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The Disruption of Prepulse Inhibition by Social Isolation in the Wistar Rat: How Robust Is the Effect?

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DOMENEY, A. AND J. FELDON. *The disruption of prepulse inhibition by social isolation in the Wistar rat: How robust is the effect?* PHARMACOL BIOCHEM BEHAV **59**(4) 883–890, 1998.—Postweaning isolation rearing in rats is shown to have consequences for the expression of numerous behaviors. The present studies investigated isolation-induced disruptions of the prepulse inhibition (PPI) response in the Wistar rat strain, as a function of exposure of the animals to locomotor activity testing. Further, repeated testing of PPI was investigated to examine the robustness of the isolation-induced disruptions. The results indicate that experimentally naive isolation-reared animals exhibit disruptions in the PPI response that are retained in a second test 7 days later. The disruptions obtained are shown to be consistent across all pulse frequencies examined and independent of effects on startle. Exposure to activity testing, however, either before or after the measurement of PPI, abolished the isolation-induced disruption of PPI in a subsequent test. In contrast, locomotor activity testing consistently revealed a hyperactivity response in isolation-reared animals that was not influenced by the temporal occurrence of the testing. The findings are discussed relative to the interpretation of data emerging from studies where both activity testing and PPI are performed in the same animals, and in the relation to the use of PPI in isolation-reared animals as representing a nonpharmacological animal model of schizophrenia. © 1998 Elsevier Science Inc.

Prepulse inhibition Social isolation Locomotor activity Schizophrenia

IN recent years researchers have focused on means by which the environment of an animal can be manipulated to produce a disturbance in the expression of normal behavior. One such environmental manipulation reported to have consequences for the expression of behavioral responses in animal species is that of postweaning social isolation. Rats subjected to early social isolation are reported to be hyperactive in an open-field environment (5,7), show increased sensitivity to amphetamine challenge (13), exhibit spatial working memory impairments in the radial maze (4), impairments in reversal learning tasks (12), in addition to showing modified responses to the rewarding effects of psychostimulants (16,26). Further, isolation rearing is reported not to affect latent inhibition (6,25) but to disrupt prepulse inhibition (9,23,25).

The measurement of sensory motor gating or prepulse inhibition (PPI) has been proposed as representing an animal model of the attentional impairments of schizophrenia (8). PPI refers to the inhibition of the startle reflex by the presentation of a weak intensity prepulse that precedes the startle stimulus (10). It is a cross-species phenomena and one that is impaired in patients with psychotic symptoms (1,2,8) and in animals following activation of central dopamine mechanisms (20). Thus, studies incorporating both environmental manipulations and the measurement of selective attention may be particularly relevant for the development of animal models of schizophrenia and as models to screen antipsychotic drugs. Indeed, it has already been suggested that non drug-induced disruptions of PPI, such as social isolation, may be a more viable approach to identify novel antipsychotics (23). This may be a particularly pertinent issue, because to obtain robust disruption of PPI by dopamine agonists a number of important methodological considerations are required. For example, complete inhibition of PPI has been demonstrated in the Wistar rat and not Sprague–Dawley derived rats (17). The effect of apomorphine on startle amplitude is reported to be influenced by inter-strain differences (18), with further inter-

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strain differences being reported in the sensitivity to the prepulse parameters (22). Such findings, therefore, support the contention that measurement of PPI in the rat is critically dependent on a number of methodological features. If the measurement of PPI in group-housed animals is already confounded by methodological issues such as those described above, then isolation rearing as an additional variable may demand careful experimental design to ensure robust results. This is particularly important if we are to accept that isolation rearing of rats and subsequent PPI measurement may represent a valid, nondrug methodology in which to investigate both physiological and pharmacological mechanisms associated with mesolimbic dysfunction.

In the majority of studies where isolation-induced disruptions of PPI have been investigated, the locomotor activity response of the animals to a novel environment has also been tested at some stage (9,23,25). It is interesting to note that in studies where both activity testing and PPI testing occurred, the detection of significant isolation-induced disruptions of PPI has often been restricted to limited prepulse frequencies, especially in the Lister Hooded rat strain (9,25). Interestingly, Geyer at al. (9), in the same study, report data obtained using both Lister Hooded and Sprague–Dawley rats, the latter of which seem to show a more consistent response over a range of prepulse frequencies. It is worthy of note, however, that in this particular study the testing was performed in different laboratories. Thus, Lister Hooded rats were exclusively used by the joint Cambridge collaborators of the study, while the San Diego group used Sprague–Dawley rats. Although isolation-induced disruptions of PPI in the Lister Hooded rat have also been reported for a full range of prepulse frequencies, these do not seem to occur in all groups of isolates tested (23). Indeed, these authors indicate that out of five separate groups of isolates significant PPI disruptions were detected in four, and these were not identical to those showing a hyperactivity response. It has been suggested that the expression of hyperactivity in isolates and PPI disruption are dissociable despite both reflecting enhanced mesolimbic dopamine function (11,25). Although this remains conceivable, additional factors may be involved. For example, it is not known if locomotor activity testing in a novel environment influences the detection of an isolation-induced disruption of PPI, an issue that may further be compromised by strain differences.

