ORIGINAL INVESTIGATION

Richard Paylor · Jacqueline N. Crawley

Inbred strain differences in prepulse inhibition of the mouse startle response

Abstract Prepulse inhibition is the phenomenon in which a weak prepulse stimulus suppresses the response to a startling stimulus. Patients with schizophrenia have impaired prepulse inhibition which is thought to reflect dysfunctional sensorimotor gating mechanisms. To investigate the potential genetic basis for differences in sensorimotor gating, the responses of 13 inbred strains of mice were evaluated using the prepulse inhibition paradigm. Ten male mice from A/J, AKR/J, BALB/cByJ, BUB/BnJ, C3H/HeJ, C57BL/6J, C57BL/10J, DBA/2J, FVB/NJ, ST/bJ, 129/J, 129/SvJ, 129/SvEvTac inbred strains were tested for acoustic prepulse inhibition of acoustic and tactile startle responses. There was a wide range of responses among the inbred strains of mice. Exact strain distributions were determined for each combination of prepulse sound level and startle stimulus. In general, mice from the 129/SvEvTac, AKR/J, 129/J, and 129/SvJ strains displayed high levels of prepulse inhibition of both the acoustic and tactile startle responses. C57BL/6J, C57BL/10J and BUB/BnJ mice showed low levels of prepulse inhibition. There was also a wide range in the amplitude of the acoustic and tactile startle responses. C57BL/10J and FVB/NJ mice displayed the greatest startle responses and DBA/2J, 129/J and 129/SvJ had the poorest startle responses. There was no correlation between the level of prepulse inhibition and the amplitude of the startle response. These findings indicate that inbred strains of mice may be a useful tool to study the genetic basis of sensorimotor gating.

Key words Inbred mice · Sensorimotor gating · Prepulse inhibition · Acoustic startle · Tactile startle

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Introduction

The startle response is an unconditioned reflexive response to a sudden environmental stimulus. Plasticity to the startle response is evident in paradigms such as prepulse inhibition and habituation. Prepulse inhibition is the phenomenon in which a weak prestimulus or prepulse suppresses the response to a startling stimulus (Ison et al. 1973; Graham 1975). A number of studies have shown that patients with schizophrenia (Braff et al. 1978; Grillon et al. 1992; McDowd et al. 1993) and schizotypal personality disorder (Cadenhead et al. 1993), obsessive-compulsive disorder (Swerdlow et al. 1993), and Huntington's disease (Swerdlow et al. 1995) have an impaired prepulse inhibition response. The prepulse inhibition impairment observed in these neuropsychiatric patients is thought to reflect an underlying problem with inhibitory mechanisms in neuronal systems used for sensorimotor gating (Freedman et al. 1987; Braff and Geyer 1990; Waldo et al. 1995). Prepulse inhibition is one of the few paradigms in which humans and rodents are tested in similar fashions. The prepulse inhibition paradigm has quickly become the test of choice for scientists developing rodent models to study the mechanisms underlying the sensorimotor gating deficit observed in schizophrenia (Geyer and Braff 1987; Geyer et al. 1990; Swerdlow et al. 1994). In addition, apomorphine-induced deficits in prepulse inhibition in rats appears to provide a useful screening paradigm for developing new antipsychotics (Rigdon and Viik 1991; Swerdlow et al. 1991, 1994; Hoffman et al. 1993; Johansson et al. 1995).

Key neuroanatomical and neuropharmacological substrates mediating prepulse inhibition have been analyzed in rats. Direct pharmacological injections and lesion studies indicate that structures contributing to prepulse inhibition include the nucleus accumbens (Wan and Swerdlow 1993; Wan et al. 1994), hippocampus (Caine et al. 1992; Koch 1996), amygdala (Decker et al. 1995), medial prefrontal cortex (Bubser and Koch 1994; Koch and Bubser 1994), pedunculopontine tegmental nucleus (Koch et al. 1993; Swerdlow and Geyer 1993), ventral

and caudodorsal striatum (Kodsi and Swerdlow 1994, 1995a), median and dorsal raphe nucleus (Sipes and Geyer 1995b), and the superior colliculus (Fendt et al. 1994). Neurotransmitters affecting prepulse inhibition include dopamine (Mansbach et al. 1988; Hoffman and Donovan 1994; Caine et al. 1995), acetylcholine (Koch et al. 1993; Stevens et al. 1993b; Wu et al. 1993; Curzon et al. 1994), serotonin (Sipes and Geyer 1994, 1995a, b; Varty and Higgins 1995), glutamate (Hoffman et al. 1993; Reijmers et al. 1995), GABA (Kodsi and Swerdlow 1995b) and norepinephrine (Stevens et al. 1993a).

A number of studies have used behavioral genetic techniques to begin to understand the genetic influences on acoustic startle (Marks et al. 1989b; Glowa and Hansen 1994; Acri et al. 1995). Inbred mice are now being used to study the genetic basis of sensorimotor gating. Using the hippocampal auditory evoked response paradigm, Stevens et al. (1996) demonstrated that there are differences in the electrophysiological response to repeated auditory stimuli in nine inbred strains of mice. Bullock et al. (1995) presented a preliminary inbred mouse strain distribution using the prepulse inhibition paradigm. Willott and colleagues (1994) showed strain dependent changes in prepulse inhibition that are associated with age-related hearing loss.

The current study was designed to characterize fully the startle response and prepulse inhibition in a large number of the inbred strains of mice used in behavioral genetics. Identifying inbred mouse strains that differ in prepulse inhibition will be an important first step to discovering genes linked to deficits in sensorimotor gating. Further, the present experiments are designed to standardize the prepulse inhibition paradigm for mice. Previous startle and sensorimotor gating studies used inbred strains of mice bred at the Institute for Behavioral Genetics, Boulder, Colo. (Bullock et al. 1995). Further, the previous studies used procedures (e.g. startle stimulus duration) that differ from those commonly used for rats. To increase the applicability of genetic information obtained using inbred strains of mice to the overall understanding of prepulse inhibition from rat and human studies, the present experiments utilized mice commercially available from the Jackson Laboratory, Bar Harbor, Maine, USA, and standard prepulse inhibition testing equipment and procedures commonly described in previous literature (e.g. Mansbach et al. 1988; Curzon et al. 1994; Bristow et al. 1996).

