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Rats Reared in Social Isolation Show Schizophrenia-Like Changes in Auditory Gating

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STEVENS, K. E., R. G. JOHNSON AND G. M. ROSE. *Rats reared in social isolation show schizophrenia-like changes in auditory gating.* PHARMACOL BIOCHEM BEHAV **58**(4) 1031–1036, 1997.—Central sensory filtering processes can be demonstrated using a paired stimulus paradigm. Normal humans show a diminished vertex-recorded midlatency auditory-evoked potential to the second of paired clicks (0.5 s apart), a phenomenon termed auditory gating. Schizophrenics routinely fail to suppress the response to the second stimulus; thus, they do not gate. Previous animal studies of auditory gating have used psychotomimetic drug administration to induce a schizophrenia-like loss. However, a nonpharmacologic model of deficient gating would be advantageous. Isolation rearing of weanling rats produces impaired prepulse startle inhibition similar to that observed in schizophrenics. The present studied examined the effects of rearing status upon auditory gating. Male Sprague–Dawley rats raised in social isolation (ISO) were compared to socially raised rats (SOC). Across 10 baseline recording sessions, SOC rats showed substantial gating, while ISO rats failed to gate. Abnormal auditory gating is transiently normalized by nicotine, but not haloperidol, in schizophrenics. ISO rats given nicotine bitartrate showed gating in the normal range for 60 min. By contrast, haloperidol failed to normalize gating in ISO rats. Thus, isolation rearing of weanling rats appears to produce a stable schizophrenia-like gating deficiency that shows the same pattern of response to pharmacological interventions. © 1997 Elsevier Science Inc.

Isolation rearing Auditory evoked potentials Auditory gating Sensory gating Schizophrenia Haloperidol Nicotine

WHEN normal humans or unmedicated rats are presented with identical auditory click stimuli, 0.5 s apart, the vertex-recorded midlatency evoked potential to the second is diminished compared to the first (3,4,10,33). This phenomenon has been termed auditory gating. Schizophrenic humans and amphetamine-treated rats show reduced inhibition of the response to the second click. The magnitude of both responses is similar; thus, they do not gate (3,4,10,33). This inability to filter sensory information has been linked to hyperalertness and poor discrimination in schizophrenics (4). Venables termed this condition sensory "flooding" and hypothesized that it may lead to decompensation (37,38).

Previous studies utilizing an animal model have relied on amphetamine or phencyclidine treatment to induce a loss of auditory gating such as is observed in schizophrenia. Although significant information has been gleaned from this model, it has an inherent disadvantage due to the fact that it requires pharmacological intervention to produce the initial deficit condition. A nonpharmacologic model of abnormal gating would provide a better system for exploring the mechanisms underlying the gating deficit. Recent studies have demonstrated that isolation rearing of weanling rats produces deficits in inhibition of prepulse acoustic startle (15,40), which resemble those observed in schizophrenia (14). An extensive literature has documented numerous changes in behavior and brain neurochemistry associated with variations in early social experience across several species (19,21,23,29). Specifically, isolation rearing of rats has been shown to produce changes in responses to novelty (13,31) and in both spontaneous and conditioned locomotor activity (12,18,30). Isolation rearing also produces impaired discrimination learning (19), increased resistance to extinction (7,24), and altered responses to drugs such as psychomotor stimulants (17,19,31).

The present study compared auditory gating in rats reared in social isolation with those raised at a commercial breeding facility in a social environment. Animals from the latter source

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have been used for all previous studies. Auditory gating in both groups was first assessed during a baseline period of recording. After this, isolation-reared rats were administered haloperidol or nicotine and the effects on auditory gating assessed. Socially reared animals were not tested with haloperidol or nicotine, as this work has been published previously (32, 35).