The number of successive PPI sessions to which animals can be exposed seems to be a contentious issue and one that certainly has important implications. Geyer et al. (9) report data from animals that have been retested in the PPI paradigm with inter-testing periods of 1 or 3 weeks. These authors, however, suggest that there were some indications that repeated testing of isolation-reared animals may yield progressively weaker effects on PPI. These findings are further supported by those of Varty and Higgins (23), who suggest that PPI sessions in isolates should be spaced at least 14 days apart, because shorter time periods beween testing seemed to diminish the deficit. Additionally, these authors point out that the number of sessions conducted in a single group of isolates may be limited, with the suggestion that up to four tests may be possible.

The present studies, therefore, investigated the disruption of PPI in Wistar rats reared in isolation or in groups as a function of (a) exposure to activity testing, and (b) repeated tesing over time. The studies used three groups of animals, all of which were subjected to activity testing both in photobeam cages and an open-field environment in addition to PPI testing. The only difference between the groups was the temporal order in which this testing took place. Thus, the first group of animals were initially subjected to activity testing that was followed by three repeated but separate PPI sessions. The second group of animals were experimentally naive prior to the first PPI session; this was followed by activity testing, and then the animals received two further PPI sessions. The third group were again experimentally naive before undergoing PPI testing, which was subsequently repeated once prior to activity testing, and this followed by a further PPI session. In each case animals received a total of three PPI test sessions, the third test session occurring 3 weeks after the previous experiment, whether this was an activity test or a PPI test session.

METHOD

Animals

The studies used male Wistar rats [Zur:Wist(HanIbm), bred at the Institute of Toxicology, Schwerzenbach]. Animals were housed under standard conditions in a temperature (21 ± 1°C)- and humidity (55 ± 5%)-controlled room. Animals received food (Nafag, 9431, Nafag Ecosan, Gossau, Switzerland) and water ad lib. The light schedule in the room was reversed, with lights on between 1900–0700 h, and all experiments were conducted between the hours of 0900–1800.

At weaning, 21 days, animals were either separated for isolation rearing into single cages (solid bottom cages, 42.5 × 26.6 × 15.0 cm, sawdust-lined) or housed in groups of four rats per cage (solid bottom cages, 59.0 × 38.5 × 20.0 cm, sawdust-lined) for group-housed rearing. All experimental groups were established concurrently. Twelve weeks elapsed before any experimental manipulations were initiated, during which time the isolated animals were disturbed only once weekly for cage cleaning, as opposed to the normal twice weekly routine adopted for the group-housed animals.

Spontaneous Locomotor Activity

Locomotor activity was measured in an activity analysis system comprising of individual infrared photocell cages. Activity cages were held in a bank of 40 cages (25 × 16 × 18 cm high) with one photocell set off center and with each photocell cage being shielded from the next by an opaque screen (Acti +, Viewpoint, Lyon, France).

Animals were allowed a minimum of 60 min to acclimatize to the experimental room before being placed into the activity cages. For testing, rats from a single experimental group, isolates and group reared, were tested at the same time, but distributed in a counterbalanced manner in the test rack. Activity was measured as photobeam breaks in 10-min bins for a total of 30 min.

Open-Field Activity

Activity (total distance travelled in cm) was recorded in an open-field environment comprising of four square arenas (76.5 × 76.5 × 49 cm) made of dark grey plastic and via a video camera fixed on the ceiling above the test arenas. The recorded information was relayed to a monitor and a video tracking motion analysis system (EthoVision, Noldus Information Technology bv, Wageningen, The Netherlands).

Each rat was individually placed into the open-field arena. Animals were tested in counterbalanced groups of four. Distance travelled within the open arena was measured in 10-min bins for a total of 60 min.

Prepulse Inhibition (PPI)

The prepulse inhibition paradigm was performed in four startle chambers (SR-LAB, San Diego Instruments, San Diego, CA), consisting of a transparent Plexiglas tube (diam. 8.2 cm, length 20 cm) mounted on a Plexiglas frame within a ventilated enclosure. Acoustic noise bursts were presented via a speaker mounted 24 cm above the tube. A piezoelectric accelerometer mounted below the frame detected and transduced motion within the tube. Startle amplitudes were defined as the average of 100 1-ms stabilimeter readings collected from stimulus onset.

