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Lead-Induced Decrements in Waiting Behavior: Involvement of D_2-Like Dopamine Receptors

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BROCKEL, B. J. AND D. A. CORY-SLECHTA. *Lead-induced decrements in waiting behavior: Involvement of D_2-like dopamine receptors.* PHARMACOL BIOCHEM BEHAV. **63**(3) 423–434, 1999.—Some behavioral changes produced by chronic postweaning lead (Pb) exposure have been linked to mesolimbic dopamine (DA) system alterations. This study sought to determine the role of DA systems in Pb-induced changes in a fixed ratio (FR) waiting-for-reward paradigm. Rats exposed chronically from weaning to 0, 50, or 150 ppm Pb acetate drinking solutions earned free reinforcers for waiting after completion of an FR, with increasing time between successive free reinforcers. Responses during the waiting period reset the FR requirement. Once performance stabilized, the effects of acute IP administration of the D_1 agonist SKF82958, the D_2 agonist quinpirole, the D_1 antagonist SCH23390, and the D_2 antagonist eticlopride were determined. Pb itself increased FR response rates and decreased mean waiting time, a pattern of behavior that increased the number of earned reinforcers, but doubled the number of responses/reinforcer. None of the DA compounds mimicked Pb effects when administered to controls. Only DA agonists altered waiting behavior and responses per reinforcer. Quinpirole, in particular, appeared to reverse Pb effects on the FR wait baseline by increasing waiting time and decreasing FR resets to control levels. These findings point to a particular role for D_2 DA function in Pb's detrimental effects on waiting. © 1999 Elsevier Science Inc.

Lead Fixed ratio Delay of reinforcement Dopamine Quinpirole SKF 82958 SCH 23390 Eticlopride

CLINICAL and experimental evidence suggests that even current very low environmental lead (Pb) exposures can have adverse effects on children (8). It is estimated that in the United States today, almost one in nine children have blood Pb (PbB) levels equal to or greater than 10 μg/dl, the currently designated PbB level of concern for pediatric populations (7). These low-level Pb exposures have been shown to produce cognitive deficits as measured by intelligence quotient (IQ) scores and other psychometric tests (3,21). Similar deficits have been observed in experimental animal models of Pb. Low-level Pb exposures selectively alter learning in a multiple schedule of repeated learning and performance in rats (9) and produce changes in both discrimination and reversal learning in primates (31). Pb exposure is associated with increased rates of responding on fixed interval (FI) (15–17,32,35) and on differential reinforcement of low rates (DRL) schedules of reinforcement (30,34). Such patterns of responding are highly inefficient because in the former case (FI) they cannot accelerate reinforcement availability, and in the latter case (DRL) can actually delay reinforcement availability and decrease reinforcement density.

Some investigators have suggested that these behavioral alterations are actually a result of attention deficits (2,31), an interpretation based in part on findings such as those reporting that low-level Pb exposures of children during development are associated with higher distractibility and impulsiveness ratings [e.g., (27)]. In addition, an enhancement of perseverative errors has been reported both in children (40) and in experimental animal studies (9,31). Alber and Strupp (1) suggested that Pb-related increases in rats in the number of errors in a delayed spatial alternation paradigm were related to the variable nature of the delays in this task possibly leading to "impatience" and an inability to inhibit prepotent responses, findings reminiscent of an attention deficit.

Surprisingly, however, the assertion that attention serves as a basis for Pb-induced cognitive deficits has not been widely confirmed nor even systematically investigated. Findings from some studies, moreover, actually argue against this assertion. For example, the continuous performance test has not been reliably associated with Pb-related deficits in children (2). Padich et al. (28) found no relationship between Pb exposures and measures of attention in children at 18 months

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of age. In an experimental study with rats, Brockel and Cory-Slechta (5) failed to find any effects of Pb exposure in rodents on a sustained vigilance paradigm, despite manipulations of interstimulus interval, stimulus duration, probability of stimulus presentation, etc.

One potentially intriguing link between lead exposure and attentional dysfunction, however, is suggested by the fact that low-level Pb exposures consistently increase fixed-interval (FI) response rates in experimental animal studies (15–17,32,35). Two recent studies by Darcheville, et al. (19,20) found that FI response rates reliably predicted performance of children on a self-control (impulsivity) paradigm, which provided a choice between a smaller but immediate reward (impulsive choice) or a larger but delayed reward (self-controlled choice). Specifically, children with higher FI response rates made significantly more impulsive choices than those with lower FI response rates. Impulsivity is one of the three diagnostic criteria for attention deficit (23,41).

Impulsive behavior, as defined using such self-control paradigms, has been postulated to result from an inability to manage delays [i.e., (39)]. In an attempt to assess the extent to which delays might also reflect the impact of chronic postweaning Pb exposure, Brockel and Cory-Slechta (6) recently evaluated Pb effects of Pb on a FR (fixed ratio) waiting-for-reward paradigm [as modified from (4)]. It provided free food deliveries after the completion of a FR requirement, with the time between deliveries increasing after each successive food delivery. Any intervening response reset the FR requirement. Interestingly, rats treated chronically from weaning with Pb reset the FR more frequently (i.e., exhibited shorter mean wait times) than did controls. Because their FR response rates were also higher than controls, this pattern of behavior resulted in the Pb-treated group obtaining a greater total number of reinforcers. This occurred, however, at a cost, because the number of responses emitted per reinforcer was almost twice as high as that required by controls. Although other explanations for these findings still remain to be ruled out, one potential basis for such an effect is likewise an inability to manage delays.

Prior studies from this laboratory have suggested that the increases in FI response rates produced by Pb exposure derive from enhanced mesolimbic dopamine (DA) availability. Blockade of DA receptors in nucleus accumbens (NAC), but not in dorsal striatum (DS), markedly decreases FI response rates; DA microinjected into NAC increases FI response rates in normal (non-Pb treated) rats (11,12). That chronic postweaning Pb exposure does indeed appear to be associated with enhanced NAC DA availability was further suggested by two studies. In an autoradiographic time course study, Pb exposure decreased D_1, D_2 and DA transporter binding sites in NAC but not in DS. These effects, at least for D_2 and DA transporter binding, were evident after only 2 weeks of exposure, and lasted for the duration of the study (12 months), findings consistent with elevated DA levels in NAC, and not in DS, with consequent NAC receptor downregulation (29). A subsequent in vivo electrochemical time course study revealed increases in amplitude of evoked DA overflow that were likewise expressed selectively in NAC and that again were consistent with enhanced NAC DA availability in response to chronic postweaning Pb exposure (44). Thus, chronic postweaning Pb exposure has been shown to alter DA function in a manner suggestive on increased DA availability expressed preferentially in mesolimbic DA systems.

The present study was designed to assess the hypothesis that altered DA function might likewise contribute to the observed changes produced by Pb in the FR waiting-for-reward paradigm (6). It compared the effects of acute systemic administration of both D1 (SKF 82958) and D_2 (quinpirole) DA agonists and antagonists (SCH 23390 and eticlopride, respectively) on this baseline in control vs. Pb-exposed rats. The use of both agonists and antagonists in this study provided the possibility of determining whether increased or decreased DA activity would either mimic Pb effects in controls or possibly counter the effects of Pb on this baseline.

