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Short-term selective breeding for High and Low prepulse inhibition of the acoustic startle response; pharmacological characterization and QTL mapping in the selected lines

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ABSTRACT

Selective breeding offers several important advantages over using inbred strain panels in detecting genetically correlated traits to the selection phenotype. The purpose of the current study was to selectively breed for prepulse inhibition (PPI) of the acoustic startle response (ASR), to pharmacologically and behaviorally characterize the selected lines and to use the lines for quantitative trait loci (QTL) mapping. Starting with heterogeneous stock mice formed by crossing the C57BL/6J, DBA/2J, BALB/cJ and LP/J inbred strains and using a short-term selective breeding strategy, animals were selected for High and Low PPI. The selection phenotype was the 80 dB prepulse tone (15 dB above the background noise). After five generations of selection, the High and Low lines differed significantly (78.1±3.1 vs. 45.2±3.9 [percent inhibition], $p<0.00001$). The effects of haloperidol and MK-801 on PPI were not different between the High and Low lines. However, at the highest dose tested (10 mg/kg), the High line was more sensitive than the Low line to the disruptive PPI effects of methamphetamine. The lines did not differ in terms of basal activity or methamphetamine-induced changes in locomotor activity. The High and Low lines were genotyped using a panel of 768 SNPs. Significant QTLs (LOD>10) were detected on chromosomes 11 and 16 that appeared similar to those detected previously [Hitzemann, R., Bell, J., Rasmussen, E., McCaughran, J. Mapping the genes for the acoustic startle response (ASR) and prepulse inhibition of the ASR in the BXD recombinant inbred series: effect of high-frequency hearing loss and cochlear pathology. In: Willott JF, editor. Handbook of mouse auditory research: From behavior to molecular biology. New York: CRC Press; 2001. p. 441–455.; Petryshen, T. L., Kirby, A., Hammer, R.P. Jr, Purcell, S., O'Leary, S.B., Singer, J.B., et al. Two quantitative trait loci for prepulse inhibition of startle identified on mouse chromosome 16 using chromosome substitution strains. Genetics 2005; 171: 1895–1904.]. Overall, the current study illustrates that the heritability of PPI is sufficient for short-term selective breeding and that the lines which are developed can be used to characterize the factors associated with the regulation of PPI.

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1. Introduction

The magnitude of the acoustic startle response (ASR) is markedly reduced if preceded 30 to 500 ms by a weak tactile or acoustic stimulus (Hoffman and Ison, 1980). This phenomenon, termed prepulse inhibition (PPI), is thought to reflect a mechanism of sensory modulation or sensorimotor gating. PPI does not appear to be a form of conditioning because it occurs on the first exposure to the prepulse stimulus and does not exhibit significant habituation or extinction over multiple trials. Because PPI can be measured under similar conditions in animals and humans, deficient PPI has been considered an isomorphic animal model for the gating deficits seen in schizophrenia and a variety of other neuropsychiatric disorders (Braff and Light, 2005; Geyer et al., 2001; Light and Braff, 1999; Van den Buuse et al., 2003). In animals, poor PPI is readily reversed by both typical and atypical antipsychotic drugs (e.g., McCaughran et al., 1997), suggesting the model has strong predictive validity (see Swerdlow and Geyer, 1993). The PPI model has construct validity given that the mesolimbic and mesocortical circuits, which are involved in the regulation of PPI, overlap with the circuits that are thought to be abnormal in schizophrenia (Braff et al., 2001; Fendt et al., 2001; Geyer et al., 2001; Koch, 1996; Swerdlow et al., 2001; Wan and Swerdlow, 1996).

In recent years, PPI has served as an important bridge between animal and human genetics. On the animal side, the majority of the studies fall into the category of reverse genetics (see e.g., Geyer et al., 2002; Klejbor

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et al., 2006; Ralph et al., 2001a). Genes of interest, sometimes generated from human linkage studies, are manipulated (under- or over-expressed), and the effects on PPI are noted. Paylor et al. (2006) used this approach to demonstrate in mice that a mutation in the transcription factor TBX1 (T-box 1) was likely to be involved in the psychiatric abnormalities associated with the 22q11 deletion syndrome. This association has been confirmed in some (e.g. Williams et al. (2007) but not all studies (e.g. Ma et al., 2007; Funke et al., 2007). In addition to the use of transgenic animals, *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis has identified animals with abnormal PPI (e.g., Cook et al., 2007). PPI has also been measured among inbred strains of laboratory mice and rats (e.g., Bullock et al., 1997; Hitzemann et al., 2001; Logue et al., 1997; Paylor and Crawley, 1997; Swerdlow et al., 2004a, b,c; Willott et al., 2003). These data can be used to detect genetically correlated traits and, when the panel of inbred strains is large, to accurately estimate heritability. Willott et al. (2003), using a panel of 40 inbred mouse strains, estimated that the heritability of PPI was on average 0.48±0.12; although this was somewhat less than the heritability of the ASR (0.62±0.25), the data still indicated that a significant component of the variance in PPI was of genetic origin. Essentially identical results were obtained when looking at PPI in a panel of C57BL/6J×DBA/2J (BXD) recombinant inbred (RI) strains (Hitzemann et al., 2001; McCaughran et al., 1999). Finally it should be noted that several groups have reported some success at mapping quantitative trait loci (QTL) for PPI (Hitzemann et al., 2001; Joober et al., 2002; Palmer et al., 2003; Petryshen et al., 2005; Vendruscolo et al., 2006).

Despite the strength of the genetic evidence, there has been to our knowledge only one successful attempt to selectively breed for High and/or Low PPI (Hadamitzky et al., 2007; Schwabe et al., 2007). Given the high level of PPI in the parent population (outbred Wistar rats), there was no significant segregation in the High line (ceiling effect); however, in the Low line, PPI was, after 6 generations of breeding, essentially zero at the highest prepulse intensity, with numerous animals showing prepulse facilitation (Schwabe et al., 2007). The ASR was also higher in the Low line, which the authors attributed to a decrease in short-term habituation. Interestingly, it was also found that the poor PPI in the Low line was more effectively reversed by haloperidol as compared to clozapine (Hadamitzky et al., 2007).