Materials and methods

Animals

Ten male mice from the following inbred strains were used: 129/J, 129/SvJ, 129/SvEvTac, A/J, AKR/J, BALB/cByJ, BUB/BnJ, C3H/HeJ, C57BL/6J. C57BL/10J. DBA/2J, and ST/bJ. All mice were obtained from Jackson Laboratories (Bar Harbor, Maine, USA) except the 129/SvEvTac mice which were obtain from Taconic Farms (Germantown, N.Y., USA). Mice were allowed 10–15 days to acclimate after arrival in the NIH vivarium and were 55–80 days of age before testing commenced. The subjects were housed five per cage, with food and water available ad libitium on a 12:12-h light:dark cycle with lights on at 0600 hours. Testing was performed during the light cycle from 0730 to 1300 hours. All testing procedures were approved by the NIMH Intramural Animal Care and Use Committee and followed the NIH Guidelines for Using Animals in Intramural Research.

Apparatus

Testing was conducted in two SR-Lab Systems (San Diego Instruments, San Diego, Calif., USA). Each system contains a 5.1-cm (outside diameter) Plexiglas cylinder mounted on a platform (20.4 cm length × 12.7 cm width × 0.4 cm thick) with a piezoelectric accelerometer unit attached below the Plexiglas cylinder. The piezoelectric unit transduces vibrations into signals that are rectified and stored by a microcomputer interface. The Plexiglas cylinder and platform are located in a sound attenuated chamber (San Diego Instruments) with a loudspeaker (28 cm above the cylinder), and house light. A piece of copper tubing was inserted into the chamber so that an air-puff stimulus could be applied directly to the body of a subject. The sensitivity of the two platforms was calibrated using a vibrating standardization unit (San Diego Instruments) that emulates an animal's response, to ensure that the sensitivity of the two chambers is not different (<5%). The average readings in the two chambers was 1100 using the standardization unit. The background noise level in each chamber was 70 dB. The sound levels for the background noise and each stimulus in both chambers were calibrated with a digital sound level meter (Radio Shack Sound Level Meter).

Acoustic prepulse inhibition of a tactile startle response

Each test session began by placing a subject in the Plexiglas cylinder where it was left undisturbed for 5 min. After the 5-min acclimation, each subject was presented with 42 trials over the 10.5-min test session. Each session consisted of seven trial types. One trial type was a 40-ms, 12-psi tactile startle stimulus. There were five different acoustic prepulse plus tactile startle stimulus trials presented so that the onset of a prepulse stimulus was 100 ms before the onset of the startle stimulus. The 20-ms prepulse stimuli were sounds of 74, 78, 82, 86, or 90 dB. Finally, there were trials where no stimulus was presented, to measure baseline movement in the cylinders. The seven trial types were presented in pseudorandom order such that each trial type was presented once within a block of seven trials. The average intertrial interval was 15 s (ranged from 10 to 20 s). The startle response was recorded for 65 ms (measuring the response every 1 ms) starting with the onset of the startle stimulus. The maximum startle amplitude recorded during the 65-ms sampling window was used as the dependent variable. A 65-ms recording window was used because it was more than twice the latency for the peak response (approximately 15–30 ms after the onset of the startle stimulus) measured during a pilot study.

Acoustic prepulse inhibition of an acoustic startle response

Seven to 14 days after being tested for acoustic prepulse inhibition of the tactile startle response, each subject was retested using the same procedures and trial types, but the startle stimulus was a 40-ms, 120-dB burst of sound. Mice from the BUB/BnJ strain were not tested for prepulse inhibition of the acoustic startle response since they had several wounds on their body from fighting during the week prior to testing. Acoustic startle stimulus alone trials, five acoustic prepulse plus acoustic startle stimulus trials, and no stimulus trials were presented.

Acoustic startle response profile

Ten naive 129/J, 129/SvJ, 129/SvEvTac, A/J, AKR/J, BALB/cByJ, C3H/HeJ, C57BL/6J, DBA/2J, and eight C57BL/10J male

mice were tested. Each test session began by placing a subject in the Plexiglas cylinder where it was left undisturbed for 5 min. After the 5-min acclimation, each subject was presented 36 trials over the 9-min test session. There were nine different sound levels (dB) presented: 70, 74, 78, 82, 86, 90, 100, 110, and 120. Each stimulus was 40 ms and presented four times in pseudorandom order such that each sound level was presented within a block of nine trials. The average intertrial interval was 15 s (ranged from 10 to 20 s). The startle response was recorded for 65 ms (measuring the response every 1-ms) starting with the onset of the startle stimulus. The maximum startle amplitude recorded during the 65-ms sampling window was used as the dependent variable.

Data analyses

Prepulse inhibition tests

The data from the tactile startle stimulus, acoustic startle stimulus, and no stimulus trials were analyzed using one-way ANOVAs. Prepulse inhibition data were analyzed using two-way ANOVAs with repeated measures. Post-hoc comparisons were made using Newman-Keuls and simple effects tests. The following formula was used to calculate % prepulse inhibition of a startle response: 100–[(startle response on acoustic prepulse plus startle stimulus trials /startle response alone trials) × 100]. Thus, a high % prepulse inhibition value indicates good prepulse inhibition, i.e. the subject showed a reduced startle response when a prepulse stimulus was presented compared to when the startle stimulus was presented alone. Conversely, a low % prepulse inhibition value indicates poor prepulse inhibition, i.e. the startle response was similar with and without the prepulse.

Pearson's correlations were used to determine if there were relationships between (1) prepulse inhibition of the tactile startle response and prepulse inhibition of the acoustic response, (2) tactile startle response and prepulse inhibition of the tactile startle, (3) acoustic startle response and prepulse inhibition of the acoustic startle, and (4) tactile and acoustic startle response.

Acoustic startle response profile

A three-way ANOVA with repeated measures was used with appropriate follow-up comparisons (Newman-Keuls and simple effects tests) to evaluate differences between the strains in the magnitude of the startle response to the various sound levels. For each strain, startle responses to the various stimuli were analyzed individually using an ANOVA with repeated measures followed by planned contrast comparisons in which the response to each stimulus intensity was compared to the response following the presentation of the 70-dB (baseline, background noise level) stimulus. In this latter analysis, the threshold for response measure was defined as the stimulus level which produces a significantly higher response ($P<0.05$) compared to the baseline response measured to the 70-dB sound. To ensure that this was a stable response, the response to each of the remaining stimuli also had to be significantly different from that observed at baseline. Pearson's correlation determined if there was a relationship between the maximum startle response observed with the 120-dB sound and the threshold for response measure among the inbred strains of mice.

