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ANTIPSYCHOTIC DRUGS DOSE-DEPENDENTLY SUPPRESS THE SPONTANEOUS HYPERACTIVITY OF THE *CHAKRAGATI* MOUSE

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Abstract—The *chakragati* (*ckr*) mouse has been proposed as a model of aspects of schizophrenia. The mice, created serendipitously as a result of a transgenic insertional mutation, exhibit spontaneous circling, hyperactivity, hypertone of the dopamine system, reduced social interactions, enlarged lateral ventricles, deficits in pre-pulse inhibition of acoustic startle and deficits in latent inhibition of conditioned learning. In this study, the dose-dependent effects of antipsychotic drugs (haloperidol, pimozide, risperidone, clozapine, olanzapine, ziprasidone, quetiapine and aripiprazole) on the spontaneous hyperactivity of the mice were investigated. All the antipsychotic drugs tested dose-dependently suppressed spontaneous hyperactivity. Aripiprazole, which is known to be a dopamine D2 receptor partial agonist, exhibited a tri-phasic dose-response, initially suppressing hyperactivity at low doses, having little effect on hyperactivity at intermediate doses, and suppressing activity again at high doses. These data suggest that the spontaneous circling and hyperactivity of the ckr mouse may allow screening of candidate antipsychotic compounds, distinguishing compounds with aripiprazole-like profiles.

Key words: *chakragati* mice, hyperactivity, antipsychotic, drug screening, schizophrenia, animal model.

Schizophrenia is a debilitating mental disorder affecting approximately 1% of the population worldwide. Animal models are important for the screening of drug candidates to predict potential efficacy in the treatment of schizophrenia. Animal models of schizophrenia typically used in drug discovery and neuropsychopharmacology research include hyperdopaminergic models, for example administration of amphetamine (Creese and Iversen, 1975; Geyer and Moghaddam, 2002), hypoglutamatergic models, for example administration of non-competitive N-methyl-D-aspartate (NMDA) receptor antagonists such as dizocilpine or phencyclidine (Geyer and Moghaddam, 2002; Murray, 2002; Seillier and Giuffrida, 2009), and neurodevelopmental models, for example rearing in isolation or intrauterine or early postnatal challenge with toxins or activators of immune responses (Geyer and Moghaddam, 2002; Koike et al., 2009; Li et al., 2009; Lipska, 2004; Lodge and Grace, 2009; Pietropaolo et al., 2008; Sams-Dodd et al., 1997; Seillier and Giuffrida, 2009; Vohs et al., 2009). These models are based on certain dopaminergic, glutamatergic or neurodevelopmental hypotheses regarding the pathophysiology of schizophrenia. As the pathogenesis of schizophrenia remains poorly understood, the validity of these hypothesis-biased models remains indeterminate and these models may limit prospects for the discovery of paradigm-shifting novel therapeutic approaches. Other limitations of these models include the labour-intensive need for intervention to create the model. In the case of the hyperdopaminergic and hypoglutamatergic models, this entails injection of drugs to create the model before injection of the compounds to be tested and so these models are likely to reveal only antipsychotic action that is mediated via neurotransmitter systems affected by the challenge paradigms. The pharmacokinetics of the drugs used to induce the model can also lead to time-dependent fluctuations in the intensity of the induced behaviors that can increase experimental variability, losing specificity and selectivity for antipsychotics. These limitations restrict the application of these models in drug screening. There is pressing need for better animal models of schizophrenia (Geyer, 2008) and in recent years there has been increasing interest in the creation of genetic animal models of schizophrenia (Chen et al., 2006; O'Tuathaigh et al., 2007; Powell et al., 2009).

The *chakragati* (*ckr*) mouse has been proposed as a genetic animal model for aspects of schizophrenia that may serve to facilitate the screening of drugs for potential application in schizophrenia (Dawe and Ratty, 2007). The *ckr* mouse was serendipitously created as a result of a transgenic insertional mutation (Ratty et al., 1990) such that in the homozygous condition the mouse exhibits an abnormal circling phenotype (Fitzgerald et al., 1991; Ratty et al., 1990). The circling is associated with increased motor activity that is similar to that induced in wild-type mice treated with NMDA receptor antagonists or amphetamine, which produce behaviors resembling the positive symptoms of schizophrenia (Fitzgerald et al., 1991, 1992, 1993; Torres et al., 2004). The *ckr* mouse also exhibits a constellation of other features that appear to mimic as-

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Abbreviations: ANOVA, analysis of variance; *ckr*, *chakragati*; NMDA, N-methyl-D-aspartate; PPI, prepulse inhibition.

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pects of the signs of schizophrenia. The mice show reduced social interactions resembling the social withdrawal that is part of the constellation of negative symptoms of schizophrenia (Torres et al., 2005a). They have lateral ventricular enlargement, which has been suggested to mirror neuropathological observations in schizophrenia (Torres et al., 2005b). They show impaired prepulse inhibition (PPI) of acoustic startle (Verma et al., 2008), which appears to mirror the deficits in PPI reported in schizophrenia and other diseases involving striatal dysfunction (Braff and Geyer, 1990; Braff et al., 2001; Kumari et al., 1999, 2002) that are thought to reflect disturbances in sensorimotor gating (Kumari and Sharma, 2002). The mice also show impaired latent inhibition of conditioned learning (Verma et al., 2008), reminiscent of the deficits in latent inhibition reported in schizophrenia (Baruch et al., 1988). Collectively, these data suggest that the *ckr* mouse, resulting serendipitously rather than as a result of deliberate hypothesis-based manipulations, may model certain aspects of the pathology of schizophrenia (Dawe and Ratty, 2007; Torres et al., 2004, 2005b, 2008).

It has previously been reported that the atypical antipsychotics, clozapine and olanzapine, reduce the circling behavior of *ckr* mice (Torres et al., 2004). This suggests the possibility that the circling behavior, and perhaps the associated hyperactivity, of the *ckr* mouse might be used to screen for antipsychotic drug activity. As the spontaneous circling and hyperactivity of the *ckr* mouse is a robust and consistent inherent characteristic of the mice it could offer an appropriate measure for the screening for antipsychotic drug activity. Therefore, in the present study, to test the predictive validity of the *ckr* model, we investigated the dose-dependent effects of a range of antipsychotic drugs, including typical antipsychotics (haloperidol and pimozide), atypical antipsychotics (risperidone, clozapine, olanzapine, ziprasidone and quetiapine), and the new D2 partial agonist antipsychotic, aripiprazole.

