Pharmacology Biochemistry & Behavior, Vol. 14, pp. 669–676, 1981. Printed in the U.S.A.

The Effect of Para-Chlorophenylalanine and Scopolamine on Passive Avoidance in Chicks[1]

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Received 8 August 1980

MATTINGLY, B. A. AND J. F. ZOLMAN. *The effect of para-chlorophenylalanine and scopolamine on passive avoidance in chicks.* PHARMAC. BIOCHEM. BEHAV. **14**(5) 669–676, 1981.—Four-day-old Vantress × Arbor Acre chicks were tested for key-peck passive avoidance (PA) learning following intraperitoneal injections of para-chlorophenylalanine (PCPA) and/or scopolamine. In Experiment 1, chicks were pre-treated with either three or five injections of PCPA (150 mg/kg) or saline across the first three posthatch days and then tested for PA learning on the fourth posthatch day. In Experiment 2, chicks were first pre-treated with three injections of PCPA (150 mg/kg) or saline, and then injected with either scopolamine (0.5 mg/kg) or saline 20 min prior to PA testing on the fourth posthatch day. Major findings were: (a) Chicks pre-treated with PCPA did not significantly differ from saline control chicks in either the acquisition or maintenance of response suppression during PA testing; (b) chicks injected with scopolamine were significantly disrupted in PA learning as compared to saline control chicks; and (c) PCPA pre-treatment did not significantly affect the scopolamine-induced disruption of PA learning. These findings, therefore, suggest that cholinergic, but not serotonergic, mechanisms are involved in PA learning of the young chick.

Chick Passive avoidance Response suppression Punishment Para-chlorophenylalanine Scopolamine Cholinergic Serotonergic

IN MAMMALIAN species, both cholinergic and serotonergic neurochemical systems have been implicated in the modulation of response suppression [1, 7, 10, 15, 17]. Typically, rats administered drugs which interfere with either cholinergic or serotonergic activity are deficient in behavioral tests, such as passive avoidance (PA) learning and extinction, which require the withholding of a prepotent response for optimal performance [2,15].

Cholinergic mechanisms also appear to be involved in the response suppression of precocial birds, as scopolamine-injected chicks are more active in an open-field, are more resistant to extinction after key-peck conditioning, and are disrupted in key-peck PA learning when compared to saline-injected control chicks [21]. Similarly, atropine-injected chicks are also disrupted in PA learning [11], and their spontaneous alternation performance is significantly below that of saline-injected control chicks [5]. These drug-induced behavioral changes in chicks are, of course, similar to the reported effects of cholinergic antagonists in rats [2], and suggest that for the precocial chick, like the altricial rat, cholinergic mechanisms may modulate response suppression.

Although serotonergic mechanisms appear to be involved in the chick's response suppression in tonic immobility tests [18], serotonergic involvement in the chicks' behavior in other response suppression tests, such as PA learning, is not known. The purpose of the present study, therefore, was to determine first whether a drug-induced interference with serotonergic functioning would retard PA learning of the young chick, and then to determine what effect the simultaneous disruption of cholinergic and serotonergic functioning would have on PA learning of the young chick.

EXPERIMENT 1

Rats pre-treated with para-chlorophenylalanine (PCPA), a compound that depletes brain serotonin [9], have been reported to be disrupted on many different PA learning tests [8, 13, 15, 16, 20]. In adult rats, 3 injections of 100 mg/kg PCPA over a 3-day period produces over a 80% decrease in brain serotonin levels [9]. Similarly, 5 injections of 150 mg/kg PCPA over a 3-day period have been reported to produce a 70% decrease in brain serotonin levels of the 5-day-old chick [14]. The purpose of Experiment 1, therefore, was to determine whether chicks pretreated with PCPA would be retarded in key-peck PA learning. Chicks were given either 3 or 5 injections of PCPA (150 mg/kg) over the first 3 posthatch

[1]This research was supported by Grant MH 24260 from the National Institute of Mental Health and by NIMH predoctoral fellowship 1 F3-MH07306 to B. A. Mattingly. We are grateful to J. E. Spivey and T. R. Zentall for their helpful comments on this manuscript.

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days, and then on the fourth posthatch day their PA performance was compared to that of saline-injected controls.

METHOD

Subjects and Rearing Procedure

Thirty-nine Vantress × Arbor Acre chicks were incubated and hatched at 37–38°C and 58–60% relative humidity. The chicks were removed from the dark hatching incubator within 4 hr after hatching, banded, and then reared socially in groups of 20–25 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 hr prior to testing at which time food was removed. The brooder room was illuminated with fluorescent light from 6 a.m. until 11 p.m.