METHOD

Animals

Male Long–Evans rats (Harlan–Blue Spruce, Indianapolis, IN), 21 days of age on arrival were divided into groups of 12 rats each of approximately equal weight and exposed to drinking water containing either 0, 50, or 150 ppm Pb acetate (Fisher Scientific, Pittsburgh, PA) dissolved in distilled deionized water. Pb exposure was sustained for the duration of the experiment. This protocol produces reliable behavioral deficits, alterations in mesolimbic DA systems [e.g., (13,29)], and mimics human exposure protocols to the extent that peak PbBs in children occur postweaning (1–3 years of age) and are then sustained over the lifetime [e.g., (7)]. Rats were provided with Purina semipurified rat chow (Purina, St. Louis, MO) ad lib until body weights reached 300 g, at which level they were sustained for the duration of the experiment. No Pb-related differences in fluid consumption or food required to maintain body weight were observed. Typical standard rodent diets maintain excessively high levels of the essential metals Ca, Fe, and Zn, which decrease oral absorption of Pb. The semipurified diet used here contains required rather than excess levels of these essential metals, thus permitting the use of lower Pb acetate drinking water concentrations to achieve target PbB concentrations. Behavioral testing procedures were implemented at approximately 60 days of age. On the day prior to behavioral training, all but two animals had reached 300 g. These animals were placed on a food schedule that allowed a 3–5 g increase in body weight per day until body weights reached 300 g. Rats were individually housed in clear 45 × 24 × 21-cm plastic cages with wood chip bedding in a room that was maintained on a 12-h light/dark cycle and monitored for temperature and humidity. All procedures and animal care followed the National Institutes of Health and the University of Rochester Animal Care and Use Committee guidelines.

Apparatus

Behaivoral testing was conducted in operant chambers (Coulbourn Instruments, Inc., Lehigh Valley, PA, Model E10-10) that were housed in light-attenuated enclosures equipped with fans for ventilation. Three response levers on the front wall of the operant chamber were 3.8 cm above a grid floor, and were separated by 3.5 cm; only the right lever was active in these experiments. A force of approximately 30 g was required to depress the lever microswitch. Food reinforcers (45 mg food pellets, P. J. Noyes Inc., Lancaster, NY) were delivered via a food trough that was located below the center lever. Extraneous sounds were masked with continuous white noise. A Digital Equipment Corporation (DEC PDP 11/73) computer was programmed with the SKED-11 system (38) to control behavioral contingencies and data collection. Events during each session were stored sequentially with a resolution of 10 ms.

Behavioral Procedures and Drug Administration

Rats were trained to press one of three levers in an operant chamber via an overnight autoshaping program used routinely in this laboratory (10). All but eight animals learned to lever press after a single session. Seven rats were trained after an additional overnight training session, and one rat required three nonconsecutive training sessions. No Pb-related differences in shaping were detected. Subsequently, a FR schedule of reinforcement was imposed, with the FR increased until 50 responses (FR 50) were required to earn a food pellet delivery. This was done on an individual rat basis, and generally required 9–10 sessions in both control and Pb-treated rats. Once rats were responding on an FR 30 schedule, a wait component was added to the schedule (see the bottom graph in Fig. 6). The wait component permitted "free" food pellets to be obtained after completion of the FR requirement until another lever response occurred which then reinitiated the FR component. "Free" pellets were delivered at increasing time intervals (i.e., 2 s, 4 s, 6 s, etc.). There was no upper limit for the waiting component; the FR component was reset only if a response on the active lever occurred. A reinforcement period of 3 s followed each pellet delivery, during which lever responding had no programmed consequences. Time spent in the reinforcement period was not included in the measurement of the waiting length between pellet deliveries. This reinforcement period was used to separate pellet delivery and consumption from waiting behavior.

Once all rats were responding on an FR 50 schedule, behavior was allowed to stabilize over 30 sessions. This stabilization period was followed by 20 behavioral baseline sessions. The resultant effects of Pb on this baseline have been reported previously (6).

After the collection of baseline data, dose–effect curves were determined for quinpirole, SKF 82958, MK 801 (data not shown), SCH 23390, and eticlopride. The MK 801 data was omitted due to the length and scope of this report, and because in general, MK 801 decreased FR response rates but had no effect on waiting behavior. Dose–effect curves were collected in the order listed, with two sessions carried out between each dose of each drug and at least five behavioral sessions conducted between each compound tested. After collection of the SKF 82958 dose–effect curve, it was observed that not even the highest dose (0.8 mg/kg) altered behavior, even though the doses utilized were found effective in pilot studies done in this laboratory using a similar paradigm. Therefore, the SKF 82958 dose–effect curve was redetermined with newly prepared drug solutions, and the results reported here for SKF 82958 are derived from this second replication. Doses of each compound were administered in a semirandomized order. Behavioral sessions were conducted during the light cycle, 5 days a week, and were 15 min in duration.

PbB Determinations

After 3 months (i.e., during the 30-day stabilization period) and again after 7 months of Pb exposure (during drug testing), a total of 100 μl of blood was obtained after the behavioral session by nicking rat's tails following immersion in warm water for determination of PbB concentrations. Whole blood was analyzed for Pb by anodic stripping voltammetry (Model 3010A Trace Metals Analyzer, Environmental Science Associates, Bedford, MA) according to the method of Morrell and Giridhar (26). The bottom limit of sensitivity of this technique is 5 μg/dl.

Data and Statistical Analysis

Total number of FR resets and total number of reinforcers earned during the wait component were tallied for each session. FR response rates were computed by dividing total number of responses by the total time spent in the FR component. Mean longest waiting time for a "free" pellet delivery (Mean Long Wait) before resetting the FR component was calculated (see the bottom graph in Fig. 6). Responses per reinforcer (Rsp/Rft), a measure of "efficiency," was equal to the total number of responses divided by the total number of reinforcers (for both the FR and Wait components). In the previous study (6), a ratio of Mean Long Wait time to the time required to complete the FR component was also calculated to provide an assessment of "efficiency" of performance, i.e., whether resets of the FR occurred as the time between free pellet deliveries exceeded the time required to complete an FR and obtain a reinforcer. Because there were no drug effects or effects of Pb performance on that measure, it is not presented in the current study.

Assessment of Pb effects on baseline performance of these rats, as presented in the Brockel and Cory-Slechta study (6), revealed that the 50-ppm group did not systematically perform differently from the control group, while the 150 ppm group exhibited considerable differences (see above), as can be seen by comparing the group means of the 5 days before quinpirole testing as listed in Table 1. Therefore, to more readily ascertain the extent to which Pb-induced alterations in dopaminergic function contributed to these performance changes, the current assessment of any differential effects of DA agonists and antagonists on this baseline were restricted to comparisons of the 0 vs. 150 ppm groups.

The means of the five behavioral sessions carried out prior to the collection of each dose–effect curve were used to determine the stability of both the baseline behavior across time and Pb-related differences relative to controls. For this purpose, repeated-measures analyses of variance (RMANOVAs) were carried out over the resulting four blocks (of five sessions each) of baseline data with Pb concentration as a between-group factor and blocks of sessions as a within-group factor.

To determine the effects of each of the DA agonists and antagonists on the FR waiting for reward baseline, RMANOVAs were carried out with Pb as a between-group factor and dose of drug as a within-group factor. Initial analyses indicated that data transformed to a proportion of the baseline did not alter or clarify the effects of this experiment; therefore, all statistical analyses were conducted on raw data. Thus, differential drug effects between Pb and controls in these analyses were signified by significant interactions between Pb and drug.

TABLE 1

MEANS ± 1 SE FOR FIVE BASELINE SESSIONS PRIOR TO PHARMACOLOGICAL TESTING

	0 ppm	50 ppm	150 ppm
Rate	88.1 ± 13.1	111 ± 16	172.3 ± 33.4
FR resets	4.3 ± 0.7	6.4 ± 1.2	11.8 ± 3.6
Wait reinforcers	42.1 ± 2.6	47.4 ± 3.6	51.8 ± 4.1
Mean long wait	25.5 ± 3.3	19.3 ± 2.4	15.6 ± 2.6
Rsp/Rft.	4.3 ± 0.5	5.6 ± 0.6	8.4 ± 1.6

For each dependent measure except Wait Reinforcers, the 150 ppm group was significantly different than controls ($p < 0.05$). On all measures, the 50 ppm group did not differ significantly from controls ($p > 0.05$) or from the 150 ppm group ($p > 0.05$).