EXPERIMENTAL PROCEDURES

Ckr mice

The *ckr* mouse was as described previously (Ratty et al., 1990). The mice were F2 animals of mixed genetic background of BCF_1 (C57BL/10Ros$^{pd}\times$C3H/HeRos) homozygous for the transgene insertion supplied by the Roswell Park Cancer Institute. BCF_1 mice were used as genetic background controls for the *ckr* mice in addition to wild-type littermates as controls. 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). Adult *ckr* adult mice were housed in same-sex, same-genotype pairs under a 12/12-h light/dark cycle (lights on at 07:00 h) with free access to food and water. The mice were never isolated before the behavioral testing. A total of 90 *ckr* mice were used. Basal locomotor activity was investigated in eight male *ckr* mice compared with eight male wild type littermates aged 3–4 months at the time of testing. Habituation of locomotor activity was investigated by continuous home cage monitoring over 5 days of six male *ckr* mice, six male heterozygous littermates and six male BCF_1 mice aged 3–4 months-old at the time of testing. The effects of haloperidol, an antipsychotic drug, or vehicle were investigated in 12 male *ckr* mice and in 13 male BCF_1 mice aged 3–4 months-old at the time of testing. The dose-dependent effects of antipsychotic drugs were investigated in two batches consisting of 32 male and female *ckr* mice aged 3–4 months-old at the time of testing and 26 male and female *ckr* mice aged 3–6 months-old at the time of testing, with equal numbers of male and female mice in each batch. The effect of imipramine, an antidepressant drug, was investigated in six male *ckr* and six male BCF_1 mice aged 2–3 months-old at the time of testing. All experiments were approved by the Institutional Animal Care and Use Committee of the National University of Singapore and were conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals.

Drugs

Haloperidol (Sigma-Aldrich, St. Louis, MO, USA), pimozide (Sigma-Aldrich), risperidone (Sigma-Aldrich), clozapine (Tocris, Bristol, UK), olanzapine (Toronto Research Chemicals, Ontario, Canada), ziprasidone (Tocris), quetiapine (Toronto Research Chemicals), and aripiprazole (Toronto Research Chemicals) were dissolved in 25% hydroxypropyl-β-cyclodextrin (TCI, Tokyo, Japan) acidified with HCl and titrated back to pH 5.5–6.0 with NaOH. The vehicle was 0.9% saline in 25% hydroxypropyl-β-cyclodextrin acidified with HCl to pH 5.5–6.0. Imipramine (Sigma-Aldrich) was dissolved in 0.9% saline and the respective vehicle control was 0.9% saline. The concentrations of the solutions were adjusted such that for all doses administered each mouse received an injection volume of 0.1 ml/10 g.

Measurement of locomotor activity in test arenas

On the day of testing, mice were brought to the behavioral testing facility and left in their cages with free access to food and water for 1 h after transportation. The mice were then placed individually in test chambers 18 cm in diameter. Between testing different mice the test chambers were cleaned and wiped down with 70% ethanol. The test arena was dimly lit with visible light ($\sim$10 lux) and illuminated with an infrared LED lamp (Tracksys, Nottingham, UK). Movement was monitored with an infrared-sensitive camera and videotaped and tracked with Ethovision 3.1 Pro (Noldus Information Technology, The Netherlands). After a period of 20 min in the test chambers the mice received an i.p. injection of drug or vehicle. After injection, the mice were immediately returned to the test chambers. In a separate experiment to investigate the effects of imipramine (20 mg/kg i.p.) or vehicle, movement was similarly tracked in a larger open field (2 m diameter) illuminated with visible light (Ethovision XT, Noldus Information Technology). All testing was done between 2 PM and 6 PM in the light phase of a 12h-12h light/dark cycle (light cycle starting at 7 AM).

Home cage locomotor activity monitoring

Mice were housed singly in cages mounted on LABORAS platforms (Metris BV, The Netherlands) with *ad libitum* access to food and water. The mice were placed in the cages at the start of the dark phase (7 PM–7 AM) of the 12h-12h dark/light cycle. Time spent in locomotion was monitored in 1 h epochs. In the first experiment to investigate habituation of locomotor activity, the mice were monitored continuously for 5 days from first introduction to the LABORAS cages. In a second experiment to investigate the effects of administration of haloperidol (0.5 mg/kg i.p.) or vehicle, the mice were housed in the LABORAS cages for 4 days before administration of the drug or vehicle and subsequent monitoring for 1 h starting from 1 h after administration of the drug.

Dose-dependent effects of antipsychotics

The drugs administered were vehicle, haloperidol (0.03, 0.1, 0.3, 1 and 3 mg/kg), pimozide (0.03, 0.1, 0.3, 1 and 3 mg/kg), risperidone (0.01, 0.03, 0.1, 0.3 and 1 mg/kg), clozapine (0.1, 0.3, 1, 3 and 10 mg/kg), olanzapine (0.6, 2, 6 and 20 mg/kg), ziprasidone (1, 3, 10, 30 and 100 mg/kg), quetiapine (6, 20, 60 and 200 mg/kg) or aripiprazole (1.67, 3, 5, 10, 15 and 30 mg/kg). As the pharmacokinetics of antipsychotics differ in rodents and humans, doses of the test compounds were selected to include doses that would approximate to 60–80% maximal D2 receptor occupancy in the rodent and thus correspond to receptor occupancy on human clinical dosing (Assié et al., 2006; Kapur et al., 2003; Sumiyoshi et al., 1995): 0.03–1 mg/kg haloperidol, 3 mg/kg pimozide, 1 mg/kg risperidone, 10 mg/kg clozapine, 2 mg/kg olanzapine, 1 mg/kg ziprasidone, 20 mg/kg quetiapine and 5 mg/kg aripiprazole. Haloperidol, pimozide, risperidone and clozapine were tested in the first batch of 32 *ckr* mice and olanzapine, ziprasidone, quetiapine and aripiprazole were tested in the second batch of 26 *ckr* mice. Each dose of each drug was tested on 5–9 mice. The mice were run in cohorts of 4–6 with a vehicle control included in each cohort such that vehicle was administered on a total of 27 trials in the first batch and 14 trials in the second batch. Each mouse received up to six treatments with a minimum of 3 days washout between treatments. Mice were randomly assigned to treatment groups but the treatments were administered in counter-balanced order such that equal numbers of mice received the highest dose first as received the lowest dose first.