Apparatus

Behavioral testing was performed in four conditioning chambers designed for testing young chicks using heat reinforcement [22]. Each chamber was housed individually in a Forma Scientific incubator (Model 3665) in which the ambient temperature was set at 10°C (±1°C). Another Forma Scientific incubator with an auxiliary 2000 W heater was set at 35°C and plastic tubing (20 and 10 cm) connected each cold incubator with this heat source. A push-pull fan arrangement (2 fans, each 500 cfm) in the heat incubator was used to maintain a balanced flow of warm air to each conditioning incubator. The temperature of the air under each conditioning chamber was maintained at 35°C and was monitored continuously by a Yellow Springs air thermometer (Model 502) connected to a Yellow Springs telethermometer. The ambient temperature on the wire floor of each chamber was maintained at 10°C and was monitored continuously. Heat onset in each chamber was controlled by two separate Ledex rotary solenoids that when activated displaced two 10 cm diameter circular butterfly valves. One valve instantaneously diverted the warm 35°C air up through the conditioning chamber whereas the other valve opened to replace in the air flow system the same amount of warm air diverted. Consequently, air flow in this system was balanced so that reinforcement delivered in any of the conditioning chambers did not affect the flow of warm air to the other chambers. A 28 V light bulb (GE 1820) located under each conditioning chamber was also turned on so that reinforcement consisted of both heat and light onset. A small Rotron whisper fan (65 cfm) located 25 cm above the open top of the conditioning chamber was turned on immediately following reinforcement and remained on during the intertrial interval. This fan dispersed any residual heat remaining in the conditioning chamber after reinforcement. 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 was generated by a Grason-Stadler white noise generator (Model 901B).

A constant current shock was supplied to each chamber by a Grass Stimulator (Model S48) connected to a Grass Stimulus Isolation unit (Model PSIU6). Shock was delivered to each chick through 12 mm Wachenfeldt nickel silver wound clips attached to the wing web near the elbow of each wing. A 10 mm female Amphenol contact was attached to each wound clip. In each conditioning box, a pair of male Amphenol contacts, connected to 25 gauge insulated wires, completed the shock circuit when mated to the female contacts. A small rubber band suspended above each conditioning chamber removed excess slack from the wires, thereby allowing the chick unrestricted movement in the small conditioning chamber.

The response keys (sensitive to less than 8 g of force) were mounted directly on IEE 12-unit inline projectors that were used to present the stimuli on the transparent keys. Two stimuli were used; one stimulus was a white bar (32×22 mm) presented vertically on a red background and the other stimulus was the same bar presented horizontally on the red background. The stimulus-reinforcement contingencies were programmed and controlled by a BRS/LVE Interact Computer Control System and response latencies in 0.1 sec were recorded on the papertape output of an ASR-33 teletype.

Procedure

All chicks were first given two autoshape sessions when 1 day old (21.8 hr; SD=2.3) and then two additional autoshape sessions followed by four PA sessions when 4 days old (97.3 hr; SD=2.5). All sessions consisted of 24 discrete trials and the intersession interval was about 20 min. The chicks were removed from their home brooder 1 hr before training and isolated in white Plexiglas cylinders (20×15 cm) to acclimate the chicks to social isolation prior to training. After each training session, the chicks were returned to their isolation cylinders to minimize experience with interfering stimuli.

The autoshaping procedure used was similar to that described by Brown and Jenkins [6] and consisted of an equal number of presentations of each of the two test stimuli in a semi-random sequence, with the restriction that each test stimulus be presented on no more than 2 trials within each 4 trial block. Two different stimuli were used during autoshaping to facilitate key-pecking of the young chick. The autoshaping sequence of events was: (a) key light onset; (b) 16-sec stimulus duration; (c) key light offset with 8-sec reinforcement (35°C air and light); (d) 5-sec intertrial interval (ITI) with house light on; (e) key light onset, etc. If the chick pecked the key at any time during the 16-sec stimulus duration, reinforcement was delivered immediately and a new trial was begun after the 5-sec ITI. During autoshaping and throughout the experiment, the chick was given a "free" reinforcement while being placed in the test box.

After the second autoshape session, chicks that responded on at least 12 trials were assigned to one of three drug treatment groups. All groups then received a total of five intraperitoneal (IP) injections of saline and/or D, L, para-chlorophenylalanine ethyl ester hydrochloride (PCPA) distributed across the first three post-hatch days. The first injection was given approximately 5 hr after the second autoshape session and the last injection was given approximately 20 hr before the third autoshape session on Day 4. The saline control group received five saline injections, the 3-PCPA group received three injections of 150 mg/kg PCPA and two saline injections, and the 5-PCPA group received five PCPA (150 mg/kg) injections. All doses were calculated as the active base of the drug and dissolved in isotonic saline daily prior to administration. Also, all doses were administered in a volume equal to 1% of body weight and treatment conditions were coded so that group assignments were unknown to the experimenter during injection and testing procedures.

