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Lack of barbering behavior in the phospholipase Cβ1 mutant mouse: a model animal for schizophrenia

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Summary

Abnormal phospholipid metabolism has been implicated in the pathogenesis of schizophrenia, and phospholipase C (PLC) β1 was shown to be reduced in specific brain areas of patients with schizophrenia. However, the causal relationship of the PLCβ1 gene with the behavioral symptoms of schizophrenia remains unclear. Recent studies with the knockout (KO) mice for the PLCβ1 gene have revealed an array of interesting phenotypes, which along with other previous information makes the PLCβ1 knockout mouse a good candidate for an animal model for schizophrenia. This also suggests that the PLCβ1-linked signaling pathways may be involved in the neural system whose function is disrupted in the pathogenesis of schizophrenia. In this chapter we will introduce various studies relevant to this issue, highlighting the social withdrawal phenotypes of the mutant, such as barbering behaviors.

Introduction

An animal model for a disease is expected to display endophenotypes, which are quantifiable phenotypes relevant to symptoms of the disease to be modeled (Braff and Freedman 2002; Gould and Gottesman 2006; van den Buuse *et al.* 2005). The endophenotypes currently pursued in schizophrenia models are: locomotive hyperactivity, sensorimotor gating deficit, deficits in social interaction, and cognitive deficits (e.g., learning and memory). Genetically modified mice

Neurobiology of Grooming Behavior, eds. Allan V. Kalueff, Justin L. LaPorte, and Carisa L. Bergner. Published by Cambridge University Press.

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targeted on candidate susceptibility genes have so far been generated as animal models for schizophrenia. These mouse models display at least one or two of the endophenotypes listed above (Gainetdinov *et al.* 2001; Gerber *et al.* 2001; Kellendonk *et al.* 2006; Lijam *et al.* 1997; Miyakawa *et al.* 2003; Robertson *et al.* 2006; Yee *et al.* 2005).

PLCβ1 is a G-protein-coupled receptor (GPCR)-associated enzyme and hydrolyzes phosphatidylinositol 4,5-bisphosphate to produce second messengers, diacylglycerol and inositol 1,4,5-trisphosphate (IP_3). The second messengers in turn activate PKC or calcium-dependent cellular components, respectively, thereby inducing a whole array of cellular responses. Three different groups of neurotransmitter receptors – muscarinic, metabotropic glutamate, and serotonin receptors – are known to be coupled to PLCβ1 for their signal transduction in neuronal cells (Chuang *et al.* 2001; Kim *et al.* 1997; Rhee and Bae 1997). PLCβ1 is expressed in select areas of the brain such as the cerebral cortex, hippocampus, amygdala, lateral septum, and olfactory bulb (Watanabe *et al.* 1998). Therefore, it is implicated for participation in diverse brain functions, and possibly for involvement in psychiatric disorders. Besides, possible genetic association of PLCβ1 with schizophrenia has been reported in linkage studies (20p12; Arinami *et al.* 2005; Peruzzi *et al.* 2002), and its abnormal expression patterns were observed in the brains of patients with schizophrenia (Lin *et al.* 1999; Shirakawa *et al.* 2001). These results implicate a derangement of the PLCβ1-dependent phospholipid signaling in schizophrenia.

In as much as PLCβ1 is an enzyme involved in phospholipid metabolism, it is interesting to note that phospholipids are required not only for the structure of neural membranes but also for the signal transduction processes that link receptor occupancy and actual neuronal response (Oude Weernink *et al.* 2006). The importance of membrane phospholipid composition in normal functioning of the brain (e.g., neurotransmission) was proposed following the observation that phospholipid composition affects the activities of ion channels, transporters, and receptors (Bourre *et al.* 1991; Spector and York 1985). Furthermore, there is evidence for abnormalities in the phospholipid metabolism in schizophrenic patients (for a review see du Bois *et al.* 2005).

All this information raised a possibility that a defect in PLCβ1 signaling may result in the development of schizophrenia-like conditions. The availability of KO mice for this gene (Kim *et al.* 1997) has allowed testing of this hypothesis. Indeed, we found that PLCβ1$^{-/-}$ mice demonstrate various endophenotypes regarded relevant to schizophrenia in humans (Koh *et al.* 2008; McOmish *et al.* 2008b). Uniquely among reported mouse models for schizophrenia, PLCβ1$^{-/-}$ mice demonstrate endophenotypes in all the four categories: locomotive hyperactivity, sensorimotor gating deficit, deficits in social interaction, and cognitive deficits.

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Furthermore, previous studies showed a derangement in the cortical development in the PLCβ1$^{-/-}$ mice (Hannan *et al.* 2001). The PLCβ1$^{-/-}$ mice, therefore, may serve as an ideal animal model for studying the brain functions disrupted in schizophrenia and other related disorders, and for developing drugs to treat the disease.

A major part of the description in this chapter is based on one of our recent reports (Koh *et al.* 2008), to which readers are referred for further details.