Results

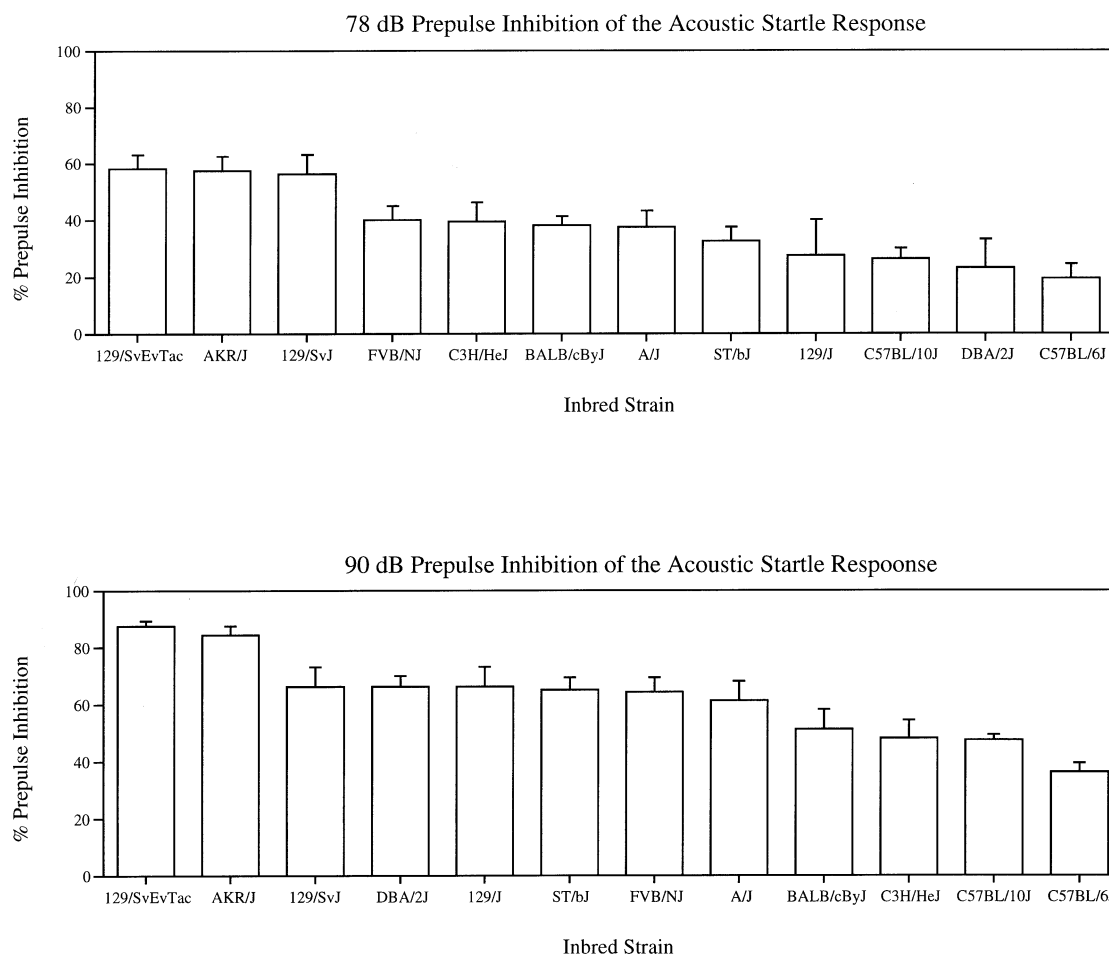Prepulse inhibition of the acoustic startle response

Figure 1 presents the strain distributions for the level of prepulse inhibition of the acoustic startle response following 78- and 90-dB prepulses. With the 78-dB pre-

pulse stimulus, 129/SvEvTac, AKR/J and 129/SvJ showed the highest levels of prepulse inhibition, and C57BL/6J, DBA/2J, and 129/J showed the lowest. With the 90-dB prepulse stimulus, 129/SvEvTac, AKR/J and 129/SvJ showed the highest levels of prepulse inhibition, and C57BL/6J, C57BL/10J and C3H displayed the lowest amounts of prepulse inhibition. The levels of prepulse inhibition obtained with each of the five different prepulses for each individual strain are presented in Fig. 2. A two-way ANOVA revealed a significant main effect of strain [$F (11, 108) = 7.054$, $P<0.0001$], indicating that overall the strains had different levels of prepulse inhibition. The main effect of prepulse sound level [$F (4, 432) = 131.032$, $P<0.0001$] was also significant. Finally, the strain × prepulse sound level interaction was significant [$F (44, 432) = 3.422$, $P<0.0001$]. Simple effects analysis of the interaction revealed that there was an effect of strain at each of the prepulse sound levels, and that the % prepulse inhibition increased with increasing prepulse sound levels in each strain except the C3H/HeJ and BALB/cByJ strains.

The current study used the peak response amplitude measure instead of the average response amplitude (e.g. Swerdlow et al. 1991). These two measurements were highly correlated for levels of prepulse inhibition of the acoustic startle response among the 12 inbred strains of mice (r values >0.95).

Prepulse inhibition of the tactile startle response

Figure 3 displays the strain distributions for the amount of prepulse inhibition of the tactile startle response following 78- and 90-dB prepulses. With the 78-dB prepulse stimulus, 129/SvEvTac, AKR/J and 129/J showed the highest levels of prepulse inhibition, and BUB/BnJ, C57BL/6J, DBA/2J, and FVB/NJ showed the poorest. With the 90-dB prepulse stimulus, 129/SvEvTac, AKR/J and 129/SvJ showed the highest levels of prepulse inhibition, and BUB/BnJ, C57BL/6J, C57BL/10J and C3H/HeJ displayed the lowest amounts of prepulse inhibition. The level of prepulse inhibition for individual strains are presented in Fig. 4. There was a significant main effect of strain [$F (12, 116) = 10.836$, $P<0.0001$], indicating that overall the strains had different levels of prepulse inhibition. The main effect of prepulse sound level [$F (4, 464) = 77.649$, $P<0.0001$] was also significant showing that prepulse inhibition increased as the prepulse sound level increased. Finally, there was a significant strain × prepulse sound level interaction [$F (48, 464) = 2.179$, $P<0.0001$]. Simple effects analysis of the interaction revealed that there was an effect of strain at each of the prepulse sound levels, and that the amount of prepulse inhibition increased with increasing prepulse sound level in each strain except for the C3H/HeJ and C57BL/10J strains. In the latter two strains, the % prepulse inhibition remained the same over the five prepulse sound levels tested. The data from one AKR/J mouse had to be excluded due to experimenter error.