These analyses were carried out separately for each dependent variable. Post hoc simple-effects ANOVAs, single degrees of freedom contrast tests, and least-squares means tests were used to further evaluate any interactions between dose of drug and Pb exposure. For these analyses, group means were used to replace missing data points, with no more than two means per Pb group per dose of drug substituted. The highest doses of SKF 82958 (0.8 mg/kg), SCH 23390 (0.2 mg/kg), and eticlopride (0.2 mg/kg) could not be used in the statistical analyses of Mean Long Wait and Rsp/Rft, because these doses suppressed behavior and produced several missing data points. Two rats in the 150-ppm group died during the course of the experiment, and data from these subjects was not included in the analyses. A criteria of $p < 0.05$ was used for both RMANOVAs and post hoc analyses. All analysis were conducted using SuperANOVA statistical software (Abacus Concepts, Inc.).

Drugs

Quinpirole HCl, SKF 82958 (chloro- APB hydrobromide), SCH 23390 HCl and eticlopride were all obtained from Research Biochemical International (RBI). Each compound was dissolved in saline and administered IP at a volume of 1 ml/kg. All compounds were administered 30 min prior to behavioral sessions, except for eticlopride, which was administered 20 min before the session.

RESULTS

PbB Analysis

PbBs increased in a concentration-related fashion, $F(2, 19) = 34.74$, $p < 0.0001$, from <5 to 9.7 ± 1.6 to 26.2 ± 2.6 μg/dl (± 1 SE) at concentrations of 0, 50, and 150 ppm, respectively. No overlap of Pb groups was observed as indicated by Fisher's PLSD (all p-values < 0.005). PbB levels remained the same after 3 and 7 months exposure, $F(1, 19) = 0.28$, $p > 0.05$, and no effect of Pb concentration by duration of exposure on PbBs was observed, $F(2, 19) = 0.86$, $p > 0.05$.

Effects of Pb and Stability of Baseline Performance Across Time

Mean rates of responding on the FR component, FR resets, Wait reinforcers, Mean Long Wait and Rsp/Rft values for the control (0 ppm) and 150 ppm groups across the four blocks of five sessions preceding the collection of each dose effect curve are presented in Fig. 1. The 50 ppm group was not utilized in the drug studies because its baseline performance did not differ from either the 0 or the 150 ppm group on any measure; see the Method section. There were changes in some of these dependent measures across the course of the experiment, but in all cases, Pb-related differences in performance were sustained. Specifically, FR response rates remained stable across the experiment, $F(3, 60) = 1.17$, $p > 0.05$ (Fig. 1A), with values of the 150 ppm group remaining significantly higher than corresponding control values by greater than twofold, $F(1, 20) = 6.04$, $p < 0.03$. The number of FR resets declined slightly although significantly across the course of the experiment, $F(3, 60) = 4.11$, $p < 0.02$ (Fig. 1B), while the nearly threefold higher number of resets in the 150 ppm exposure group relative to controls remained stable, $F(1, 20) = 4.62$, $p < 0.05$. Wait reinforcers also decreased across time, $F(3, 60) = 8.55$, $p < 0.0001$, although the 150 ppm group continued to earn approximately 10 more wait reinforcers per session than

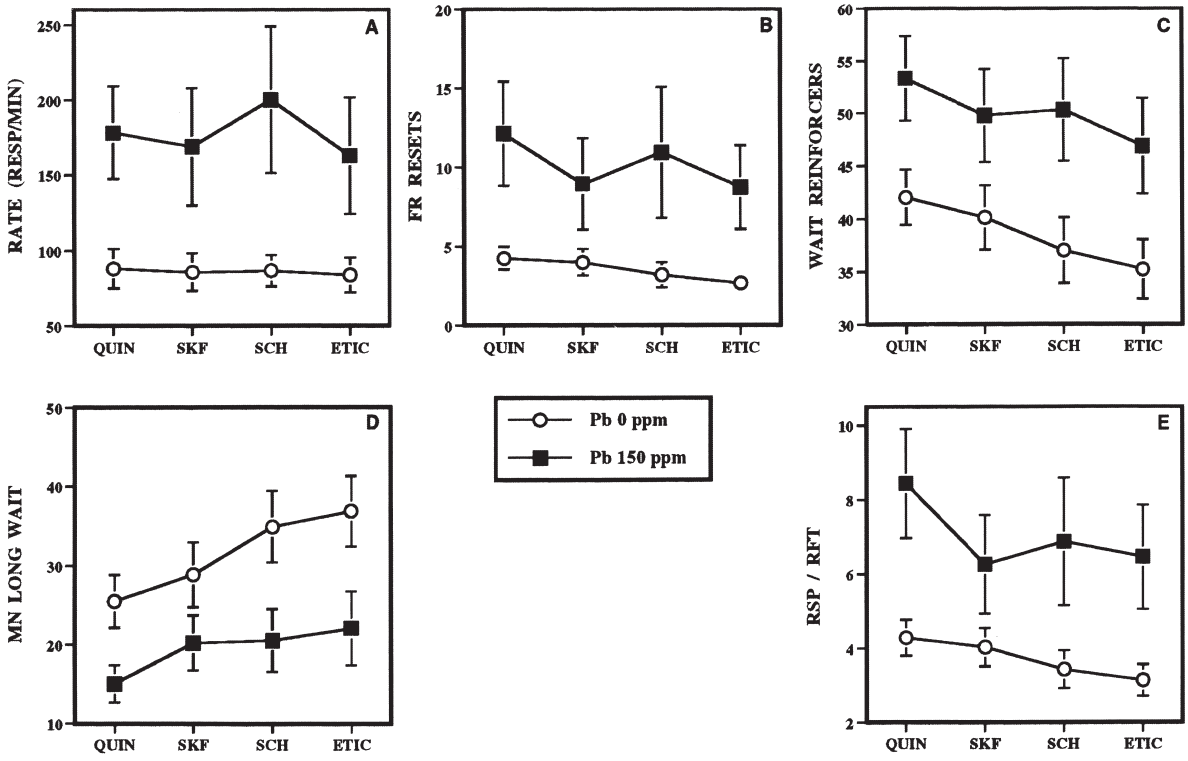

FIG. 1. The effects of Pb exposure on baseline sessions across pharmacological testing. Each point represents a group mean of three predrug baseline sessions with each bar indicating ±1 SE (n = 12, 10 for the control and 150 ppm groups, respectively).