Locomotive hyperactivity

Among the positive symptoms of human schizophrenia, locomotive hyperactivity may be the only endophenotype that can be easily measured in the mouse model of the disease. Casual inspection of home-cage behaviors suggested that PLCβ1-KO mice are more active than their wild-type (WT) littermates. To confirm their hyperactivity, locomotor activity in an open-field arena (a square-floored rectangular box made of white acrylic, 40 × 40 × 50 cm) was monitored. To start the test each mouse was gently placed at the center of the open-field kit under diffused lighting. The distance of spontaneous movement during a one-hour period was monitored at five-minute intervals via digital video recording. The video data were analyzed by software that tracks the horizontal movement of the weight center of the object using the contrast between the object and the background. PLCβ1$^{-/-}$ mice showed increased locomotor activity for most of the monitoring period relative to WT mice. The total distance traveled by PLCβ1$^{-/-}$ mice in one hour was significantly higher than that of WT mice. PLCβ1$^{-/-}$ mice showed a tendency of early increase in locomotor activity and an evident habituation. After habituation, at 55- and 60-minute bins, the locomotor activities were not significantly different between WT and PLCβ1$^{-/-}$ mice. These results show that the PLCβ1$^{-/-}$ mice show locomotor hyperactivity in a novel environment.

In both humans and rodents, amphetamine-induced increase in the locomotor activity is known to involve increased dopamine release in the ventral striatum (Creese and Iversen 1975; Drevets *et al.* 2001). Amphetamine-induced neurochemical effect in the striatum was found to be greater in patients with schizophrenia than in controls (Laruelle *et al.* 1996). Especially, this enhancement was correlated with psychosis (Laruelle *et al.* 1999). These findings suggested that an enhanced striatal dopamine release is the main neural correlate of psychosis, which became the basis for using locomotor hyperactivity as a model for positive symptoms of schizophrenia. In the open-field test, PLCβ1$^{-/-}$ mice exhibited increased locomotor activity, even without treatment with psychostimulants. Many other putative mice models have been known to exhibit locomotor hyperactivity at baseline and/or in response to novelty.

Sensorimotor gating deficit and its reversal by an antipsychotic drug

Sensorimotor gating is essentially a protection mechanism against sensory information overload (Geyer *et al.* 2001). Measures of failure in such inhibition include prepulse inhibition of the acoustic startle response (PPI), where a weaker and shorter prepulse stimulus suppresses the response to a subsequent startle stimulus (Turetsky *et al.* 2007). Human patients with schizophrenia are impaired in PPI, and it has been reported that there is a substantial covariation between the severity of positive symptoms and the degree of the PPI deficit (Weike *et al.* 2000).

The PPI test is one of the most widely used neurological tests in animals with suspected neurological defects. Mice of around 11 to 15 weeks old, were tested for PPI by using an acoustic startle chamber (Coulbourn Instruments, Allentown, PA, USA). All the animals used were behaviorally naïve in that no other kinds of tests had been performed on them previously, and only a single session of the PPI test was performed on each animal. The startle reflex was triggered by a pulse stimulus in the form of a 40-ms, 120-dB burst of white noise (startle stimulus, SS). Inhibition of the SS-elicited startle response was achieved by using a 20-ms prepulse stimulus (PP) of various intensities (74, 82, and 90 dB of white noise) that preceded the SS by 100 ms. The test was composed of a series of seven blocks, each of which was a "semi-random" mixture of eight different trial types (no stimulus, SS only, three PP only, three PP plus SS), separated by 10 to15-s intertrial intervals. The percentage prepulse inhibition (% PPI) was calculated as [1 − (response to PP–SS coupling/response to SS only)] × 100. In the pulse-alone trials, the acoustic startle response (ASR) of the PLCβ1$^{-/-}$ mice was somewhat lower than that of the WT, but the difference was not statistically significant. However, a significant attenuation of PPI was observed in the PLCβ1$^{-/-}$ mice compared to the WT at all prepulse intensities.

Haloperidol is a dopaminergic D2 receptor antagonist and is used to treat schizophrenia. Furthermore, it has been observed that the PPI in antipsychotics-medicated patients does not significantly differ from that of the healthy control group (Weike *et al.* 2000). Therefore, we tried to see if the PPI impairment of PLCβ1$^{-/-}$ mice can be ameliorated by treatment with haloperidol. Haloperidol (0.2 mg/kg body weight) was intraperitoneally administered 45 minutes before the test. There was no significant effect of haloperidol on the ASR measured in SS pulse-alone trials. However, the haloperidol treatment reversed the decreased PPI in the PLCβ1$^{-/-}$ mice to a level similar to that of the WT mice treated with either vehicle or haloperidol. The responsiveness to haloperidol of the impaired PPI phenotype of PLCβ1$^{-/-}$ mice may be analogous to that in human schizophrenia patients. Like locomotor hyperactivity, PPI deficit has been observed in most of the

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putative mice models of schizophrenia, although its responsiveness to antipsychotics has been rarely reported (Yee *et al.* 2005; Russig *et al.* 2004).

