warren Sex-Sal-Linked Brown eggs and 96 DEKALB XL White Leghorn eggs were incubated, chicks hatched, and reared under the same conditions as those described for Experiment 1. These strains of chicks were both bred for egg production: the Brown chicks are calm, easy to handle, and have a relatively slow metabolism and low energy maintenance requirement; whereas, the White Leghorns are smaller, aggressive, react to handling, and have a high activity level and a high metabolic rate (28).

Procedure and experimental groups. The apparatus and behavioral procedures were the same as those in Experiment 1. Eighteen hours before the autoshaping session, 1- and 4-day-old chicks were injected SC with 5 mg/kg reserpine. Chicks from each age were then injected IP 20 min before testing with either distilled water, 10 mg/kg SKF 38393, 2 mg/kg quinpirole, or both 10 mg/kg SKF 38393 and 2 mg/kg quinpirole.

Results

White leghorns. Because chicks of the two strains were not tested in a counterbalanced order, separate ANOVAs were performed for each strain. The mean percentages of response trials during the autoshaping session for the 1- and 4-day-old Leghorns are presented in Fig. 2. Chicks given both SKF 38393 and quinpirole responded on more trials than chicks receiving distilled water or single drug injections [drug effect, $F(3, 88) = 11.04$, $p < 0.001$, and Bonferroni tests, $p < 0.05$]. Chicks injected with either distilled water, SKF 38393, or quinpirole did not significantly differ from each other. The main effect of age and the age × drug interaction were not significant.

Brown chicks. The mean percentages of response trials during the autoshaping session for the 1- and 4-day-old Brown chicks are presented in Fig. 3. The codrug chicks responded on significantly more trials than chicks in all of the other groups [drug effect, $F(3, 88) = 33.98$, $p < 0.001$, and Bonferroni tests, $p < 0.001$]. Moreover, the quinpirole-treated chicks responded on more trials than chicks in the control and SKF 38393 groups (Bonferroni tests, $p < 0.002$ and $p <$

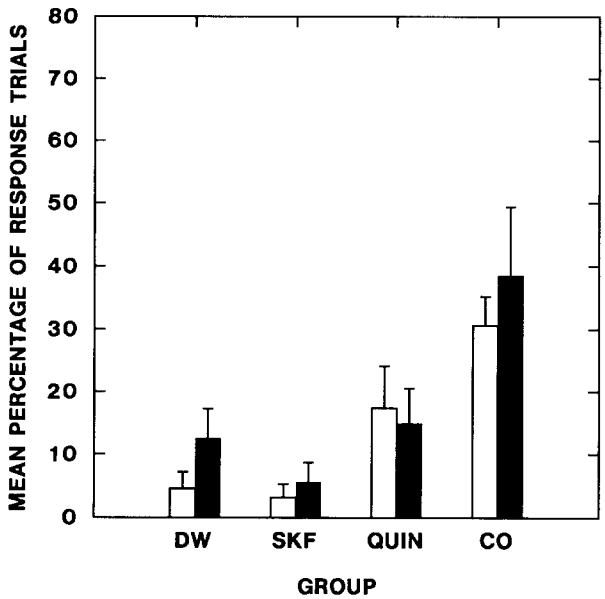

FIG. 2. Mean percentage of key-peck responses (±SEM) during a 24-trial autoshape session for 1- and 4-day-old White Leghorns pretreated with 5 mg/kg reserpine 18 h before testing. Chicks were then injected 20 min before testing with either distilled water (DW), 10 mg/kg SKF 38393 (SKF), 2 mg/kg quinpirole (QUIN), or 10 mg/kg SKF 38393 and 2 mg/kg quinpirole (CO). One-day-old chicks, open bars; 4-day-old chicks, black bars.

0.001, respectively). The control chicks and the SKF 38393-treated chicks did not significantly differ from each other. The main effect of age and the age × group interaction were not significant.

In summary, chicks of both strains given both dopamine agonists (SKF 38393 and quinpirole) made significantly more key-peck responses than chicks given either distilled water, SKF 38393, or quinpirole alone. In addition, the Brown chicks treated with quinpirole responded on significantly more trials than chicks treated with either distilled water or SKF 38393. The White Leghorns responded in a similar way to quinpirole as the Brown chicks, but did not make significantly more responses than controls (see Fig. 2). No significant age effects were observed as 1- and 4-day-old chicks of both strains responded similarly to the dopamine agonists.

GENERAL DISCUSSION

Coadministration of the dopamine D_1 agonist SKF 38393 and the D_2 agonist quinpirole produces an increase in key-peck responding for heat reinforcement in young chicks when compared with controls given distilled water or either agonist alone. This coupling of D_1 and D_2 receptors was found in both 1- and 4-day-old chicks, indicating that receptor interactions are functional within at least 24 h after hatching. In addition, chicks of two strains showed this drug-induced increase in pecking suggesting that early functional coupling of D_1 and D_2 receptors for pecking may occur in other precocial birds. These ontogenetic findings on the separate and combined effects of dopamine D_1 and D_2 receptor agonists on the young chick's key pecking are consistent with the early functional coupling found in altricial rat pups (22–24,26,27).