On the fourth post-hatch day, all chicks were wing-clipped before being placed in their isolation cylinder prior to training. Before the fourth autoshape session, the shock

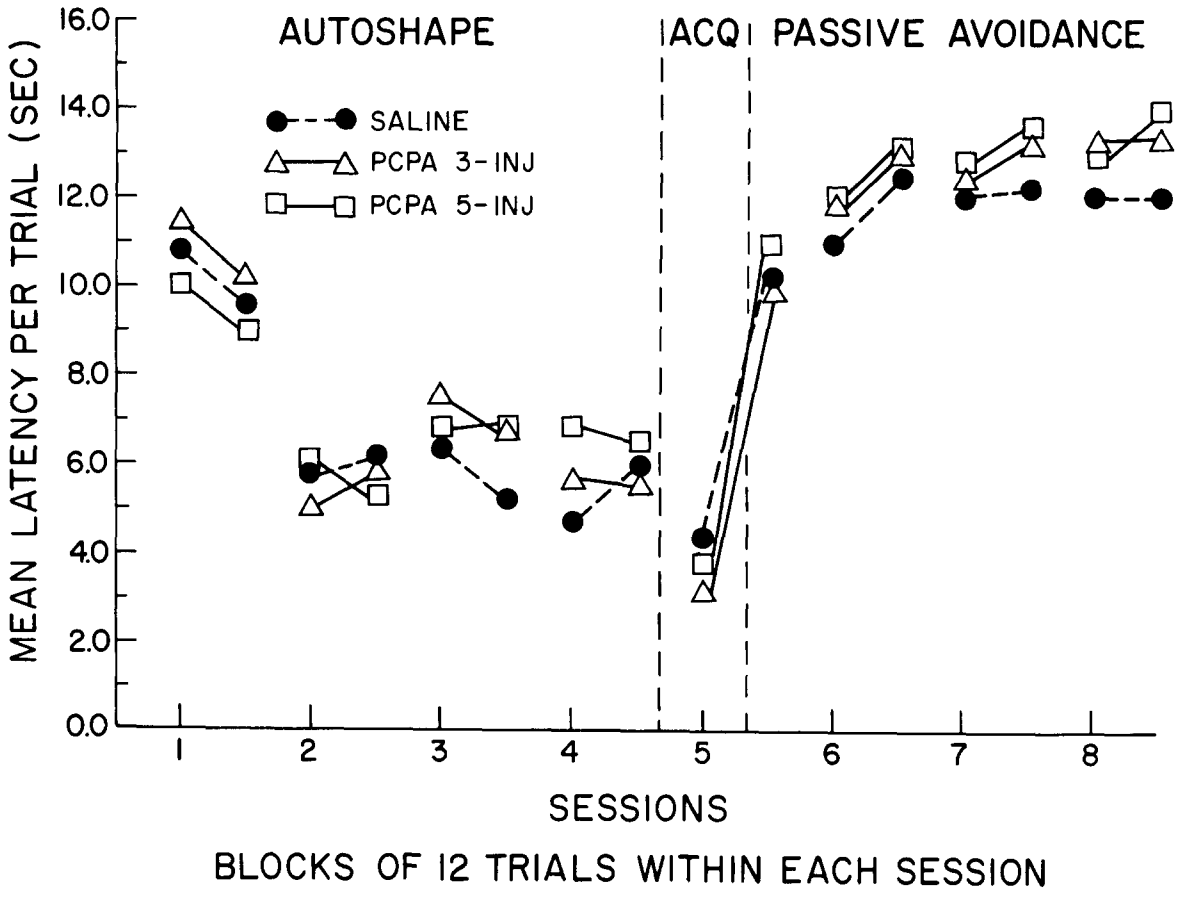

FIG. 1. Mean response latencies per trial across blocks of 12 trials for the saline- and PCPA-injected chicks during the four autoshape and four PA sessions.

wires were attached to the chicks' wing-clips to adapt all chicks to the shock harness before PA testing.

The first PA test session was given following the fourth autoshape session. The response-punishment contingencies, however, did not begin until the 13th trial of the first PA session. The first 12 trials of this session consisted of reinforced acquisition trials. Acquisition trials were the same as autoshaping trials except reinforcement was response-contingent. If the chick did not respond during the 16-sec stimulus duration, no "free" reinforcements were given. The PA trials were the same as acquisition trials except a response-contingent wing-shock (5 mA—0.5 sec) was delivered simultaneously with heat reinforcement. On the 2nd, 3rd, and 4th PA sessions, the response-shock contingency was in effect beginning on the first trial.