In addition to haloperidol, clozapine has also been used to reverse the impaired PPI of PLCβ1$^{-/-}$ mice (McOmish *et al.* 2008a). In this study, however, haloperidol was ineffective in reversing the PPI impairment, presumably due to inadequate drug doses and the different protocols used.

Social withdrawal phenotypes of PLCβ1$^{-/-}$ mice

From anecdotal observations of the mice housed as uniform genotypes, it appeared that PLCβ1$^{-/-}$ mice interacted less frequently among themselves than WT mice, suggesting a possible abnormality in social interaction in PLCβ1$^{-/-}$ mice. Therefore, we have tried to examine the social behavior of the mutant mouse.

Lack of barbering (whisker trimming) behavior

Casual inspection of physical appearance revealed a striking difference between PLCβ1$^{-/-}$ and WT mice. Most WT male and female mice were completely devoid of long whiskers (Figure 7.1A left), whereas all the PLCβ1$^{-/-}$ mice had full sets of long whiskers (Figure 7.1A right). At the age of weaning, all PLCβ1$^{-/-}$ and WT mice had full sets of long whiskers, but as they got older WT mice lost long whiskers, probably resulting from mutual whisker trimming. These preliminary observations suggested that PLCβ1$^{-/-}$ mice lack whisker trimming behavior, which may indicate reduced social interaction.

To quantify this behavior, WT and PLCβ1$^{-/-}$ mice were housed in pairs as either uniform or mixed genotypes and were scored for the presence of whiskers longer than 0.5 cm at three months of coupling. Five pairs of WT;WT, five pairs of WT;PLCβ1$^{-/-}$, and four pairs of PLCβ1$^{-/-}$; PLCβ1$^{-/-}$ were tested. At three months of coupling, the relative amount of long whiskers (longer than 0.5 cm) on individual mice were obtained by cutting all the whiskers and measuring the lengths [(number of long whiskers/number of all whiskers) × 100], and the results were compared between groups. In the uniform genotype housing, the relative amount of long whiskers was significantly greater in PLCβ1$^{-/-}$ mice (92.4 ± 2.76%) compared to that in WT mice (10.3 ± 3.1%) ($t = 18.63$, $df = 16$, $p < 0.0001$) (Figure 7.1B, +/+;+/+, −/−;−/−). While WT mice had significantly more long whiskers in the mixed (76.8 ± 8.6 %) than in the uniform genotype housing ($t = 7.1$, $df = 13$, $p < 0.0001$) (Figure 7.1B, +/+;+/+, +/+;−/−), PLCβ1$^{-/-}$ mice had significantly more long whiskers in the uniform than in the mixed genotype housing (6.3 ± 1.4 %) ($t = 20.28$, $df = 11$, $p < 0.0001$) (Figure 7.1B, +/+;−/−, −/−;−/−). These results demonstrated that WT mice trimmed the whiskers of their cage-mates,

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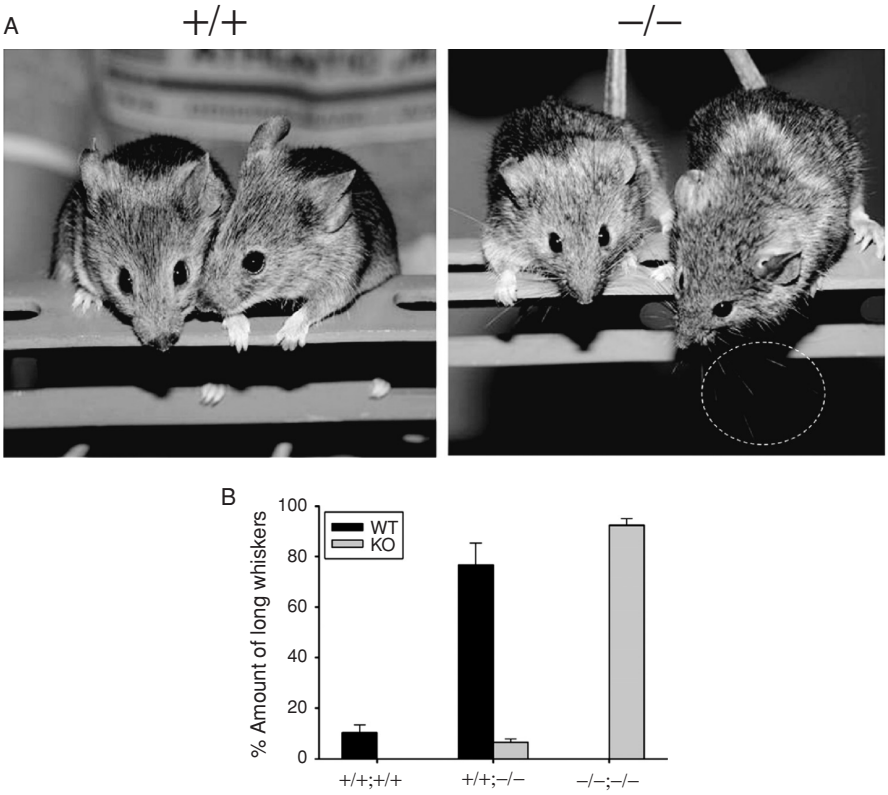