78 dB Prepulse Inhibition of the Acoustic Startle Response

90 dB Prepulse Inhibition of the Acoustic Startle Respoonse

Fig. 1 Strain distributions for prepulse inhibition of the acoustic startle response with the 78-dB (*top panel*) and 90-dB (*bottom panel*) prepulse stimuli for 12 inbred strains of mice. Data represent the mean (±SEM) % prepulse inhibition of ten male mice from each strain

Acoustic startle response

The acoustic startle responses from the 12 inbred strains obtained during the testing session to evaluate prepulse inhibition of the acoustic startle response are presented in Fig. 5. The overall differences in the acoustic startle was statistically significant [F (11, 108) = 27.567, $P<0.0001$]. In general, the C57BL/10J, FVB/NJ, BALB/cByJ, and ST/bJ showed the greatest response and the DBA/2, 129/J, and 129/SvJ had the poorest acoustic startle response.

Tactile startle response

The tactile startle responses from the 12 inbred strains obtained during the testing session to evaluate prepulse inhibition of the tactile startle response are presented in Fig. 5. The overall difference in tactile startle response was statistically significant [F (12, 116) = 20.622, $P<0.0001$]. In general, the C57BL/10J had the greatest tactile startle

response and the DBA/2, 129/J, and 129/SvJ showed the poorest response.

No stimulus trials

Data from the no stimulus trials indicate that the different inbred strains of mice have significantly different levels of basal activity in the restraining tube ($P<0.0001$; data not presented). In general, DBA/2J mice were the most active and 129/SvJ and 129/SvEvTac were the least active. The values obtained during no stimulus trials were less than 5% of the responses observed during startle stimulus trials, and therefore cannot account for strain differences in startle or prepulse inhibition.

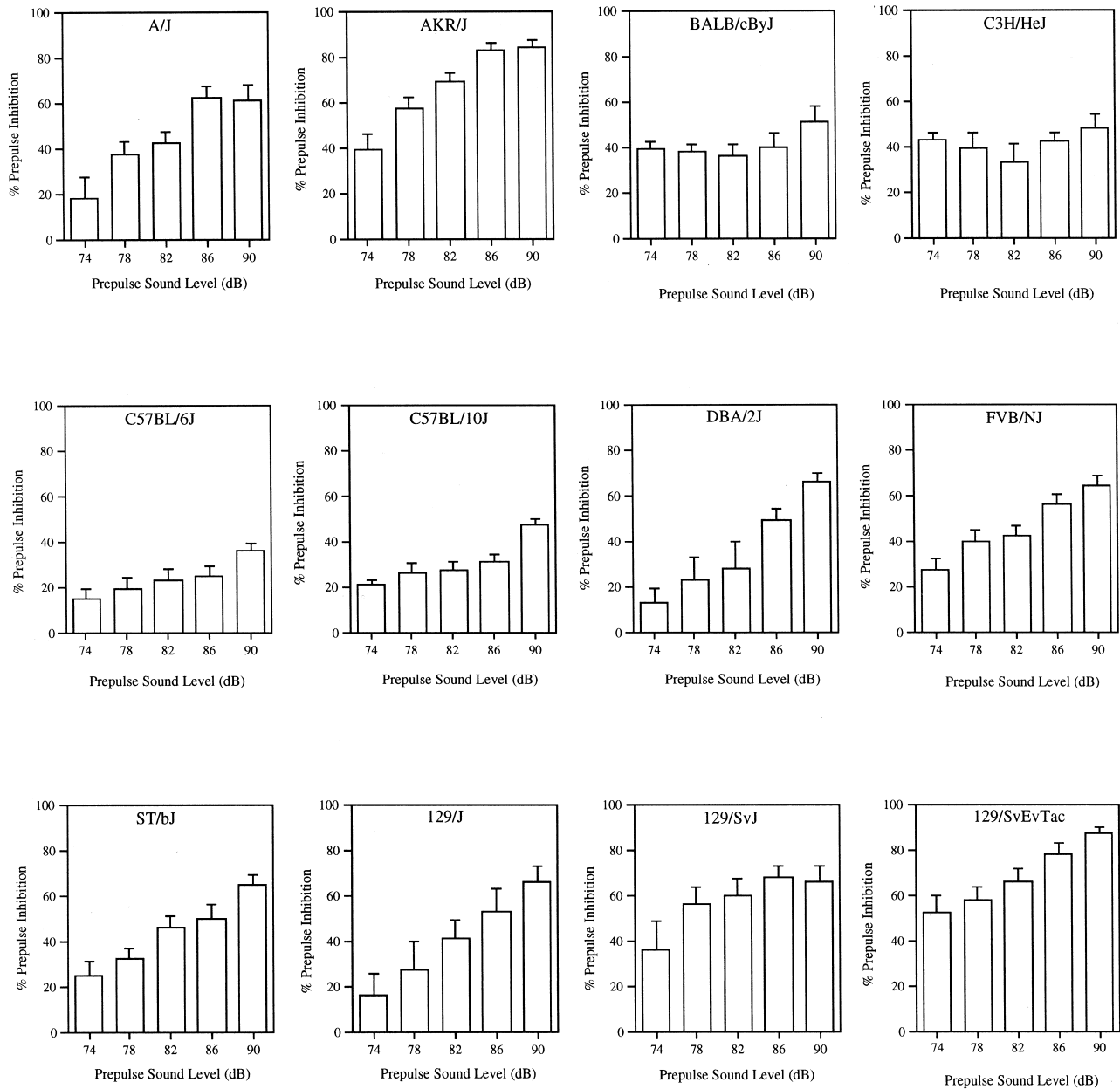## Correlational analyses of startle and prepulse inhibition