Data analysis

In the experiments to compare locomotor activity in *ckr* mice and wild-type littermates, to investigate the dose-dependent effects of antipsychotic drugs and to investigated the effect of imipramine, spontaneous locomotor activity was measured as the total distance moved during a 5 min epoch starting 30 min after injection of the drug. All statistical analysis was performed with JMP 8.0.1 (SAS Institute Inc., USA). The locomotor activity in the *ckr* mice and wild type littermates was compared by *t*-test. The duration of locomotion in 1 h epochs over 5 days in BCF_1, heterozygous and *ckr* mice was compared by repeated measures analysis of variance (ANOVA) with planned contrasts between genotypes. The mean duration of locomotion per hour during the dark phase after habituation was compared by one-way ANOVA with post-hoc Tukey HSD comparisons. In the dose-response experiments, for each drug, one-way ANOVA was used to compare total distance across doses, including the vehicle treatment condition, in the event of significance the drug groups were compared with the vehicle control with Dunnett's post hoc comparisons. Dose-response relationships were investigated by expressing the response as a percentage of the distance moved under saline treatment and logistic regression to fit a four parameter function: $\text{response}=E_{min}+(E_{max}-E_{min})/(1+\text{Exp}(\text{slope}\times(\log_{10}\text{ dose—theta})))$, where the lower parameter bound for the minimum response, E_{min}, was fixed at 0% and the maximum effect, $E_{max.}$, was fixed at 100%. The goodness of the fit was assessed by investigation of the correlation of the predicted and actual values. The ED_{50} was then estimated. To allow for the case that the maximal drug effect might reverse the *ckr* hyperactivity but leave normal basal activity intact, the ED_{50} was calculated by solving the equation for inverse prediction of the dose producing the response $((E_{max}-E_{min})/2)+E_{min}$. Where the logistic regression could fit the *F* quantile for the confidence intervals, the ED_{50} values are given±standard error. In the experiment on imipramine, the data were analyzed by two-way ANOVA with drug treatment as a repeated measure with planned contrasts of genotype and post-hoc *t*-test comparison of genotype under the vehicle treatment condition. All data are presented as mean±standard error unless otherwise stated.

RESULTS

Locomotor activity in chakragati mice

Chakragati mice exhibit significant enhancement of spontaneous open field locomotor activity (Dawe and Ratty, 2007; Fitzgerald et al., 1991; Ratty et al., 1990; Torres et al., 2004). We replicated the hyperactivity of *ckr* mice (3720±604 cm, $n=8$) compared with wild-type littermate control mice (811±288 cm, $n=8$) in the same experimental system used for the studies of dose-dependent responses to antipsychotic drugs reported below ($t=4.35$, $df=14$, $P<0.001$; Fig 1A). As both male and female mice were used, we also investigated whether there was sex difference in locomotor activity in the first cohort of 32 *ckr* mice (16 male mice and 16 female mice) used for the investigation of dose-dependent effects of antipsychotic drugs. Since there was no significant sex difference in locomotor activity of *ckr* mice (male=3510±565 cm compared with female=3225±719 cm, mean±SEM; $t=0.312$, $df=30$, n.s.), male and female mice were pooled in all subsequent analysis. Additionally, we use continuous home cage monitoring over 5 days to investigate whether the hyperactivity of *ckr* mice habituated over time. In this experiment, analysis of the duration of locomotion again confirmed a significant effect of genotype ($F_{2,15}=2.47$, $P<0.0001$) and planned contrasts revealed that *ckr* mice exhibited hyperactivity compared with heterozygous ($F_{1,15}=2.13$, $P<0.0001$) and BCF_1 control mice ($F_{1,15}=1.53$, $P<0.0005$; Fig 1C). Although there was habituation of locomotor activity over time in both wild type and *ckr* mice, the habituation approached asymptote by the third day and the *ckr* mice continued to exhibit marked hyperactivity compared with heterozygous and BCF_1 control mice (Fig 1C). During the dark cycle of the fifth day there was still a significant genotype effect on the duration spent in locomotion ($F_{2,15}=7.04$, $P<0.01$) and *ckr* mice (201±42.4 s, mean±SEM) still spent significantly more time than heterozygous (71.7±13.8 s; post-hoc Tukey HSD, $P<0.01$) and BCF_1 (95.9±6.58 s; post-hoc Tukey HSD, $P<0.05$) control mice in locomotor activity (Fig 1B).

Haloperidol

We compared the effects of administration of 0.5 mg/kg haloperidol, a dose expected to produce 60–80% maximal D2 receptor occupancy in the rodent and thus to correspond to receptor occupancy on human clinical dosing (Assié et al., 2006; Kapur et al., 2003), on locomotor activity in *ckr* and BCF_1 mice. Mice were habituated to the home cage monitoring system for 4 days before injection with vehicle or haloperidol (0.5 mg/kg) at the start of the dark cycle. Following vehicle treatment, the *ckr* mice again showed greater locomotor activity than BCF_1 mice (278±63.6 s and 41.6±21.4 s, respectively; $t=3.76$, $df=11$, $P<0.005$). Haloperidol tended to reduce the time spent in locomotor activity in both BCF_1 mice (41.6±21.4 s after vehicle compared with 22.0±4.32 s after haloperidol; $t=0.757$, $df=10$, n.s.; Fig 2A) and *ckr* mice (278±63.6 s after vehicle compared with 45.5±19.4 s after haloperidol; $t=3.497$, $df=10$, $P<0.01$; Fig 2B). The initial levels of locomotor activity were lower in the BCF_1 mice and the reduction in locomotor activity only reached significance in the *ckr* mice. The following experiments on dose-dependent effects of antipsychotics were only conducted in *ckr* mice.