Figure 7.1 Lack of mutual barbering behavior in PLCβ1$^{-/-}$ mice. Wild-type and PLCβ1$^{-/-}$ mice housed in pairs of either uniform or mixed genotypes were scored for the presence of whiskers longer than 0.5 cm at three months of coupling. (A) In the uniform genotype housing, the WT mice were completely devoid of long whiskers (left, +/+). However, the PLCβ1$^{-/-}$ mice had full sets of long whiskers (right, −/−). (B) In the uniform genotype housing (+/+;+/+, −/−;−/−), the relative amount of long whiskers was significantly higher in the PLCβ1$^{-/-}$ mice (KO) compared to the WT. While WT mice had significantly more long whiskers in the mixed (+/+;−/−) than in the uniform genotype housing (+/+;+/+), PLCβ1$^{-/-}$ mice had significantly more long whiskers in the uniform (−/−;−/−) than in the mixed genotype housing (+/+;−/−). All bars with error bars are mean ± SEM.

but PLCβ1$^{-/-}$ mice rarely did so. This interpretation was confirmed by $2 \times 2 \times 2$ (genotype × gender × pairing) ANOVA for percentage control of long whiskers, which showed a significant interaction between genotype and pairing ($F_{1,20} = 184$, $p < 0.001$). No interaction was observed between gender and either genotype or pairing ($F = 0.171$ and 0.011, respectively, $p > 0.05$).

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Socially recessive trait determined by the tube test for social dominance

Social dominance was tested for 24 WT and 24 PLCβ1$^{-/-}$ mice as described (Messeri *et al.* 1975). The whole social dominance tube kit was made of clear acrylic. Two waiting chambers, 10 × 10 × 10 cm, were connected through a tube, 30 × 3 × 3 cm, between them with a sliding door at the entrance to each chamber. A WT and a PLCβ1$^{-/-}$ mouse of the same gender were put in each of the waiting chambers, and then were released to enter the tube by opening the doors. A subject was considered a winner when it remained in the tube while its opponent completely retreated from the tube. The winner was given a score "1," and the loser, "0." Each mouse went through a single ten-minute session. In most cases, a single contact between the two mice happened during a session. In cases where multiple contacts happened during a session, a subject was declared winner if it won in more than one out of three contacts. Since the scores of the WT and PLCβ1$^{-/-}$ subjects in a pair were not independent, a χ^2 one-sample analysis was used to determine whether the number of wins by PLCβ1$^{-/-}$ mice was significantly different from an outcome expected by chance. Each mouse was tested once with a mouse of the opposite genotype and the same gender. Only two of 24 PLCβ1$^{-/-}$ mice tested (8.33 %) won over the opponent, which is significantly less than expected by chance ($\chi^2 = 16.7$, $p < 0.001$; Figure 7.2). This result demonstrates that PLCβ1$^{-/-}$ mice are socially recessive to WT mice when matched against each other.

Lack of nesting behavior

Casual inspection of mice cages housing uniform genotypes (four or five mice per cage) revealed that WT mice always build fluffy nests with the wooden chips provided, at a corner of the cage floor, whereas PLCβ1$^{-/-}$ mice do not build anything so that the cage floor always looks even and flat. Based on this preliminary observation, nesting behavior was quantified using commercial cotton nesting material. Each mouse was placed alone in a cage with 3 × 3 cm pieces of cotton nesting material evenly spread on top of the ordinary wooden chips. An hour later, photographs were taken of the floor of each cage to inspect whether there was a nest made of the cotton material. Within an hour after being placed in a cage with the cotton pieces, each of the nine WT mice tested built a nest, but none of the 9 PLCβ1$^{-/-}$ mice tested did (Figure 7.3).

Social withdrawal is one of the negative symptoms of human schizophrenia. Whisker trimming, also called barbering behavior, is observed in both male and female mice from many of the commonly used inbred mouse strains. This behavior seems to reflect a cooperative social activity, and also to be associated with social dominance (Strozik and Festing 1981). PLCβ1$^{-/-}$ mice that lack barbering behavior,

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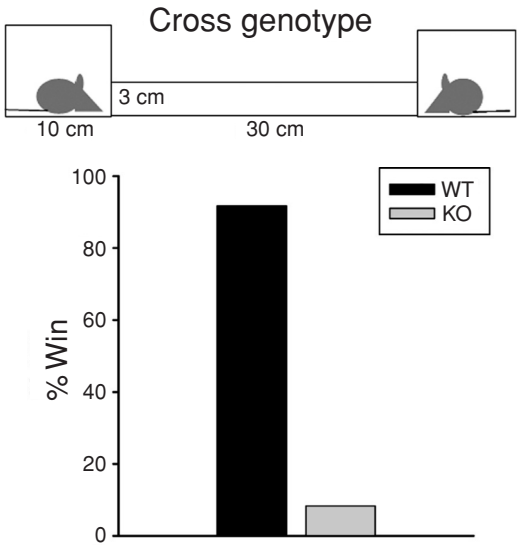