METHOD

Sprague–Dawley rat pups were delivered from pregnant dams (Harlan Laboratories, Indianapolis, IN) and allowed to remain with the mother and siblings until weaning (21 days). Male pups were then placed in individual clear polycarbonate cages with in-cage litter. They were housed in the regular colony where they could hear, see, and smell other rats. Because previous studies had shown that least 90% of rats raised in social groups (as are found in commercial breeding facilities) show normal auditory gating (16), additional male Sprague–Dawley rats were also obtained from Harlan Laboratories (at ~250–275 g body weight) and were grouped housed (three per cage; SOC) until implantation surgery. After 7 weeks of social isolation, or about 2 weeks after arrival for SOC rats, reference and recording electrode implantation surgery took place under sodium pentobarbital anesthesia (50 mg/kg, IP) with methoxyflurane as auxiliary. The brain surface recording electrode consisted of a stainless steel screw (00-80 × 1/8′) soldered to a length of 0.005′ diameter Teflon-coated stainless steel wire terminated with an Amphenol Relia-tac pin. The recording electrode was placed 4 mm posterior to bregma on the midline ("vertex") with the end in contact with the dura. The reference electrodes were a pair of 0.010′ diameter Teflon-coated stainless steel wires crimped to a single Amphenol Relia-tac pin at one end, and stripped of insulation for the terminal 4 mm at the other. The uninsulated ends were placed in the frontal cortex through burr holes drilled 3 mm anterior to bregma and ±1.5 mm lateral to midline. The pins from both electrodes were inserted into a Carlton socket connector (Carlton University, Ottawa, Canada), which was secured to the skull with four stainless steel screws and dental acrylic cement. All rats were individually housed after surgery. Rats were allowed at least 1 week to recover following surgery before baseline recordings were begun.

Auditory evoked potential recordings were performed with the rat in a plexiglas chamber (21 × 22 cm) housed in a sound-attenuating enclosure. The implanted socket was connected to a plug/locking ring assembly that contained a unity-gain FET operational amplifier. This assembly was, in turn, attached by cable to a slip-ring commutator mount at the top of the recording chamber, thus allowing full freedom of movement for the animal. The signal from the recording electrode was sent to a second-stage amplifier that increased the signal gain to a total of 5000.

Auditory stimuli were delivered through a speaker located in the ceiling of the recording chamber, 45 cm above the chamber floor. The stimuli consisted of paired 500-μs duration clicks, presented 0.5 s apart, at 87 dB (SPL). White noise from a fan provided a background noise level of 52 dB (SPL). Click pairs (a conditioning click followed by a test click) were automatically presented at 15-s intervals. Evoked potentials were computer digitized at 1 kHz over 412-ms epochs, beginning 100 ms preceding stimulus onset, and stored for later analysis.

After handling for 5–10 min, rats were connected to the cable, placed in the recording chamber, and allowed an additional 5–10 min to acclimate to the environment. For each trial, the behavior of the rat was noted at the onset of the first click and classified as to behavioral state: either alert-still, moving, or asleep. Pairs of clicks were presented until 30 alert-still trials had been recorded. Ten recordings were performed on each animal over at least 10 days (one recording session/day, maximum). The trials from a single session were averaged together, and gating parameters were determined from the average. Measurements of waveform latency were taken from stimulus onset to the peak of the evoked potential; amplitudes were measured from a baseline calculated as the average for the 100 ms immediately preceding click delivery. In addition, a TC ratio was calculated by dividing the amplitude of the test evoked potential by the amplitude of the conditioning evoked potential. A ratio of less than 1.0 indicated that the response to the test click was suppressed compared to the conditioning click. Normal rats have a TC ratio of 0.40 or less (33).

Pharmacological studies on ISO rats were conducted after completion of the baseline data collection. Rats were administered either nicotine bitartrate (0.45 mg/kg, SC) or haloperidol (1 mg/kg, SC) and evoked potential data collected for three consecutive 20 min periods following injection. On another day, each rat received the drug not previously injected and data were collected in a similar fashion. A minimum of 3 days elapsed between drug trials.

The baseline data to assess any differences in auditory gating between ISO and SOC rats were analyzed by repeated measures analysis of variance with recording session as the repeated measure and rearing as the between groups measure. For assessment of drug effects in the ISO group, recording session was again the repeated measure and drug was the between groups measure. Newman–Keuls a posteriori analysis was used when appropriate. An alpha level of $p < 0.05$ was maintained throughout the analysis.

