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Acoustic startle and disruption of prepulse inhibition by dizocilpine in selectively bred mice

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In this study we examined the relationship between genetically produced differences in the magnitude of prepulse inhibition (PPI) of the acoustic startle response (ASR) and stress induced swim analgesia in genetically different strains of mice. Prepulse inhibition of the ASR and its changes due to dizocilpine (MK-801) injection were studied in 180 mice. The animals used in this study were obtained from our colony of 54 generation, Swiss-Webster mice selectively bred for high and low magnitude of analgesia. Three month old male mice of the high analgesia (HA) and the low analgesia (LA) lines, in addition to randomly bred controls (C), were used in the experiment. Thirty minutes before the ASR session the mice were injected intraperitoneally with saline or with 0.15, 0.25, 0.5 mg/kg of dizocilpine maleate. Prepulses suppressed the acoustic startle response in all lines in a prepulse intensity-dependent manner, but only the differences between the weakest and the strongest prepulses appeared significant. Two-way ANCOVA performed separately for each line revealed a significant effect of dizocilpine and prepulse intensity. Only in the HA line, however, the disruption of PPI from the injection of dizocilpine was evidenced by significant treatment by prepulse interaction. That means the prepulses decreased ASR significantly less in dizocilpine- treated animals than in saline-treated animals. The results confirmed that the mouse lines manifesting differential ASR magnitudes along with different degrees of PPI sensitivity to dizocilpine, might be suitable for pharmacogenetic studies on the glutaminergic mechanism of the startle response.

Key words: acoustic startle response, prepulse inhibition, dizocilpine, mouse behavior, analgesia

INTRODUCTION

Prepulse inhibition (PPI) of the acoustic startle reflex (ASR) is the reduction of the startle response, which occurs when a weak sensory stimulus (prepulse) is presented 30–500 ms before the startling pulse (Ison and Hammond 1971, Swerdlow et al. 1986, 1994, Koch 1999, Fendt et al. 2001, Yeomans et al. 2006). PPI is commonly viewed as an operational measure of a process called 'sensorimotor gating', by which excess or trivial stimuli are screened or 'gated out' of awareness (Braff et al. 1992, Curzon and Decker 1998, Arai et al. 2008). The fast excitatory pathway of the acoustic startle system involves serial connections linking the auditory nerve, cochlear root neurons, the caudal pontine reticular nucleus, and spinal motor neurons (Koch 1999, Fendt et al. 2001). Results of neurophysiological studies confirmed that the caudal pontine reticular nucleus is a key locus of PPI modulation and its neurons are markedly inhibited by an acoustic prepulse in mice (Willot et al. 1994). Recent findings suggest that the fast excitatory pathway of the acoustic startle system may be activated even in the presence of prepulse stimulus if dopaminergic synaptic transmission is blocked by dizocilpine (Arai et al. 2008).

Animal models provide a way to help understand and find ways to alleviate human diseases. The large interest in PPI has developed because clinical observations have shown a deficit of this phenomenon in several psychiatric diseases, especially in schizophrenia (Braff et al. 1978, 1992, Geyer et al. 1990, Swerdlow et al. 1994, McAlonan et al. 2002). The PPI loss in schizophrenic patients is thought to reflect a deficient sensorimotor gating, leading to "sensory overload" and cog-

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nitive intellectual impairment. Like the startle reflex itself, PPI is also a cross-species phenomenon (Swerdlow et al. 1999). The PPI deficits seen in schizophrenics can be mimicked in rodents by treatment with psychostimulants such as dizocilpine, also known as MK-801 (Curzon and Decker 1998, Swerdlow and Geyer 1998, Cadenhead et al. 1999, Eyjolfsson et al. 2006). Dizocilpine is a non-competitive antagonist of the NMDA glutamate receptor and it has a great deal of potential for being used in research to create animal models of schizophrenia (Eyjolfsson et al. 2006, Arai et al. 2008, Gururajan et al. 2010). Unlike other dopaminergic agonists, which mimic only the positive symptoms of schizophrenia, a single injection of dizocilpine was successful in modeling both the positive and negative symptoms (Eyjolfsson et al. 2006, Pratt et al. 2008). Recently, Arai and colleagues demonstrated that in mice, the fast excitatory pathway of the acoustic startle may be activated even in the presence of prepulse stimulus if dopaminergic transmission is blocked by dizocilpine (Arai et al. 2008). They documented that PPI disruption caused by dizocilpine is associated with the dysfunction of pallidotegmental neurons. The administration of dizocilpine results also in an increase in the amounts of glutamate, glutamine and succinate in the temporal lobe (Eyjolfsson et al. 2006).

