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Modeling the Positive Symptoms of Schizophrenia in Genetically Modified Mice: Pharmacology and Methodology Aspects

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In recent years, there have been huge advances in the use of genetically modified mice to study pathophysiological mechanisms involved in schizophrenia. This has allowed rapid progress in our understanding of the role of several proposed gene mechanisms in schizophrenia, and yet this research has also revealed how much still remains unresolved. Behavioral studies in genetically modified mice are reviewed with special emphasis on modeling psychotic-like behavior. I will particularly focus on observations on locomotor hyperactivity and disruptions of prepulse inhibition (PPI). Recommendations are included to address pharmacological and methodological aspects in future studies. Mouse models of dopaminergic and glutamatergic dysfunction are then discussed, reflecting the most important and widely studied neurotransmitter systems in schizophrenia. Subsequently, psychosis-like behavior in mice with modifications in the most widely studied schizophrenia susceptibility genes is reviewed. Taken together, the available studies reveal a wealth of available data which have already provided crucial new insight and mechanistic clues which could lead to new treatments or even prevention strategies for schizophrenia.

Key words: schizophrenia risk gene/dopamine/glutamate/neuregulin-1/DISC-1/dysbindin/locomotor hyperactivity/prepulse inhibition

Introduction

In the last 10 years or so, there have been huge advances in the use of genetically modified mice to study pathophysiological mechanisms involved in schizophrenia. Much of that progress has been driven by rapid developments in molecular biology techniques, allowing both better identification of neurogenetic mechanisms putatively involved in this illness, as well as generating more and more sophisticated gene modifications in mice. Thus, there has been rapid progress in our understanding of the role of several proposed gene mechanisms in schizophrenia, and yet this research has also revealed how much still remains unresolved.

This review article addresses pharmacological and methodological aspects of behavioral studies in genetically modified mice with special emphasis on modeling psychotic-like behavior. This article is not about the validity or strength of the evidence for an association of various genetic factors with schizophrenia; the reader is referred to several excellent other review articles which address those aspects. [1–14]

There have been many discussion papers on the need for more comprehensive phenotyping and the use of standard behavioral test ''batteries'' to reveal behavioral effects of genetic modifications in mice,[3,13–19] but pharmacological characterization of behavioral changes in a particular mouse model is not always part of that. This is an unfortunate shortcoming of some studies because including relevant pharmacological challenges in the behavioral phenotyping battery may reveal changes in behavioral reactivity which may go unnoticed if only baseline behaviors are assessed. Here, I will particularly focus on psychotropic drug-induced locomotor hyperactivity and disruptions of prepulse inhibition (PPI) for reasons which will be outlined below. If unavailable, I will also include observations on baseline locomotor activity, baseline PPI, and some other relevant behaviors and neurochemical measures. I will focus on detailing the results of behavioral testing of mutant mice of 2 main groups of factors, including the most important neurotransmitter systems and candidate/risk genes in schizophrenia, respectively.[2–7,9,11–14] Other symptom domains, including behavioral methods with relevance to negative symptoms of schizophrenia, or cognitive deficits, will be addressed in other reviews in this series.

Animal Models of Psychosis: General Features and Methodological Considerations

While the positive symptoms of schizophrenia, such as auditory hallucinations and delusions, are uniquely

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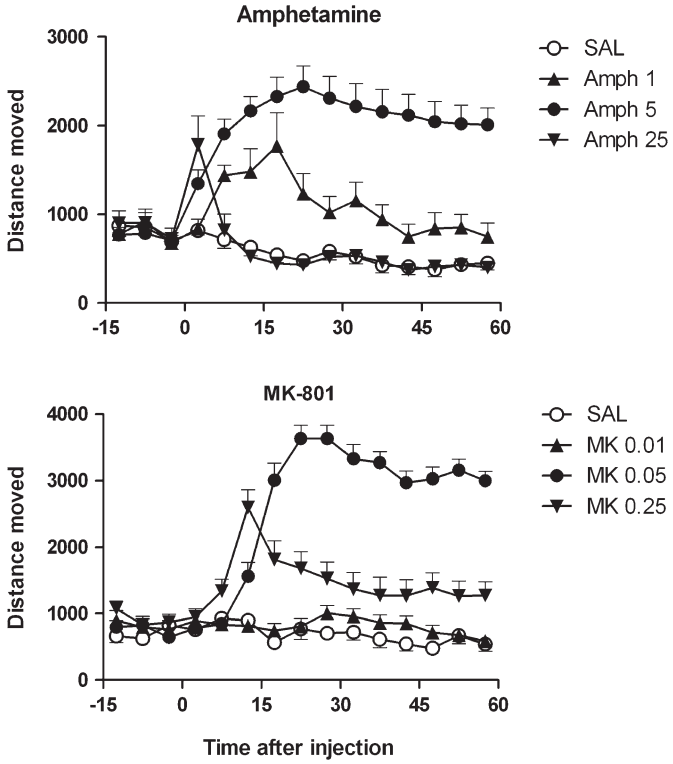