Statistical Evaluation

An analysis of variance with repeated measures was used to determine significance levels for response latencies during the autoshape sessions and for both response latencies and the percentage of trials on which the chicks responded (response trials) during the PA test sessions. All analysis were performed on means of 12 trial blocks. Since the response-punishment contingency did not begin until the 13th trial of the first PA session, this session was analyzed separately from the subsequent three PA sessions which consisted of all punishment trials. These analyses were supplemented, when appropriate, by Newman-Keuls tests.

RESULTS AND DISCUSSION

Autoshape Sessions

Mean response latencies across the four autoshape and four PA sessions for the three groups are presented in Fig. 1. Across the four autoshape sessions, the mean response latencies of the various groups did not differ as neither the main effect of group nor any of the interactions including group were significant. The session effect, however, was significant, $F(3,108)=17.61$, $p<0.0001$, as the chicks significantly decreased their response latencies from the first to second autoshape session, Newman-Keuls test, $p<0.05$. Although the chick's response latencies were slightly higher on Sessions 3 and 4 than on Session 2, this increase in response latencies was not significant, Newman-Keuls tests, $p>0.05$ in each case. These findings indicate that: (a) the chicks of the various groups were responding similarly before the

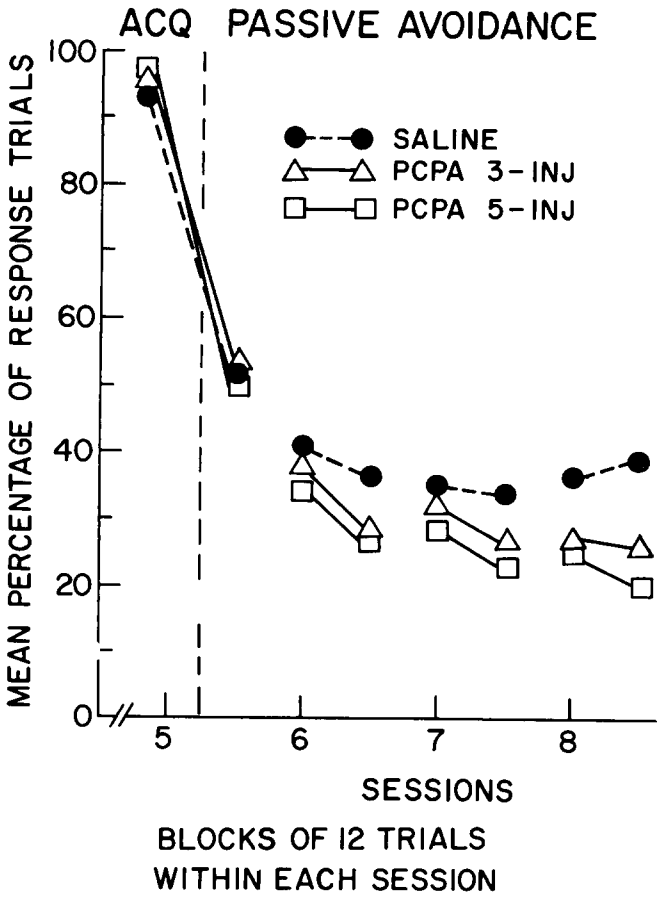

FIG. 2. Mean percentage of response trials across blocks of 12 trials for the saline- and PCPA-injected chicks during the four PA sessions.

treatment conditions were introduced (Sessions 1 and 2); (b) the PCPA injections did not significantly affect the chicks' retention or performance of key-pecking (Sessions 2 and 3); and (c) the key-peck performance of the saline and PCPA groups of chicks did not significantly differ prior to the first PA session (Sessions 3 and 4).

PA Sessions

As may be seen in Fig. 1, response latencies of all groups significantly increased when the response-punishment contingency was initiated in the first PA session, block effect, $F(1,36)=185.11$, $p<0.0001$. More important, the saline- and PCPA-treated chicks did not significantly differ in this initial increase in response latencies following punishment onset, group effect, $F(2,36)=0.72$; Group × Block interaction, $F(2,36)=0.68$.

On the subsequent three PA sessions, the groups increased response latencies across blocks, $F(1,36)=17.77$, $p<0.001$, but this increase was greater on the second PA session than on the last two PA sessions, Session × Block interaction, $F(2,72)=3.87$, $p<0.05$. The group effect was not significant, $F(2,36)=0.92$, but the Group × Session interaction did approach significance, $F(4,72)=2.23$, $p<0.08$. As shown in Fig. 1, the two PCPA groups continued to increase response latencies across the last three PA sessions, whereas the saline group showed a slight decrease in response latencies across these three sessions. Consequently, the PCPA groups responded more slowly than the saline group on the latter sessions.