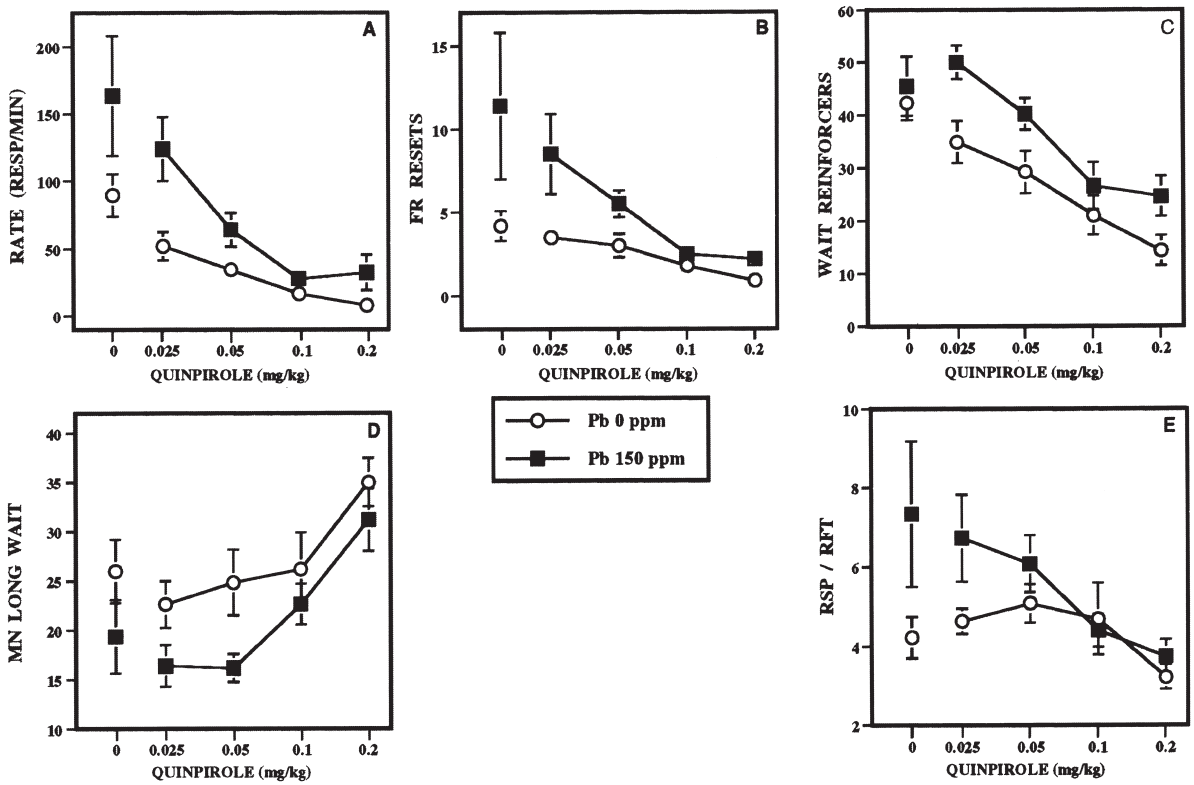

FIG. 2. Dose–response curves of quinpirole for control ($n = 12$) and the 150-ppm exposure group ($n = 10$). Each point represents a group mean with each bar indicating ±1 SE.

controls, $F(1, 20) = 5.03$, $p < 0.04$ (Fig. 1C). The duration of waiting behavior (Mean Long Wait) actually increased across experimental sessions for both the 0 and 150 ppm groups, $F(3, 60) = 12.83$, $p < 0.0001$ (Fig. 1D) with the control group waiting on average 150% longer than the 150-ppm group, $F(1, 20) = 5.01$, $p < 0.04$. The number of Rsp/Rft decreased during the experiment, $F(3, 60) = 7.30$, $p < 0.0003$ (Fig. 1E), even while the 150 ppm group continued to emit nearly twice as many Rsp/Rft as required by the control group, $F(1, 20) = 5.27$, $p < 0.04$.

Effects of the D_2 Agonist Quinpirole

Quinpirole dose-dependently decreased FR response rates, $F(4, 80) = 16.19$, $p < 0.001$ (Fig. 2A), FR resets, $F(4, 80) = 7.68$, $p < 0.0001$ (Fig. 2B), and wait reinforcers, $F(4, 80) = 20.19$, $p < 0.0001$ (Fig. 2C) over the dose range of 0.025 to 0.20 mg/kg. FR response rates declined by 80–90% across this dose range, while corresponding declines for wait reinforcers ranged from 46–67%, and for FR resets about 80%. These effects of quinpirole were not modified by concurrent Pb exposure. Mean long wait time actually increased in response to quinpirole administration, $F(4, 76) = 12.13$, $p < 0.0001$ (Fig. 2D). Collapsed across the 0 and 150 ppm groups, the dose–effect curve was U-shaped, as indicated by its significant quadratic component ($p < 0.0001$), with low doses of quinpirole decreasing waiting behavior and higher doses increasing waiting behavior. These biphasic effects were comparable in both Pb exposure groups, $F(4, 76) = .58$, $p > 0.05$. Quinpirole administration also decreased the number of Rsp/Rft, $F(4, 76) = 5.49$, $p < 0.0006$ (Fig. 2E), an effect that was significantly enhanced by Pb exposure, $F(4, 76) = 3.19$, $p < 0.02$. In the 0 ppm group, quinpirole tended to slightly increase Rsp/Rft at intermediate doses (e.g., by 29% at 0.05 mg/kg), before values declined, but only slightly at higher doses (e.g., by 18% at 0.20 mg/kg). This profile of effects was confirmed by a significant quadratic ($p < 0.004$) but not linear component in post hoc contrast tests. To further evaluate this biphasic effect of quinpirole, least-squares means were used to compare doses of quinpirole within the 0 ppm group. Although not statistically significant ($p < 0.08$), 0.05 mg/kg quinpirole increased Rsp/Rft from vehicle levels, but the 0.2 mg/kg dose had lower Rsp/Rft values than either 0.025 mg/kg ($p < 0.04$), 0.05 mg/kg ($p < 0.006$), and 0.1 mg/kg ($p < 0.03$). In contrast, quinpirole dose dependently decreased Rsp/Rft in the 150 ppm Pb group, by as much as 49% at 0.20 mg/kg relative to 0 mg/kg (vehicle) values, and this was confirmed in post hoc contrasts by a significant linear ($p < 0.0001$) but not quadratic component. Least-squares means indicated that 0.1 mg/kg was significantly lower than vehicle ($p < 0.005$) and 0.025 ($p < 0.03$); whereas, 0.2 mg/kg significantly reduced Rsp/Rft when compared to vehicle ($p < 0.0008$), 0.025 ($p < 0.005$), and 0.05 ($p < 0.03$).

Effects of the D_1 Agonist SKF 82958

Effects of SKF 82958 on the FR waiting for reward paradigm were modest. When collapsed across the two Pb exposure groups, SKF 82958 dose dependently decreased FR response rates, $F(3, 60) = 7.06$, $p < 0.0004$ (Fig. 3A) and number of FR resets, $F(3, 60) = 6.77$, $p < 0.0005$, (Fig. 3B), effects that