Fig. 1. The Effect of Different Doses of Amphetamine (amph, Top Panel) and MK-801 (MK, Bottom Panel) on Locomotor Activity of C57BL/6 Mice (M. van den Buuse, unpublished data). Both drugs showed little effect at the lowest dose, markedly increase locomotor distance moved at the middle dose, but induced low scores at the highest dose, presumably because of the induction of stereotyped responses which disrupted ambulatory activity. Depending on the dose of the drug, an increase of locomotor distance moved displayed by a genetically modified mouse model could either mean hypersensitivity or hyposensitivity to the treatment. Locomotor distance moved was assessed using automated photocell cages (see van den Buuse et al[175] for details). Doses indicated are in milligram per kilogram. There were 8–20 mice per group, and data are expressed as mean ± standard error of the mean.

human, the literature on genetically modified mouse models of this symptom cluster has focused on 2 main categories of behavior: locomotor hyperactivity and disruptions of PPI.

Locomotor Hyperactivity

Some insight is available into brain neurotransmitter mechanisms involved in psychotic symptoms, and these neurotransmitter changes can potentially be "recreated" in rodents with drug treatments. Historically, subcortical hyperdopaminergia was postulated in schizophrenia mostly on the basis of the neuropharmacological action of antipsychotic drugs, which are virtually all dopamine receptor antagonists (with varying affinity for other neurotransmitter receptors).[20,21] The other line of evidence comes from imaging studies which have shown enhanced dopaminergic reactivity and enhanced effects of amphetamine in the forebrain of subjects with schizophrenia (eg, Drevets et al[22] and Laruelle et al[23,24]). It is reasonable to state that changes in dopaminergic activity are unlikely to be the primary cause of schizophrenia—or even the positive symptoms of schizophrenia—but there may be a final common dopaminergic pathway through which genetic, environmental, and developmental factors combine to result in varying degrees of symptomatology.[25,26] With respect to animal models, it then makes sense to assess for changes in dopamine-related behaviors, an approach which has construct validity rather than face validity, as between humans and mice the underlying neuropharmacological mechanisms may be the same, but the behavioral consequences are quite different. It has been suggested that locomotor hyperactivity may have some face validity for certain components of the positive symptoms of schizophrenia, such as psychotic agitation.[12] However, here I will focus mainly on the use of locomotor hyperactivity to reveal underlying neurotransmitter changes.

Because of its relative ease of quantification, locomotor activity testing has been widely used in modeling the positive symptoms of schizophrenia. Although complex and multifactorial, the role of dopamine in movement control is reasonably well defined, with a predominant involvement of the mesolimbic and nigrostriatal dopamine systems and a relatively clear pharmacology. In its simplest form, the concept of testing for locomotor hyperactivity is based upon the premises that enhanced dopaminergic activity in rodents leads to enhanced motor activity, be it horizontal locomotor activity, rearing, or, at higher doses, stereotyped behaviors (see figure 1). Most of these behaviors can be measured by automated photocell cages or scored by observation. More sophisticated methodology includes ethological assessment of a range of natural behaviors, including motor activity, or qualitative analysis of patterns and perseverative aspects of behavior.[27,28]

Classic experiments have shown the role of different parts of the dopamine system in locomotor hyperactivity in rats.[29] For example, 6-hydroxydopamine (6-OHDA)–induced lesions of the nucleus accumbens abolished amphetamine-induced hyperactivity in this species.[30,31] Thus, altered amphetamine-induced locomotor hyperactivity can then be used as a measure of altered dopaminergic neurotransmission in the mesolimbic system and has construct validity for enhanced dopaminergic activity in schizophrenia. Importantly, it should be noted that amphetamine also stimulates extracellular levels of other neurotransmitters, such as noradrenaline and serotonin, and the possible involvement of those systems should therefore not be ignored.[32–34] Similar, but not identical anatomical and pharmacological substrates are involved in the action of cocaine on locomotor activity.[32,35] In all this, it is important to note that the vast majority of the evidence for the involvement of mesolimbic

dopaminergic activity in amphetamine-induced locomotor hyperactivity has been obtained in rats and that this same relationship has not yet been thoroughly studied in mice.[36]