The prepulse inhibition of the tactile startle response was positively correlated to the prepulse inhibition of the acoustic startle response using the 82-($r = 0.768$, $P<0.001$), 86-($r = 0.824$, $P<0.001$), and 90-($r = 0.856$, $P<0.001$) dB prepulses, but not with the 74-($r = 0.299$, $P>0.05$) or 78-($r = 0.481$, $P>0.05$) dB prepulses. In addition, the tactile startle response was positively correlated with the acoustic startle response ($r = 0.896$, $P<0.001$). However, there were
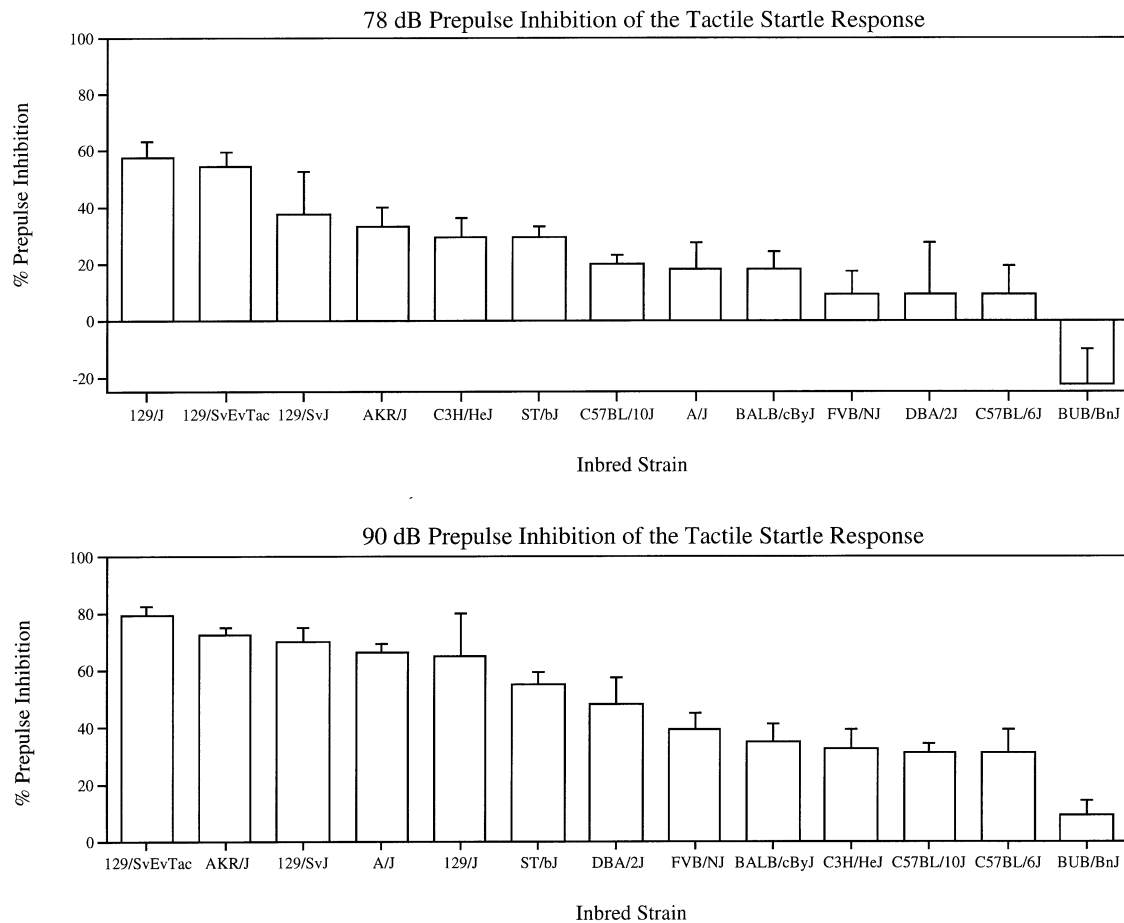
Fig. 2 Percent prepulse inhibition of the acoustic startle response for the 12 inbred strains of mice. The level of prepulse inhibition of the acoustic startle response obtained with each of the five prepulse stimuli is presented for each individual inbred strain. Data represent the mean (±SEM) % prepulse inhibition of ten male mice from each strain

no significant correlations between the tactile startle response and the level of prepulse inhibition (r values ranged from 0.099 to 0.427, $Ps>0.05$). The correlations between the acoustic startle response and the level of prepulse inhibition were also not significant (r values ranged from 0.013 to 0.411, $Ps>0.05$).

Acoustic startle amplitude and threshold

The acoustic startle response to each of the sound levels and the threshold for response value for each of the inbred strains are presented in Fig. 6. The magnitude of the acoustic startle response was determined by both strain and stimulus sound level. A three-way ANOVA with repeated measures revealed a significant main effect of strain [$F (10, 97) = 14.972$, $P<0.0001$], stimulus level [$F (8, 776) = 358.617$, $P<0.0001$], and a significant strain × stimulus level interaction [$F (80, 776) = 15.04$, $P<0.0001$]. Overall, the C57BL/10J, FVB/NJ, A/J, and BALB/cByJ had the greatest startle response amplitude, while the 129/J and 129/SvJ had the smallest startle response amplitude. Simple effects analysis of the strain × stimulus level interaction showed that the difference in the startle response between the inbred strains of

Fig. 3 Strain distributions for prepulse inhibition of the tactile startle response with the 78-dB (*top panel*) and 90-dB (*bottom panel*) prepulse stimuli for 13 inbred strains of mice. Data represent the mean (±SEM) % prepulse inhibition of ten male mice from each strain, except the AKR/J strain which had data obtained from nine mice