It is well documented that the parameters of ASR depend on the genetic makeup of animals. ASR amplitudes differ among inbred and outbred rat strains (Glowa and Hansen 1994, Bast et al. 2000, Conti et al. 2001). Large strain differences in the magnitude of startle, as well as in the amount of PPI, were described in mice (Bullock et al. 1997, Logue et al. 1997, Paylor and Crawley 1997, Dulawa and Geyer 2000). Rat and mouse strains were also found to display different degrees of PPI disruption by apomorphine, amphetamine, dizocilpine and phencyclidine (Varty and Higgins 1994, Bast et al. 2000, Ralph et al. 2001, Varty et al. 2001). These observations are important in view of the evidence for genetic transmission of schizophrenia in families (Faraone and Tsuang 1985).

A way to study the genetics of behavioral, physiological, biochemical or pharmacological traits is an artificial selection of animals for a discrete phenotype. For several years we have been conducting a bidirectional selection of mice for magnitude of swim stress-induced analgesia (SSIA), as assessed with the hot-plate method. Using this strategy, we developed a high analgesia (HA) line, and a low analgesia (LA) line. The (HA) line manifests a pronounced loss of nociception after swim stress. In the (LA) line, the hot-plate latencies after swimming barely exceed the preswim baseline (Panocka et al. 1986). In our previous paper we described that the selected mouse lines dramatically differ in the magnitude of the ASR which is significantly higher in the HA than in the LA line (Błaszczyk et al. 2000). Since HA mice also appeared less active than LA mice in the open field test, we linked their higher startle with enhanced emotionality. Objectives of the present study were to investigate whether along with the divergence of ASR magnitude, the selected mouse lines manifest differential sensitivity to PPI disruption by dizocilpine. We were particularly interested in the influence of this compound on PPI in our selected mice, because we had earlier found the nonopioid SSIA in both lines to be antagonized by a low dose of dizocilpine (Marek et al. 1992). Since the nonopiod component of SSIA in HA mice is greater in magnitude than the overall nonopioid SSIA in LA mice, this can point to differential involvement of glutaminergic transmission in the nonopioid form of swim analgesia in these lines. It may also point to the control of other physiological functions, including the sensorimotor gating mechanisms.

METHODS

Animals

The subjects used in this study were obtained from our colony of 54 generation, Swiss-Webster mice selectively bred for high and low magnitude of analgesia induced by 3- min swimming in 20°C water. The details of the selection protocol were described earlier (Panocka et al. 1986). A total of one hundred eighty male, 3 month old mice of the HA and the LA line, including randomly bred controls (C), were used. Their mean body mass was 37.9±4.0 (SD) g. Body mass did not differ between the lines. Four – six mice were kept in a cage, in same-litter (family) groups at an ambient temperature of 22±1ºC, on 0600-lights on/1800-lights off photoperiod, with unlimited access to murine chow and water. All experiments were conducted between 0900 and 1500.

The protocols of the selective breeding and the experimentation on live vertebrates were approved by an authorized Ethics Commission. The rules of intramural humane maintenance of experimental animals and animal welfare were strictly observed in compliance with Polish law.

Treatments

Thirty minutes before the ASR session the mice were injected intraperitoneally with 0.15, 0.25 or 0.5 mg/kg of dizocilpine maleate (Sigma) freshly dissolved in 10 ml/kg of saline, or with equal volume of saline. Twelve line/treatment groups were formed, each containing 15±2 randomly assigned animals.

ASR testing

ASR testing was performed in a Coulbourn apparatus equipped with four force-sensitive platforms placed in a 0.8×0.8×1.1 m sound-proof ventilated chamber. The ventilation system provided a steady 46 dB background noise. Each mouse was tested only once. A loudspeaker located 10 cm above the cages generated 112 dB SPL 20-ms white noise pulses with 2-ms rise time, which were the startle stimuli. In some trials the same loudspeaker also emitted a weaker 20-ms white noise prepulse preceding the startle stimulus by 100 ms (onset-to-onset). The vertical component of the reactive force exerted on the platform by the animal's startle, produced an electric signal that was amplified, rectified, passed through a 40 Hz filter and was then sampled at 400 Hz for 200 ms. To assure better transfer of an animal's startling force to the body of the platform, each mouse was confined to a plastic cage (100×60×70 mm). Holes for ventilation were drilled in the walls of the cage. This was also believed to minimize possible ultrasound communication between the simultaneously tested four mice. Before each session the cages were thoroughly washed and wiped to eliminate odors.