The second main line of research using locomotor hyperactivity as an *in vivo* measure of central neurotransmitter system activity has been to assess the effect of N-methyl-D-aspartate (NMDA) receptor antagonists, such as phencyclidine and MK-801.[37,38] Construct validity for this approach stems from the effect of dissociative anesthetics, such as ketamine and phencyclidine, to induce hallucinations with similarities to the positive symptoms of schizophrenia.[39,40] In rats and mice, moderate doses of these drugs induce locomotor hyperactivity, while at higher doses, sedative and anesthetic effects or the emergence of stereotyped behaviors lead to a apparent reduction of locomotor counts, similar to that seen with high doses of amphetamine (see Yates et al[41] and figure 1). While these compounds indirectly activate dopaminergic activity in humans[42] and rats,[43] locomotor hyperactivity induced by these drugs in rodents is largely independent of dopaminergic activation. For example, phencyclidine-induced locomotor hyperactivity is temporally dissociated from its effect on dopamine release.[43] Moreover, phencyclidine effects on locomotor activity are not readily attenuated by pretreatment with dopaminergic antagonists, such as haloperidol, unless these drugs are administered at high doses which may nonspecifically cause general motor inhibition and catatonia.[37,38]

PPI of Startle

As reviewed previously, loss of normal PPI is widely accepted as an endophenotype of schizophrenia[44] and considered indicative of disrupted sensorimotor gating, a precognitive process to prevent sensory overload and cognitive fragmentation (for references, see Powell et al,[12] van den Buuse et al,[14] Geyer et al,[17] and Geyer[45]). It should not be considered as a straightforward model of positive symptoms of schizophrenia but is more likely to represent the ''interface of psychosis and cognition.''[4] Moreover, disruptions of PPI have been described in other neurological and psychiatric diseases.[12,46]

Several studies have suggested overlapping neural substrates and pharmacological mechanisms between PPI in rodents and in humans, and PPI is therefore usually referred to as a ''cross-species'' measure of sensory gating. At the same time, it should be recognized that the pharmacology of PPI appears to be different at a number of levels between rodents and humans[47] and even between mice and rats. Administration of direct dopamine D1 and D2 receptor agonists, such as apomorphine, indirect dopamine agonists, such as amphetamine, and NMDA receptors antagonist generally results in disruption of PPI in mice[12,47] (also see figure 2). Thus, PPI can be used to model both a hyperdopaminergic and a hyperglutamatergic state. However, the role of the nucleus accumbens in the effects of dopamine D2 receptor agonists on PPI appears to be opposite in rats and mice.[48,49] Similarly, some drugs, such as serotonin-1A receptor agonists, disrupt PPI in rats but increase PPI in mice.[47,50] In addition, baseline PPI is different between mouse strains[51] which likely reflects differences in the inherent activity of dopaminergic or other neurotransmitter systems in these animals (see figure 2). Indeed, in a mouse strain with particularly low baseline PPI, the DBA/2J line, antipsychotic treatment increased PPI to a much greater extent than in C57BL/6 where baseline PPI was already higher.[52] Also the extent of other drug-induced changes in PPI appear to be strain specific in mice.[17,47]

PPI of acoustic startle can be assessed using automated startle boxes, and there is reasonable agreement in the literature as to the protocols and equipment used for these kinds of experiments.[45,53] However, some seemingly minor differences in the details of PPI protocols can impact on the results, including technical details such as prepulse-pulse interval and stimulus modalities, and experimental details such as mouse background strain,[50,54] sex of the animals, and drug doses used.[17,45,50,55,56] Overall, while several studies on genetically modified mouse models of schizophrenia have included PPI testing,[12,17] many others have not and few include pharmacological testing. The latter is important as it is very well conceivable that mice with a given gene mutation show apparently normal PPI and startle because of compensatory mechanisms in the brain such as receptor upregulation or altered activity in parallel neurotransmitter systems.[47,57] In that situation, the animal may respond more or less to specific drug challenges (figure 2), similar to locomotor hyperactivity. Conversely, it could be argued that mice with altered baseline PPI represent only the more severe perturbations of regulatory mechanisms which cannot readily be compensated for. In either case, whether there is altered baseline PPI or not, pharmacological studies can identify subtle shifts in the relative activity of its neurotransmitter control.