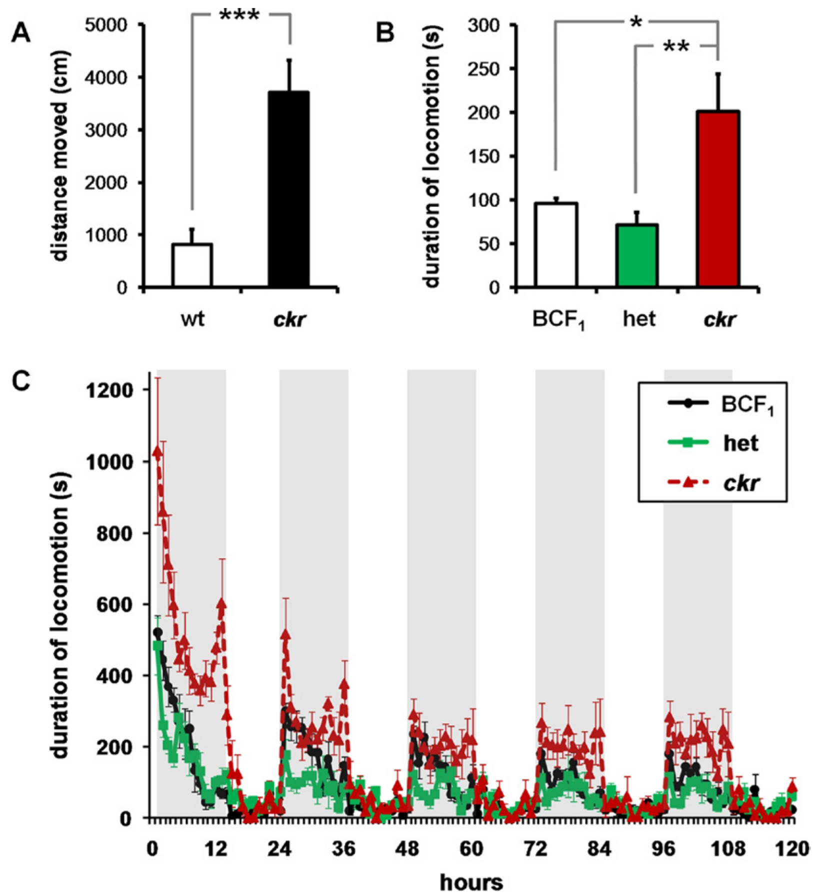

Fig. 1. (A) *Ckr* mice showed significantly greater locomotor activity than wild-type littermates (*t*-test: *** $P<0.001$) in a novel test chamber during the light phase of the light/dark cycle. (B) Mean duration of locomotion per hour during the dark phase of the light/dark cycle on the 5th day of continuous home cage monitoring. There was a significant genotype effect on the duration of locomotion ($F_{2,15}=7.04$, $P<0.01$) and *ckr* mice spent significantly greater time in locomotion than both BCF_1 control mice (post-hoc Tukey HSD, * $P<0.05$) and heterozygous mice (post-hoc Tukey HSD, ** $P<0.01$). (C) Duration spent in locomotion in 1 h epochs over 5 d. The gray shading represents the dark phases of the 12h-12h light/dark cycle. Overall genotype had a significant effect on locomotor activity ($F_{2,15}=2.47$, $P<0.0001$) and planned contrasts revealed that *ckr* mice exhibited hyperactivity compared with heterozygous ($F_{1,15}=2.13$, $P<0.0001$) and BCF_1 control mice ($F_{1,15}=1.53$, $P<0.0005$).

Administration of haloperidol dose-dependently reduced the locomotor activity of *ckr* mice ($F_{5,66}=16.43$, $P<0.0001$; Fig 2C). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 0.1 mg/kg and above significantly reduced locomotor activity. Suppression of locomotor activity reached asymptote at a dose of 1 mg/kg. It was noted that the mice appeared severely cataleptic at doses of 1 mg/kg and above. The fitted dose-response curve (Fig 2D) correlated well with the actual values observed ($R^2=0.998$, $P<0.0001$) and predicted an ED_{50} of $0.093+0.008/-0.007$ mg/kg.

Pimozide

Administration of pimozide dose-dependently reduced the locomotor activity of *ckr* mice ($F_{5,64}=5.904$, $P<0.0005$; Fig 3A). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 1 mg/kg and above significantly reduced locomotor activity. There was marginally less suppression of locomotor activity at 0.3 mg/kg than at 0.1 mg/kg but this was not significant. The dose-response curve function that fitted to all data points did not correlate significantly with the actual values observed. However, when the logistic regression was performed only for doses from 0.3 to 3 mg/kg (Fig 3B), the dose-response curve function correlated across all the actual values observed ($R^2=0.896$), albeit weakly ($P<0.05$). The predicted ED_{50} was 0.784 mg/kg but it was not possible to estimate the confidence intervals. Observationally it was noted that at doses of 0.3 mg/kg and above the mice developed a tendency to jump, typically executing backflips, which was not noted with any of the other antipsychotic treatments.

Risperidone

Administration of risperidone dose-dependently reduced the locomotor activity of *ckr* mice ($F_{5,66}=7.669$, $P<0.0001$; Fig 4A). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 0.3 mg/kg and above significantly reduced locomotor activity. Doses of 0.03 and 0.1 mg/kg which encompass the range of doses likely to result in clinically equivalent D_2 receptor occupancy (Kapur et al., 2003), did not significantly reduce locomotor activity. The fitted dose-response curve (Fig 4B) correlated well

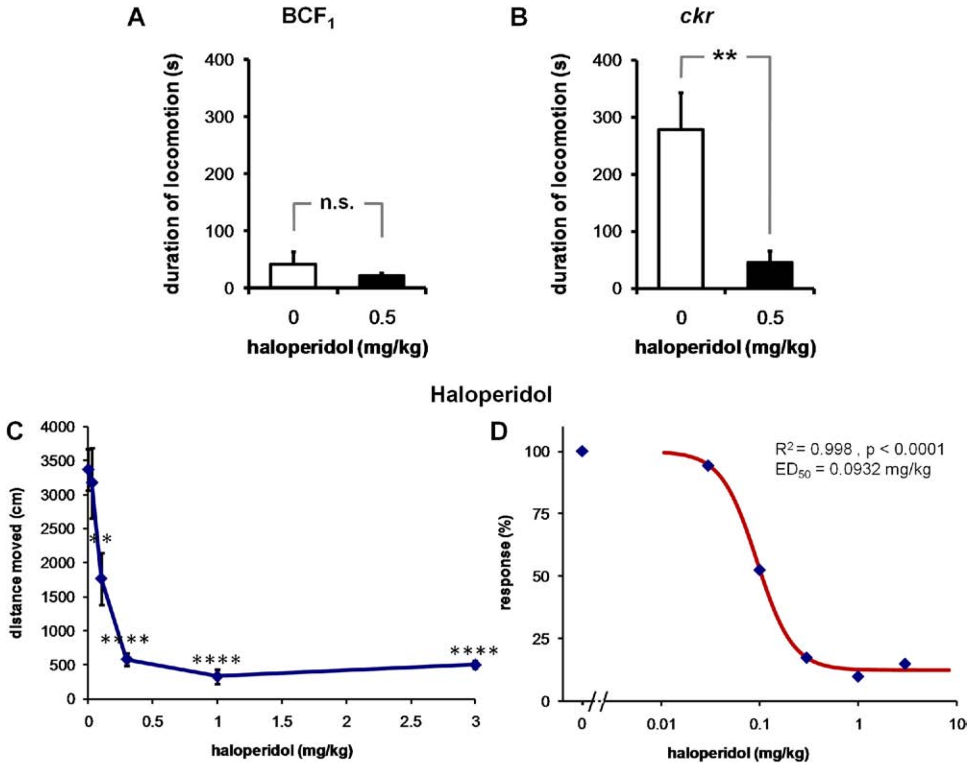

Fig. 2. Administration of 0.5 mg/kg haloperidol (A) did not significantly effect locomotor activity in BCF_1 control mice (*t*-test: n.s.) during the dark phase of the 12h-12h light/dark cycle in the LABORAS but (B) did reduce locomotor activity in *ckr* mice (*t*-test: ** $P<0.01$). On video tracking of distance moved in an 18 cm diameter chamber to test for dose-dependent effects of antipsychotic drugs, (C) haloperidol significantly decreased locomotor activity ($F_{5,66}=16.43$, $P<0.0001$). Dunnett's comparison with vehicle control (0 mg/kg haloperidol): ** $P<0.01$; **** $P<0.001$. (D) The fitted dose-response curve correlated with the actual values observed ($R^2=0.998$, $P<0.0001$) and predicted an ED_{50} of 0.093+0.008/−0.007 mg/kg.

with the actual values observed ($R^2=0.997$, $P<0.0005$) and predicted an ED_{50} of 0.194+0.036/−0.030 mg/kg.