Figure 7.2 PLCβ1$^{-/-}$ mice are socially recessive. Social dominance was tested using the acrylic tube kit (upper panel). Each mouse was tested once with a mouse of the opposite genotype and the same gender. Only 2 of 24 PLCβ1$^{-/-}$ mice tested (KO, 8.33%) won, showing that wild-type mice (WT) are more dominant than PLCβ1$^{-/-}$ mice.

also exhibited a socially recessive trait in the social dominance tube test, suggesting that the lack of barbering in PLCβ1$^{-/-}$ mice is related to a low level of social interaction. Nest building is an activity shared by all members of the home cage and it provides an area for group sleep/huddling (Schneider and Chenoweth 1970). Thus, it is regarded as a behavioral measure of social interaction (Crawley 2004; Long *et al.* 2004). The lack of barbering and nesting behavior, and the socially recessive trait, can be endophenotypes relevant to the negative symptoms found in many schizophrenia patients. A similar set of phenotypes relevant to social withdrawal were also observed in mice lacking disheveled homolog 1 (Dvl1-KO) (Lijam *et al.* 1997).

Cognitive deficits of the PLCβ1$^{-/-}$ mice

Working memory deficit: delayed non-match to sample (DNMTS) T-maze test

Working memory deficit is often the major contributor to the morbidity of schizophrenia. We have evaluated PLCβ1$^{-/-}$ mice for the working memory capacity using the DNMTS T-maze test according to the procedure as previously described (Kellendonk *et al.* 2006; Dias and Aggleton 2000) with minor modifications. In this test, in order to obtain food, a mouse has to remember the arm in the T-maze that

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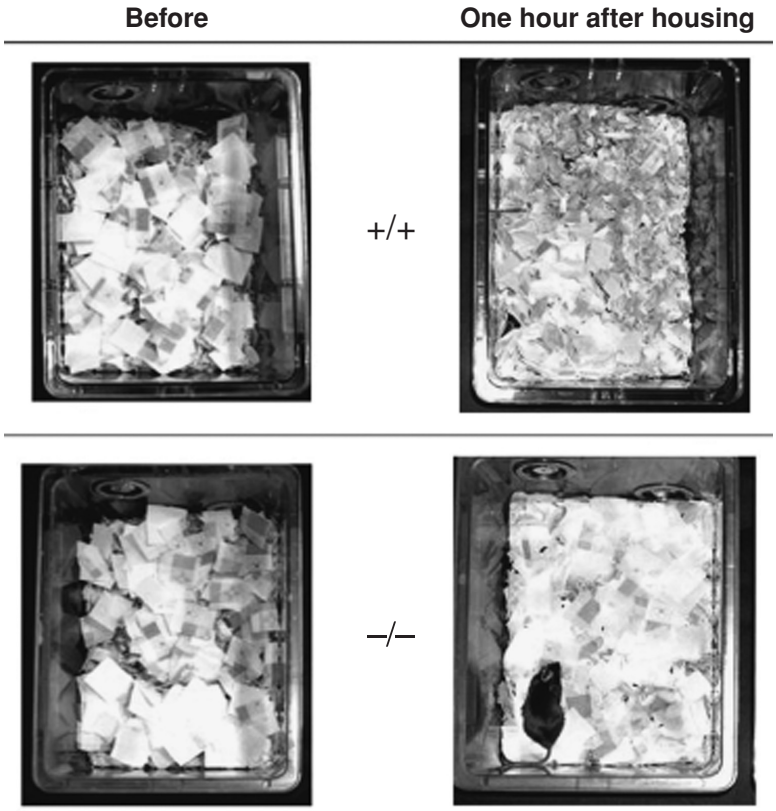

Figure 7.3 Lack of nest building behavior in PLCβ1$^{-/-}$ mice. Nesting behavior was tested using commercial cotton nesting material acutely provided in the cage. Within an hour after being placed in a cage with the cotton pieces, each of all the wild-type mice (+/+, n = 9) tested built a nest, but none of the PLCβ1$^{-/-}$ mice (–/–, n = 9) tested did.

it has just visited and choose to go to the other arm of the maze. A correct choice is scored when the mouse visits the alternate arm in the choice run. The criterion for completing the task was reached when 11 correct choices out of 12 consecutive trials (92%) were made. Each mouse was tested for up to 28 days, during which the sequence of baiting sides (right or left) was randomized. All of the eight WT mice tested reached the criterion (11 correct choices out of 12 consecutive trials) with 6.38 ± 0.34 days of delay. In contrast, none of the eight PLCβ1$^{-/-}$ mice tested ever reached the criterion within 28 days. However, PLCβ1$^{-/-}$ mice performed normally in the simple right–left discrimination T-maze test where the baiting target was fixed at one side, either left or right, for all trials throughout the whole experimental period.