TABLE 1

MEAN GATING PARAMETERS

	Conditioning Latency (msec)	Test Latency (msec)	Conditioning Amplitude (μvolts)	Test Amplitude (μvolts)	TC Ratio
Socially reared‡	33.7 ± 1.07	32.7 ± 1.21	125.10 ± 5.20	35.80 ± 3.73	0.29 ± 0.03
Isolation reared‡	37.4 ± 2.14*	35.9 ± 2.67	83.71 ± 10.89*	68.90 ± 5.47*	0.91 ± 0.09*
Isolation-reared + Nicotine§	35.2 ± 2.49	30.7 ± 2.20†	130.97 ± 10.56†	40.33 ± 4.03†	0.32 ± 0.04†
Isolation-reared + Haloperidol§	42.5 ± 1.92†	40.0 ± 2.19†	121.93 ± 8.84†	92.27 ± 8.57†	0.75 ± 0.04

Data are mean ± SEM; $n = 10$ for all groups.

*$p < 0.05$ as compared to socially reared rats.

†$p < 0.05$ as compared to unmediated, isolation reared rats.

‡Data are from the 10th baseline session.

§Data are from the 20–40 min time frame postinjection.

RESULTS

ISO rats were minimally more behaviorally reactive than SOC rats at the initiation of the recording experiments. By the third to fourth recording session, they were behaviorally indistinguishable from SOC rats.

The most prominent component of the vertex-recorded auditory evoked response was a negative-going potential that peaked 33 ms after click onset for SOC rats and 38 ms after click onset for ISO rats. This agrees with previous studies that found a similar negative-going wave in the same general time frame (35,37).

Examination of TC ratios for ISO and SOC rats over the first 10 unmedicated recording sessions showed a significant effect of rearing status, $F(1, 18) = 22.84$, $p < 0.001$, but no interaction of rearing status by recording session, $F(9, 162) = 0.66$, $p = 0.745$. Basically, ISO rats had high TC ratios (indicating poor gating) at the beginning of the baseline period and showed no improvement over the 10 recording sessions, while SOC rats showed good gating initially, which improved slightly over the baseline sessions (Table 1, Fig. 1).

Analysis of conditioning amplitudes showed that ISO rats had significantly lower conditioning amplitudes than SOC rats throughout the baseline recording sessions, $F(1, 18) = 8.73$, $p = 0.008$ (Fig. 2). Again, there was no interaction effect of rearing status by recording session. ISO rats also differed from SOC rats in their test amplitude responses [rearing status by recording session, $F(9, 162) = 2.21$, $p = 0.024$]. SOC rats showed a significant decrease in test amplitude over course of the baseline sessions, while ISO rats showed consistently high test amplitudes which did not change over recording session (Fig. 2).

Analysis of conditioning response latency showed that ISO rats had latencies which were significantly longer than those observed for SOC rats, $F(1, 18) = 7.17$, $p = 0.015$; neither changed over the baseline sessions. Analysis of test response latency revealed no significant effect of rearing status, $F(1, 18) = 3.76$, $p = 0.068$. Figure 3 illustrates representative evoked potentials for both SOC and ISO rats.

When ISO rats were given either nicotine bitartrate or haloperidol, significant changes in the TC ratio were observed across all three time frames tested, $F(3, 54) = 5.61$, $p = 0.002$. Newman–Keuls a posteriori analysis showed significantly lower TC ratios (e.g., better gating) for all three time frames when nicotine was administered ($p < 0.01$), but no change with haloperidol (Figs. 4 and 5). Both nicotine and haloperidol caused a significant increase in conditioning amplitude, compared to control, over all time frames tested, $F(3, 27) =$