The mean percentages of response trials during the four PA sessions are presented in Fig. 2. On the first PA session, the number of trials on which the chicks responded decreased significantly following the onset of the punishment contingency, block effect, $F(1,36)=149.92$, $p<0.0001$, and the saline- and PCPA-treated chicks did not significantly differ in this punishment-induced decrease in responding, group effect, $F(2,36)=0.01$; Group × Block interaction, $F(2,36)=0.18$. Similarly, across the last three PA sessions the chicks continued to decrease their responding over both sessions, $F(2,72)=3.27$, $p<0.05$, and blocks, $F(1,36)=9.62$, $p<0.01$, but again the saline and PCPA groups did not significantly differ in this decrease.

It is evident from these results that chicks pretreated with three or five injections of 150 mg/kg PCPA learned to suppress responding during PA testing as well as the saline-injected control chicks. Indeed, PCPA treated chicks learned to withhold responding as quickly as saline treated chicks following punishment onset, and then maintained the same magnitude of response suppression across trials as the saline control chicks.

EXPERIMENT 2

In Experiment 1, PCPA pretreatments did not significantly affect the subsequent PA performance of the 4-day-old chick. However, if cholinergic control of response suppression is predominant (see [17]) then any disruptive effects of PCPA on the PA performance of the chick could have been masked by the functioning cholinergic system. The purpose of Experiment 2, therefore, was to determine whether PCPA pretreatments would significantly increase the disruptive effects of a cholinergic antagonist on PA learning of the young chick. Two groups of chicks were given 3 injections of PCPA (150 mg/kg) or saline over the first three posthatch days, and then one half of the chicks from each group were injected with either scopolamine (0.5 mg/kg) or saline prior to PA testing on the fourth posthatch day. This dose (0.5 mg/kg) of scopolamine has been shown to significantly retard PA learning of the 4-day-old chick [11].

METHOD

Fifty-two Vantress × Arbor Acre chicks were hatched, reared, and tested as described in Experiment 1. All chicks were given two autoshape sessions when 1 day old (22.3 hr; SD=1.9) and then two additional autoshape and four PA sessions when 4 days old (95.8 hr; SD=3.1). Following the first two autoshape sessions the chicks were assigned in equal numbers to either the PCPA (150 mg/kg) or saline pretreatment condition. The chicks then received three IP injections of the appropriate drug. The first injection was given approximately 2 hr after autoshaping on Day 1, and the second and third injections were given 24 hr and 48 hr later, respectively. On the fourth posthatch day, immediately following the fourth autoshape session, one-half the chicks of each pre-treatment condition were assigned to either a scopolamine (0.5 mg/kg scopolamine hydrobromide as the active base) or saline post-treatment condition and injected IP about 20 min before PA testing. Thus, a 2×2 factorial design combining two pre-treatment conditions (PCPA vs