The delayed alternation tasks such as DNMTS T-maze have been widely used to assess working memory function in rats and mice, and impaired working memory is considered a core cognitive deficit in schizophrenia (Elvevag and Goldberg 2000). The inability of PLCβ1$^{-/-}$ mice to reach the criterion within a given period of time, with no significant impairment in the simple right–left discrimination task, suggests that they may have a working memory deficit. Similar deficit was observed in striatal dopamine receptor D2 knockup mice (Kellendonk *et al.* 2006).

Deficits in hippocampus-dependent long-term memory

PLCβ1$^{-/-}$ mice also showed an impaired performance in the Morris water maze, along with a lack of cholinergic, Type-II, theta rhythms on the hippocampal field recordings (Shin *et al.* 2005). A similar behavioral deficit was observed in human schizophrenic patients in tests with a virtual Morris water maze (Hanlon *et al.* 2006). Impaired spatial learning has also been observed in dopamine transporter knockout mice (DAT-KO) in a study using the eight-arm radial maze (Gainetdinov *et al.* 1999). Recently, the hippocampus-dependent fear conditioning was also shown to be impaired in PLCβ1$^{-/-}$ mice (McOmish *et al.* 2008a).

Discussion

Schizophrenia is characterized by positive symptoms (delusion, hallucination, disorganized speech, and psychomotor hyperactivity), negative symptoms (flat affect, avolition, poverty of speech and language, and social withdrawal), and cognitive impairments (deficits in attention, planning and abstract thinking, and short- and long-term memory deficits) (Andreasen 1995; Lewis and Lieberman 2000). Due to the heterogeneity in potential pathogenetic mechanisms suggested by heavy genetic linkage studies that identified multiple susceptibility loci and alleles (Gogos and Gerber 2006), there can not exist a single ideal mouse model of schizophrenia that can represent all the aspects of this disease. Instead, behavioral paradigms with relevance to schizophrenia are sought on the basis of multiple overlapping criteria. These are indirect behavioral measures that resemble the features of the disorder, and abnormalities in a behavioral pattern found in already existing models, as well as directly measurable abnormalities that are almost exactly the same in mice and human patients (Arguello and Gogos 2006; Powell and Miyakawa 2006).

PLCβ1$^{-/-}$ mice exhibited some of the endophenotypes related to all the three categories of symptoms of schizophrenia – positive, negative, and cognitive symptoms. The pattern of severe behavioral abnormalities of these knockout mice is strikingly similar to those of existing putative mice models of schizophrenia. This

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finding is another encouraging example supporting the idea that various kinds of genetic mutations could result in a similar behavioral symptom in mice, which may potentially correspond to psychiatric disorders in humans. The PLCβ1$^{-/-}$ mouse is still among the very few cases of animal models of schizophrenia proposed to date, e.g., NMDA receptor subunit NR1 knockdown (Cheli *et al.* 2006; Mohn *et al.* 1999), stable tubule only peptide (STOP) knockout (Andrieux *et al.* 2002; Brun *et al.* 2005; Fradley *et al.* 2005), and conditional calcineurin (CN) knockout mice (Miyakawa *et al.* 2003; Zeng *et al.* 2001).

The results suggest that PLCβ1-linked signaling pathways are relevant to the physiology of neural functions disrupted in schizophrenia, and thus add significance to the previous works implicating PLCβ1 and related phospholipid metabolism in the pathogenesis of schizophrenia (Arinami *et al.* 2005; du Bois *et al.* 2005; Peruzzi *et al.* 2002; Lin *et al.* 1999; Shirakawa *et al.* 2001). In addition, some of the endophenotypes of PLCβ1$^{-/-}$ mice, the locomotor hyperactivity and sensorimotor gating deficits, are subject to beneficial modulation by environmental enrichment (McOmish *et al.* 2008b): an observation with important implications in the management of schizophrenia patients. PLCβ1$^{-/-}$ mice may be used for future experiments to discover basic pathogenetic mechanisms underlying schizophrenia, which will eventually help develop novel therapeutics.

References

Andreasen NC (1995): Symptoms, signs, and diagnosis of schizophrenia. *Lancet* **346**:477–81.

Andrieux A, Salin PA, Vernet M *et al.* (2002): The suppression of brain cold-stable microtubules in mice induces synaptic defects associated with neuroleptic-sensitive behavioral disorders. *Genes Dev* **16**:2350–64.

Arguello PA and Gogos JA (2006): Modeling madness in mice: one piece at a time. *Neuron* **52**:179–96.

Arinami T, Ohtsuki T, Ishiguro H *et al.* (2005): Genomewide high-density SNP linkage analysis of 236 Japanese families supports the existence of schizophrenia susceptibility loci on chromosomes 1p, 14q, and 20p. *Am J Hum Genet* **77**: 937–44.

