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The *chakragati* mouse shows deficits in prepulse inhibition of acoustic startle and latent inhibition

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Abstract

The *chakragati* (*ckr*) mouse, which was serendipitously created as a result of a transgenic insertional mutation, has been proposed as a model of aspects of schizophrenia. The mice exhibit circling, hyperactivity, reduced social interactions, and enlarged lateral ventricles, which parallel aspects of the pathophysiology of schizophrenia. Deficits in sensorimotor gating and processing of the relevance of stimuli are core features of schizophrenia, which underlie many of the symptoms presented. Measures of prepulse inhibition (PPI) and latent inhibition (LI) can assess sensorimotor gating and processing of relevance in both humans and animal models. We investigated PPI of acoustic startle and LI of aversive conditioning in wild-type, heterozygous, and *ckr* mice. The *ckr* mice, which are homozygous for the transgene insertion, but not heterozygous littermates, showed impaired PPI in the absence of any difference in acoustic startle amplitude and showed deficits in LI of conditioning of a light stimulus to footshock, measured as suppression of licking for water in water-restricted mice. Together with the previous evidence for hyperactivity, reduced social interactions, and enlarged lateral ventricles, these data lend further support to the suggestion that the *ckr* mouse has utility as an animal model of aspects of schizophrenia.

Keywords: *Chakragati* mice; Acoustic startle; Prepulse inhibition; Latent inhibition; Schizophrenia; Animal model

1. Introduction

Schizophrenia, which affects approximately 1% of the population, is one of the most debilitating of psychiatric disorders. There are few animal models for the investigation of new therapeutic approaches to schizophrenia. The animal models currently used in drug discovery and pharmacological research are based on certain hypotheses regarding the pathophysiology of schizophrenia. These include models based on dopaminergic, glutamatergic and neurodevelopmental hypotheses, which mimic various symptoms of schizophrenia. A hyperdopaminergic model of positive symptoms of schizophrenia such as hyperactivity and behavioral disinhibition can be elicited by administration of amphetamine, which also has similar psychomimetic effects in humans (Creese and Iversen, 1975; Geyer and Moghaddam, 2002). A hypoglutamatergic model of aspects of the symptomatology of schizophrenia can be elicited by administering non-competitive *N*-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine (PCP), which also have similar psychomimetic effects in humans (Krystal et al., 1994; Malhotra et al., 1996; Jentsch et al., 1997; Geyer and Moghaddam, 2002). As the pathogenesis of

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schizophrenia remains poorly understood, these hypothesis-biased models have incomplete or unproven construct validity. Being hypothesis-biased, they may limit prospects for the discovery of paradigm-shifting novel therapeutic approaches.

In recent years, attention has shifted towards the creation of genetic animal models of schizophrenia. One approach entails making genetic changes and screening for the associated behavioral correlates, another entails looking for characteristics reminiscent of schizophrenia in an animal first and then proceeding to understand the underlying mechanisms through a comprehensive analysis of the genetic correlates (Tarantino and Bucan, 2000; Kilts, 2001).

The *chakragati* (*ckr*) mouse was serendipitously created as a result of a transgenic insertional mutation (Ratty et al., 1990) resulting in a mouse that in the homozygous condition, exhibited an abnormal circling phenotype (Ratty et al., 1990; Fitzgerald et al., 1991). The *ckr* mouse line was generated by introduction of a 24-kb fragment of the mouse *Ren-2*^{d} renin gene (Mullins et al., 1989), however there was no evidence for transgene expression in the brain, kidney, submaxillary gland or liver. The behavioral phenotype appears to be linked to the integration of the transgene sequences between *D16Ros1* and *D16Ros2* on mouse chromosome 16 and associated rearrangements (Ratty et al., 1992; Smiraglia et al., 1997a,b). The increased motor activity in these mice is similar to that observed in wild-type mice treated with NMDA receptor antagonists, which produce behaviors resembling the positive symptoms of schizophrenia (Fitzgerald et al., 1991, 1992, 1993; Torres et al., 2004). Moreover, the atypical antipsychotics, clozapine and olanzapine, have been shown to reduce the circling behavior (Torres et al., 2004). The *ckr* mouse also appears to show reduced social interactions resembling the social withdrawal that is part of the constellation of negative symptoms of schizophrenia (Torres et al., 2005a). Additionally, the mouse shows lateral ventricular enlargement, which has been suggested to mirror neuropathological observations in schizophrenia (Torres et al., 2005b). These data collectively suggest that the *ckr* mouse may model certain aspects of the pathology of schizophrenia.

Dysfunctions in information processing and attentional processes are important aspects of the deficits in schizophrenia. Deficits in sensorimotor gating and processing of the relevance of stimuli are central to many aspects of the symptomatology of schizophrenia. It is therefore important that animal models of schizophrenia also model these deficits in sensory information processing (Kilts, 2001).