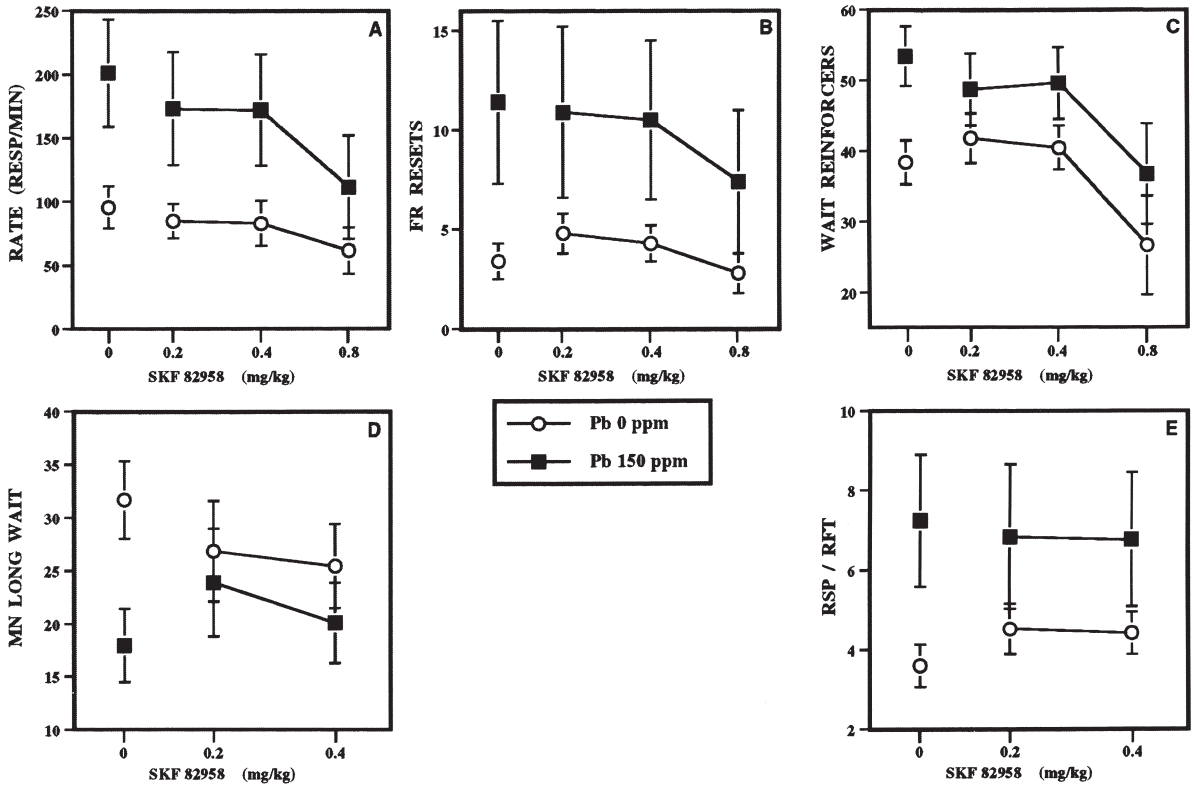

FIG. 3. Dose–response curves of SKF 82958 for control ($n = 12$) and the 150 ppm exposure group ($n = 10$). Each point represents a group mean with each bar indicating ±1 SE.

were primarily evidenced at the 0.8 mg/kg dose. These decreases produced by SKF 82958 were similar in both Pb groups. Wait reinforcers in both Pb groups were also reduced particularly by the high dose of SKF 82958, $F(3, 60) = 8.63$, $p < 0.0001$ (Fig. 3C), decreasing by values of 31% in both the 0 and 150 ppm groups. The effect of SKF 82958 on Mean Long Wait differed significantly in the two Pb exposure groups, $F(2, 40) = 4.84$, $p < 0.02$. As can be seen in Fig. 3D, SKF 82958 decreased Mean Long Wait in the control group but increased Mean Long Wait times in the 150 ppm group. This interaction was confirmed by post hoc single degree of freedom contrasts that indicated a significant linear ($p < 0.03$) but not quadratic component in the 0-ppm group, while the 150 ppm group evidenced a significant quadratic ($p < 0.04$) but not a linear component. Least-squares means indicate that SKF 82958 produced a slight decrease in Mean Long Wait at 0.2 mg/kg ($p < 0.09$) and a significant decrease at 0.4 mg/kg ($p < 0.03$) in controls. In the 150 ppm group, 0.2 mg/kg increased Mean Long Wait relative to vehicle ($p < 0.03$), but 0.4 mg/kg did not differ from either vehicle or 0.2 mg/kg. The effects of SKF 82958 administration on Rsp/Rft also depended upon Pb exposure, $F(2, 40) = 4.11$, $p < 0.03$, (Fig. 3E). Specifically, Rsp/Rft were actually increased by SKF 82958, but only in the control (0 ppm) group. This was indicated by a significant main effect of SKF 82958 in a one-way RMANOVA in the control group, $F(2, 22) = 5.00$, $p < 0.02$) accompanied by a significant linear trend ($p < 0.02$) based on a slight (approximately 25% increase) at the two SKF 82958 doses relative to vehicle and the absence of a main effect of SKF 82958 in a corresponding RMANOVA carried out in the 150-ppm group.

Effects of the D_2 Antagonist Eticlopride

Eticlopride dose dependently decreased FR response rates, $F(4, 80) = 8.32$, $p < 0.0001$). Figure 4A shows that the rate-decreasing effects of eticlopride were apparent in both exposure groups but were suggestively potentiated by 150 ppm Pb exposure, an effect that narrowly missed achieving conventional levels of statistical significance, $F(4, 80) = 2.29$, $p < 0.07$. Rates declined in the 0 ppm group by approximately 39%, whereas they decreased by 71% in the 150-ppm group. Eticlopride also significantly reduced the number of FR resets, $F(4, 80) = 3.50$, $p < 0.02$ (Fig. 4B), and these effects were significantly enhanced by 150 ppm Pb, $F(4, 80) = 3.08$, $p < 0.03$. In fact, subsequent one-way RMANOVAs carried out separately in each group confirmed that eticlopride-induced decreases were observable only in the 150 ppm group, $F(4, 36) = 3.15$, $p < 0.03$, with values decreasing by 69% relative to vehicle in this group. The administration of eticlopride likewise decreased wait reinforcer, $F(4, 80) = 9.67$, $p < 0.0001$ (Fig. 4C), and this effect was again significantly modulated by Pb exposure, $F(4, 80) = 3.20$, $p < 0.02$. As with FR resets, the decrease produced by eticlopride was restricted to the 150 ppm group, as indicated by subsequent one-way RMANOVAs, $F(4, 36) = 8.49$, $p < 0.0001$, with wait reinforcers decreasing by approximately 66%. Although the high dose (0.2 mg/kg) of eticlopride could not be used in the analyses, eticlopride had no effect on either waiting behavior, $F(3, 60) = 2.59$, $p > 0.05$ (Fig. 4D), nor on Rsp/Rft, $F(3, 60) = 1.20$, $p > 0.05$ (Fig. 4E), nor were any modulatory effects of Pb exposure on eticlopride noted for either of these dependent variables (both ps > 0.05).