Bourre JM, Dumont O, Piciotti M *et al.* (1991): Essentiality of omega 3 fatty acids for brain structure and function. *World Rev Nutr Diet* **66**:103–17.

Braff DL and Freedman R (2002): *Endophenotypes in Studies of the Genetics of Schizophrenia*. Philadelphia: Lippincott Williams & Wilkens.

Brun P, Begou M, Andrieux A *et al.* (2005): Dopaminergic transmission in STOP null mice. *J Neurochem* **94**:63–73.

Cheli V, Adrover M, Blanco C *et al.* (2006): Knocking-down the NMDAR1 subunit in a limited amount of neurons in the rat hippocampus impairs learning. *J Neurochem* **97** Suppl 1:68–73.

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CUUK860-07 cuuk860/Kalueff ISBN: 978 0 521 11638 1 September 4, 2009 17:3

Chuang SC and Bianchi R, Kim D, Shin HS and Wong RK (2001): Group I metabotropic glutamate receptors elicit epileptiform discharges in the hippocampus through PLCbeta1 signaling. *J Neurosci* **21**:6387–94.

Crawley JN (2004): Designing mouse behavioral tasks relevant to autistic-like behaviors. *Ment Retard Dev Disabil Res Rev* **10**:248–58.

Creese I and Iversen SD (1975): The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res* **83**:419–36.

Dias R and Aggleton JP (2000): Effects of selective excitotoxic prefrontal lesions on acquisition of nonmatching- and matching-to-place in the T-maze in the rat: differential involvement of the prelimbic-infralimbic and anterior cingulate cortices in providing behavioural flexibility. *Eur J Neurosci* **12**:4457–66.

Drevets WC, Gautier C, Price JC *et al.* (2001): Amphetamine-induced dopamine release in human ventral striatum correlates with euphoria. *Biol Psychiatry* **49**: 81–96.

du Bois TM, Deng C and Huang XF (2005): Membrane phospholipid composition, alterations in neurotransmitter systems and schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **29**:878–88.

Elvevag B and Goldberg TE (2000): Cognitive impairment in schizophrenia is the core of the disorder. *Crit Rev Neurobiol* **14**:1–21.

Fradley RL, O'Meara GF, Newman RJ *et al.* (2005): STOP knockout and NMDA NR1 hypomorphic mice exhibit deficits in sensorimotor gating. *Behav Brain Res* **163**:257–64.

Gainetdinov RR, Wetsel WC, Jones SR *et al.* (1999): Role of serotonin in the paradoxical calming effect of psychostimulants on hyperactivity. *Science* **283**:397–401.

Gainetdinov RR and Mohn AR and Caron MG (2001): Genetic animal models: focus on schizophrenia. *Trends Neurosci* **24**:527–33.

Gerber DJ, Sotnikova TD, Gainetdinov RR *et al.* (2001): Hyperactivity, elevated dopaminergic transmission, and response to amphetamine in M1 muscarinic acetylcholine receptor-deficient mice. *Proc Natl Acad Sci USA* **98**:15312–17.

Geyer MA, Krebs-Thomson K, Braff DL and Swerdlow NR (2001): Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology (Berl)* **156**:117–54.

Gogos JA and Gerber DJ (2006): Schizophrenia susceptibility genes: emergence of positional candidates and future directions. *Trends in Pharmacological Sciences* **27**:226–33.

Gould TD and Gottesman, II (2006): Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav* **5**:113–19.

Hanlon FM, Weisend MP, Hamilton DA *et al.* (2006): Impairment on the hippocampal-dependent virtual Morris water task in schizophrenia. *Schizophr Res* **87**:67–80.

Hannan AJ, Blakemore C, Katsnelson A *et al.* (2001): PLC-beta1, activated via mGluRs, mediates activity-dependent differentiation in cerebral cortex. *Nat Neurosci* **4**:282–8.

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CUUK860-07 cuuk860/Kalueff ISBN: 978 0 521 11638 1 September 4, 2009 17:3

Kellendonk C, Simpson EH, Polan HJ *et al.* (2006): Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* **49**:603–15.

Kim D, Jun KS, Lee SB *et al.* (1997): Phospholipase C isozymes selectively couple to specific neurotransmitter receptors. *Nature* **389**:290–3.

Koh HY, Kim D, Lee J and Lee S and Shin HS (2008): Deficits in social behavior and sensorimotor gating in mice lacking phospholipase Cβ1. *Genes Brain Behav* **7**: 120–8.

Laruelle M, Abi-Dargham A, van Dyck CH *et al.* (1996): Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci USA* **93**:9235–40.

Laruelle M, Abi-Dargham A, Gil R, Kegeles L and Innis R (1999): Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry* **46**:56–72.

Lewis DA and Lieberman JA (2000): Catching up on schizophrenia: natural history and neurobiology. *Neuron* **28**:325–34.