PPI is a sensorimotor gating phenomenon, which results in reduced responses to a strong stimulus when it is preceded by a prepulse exposure to the stimulus at a lower intensity that does not elicit the response. PPI is commonly measured as the reduction of the startle response to a loud white-noise pulse by pre-exposure to a weaker white-noise prepulse. PPI is deficient in patients with schizophrenia (Braff et al., 1978; Braff and Geyer, 1990; Kumari et al., 1999, 2002). This deficiency in PPI is generally considered to reflect disturbances in sensorimotor gating (Kumari and Sharma, 2002). In animal models, the PPI test is considered to have good face, predictive, and construct validity for sensorimotor gating deficits in schizophrenia (Braff and Geyer, 1990) and PPI deficits have been an important criterion in the assessment of animal models of schizophrenia, including both hypoglutamatergic and hyperdopaminergic models (Mansbach and Geyer, 1989; Swerdlow et al., 1990, 1996a; Keith et al., 1991; Bakshi et al., 1994).

LI is the retardation or inhibition of learning that one stimulus predicts the occurrence of another due to pre-exposure to the first stimulus. Although the neural and psychological basis of the phenomenon is still debated, LI is generally accepted to reflect processing of the salience or relevance of stimuli. LI can be absent or much reduced in people with schizophrenia resulting in enhanced learning of associations with pre-exposed stimuli (Baruch et al., 1988). The relevance of LI to chronic schizophrenia is less clear since antipsychotic medication can reverse deficits in LI or even enhance LI (Swerdlow et al., 1996b; Weiner, 2003; Gray and Snowden, 2005). Administration of amphetamine, which models aspects of the positive symptoms of schizophrenia, can mimic the LI deficits seen in acute schizophrenia in both healthy humans (Gray et al., 1992) and animals (Solomon et al., 1981; Weiner et al., 1984).

In the present study, we investigated PPI of acoustic startle and LI of conditioning of a light stimulus to footshock in wild-type, heterozygous, and *ckr* mice.

2. Materials and methods

2.1. Animals

The *ckr* mouse was generated as described previously (Ratty et al., 1990). The mice were male and female F2 animals of mixed genetic background of BCF_1 (C57BL/10Ros^{pd} × C3H/HeRos) supplied by the Roswell Park Cancer Institute. Wild-type mice were BCF littermates with no transgene insertion, heterozygous *ckr* mice were hemizygous for the transgene insertion, and *ckr* mice were homozygous for the transgene insertion. Mice were 4–5-month-old at the time of behavioral testing on the PPI task and another batch was 7-month-old at the time of behavioral testing on the LI task. The mice were genotyped by restriction fragment-length polymorphism analysis of biopsied tail DNA taken during the first week of postnatal life (Ratty et al., 1990). Wild-type, heterozygous, and *ckr* adult mice were housed in same-sex, same-genotype pairs under a 12/12 h light/dark cycle (lights on at 07:00) with free access to food and water. The mice were never isolated prior to the behavioral testing. All experiments were approved by the institutional animal ethics review board of the National University of Singapore and were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

2.2. Antipsychotic drug treatment

Haloperidol (Sigma–Aldrich, St. Louis, MA), risperidone (Sigma–Aldrich), and clozapine (Tocris, Bristol, UK) were dissolved in distilled water acidified to pH 4.5–5.0 with acetic acid. As a vehicle control, distilled water was likewise acidified to pH 4.5–5.0 with acetic acid. In the experiment to investigate the effects of antipsychotic drug treatment, mice received intraperitoneal injection of either antipsychotic drug in 0.1 ml/10 g or an equivalent volume of vehicle 20 min prior to testing of PPI of acoustic startle. Haloperidol was administered at 0.1, 0.5 and 1 mg/kg. Risperidone was administered at 0.1, 0.5 and 1 mg/kg. Clozapine was administered at 1, 4 and 10 mg/kg. The pharmacokinetics of antipsychotic drugs differs in rodents and humans. In rodents, single doses of 0.04–0.08 mg/kg haloperidol, 0.5–1 mg/kg risperidone and 5–15 mg/kg clozapine are expected to achieve clinically comparable in vivo dopamine D_2 receptor occupancies (Kapur et al., 2003).

2.3. Prepulse inhibition of acoustic startle

2.3.1. Apparatus

Startle reactivity was measured using a startle chamber (SR-LAB, San Diego Instruments, San Diego, CA). The chamber consisted of a clear plexi-glass cylinder resting on a platform inside a ventilated, sound-attenuating chamber. A high frequency loudspeaker inside the chamber produced a continuous background noise of 65 dB. The same loudspeaker produced the various acoustic stimuli. Vibrations of the plexi-glass cylinder, caused by the whole body startle response of the animals, were transduced into analog signals (0–5000 mV range) by a piezoelectric unit attached to the platform. These signals were then digitized for analysis.