After a 3-min adaptation, the mice were given seven startle stimulus-alone trials, intermingled with seven exposures to each of three other types of trials in which the startle stimulus was preceded by a 73, 83 or 89 dB prepulse. This made a total of 28 trials per session arranged in a pseudorandom sequence, and spaced by intertrial intervals of pseudorandom duration from 18 to 60 seconds.

Statistics

From preliminary observations we estimated that the movement of the mouse on the platform can be reliably qualified as a genuine ASR only when the peak latency of the response is not shorter than 15 and not longer than 50 ms. When the latency response is different, the records may represent locomotion or other casual motor activities (e.g., grooming) rather than startle. Therefore, we averaged maximum ASR amplitudes for each of the four trial types only from those trials that met the above criterion.

The data were analyzed with Statistica software (StatSoft, USA, version 5.1), supplemented with our own custom developed macros. ASR magnitudes, transformed to square roots to equalize variances, were analyzed with appropriate models of ANCOVA, in which mouse lines and treatments were independent factors, prepulse intensities were a repeated measure (12 line/treatment groups), and body mass was a covariate. The variances compared between treatments within each mouse line satisfied Barthlett's criterion of homogeneity in 9 out of 12 groups, and compared between prepulse intensities, appeared homogenous in 11 out of 12 line/treatment groups. ASR magnitudes, tested across prepulse intensities did not significantly deviate from sphericity in 7 out of these latter groups (Mauchley's test). Since the amplitudes of ASR did not significantly differ between families in any treatment group, the family factor was not included into the analyses.

The Bonferroni test was used for all *post-hoc* comparisons. In order to compare the amounts of PPI between the mouse lines, percent PPI scores were computed for each mouse as (prepulse + pulse)/(startle pulse-alone) ratios according to the formula: %PPI =100×(ASR magnitude without prepulse – ASR magnitude after prepulse)/ASR without prepulse. To improve normality, the percentages (p) were converted to arcsins according to the formula: $\arcsin\sqrt{p}$, and were analyzed with one-way ANOVA. The accepted level of significance in all analyses was $P<0.05$.

RESULTS

Prepulse inhibition (PPI) and basal amplitude of ASR

Administration of a prepulse suppressed ASR in all lines in a prepulse intensity-dependent manner, $F_{2,104}=4.91$, $P<0.01$, one-way ANOVA of percentual data (Fig. 1). Only the difference between the weakest (73 dB) and the strongest (89 dB) prepulse appeared significant using the Bonferroni comparison, $P<0.05$. The slightly smaller amount of PPI seen in LA than in

HA mice after the 73 dB and the 89 dB prepulse did not reach the criterion of statistical significance. The white bars in Fig. 2 representing startle-alone pulses in saline-injected mice show that the mouse lines displayed marked difference in basal ASR magnitude. This is confirmed by one-way ANCOVA of these data: $F_{2,51}$=31.73, P<0.0001. The magnitude of ASR was greater in HA mice than in each of the other lines (P<0.001, Bonferroni), whereas no significant difference was found between C and LA mice. Body mass was insignificant as a covariate.