Independent of the above selection, we initiated and have completed a short-term selective breeding (STSB) experiment for PPI, beginning with heterogeneous stock (HS) mice. This HS population, designated HS4, was formed by crossing the C57BL/6J, DBA/2J, BALB/cJ, and LP/J inbred mouse strains. The basic elements of STSB are described elsewhere (Belknap et al., 1997). Here we simply note that STSB maximizes selection pressure at the expense of genetic drift. The current study focused on how selection for High and Low PPI 1) affected the ASR and other behavioral parameters (e.g. haloperidol-induced catalepsy and 2) on how the High and Low lines differed in terms of the effects haloperidol, methamphetamine and MK-801 on PPI. These studies extended our long-standing interest in the genetic relationships between catalepsy and PPI (e.g. McCaughran et al., 1997), provided a bridge to both rodent and clinical studies examining drug-effects in strains or individuals with High and Low PPI (e.g. Varty et al., 2001; Swerdlow et al., 2003, 2004a,b,c; Bitsios et al., 2005; Csomor et al., 2008) and provided a link to work from this laboratory and elsewhere examining the genetics of haloperidol and methamphetamine responses (e.g. Hitzemann et al., 2001; Janowsky et al., 2001; Palmer et al., 2005; Phillips et al., 2008) Finally, the selected lines were used to map PPI associated quantitative trait loci (QTL).

2. Materials and methods

2.1. Animals

All mice were maintained in a temperature-controlled colony room (21 °C–23 °C) on a 12-hour light–dark cycle and were allowed free access to food and water. Details concerning the formation of the HS4 colony are found elsewhere (Malmanger et al., 2006). Briefly, the colony is maintained as 48 families; the standard circle design is used for breeding. G_{27} animals were used as the founding population for STSB. Two to 3 males and females from each of 44 families were used for a mass selection; details of the ASR and PPI phenotypes follow. The selection phenotype was the PPI to the 80 dB prepulse. This phenotype was chosen because (a) the test–retest reliability was good (see Results) and (b) this response allowed "room" to select in the high as well as the low direction. Animals with ASRs < > 2 SD from the mean were not included in the selection. Animals were selected to form 10 High-response and 10 Low-response families; brother–sister matings were avoided even if it meant using an animal that was not in the highest or lowest tier. To the extent possible, animals were mated to balance differences in the ASR. The selection procedure was followed for each subsequent generation. Selection was stopped at S_5. All animal care, breeding, and testing procedures were approved by the Laboratory Animal Users Committees at the Veterans Affairs Medical Center, Portland, OR and Oregon Health & Science University, Portland, OR.

2.2. Behavioral testing

For the selection experiments, animals were tested for the ASR and PPI on 2 consecutive days using the San Diego Instruments SR-LAB startle response system (San Diego, CA). Each session consisted of 12 blocks of 5 trial types: startle stimulus alone, prepulses of 72, 80, or 84 dB followed by the startle stimulus, and a null stimulus (no stimulus presented). In addition, there were 2 startle stimulus trials to start the session and 3 trials of the 84 dB prepulse stimulus to end each session. No animal in the current study exhibited a startle response to the 84 dB prepulse stimulus. The trial types were presented in pseudorandom order and separated by an interval between 5 and 15 s. Each startle session took 12 min.

A background noise of 65 dB was constant throughout the session. The startle stimulus was a 60 ms 115 dB white noise. Prepulses were delivered as 20 ms white noise pulses 100 ms prior to the startle stimulus. Data were collected for 200 ms from the onset of the startle stimulus. Startle data are presented in relative machine units as the difference between the null and startle trials. PPI data were calculated as % Acoustic PPI = 100 − {[(startle response for PREPULSE + PULSE)/(startle response for PULSE-ALONE)] × 100}. Data are reported as the average across all 12 trials. Animals were run 4 at a time (each housed individually in a sound-attenuated chamber). Care was taken to balance the animals in any given session for sex and to avoid having animals from a single family.

Animals from the fifth generation of selection (S_5) were administered i.p. saline (10 ml/kg), methamphetamine (1, 3, and 10 mg/kg), haloperidol (0.1, 0.3, and 1.0 mg/kg), or MK-801(0.03, 0.10, and 0.30 mg/kg) 15 min prior to testing for the ASR and PPI. Testing then proceeded as described above except that the animals were only tested once.

Additional S_5 animals were used to test for the locomotor response to saline and methamphetamine. On day 1, animals were administered saline i.p. (10 ml/kg) and immediately placed in an activity monitor. The floor of the testing device was covered with standard laboratory bedding, which was changed after each testing period. Activity was monitored for 20 min under standard laboratory lighting conditions. The following day, animals were administered 1 or 3 mg/kg methamphetamine, and the activity measurements were repeated. The methamphetamine response is the difference in activity between days 2 and 1 (reported as distance [cm] traveled). Locomotor activity was assessed in a San Diego Instruments Flex Field locomotor system (San Diego, CA). The apparatus comprised a 4×8 array of photocells mounted in a 25×47 cm metal frame, situated 1 cm off the floor, and surrounding a 22×42×20 cm high plastic arena. Activity was recorded over eight 2.5 minute blocks.

Haloperidol-induced catalepsy was measured in S_5 animals as described elsewhere (Kanes et al., 1996).