2.3.2. Procedure

The protocol for measuring PPI was adapted from that described by Geyer and coworkers (Dulawa and Geyer, 1996; Geyer and Swerdlow, 1998). In the experiment to characterize PPI in mice without drug treatment, there were eight mice in each group. In the experiment to investigate the effects of antipsychotic drug treatment, there were six mice in each group. The mice were acclimatized for 60 min in the behavioral test room prior to measurement of PPI. They were then placed in the plexi-glass cylinder and exposed to 65 dB background white-noise. After 5 min, the mice were exposed to a series of five different types of trials involving exposure to pulses of white-noise: (1) pulse-alone trials, during which a 120 dB stimulus was presented for 40 ms; (2) +3 dB prepulse trials, during which a 20 ms, 68 dB (+3 dB above 65 dB background) prepulse preceded the 120 dB pulse by the prepulse-to-pulse interval; (3) +6 dB prepulse trials, during which a 20 ms, 71 dB (+6 dB above 65 dB background) prepulse preceded the 120 dB pulse by the prepulse-to-pulse interval; (4) +12 dB prepulse trials, during which a 20 ms, 77 dB (+12 dB above 65 dB background) prepulse preceded the 120 dB pulse by the prepulse-to-pulse interval; and (5) no pulse trials. For the measurement of differences in PPI between the wild-type, heterozygous and *ckr* mice, the prepulse-to-pulse interval was set at 100 ms, an interval which has previously been used to investigate PPI deficits in mice (Ralph et al., 1999; Yee et al., 2004; Gould et al., 2004). In one session, a total of 52 trials were conducted in pseudorandom order: 20 pulse-alone trials, and eight each of the other four trials. These were preceded by four pulse-alone trials, which were discarded. The average inter-trial interval was 15 s (9–21 s range). The startle response was recorded as the average movement detected over 65 ms following the pulse.

The startle amplitude was measured as the average startle response for the pulse-alone trials. Prepulse inhibition was calculated as percentage PPI, namely as $((A - B)/A) \times 100$, where A was the average startle response amplitude on pulse-alone trials and B was the average startle response amplitude on prepulse trials. Use of this measure, in preference to absolute difference scores, minimizes the possible effects of individual differences in startle amplitude on PPI (Mansbach et al., 1988).

2.4. Latent inhibition

2.4.1. Apparatus

The apparatus consisted of a 159 mm × 165 mm × 175 mm mouse operant behavior box (Model 259900-SK-MAU-ST/2, TSE Systems, Germany) in a sound-attenuating housing equipped with a ventilation fan (Model 259900-Hou-SK-M, TSE Systems, Germany). Fluid was delivered by a drop dispenser with a software-controlled magnetic valve. One of the walls of the chamber housed the receptacle for the liquid dispenser. Numbers of licks were monitored by infra-red sensors fitted at the opening of the receptacle. The pre-exposed, to-be-conditioned stimulus was a 2 W white house-light. Footshocks (0.1 mA, 1 s) generated by a shock scrambler module (Model 259900-SHOCK, TSE Systems, Germany) were delivered through a cage floor grid.

2.4.2. Procedure

The protocol for LI in mice was adapted from that previously described with minor modifications (Gould and Wehner, 1999; Lipina et al., 2005; Meyer et al., 2006). From 1 week prior to the start of the experiment and throughout the experiment, the mice were placed on a 23-h water restriction schedule. For 5 days prior to the start of the experiment, the animals were handled for 5 min daily. The animals were tested between 08:00 and 17:00. There were eight mice in each group.

During initial baseline exposure, the mice were placed in the experimental chamber and allowed free access to water for 20 min daily for 5 days. Pre-exposure, conditioning, re-baseline, and test sessions were then administered 24 h apart. During the pre-exposure session, the mice were placed in the experimental chamber without access to water. The pre-exposed (PE) group received forty 10 s house-light exposures with a variable inter-stimulus interval (ISI) with a mean of 35 s. The non-pre-exposed (NPE) animals were confined to the chamber for an identical period of time, but they did not receive the light stimuli. During the conditioning session, the mice were again placed in the experimental chamber without access to water. Each animal received two light-shock pairings 5 and 10 min after the start of the session. The light stimulus parameters were identical to those used during pre-exposure. The footshock followed immediately after termination of the light stimulus. After the second pairing, the animal was left in the experimental chamber for an additional 5 min. During the re-baseline session, the mice were allowed free access to water as in the baseline condition. Latency to first lick and the total number of licks were recorded for each mouse. During the test session, the mice were again allowed to drink water from the receptacle. When the animal completed 75 licks, the house light was presented for 5 min. The time to first lick, time to complete 1–50 licks, time to complete 50–75 licks (pre-light), latency to first lick after light presentation and the time to complete 75–100 licks (light on) were recorded. Animals that failed to complete 25 licks within the 5 min duration when the light was on were given a score of 300 s.