Methodological Considerations

As will become obvious from the available literature on genetically modified mouse models of aspect of psychosis (see below), some methodological recommendations may be useful. Many excellent reviews for other behavioral domains and psychiatric illnesses have discussed discrepancies between behavioral phenotyping studies caused by methodological factors.[10,15,18,19,51,53,58] It is therefore important that details are reported on housing conditions, age, and male/female ratio of the mice. Solitary housing has profound effects on locomotor activity and PPI in rats,[46] and comparable effects are found in mice.[59] As outlined below, housing conditions can

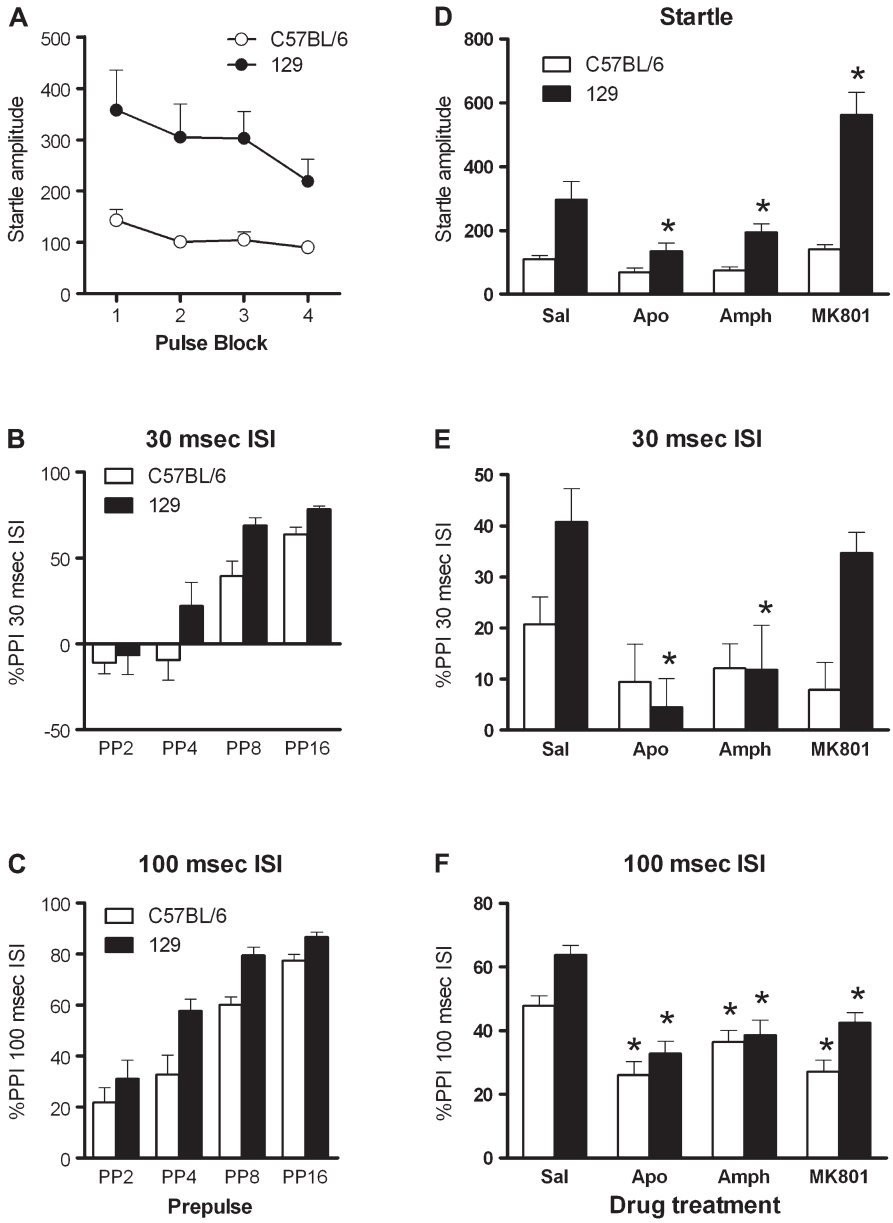

Fig. 2. Comparison of PPI of C57BL/6 and 129Sv Mice (M. van den Buuse, unpublished data). Startle amplitude was much greater in 129Sv mice than in C57BL/6 although startle habituation was not different (panel A). PPI tended to be higher in 129Sv mice than in C57BL/6 at both the 30-ms ISI (panel B) or 100 ms ISI (panel C). There were differential as well as similar effects between the strains, depending on the parameter measured and drug tested. Genetic modifications on either a C57BL/6 or 129Sv genetic background may have profoundly different effects on these baseline levels. Experiments included the effect of 5 mg/kg of apomorphine, 5 mg/kg of amphetamine, and 0.25 mg/kg of MK-801 on average startle (panel D), PPI at the 30-ms ISI (panel E), and PPI at the 100-ms ISI (panel E). For methodological details, see van den Buuse et al.[56,175] Data are expressed as mean ± SEM of $n = 8$–12. *$P < .05$ compared with the saline condition in the same strain (analyzed by analysis of variance).

in fact become a second neurodevelopmental "hit," and then the experimental model becomes a gene/environment model instead of just the effect of the gene. In order to be able to replicate results between laboratories, it is also important that experimental details, such as open field dimensions and testing conditions (eg, light), are reported. For PPI, where possible, different interstimulus intervals (ISIs) or stimulus modalities should be used, and effects on startle should always be analyzed and included.

Another factor of importance in studying genetically modified mouse models of psychiatric illnesses is background strain. The majority of studies report the background strain that a given genetic modification is on. However, this information also reveals variability of genetic backgrounds used, and in some cases, this can