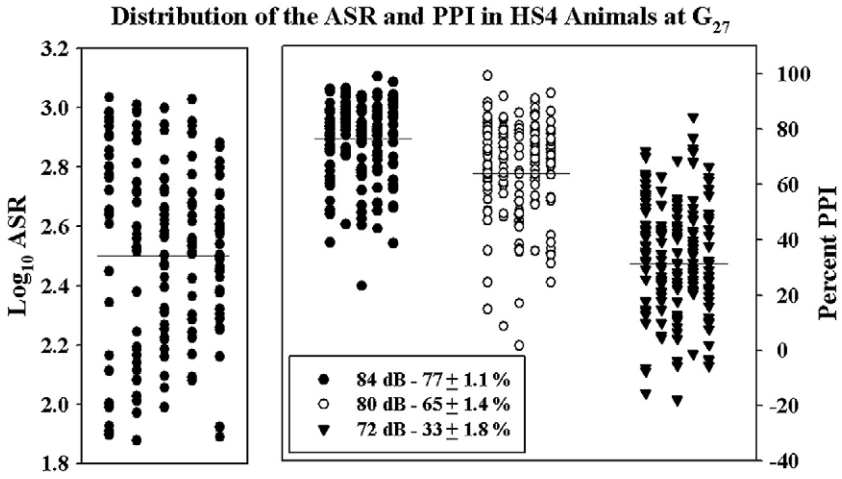

Fig. 1. Distribution of the acoustic startle reflex (ASR) and prepulse inhibition (PPI) of the ASR in generation 27 (G_{27}) HS4 mice. Two to 3 males and females from 44 different HS4 families were selected for phenotyping. Animals with an ASR values > and <2 SD from the mean are not included in the figure. Data are presented for a total of 167 animals. The means ± SE for each of the 3 prepulse intensities are presented in the graph. Test/retest reliability data are found in the text.

With the exception of the catalepsy response, all behavioral data were analyzed using a standard factorial or repeated measures ANOVA; Tukey's HSD test was used for the post-hoc analysis. These analyses were run using Statistica (StatSoft Inc., Tulsa, OK). For haloperidol-induced catalepsy, the ED_{50} values in the High and Low lines were determined and compared using the "up and down method" (Dixon, 1965).

2.3. Genotyping the selected lines

DNA was extracted as described elsewhere (Malmanger et al., 2006). Mice were genotyped using a custom SNP array and the Illumina Golden Gate Assay (San Diego, CA). The array was derived from the Illumina high density mouse array. The 1449 SNPs on this array were culled to include only those that would be informative for the 4 strains of interest. The genome was then divided into ~13 Mbp bins; our goal was to ensure that each bin had at least 3 informative SNPs, roughly evenly spaced, and when possible, one SNP that discriminated the B6 strain from the other 3. This process culled the number of SNPs to 695. Seventy-three additional SNPs were added from a list of 13,549 SNPs that had been validated using the Illumina genotyping platform (http://www.well.ox.ac.uk/mouse/INBREDS). Samples were run locally using the Illumina BeadStation genotyping platform. All procedures were exactly as described by the manufacturer. The 768 SNPs were validated using DNA from the 4 inbred strains and the 6 possible mixtures of DNA. All of the SNPs performed as expected. The SNP data for the High and Low lines were analyzed using a marker-by-marker χ^2 analysis. In the absence of a correction for drift, the nominal LOD threshold (4.2) is obtained by correcting for the number of multiple comparisons.

The drift correction was patterned after that of Belknap et al. (1997), which was explicitly designed for short-term selection line data. We refer to the most common allele frequency as q and the sum of remaining alleles as p, such that $p+q=1$. Selection for a trait will cause q for all QTLs influencing the selected trait to increase in 1 line and to decrease in the oppositely selected line. (Because the expected outcome for p is the mirror image of q, we can focus only on q.) Evidence for the presence of a QTL will be gained from the difference in relative allele frequencies between the High and Low lines at a nearby marker ($\delta = q_H - q_L$) exceeding that expected from random drift and sampling error. The value of Z, the normal deviate, will be calculated as follows for each marker used to test for QTL significance:

$$Z = \delta / [p_0 q_0 F + p_H q_H / 2n_H + p_L q_L / 2n_L]^{0.5}$$

where the 1st term in the denominator is the expected random drift variance (Falconer and Mackay, 1996); the 2nd and 3rd terms are the variances due to sampling error in the High- and Low-selected lines, respectively; n_L and n_H are the sample sizes in each line; p_H, q_H, p_L, q_L are the allele frequencies in each line; F is the inbreeding coefficient at a given selected generation (Falconer and Mackay, 1996); and p_0 and q_0 are the initial allele frequencies in the founding population.

To correct for drift, we simply estimated what Z would be both in the presence and absence of drift and then translated these values of Z to $-\log(p)$ values. For the experiment described here, multiplying the observed $-\log(p)$ values by 0.4 gives the estimated values corrected for drift. Thus, the $-\log P$ threshold for a significant QTL is 10.5.

3. Results

3.1. Characteristics of the ASR and PPI of the ASR in HS4 animals

Two to 3 males and females from 44 HS4 families at G_{27} were phenotyped for the ASR and PPI of the ASR. The data were censored for individuals with extreme ASR values as described in Materials and methods. After censoring, data were available for 167 individuals. The data in Fig. 1 illustrate the distribution of the ASR and PPI data. Note the ASR data were log transformed to normalize the distribution. The ANOVA of the PPI data revealed a significant effect for prepulse intensity ($F(2,495)=250$, $p<<10^{-10}$). The post-hoc analysis (Tukey's HSD) showed that, for all comparisons, the means (see Fig. 1) for the prepulse intensities differed significantly ($p<2\times10^{-5}$). Test/retest reliability data were 0.53 for PPI-84dB, 0.48 for PPI-80dB, and 0.33 for PPI-72dB. Assuming that the PPI data were not independent, the test/retest coefficients for the PPI-84dB and PPI-80dB data were significantly different from the PPI-72dB coefficient at $p<0.05$ or better. Given that the reliability of the 80 and 84 dB data were similar and given the greater dynamic range of the 80 dB data (the ceiling effect would be avoided to a somewhat greater degree), the 80 dB data were chosen as the selection phenotype. Male and female mice did not differ significantly for the 80 dB data (63.6 ± 2.0 vs. 67.2 ± 1.7 [percent inhibition]).

Test/retest reliability data were 0.77 for the ASR. Male and female mice did not differ significantly ($p>0.1$) for the ASR (2.49 ± 0.27 vs. 2.48 ± 0.32 [log ASR units]). The relationship between the ASR and the 80 dB data is illustrated in Fig. 2. The correlation ($r=0.10$) was not significant ($p>0.20$).