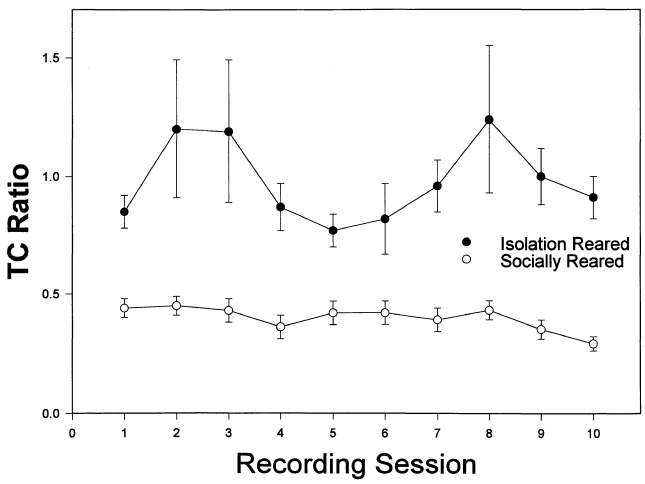

FIG. 1. Comparison of TC ratios for socially- and isolation-reared rats over the first 10 unmedicated baseline recording sessions. Socially reared rats had low TC ratios initially and improved slightly, but not significantly, over the course of the baseline sessions. Isolation-reared rats maintained consistently high TC ratios, never showing improvement. Data are the mean ± SEM, $n = 10$ for each group. TC ratios between groups are significantly different ($p < 0.05$) for all recording sessions.

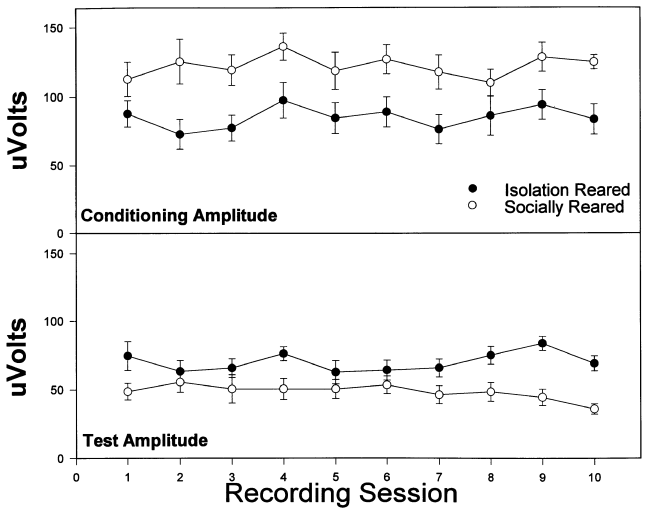

FIG. 2. Conditioning amplitude and test amplitude for vertex-recorded auditory evoked potentials from socially- and isolation-reared rats over the first 10 unmedicated baseline recording sessions. Socially-reared rats had consistently higher conditioning amplitudes than isolation-reared rats. Neither group show a significant change over the baseline period. In contrast, socially-reared rats had lower test amplitudes than isolation-reared rats, and the amplitudes deceased significantly over the baseline period. Isolation-reared rats had no change in test amplitude. Data are the mean ± SEM, $n = 10$ for each group.

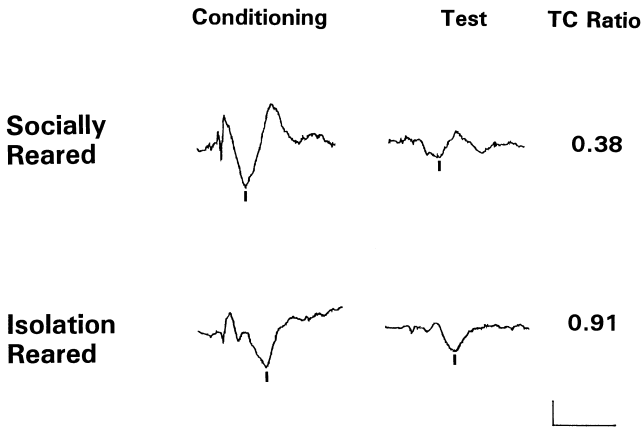

FIG. 3. Representative auditory evoked potentials recorded from vertex in a socially reared and an isolation-reared rat. Socially-reared rats had larger conditioning amplitudes and smaller test amplitudes than the isolation-reared animals. Latencies for both conditioning and test potentials were longer for isolation-reared rats. The tick marks note the peak of the wave studied. Calibration: 50 μV, 50 ms.