strongly influence the result.[51,56] We compared 2 of the most commonly used inbred mouse lines, C57BL/6 and 129Sv, for baseline PPI and the effect of apomorphine, amphetamine, and MK-801, and found marked differences in behavioral responses (M. van den Buuse, unpublished data, see figure 2) which could influence the impact of genetic modifications on these genetic backgrounds. In the literature, mouse strains used range from "pure" 129Sv, 129/C57BL/6 mixed to "pure" C57BL/6, while some studies include FVB or BALB/c background. Although backcrossing onto a C57BL/6 background is commonly recommended, it should be noted that even after prolonged backcrossing, there is still a chance of flanking genes influencing the behavioral outcomes.[60] In addition, C57BL/6 are clearly different in several behavioral tests from other strains (eg, figure 2 and Kalueff et al[19] and Paylor and Crawley[51]), and this could mask a relatively subtle effect of a genetic modification.

In several otherwise excellent studies, only baseline behaviors are reported. Indeed, a major caveat in the literature is the common use of baseline locomotor activity in the same way as drug-induced locomotor hyperactivity. Thus, if genetically modified mice display locomotor hyperactivity at baseline, it is often interpreted to indicate enhanced dopaminergic activity or "psychotic-like" behavior. This is clearly a simplification as the pharmacology of baseline (ie non-drug induced) locomotor activity, and amphetamine-induced locomotor hyperactivity is likely to be different. While the effect of amphetamine on locomotor activity may involve neurotransmitters other than just dopamine, baseline activity may involve many other transmitter systems again. For example, glutamatergic pathways are involved in non-dopaminergic modulation of motor activity (see above). Furthermore, manipulation of the activity of several other neurotransmitter systems, such as noradrenaline and serotonin, can induce changes in locomotor activity. These may involve dopaminergic activation, but the primary cause for the altered behavior then lies outside the dopamine system itself.

In general, it is fair to say that the pharmacology of behavior in mice is less well studied than that in rats. It is important to note that mice are not simply "small rats" and do not necessarily respond to the same doses of drugs. Indeed, there are large differences in dose ranges between rats and mice for some drugs, eg, amphetamine needs to be administered at milligram per kilogram doses about 10× in mice than in rats to elicit a significant hyperactivity response; however, clozapine doses are generally lower in mice than in rats. These species variations may be explained by differences in the neural substrates and neuropsychopharmacological mechanisms involved in the regulation of locomotor hyperactivity and PPI in mice vs rats. In addition, species differences in mechanisms outside the central nervous system, such as drug metabolism and pharmacokinetics, always need to be considered as well.