The data for individual families are illustrated in Fig. 3. The analysis of variance for family effect revealed no significant effect for

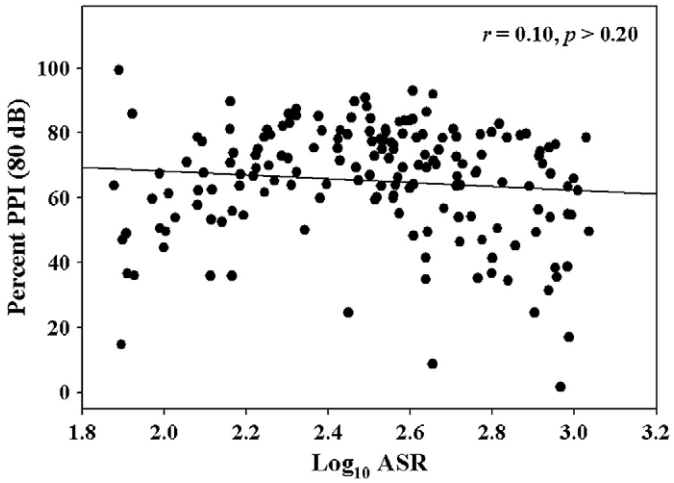

Fig. 2. The correlation between the acoustic startle reflex (ASR) and prepulse inhibition (PPI) (80 dB) in HS4 mice. Details are similar to those found in the legend to Fig. 1. The correlation coefficient (r=0.10) was not significant.

the ASR (F(43,122)=1.3, p>0.14); however, a significant family effect was observed for the 80 dB data (F(43,122)=2.1, p<0.0007). The range in mean PPI was >130% from the lowest to the highest family. Family data can be used to estimate heritability (DeFries et al., 1989) in essentially the same way as the data from multiple inbred or recombinant inbred strains (see e.g., Demarest et al., 2001). The estimated heritability of the 80 dB phenotype was 0.30.

3.2. Selection of the High and Low PPI lines

The selection of the Low and High PPI lines is illustrated in Fig. 4. The ANOVA for the line×generation interaction revealed a significant effect (F(4,475)=4.7, p<0.001). Notably, the post-hoc analysis illustrated that there was a significant difference in PPI when comparing the Low line at S_1 and S_5 (59.4±2.2 vs. 45.2±3.9 [percent inhibition], p<0.013) and a highly significant difference between the High and Low lines at S_5 (78.1±3.1 vs. 45.2±3.9 [percent inhibition], p<0.00001). Fig. 5 illustrates the data for all 3 prepulse intensities in the High and Low lines at S_5. The prepulse data were entered into the analysis as a repeated measure. The ANOVA revealed a significant effect for the line×intensity interaction (F(2,88)=3.8, p<0.025). The post-hoc analysis showed that, for each prepulse intensity, the High and Low lines differed at p<0.0005 or better.

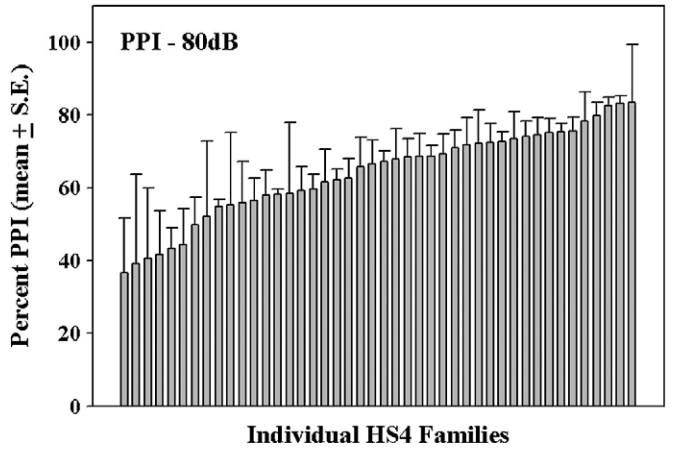

Fig. 3. Average prepulse inhibition (PPI) (80 dB) among 44 HS4 families. Details in the legend to Fig. 1. Forty-four of the 48 families in the HS4 colony were entered into the analysis. No family had fewer than 3 or more than 6 members. Data are the average PPI±SE for each family. The difference between the highest and lowest family was >130%.

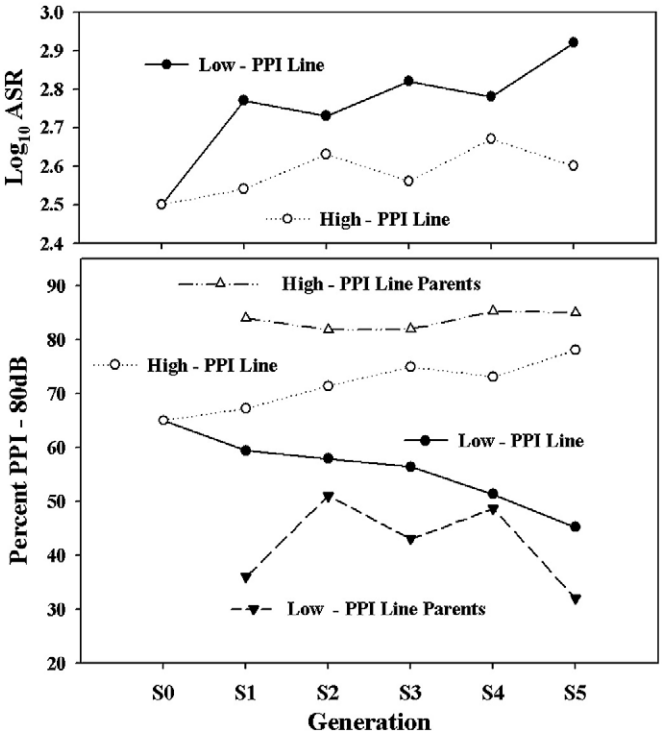

Fig. 4. The selection of the High and Low prepulse inhibition (PPI) lines. The graphs plot the segregation of the acoustic startle reflex (ASR) and PPI across 5 generations of selection. The average PPI of the parents for the High and Low PPI lines at each generation of selection is also illustrated. The selection criterion was the 80 dB PPI response. Parental breeding pairs were censored for animals with ASR values < > 2 SD from the mean. Brother–sister matings were not allowed, even if it meant taking animals that were not in the highest or lowest tier. There were 10 families for the High and Low lines at each generation of selection.