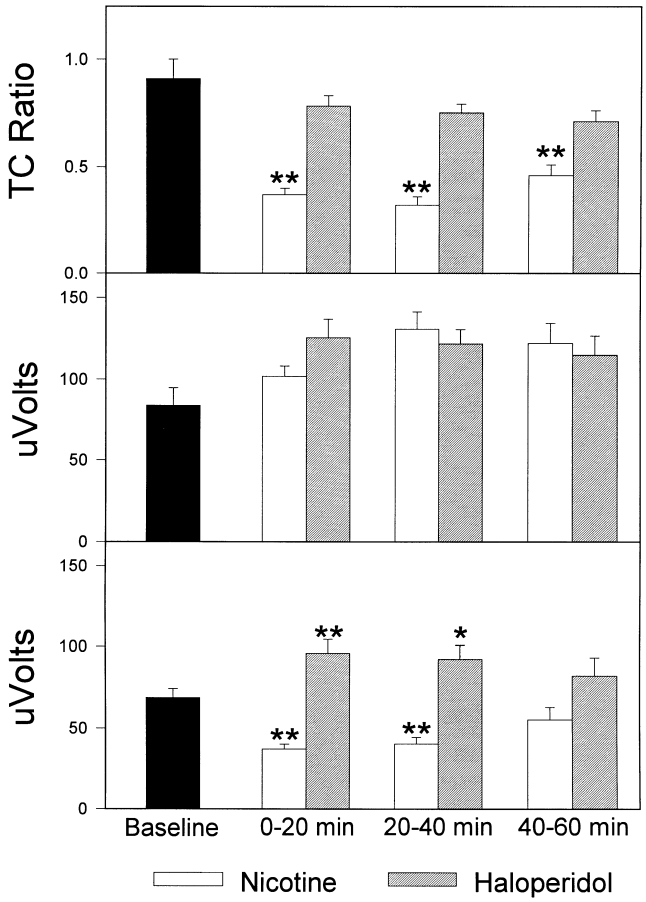

FIG. 4. The effects of nicotine bitartrate (0.45 mg/kg, SC) or haloperidol (1 mg/kg, SC) administration on TC ratio (top panel), conditioning amplitude (middle panel), and test amplitude (bottom panel) of isolation-reared rats over three time frames after injection. Nicotine significantly lowered the TC ratio at all time frames, while haloperidol had no significant effect. Conditioning amplitude was significantly increased over baseline for all three time frames for both nicotine and haloperidol injections. Nicotine significantly reduced, and haloperidol significantly increased, test amplitude over the first two time frames only. Data are mean ± SEM. *$p < 0.05$; **$p < 0.01$.

6.48, $p = 0.002$; $F(3, 27) = 5.17$, $p = 0.006$, respectively (Fig. 4). Test amplitudes showed a significant interaction between drug and recording time frame, $F(3, 54) = 13.94$, $p < 0.001$. Newman–Keuls a posteriori analysis revealed significant decreases in test amplitude in the first and second time frames after nicotine administration ($p < 0.01$), while significant increases were found over the same time frames after haloperidol administration ($p < 0.05$) (Fig. 4). Analyses of latencies following nicotine or haloperidol administration showed significant drug by recording time frame interactions for both conditioning and test latencies, $F(3, 54) = 11.45$, $p < 0.001$; $F(3, 54) = 8.02$, $p < 0.001$; respectively (Table 1). A posteriori analysis showed a significant increase in conditioning latency for all three time frames following haloperidol administration ($p < 0.01$) but no change following nicotine injection. Test latency decreased significantly following nicotine only in the second time frame ($p < 0.05$) but showed a significant increase in both the second and third time frames following haloperidol injection ($p < 0.05$) (Table 1).

