Interaction of reelin and stress on immobility in the forced swim test but not dopamine-mediated locomotor hyperactivity or prepulse inhibition disruption: Relevance to psychotic and mood disorders

Michael J. Notaras a,1, Billie Vivian b,1, Carey Wilson b,1, Maarten van den Buuse b,c,d,*

a Florey Institute of Neuroscience & Mental Health, Melbourne, Victoria, Australia.
1 School of Psychology and Public Health, La Trobe University, Melbourne, Victoria, Australia
b Department of Pharmacology, University of Melbourne, Victoria, Australia
c Florey Institute of Neuroscience & Mental Health, Melbourne, Victoria, Australia
* Corresponding author at: La Trobe University, School of Psychology and Public Health, Kingsbury Drive, Bundoora, Melbourne, Victoria 3086, Australia.
E-mail address: m.vandenbuuse@latrobe.edu.au (M. van den Buuse).

1 Authors contributed equally.

Rationale: Psychotic disorders, such as schizophrenia, as well as some mood disorders, such as bipolar disorder, have been suggested to share common biological risk factors. One such factor is reelin, a large extracellular matrix glycoprotein that regulates neuronal migration during development as well as numerous activity-dependent processes in the adult brain. The current study sought to evaluate whether a history of stress exposure interacts with endogenous reelin levels to modify behavioural endophenotypes of relevance to psychotic and mood disorders.

Methods: Heterozygous Reeler Mice (HRM) and wildtype (WT) controls were treated with 50 mg/L of corticosterone (CORT) in their drinking water from 6 to 9 weeks of age, before undergoing behavioural testing in adulthood. We assessed methamphetamine-induced locomotor hyperactivity, prepulse inhibition (PPI) of acoustic startle, short-term spatial memory in the Y-maze, and depression-like behaviour in the Forced-Swim Test (FST).

Results: HRM genotype or CORT treatment did not affect methamphetamine-induced locomotor hyperactivity, a model of psychosis-like behaviour. At baseline, HRM showed decreased PPI at the commonly used 100 msec interstimulus interval (ISI), but not at the 30 msec ISI or following challenge with apomorphine. A history of CORT exposure potentiated immobility in the FST amongst HRM, but not WT mice. In the Y-maze, chronic CORT treatment decreased novel arm preference amongst HRM, reflecting reduced short-term spatial memory.

Conclusion: These data confirm a significant role of endogenous reelin levels on stress-related behaviour, supporting a possible role in both bipolar disorder and schizophrenia. However, an interaction of reelin deficiency with dopaminergic regulation of psychosis-like behaviour remains unclear.

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symptoms which include hallucinations and delusions (Potash et al., 2001). In some cases, especially in cases of early onset, bipolar disorder is commonly misdiagnosed as schizophrenia (Joyce, 1984) – a psychotic disorder that also typically has an early age of onset (Maurer and Riecher-Rossler, 1993) and can broadly be defined by the apodictic clustering of symptoms into positive (Lewine et al., 1983; Addington and Addington, 1991), negative (Andreasen, 1982; Foussias and Remington, 2010) and cognitive (Addington et al., 1991, Goldman-Rakic, 1994, Simpson et al., 2010) domains. Given the partial overlap in symptomology (Green, 2006) and genetic risk loadings (Lichtenstein et al., 2009; Purcell et al., 2009) between these disorders, it is not surprising that reelin has been rather consistently implicated in the pathophysiology of both bipolar disorder and schizophrenia (Fatemi, 2001). For instance, decreased expression levels of reelin within the post-mortem brain of bipolar and schizophrenia (Impagnatiello et al., 1998, Fatemi et al., 2000, Guidotti et al., 2000, Fatemi et al., 2005b) patients has been observed across multiple studies. Polymorphisms within the RELN gene have also been associated with both bipolar disorder (Goes et al., 2012) and schizophrenia (Shifman et al., 2008; Liu et al., 2010), and there is evidence that the RELN gene may also undergo epigenetic modification in schizophrenia (Tochigi et al., 2008).

While it is difficult for human studies to control for covariates that may shape gene-environment interactions, animal model studies are able to control for these factors allowing for rigorous control of clinically-relevant biological and environmental risk factors. Heterozygote Reeler Mice (HRM), which carry a naturally-occurring mutation that has been independently replicated the effect of chronic CORT treatment in HRM on several behaviours of relevance to both mood and psychotic disorders. To explore if these factors interact to modify psychosis-related behaviour, we tested mice for methamphetamine-induced locomotor hyperactivity, and for PPI at baseline and following acute challenge with MK-801 and apomorphine. Given inconclusive data on the effect of HRM genotype on the Y-maze, and the relatively few studies that have assessed the FST performance of this mouse model, these two behaviours were additionally included here to resolve discrepancies in the literature and probe for a potential interaction of HRM genotype and chronic CORT treatment.