The amount of suppression of licking was measured using a suppression ratio, $A/(A + B)$, where A was the period prior to the presentation of the house-light (licks 51–75) and B was the period of the house-light presentation (licks 76–100). A suppression ratio of 0.01 indicates complete suppression (no LI) and a suppression ratio of 0.50 indicates no change in response rate from the period prior to the presentation of the stimulus to the period of stimulus presentation (complete LI).

2.5. Statistical analysis

The startle amplitudes of the wild-type, heterozygous, and *ckr* mice were compared by one-way analysis of variance (ANOVA). The PPI data were analyzed by two-way ANOVA with genotype as a between-subject factor and the prepulse intensity as a repeated measure. The data on the effects of the antipsychotic drugs on PPI were analyzed by two-way ANOVA with both genotype and drug treatment as between-subjects measures. The results of the LI experiments were analyzed using a two-way ANOVA with exposure (PE and NPE) and the genotype (wild-type, heterozygous and *ckr*) being fixed factors. Post hoc tests were conducted using Tukey's Honestly Statistically Different (HSD) test. The alpha level was set at 0.05.

3. Results

3.1. Acoustic startle response

The amplitude of the acoustic startle response of wild-type, heterozygous and *ckr* mice was compared on pulse-alone trials. The startle amplitude was recorded as the average voltage measured by the piezoelectric transducer over 65 ms following the 40 ms, 120 dB pulse. Although the *ckr* mice showed slightly greater startle amplitudes (266.87 ± 51.53 mV) compared to the wild-type (221.62 ± 31.86 mV) and the heterozygous mice (218.75 ± 50.25 mV), the startle amplitudes did not significantly differ (Fig. 1).

3.2. Prepulse inhibition of acoustic startle

PPI was compared in wild-type, heterozygous and *ckr* mice across three prepulse intensities. Two-way ANOVA revealed

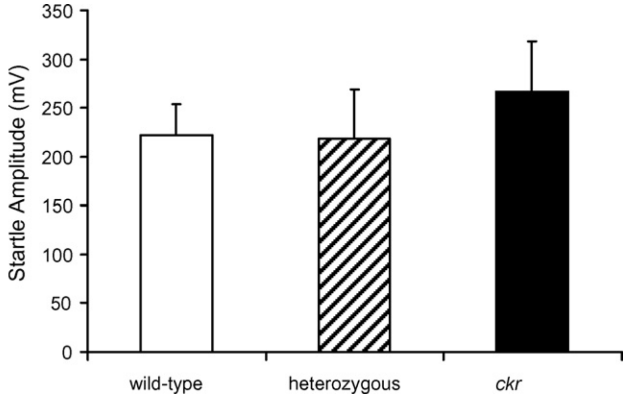

Fig. 1. Acoustic startle in wild-type, heterozygous and *ckr* mice. Movement resulting from acoustic startle responses was averaged over 65 ms following the 120 dB pulses in pulse-alone trials. The magnitude of acoustic startle is expressed as the mean response amplitude measured by the piezoelectric transducer (mV). Data are plotted as mean + S.D. $n = 8$ male/female mice/genotype.

that genotype had a significant effect on PPI ($F_{(2,21)} = 32.36$, $p < 0.001$). Prepulse intensity significantly influenced PPI ($F_{(2,42)} = 30.91$, $p < 0.001$), but there was no prepulse intensity × genotype interaction (n.s.). Post hoc Tukey's HSD tests showed that the genotype effect was attributable to a significant reduction in PPI in *ckr* mice compared to wild-type mice across all prepulse intensities (Fig. 2). Heterozygous mice did not show significant deficits in PPI compared to wild-type mice.

3.3. Effect of antipsychotic drug treatment on PPI

The effect of administering antipsychotic drugs on PPI produced by a +12 dB prepulse was investigated in wild-type and *ckr* mice. Administration of haloperidol (0.1–1 mg/kg) did not significantly affect PPI (Fig. 3A). Overall two-way ANOVA was significant ($F_{(7,56)} = 10.56$, $p < 0.0001$) but, while there was a significant genotype effect ($F_{(1,56)} = 69.44$, $p < 0.0001$), the dose effect was not significant ($F_{(3,56)} = 0.53$, n.s.) and there was no genotype–dose interaction ($F_{(3,56)} = 0.22$, n.s.). Post hoc Tukey's HSD comparisons on genotype confirmed that the difference between wild-type and *ckr* mice remained significant across all doses of haloperidol.