mice was determined by the stimulus sound level. For example, the DBA/2 strain which had one of the smallest responses to the 110- and 120-dB stimuli, had the largest response to the 82- and 86-dB stimuli.
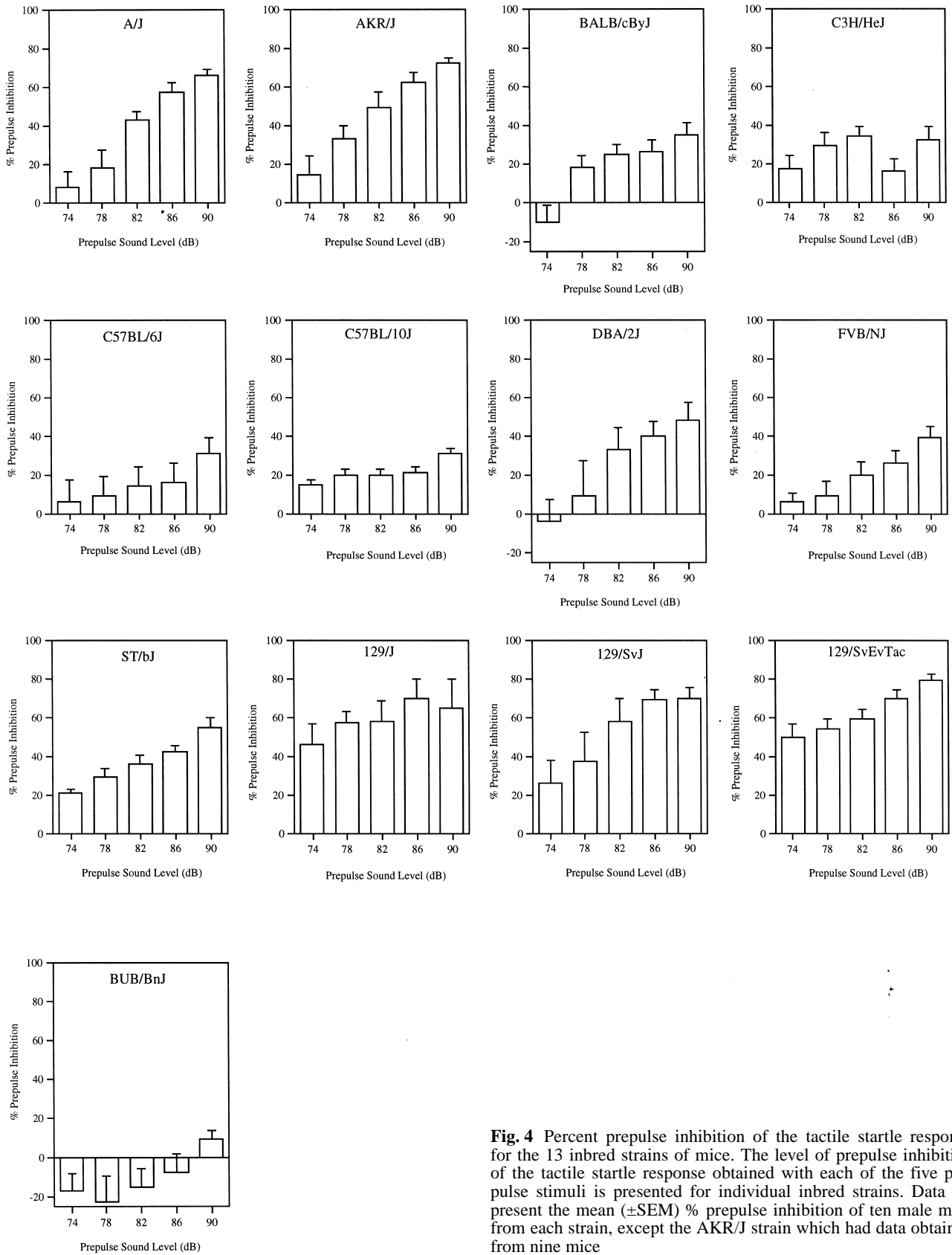
The minimum sound level needed to produce a significant response (e.g. threshold for response measure) was different among the strains of mice. Some strains of mice which have small startle response amplitudes to the 120-dB stimulus actually emit a response to a lower sound level than strains which show much greater overall startle amplitudes (see Fig. 5). In fact, the correlation between the acoustic startle response to the 120-dB sound and the threshold for response measure was not significant ($r = 0.425$, $P>0.05$), suggesting that there is little relationship between these two parameters.
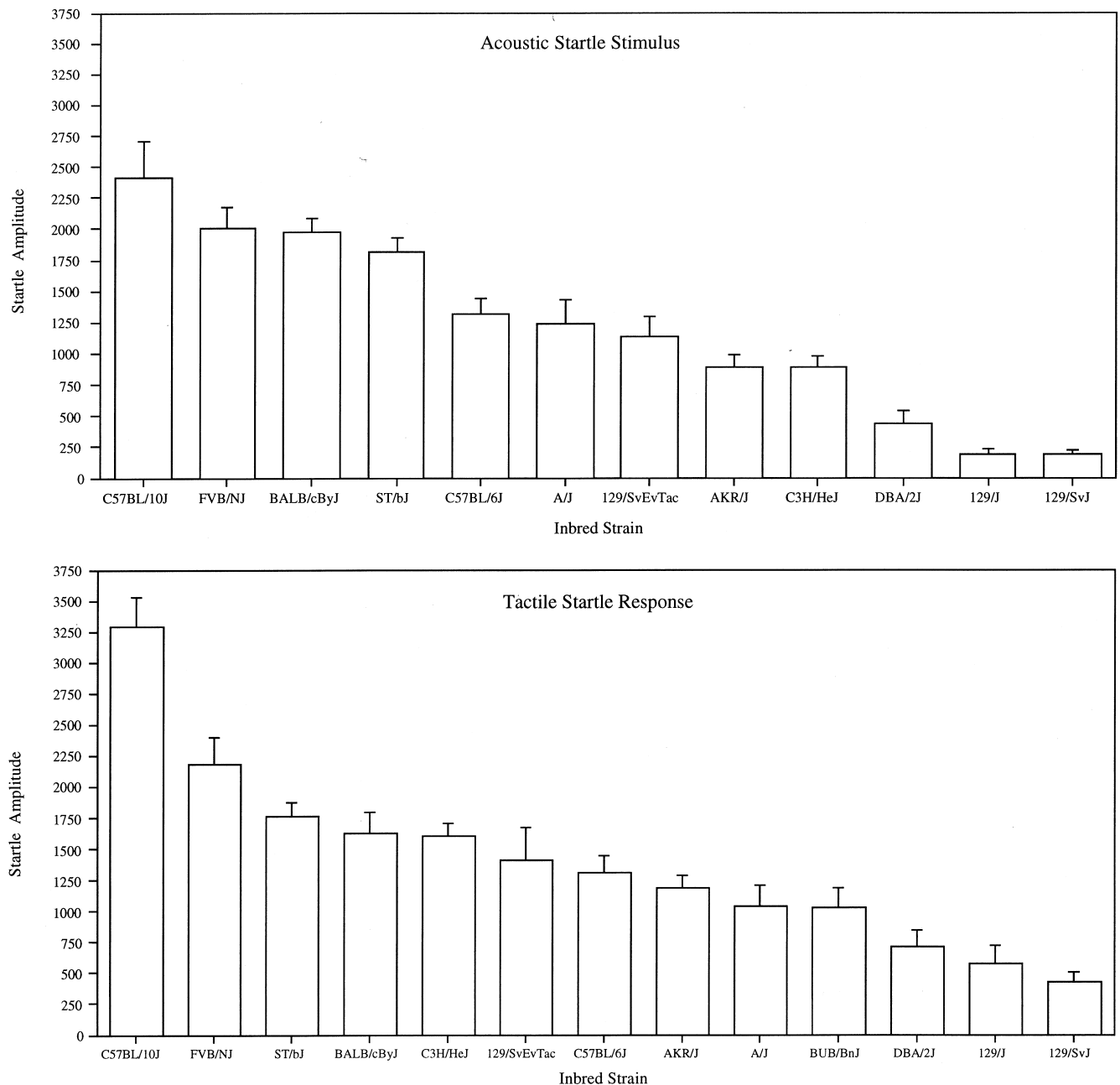
Discussion