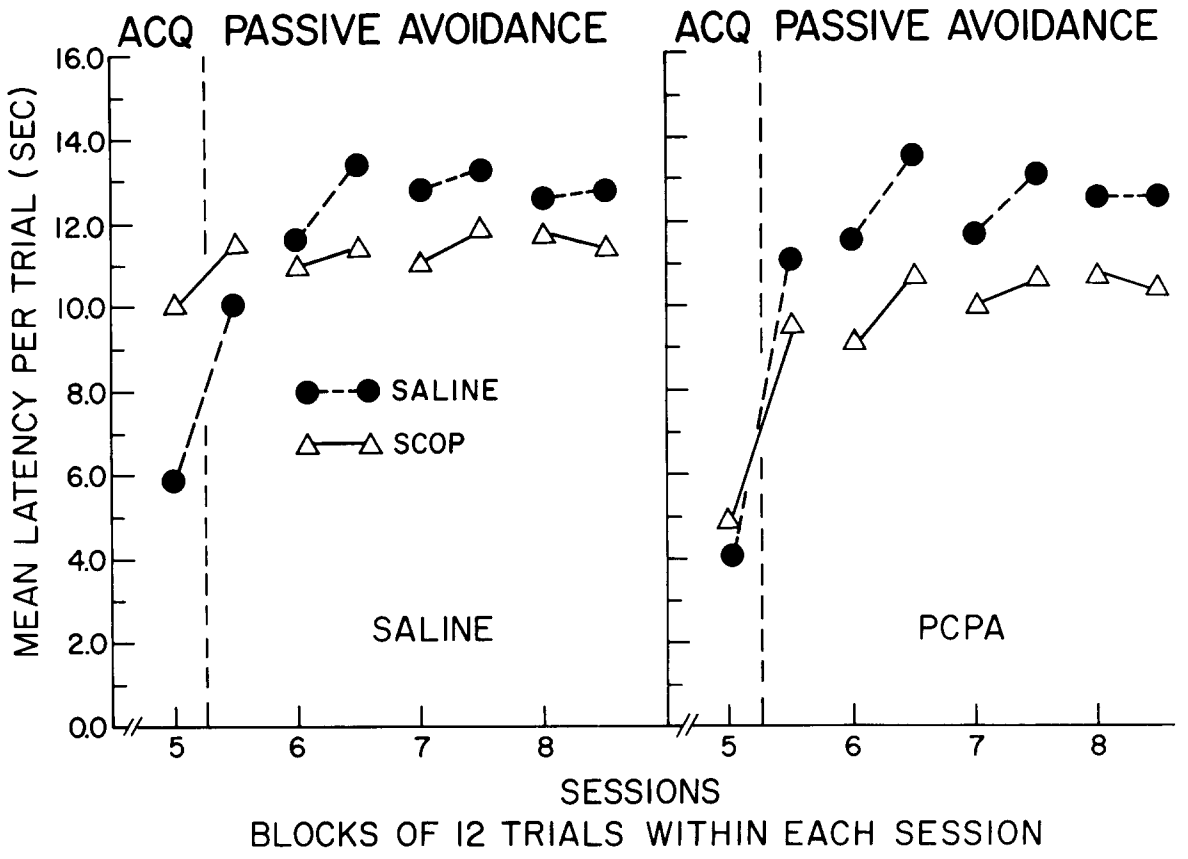

FIG. 3. Mean response latencies per trial across blocks of 12 trials during the four PA sessions for the saline- and scopolamine (SCOP)-injected chicks in the saline (left panel) and PCPA (right panel) pre-treatment conditions.

Saline) and two post-treatment conditions (SCOP vs Saline) with repeated measures was used.

RESULTS AND DISCUSSION

Autoshape Sessions

Response latencies decreased for all groups across the four autoshape sessions, session effect, $F(3,144)=29.48$, $p<0.0001$. Overall, the chicks decreased response latencies from the first to second block of 12 trials, block effect, $F(1,48)=6.77$, $p<0.05$, but this decrease was greater on the last two autoshape sessions than on the first two sessions, Session × Block interaction, $F(3,144)=2.81$, $p<0.05$. Neither the main effect of pre-treatment (Saline vs PCPA), post-treatment (Saline vs SCOP), nor any of the interactions were significant. Consequently, the performance of the various groups was equivalent on the first two autoshape sessions prior to the introduction of the pre-treatment conditions and also on the last two autoshape sessions prior to the administration of the post-treatment conditions. Furthermore, consistent with the results of Experiment 1, PCPA did not significantly affect either the retention or the performance of key-pecking.

PA Sessions

Mean response latencies for the four groups of chicks across the four PA sessions are presented in Fig. 3. Overall, on the first PA session, the chicks pretreated with PCPA responded more quickly than chicks pre-treated with saline, pre-treatment effect, $F(1,48)=6.62$, $p<0.05$, but this difference between pre-treatment groups was larger for chicks in the scopolamine post-treatment condition than for those in the saline post-treatment condition, Pre-treatment × Post-treatment interaction, $F(1,48)=3.67$, $p<0.06$. Further, although all groups increased response latencies following the onset of punishment in the first PA session, block effect, $F(1,48)=69.78$, $p<0.0001$, this punishment-induced increase in response latencies was greater for chicks in the PCPA pre-treatment condition than for chicks in the saline pre-treatment condition, Pre-treatment × Block interaction, $F(1,48)=8.48$, $p<0.001$, and also for chicks in the saline post-treatment condition than for chicks in the scopolamine post-treatment condition, Post-treatment × Block interaction, $F(1,48)=6.2$, $p<0.05$. These interactions, however, were mainly due to the quicker responding of the PCPA pre-treatment groups and the saline post-treatment groups on the first block of 12 acquisition trials as the response latencies of the various groups following punishment onset were very similar. Basically, the significant effect of the two drugs on the first PA session was confined to the first block of 12 acquisition trials. That is, scopolamine produced the characteristic disruption in key-pecking on the first block of 12 trials in chicks pre-treated with saline (see [11,21]) but not in chicks pre-treated with PCPA.