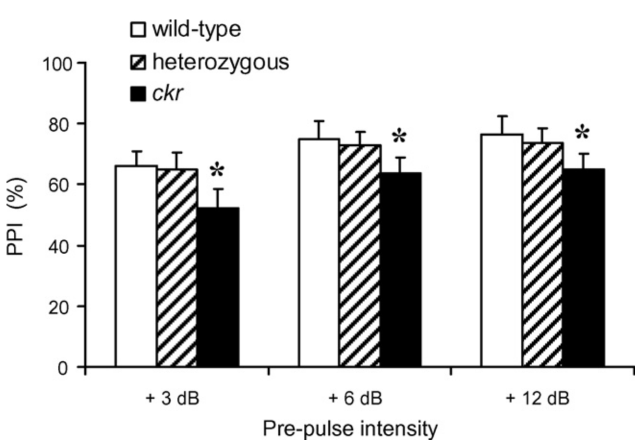

Fig. 2. Prepulse inhibition (PPI) of acoustic startle in wild-type, heterozygous and *ckr* mice. Data are plotted as mean + S.D. $n = 8$ male/female mice/genotype. *$P < 0.05$, post hoc Tukey's HSD comparison with wild-type.

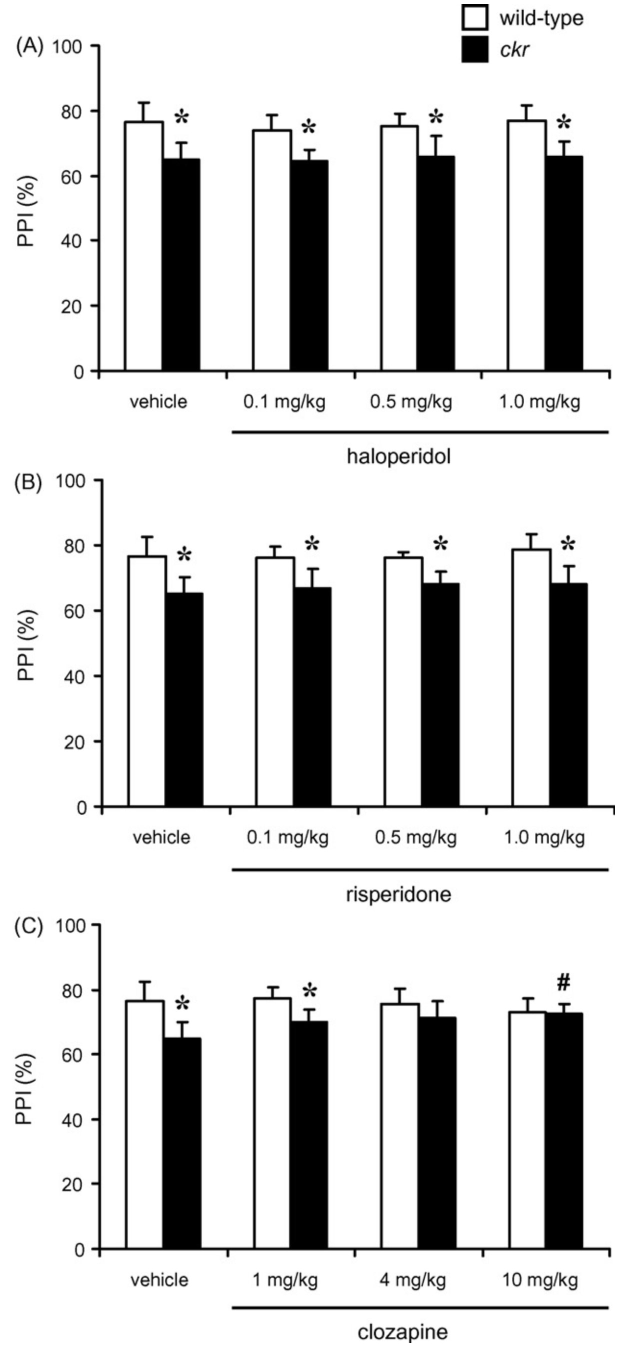

Fig. 3. Effect of administration of (A) haloperidol (0.1–1 mg/kg, i.p.), (B) risperidone (0.1–1 mg/kg, i.p.), and (C) clozapine (1–10 mg/kg, i.p.) on prepulse inhibition (PPI) of acoustic startle by a +12 dB prepulse in *ckr* mice. Data are plotted as mean + S.D. $n = 8$ male/female mice/genotype. *$p < 0.05$, post hoc Tukey's HSD comparison with wild-type. $^{\#}p < 0.05$, post hoc Tukey's HSD comparison with vehicle-treated *ckr* mice.

Likewise, administration of risperidone (0.1–1 mg/kg) did not significantly affect PPI (Fig. 3B). Overall two-way ANOVA was significant ($F_{(7,56)} = 10.52$, $p < 0.0001$) but, while there was a significant genotype effect ($F_{(1,56)} = 70.11$, $p < 0.0001$), the dose effect was not significant ($F_{(3,56)} = 0.83$, n.s.) and there was no genotype–dose interaction ($F_{(3,56)} = 0.34$, n.s.). Post hoc Tukey's HSD comparisons on genotype confirmed that the difference between wild-type and *ckr* mice remained significant across all doses of risperidone.