Zarrindast and Amin (1992) have proposed that pecking in 7-day and older chicks is a D_2-mediated behavior that requires D_1 receptor activation (i.e., D_1 receptor tone). The enhanced responding to quinpirole of reserpinized 1- and 4-day-old chicks of the Brown strain compared with their distilled water controls (Fig. 3) was probably caused by residual brain dopamine. Sufficient endogenous brain dopamine would affect both D_1 and D_2 receptors, and D_1 stimulation would enable the D_2 agonist quinpirole to increase the Brown chicks' key pecking. Similar enhanced responding was found for quinpirole-injected White Leghorns compared with their controls, but this increase in key pecking was not significant (Fig. 2).

Different strains of chickens have been genetically selected for domestic purposes and, therefore, possess different physiological and behavioral characteristics (34). As examples, Brown chicks are calm, easy to handle, and have a lower metabolism when compared with the White Leghorns (28). Dramatic strain differences in catecholamine concentrations in specific brain regions are also found in newly hatched chicks (3,18). Presumably, endogenous brain dopamine levels after reserpine pretreatment were different in the Brown chicks and White Leghorns. Similar to the findings with reserpinized Brown chicks (Experiment 2), reserpine pretreatment and subsequent quinpirole treatment in 7-day and older chicks produce substantial increases in pecking (32). When these older chicks were pretreated with both reserpine and AMPT (a combination that depletes dopamine stores and inhibits dopamine synthesis producing more substantial dopamine depletion), their quinpirole-induced pecking was significantly reduced. Therefore, reserpine pretreatment alone in the Brown chicks (Experiment 2) probably was not sufficient to prevent D_1 receptor activation. Dopamine D_1 receptor stimulation by SKF 38393 had no effect on key pecking in the young chick

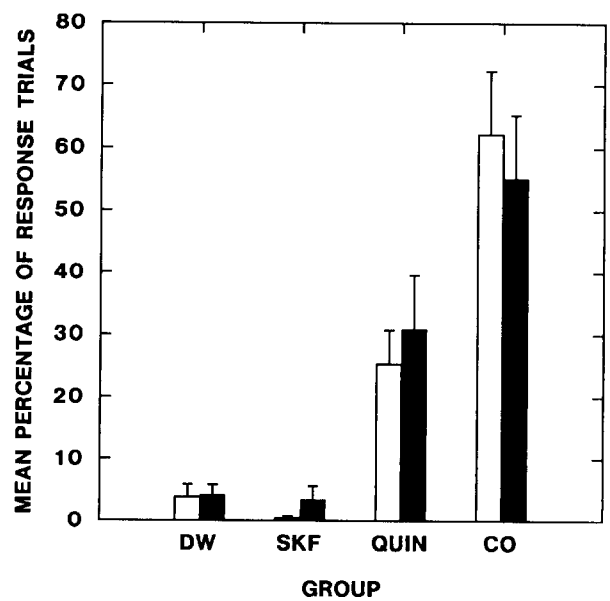

FIG. 3. Mean percentage of key-peck responses (±SEM) during a 24-trial autoshape session for 1- and 4-day-old Brown chicks pretreated with 5 mg/kg reserpine 18 h before testing. Chicks were then injected 20 min before testing with either distilled water (DW), 10 mg/kg SKF 38393 (SKF), 2 mg/kg quinpirole (QUIN), or 10 mg/kg SKF 38393 and 2 mg/kg quinpirole (CO). One-day-old chicks, open bars; 4-day-old chicks, black bars.

(Figs. 2 and 3). Other doses of this D_1 agonist do not increase key pecking (13). Apparently, D_1 receptor stimulation, although necessary for the expression of D_2-induced pecking in the chick, has no effect by itself.

Age-dependent key-peck responding was not produced by either SKF 38393 or quinpirole alone or by these D_1 and D_2 agonists together. In contrast to these agonist findings, both nonselective and selective D_2 antagonists produce age-dependent responding in 1- and 4-day-old chicks (35). Why dopamine antagonists, but not agonists, produce age-dependent responding in the young chick is not known. Most of the antagonist effects were found when learned key pecks were punished, whereas, the effects of agonists were found during key-peck acquisition (Experiments 1 and 2). Punishment of key pecks in newly hatched chicks would produce more nonspecific arousal than would key-peck acquisition. Haloperidol did produce age differences in acquisition of key pecking; however, a long intertrial interval averaging 60 s was used in this study which would increase cold stress, and thereby increase arousal of younger chicks (35). Apparently, the arousal/motivational levels of chicks are important for understanding the effects of dopamine agonists and antagonists on key-peck conditioning. This assumption receives support from experiments using weakly reinforced learning and ACTH1-24 in young chicks (9,10). In conclusion, these results with young chicks are consistent with the hypothesis that in many vertebrate species D_1 receptors are permissive and provide the necessary background tone for the induction of D_2-mediated behaviors.

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