The startle session started with a 5-min acclimatization period with a 68 dB[A] background noise level that continued throughout the session. After the acclimatization period, four startle pulses of 120 dB[A] broad band burst for 30 ms were presented to test for basal startle responsiveness. Next, six blocks of 11 trials were presented to measure prepulse inhibition. Each block included four different trial types: no stimulus, pulse alone, prepulse alone, and prepulse followed by pulse. Prepulses, 20 ms of broad band burst, had an intensity of either 72, 76, 80, or 84 dB[A]. The interstimulus interval, the time between prepulse offset and pulse onset, was 100 ms. Trial types were presented in a pseudorandom order within each block. The percentage prepulse inhibition induced by each prepulse intensity was calculated as: [100 − (100 × startle amplitude on prepulse trial)/(startle amplitude on pulse alone trial)].

Experimental Design

The studies used three separate groups of animals (groups A, B, and C) each comprising of isolation reared ($n = 10$) and group-housed ($n = 10$) rats. The animals of each group were tested in locomotor activity boxes, open-field and prepulse inhibition (PPI) during the study. The temporal order of testing, however, was different for each group such that 6 days elapsed between testing in the open field and subsequent PPI testing, but that one or three weeks elapsed between consecutive PPI tests. Each group received a total of three PPI sessions.

Group A
- Day 1: Locomotor activity boxes
- Day 3: Open field
- Day 9: PPI—test 1
- Day 16: PPI—test 2
- Day 37: PPI—test 3

Group B
- Day 1: PPI—test 1
- Day 8: Locomotor activity boxes
- Day 10: Open field
- Day 17: PPI—test 2
- Day 38: PPI—test 3

Group C
- Day 1: PPI—test 1
- Day 8: PPI—test 2
- Day 15: Locomotor activity boxes
- Day 17: Open field
- Day 38: PPI—test 3

Statistical Analysis

The data were analyzed using an analysis of variance (ANOVA), calculated with the StatView and SuperANOVA software system (Abacus Concepts, Inc., Berkeley, CA, 1992).

Locomotor activity. Activity measured in locomotor activity boxes and registered as photocell counts was analyzed using a 2×3 ANOVA consisting of a between subjects factor of housing condition (isolated, grouped) and a repeated measurements factor of three 10-min bins.

Open field. Behavior in the open field was analyzed using a 2×6 ANOVA with a between-subjects factor of housing condition and a repeated measurements factor of six 10-min bins conducted on distance moved.

Startle response. Data was analyzed in two ways. Firstly, a 2×16 ANOVA consisting of a between-subjects factor of housing condition (isolated, grouped) and a repeated measurements factor of the 16 pulse-alone presentations was conducted on the amplitude of the startle response.

Second, a further analysis comprising of a 2×4 ANOVA consisting of a between-subjects factor of housing condition (isolated, grouped) and a repeated measurements factor of four prepulse intensities was conducted on the percentage prepulse inhibition.

RESULTS

Locomotor Activity, Photocell Cages

There was a significant main effect of housing condition for group A, $F(1, 18) = 4.85$, $p < 0.05$, group B, $F(1, 18) = 5.15$, $p < 0.04$, and group C, $F(1, 18) = 14.84$, $p < 0.001$, revealing that isolated animals in each experimental group demonstrated higher overall locomotor activity compared with their group-housed counterparts. In each experiment the analysis revealed a significant effect of bin, $F(2, 36) = 41.72$, $p < 0.001$, $F(2, 36) = 19.92$, $p < 0.001$, and $F(2, 36) = 67.27$, $p < 0.001$, for experimental groups A, B, and C, respectively, indicating an overall habituation over the three time periods examined. For none of the experimental groups was there a significant housing condition × bin interaction. The locomotor activity data obtained for groups A, B, and C is presented in Table 1.

TABLE 1

LOCOMOTOR ACTIVITY MEASURED IN INDIVIDUAL ACTIVITY BOXES FOR ISOLATES AND GROUP-HOUSED RATS OF EXPERIMENTAL GROUPS A, B, AND C

Locomotor Activity (counts/10min)	A			B			C		
	10	20	30	10	20	30	10	20	30
Isolates	43 ± 3	25 ± 4	18 ± 4	47 ± 4	24 ± 3	25 ± 2	51 ± 4	38 ± 2	19 ± 2
Group-housed	36 ± 2	16 ± 2	10 ± 3	35 ± 3	24 ± 4	14 ± 5	36 ± 3	24 ± 2	15 ± 2

Data is shown as mean ± SEM counts/10-min time bins overs a 30-min test period. $n = 10$ animals per group.