In contrast, administration of clozapine (1–10 mg/kg) reduced the difference between wild-type and *ckr* mice (Fig. 3C). Overall two-way ANOVA was significant ($F_{(7,56)} = 6.09$, $p < 0.0001$) and both the genotype effect ($F_{(1,56)} = 26.39, p < 0.0001$) and the genotype–dose interaction were significant ($F_{(3,56)} = 4.09$, $p < 0.05$). Post hoc Tukey's HSD comparisons confirmed that while the difference between wild-type and *ckr* mice was significant on administration of vehicle and 1 mg/kg clozapine, there was no significant difference between wild-type and *ckr* mice after administration of 4 mg/kg and 10 mg/kg clozapine. Post hoc Tukey's HSD comparisons also confirmed that administration of 10 mg/kg significantly increased PPI in *ckr* mice compared to that seen after administration of vehicle. Additionally, one-way ANOVA on the *ckr* data alone ($F_{(3,28)} = 4.42$, $p < 0.05$) confirmed that clozapine altered PPI in the *ckr* mice and post hoc comparison with vehicle (65.00 ± 5.01% PPI, mean ± S.D.) confirmed that 10 mg/kg clozapine significantly increased PPI in *ckr* mice (72.38 ± 3.34% PPI, mean ± S.D.; $p < 0.05$). Furthermore, one-way ANOVA on the difference between the PPI in the *ckr* mice and the mean PPI in wild-type mice under the same treatment conditions ($F_{(3,28)} = 8.89$, $p < 0.0005$) further confirmed that the clozapine treatment reduced the difference between *ckr* and wild-type mice and post hoc comparison with vehicle confirmed that 10 mg/kg clozapine reduced the difference in PPI (−11.50 ± 5.01% PPI and −0.63 ± 3.34% PPI, respectively; $p < 0.05$).

3.4. Latent inhibition

The LI data were analyzed by two-way ANOVA of genotype (wild-type, heterozygous, and *ckr*) and exposure (non-pre-exposure, NPE, and pre-exposure conditions, PE). There were significant effects of genotype ($F_{(2,18)} = 24.47$, $p < 0.001$) and exposure ($F_{(1,18)} = 411.46$, $p < 0.001$). There was also a significant genotype × exposure interaction ($F_{(2,18)} = 55.09$, $p < 0.001$), indicating an effect of genotype on LI. Post hoc Tukey's HSD tests showed that within the wild-type and heterozygous mice, the suppression ratios were significantly greater in the PE condition than in the NPE condition, indicating that LI had occurred (Fig. 4). In contrast, in the *ckr* mice, there was no significant difference between the PE and NPE conditions, indicating a deficit in LI. The pre-exposed *ckr* mice also had significantly lower suppression ratios than pre-exposed wild-type and pre-exposed heterozygous mice.

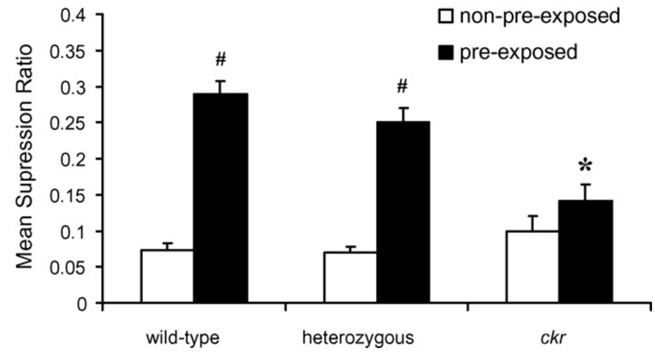

Fig. 4. Latent inhibition in wild-type, heterozygous and *ckr* mice. Mice were assigned to pre-exposure to a house-light or non-pre-exposure to the house-light. The house-light was subsequently paired with a footshock. Learning of the association between the house-light and the footshock was measured by recording licks of water and calculating the mean suppression ratio of licking in absence and presence of the light. Data are plotted as mean + S.D. $n = 8$ male/female mice/genotype. *$p < 0.001$, post hoc Tukey's HSD comparison with wild-type pre-exposed group; #$p < 0.001$, post hoc Tukey's HSD comparison with non-pre-exposed condition.

4. Discussion

Although *ckr* mice did not show any changes in acoustic startle amplitude, we found a significant reduction in the PPI of the acoustic startle reflex in *ckr* mice compared to the wild-type and heterozygous littermates. The absence of any changes in the amplitude of acoustic startle suggests that the observed effects in the PPI paradigm are not attributable to general changes in reactivity to stimuli.