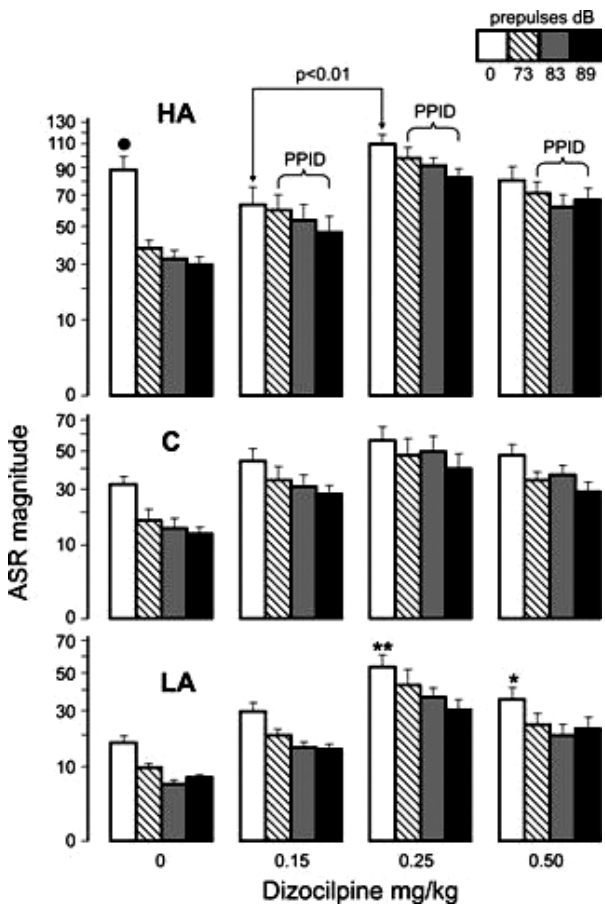

Fig. 1. Mean + SEM percent inhibition of ASR by prepulses of different intensity (white noise of 73, 83 or 89 dB) in high analgesia (HA), control (C) and low analgesia (LA) mouse lines. Filled-in circle denotes significant difference between HA and both C and LA lines (P<0.0001); *, ** denote significant differences from saline (P<0.05 and P<0.001, respectively). PPID - disruption of prepulse inhibition by dizocilpine; P<0.05 or better. Please note that only in the HA line the level of PPI disruption was strongly dependent on dizocilpine dose and prepulse intensity (significant treatment and intensity of prepulse interaction).

Dizocilpine-induced disruption of PPI

Two-way ANCOVA performed separately for each line revealed the significant effect of dizocilpine (HA: $F_{3,54}$=9.89, P<0.0001; C: $F_{3,55}$=6.28, P<0.001; LA: $F_{3,56}$=15.62, P<0.0001) and prepulse intensity (HA: $F_{3,165}$=61.78; C: $F_{3,168}$=32.29; LA: $F_{3,171}$=47.88, all P<0.0001). However, only in the HA line was the disruption of PPI from the use of dizocilpine confirmed in significant treatment by intensity of prepulse interaction, $F_{9,165}$=12.49, P<0.0001. This means that the prepulses decreased ASR significantly less in dizocilpine-treated animals than in saline-treated animals (Fig. 2). This interpretation is supported by significant simple interactions between each dose of dizocilpine vs. saline, and each prepulse and startle pulse vs. startle pulse alone, all P<0.0001 after Bonferroni correction for a total of 9 comparisons. Dizocilpine affected basal ASR in the HA line, $F_{3,54}$=4.78, P<0.01 (one-way ANCOVA of pulse-alone trials), but a significant difference was confirmed only between magnitudes of the lowest startle after 0.15 mg/kg and the highest startle after 0.25 mg/kg (P<0.01, Bonferroni), and not between any dose of dizocilpine vs. saline. The same analyses applied to the other lines showed that dizocilpine significantly augmented basal ASR in LA mice, $F_{3,56}$=9.10, P<0.0001, so that they startled with higher amplitudes after 0.25 mg/kg (P<0.0001) and after 0.5 mg/kg of dizocilpine (P<0.05, Bonferroni) than after saline. Although the same profile of dizocilpine action was seen in the C line, the change barely approached the criterion of statistical significance, $F_{3,55}$=2.46, P=0.072. Significant dizocilpine by prepulse interaction was revealed neither in the C ($F_{9,168}$=1.67, P=0.10) nor in the LA line ($F_{9,171}$=0.67, P=0.73, two-way ANCOVA). It then appears that in these lines dizocilpine did not affect PPI, but augmented ASR magnitudes in prepulse and startle pulse trials to the same extent as it did in startle-alone trials. The body mass was significant as a covariate in most within-line comparisons.

DISCUSSION

In this paper we report a study that examines the relationship between genetically produced differences in the magnitude of prepulse inhibition of the acoustic startle response and stress induced swim analgesia in genetically different strains of mice. The most impor-

tant finding of our study was related to different effects of dizocilpine disruption of PPI, observed in the mouse lines selected for SSIA (C, HA and LA). Although nonsignificant differences between lines were found in the percent scores of PPI (see Fig. 2), clear increase of ASR amplitudes (the effect related to disruption of PPI) by dizocilpine was seen only in the HA line (see Fig. 1). In these animals the prepulses decreased ASR significantly less in dizocilpine- treated animals than in saline-treated animals. The effect was confirmed with significant treatment by intensity of prepulse interaction.