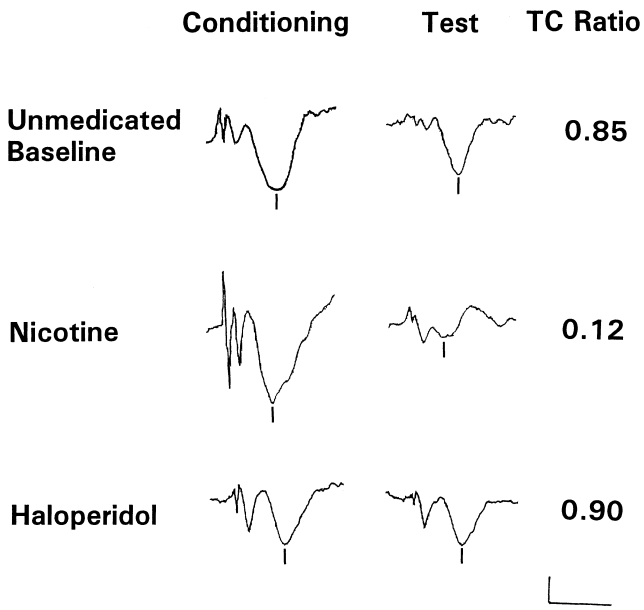

FIG. 5. Representative evoked potentials for one isolation-reared rat in the unmedicated state, 20–40 min after nicotine (0.45 mg/kg, SC) or haloperidol (1 mg/kg, SC). Nicotine lowered the TC ratio while haloperidol had no effect. Tick marks note the peak of the wave of interest. Calibration: 50 μV, 50 ms.

DISCUSSION

In the present study, isolation-reared rats (ISO) showed only minimal hyperactivity, in the form of increased nervousness during prerecording handling, which dissipated after the first few recording sessions. This agrees with previous reports of minimal increases in behavioral reactivity after isolation rearing of Sprague–Dawley rats (15), but contrasts with the significant increases in reactivity seen in the Lister-Hooded strain (28). The results of the auditory gating analyses demonstrated deficits in gating of the midlatency negative component of the auditory evoked potential in unanesthetized ISO rats, a result that resembles that observed in schizophrenia patients (4,9). In both cases, the amplitude of the conditioning evoked potential was somewhat reduced compared to controls, while the test amplitude was increased. This pattern is also similar to that observed after administration amphetamine, a psychotomimetic agent, to normal gating rats (3,33, 35). Additionally, the loss of auditory gating is in concert with recent studies of ISO rats that demonstrated deficits in prepulse inhibition of acoustic startle response (15,40), another model of gating deficits observed in schizophrenia patients (14).

When auditory gating parameters of ISO rats were compared to those raised in social environments (SOC) over the first 10 unmedicated baseline recording sessions, the ISO rats were found to show consistently higher TC ratios that did not change significantly over the 10 sessions. In contrast, SOC rats began with significantly lower TC ratios that improved over the baseline sessions. The improvement in TC ratio in SOC rats came from a significant decrease in test amplitude over the course of the baseline recording period. This is consistent with previous studies in which there is a progressive improvement in gating over the baseline, unmedicated recording sessions which asymptotes around the eighth session (33,35).

It has long been known that administration of classic neuroleptics to schizophrenia patients produces an improvement in some symptoms, but fails to normalize auditory gating (9, 10). Administration of the classic neuroleptic, haloperidol, to ISO rats produced significant increases in both conditioning and test amplitudes. However, because these increases were of similar magnitude, there was no overall change in auditory gating. This is comparable to the effect of haloperidol in socially reared rats (32). Although this result parallels the effects of neuroleptic administration to schizophrenics (10), it stands in contrast to the effect of haloperidol upon amphetamine-induced loss of gating in rats. In the latter studies, which utilized socially-reared rats, haloperidol normalized amphetamine-induced loss of gating via a selective enhancement of the conditioning evoked potential (3).

Recent studies have suggested a role for central nicotinic receptors in pathophysiology of schizophrenia (8,11). Studies of nicotine administration in schizophrenics and their normal nongating relatives has shown transient normalization of auditory gating following chewing of nicotine gum or smoking cigarettes (1,2). Animal studies have shown a loss of auditory gating following central administration of either *d*-tubocurarine or α-bungarotoxin in anesthetized rats (22). Additional studies have correlated auditory gating with the number of hippocampal α-bungarotoxin receptors present in inbred mouse strains (32). Administration of nicotine has been shown to induce transient normal gating in amphetamine-treated rats (35), in spontaneously nongating rats (16), in anesthetized fimbria-fornix–lesioned rats (5), and in certain strains of inbred mice when studied in an anesthetized paradigm (36). At the dose tested in the present study, nicotine had no effect on socially-reared rats (33). However, when administered to ISO rats, this dose of nicotine produced normal gating that persisted throughout the one hour of observation. The normalization of gating was accomplished through a combination of a significant increase in conditioning amplitude and a significant decrease in test amplitude. Studies of nongating normal humans given nicotine gum or neuroleptic-treated schizophrenic patients who smoked cigarettes indicate that, in these cases, nicotine transiently normalized gating primarily through a decrease in test amplitude (1,2).