Turning and hyperactivity can be overt phenotypes associated with hearing or vestibular dysfunction (Jones et al., 2005). If *ckr* mice have a hearing deficit then it might be argued that difficulty in detecting the prepulse could explain the reduction in PPI seen in *ckr* mice. Willott et al. (2003) investigated correlations between hearing sensitivity, acoustic startle responses and PPI in mice and concluded that hearing loss must be severe to influence PPI in mice. There is no evidence that *ckr* mice have any hearing deficit or vestibular abnormality (Ratty et al., 1990; Fitzgerald et al., 1991). In our study, we investigated the effects of varying the prepulse intensity on PPI. If the deficit in PPI seen in the *ckr* mice was attributable to a hearing deficit, then it would be predicted that the *ckr* mice would be more sensitive to increasing the intensity of the prepulse. PPI would be predicted to increase with increasing prepulse intensities until the prepulse was loud enough to overcome the hearing deficit and be reliably detected by the *ckr* mice, resulting in the same level of PPI as in wild-type mice. However, we found no evidence for this pattern of change in PPI across prepulse intensities. The prepulse intensity × genotype interaction was not significant, which shows that *ckr* mice have a similar pattern of change in PPI across prepulse intensities to the wild-type and heterozygous mice. There was no further increase in PPI on increasing the prepulse intensity from +6 dB to +12 dB, yet the PPI deficit in *ckr* mice had not been abolished at these prepulse intensities. Furthermore, administration of the antipsychotic drug, clozapine, reversed the deficit in PPI in the *ckr* mice. Together these data imply that the PPI deficits in *ckr* mice are not attributable to gross sensory abnormalities.

PPI deficits may serve as a good model of the sensorimotor gating problems associated with schizophrenia (Geyer and Moghaddam, 2002). There are various ways in which PPI deficits can be induced in animals. PPI deficits can be produced by stimulation of D_2-like dopamine receptors by amphetamine, apomorphine and D_2 receptor agonists (Schwarzkopf et al., 1993; Caine et al., 1995; Ralph et al., 1999); by the activation of the serotonergic system with 5-HT releasers or direct agonists at multiple serotonin receptors (Padich et al., 1996; Kehne et al., 1996); by blocking of *N*-methyl-D-aspartate (NMDA) receptors with drugs like phencyclidine (PCP) (Johansson et al., 1995); or by developmental manipulations, such as rearing in isolation (Wilkinson et al., 1994; Varty et al., 1999). Like the hyperdopaminergic and hypoglutamatergic animal models of aspects of schizophrenia (Mansbach and Geyer, 1989; Swerdlow et al., 1990, 1996a; Keith et al., 1991; Bakshi et al., 1994), *ckr* mice show a deficit in PPI. Although the *ckr* mouse is the result of a serendipitous transgene-insertional mutation and was not created as a hyperdopaminergic model, it may involve alterations in dopaminergic neurotransmission (Fitzgerald et al., 1992, 1993). However, the PPI deficit in the *ckr* mouse is not identical to that seen in hyperdopaminergic models. For example, while PPI in the amphetamine-induced hyperdopaminergic model is generally more robust with weak prepulses and disappears with stronger prepulses (Sills, 1999), the *ckr* mouse showed no evidence of a prepulse intensity × genotype interaction. In this respect, the *ckr* mouse may be a better model of PPI in schizophrenia than the amphetamine-induced hyperdopaminergic model as Braff et al. (1999) found no evidence for a prepulse intensity × diagnosis interaction when they compared male patients with schizophrenia with control subjects.

We found that clozapine dose-dependently increased PPI in *ckr* mice and that after 10 mg/kg clozapine-treatment there was no difference in PPI between wild-type and *ckr* mice. Although 10 mg/kg clozapine may not be directly comparable on a per weight basis to the doses typically administered to humans, due to the differences in pharmacokinetics in humans and rodents, the dose is in the range that is likely to reach clinically comparable dopamine D_2 receptor occupancies on single dosing in rodents (Kapur et al., 2003). A typical or first generation antipsychotic, haloperidol (0.1–1 mg/kg) and another atypical or second generation antipsychotic, risperidone (0.1–1 mg/kg) did not affect PPI in the *ckr* mouse. The doses of these antipsychotics encompass or exceed those likely to achieve clinically comparable dopamine D_2 receptor occupancies on single dosing in rodents (Kapur et al., 2003). That haloperidol and risperidone did not affect PPI in the *ckr* mouse suggests that the PPI deficit observed in the *ckr* mouse is not a purely dopaminergic phenomenon. Notably, patients with schizophrenia medicated with a range of typical antipsychotics, including haloperidol, still show substantial disruption of PPI (Kumari et al., 1999, 2002; Kumari and Sharma, 2002; Mackeprang et al., 2002; Duncan et al., 2003a,b). In contrast, patients on the atypical antipsychotic, clozapine, are reported to show improvements in PPI (Kumari et al., 1999), while the evidence for improvement in PPI with risperidone has been inconclusive and controversial (Kumari et al., 2002; Kumari and Sharma, 2002; Mackeprang et al., 2002; Duncan et al., 2003b). This lends further support to the notion that the PPI deficit in the *ckr* mouse may offer a model predicting pharmacological efficacy against some aspects of the symptomatology of schizophrenia.