Clozapine

Administration of clozapine dose-dependently reduced the locomotor activity of *ckr* mice ($F_{5,66}=7.054$, $P<0.0001$; Fig 5A). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 3 mg/kg and above significantly reduced locomotor activity. There appeared to be a marginal tendency towards a bi-phasic response as there was little difference in the degree of suppression of motor activity at 0.3 and 1 mg/kg but this was not significant. The fitted dose-response curve (Fig 5B) correlated well with the actual values observed ($R^2=0.992$, $P<0.001$) and predicted an ED_{50} of 3.04+0.894/−0.691 mg/kg.

Olanzapine

Administration of olanzapine dose-dependently reduced the locomotor activity of *ckr* mice ($F_{4,44}=5.343$, $P<0.005$;

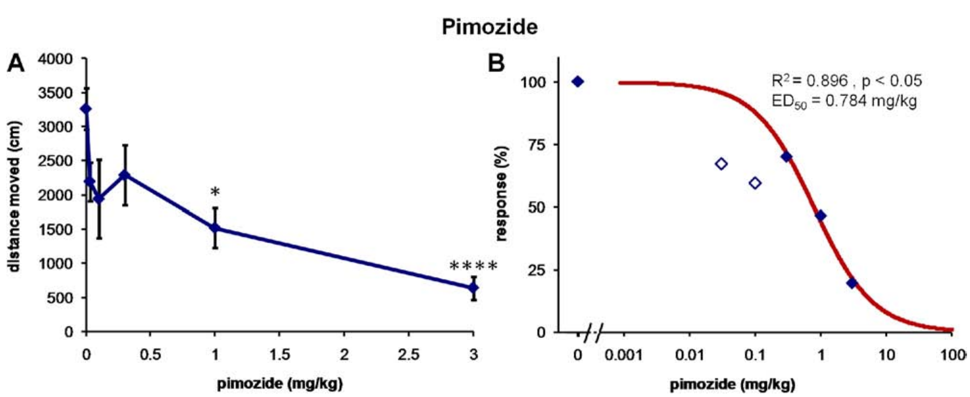

Fig. 3. (A) Pimozide significantly decreased locomotor activity ($F_{5,64}=5.904$, $P<0.0005$). Dunnett's comparison with vehicle control (0 mg/kg pimozide): * $P<0.05$; **** $P<0.001$. (B) The fitted dose-response curve correlated with the actual values observed ($R^2=0.896$, $P<0.05$) and predicted an ED_{50} of 0.784 mg/kg.

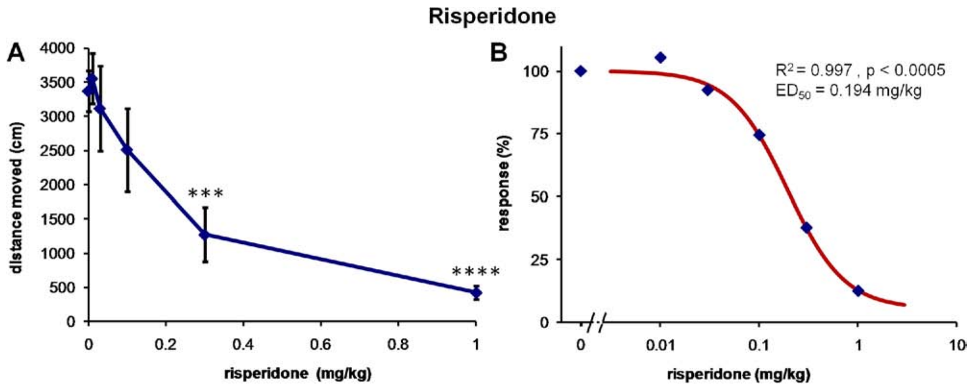

Fig. 4. (A) Risperidone significantly decreased locomotor activity ($F_{5,66}$=7.669, $P<0.0001$). Dunnett's comparison with vehicle control (0 mg/kg risperidone): *** $P<0.005$; **** $P<0.001$. (B) The fitted dose-response curve correlated with the actual values observed (R^2=0.997, $P<0.0005$) and predicted an ED_{50} of 0.194+0.036/−0.030 mg/kg.

Fig 6A). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 2 mg/kg and above significantly reduced locomotor activity. Notably 2 mg/kg is the upper end of the dose range likely to produce clinically equivalent D_2 receptor occupancy in rodents (Kapur et al., 2003) and near maximal suppression of motor activity was not achieved until a dose of 20 mg/kg. The fitted dose-response curve (Fig 6B) correlated well with the actual values observed (R^2=0.999, $P<0.0005$) and predicted an ED_{50} of 0.659 mg/kg.

Ziprasidone

Administration of ziprasidone dose-dependently reduced the locomotor activity of *ckr* mice ($F_{5,37}$=5.526, $P<0.001$; Fig 7A). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 3 mg/kg and above significantly reduced locomotor activity. Notably 3 mg/kg is likely beyond the upper end of the dose range likely to produce clinically equivalent 60–80% D_2 receptor occupancy in the striatum of rodents (Assié et al., 2006). Maximal suppression of locomotor activity was not reached until doses of 10 mg/kg and above. The fitted dose-response curve (Fig 7B) correlated well with the actual values observed (R^2=0.984, $P<0.005$) and predicted an ED_{50} of 0.328+5.862/−0.310 mg/kg.

Quetiapine

Administration of quetiapine dose-dependently reduced the locomotor activity of *ckr* mice ($F_{4,34}$=5.287, $P<0.005$; Fig 8A). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 20 mg/kg and above significantly reduced locomotor activity. Notably, 20 mg/kg is near the upper end of the dose range likely to produce clinically equivalent 60–80% D_2 receptor occupancy in rodents (Kapur et al., 2003). Maximal suppression of locomotor activity was not reached until a dose of 60 mg/kg and above. The fitted dose-response curve (Fig 8B) correlated with the actual values observed (R^2=0.951, $P<0.05$) and predicted an ED_{50} of 7.929 mg/kg but it was not possible to estimate the confidence intervals. Observationally it was noted that the highest dose (200 mg/kg) appeared to be associated with some lose of hind limb motor function.