The present results confirmed that mouse lines selectively bred in our laboratory for divergent amounts of SSIA substantially differ in ASR magnitude. The between-line difference in ASR magnitude was even greater in the present 54th generation than previously reported in mice of the 46th generation (Błaszczyk et al. 2000). Our results are then congruent with the data showing that the expression of ASR parameters varies not only among outbred or inbred strains, but also among members of genetically heterogenous populations. Our findings are consistent with previous studies, documenting that ASR magnitudes were found differentiated in rats bred for high vs. low acquisition of two-way avoidance (Schwegler et al. 1997) and for response vs. nonresponse to neuroleptic-induced catalepsy (Kline et al. 1998). Rats selected for hyper- vs. hypocholinergia, however, manifested differences in ASR thresholds (Markou et al. 1994). To our knowledge, only one protocol, which is the selective breeding of Wistar rats for susceptibility to apomorphine, can be regarded as more directly related to the mechanism of startle. This is because along with the differentiation of the central dopaminergic mechanisms, the selected lines display different amounts of PPI (Ellenbroek et al. 1995).

It is also well documented that in rodents dizocilpine dose, dependently disrupts PPI with a concomitant increase in the magnitude of the startle response at the lower and intermediate doses (Long et al. 2006). Therefore, in our experiments an observed pronounced PPI disruption in HA mice cannot be attributed to a ceiling effect of dizocilpine on ASR magnitude. This is because in startle pulse-alone trials the animals performed significantly more after 0.25 than after 0.15 mg/kg of dizocilpine, yet manifested equal degree of PPI disruption by the two doses. Since replicated sublines were not included in our breeding program, we cannot estimate with reliable statistics the probability of genetic drift involvement in within-line transmission of the unselected ASR traits. However, the large between-line difference in ASR magnitude, similar in its extent to the difference in the magnitude of SSIA, and the pronounced dizocilpine-produced PPI deficit in HA mice, contrasting with no such deficit in the other selected line, argue against only casual coexistence of these phenomena. Instead there is a claim for a genuine genetic correlation between the selected (SSIA) and the unselected (ASR) phenotypic traits (Henderson 1989).

Some methodological constrains should be given particular attention when discussing the results. Our results may be confounded by both: the testing conditions and the doses of dizocilpine. The testing conditions appear to have a significant impact on the outcome of experiments aimed at observing the propsychotic action of dizocilpine (Gururajan et al. 2010). Theses authors showed, for example, that in rats the habituating to injection procedure had no effect on their social behavior or locomotor activity, but significantly lowered the PPI, albeit with a non-significant lowering of the ASR. With the increasing dose of dizocilpine, however, the risk of dizocilpine dependency having an effect on the ASR was probably diminished by the tendency for dizocilpine to potentiate the ASR.

It is also important to note that the continuous noise emitted by the ventilation system in the Coulburn chamber was far below the 65 dB acoustic ambience purposefully imposed by other investigators. By using a lower noise intensity we wanted to avoid the known

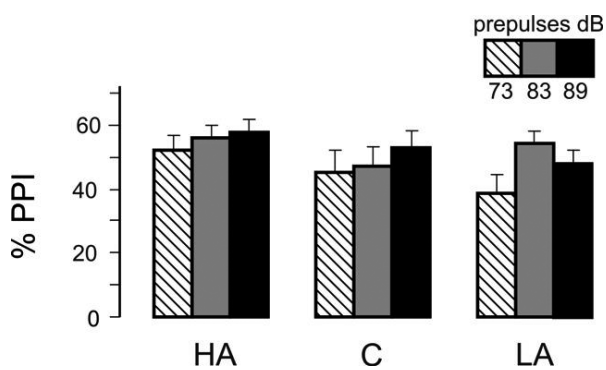

Fig. 2. Mean ASR magnitudes after square root transformation in high analgesia (HA), control (C) and low analgesia (LA) mouse lines to startle pulse alone (white columns) and prepulse + startle pulse (hatched and gray columns) trials. Prepulse intensity denotations as in Fig. 1.

effect of background noise on ASR (Davis 1974) which might substantially differ between the selected lines. Such a difference could obscure the genuine between-line difference in the ASR magnitude and in the amount of PPI. As it turned out, in our study, the relative loudness of the prepulses with respect to background became much greater than that commonly used in pharmacological work with PPI.