LI may be envisaged as a measure of ability to ignore irrelevant stimuli (Lubow, 1973; Lubow and Gewirtz, 1995). The function of LI is probably to focus attention on more recent inputs with potential salience rather than on earlier or older inputs with no established salience (Lubow, 2005). Various studies have found deficits in LI in patients with schizophrenia while others have not and the relevance of deficits in LI to schizophrenia remains hotly debated (Weiner, 2003; Gray and Snowden, 2005). The relationship between LI and schizophrenia is strengthened by the fact that amphetamine, which mimics positive symptoms of schizophrenia in normal human subjects, decreases LI both in healthy humans (Gray et al., 1992) and in rodents (Solomon et al., 1981; Weiner et al., 1984). Similarly, it has been reported that atypical antipsychotics like clozapine (Moran et al., 1996), olanzapine (Gosselin et al., 1996) and remoxipride (Trimble et al., 1997) either produced the expected increases in LI or prevented the LI lowering effect of indirect dopamine agents (Moser et al., 2000; Weiner, 2000). Thus, although arguably these models also have construct validity for attentional processes in schizophrenia (Lubow, 2005), regardless of whether or not deficits in LI occur in schizophrenia, LI in animals provides a test with good predictability for pharmacological effects on some of the symptoms of schizophrenia.

In our experiments, we observed that (i) pre-exposed *ckr* mice showed significantly lower suppression ratios than pre-exposed wild-type and pre-exposed heterozygous littermates, and (ii) in *ckr* mice the difference in the suppression ratio between the pre-exposed and non-pre-exposed conditions was not significant, whereas in wild-type mice and heterozygous littermates there was a significant suppression of learning in the pre-exposed condition. This indicated that the *ckr* mice are deficient in LI, whereas the wild-type and heterozygous mice showed LI. Notably, LI deficits are not seen in the rearing in periodic social isolation model of schizophrenia (Wilkinson et al., 1994). Thus the LI deficit seen in *ckr* mice cannot be attributed to isolation secondary to the hyperactivity and circling or to the reduced social interactions that these mice exhibit (Torres et al., 2005a).

The pathophysiological bases for the deficits in PPI and LI in the *ckr* mouse remain to be elucidated. Torres et al. (2004, 2005b) have reported that *ckr* mice show enlarged lateral ventricles, agenesis of the corpus callosum, and depletion of myelinated axons in the vicinity of the ventricles. However, these neuroanatomical abnormalities were observed both in *ckr* mice and in heterozygous mice. It is therefore highly unlikely that the PPI and LI deficits which were observed in *ckr* mice, but not heterozygous mice, relate directly to these neuroanatomical abnormalities. Torres et al. (2004) have also drawn qualitative and quantitative parallels between the hyperactivity observed in *ckr* mice and NMDA antagonist-induced hyperactivity. However, although administration of the NMDA receptor antagonist produces deficits in PPI (Lubow, 2005) it does not disrupt (Weiner and Feldon, 1992) and may even enhance LI (Palsson et al., 2005). The behavioral profile of the *ckr* mouse, which shows deficits in both PPI and LI, is therefore not that of a hypoglutamatergic model of schizophrenia. The parallel deficits in both PPI and LI are consistent with the deficits seen in the amphetamine-induced hyperdopaminergic model. As the circling of the *ckr* mouse has been attributed to a hemispheric dopaminergic imbalance (Fitzgerald et al., 1992, 1993), it may be that dopaminergic mechanisms contribute to the deficits in LI and PPI seen in the *ckr* mouse. However, as yet there is no evidence that the insertional mutation in the *ckr* mouse directly disrupts any genes associated with dopaminergic neurotransmission. The pattern of antipsychotic sensitivity of the deficit in PPI also differed from that reported for the amphetamine-induced hyperdopaminergic model. It is likely that the changes in dopaminergic function and the behavioral changes, including the disruption of PPI and LI, are part of a complex manifestation of the insertional mutation that may involve multiple neurotransmitter systems.

Together these findings on deficits in PPI and LI in *ckr* mice lend further support to the suggestion that *ckr* mice may model aspects of schizophrenia.

5. Conflict of interest statements

Anil K. Ratty is the Chief Scientific Architect of Chakra Biotech Pte Ltd. Anil K. Ratty and Kenneth W. Gross are inventors on U.S. Patent 5,723,719 (3 March 1998) ‘‘Transgenic mouse as model for diseases involving dopaminergic dysfunction’’. Gavin S. Dawe is a consultant to Chakra Biotech Pte Ltd.

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