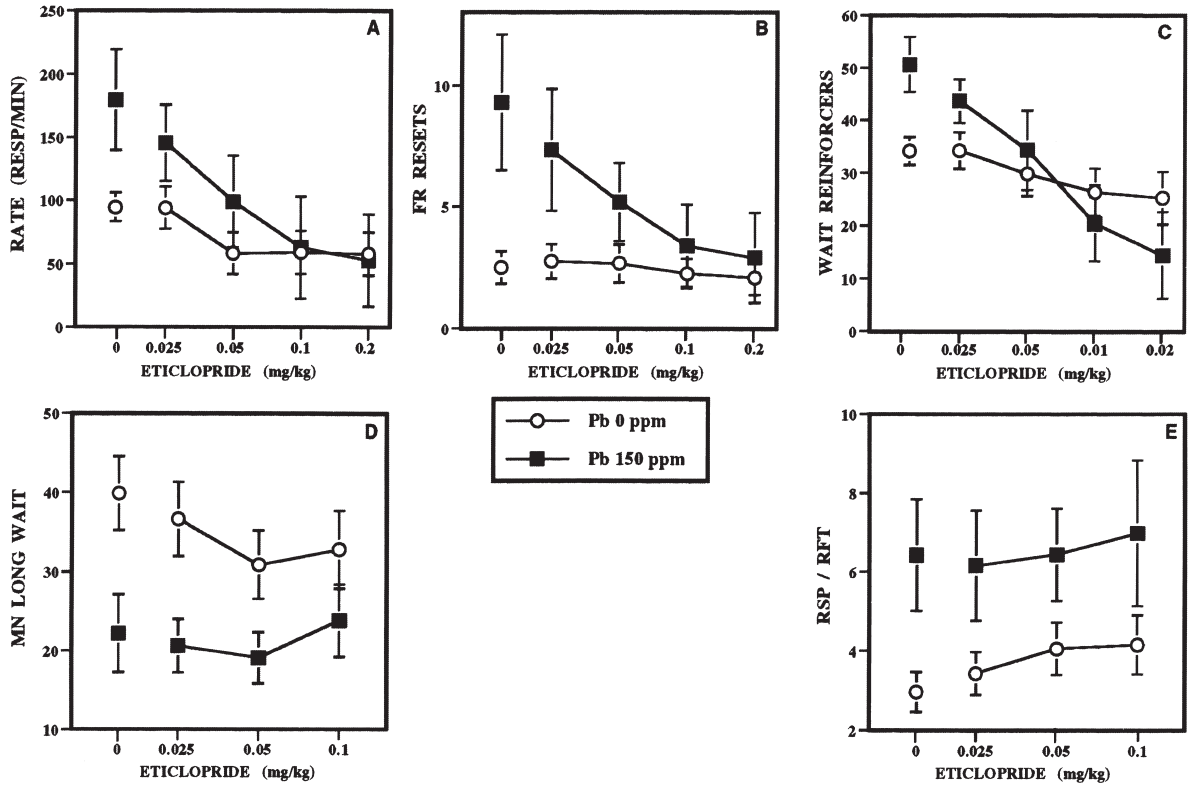

FIG. 4. Dose–response curves of eticlopride for control (n = 12) and the 150-ppm exposure group (n = 10). Each point represents a group mean with each bar indicating ±1 SE.

Effects of the D_1 Antagonist SCH 23390

FR response rates decreased with increasing doses of SCH 23390, $F(4, 80) = 5.22$, $p < 0.0009$ (Fig. 5A). Response rates declined to mean values of approximately 51–73% below vehicle. SCH 23390 also decreased FR resets, an effect that narrowly missed achieving conventional levels of statistical significance, $F(4, 80) = 2.46$, $p = 0.52$ (Fig. 5B), by values of 34–78%. Wait reinforcers likewise decreased in response to SCH 23390 administration, $F(4, 80) = 5.91$, $p < 0.0003$, (Fig. 5C), with values declining to levels of 33–57% relative to control. Although the highest dose of SCH 23390 (0.2 mg/kg) could not be used in the analyses, neither Mean Long Wait, $F(3, 48) = 0.16$, $p > 0.05$ (Fig. 5D) nor Rsp/Rft, $F(3, 48) = 1.55$, $p > 0.05$ (Fig. 5E) was altered by doses of SCH 23390. Pb exposure had no effect on any of the changes produced by SCH 23390 administration.

DISCUSSION

This study was designed to examine the hypothesis that DA system alterations would contribute to previously reported Pb-associated changes in a FR-waiting for reward paradigm (6), in which Pb exposure decreased mean waiting time relative to control levels. The pattern of Pb-associated changes on this baseline actually increased the total number of reinforcer deliveries, but concurrently doubled the number of responses for each reinforcer obtained. The extent to which these effects could be considered to reflect an inability to manage delays remains to be fully evaluated. However, the fact that Pb exposure modified the effects of some DA compounds on various measures of FR-waiting for reward performance, as summarized in Table 2, does provide evidence consistent with the possibility that DA system alterations contribute to these Pb-induced behavioral changes. Neither the DA agonists or antagonists, when administered to controls, produced a pattern of behavior mimicking the effects of Pb on this baseline. Doses of 0.05–1.0 mg/kg of the D_2 agonist quinpirole generally reversed the performance changes produced by Pb, decreasing FR response rates, FR resets, and wait reinforcers, while concurrently increasing Mean Long Wait time and decreasing the Rsp/Rft ratio to control levels (Fig. 2), suggesting a particular role for DA D_2 receptors in Pb's effects. In addition, D_2-based compounds generally exerted greater magnitude effects than did D_1-mediated compounds on this baseline. Finally, the current findings demonstrate that Pb effects on the FR component of the schedule are dissociable from its effects on mean waiting time, because all drugs decreased FR response rates but only quinpirole also altered mean waiting time. Mean waiting time was found to be more susceptible to DA agonists than antagonists, and thus presumably sensitive to enhanced DA function.

Pb exposure per se produced increased FR response rates and FR resets, which resulted in a greater total number of wait reinforcers. In addition, Mean Long Wait was significantly shorter in the 150 ppm group, but this response pattern also doubled the number of Rsp/Rft, thus resulting in a highly inefficient pattern of behavior. Possible explanations posed for the shorter Mean Long Wait times in Pb-treated rats, also detailed in the previous study [(6); see also Fig. 1] include an inability to inhibit responding or an inability to manage de-

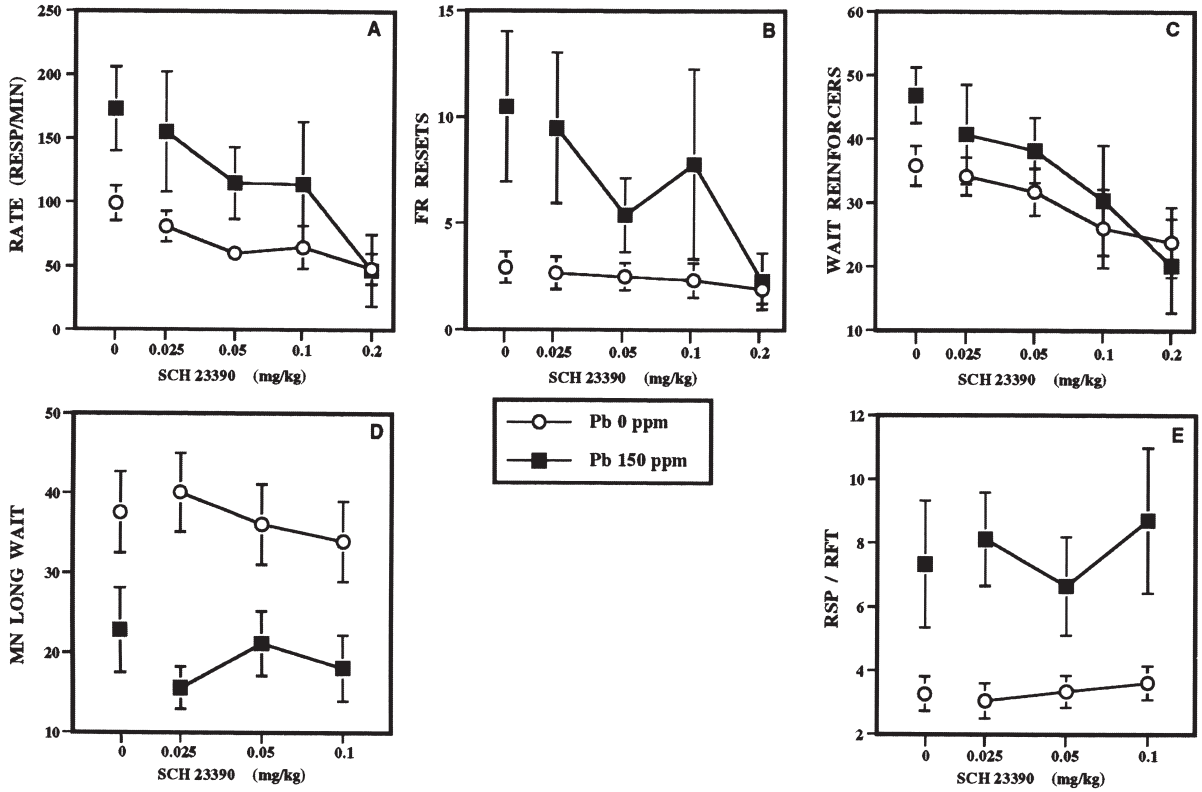

FIG. 5. Dose–response curves of SCH 23390 for control (n = 12) and the 150 ppm exposure group (n = 10). Each point represents a group mean with each bar indicating ±1 SE.