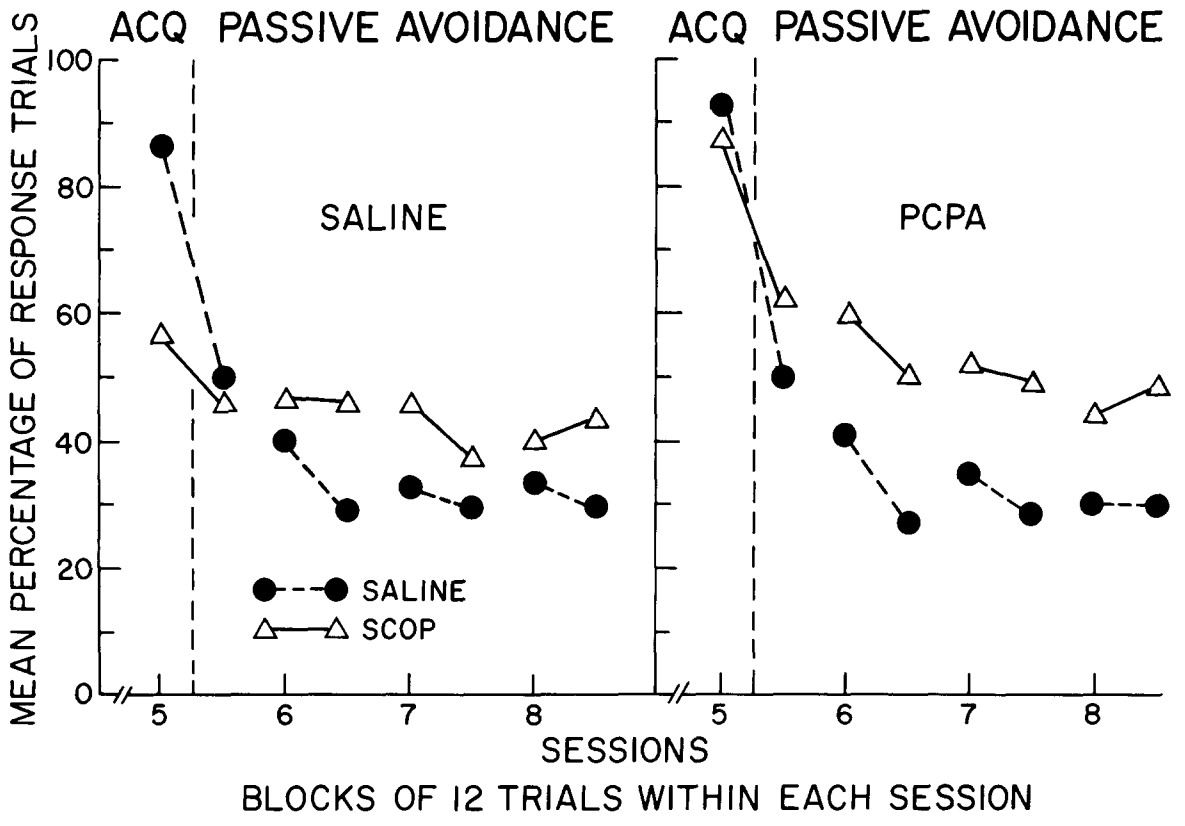

FIG. 4. Mean percentage of response trials across blocks of 12 trials during the four PA sessions for the saline- and scopolamine-injected chicks in the saline (left panel) and PCPA (right) pre-treatment conditions.

Overall, the chicks increased response latencies from the first to second block of trials across the second and third PA sessions, block effect, $F(1,48)=9.73$, $p<0.01$, and Session × Block interaction, $F(2,96)=7.70$, $p<0.001$. More important, the scopolamine-injected chicks in both pre-treatment conditions responded more quickly than chicks in the saline post-treatment condition, post-treatment effect, $F(1,48)=4.82$, $p<0.05$. Although this scopolamine-induced disruption in PA learning appeared to be slightly greater for chicks pre-treated with PCPA than for chicks pre-treated with saline, neither the main effect of pre-treatment condition nor the Pre-treatment × Post-treatment interaction approached significance, $F(1,48)=0.65$, and $F(1,48)=0.39$, respectively.

The mean percentage of response trials during the four PA sessions for the four groups are presented in Fig. 4. Chicks pre-treated with PCPA responded on more trials overall than chicks pre-treated with saline on the first PA session, pre-treatment effect, $F(1,48)=6.66$, $p<0.05$, but this pre-treatment effect was greater for chicks in the scopolamine post-treatment condition than for chicks in the saline post-treatment condition, Pre-treatment × Post-treatment interaction, $F(1,48)=4.41$, $p<0.05$. Also, although the number of response trials decreased for all groups following punishment-onset, block effect, $F(1,48)=59.67$, $p<0.0001$, this decrease was greater for chicks in the saline post-treatment condition than for chicks in the scopolamine post-treatment condition, Post-treatment × Block interaction, $F(1,48)=7.54$, $p<0.01$.