Fig. 4 also illustrates the change in the ASR during selection. The ANOVA revealed no significant effect for the line×generation interaction (F(4,475)=0.95, p>0.43), but there was a significant effect for line (F(1,475)=29, p<0.000001, ASR_{Low}>ASR_{High}).

3.3. Characterization of the High and Low PPI lines

The effects of methamphetamine on PPI in the High and Low PPI lines are illustrated in Fig. 6 A. The line×dose interaction (illustrated in

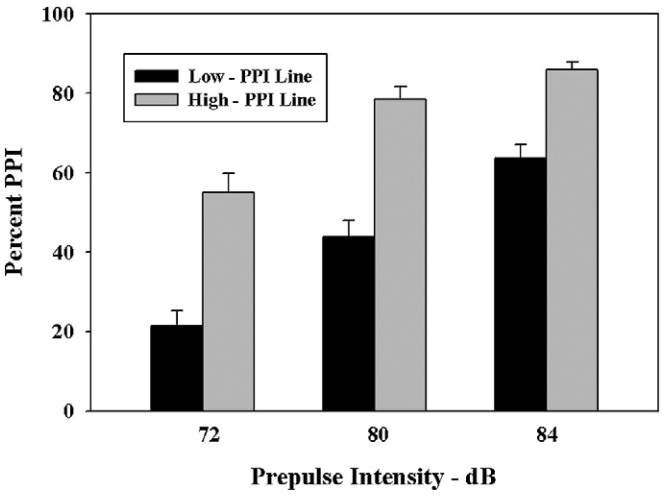

Fig. 5. The average prepulse inhibition (PPI) across 3 prepulse intensities for the High and Low PPI selection lines. The data presented are for the S_5 animals. Selection details are found in the legend to Fig. 4. The High and Low lines at each intensity were significantly different from each other at p<0.00005. n=30/line.

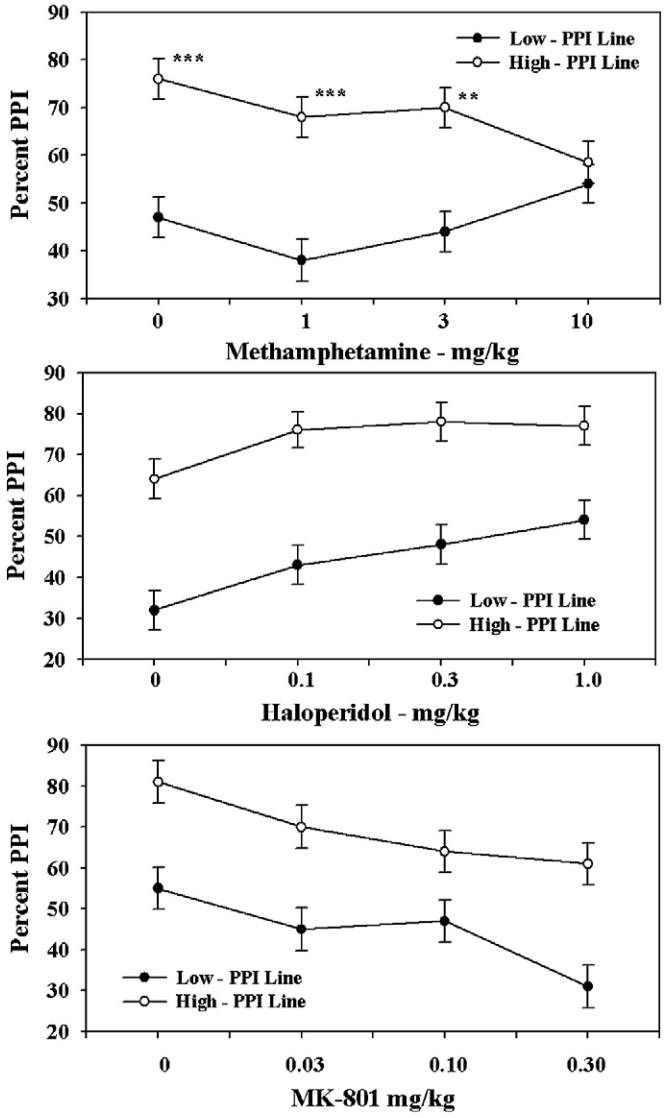

Fig. 6. The effects of methamphetamine, haloperidol, and MK-801 on prepulse inhibition (PPI) in the High and Low PPI lines. Drugs were administered at the doses indicated 15 min prior to the assessment of PPI. For no treatment was there a dose × line × prepulse intensity interaction. The line × dose interactions are presented in the figure; this interaction was significant only for the effects of methamphetamine. At 0, 1, and 3 but not 10 mg/kg the difference between the High and Low lines was statistically significant. ***$p<0.0003$; **$p<0.01$. For haloperidol and MK-801, only the dose effect was significant (see text for details). $n=8$–10/dose/treatment.

the figure) was significant ($F(3,71)=3.8$, $p<0.01$) but the line × dose × prepulse intensity interaction was not significant ($p>0.56$). The post-hoc analysis revealed a significant difference between the High and Low lines at 0, 1, and 3 but not 10 mg/kg i.e. methamphetamine at 10 mg/kg disrupted PPI in the High but not the Low line.

The effects of haloperidol on PPI in the High and Low lines are illustrated in Fig. 6 B. Neither the line × dose interaction (illustrated in the figure) nor the line × dose × prepulse intensity interaction was significant ($p>0.7$). However, the effect of dose was significant ($F(3,72)=5.0$, $p<0.003$); haloperidol increased PPI.