In previous studies utilizing unanesthetized rats to study auditory gating, amphetamine had been used to induce schizophrenia-like changes in gating parameters (3,33,35). This model has certain inherent drawbacks. It requires drug administration to produce the deficit, after which other drugs are administered to study their ability to normalize the amphetamine-induced loss of gating. This sort of polypharmacy can obfuscate relevant results and render a mechanistic interpretation difficult to impossible, particularly when the drugs have multiple actions at a variety of receptors. In addition, as was stated earlier, haloperidol will normalize amphetamine-induced loss of gating, which is not consistent with the effect of neuroleptics in schizophrenics. Thus, the amphetamine model of schizophrenia-like auditory gating deficits is not likely to be optimal. An apparently better model would be an animal that demonstrated schizophrenia-like deficits in auditory gating without prior drug administration. The population of outbred Sprague–Dawley rats has been shown to contain 10% or less spontaneously nongating animals (16). Unfortunately, there is no reliable method for predicting, a priori, which animals will be nongaters and which will be normal gating animals. Thus, a reliable, nongating, nonpharmacologic model of schizophrenia-like auditory gating deficits would be a significant advance in this research area. The isolation-reared rat appears to be such a model. The behavioral manipulation of rearing the rat pup from weaning to adulthood in physical isolation from other rats produces a stable, long-term deficit in auditory gating that appears to have much in common with the deficit observed in schizophrenia. ISO rats show decreased conditioning amplitude, coupled with increased test amplitude, to produce a large TC ratio similar to that observed in schizophrenia. Studies of prepulse startle inhibition also show schizophrenia-like deficits in rats that have been isolation-reared (15,40). However, studies of latent inhibition, a model of attention deficits present in schizophrenia, did not show changes in ISO rats (40). In the present studies, pharmacological interventions also showed significant parallels to schizophrenia. Haloperidol does not normalize gating in either the ISO rats or in schizophrenia patients, while nicotine produces normal auditory gating in both.

The mechanism underlying the loss of gating observed in ISO rats is not known. Earlier work has shown increased levels of norepinephrine and dopamine (6,25) as well as decreased turnover of these neurotransmitters (27,39); previous studies in our laboratory have shown that increased levels of either of these neurotransmitters produces a loss of gating (33,34). The present study did not address changes in the norepinephrine system produced by social isolation, but the failure of haloperidol to improve gating in these animals suggests that increased central dopamine is not responsible for the deficient gating. An alternate explanation is changes in the cholinergic system, as suggested by the normalization of gating following nicotine administration to ISO rats. Previous studies have shown a loss of gating in anesthetized rats with central α-bungarotoxin or *d*-tubocurarine administration (22). Studies in mice have shown that a reduction in hippocampal α-bungarotoxin receptors is correlated with deficient gating (32) and that chronic corticosterone treatment reduces hippocampal α-bungarotoxin receptor populations (26). Because rearing of rats in social isolation has been suggested to be a chronic stressor (20), ISO rats may show stress-induced decreases in hippocampal α-bungarotoxin receptor numbers. This possibility is currently under investigation. Additional studies to assess the possible role of serotonergic receptors in the modulation of auditory gating, as well as assessment of the newer atypical neuroleptics (i.e., clozapine and risperidone) in the isolation-reared rat model are planned.

In conclusion, the present data show schizophrenia-like deficits in auditory gating in rats raised in social isolation, and subsequent improvement in gating with administration of nicotine but not haloperidol. These data, coupled with previous studies, suggest that rearing of rats in social isolation may be a superior model for studying certain dysfunctions present in schizophrenia, such as the auditory gating deficit.

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