lays in reward. It could be argued, though, that Pb animals would have exhibited longer wait times had they been forced to experience the "free" pellets associated with longer delays, i.e., forced long-delay experience. This assertion seems unlikely, however, because even while waiting behavior increased to mean values in excess of 30 s at the highest dose of quinpirole in both control and Pb-treated groups (Fig. 2D), these values generally returned to pre-quinpirole levels in both groups (Fig. 1D) during the baseline sessions that preceded the determination of the subsequently collected SKF 82958 dose–effect curve. Further, although Mean Long Wait did slowly increase over the course of this experiment, the increase was not differentially affected by Pb exposure. Another potential explanation for the Pb-related shortening of mean waiting behavior is that it is directly related to FR response rates, and therefore, decreasing FR response rates alone should increase Mean Long Wait. However, this relationship was not found in the current experiment. All compounds tested decreased FR response rates, but only quinpirole notably increased waiting time, indicating a dissociation between these two components of performance on this baseline. This would suggest that decreased waiting behavior is a direct effect of Pb exposure. Finally, given that Pb has been shown to produce perseveration in humans (40), rats (9,14) and primates (30,33,36), the observed pattern of behavior might be considered to reflect repetitive motor responses

TABLE 2

SUMMARY OF THE COMPARISON OF 0 AND 150 ppm Pb DURING BASELINE AND DOSE–EFFECT DETERMINATIONS

	Rate		FR Resets		Wait Reinforcers		MN Long Wait		Rsp/Rft	
	0 ppm	150 ppm	0 ppm	150 ppm	0 ppm	150 ppm	0 ppm	150 ppm	0 ppm	150 ppm
Baseline		↑		↑		↑		↓		↑
Quinpirole	↓	↓	↓	↓	↓	↓	↓↑	↓↑	↑↓	↓
SKF 82958	↓	↓	↓	↓	↓	↓	↓	↑	↑	—
Eticlopride	↓	↓	—	↓	—	↓	—	—	—	—
SCH 23390	↓	↓	ns↓	ns↓	↓	↓	—	—	—	—

↑ = increase, ↓ = decrease, ↓↑ indicates a decrease at low doses followed by an increase at higher doses, ↑↓ indicates an increase at low doses followed by a decrease at higher doses, ns means non-significant and – means no effect. Although both DA agonists attenuated the effects of 150 ppm Pb, only quinpirole showed a reversal of 150-ppm Pb on each dependent measure.

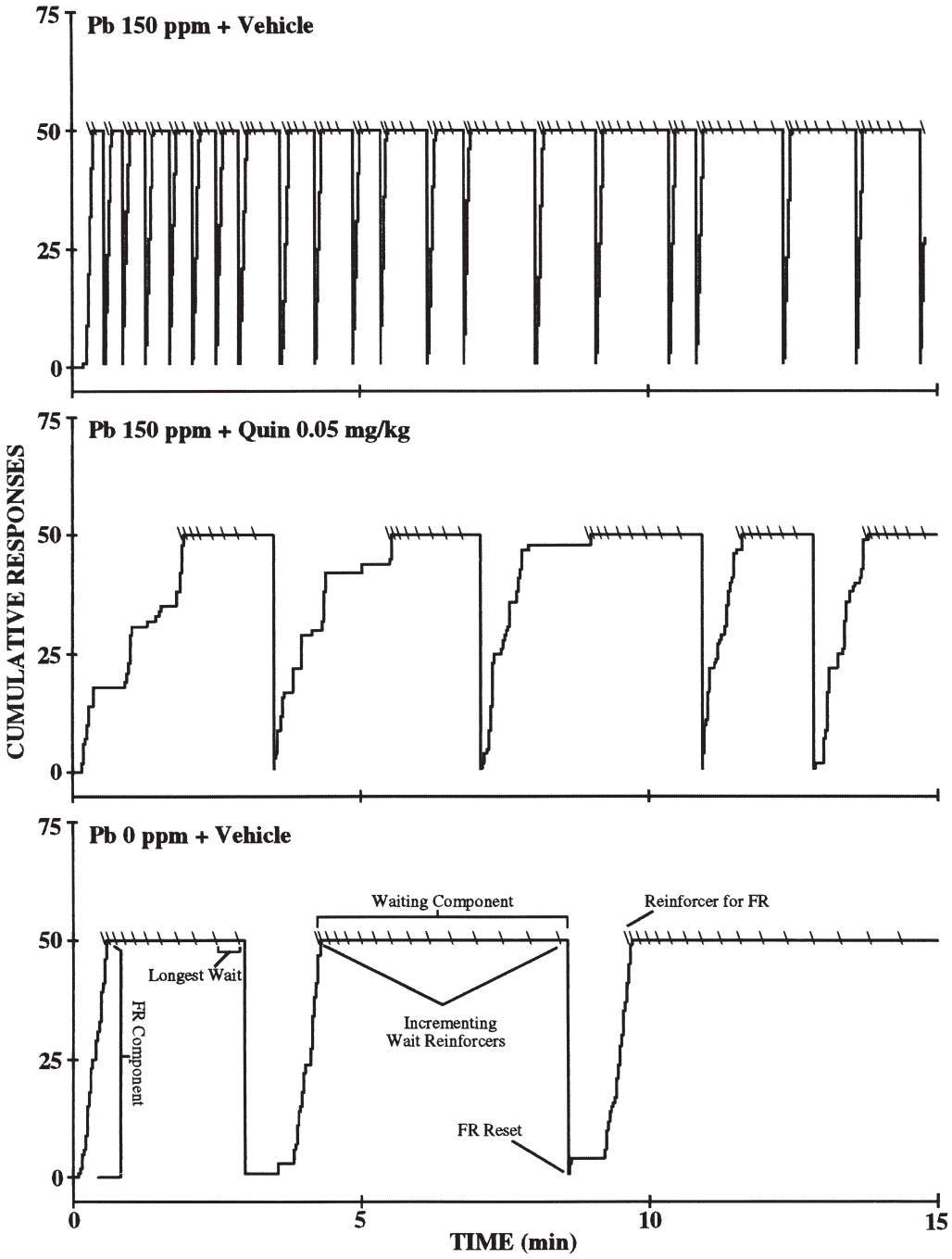

FIG. 6. Cumulative records for a rat from the 150 ppm Pb group (top panel), the same rat after receiving 0.05 mg/kg quinpirole (middle panel), and an animal from the 0 ppm group (bottom panel). Backslashes indicate reinforcers. The bottom panel is labeled to illustrate the various parameters and behavioral measures of the FR 50 waiting-for-reward procedure.

rather than an inhibitory deficit (24). However, Pb exposure does not routinely increase responding during time-out periods or delays, as would be predicted from a repetitive motor response deficit, (9,14,30,33), arguing against such an interpretation.

One of the most provocative outcomes of the current study was the finding that administration of the D_2 agonist quinpirole resulted in an apparent reversal of the effects of Pb exposure on FR waiting for reward performance. Specifically, quinpirole decreased FR response rates, number of FR resets, wait reinforcers, and responses per reinforcer while increasing Mean Long Wait time in Pb-exposed rats to values that were generally indistinguishable from controls. In Fig. 6, cumulative records show the effects of 0.05 mg/kg quinpirole

(middle panel) on the behavior of a rat exposed to 150 ppm Pb relative to its own vehicle performance (top panel) and in comparison to a control animal (bottom panel). Indeed, 7 of the 10 Pb-exposed rats showed, at least at one quinpirole dose, this restorative effect; the examples in Fig. 6 show the most pronounced effect of quinpirole on the Pb-induced baseline performance. The similarities between the performance of the Pb-exposed rat after quinpirole administration and the control rat under vehicle conditions is striking. However, it is also clear from this figure that quinpirole did not reverse the deficits produced by 150 ppm Pb completely or without producing adverse effects. For example, quinpirole not only reduced FR response rates but disrupted the usually smooth FR run into segments of bursts of responding and pausing. The interruptions in FR responding could be a result of a disruption of motor function. While this seems unlikely, because all the DA compounds examined decreased FR response rates but only quinpirole also increased waiting behavior in Pb-exposed rats, this interpretation cannot be fully ruled out.