The effects of MK-801 on PPI in the High and Low lines are illustrated in Fig. 6 C. Neither the line × dose interaction (illustrated in the figure) nor the line × dose × prepulse interaction were significant. The effect of dose was significant ($F(3,40)=5.9$, $p<0.002$); MK-801 decreased PPI.

The locomotor responses of the High and Low lines to a novel environment are illustrated in Fig. 7. The line × time interaction was

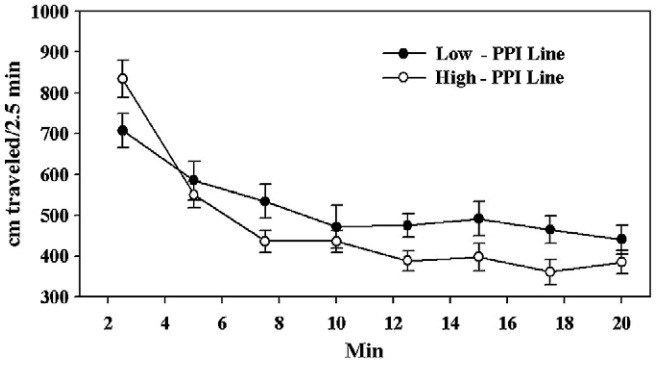

Fig. 7. Locomotor response to a novel environment in the High and Low prepulse inhibition (PPI) lines. Details are found in the Materials and methods. Briefly, animals were removed form the home cage, administered saline (10 ml/kg), and immediately placed in the apparatus for measuring locomotor activity. The trial lasted 20 min. $n=16$–20/line.

significant ($F(7,266)=4.9$, $p<0.00003$). Although the High line was somewhat less active, at no time point in the 20 min trial was the High line different from the respective value in the Low line.

The High and Low lines were challenged with 1 and 3 mg/kg methamphetamine, and the effects on locomotor activity were examined; the response was calculated as a difference score (see Materials and methods). The line × dose interaction was not significant ($p>0.6$). The dose effect was also not significant because the HS4 mice appeared to be just as likely to show an inhibitory as an excitatory response to methamphetamine (Fig. 8).

Haloperidol-induced catalepsy was measured in the High and Low lines as described elsewhere (Kanes et al., 1996). The ED_{50} values were 1.35 ± 0.15 and 1.82 ± 0.26 mg/kg for the High and Low lines, respectively; these values were not significantly different ($p>0.3$).

3.4. QTL analysis in the High and Low lines

The purpose of the QTL analysis was to determine which PPI QTLs detected in previous studies (see Introduction) and replicated at least once, would also be detected by comparing the High and Low lines. Four and perhaps 5 QTLs for PPI have been mapped in 2 or more independent studies; these QTLs are found on chromosomes 3, 11, and 16 (see Table 1). Seventy-nine High line and 47 Low line animals were genotyped using a genome-wide SNP panel. Data were analyzed using a marker-by-marker analysis. Because of genetic drift (see Materials

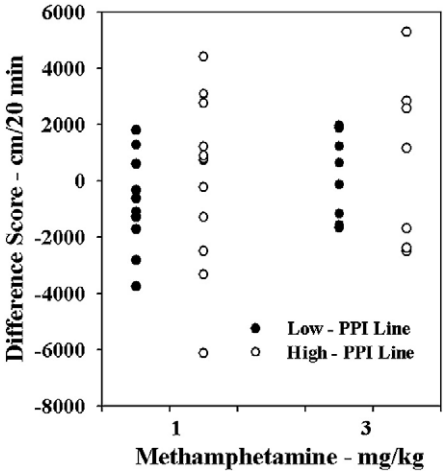

Fig. 8. The effects of methamphetamine on locomotor act The effects of methamphetamine on locomotor activity in the High and Low lines. Data are reported as the difference score between the saline and methamphetamine trials (see Materials and methods).

Table 1
Quantitative trait loci (QTLs) for prepulse inhibition (PPI) detected in multiple independent experiments

Chr (Mbp)[a]	References	Comments
3 (100)	Liu et al. (2003) Palmer et al. (2003) Joober et al. (2002) Hitzemann et al. (2008)[b]	The Liu et al. (2003) data suggest that there may be 2 QTLs present, one more proximal and one more distal than 100 Mbp. Palmer et al. (2003) detected a QTL on rat Chr 2; the homologous region is on mouse Chr 3 at approximately 150 Mbp. Both Liu et al. (2003) and Joober et al. (2002) are in agreement that the B6 allele(s) are associated with decreased PPI. The QTL detected in the current study is in approximately the right position for the proximal QTL but the B6 allele(s) are associated with increased PPI.
11 (70)	Joober et al. (2002) Hitzemann et al. (2001) Hitzemann et al. (2008)	Hitzemann et al. (2001) detected the Chr 11 QTL in both the BXD recombinant inbred panel and a B6XD2 F2 intercross. Joober et al. (2002) confirmed the presence of a QTL on Chr 11 where the B6 allele(s) are associated with increased PPI. Hitzemann et al. (2008) suggest the presence of 2 QTLs with the appropriate signature.
16 (45,80)	Joober et al. (2002) Petryshen et al. (2005)	Petryshen et al. (2005) first identified a QTL on Chr 16 using a chromosome substitution strain. Subsequent work suggests that 2 QTLs are present and that the B6 allele(s) are associated with decreased PPI. Joober et al. (2002) also detected at least one QTL on Chr 16 with the same signature. Hitzemann et al. (2008) detected 3 QTLs on Chr 16, one with the correct and two with the opposite signature.

[a] The Mbp position is that of the approximate peak for the QTL(s). The 2-LOD support region for all of these QTLs is broad.
[b] Hitzemann et al. (2008) is the current study.