Aripiprazole

Administration of aripiprazole dose-dependently reduced the locomotor activity of *ckr* mice ($F_{6,54}$=4.626, $P<0.001$; Fig 9B). Post-hoc Dunnett's test comparisons with the vehicle control revealed that doses of 3–10 mg/kg significantly reduced locomotor activity. The response appeared

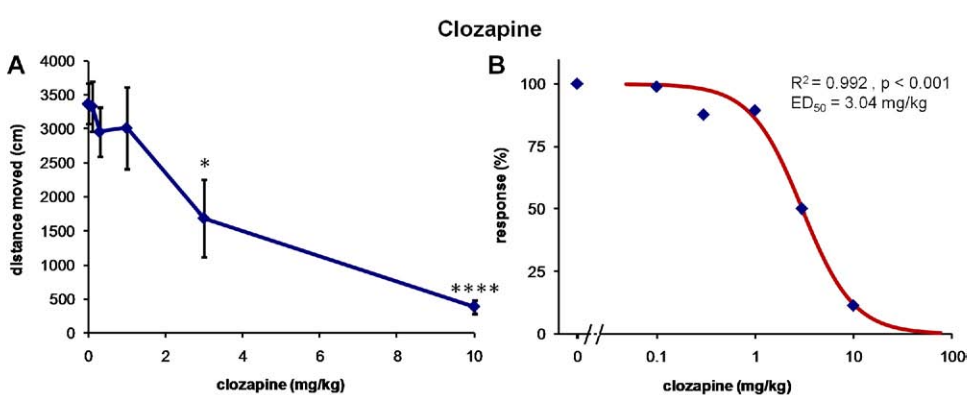

Fig. 5. (A) Clozapine significantly decreased locomotor activity ($F_{5,66}$=7.054, $P<0.0001$). Dunnett's comparison with vehicle control (0 mg/kg clozapine): * $P<0.05$; **** $P<0.001$. (B) The fitted dose-response curve correlated with the actual values observed (R^2=0.992, $P<0.001$) and predicted an ED_{50} of 3.04+0.894/−0.691 mg/kg.

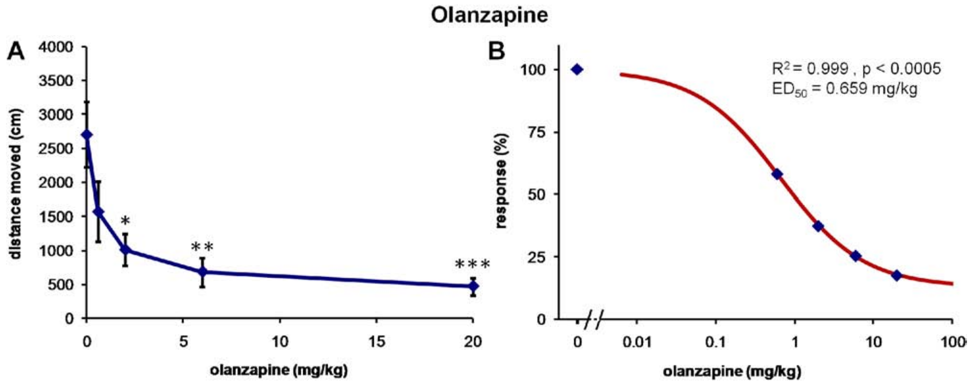

Fig. 6. (A) Olanzapine significantly decreased locomotor activity ($F_{4,44}$=5.343, P<0.005). Dunnett's comparison with vehicle control (0 mg/kg olanzapine): * P<0.05; ** P<0.01; *** P<0.005. (B) The fitted dose-response curve correlated with the actual values observed (R^2=0.999, P<0.0005) and predicted an ED_{50} of 0.659 mg/kg.

to be multiphasic as a higher dose of 15 mg/kg did not significantly suppress locomotor activity while a higher still dose of 30 mg/kg again significantly suppressed locomotor activity. Observationally, the dose of 30 mg/kg appeared to be associated with marked overall suppression of motor function suggestive of severe sedation. Although it was not possible to fit the dose-response curve function to the complete data set; it was possible to fit a subset of the data describing the initial suppression of activity at doses from 1.67 to 10 mg/kg with a curve predicting an ED_{50} of 2.695 mg/kg (Fig 9B). However, the responses predicted by the function fitted failed to correlate with the actual values observed (R^2=0.811, P=0.189).

Imipramine

Imipramine (20 mg/kg i.p.), an antidepressant with sedative effects, or vehicle was administered to *ckr* (n=6) and BCF_1 mice (n=6). The vehicle-treated groups once again confirmed the increase in locomotor activity in *ckr* mice (6556±1692 cm; mean±SEM) compared with BCF_1 mice (1529±145.8 cm; t=2.959, df=10, P<0.05; Fig 10). Overall there was a significant genotype effect ($F_{1,10}$=1.49, P<0.005) but no significant drug effect ($F_{1,10}$=0.689, n.s.) or drug×genotype interaction ($F_{1,10}$=0.002, n.s.). In BCF_1 mice, imipramine (20 mg/kg) produced a trend towards decreased locomotor activity (1529±145.8 cm after vehicle compared with 1003±200.4 cm after imipramine) but this was not significant (t=2.123, df=10, P=0.0597). There was no effect on locomotor activity in *ckr* mice (t=0.120, df=10, n.s.; Fig 10).

DISCUSSION

We investigated the effects of antipsychotics on the hyperactivity seen in the *ckr* mouse. We confirmed yet again the previously reported hyperactivity of *ckr* mice (Dawe and Ratty, 2007; Fitzgerald et al., 1991; Ratty et al., 1990; Torres et al., 2004). We used three different experimental systems to monitor locomotor activity (video tracking in 18 cm diameter test chambers, video tracking in a 2 m diameter arena and LABORAS home cage monitoring) and various batches of animals, including both males and females and mice of ages ranging from 2 to 6 months old. There were differences in the level of locomotor activity, for example younger (2–3 months old) *ckr* mice video tracked in the 2 m diameter arena showed much greater locomotor activity (6556±1692 cm) than older (3–4 months old) *ckr*

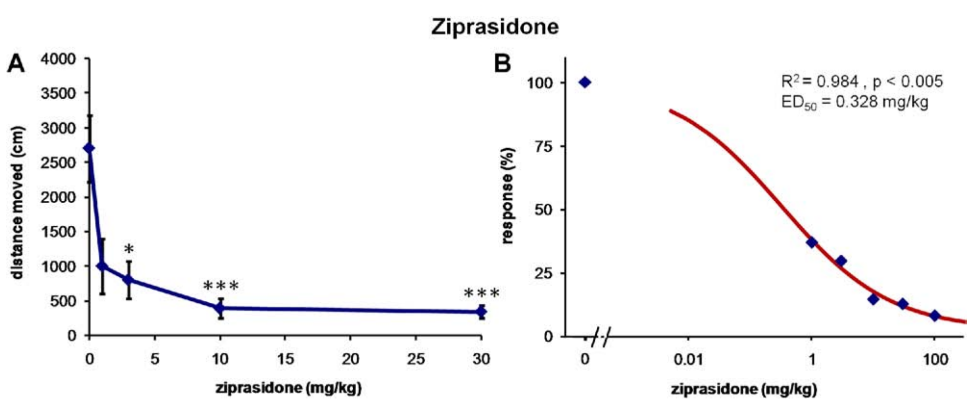

Fig. 7. (A) Ziprasidone significantly decreased locomotor activity ($F_{4,44}$=5.343, P<0.005). Dunnett's comparison with vehicle control (0 mg/kg ziprasidone): * P<0.05; *** P<0.005. (B) The fitted dose-response curve correlated with the actual values observed (R^2=0.984, P<0.005) and predicted an ED_{50} of 0.328+5.862/−0.310 mg/kg.