Open Field

Analysis of data obtained from the open-field test revealed a significant main effect of housing condition for group A, $F(1, 18) = 13.58$, $p < 0.002$, group B, $F(1, 18) = 8.17$, $p < 0.015$, and group C, $F(1, 18) = 9.91$, $p < 0.006$. Further, for each experimental group a significant effect of bin, and a housing condition × bin interaction was obtained: group A, bin, $F(5, 90) = 101.57$, $p < 0.001$, housing condition × bin interaction, $F(5, 90) = 8.94$, $p < 0.001$. Group B, bin, $F(5, 90) = 31.77$, $p < 0.001$, housing condition × bin interaction, $F(5, 90) = 10.02$, $p < 0.001$. Group C, bin, $F(5, 90) = 32.12$, $p < 0.001$, housing condition × bin, $F(5, 90) = 2.70$, $p < 0.03$.

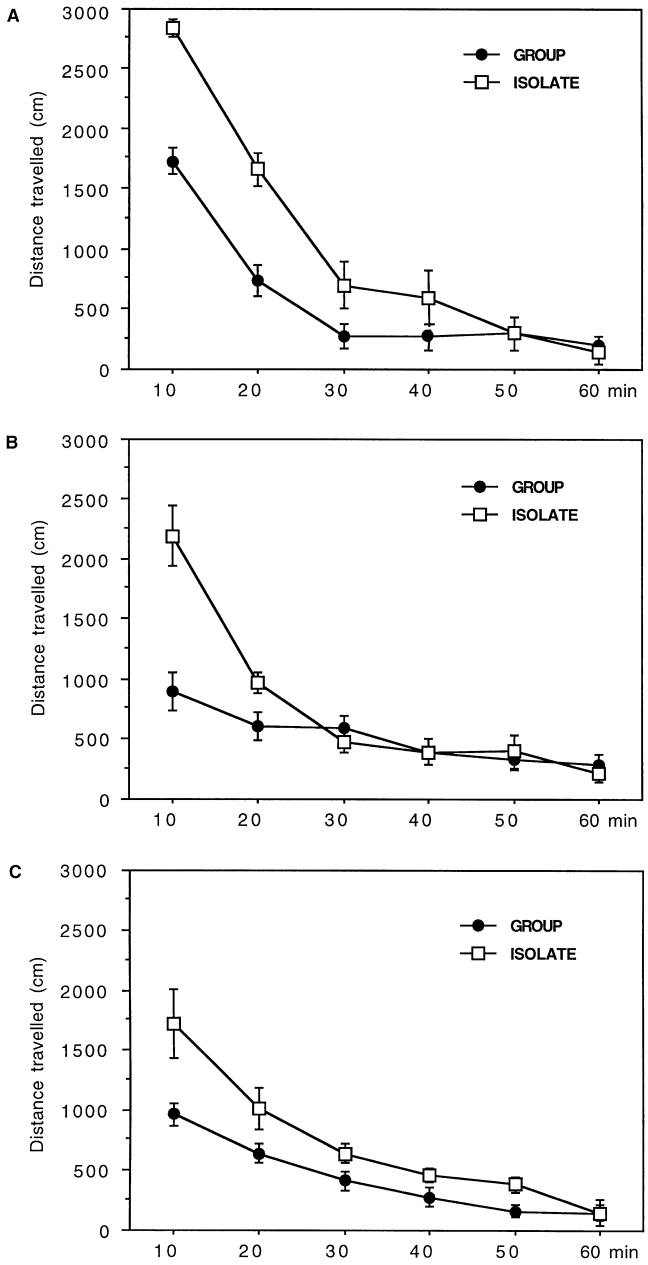

FIG. 1. The activity of group-housed (GROUP) and isolation-reared (ISOLATE) animals from experimental groups A, B, and C, measured as distance travelled (cm) in an open field in 10-min time bins over a 60-min test period.

Figure 1 depicts the distance travelled by the grouped and isolated animals of experimental groups A, B, and C over six bin periods of 10 min. The isolated animals of each group showed enhanced activity at least during the early section of the measurement session. Isolates of group C, however, showed an increased activity that lasted up to the fifth bin. In all experimental groups tested both isolated and grouped animals showed an habituation response to the novel environment during the test session.

PPI Testing

Group A. There were no significant effects of housing condition on the mean startle response in test 1 (isolated subjects 1276 ± 94 and grouped subjects 1347 ± 142), or test 2 (isolated subjects 1219 ± 127 and grouped subjects 1207 ± 121). Analysis of the data obtained in test 3, however, revealed enhanced startle responses of the isolation-reared subjects (1654 ± 185) compared with the group-reared subjects (1226 ± 156) to the first eight pulse-alone presentations. No such effect was evident for the last eight pulse-alone presentations (isolates 1520 ± 145, grouped 1422 ± 180). This was supported by a significant housing condition × pulse presentation interaction, $F(15, 270) = 1.92$, $p < 0.025$.