The present data show that different inbred strains of mice display different levels of prepulse inhibition. In

general, AKR/J and 129/SvEvTac mice had high levels of prepulse inhibition and C57BL/6J, C57BL/10J had low levels of prepulse inhibition of both the acoustic and tactile startle response. Exact strain distributions, however, depended on the prepulse sound level. The DBA/2J strain showed poor prepulse inhibition of both the tactile and acoustic startle response with a 74-dB prepulse sound, but displayed intermediate to high levels of prepulse inhibition with the 90-dB prepulse sound level. The C3H/HeJ strain showed moderate levels of prepulse inhibition that did not change significantly across the five prepulse sound levels. The 129/J strain showed high levels of prepulse inhibition of the tactile startle response with every prepulse sound level, but displayed poor prepulse inhibition of the acoustic startle response with the 74- and 78-dB prepulses. The observations that strain differences in prepulse inhibition are determined by the prepulse sound level and the modality of the startle stimulus is supported by correlational analyses. The level of prepulse inhibition of the tactile startle response was significantly correlated to the prepulse inhibition of the acoustic startle response, but only when 82-, 86-, or 90-dB prepulse sound levels were used.

Taken together, the findings from the prepulse inhibition experiment indicate that (a) prepulse inhibition is under genetic control, (b) some of the same genes may be linked to both prepulse inhibition of an acoustic startle response and inhibition of a tactile startle response, and

Fig. 4 Percent prepulse inhibition of the tactile startle response for the 13 inbred strains of mice. The level of prepulse inhibition of the tactile startle response obtained with each of the five prepulse stimuli is presented for individual inbred strains. Data represent the mean ($\pm$SEM) % prepulse inhibition of ten male mice from each strain, except the AKR/J strain which had data obtained from nine mice
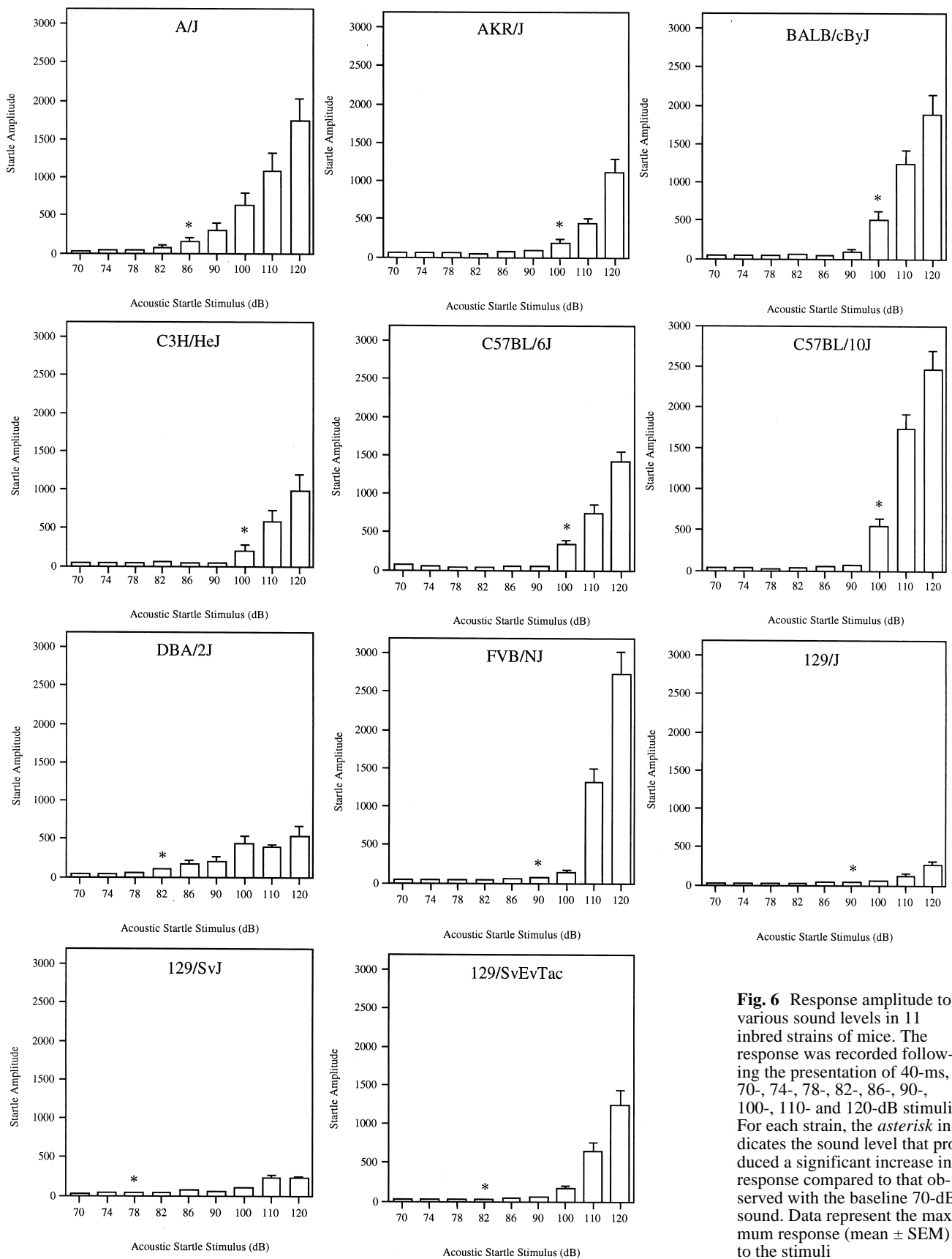
Fig. 5 Acoustic and tactile startle response strain distributions. The acoustic startle response from 12 inbred strains (*top panel*) was recorded following the presentation of a 40-ms, 120-dB sound. The tactile startle response from 13 inbred strains (*bottom panel*) was recorded following the presentation of a 40-ms, 12-psi air-puff. Data represent the maximum startle response (mean ± SEM) to the startle stimuli

(c) the genes contributing to prepulse inhibition of tactile and acoustic startle stimuli obtained using low prepulse sound levels may be different than those genes contributing to inhibition with louder prepulse sound levels.