Finally, the importance of prepulse intensity was raised years ago as a controversy arose whether dopaminergic agonists disrupt PPI in rats (Mansbach et al. 1988) or not (Davis 1988). A comparative study made simultaneously in these two laboratories led to a conclusion that for apomorphine blockade of PPI to occur, the prepulse intensity should be maintained at stimulus detection level. This means that the prepulse intensity must not exceed the background noise by more than 10 dB (Davis et al. 1990). The same low prepulse intensity was later found important for the antagonism of PPI by PCP-like compounds which appeared effective with 10 dB, but not with 20 dB prepulses (Al-Amin and Schwarzkopf 1996). In accordance with these data, dizocilpine did not block PPI in our C and LA mice. However, the postulate of low prepulse intensity for pharmacological disruption of PPI, as stated in several reports, should be accepted with caution. In Wistar rats, unlike as in Sprague-Dawley rats, apomorphine was found to attenuate PPI at prepulse intensity more then 20 dB over background (Rigdon 1990). Such a finding argues that the intrinsic mechanism of sensorimotor gating can be subject to subtle genetic control, differing among the strains. Later on, Campeau and Davis (1995) demonstrated that the disruption of PPI produced in rats by apomorphine can be removed by merely changing the frequency, and not the intensity of background noise. This result based on changing the frequency, suggests that not the relative strength of the prepulse, but rather its interaction with the acoustic ambience can play a role in the sensitivity of PPI to pharmacological agents. Finally, the main objective comes from studies in schizophrenic patients, found to exhibit steady deficits of PPI at a wide range of prepulse intensities from 5 up to 20 dB over continuous background noise (Grillon et al. 1992). Since the PPI disruption by PCP-like compounds in rats, as the PPI deficit in schizofrenia, relatively little varies with increasing the intensity of the prepulse, it is supposed to better mimic the sensorimotor gating impairment in this disease than does the prepulse intensity dependent profile of PPI antagonism by dopaminergic agonists (Al-Amin and Schwarzkopf 1996).

According to many observations, higher prepulse intensities are usually required in mice than in rats to elicit similar amounts of PPI. Thus, inbred mouse strains were found to differ in PPI with prepulses up to 20-25 dB (Paylor and Crawley 1997) or even 30 dB (Bullock et al. 1997) above background. Targeted mutants of mice, manifested differential PPI as compared to wild forms when tested with up to 25 dB prepulse intensity (Petitto et al. 2002). Accordingly, the use of acoustic prepulses differing from background even by 16 dB from background, is not uncommon in pharmacological research with mice (for example see: Ralph et al. 2001 and Varty et al. 2001). Since a pronounced disruption of PPI by dizocilpine in HA mice occurred at far larger prepulse intensities, we conceive that in this line dizocilpine directly affected the intrinsic mechanism of NMDA receptor-mediated inhibition of PPI. Dizocilpine did not solely lessen the animals' ability to detect weak environmental stimuli. The outcome being that the PPI disruption by dizocilpine in the HA line appears to be similar in nature to the PPI deficit in schizophrenia. The PPI deficit in schizophrenia is thought to reflect more of a general impairment of intrinsic brain inhibitory processes than only the patients' inability to perceive signals minimally different from background noise (Grillon et al. 1992).

CONCLUSIONS

The mouse lines manifesting differential ASR magnitudes along with differential sensitivity of PPI to dizocilpine might be suitable for studies on sensory gaiting mechanisms. Our results advocate that disruption of PPI by dizocilpine in HA might be suitable for pharmacogenetic studies on the glutaminergic mechanism of the startle response. Disruption of PPI by dizocilpine in HA mice may also serve as an useful animal model of schizophrenia.

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REFERENCES

Al-Amin HA, Schwarzkopf SB (1996) Effects of the PCP analog dizocilpine in sensory gating, potential relevance to clinical subtypes of schizophrenia. Biol Psychiat 40: 744–754.

Arai S, Takuma K, Mizoguchi H, Ibi D, Nagai T, Takahashi K, Kamei H, Nabeshima T, Yamada K (2008) Involvement of pallidotegmental neurons in methamphetamine- and MK-801-induced impairment of prepulse inhibition of the acoustic startle reflex in mice: reversal by GABAB receptor agonist Baclofen. Neuropsychopharmacol 33: 3164–3175.

Bast T, Zhang W, Feldon J, White IM (2000) Effects of MK801 and neuroleptics on prepulse inhibition: re-examination in two strains of rats. Pharmacol Biochem Behav 67: 647–658.