2. Methodology

2.1. Heterozygous Reeler Mice (HRM)

Mice were bred and housed at the La Trobe Animal Research and Teaching Facility (LARTF) at La Trobe University’s Bundoora campus. Heterozygous Reeler Mice (HRM) were of a C57Bl/6j background, and were originally acquired from the Jackson Laboratory (Bar Harbor, Maine, USA). Mice were weaned at 3 weeks of age and moved to a dedicated housing room within the behavioural facility of LARTF. All mice were housed in individually-ventilated cages (IVC, Tecniplast, Italy) in groups of two to five. Six male mice had to be isolated due to persistent aggression, independent of genotype. All mice were kept on a 12-h light/dark cycle, at 20–22 °C, and were provided ad libitum access to standard pellet food and water. Housing, handling and experimental procedures were approved by, and carried out in compliance of, the La Trobe University Animal Ethics Committee.

2.2. Chronic corticosterone (CORT) treatment

We chose to model chronic stress via a bottom-up, pharmacological, approach by administering the mouse stress hormone corticosterone (CORT) in the drinking water of mice. The benefits of this model of chronic stress is that glucocorticoid-dependent effects can be isolated outside of other brain and circulatory factors that may confound the investigation of how stress hormones may impact the brain. Indeed, prior engagement of the hypothalamus-pituitary (HPA) axis. In recent years, it has been suggested that endogenous reelin expression may determine resilience to stress (Fatemi, 2011), and it is now well established that stress hormones are able to down-regulate reelin expression in several regions including the hippocampus (Fenton et al., 2015). In particular, we recently observed that the dorsal, but not ventral hippocampus, of HRM mice is particularly vulnerable to the effects of the mouse stress hormone corticosterone (CORT) (Buret and van den Buuse, 2014). We furthermore observed recently that chronic CORT treatment reduces prepulse inhibition (PPI) (Barr et al., 2008), a model of sensorimotor gating which is an endophenotype of psychosis (Tueting et al., 1999). However, not all studies have observed a baseline PPI deficit amongst HRM mice (Kutiyanawalla et al., 2012; van den Buuse et al., 2014, Schroeder et al., 2015). Moreover, against a background of normal baseline PPI, we observed that disruption of PPI by treatment with the NMDA receptor antagonist, MK-801, or with the dopamine receptor agonist, apomorphine, was not different between HRM and wildtype controls (van den Buuse et al., 2012). These drugs are used to mimic NMDA receptor hypofunction and dopaminergic hyperactivity, respectively, which have been posited to underlie positive symptoms of schizophrenia (van den Buuse, 2010).

Another psychosocial endophenotype, drug-induced locomotor hyperactivity, has also been used to show that male HRM are selectively more vulnerable to MK-801-induced hyperactivity relative to wildtype (WT) mice (van den Buuse et al., 2012). However, surprisingly there were no genotype differences in amphetamine-induced locomotor hyperactivity (van den Buuse et al., 2012), a model of dopaminergic hyperactivity (van den Buuse, 2010). With respect to cognitive deficits in bipolar disorder and schizophrenia, deficits in hippocampus-dependent memory function have also been observed in HRM, specifically on the Y-maze (Kutiyanawalla et al., 2012) as well as using a contextual fear conditioning paradigm (Qiu et al., 2006). However, this too remains controversial as more complex forms of hippocampal learning and memory – such as those that can be tested using the Morris Water Maze – have not been found to be robustly associated with HRM genotype (Qiu et al., 2006). When taken as a whole, these core phenotypes qualify HRM as a powerful tool to screen bipolar- and schizophrenia-related endophenotypes (Costa et al., 2002), it is likely that additional factors than genotype alone determine the qualitative and quantitative differences between these mice and controls.

Relatively few studies have attempted to model gene-environment interactions in bipolar disorder or schizophrenia using HRM. One environmental risk factor for both bipolar disorder (Dienes et al., 2006) and schizophrenia (Corcoran et al., 2003) is stress, defined here as the physiological adaptation to environmental challenges that elicits...
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