Consistent with the existing literature (Marks et al. 1989b), the magnitude of the acoustic startle response increased as the sound level increased for each strain of mouse tested, but the absolute startle response to the loudest sound (120 dB) was different between the strains. C57BL/10J and FVB/NJ showed the greatest startle response amplitude and the DBA/2J, 129/J, and 129/SvJ displayed the lowest startle response. Interestingly, the 10J and 6J, which are substrains of the C57BL strain, show different levels of startle. Similarly, there is considerable difference in the amount of startle among the 129/J and 129/SvJ strains compared to the 129/SvEvTac strain. The threshold for response measure, which can be used as an indicator of startle response sensitivity, also differed among the various inbred strains. 129/SvJ, DBA/2J and 129/SvEvTac showed a significant startle response to low stimulus sound levels (78–82 dB), while AKR/J, BALB/cByJ, C3H/HeJ, C57BL/6J, and

Fig. 6 Response amplitude to various sound levels in 11 inbred strains of mice. The response was recorded following the presentation of 40-ms, 70-, 74-, 78-, 82-, 86-, 90-, 100-, 110- and 120-dB stimuli. For each strain, the *asterisk* indicates the sound level that produced a significant increase in response compared to that observed with the baseline 70-dB sound. Data represent the maximum response (mean ± SEM) to the stimuli

C57BL/10J did not show a response until the startle stimulus was 100 dB. There was no correlation between the startle response to the 120-dB sound and the threshold for response measure, suggesting that the genetic substrates for these two measurements are different.

The tactile startle response also varied among the inbred strains of mice. The maximum tactile and acoustic startle responses were significantly correlated among 12 inbred strains, indicating that these two startle responses are related and under similar genetic control.

An important finding is that the magnitude of either the tactile or the acoustic startle response appears to be independent of the level of prepulse inhibition. Correlations between the startle response and prepulse inhibition were not significant. Some strains that show poor startle amplitude show high levels of prepulse inhibition (e.g. 129/J and 129/SvJ), some strains show moderate levels of startle and prepulse inhibition (e.g. ST/bJ), while other strains have a large startle response and poor prepulse inhibition (e.g. C57BL/10J). This dissociation between startle and prepulse inhibition has been reported previously in studies using rats (e.g. Mansbach et al. 1988; Bakshi et al. 1994; Johansson et al. 1994, 1995). The current findings support the previous research and indicate that startle and prepulse inhibition are likely to be under different genetic control.

Though some strains of mice showed a response to several acoustic stimuli (see Fig. 6), at dB levels (82–90) that were used as prepulse stimuli (see Fig. 2), it is unlikely that this response contributed to the strain differences in prepulse inhibition. There was no correlation (r values <0.17, P>0.05) between the response to the 90-dB stimulus (Fig. 6) and the level of prepulse inhibition obtained with the 90-dB prepulse (Figs. 1 and 3). Similarly, the threshold for response measure and the level of prepulse inhibition of the acoustic startle response with any of the prepulse stimuli were not significantly correlated (r values <0.53, P>0.05).

The present findings confirm and extend previous reports. Acoustic startle and prepulse inhibition have been reported to differ across inbred strains of mice (Bullock et al. 1995). In addition, the hippocampal auditory evoked response measure of sensory gating was recently shown to vary among inbred strains of mice (Stevens et al. 1996). Comparison between the prepulse inhibition strain distribution by Bullock and co-workers (1995) with the present results shows some minor differences in the level of prepulse inhibition with the C3H and DBA/2 strains. In the current study, DBA/2J mice showed poor prepulse inhibition with the 74-dB prepulse and intermediate to high levels with the 90-dB prepulse. The C3H/HeJ mice showed intermediate levels of prepulse inhibition with all prepulse sound stimuli. Bullock et al. (1995) reported that C3H/2Ibg mice displayed more prepulse inhibition than DBA/2J/Ibg mice. In addition, DBA/2Ibg mice have poorer sensory gating compared to C3H as measured using the hippocampal auditory evoked response (Stevens et al. 1996). Reasons for these differences may include (1) different substrains from the Institute for Behavioral Genetics and the Jackson Laboratory, and (2) greater sensitivity of the prepulse equipment in the present methods.

There are age-related hearing impairments among inbred strains of mice. DBA/2J mice have hearing loss by 4 months of age, C57BL/6J have hearing loss by 1 year and BALB/cByJ have hearing loss by 2 years (Erway et al. 1993). It is possible that some of these late developmental impairments in audition could account for differences in the acoustic startle response and in levels of prepulse inhibition observed in the current study. However, we found that the tactile startle response was poor in the same strains that showed the poorest acoustic startle response. Further, the magnitude of the acoustic startle response and the level of prepulse inhibition were not correlated. Thus, possible hearing impairments in these mice could not account for differences in prepulse inhibition. In addition, mice in the current study were tested when they were approximately 2 months old, which is younger than the age reported for auditory system impairments.

Future studies will be needed to identify the neural substrates and transmitter system or combination of systems that contribute to inbred mouse strain differences in prepulse inhibition. Reported inbred strain differences in dopaminergic (Fink et al. 1982; Vadasz et al. 1992; Kanes et al. 1993), nicotinic (Marks et al. 1989a), and/or serotonergic (Popova and Kulikov 1995) receptor systems could contribute to the range of prepulse inhibition observed in the current study. Induced genetic mutations (e.g. knockout and transgenic mice) provide one approach to study the role of genes in prepulse inhibition. For example, $5HT_{1B}$ knockout mice have been reported to display increased levels of prepulse inhibition and reduced startle compared to wild-type controls (Dulawa et al. 1995). This gene targeting approach can be used to evaluate the role of candidate genes in prepulse inhibition and startle.

Using quantitative trait loci techniques (QTL), genes linked to the phenotype of high and low levels of prepulse inhibition can be identified. The present study has shown that there is a large range in the level of prepulse inhibition among inbred mice strains, which makes it a good behavioral trait for QTL analysis. Future studies will use QTL analysis to identify chromosomal loci contributing to differences in prepulse inhibition between the low responding C57BL/6J and the high responding AKR/J mice. Results from these QTL studies will have implications for the genetic basis of schizophrenia, and possibly for obsessive-compulsive disorder and Huntington's disease, since patients with these maladies also have abnormal levels of prepulse inhibition (Swerdlow et al. 1993, 1995).

Finally, identified strains of mice that show poor prepulse inhibition may prove to be a useful tool for identifying new putative antipsychotics. Future investigations will test the hypothesis that antipsychotic drug treatment can improve prepulse inhibition in low responding inbred strains of mice.

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