These reversal effects of quinpirole were evident in some Pb-treated rats at doses that are consistent with presynaptic activity [i.e., 0.05 mg/kg, (18,43)], an outcome that could suggest an apparent attenuation of DA synthesis/release as the basis of this reversal, and thus enhanced DA function as a basis of the Pb-related alterations in this performance. Such an underlying mechanism would be entirely compatible with recent studies from this laboratory that have pointed to enhanced DA function, particularly in mesolimbic DA systems, as a basis of another repeatedly described behavioral manifestation of Pb exposure, increases in response rates on FI schedules of reinforcement. Studies based on microinjections of DA agonists and antagonists into NAC vs. DS (11,12) show that injection of DA itself into NAC likewise increases FI response rates, while dopamine antagonists suppress response rates. Evidence for selective mesolimbic DA system vulnerability to the chronic postweaning Pb exposure regimen used here was also obtained from recent autoradiographic and in vivo electrochemistry time-course studies (29,44). The autoradiographic studies revealed decreases in DA D_1, D_2, and DA transporter binding in NAC but not in DS, with such effects occurring after as little as 2 weeks of exposure and being sustained over a 12-month exposure duration. Decreases in binding expressed selectively in NAC are consistent with a selective increase in DA in this region. These results were buttressed by the results of in vivo electrochemistry studies that showed increases in KCl-evoked DA release in NAC but not in DS at both 11 weeks and 11 months of Pb exposure. However, assessment of the extent to which the current results reflect mesolimbic DA system function, combined nigrostriatal and mesolimbic DA system function, or even indirect DA system effects must await regional administration studies.

Interestingly, the effects of Pb on the FR waiting-for-reward paradigm used in the present study and on FI schedules are in some respects similar. On an FI schedule, Pb is associated with higher response rates that cannot increase reinforcement density. In this study, Pb produced more frequent resets of the FR component and decreased waiting behavior, but also increased Rsp/Rft. Thus, increased Rsp/Rft or inefficient response patterns are produced by Pb on both tasks. Taken together, these data strongly suggest that the behavioral deficits associated with low-level Pb exposure may be related to changes in the mesolimbic DA system.

However, the most pronounced effects of the interaction between quinpirole and Pb were seen at a dose of 0.1 mg/kg of quinpirole, which could be considered a postsynaptic D_2 agonist dose (22), suggesting the converse interpretation, i.e., Pb-related deficits are associated with insufficient DA activity. In that regard, the findings are reminiscent of those previously reported by Levin et al. (25) showing that treatment with the DA precursor l-dopa could attenuate Pb-induced deficits on a delayed spatial alternation task. Ascertaining the exact mechanism associated with this reversal is complicated by the fact that both the current study and that of Levin et al. (25) were based on systemic injections that undoubtedly resulted in widespread DA effects across brain regions. Certainly, as noted above, only regional administrations will facilitate the understanding of the specific DA mechanisms and systems involved.

Nevertheless, the current results do point to an important role for D_2 receptor function in the Pb-related changes in the FR-waiting for reward paradigm. Although interactions between Pb and both the D_1 agonist SKF 82958 and the D_2 agonist quinpirole were observed, these interactions were clearly more dramatic for quinpirole. In comparing effects across the two antagonists used in the current study, it is notable that while SCH 23390 and eticlopride both decreased FR response rates, FR resets, and number of wait reinforcers obtained, these effects were generally observed only in the Pb group following eticlopride administration but appeared to occur to an equal extent in the control and Pb-treated groups following SCH 23390.

Only DA agonists produced changes in waiting behavior and the global measure of Rsp/Rft (Table 2). As noted above, quinpirole increased Mean Long Wait in controls and in the 150-ppm group, while Rsp/Rft were altered differentially with respect to Pb exposure, with controls exhibiting a biphasic effect: the 0.05 mg/kg dose slightly increased Rsp/Rft relative to vehicle, while high doses (0.1 and 0.2 mg/kg) decreased Rsp/Rft. Quinpirole at 0.1 and 0.2 mg/kg decreased number of Rsp/Rft in the 150 ppm group relative to controls. SKF 82958 at 0.2 mg/kg showed a tendency to increase Mean Long Wait in the 150-ppm group, while 0.4 mg/kg decreased this measure in the controls. Rsp/Rft were increased slightly by SKF 82958 in the control but not in the Pb-exposed groups. The ability to modulate these performance measures with agonists but not antagonists is interesting, and although the exact basis for this difference cannot be discerned from the present study, it could be related to the greater difficulty in eliminating receptor function sufficiently with antagonists compared to enhancing function with DA agonists, i.e., receptor reserve issues.

In contrast, both dopamine agonists and antagonists decreased FR response rates. These rate-decreasing effects were not altered by Pb exposure after accounting for baseline differences between these groups. At least for DA agonists, such effects may reflect rate-dependency phenomena [e.g., (37,42)]. FR schedules, of course, including that used in the current study, produce very high rates of responding. and such high response rates tend to be decreased by DA agonists, whereas low response rates tend to be increased. FR resets were also decreased by both DA agonists and antagonists. The latter effect may be directly related to the rate decreasing effects of these compounds, such that when response rates are reduced, there are fewer opportunities in the session to reset the FR. This same sequence of events could, therefore, decrease the number of wait reinforcers that could be obtained, an effect that was also noted in response to both DA agonist and antagonist administration. The fact that both enhancing and blocking DA function can alter these components of FR performance could suggest that DA levels may modulate this performance, with a certain level of DA func-

tion resulting in "normal" levels of performance. Increasing DA function might result in behaviors incompatible with lever pressing, and thereby reduce rates, while decreasing DA function below these suitable levels alter FR response rates by other mechanisms. We have recently hypothesized a similar relationship between NAC DA function and FI response rates (11).

If postweaning Pb exposure produces increases in DA availability as suggested by Cory-Slechta et al. (29,44), then it might also be expected that DA agonists would produce Pb-like effects in controls, and DA antagonists would reverse the effects of Pb. As noted above and from the summary presented in Table 2, such a pattern of effects was not observed in the present study. However, it must be stressed that only the acute effects of these drugs were examined here, and the effects of Pb on the DA system are the result of chronic exposure occurring during development and during the acquisition of the behavioral baseline. Such hypotheses might be better approached based on chronic dosing regimes with the DA compounds. Moreover, our previous findings with respect to the preferential involvement of NAC and mesolimbic DA systems in these dopaminergic changes produced by Pb exposure point to the importance of subsequent efforts examining changes following regional administration of such compounds to further delineate the neurochemical bases of these Pb-associated behavioral changes.

Finally, these patterns of Pb-induced changes in FR waiting-for-reward and their DA-based modulation were based on an exposure protocol that was implemented in the rodent at weaning, i.e., 21 days of age. The residual contamination from prolonged use of Pb in gasoline and paint means that human Pb exposure begins at conception, and is then sustained over life. How that difference in exposure pattern might alter the nature of DA system changes and behavioral toxicity remains a critical question to be addressed.

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