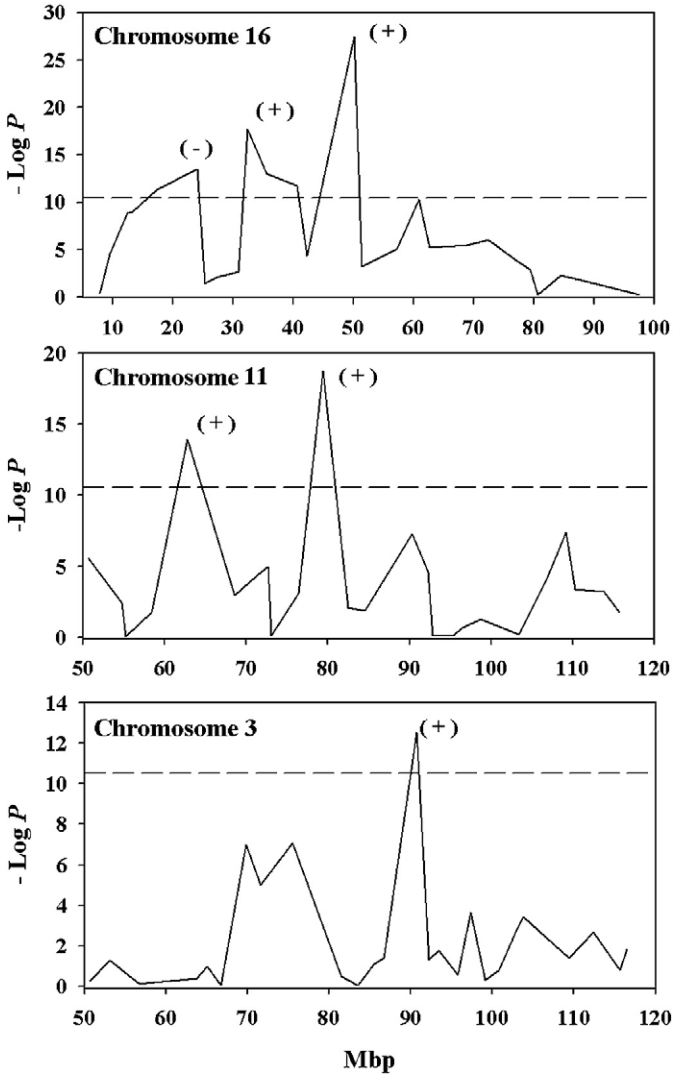

Fig. 9. Quantitative trait locus (QTL) plots on Chr 3, 11, and 16 for prepulse inhibition (PPI) (80dB). QTLs on Chr 3, 11, and 16 have been repeatedly detected in at least 2 independent investigations (see Table 1). Seventy-nine High and 47 Low animals were genotyped using a genome-wide SNP panel as described in the Materials and methods. Data were analyzed using a marker-by-marker analysis. Because of genetic drift, the threshold for a significant QTL was −log P=10.5 (dotted line). Each of the peaks exceeding the threshold were characterized as to whether the B6 allele increased (+) or decreased (−) PPI.

and methods), the threshold for a significant association is −log P=10.5. The results of this analysis for the regions of interest on chromosomes 3, 11 and 16 are illustrated in Fig. 9. Significant QTLs were detected on all 3 chromosomes in the expected regions. The QTLs were characterized as to whether or not the direction of the effect for the B6 allele was similar to that reported previously. The QTL on proximal Chr 16 and the 2 QTLs on Chr 11 had the expected B6 effect (see Table 1).

4. Discussion

Schwabe et al. (2007) were the first to demonstrate that animals (outbred Wistar rats) can be selectively bred for differences in PPI (see also Hadamitzky et al., 2007). The selection was asymmetric such that after 6 generations of selection, the Low line, on average, showed no PPI; the High line showed no segregation, the likely result of a ceiling effect. The poor PPI in the Low line was readily reversed by the typical antipsychotic drug haloperidol. The current study confirms that it is possible to breed for differences in PPI and extends the observation to mice. Similar to Schwabe et al. (2007), most of the selection differential was associated with the Low line, which showed a significant decrease in PPI from S_1 to S_5. A significant concern when breeding for an auditory response in mice is that one will actually select for hearing differences and not differences in PPI. All of the 4 strains used to form the HS4 are known to have some degree of cochlear pathology (e.g., Henry and McGinn, 1992). Previously, we reported (McCaughran et al., 1999) that it was possible to disassociate cochlear pathology from differences in PPI providing the animals were tested at 6–7 weeks (as in the current study).

The current study focused in part on the pharmacological characterization of the High and Low lines. Of the four strains used to form the HS4, two of the strains (DBA/2J and C57BL/6J) have been widely studied for the effects of haloperidol (or related typical antipsychotic drugs), methamphetamine (or amphetamine) and MK-801 (or the related drugs, ketamine and phencyclidine) (e.g. McCaughran et al., 1997; Olivier et al., 2001; Ralph et al., 2001b; Varty et al., 2001;Ouagazzi et al., 2001; Brody et al., 2003, 2004; Yee et al., 2004; Andreasen et al., 2006). For example, the DBA/2J mouse which has poor PPI shows a haloperidol-induced increase in PPI (McCaughran et al., 1997; Olivier et al., 2001); similar results were obtained in the Low line. The BALB/cJ and LP/J strains have received little attention. However, Varty et al. (2001) and Andreasen et al. (2006) have examined the PPI disruptive effects of MK-801 and phenchylidine, respectively, in the BALB/cByJ mouse which is closely related to the BALB/cJ (Beck et al., 2000). While we know of no data examining the effects of dopamine agonists and antagonists and NMDA antagonists on PPI in LP/J mice, there are numerous reports on the effects of such drugs in the closely related 129 strains (e.g. Varty et al., 2001; Ralph et al., 2001b; Brody et al., 2003, 2004). Overall, the data suggest that the strains used to form the HS4 (or their close surrogates) are drug responsive.