A significant effect of prepulse intensity was obtained for test 1, $F(3, 54) = 37.53$, $p < 0.001$, test 2, $F(3, 54) = 40.13$, $p < 0.001$, and test 3, $F(3, 54) = 30.68$, $p < 0.001$. This reflected the increasing effectiveness of more intense prepulses in inducing prepulse inhibition. There were no significant effects of housing condition on the mean prepulse inhibition in any of the three PPI tests. For test 1, the mean prepulse inhibition of the isolated group was 20 ± 8% compared with the group-housed subjects 28 ± 5%. For test 2, overall mean prepulse inhibition was 48 ± 8% (isolates) compared with 46 ± 7% (grouped-housed animals) and for test 3, the overall mean prepulse inhibition was 48 ± 6% (isolates) and 46 ± 6% (grouped-housed). All PPI testing was performed subsequent to testing the animals in locomotor activity boxes and the open field. Data for each test is presented in Fig. 2.

Group B. There was no significant effect of housing condition on the startle response of animals in PPI test 1, which was conducted prior to any other behavioral evaluation (isolated subjects 1447 ± 137 and grouped subjects 1563 ± 143). In subsequent PPI tests, however, that were conducted after locomotor activity and open-field testing, analysis of the startle response revealed for test 2 a significant main effect of housing condition, $F(1, 18) = 4.6$, $p < 0.05$. The mean startle amplitude of the isolates (1293 ± 152) being significantly lower than the mean of the group-housed animals (1690 ± 105). Similarly for test 3, analysis of the startle response yielded a significant main effect of housing condition, $F(1, 18) = 5.46$, $p < 0.04$. The isolation-reared animals again exhibited lower startle responses to the 16 alone pulse presentations (mean 1300 ± 170) compared to the group-housed subjects (mean 1791 ± 127).

A significant effect of prepulse intensity was obtained for test 1, $F(3, 54) = 17.46$, $p < 0.001$, test 2, $F(3, 54) = 36.98$, $p < 0.001$, and test 3, $F(3, 54) = 42.67$, $p < 0.001$, reflecting the increasing effectiveness of more intense prepulses in inducing prepulse inhibition.

In test 1 there was also a significant main effect of housing condition, $F(1, 18) = 6.38$, $p < 0.025$. As can be seen in Fig. 3, the isolated animals demonstrated a significant reduction of overall mean prepulse inhibition (8 ± 4%) compared with the grouped animals (32 ± 5%). This reduction was evident in all