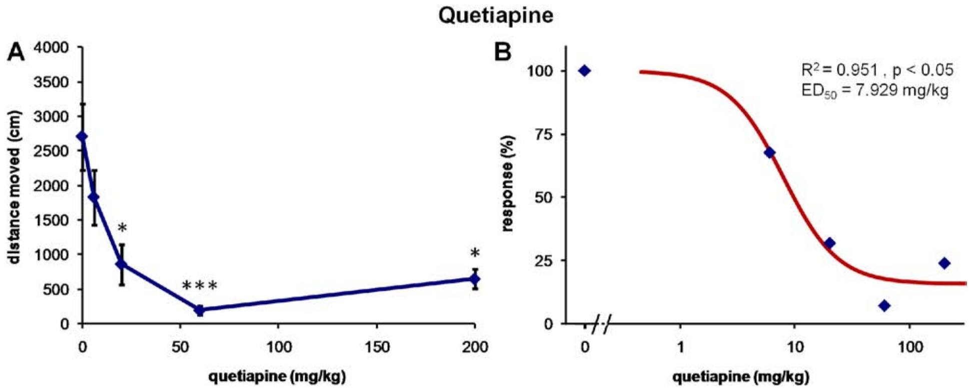

Fig. 8. (A) Quetiapine significantly decreased locomotor activity ($F_{4,44}$=5.343, $P<0.005$). Dunnett's comparison with vehicle control (0 mg/kg quetiapine): * $P<0.05$; *** $P<0.005$. (B) The fitted dose-response curve correlated with the actual values observed (R^2=0.951, $P<0.05$) and predicted an ED_{50} of 7.929 mg/kg.

mice video tracked in the 18 cm diameter chamber (3720±604 cm). But in all cases, the observation of increased locomotor activity in *ckr* mice was robustly replicated.

The antipsychotic haloperidol (0.5 mg/kg) produced a trend towards reduced locomotor activity in BCF_1 control mice. Although the experiment was conducted by home cage monitoring in the dark during the dark phase of the light cycle to maximize spontaneous activity, the baseline locomotor activity of the control mice was so low that it was impossible to detect a significant reduction in response to haloperidol. The greater locomotor activity in *ckr* mice allowed for more sensitive detection of antipsychotic-induced reductions in locomotor activity.

The typical antipsychotics, haloperidol and pimozide, and the atypical antipsychotics, clozapine, olanzapine, risperidone, ziprasidone and quetiapine, suppressed the elevated hyperactivity of the *ckr* mouse in a dose-dependent manner. Imipramine, an antidepressant with sedative effects, did not alter locomotor activity. Among the antipsychotics, pimozide was unique in that it produced an initial reduction in activity at lower doses (0.03 and 0.1 mg/kg) followed by a more clearly dose-dependent suppression of activity together with an unusual jumping response at higher doses (0.3–3 mg/kg).

Aripiprazole, an antipsychotic of a novel class acting as a partial and selective dopamine agonist, produced a different pattern of change in locomotor activity across doses. At lower doses (1.67–10 mg/kg) it produced an apparently dose-dependent reduction in motor activity followed by an increase in motor activity (15 mg/kg) and a subsequent suppression of motor activity (30 mg/kg). It a may be that this multiphasic pattern of change in motor activity across doses reflects the dopamine receptor partial agonist activity of aripiprazole. Thus, the nature of the dose-dependent response in *ckr* mouse would be expected to differentiate aripiprazole-like drugs from typical and atypical antipsychotic drugs. It is possible that wild type mice would express a similar dose-dependent pattern of motor disturbance but the low level of basal activity in wild type mice would make this difficult to detect. Even haloperidol, which is associated with far stronger extrapyramidal motor side effects than aripiprazole, did not produce a significant suppression in the locomotor activity of control mice monitored during the dark cycle when they are most active.

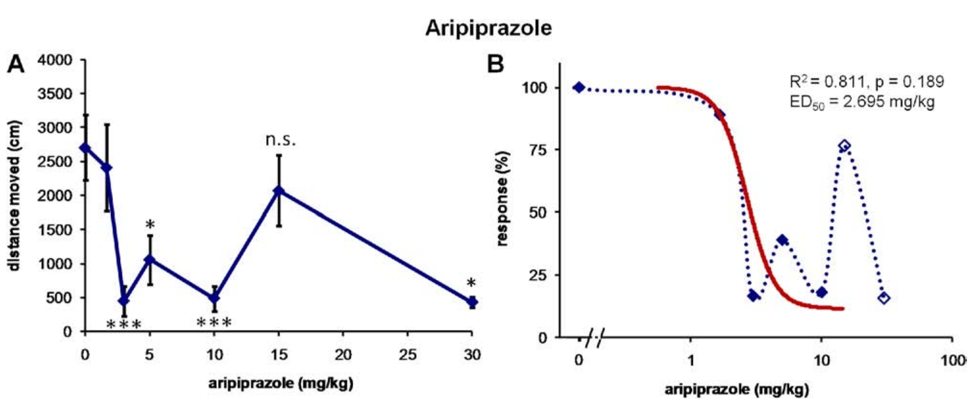

Fig. 9. (A) Aripiprazole significantly decreased locomotor activity ($F_{6,54}$=4.626, $P<0.001$). Dunnett's comparison with vehicle control (0 mg/kg aripiprazole): * $P<0.05$; *** $P<0.005$. (B) It was not possible to fit a sigmoid dose-response curve to the complete dataset. A dose-response curve fitted to the responses to doses from doses from 1.67 to 10 mg/kg predicting an ED_{50} of 2.695 mg/kg but no correlating significantly with the actual values observed (R^2=0.811, P=0.189).

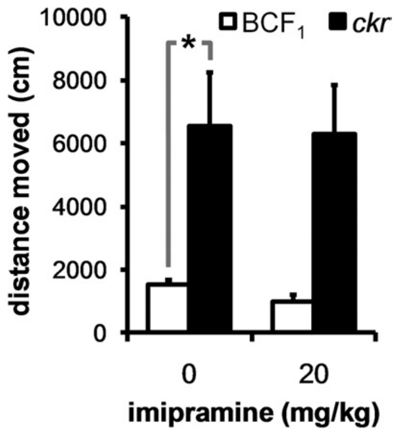

Fig. 10. Video tracking of distance moved in a 2 m arena confirmed that *ckr* mice exhibited greater locomotor activity than BCF_1 control mice (*t*-test: * $P<0.05$) but did not reveal any significant effect of imipramine (20 mg/kg) on locomotor activity in either *ckr* or BCF_1 mice.