Błaszczyk JW, Tajchert K, Łapo I, Sadowski B (2000) Acoustic startle and open field behavior in mice bred for magnitude of swim analgesia. Physiol Behav 70: 471–476.

Braff DL, Stone C, Callaway E, Geyer MA, Glick I, Bali L (1978) Prestimulus effects on human startle reflex in normals and schizophrenics. Psychophysiol 15: 339–343.

Braff DL, Grillon C, Geyer MA (1992) Gating and habituation of the startle reflex in schizophrenic patients. Arch Gen Psychiat 49: 206–215.

Bullock AE, Slobe BS, Vazquez V, Collins AC (1997) Inbred mouse strains differ in the regulation of startle and prepulse inhibition of the startle response. Behav Neurosci 111:1353–1360.

Cadenhead KS, Carasso BS, Swerdlow NR, Geyer MA, Braff DL (1999) Prepulse inhibition and habituation of the startle response are stable neurological measures in normal male population. Biol Psychiatry 45: 360–364.

Campeau S, Davis M (1995) Prepulse inhibition of the acoustic startle reflex using visual and auditory prepulses, disruption by apomorphine. Psychopharmacol 117: 267–274.

Conti LH, Palmer AA, Vanella JJ, Printz MP (2001) Latent inhibition and conditioning in rat strains which show differential prepulse inhibition. Behav Genet 31: 325–333.

Curzon P, Decker MW (1998) Effects of phencyclidine (PCP) and (+)MK-801 on sensorimotor gating in CD-1 mice. Prog Neuropsychopharmacol Biol Psychiatr 22: 129–146.

Davis M (1974) Sensitization of the rat startle response by noise. J. Comp Physiol Psychol 87:571–581.

Davis M (1988) Apomorphine, d-amphetamine, strychnine and yohimbine do not alter prepulse inhibition of the acoustic startle reflex. Psychopharmacol 95: 151–156.

Davis M, Mansbach RS, Swerdlow NR, Campeau S, Braff DL, Geyer MA (1990) Apomorphine disrupts the inhibition of acoustic startle induced by weak prepulses in rats. Psychopharmacol 102: 1–4.

Dulawa SC, Geyer MA (2000) Effects of strain and serotonergic agents on prepulse inhibition and habituation in mice. Neuropharmacol 39: 2170–2179.

Ellenbroek BA, Geyer MA, Cools AR (1995) The behavior of APO-SUS rats in animal models with construct validity for schizophrenia J Neurosci 15: 7604–7611.

Eyjolfsson EM, Brenner E, Kondziella D, Sonnewald U (2006) Repeated injection of MK801: An animal model of schizophrenia? Neurochem Int 48: 541–546.

Faraone SV, Tsuang MT (1985) Quantitative models of the genetic transmission of schizophrenia. Psychol Bull 98: 41–66.

Fendt M, Li L, Yeomans JS (2001). Brain stem circuits mediating prepulse inhibition of the startle reflex. Psychopharmacol 156: 216–224.

Geyer MA, Swerdlow NR, Mansbach RS, Braff DL (1990) Startle response models of sensorimotor gating and habituation deficit in schizophrenia. Brain Res Bull 25: 485–498.

Glowa JR, Hansen CT (1994) Differences in response to an acoustic startle stimulus among forty-six rat strains. Behav Genet 24: 79–84.

Grillon C, Ameli R, Charney DS, Krystal J, Braff DL (1992) Startle gating deficits occur across prepulse intensities in schizophrenic patients. Biol Psychiat 32: 939–943.

Gururajan A, Taylor DA, Malone DT (2010) Effect of testing conditions on the propsychotic action of MK-801 on prepulse inhibition, social behaviour and locomotor activity. Physiol Behav 99: 131–138.

Henderson ND (1989) Interpreting studies that compare high- and low-selected lines on new characters. Behav Genet 19: 473–502.

Ison JR, Hammond GR (1971) Modification of the startle reflex in the rat by changes in the auditory and visual environments. J Comp Physiol Psychol 75: 435–452.

Kline L, Decena E, Hitzemann R, McCaughran J (1998) Acoustic startle, prepulse inhibition, locomotion, and latent inhibition in the neuroleptic-responsive (NR) and neuroleptic-nonresponsive (NNR) lines of mice. Psychopharmacol 139: 322–331.

Koch M (1999) The neurobiolology of startle. Progr Neurobiol 59: 107–128.