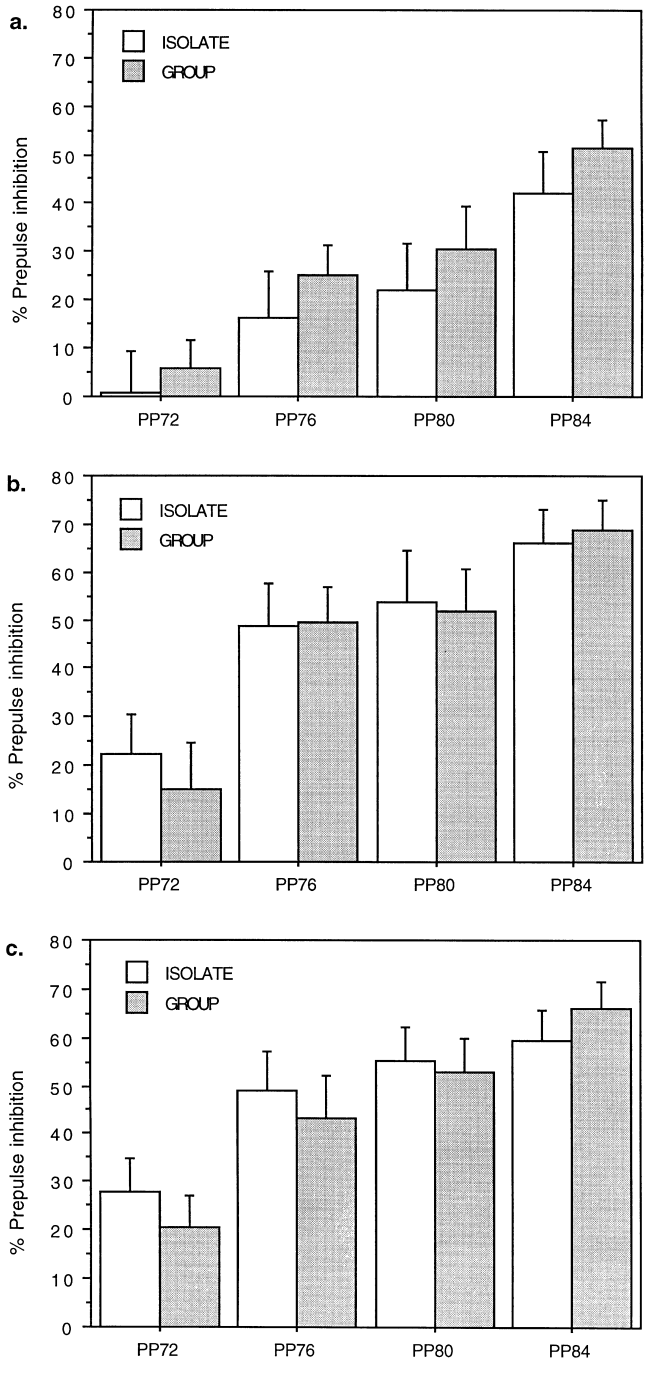

FIG. 2. Means ± SEM of percentage PPI in isolation-reared (ISOLATE) and group-housed (GROUP) animals of experimental group A for prepulse intensities 72, 76, 80, and 84 dB[A]. PPI was tested on three separate sessions: (a) test 1, (b) test 2, and (c) test 3. All three PPI tests were conducted after the animals had been tested in locomotor activity boxes and the open field. The first PPI test was performed 6 days after open-field testing. Subsequent PPI tests were separated by 7 and 14 days, respectively.

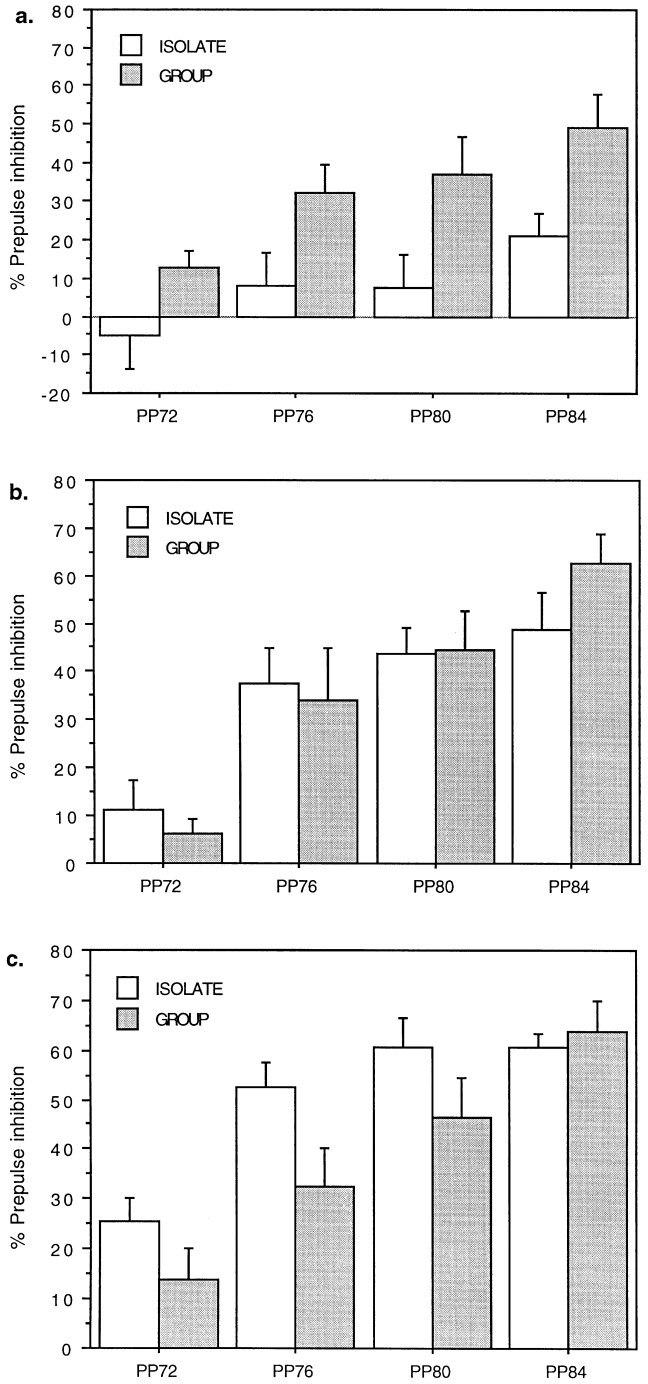

FIG. 3. Means ± SEM of percentage PPI in isolation-reared (ISOLATE) and group-housed (GROUP) animals of experimental group B for prepulse intensities 72, 76, 80, and 84 dB[A]. PPI was tested on three separate sessions: (a) test 1, conducted 7 days prior to testing the animals in locomotor activity boxes and the open field; (b) test 2 conducted 6 days after open-field testing; and (c) test 3 conducted 14 days after test 2.

four prepulse type intensities. In test 2, however, there was no difference between the overall mean of the isolated (35 ± 5%) compared with the grouped (37 ± 7%) in the percentage prepulse inhibition. A significant interaction of housing condition × prepulse intensity, $F(3, 54) = 3.06$, $p < 0.04$, was again demonstrated in test 3, as can be seen in Fig. 3. Isolated animals in this test session demonstrated a higher mean prepulse inhibition compared to the group-housed subjects for prepulse intensities of 76 and 80 dB[A].