In previous studies and depending on genotype, we have both detected and not detected an association between PPI and

haloperidol-induced catalepsy (Kline et al., 1998; McCaughran et al., 1997, 1999). Kline et al. (1998) observed that in mice selectively bred from HS-NPT mice for the catalepsy response, the haloperidol nonresponsive line had poor PPI compared to the haloperidol responsive line. In contrast, in the BXD recombinant inbred series, there was no correlation between catalepsy and PPI (compare Kanes et al., 1996 and McCaughran et al., 1999; these data are available at http://www.genenetwork.org). In the current study, while there is a trend for the Low line to be less responsive to haloperidol-induced catalepsy, the difference was not significant. The hypothesis that there would be an association largely rests on the repeated observation that dopamine-receptor agonists reduce PPI (e.g., Swerdlow et al., 2004a,b, c). Thus, the poor PPI seen in the Low line could be associated with increased dopaminergic activity, which in turn would antagonize the effects of haloperidol. Obviously, the data presented here do not preclude the possibility that the poor PPI in the Low line was associated with increased dopaminergic activity; however, the data would suggest that if the increase was present, it was not sufficient to antagonize the effects of haloperidol.

Interestingly, the data suggest that the Low line was resistant to the disruptive effects of methamphetamine on PPI. At the highest dose tested (10 mg/kg), methamphetamine significantly decreased PPI in the High line but had no effect in the Low line. The heritability of differences in the effects of dopamine agonists on PPI has been most extensively studied in rats and, in particular, by Swerdlow and colleagues comparing the Harlan Sprague–Dawley (SD) and Long Evans (LE) strains (see Swerdlow et al., 2006 and references therein). Crosses and backcrosses between SD and LE animals have revealed an orderly pattern of PPI apomorphine sensitivity (SD>N_2>F_1>LE), suggesting the differences may be associated with a relatively small number of genes (Swerdlow et al., 2004a,b). As summarized in Swerdlow et al. (2006), greater sensitivity to the disruptive effects of dopamine agonists was found to be associated with (1) lower basal levels of basal ganglia dopamine turnover (Swerdlow et al., 2005, (2) lower levels of dopamine-stimulated [^{35}S]GTPγS binding (Swerdlow et al., 2006), (3) lower sensitivity to the locomotor-activating effects of dopamine agonists (Swerdlow et al., 2006), (4) higher sensitivity to the motor suppressant effects of apomorphine (Swerdlow et al., 2006), and (5) relatively less fur pigmentation (Swerdlow et al., 2006). More recently, this group has observed an inverse relationship between dopamine agonist induced c-Fos expression and PPI disruption (Saint Marie et al., 2006) and that the intracerebral injection of amphetamine mimics the effects seen after s.c. drug injection in the SD and LE animals (Swerdlow et al., 2007). We observed that the High and Low lines do not seem to differ in terms of the methamphetamine effects on locomotor activity. Furthermore, there was no difference in coat color between the lines (data not shown). Effects on c-Fos expression are currently under investigation.

Noncompetitive NMDA receptor antagonists such as MK-801 (dizocilpine) and phencyclidine disrupt PPI (e.g., Curzon and Decker, 1998; Yee et al., 2004), and this effect is reversed by both typical and atypical antipsychotic drugs (Kline et al., 1998; Brody et al., 2004). Similarly, a mouse line (NR1−/−) with low levels of NR1 receptor density has poor PPI that is readily reversed by typical and atypical antipsychotic drugs; furthermore, the NR1−/− mouse is more sensitive to the disruptive effects of amphetamine (Duncan et al., 2006; Moy et al., 2006). In addition, some data suggest that among-strain differences in PPI are associated with differences in NMDA receptor density (Wolf et al., 2006). The data collected in the current study suggest that the High and Low lines are equally sensitive to the disruptive effects of the MK-801 challenge.

As noted by Belknap and Atkins (2001), STSB is an effective strategy for confirming known QTLs. As summarized in Table 1, QTLs on 3 different chromosomes (Chr 3, 11, and 16) have been detected and confirmed in independent investigations. The QTL on Chr 3 has not only been detected in multiple mouse studies but also detected in the homologous region of rat Chr 2 (Palmer et al., 2003). Significant QTLs were detected in the STSB lines for all 3 chromosomes in the expected regions. The question arises as to whether these are the same QTLs detected in the previous studies. In lieu of actually isolating the quantitative trait gene across studies, answering this question relies on indirect approaches. In the current study, we asked whether the B6 allele had the expected effect on PPI. The expected effect was observed on Chr 11 and the proximal region of Chr 16. Although the precision of the analysis here is no better than one would obtain in an F_2 intercross, the data suggest that it should be possible to map these QTLs in a large HS4 population where 1–2 cM precision can be easily obtained (see Malmanger et al., 2006). The failure to find the expected B6 allele effect on Chr 3 and the mid region of Chr 16 could be because of a variety of factors, including the greater genetic complexity of the HS4 mice that were used to generate the High and Low lines.

Although PPI in rodents and humans appears isomorphic and apparently associated with similar neural circuits, differences in drug responses e.g. the disruptive effects of amphetamine on PPI have been noted (Swerdlow et al., 2003). Some of the differences between rodents and humans appear to be related to the baseline level of PPI. Swerdlow et al. (2003) and Bitsios et al. (2005) have noted that dopamine agonists (direct and indirect) disrupt PPI in normal healthy volunteers with High but not Low PPI. The lines developed in the current selection mimicked these data; methamphetamine decreased PPI in the High but not the Low line. In contrast, while Csomor et al. (2008) found that haloperidol did not increase PPI in normal volunteers with Low PPI and actually decreased PPI in normal volunteers with High PPI, we observed that haloperidol increased PPI in both the High and Low lines. The reasons for these differences are unclear but may reflect differences in methods including the route of drug administration.

Given the widespread use of the PPI phenotype to model the sensory gating deficits found in schizophrenia and other psychiatric disorders, it would seem logical that selective breeding for PPI would have occurred much sooner. Although the heritability (in mice) for PPI is not high, it is similar to other phenotypes for which selective breeding has been quite successful, e.g., ethanol-induced activation (Phillips et al., 1991). Importantly, the current study and that of Schwabe et al. (2007) confirm the feasibility of selectively breeding for PPI. We strongly recommend that the next step should be to breed, in replicate, High and Low lines of mice using the familiar within-family selection design (Falconer and Mackay, 1996). This design minimizes the effects of genetic drift and allows one to establish selection lines that can be maintained long term.

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