As it has been noted that the circling of *ckr* mice appears to be triggered by environmental stimuli and stress (Dawe and Ratty, 2007; Ratty et al., 1990), the hyperactivity recorded on initial exposure to a novel environment might be predicted to habituate as the environment becomes familiar. We investigated this concern by continuous home cage monitoring of locomotor activity over 5 days. While there was evidence for habituation of locomotor activity in *ckr* mice, heterozygous mice and BCF_1 background strain mice, the *ckr* mice consistently showed markedly greater locomotor activity. The elevated locomotor activity of the *ckr* mice persisted even after the habituation approached asymptote from about the third day. Importantly, in the design of the experiments to study the dose-dependent effects of antipsychotics, the mice were randomly assigned to treatment groups and the treatments were administered in counterbalanced order to avoid any possible bias caused by habituation over time.

Imipramine, a non-antipsychotic drug known to produce sedation in rodents (Ögren et al., 1981; Zebrowska-Lupina et al., 1980), did not decrease locomotor activity in *ckr* mice. Interestingly, in other animal models used for screening antipsychotic drugs, antidepressant drugs, including imipramine, have been reported to increase rather than decrease locomotor activity. For example, imipramine was reported to acutely increase locomotor activity in dizocilpine (MK-801)-treated rats (Maj et al., 1991, 1992) and to chronically increase locomotor activity in response to amphetamine administered into the nucleus accumbens (Maj and Wedzony, 1985). Although the *ckr* mouse did not exhibit increased locomotor activity in response to imipramine, it is interesting that they did not exhibit significant sedation.

With the exception of aripiprazole, the ED_{50} for suppression of hyperactivity in the *ckr* mouse correlated well with typical clinical doses of the various antipsychotics (Fig 11A; $R^2=0.855$, $P<0.005$). Clinical doses of antipsychotic drugs have long been known to correlate with D2 receptor antagonism (Creese et al., 1976; Peroutka and Synder, 1980; Seeman et al., 1976). When the ED_{50} was expressed in micromoles per body weight, the ED_{50} also correlated well with the published affinities of the various antipsychotic drugs at the D2 receptor (Fig 11B; $R^2=0.902$, $P=0.001$). Thus, the effect of a drug on motor activity in the *ckr* mouse would be expected to predict efficacy as an antipsychotic and allow an approximate estimation of the likely human clinical dose. There was no evidence of any correlation of the ED_{50} with 5-HT_{2A}, 5-HT_{2C} and H_1 receptor binding affinity (Table 1).

CONCLUSION

Together these data indicate that the effects of drugs on hyperactivity in the *ckr* mouse predict antipsychotic efficacy. The *ckr* mouse also showed a multiphasic response to aripiprazole, which suggest that the profile of the response of the *ckr* mouse may be able to predict aripiprazole-like partial agonist properties. While the *ckr* mouse was not created as a dopaminergic model of schizophrenia, the *ckr* mouse develops a dopaminergic imbalance in the striatum that likely contributes to the circling phenotype (Dawe and Ratty, 2007). As antipsychotic efficacy correlates with D_2-like dopamine receptor affinity (Creese et al., 1976; Peroutka and Synder, 1980; Seeman et al., 1976), the mouse model is able to predict antipsychotic efficacy. Importantly, newer candidate antipsychotics selected for

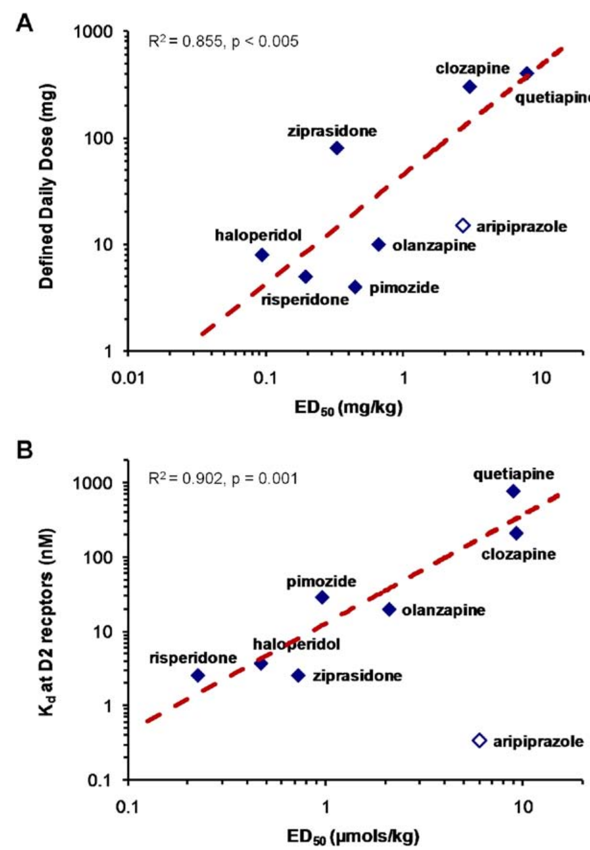

Fig. 11. Correlation of the ED_{50} values predicted by the response of the *ckr* mouse with (A) daily defined dose ($R^2=0.855$, $P<0.005$) and (B) K_d at D_2 receptors ($R^2=0.902$, $P=0.001$).

Table 1. Summary of response of *ckr* mice to antipsychotics and comparison with clinical dose and receptor binding affinities

Drug	Parameters of dose-response curved fitted by logistic regression			Correlation of predicted with observed		ED_{50}		DDD[a] mg	Receptor binding affinity (nM)[b]			
	E_{min}	Slope	Theta	R^2	*P*	mg/kg	μmol/kg		D_2	5-HT_{2A}	5-HT_{2C}	H_1
Haloperidol	12.186	5.503	−4.031	0.998	<.0001	0.093	0.226	8	2.6	61	4700	260
Pimozide	0	2.215	−3.106	0.896	0.0398	0.784	1.698	4	29	14.3	570	25
Risperidone	5.307	3.466	−3.713	0.997	0.0002	0.194	0.472	5	3.77	0.15	32	5.2
Clozapine	0	3.819	−2.517	0.992	0.0009	3.039	9.299	300	210	2.59	4.8	3.1
Olanzapine	12.877	1.894	−3.181	0.999	0.0002	0.659	2.109	10	20	1.48	4.1	0.087
Ziprasidone	2.319	1.136	−3.485	0.984	0.0024	0.328	0.729	80	2.6	0.12	0.9	4.6
Quetiapine	15.739	4.227	−2.101	0.951	0.0487	7.929	8.979	400	770	31	3500	19
Aripiprazole	11.595	9.451	−2.569	0.811	0.1890	2.695	6.011	15	0.34	3.4	15	61

[a] Defined daily dose from the Anatomical Therapeutic Chemical (ATC) Classification maintained by the World Health Organization (WHO) Collaborating Center for Drug Statistics Methodology (http://www.whocc.no/atcddd/).
[b] From Richelson E, Souder T (2000) Life Sciences 68:29–39, except for apripiprazole from Buckley PF (2007) J Clin Psychiatry 68[Suppl 6]:5–9.

mGlur receptor targeting have recently been reported to act also as D_2 receptor antagonists (Seeman and Guan, 2009a,b) and D_2 receptor antagonism is arguably a core feature of all current antipsychotics (Seeman, 2009).

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