Group C. There were no significant effects of housing condition on the startle response in test 1 (isolated subjects 1548 ± 131 and grouped subjects mean 1713 ± 143), test 2 (isolated subjects 1400 ± 154 and grouped subjects 1412 ± 175), or test 3 (isolated subjects 1400 ± 136 and grouped subjects 1091 ± 195).

A significant main effect of prepulse intensity, $F(3, 54) = 30.72$, $p < 0.001$, was obtained for test 1, test 2, $F(3, 54) = 37.15$, $p < 0.001$, and test 3, $F(3, 54) = 42.5$, $p < 0.001$, reflecting the increasing effectiveness of more intense prepulses in inducing prepulse inhibition. Further, a significant main effect of housing condition was obtained for test 1, $F(1, 18) = 11.43$, $p < 0.04$, and for test 2, $F(1, 18) = 7.18$, $p < 0.02$, but not for test 3. As can be seen in Fig. 4, the isolated animals showed a decrease in prepulse inhibition in all four intensities of the prepulse in test 1 (isolates overall mean 8 ± 4%) compared with group housed animals (overall mean 35 ± 6%). In test 2, (isolates 35 ± 7%) compared with group-housed subjects (overall mean 57 ± 5%). Although percentage PPI was greater in both isolates and group-housed rats in test 2 compared to test 1, a separate within subjects repeated measures ANOVA performed on the data obtained revealed that these differences were not significant. There was no difference between the housing conditions in test 3. The overall mean prepulse inhibition for the isolated group was 52 ± 4%, and for the group housed condition 47 ± 6%.

DISCUSSION

The results of our studies confirm those reported in the literature on two levels. First, that animals reared in isolation from weaning show locomotor hyperactivity when exposed to a novel environment relative to their socially reared counterparts (5,7,9,14,23,25). Second, that isolation-reared animals exhibit PPI deficits compared to animals reared in social groups (9,23,25).

A number of observations can be made regarding the PPI data obtained in our studies. First, the PPI deficit in isolation-reared Wistar rats was evident at all four prepulses tested. This contrasts with the findings of Geyer at al. (9) and Wilkinson et al. (25), who report disruption of PPI at one prepulse intensity only (8 dB[A] above a background of 65 dB[A]) in Lister Hooded rats. Interestingly, Varty and Higgins (23) report a more robust effect in three out of four prepulse intensities using the same rat strain. Further, in the studies of Geyer et al. (9), where half the studies were conducted in another laboratory using the Sprague–Dawley rat strain, again an isolation-induced deficit was seen for three out of four prepulse intensities.

Second, an analysis of the startle response to the 16 pulse-alone presentations in our study revealed that in six out of nine replications there was no overall effect. In the remaining three cases there was a significant main effect of housing condition, with startle being lower in isolates in two experiments while being higher in the other. None of these cases, however, was accompanied by a significant PPI disruption effect, supporting the contention that effects on startle are independent of percentage disruption of PPI (9,23).

Third, repeated testing of PPI with an inter-test interval of 7 days does not seem to influence detection of the isolation-induced PPI disruption in a subsequent session. While agreeing with the literature (9,23,25), our studies, however, demonstrate, that prior exposure to activity testing abolishes isolation-induced PPI deficits. Thus, PPI deficits can be demonstrated in experimentally naive isolation-reared animals, but not in animals that have first been exposed to activity testing. Further, a PPI deficit was still not detected in such animals even when several weeks elapsed between activity testing and a subsequent PPI session. Additionally, an isolation-induced PPI deficit demonstrable for group C during two indepen-