Logue SF, Owen EH, Rasmussen DL, Wehner JM (1997) Assessment of locomotor activity, acoustic and tactile startle, and prepulse inhibition of startle in inbred mouse strains and F1 hybrids, implications of genetic background for single gene and quantitative trait loci analyses. Neuroscience 80**:** 1075–1086.

Long LE, Malone DT, Taylor DA (2006) Cannabidiol reverses MK-801-induced disruption of prepulse inhibition in mice. Neuropsychopharmacol 31: 795–803.

McAlonan GM, Daly E, Kumari V, Critchley HD, van Amelsvoort T, Suckling J, Simmons A, Sigmundsson T, Greenwood K, Russell A, Schmitz N, Happe F, Howlin P, Murphy DGM (2002) Brain anatomy and sensorimotor gating in Asperger's syndrome. Brain 127: 1594–1606.

Mansbach RS, Geyer MA, Braff DL (1988) Dopaminergic stimulation disrupts sensorimotor gating in the rat. Psychopharmacol 94: 507–514.

Marek P, Mogil JS, Sternberg WF, Panocka I, Liebeskind JC (1992) N-Methyl-Daspartic acid receptor antagonist MK-801 blocks nonopioid stress-induced analgesia. II. Comparison across three swim-stress paradigms in selectively bred mice. Brain Res 578: 197–203.

Markou A, Matthews K, Overstreet DH, Koob GF, Geyer MA (1994) Flinders resistant hypocholinergic rats exhibit startle sensitization and reduced startle thresholds. Biol Psychiat 36: 680–688.

Panocka I, Marek P, Sadowski B (1986) Inheritance of stress-induced analgesia in mice, selective breeding study. Brain Res 397: 152–155.

Paylor R, Crawley JN (1997) Inbred strain differences in prepulse inhibition of the mouse startle response. Psychopharmacol 132: 169–180.

Petitto JM, Huang Z, Lo J, Beck RD jr, Rinker C, Hartemink DA (2002) Relationship between the development of autoimmunity and sensorimotor gating in MRL-lpr mice with reduced IL-2 production. Neurosci Letters 328: 304–308.

Pratt JA, Winchester C, Egerton A, Cochran SM, Morris BJ (2008) Modelling prefrontal cortex deficits in schizophrenia: implications for treatment. Br J Pharmacol 153 (Suppl 1): S465–470. Ralph RJ, Paulus MP, Geyer MA (2001) Strain-specific effects of amphetamine on prepulse inhibition and patterns of locomotor behavior in mice. J Pharmacol Exp Ther 298: 148–155.

Rigdon GC (1990) Differential effects of apomorphine on prepulse inhibition of acoustic startle reflex in two rat strains. Psychopharmacol 102: 419–421.

Schwegler H, Pilz PK, Koch M, Fendt M, Linke R, Driscoll P (1997) The acoustic startle response in inbred Roman high- and low-avoidance rats. Behav Genet 27: 579–582.

Swerdlow NR, Braff DL, Geyer MA, Koob GF (1986) Central dopamine hyperactivity in rats mimics abnormal acoustic startle response in schizophrenics. Biol Psychiat 21: 23–33.

Swerdlow NR, Braff DL, Taaid N, Geyer MA (1994) Assessing the validity of an animal model of deficient sensorimotor gating in schizophrenic patients. Arch Gen Psychiat 51: 139– 154.

Swerdlow NR, Geyer MA (1998) Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. Schiz Bull 24: 285–301.

Swerdlow NR, Braff DL, Geyer MA (1999) Cross-species studies of sensorimotor gating of the startle reflex. Review. Ann N Y Acad Sci 877: 202–216.

Varty GB, Higgins GA (1994) Differences between three rat strains in sensitivity to prepulse inhibition of an acoustic startle response, influence of apomorphine and phencyclidine pretreatment. J Psychopharmacol 8: 148–156.

Varty GB, Walters N, Cohen-Williams M, Carey GJ (2001) Comparison of apomorphine, amphetamine and dizocilpine disruptions of prepulse inhibition in inbred and outbred mice strains. Eur J Pharmacol 424: 27–36.

Willott JF, Carlson S, Chen H (1994) Prepulse inhibition of the startle response in mice: relationship to hearing loss and auditory system plasticity. Behav Neurosci 108: 703–713.

Yeomans JS, Lee J, Yeomans MH, Steidl S, Li L (2006). Midbrain pathways for prepulse inhibition and startle activation in rat. Neuroscience 142: 921–929.