Lijam N, Paylor R, McDonald MP *et al.* (1997): Social interaction and sensorimotor gating abnormalities in mice lacking Dvl1. *Cell* **90**:895–905.

Lin XH, Kitamura N, Hashimoto T, Shirakawa O and Maeda K (1999): Opposite changes in phosphoinositide-specific phospholipase C immunoreactivity in the left prefrontal and superior temporal cortex of patients with chronic schizophrenia. *Biol Psychiatry* **46**:1665–71.

Long JM, LaPorte P, Paylor R and Wynshaw-Boris A (2004): Expanded characterization of the social interaction abnormalities in mice lacking Dvl1. *Genes Brain Behav* **3**:51–62.

McOmish CE, Burrows EL, Howard M and Hannan AJ (2008a): PLC-beta1 knockout mice as a model of disrupted cortical development and plasticity: behavioral endophenotypes and dysregulation of RGS4 gene expression. *Hippocampus* **18**:824–34.

McOmish CE, Burrows E, Howard M *et al.* (2008b): Phospholipase C-beta1 knockout mice exhibit endophenotypes modeling schizophrenia which are rescued by environmental enrichment and clozapine administration. *Mol Psychiatry* **13**:661–72.

Messeri P, Eleftheriou BE and Oliverio A (1975): Dominance behavior: a phylogenetic analysis in the mouse. *Physiol Behav* **14**:53–8.

Miyakawa T, Leiter LM, Gerber DJ *et al.* (2003): Conditional calcineurin knockout mice exhibit multiple abnormal behaviors related to schizophrenia. *Proc Natl Acad Sci USA* **100**:8987–92.

Mohn AR, Gainetdinov RR, Caron MG and Koller BH (1999): Mice with reduced NMDA receptor expression display behaviors related to schizophrenia. *Cell* **98**:427–36.

Oude Weernink PA, Han L, Jakobs KH and Schmidt M (2006): Dynamic phospholipid signaling by G protein-coupled receptors. *Biochim Biophys Acta* **1768**:888–900.

Peruzzi D, Aluigi M, Manzoli L *et al.* (2002): Molecular characterization of the human PLC beta1 gene. *Biochim Biophys Acta* **1584**:46–54.

Powell CM and Miyakawa T (2006): Schizophrenia-relevant behavioral testing in rodent models: a uniquely human disorder? *Biol Psychiatry* **59**:1198–207.

Rhee SG and Bae YS (1997): Regulation of phosphoinositide-specific phospholipase C isozymes. *J Biol Chem* **272**:15045–8.

Robertson GS, Hori SE and Powell KJ (2006): Schizophrenia: an integrative approach to modelling a complex disorder. *J Psychiatry Neurosci* **31**:157–67.

Russig H, Spooren W, Durkin S, Feldon J and Yee BK (2004): Apomorphine-induced disruption of prepulse inhibition that can be normalised by systemic haloperidol is insensitive to clozapine pretreatment. *Psychopharmacology (Berl)* **175**:143–7.

Schneider CW and Chenoweth MB (1970): Effects of hallucinogenic and other drugs on the nest-building behaviour of mice. *Nature* **225**:1262–3.

Shin J, Kim D, Bianchi R, Wong RK and Shin HS (2005): Genetic dissection of theta rhythm heterogeneity in mice. *Proc Natl Acad Sci USA* **102**:18165–70.

Shirakawa O, Kitamura N, Lin XH, Hashimoto T and Maeda K (2001): Abnormal neurochemical asymmetry in the temporal lobe of schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **25**:867–77.

Spector AA and Yorek MA (1985): Membrane lipid composition and cellular function. *J Lipid Res* **26**:1015–35.

Strozik E and Festing MF (1981): Whisker trimming in mice. *Lab Anim* **15**:309–12.

Turetsky BI, Calkins ME, Light GA *et al.* (2007): Neurophysiological endophenotypes of schizophrenia: the viability of selected candidate measures. *Schizophr Bull* **33**:69–94.

van den Buuse M, Garner B, Gogos A and Kusljic S (2005): Importance of animal models in schizophrenia research. *Aust N Z J Psychiatry* **39**:550–7.

Watanabe M, Nakamura M, Sato K *et al.* (1998): Patterns of expression for the mRNA corresponding to the four isoforms of phospholipase C beta in mouse brain. *Eur J Neurosci* **10**:2016–25.

Weike AI, Bauer U and Hamm AO (2000): Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. *Biol Psychiatry* **47**:61–70.

Yee BK, Keist R, von Boehmer L *et al.* (2005): A schizophrenia-related sensorimotor deficit links alpha 3-containing GABAA receptors to a dopamine hyperfunction. *Proc Natl Acad Sci USA* **102**:17154–9.

Zeng H, Chattarji S, Barbarosie M *et al.* (2001): Forebrain-specific calcineurin knockout selectively impairs bidirectional synaptic plasticity and working/episodic-like memory. *Cell* **107**:617–29.