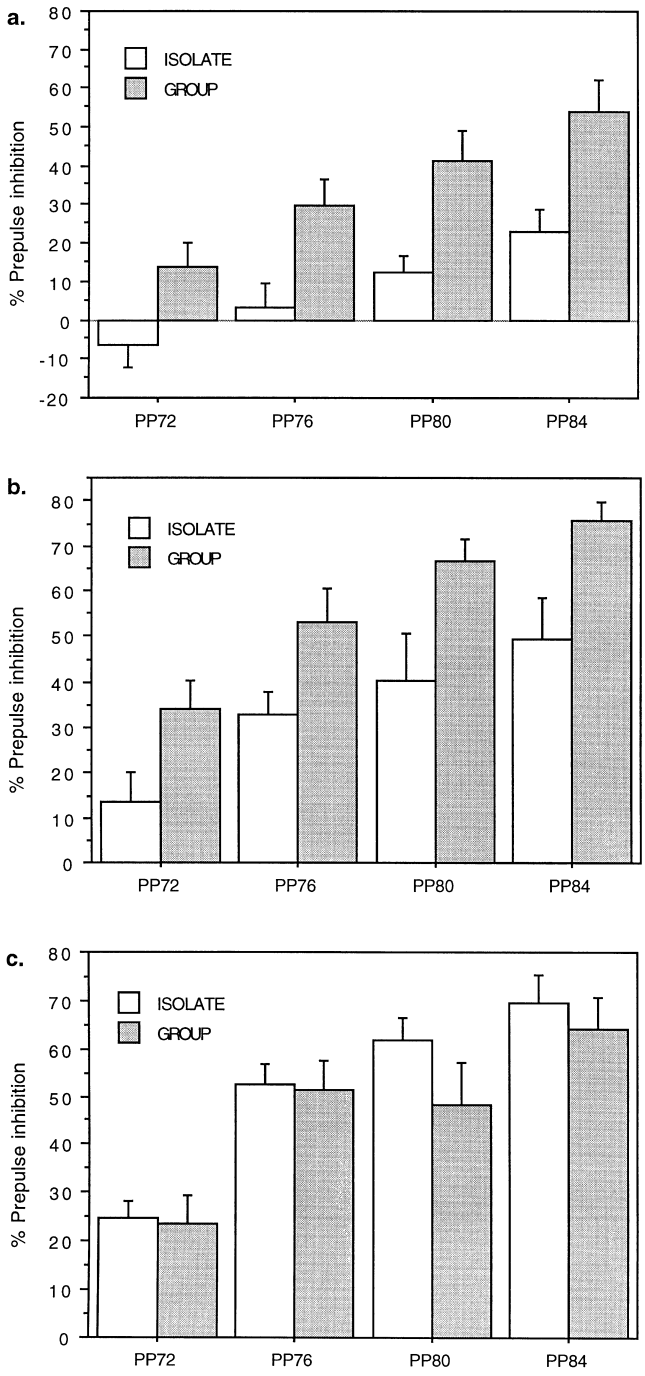

FIG. 4. Means ± SEM of percentage PPI in isolation-reared (ISOLATE) and group-reared (GROUP) animals of experimental group C for prepulse intensities 72, 76, 80, and 84 dB[A]. PPI was tested on three separate sessions: (a) test 1, (b) test 2, and (c) test 3. Tests 1 and 2 were conducted at 7-day intervals prior to testing the animals in locomotor activity boxes and the open field. The third test was conducted 14 days after open-field testing.

dent, but consecutive test sessions, was abolished by interim activity testing. The mechanism by which activity testing can so markedly influence the expression of a PPI deficit in isolation-reared animals is not known. Certainly existing reports on PPI measurement in isolates have always included data from experiments where locomotor activity was also measured (9,23,25). Although it is not always easy to ascertain the precise temporal occurrence of locomotor activity testing relative to that of PPI, in general it has been carried out prior to testing animals in the PPI paradigm. Thus, either 1 h immediately before the PPI session in a proportion of the experiments, or an unspecified time beforehand in the remainder [(9); Cambridge/San Diego study]. In other studies incorporating both behavioral measures, and where activity is measured before PPI, it is also difficult to deduce the precise temporal difference between the tests (23,25). In each of the aforementioned studies isolation-induced PPI deficits are reported for the same animals whether this be across the majority of prepulse intensities tested (9,23) or in a limited number (9,25).

It is perhaps interesting to consider to what the differences in results could be attributed. In our own studies, animals were tested in two different locomotor activity systems: small photobeam cages and a much larger open-field environment. It is not known to what extent, or indeed, which of those measurements influenced the subsequent detection of a PPI deficit in the isolation-reared animals. Clearly, if prior locomotor activity testing is able to so markedly effect the expression of a PPI defict in isolation-reared animals this may explain why some studies report a reduced effect to only one, or at least less than four prepulse intensities. That locomotor activity is modulated by several neurotransmitter mechanisms that are also reported to influence PPI (3,15,19,21,24) cannot be excluded as a contributory factor either.

Additional critical factors may include the provenance of the animals, and the conditions under which they are reared. In our studies, animals are bred on site in the same building where the laboratories are situated. Thus, transportation to the experimental holding rooms, we could assume, poses minimal disturbance. Under such conditions our animals may be particularly sensitive to any form of novel sensory stimulation, for example, first exposure to an experimental situation. How such experiences may act to dampen or indeed abolish the expression of a PPI deficit is not known. It suggests, however, that data emerging from studies where activity measurements are incorporated to evaluate the behavioral consequences of environmental manipulations should be subjected to careful analysis before precise interpretations are made.

At present, the precise biological substrates for PPI remain unknown. With respect to animals reared in isolation, however, prior experimental history could have important physiological and pharmacological implications. These findings may also have important implications for other studies that seek to further elucidate the biological substrates involved in PPI by brain lesions or pharmacological manipulations in normally socially reared animals.

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