Across the last three PA sessions, the chicks responded on fewer trials on the first block of 12 trials than the last block of 12 trials, block effect, $F(1,48)=7.31$, $p<0.01$, and this decrease in responding across blocks was greater on the second PA session than on the last two PA sessions, Session × Block interaction, $F(2.96)=6.36$, $p<0.01$. Furthermore, as may be seen in Fig. 4, the chicks treated with scopolamine responded on significantly more trials than did chicks in the saline post-treatment conditions, Post-treatment effect, $F(1,48)=6.01$, $p<0.05$, and although PCPA appeared to increase this difference in responding between chicks in the scopolamine and saline post-treatment conditions, neither the main effect of pre-treatment nor any of the interactions approached significance.

In summary, chicks injected with 0.5 mg/kg scopolamine 20 min before PA testing responded more quickly and on more trials across the last three PA sessions than chicks injected with saline 20 min before PA testing. Furthermore, consistent with the results of Experiment 1, chicks pre-treated with three daily injections of 150 mg/kg PCPA and then given a saline injection prior to PA testing did not significantly differ from chicks administered only saline. More important, the scopolamine-injected chicks pre-treated with PCPA did not significantly differ from the scopolamine-injected chicks pre-treated with saline. Interestingly, the

only significant effect PCPA pre-treatment had was to prevent the scopolamine-induced disruption of key-pecking on the first 12 acquisition trials of the first PA session.

GENERAL DISCUSSION

The results of the present study suggest that cholinergic, but not serotonergic, mechanisms are involved in PA learning of the young chick. Although chicks injected with scopolamine were significantly disrupted in PA learning, chicks pre-treated with doses of PCPA which have been reported to produce over a 70% decrease in brain serotonin levels did not significantly differ from saline control chicks in either the acquisition of response suppression or in the asymptotic level of response suppression during PA testing. Furthermore, PCPA pre-treatment did not significantly enhance the scopolamine-induced disruption of PA learning of the young chick.

Some neurochemical models of behavior propose that serotonergic mechanisms mediate the selective inhibition or suppression of behaviors which are nonreinforced or punished (e.g. [15,19]). Support for this view that serotonergic mechanisms mediate punishment-induced response suppression has been primarily from those studies reporting that chronic PCPA pretreatments of rats attenuate the suppressive effects of punishment on responding in PA tests (e.g. [8,13]). But not all studies of PA learning in rats have found a PCPA induced disruption in response suppression (e.g. [3,4]). Therefore, it is not clear whether the reported PCPA-induced disruption of PA learning in rats is a general phenomena or is restricted to specific, and perhaps inappropriate, methodological procedures (see [3]). For instance, most of the studies reporting a PCPA-induced attenuation of response suppression in rats have used a discriminated punishment paradigm in which response-dependent punishment was delivered only during the presentation of an exteroceptive warning stimulus (e.g. [8, 13, 20]). Consequently, in these studies the continued responding of PCPA-treated rats when punished may have been because of hyperreactivity to the warning signal (see [20]), rather than because of an inability to suppress a specific prepotent response. In our PA experiments all of the chicks' key-peck responses were punished during the PA sessions, and a warning signal was not presented. These procedural differences may account for the apparent discrepancy between the effects of PCPA on PA learning of the rat and the young chick.

In contrast to the lack of effect of PCPA on the chicks' PA performance, chicks injected with scopolamine responded significantly quicker and on more trials during PA testing than saline-injected control chicks. This finding is consistent with previous findings of anti-cholinergic effects on PA learning in chicks [11,21] and rats [2], and, therefore, supports the view that cholinergic mechanisms mediate response suppression. It should be emphasized, however, that PA learning, like most response suppression tests used in psychopharmacological research, can not differentiate among inhibitory, memory, or discriminative processes. Consequently, it cannot be concluded from such tests that cholinergic antagonists effect only inhibitory processes (see [21]).

In conclusion, chronic PCPA pretreatments did not significantly affect the subsequent PA performance of the young chick; results which do not support the view that serotonergic mechanisms mediate punishment-induced response suppression. However, consistent with previous studies, scopolamine did significantly attenuate the chicks' response suppression during PA testing; results which are consistent with a cholinergic involvement in response suppression. But the scopolamine-induced disruption in PA learning was not very large, and consequently, other neurochemical systems, beside cholinergic, probably play a more fundamental role in response suppression in chicks.

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