Ideally, genetically modified mice should be tested for changes in both baseline activity and locomotor hyperactivity induced by a predominantly dopaminergic stimulus, such as amphetamine, and NMDA receptor antagonists, such as phencyclidine or MK-801. Pharmacological mechanisms can be further identified by the use of appropriate antagonists drugs, including, eg, antipsychotics such as haloperidol. Where this is done, the effect of the antipsychotics on baseline behavior should also be assessed to ascertain that any inhibition of psychotropic drug-induced hyperactivity is specific. Unfortunately, with some excellent exceptions, not many studies adopt such an approach. The result of such drug testing can be that it is found that a mouse model does not display changes in baseline behaviors, but responses to certain drugs are enhanced or reduced. It is important to test multiple doses of drugs, which can cause locomotor hyperactivity as well as reduced activity due to stereotyped responding. Thus, with drug such as amphetamine or MK-801 (see figure 1), it is important to ascertain whether enhanced locomotor activity scores in fact reflect increased or decreased sensitivity to the treatment. Antagonist treatment, including antipsychotic drugs, can also be used as tools to probe for pharmacological specificity; however, it is important to assess the effect of these drugs on baseline behavior to exclude nonspecific effects, such as sedation, catatonia, or stereotyped responses. If automated photocell cages are to be used, such responses may easily be missed and interpreted as a reduced locomotor hyperactivity response, where it is in fact *enhanced* responding. In PPI experiments, some of these effects could be reflected by reduced startle responses.

Neurotransmitter Models of Psychosis

Dopamine

In accordance with the widespread historical interest in the "hyperdopaminergic hypothesis" of schizophrenia, many mouse models have been developed which address virtually all components of dopaminergic activity in the brain, from its synthesis by tyrosine hydroxylase, to release and the regulation of extracellular levels, including by dopamine transporters and catabolic enzymes, and the role of the 5 dopamine receptors.

Dopamine D1 Receptors. Dopamine D1 receptor knockouts were generated as early as 1994 by 2 separate laboratories.[61,62] One of these mouse lines showed reduced horizontal locomotion[61] and the other baseline locomotor hyperactivity.[62–64] Both D1 knockout lines showed a reduced hyperactivity response to acute and chronic treatment with cocaine[63,65] or amphetamine[66,67] (table 1).

Table 1. Summary of the Effect of Dopaminergic Drugs on Locomotor Activity and PPI in Dopamine Receptor Mutant Mice

	Wild type	D1 KO	D2 KO	D3 KO	D4 KO	D5 KO
Locomotor activity						
Baseline (vs wild type)		↓/↑[61,62]	↓↓/↓[71,73]	↑[84,86]	↓[91]	0
Amphetamine (vs saline)	↑↑	↑[66,67]	↑/0[73]	↑↑↑[86]	↑↑↑[91,93]	ND
Cocaine (vs saline)	↑↑	0[63,65]	↑[74]	↑↑↑[86,89]	↑↑↑[91,92]	↑/0[96,97]
PCP/MK-801 (vs saline)	↑↑	ND	ND	↑/0[90]	ND	ND
PPI						
Baseline (vs wild type)		0	↓[68]	0	0	0
Apomorphine (vs saline)	↓↓	0[68]	↓↓[68]	ND	ND	ND
Amphetamine (vs saline)	↓↓	↓↓[68]	0[68,83]	↓↓[83]	↓↓[83]	ND
Cocaine (vs saline)	↓↓	0[69]	↓[69]	↓↓↓[69]	ND	ND
PCP/MK-801 (vs saline)	↓↓	↓↓[68]	↓↓[68]	ND	ND	ND

Note: KO, knockout; ND, not determined. Drug effects in wild-type mice have been schematically "normalized" to 2 arrows. A "0" then indicates virtual or complete abolition of the locomotor stimulation or PPI disruption, with single arrows indicating partial changes.

PPI was similar in D1 receptor knockout mice as in wild-type controls.[68] In contrast to the loss of its effect on locomotor activity in D1 receptor knockouts,[66,67] the effect of amphetamine to disrupt PPI was not altered in these animals.[68] The effect of MK-801 to disrupt PPI was also not altered; however, in contrast, the effect of the dopamine D1/D2 receptor agonist, apomorphine, was absent in D1 receptor knockouts.[68] Surprisingly, and in contrast to amphetamine, the effect of cocaine to disrupt PPI was completely absent in D1 receptor knockouts.[69] These results (table 1) suggest that the dopamine receptors involved in amphetamine-induced locomotor hyperactivity and disruption of PPI are not the same in mice, with the D1 receptor being involved in the former but not the latter. The effect of cocaine was equally absent for locomotor hyperactivity or PPI disruption in D1 knockouts. Finally, the results confirm studies with antipsychotic drugs and receptor antagonists that dopamine D1 receptors are not involved in the effect of MK-801 on PPI.

In addition to D1 receptor knockouts, a mouse line overexpressing D1 receptors has also been developed.[70] These transgenic animals had 2- to 5-fold increases in D1 receptor levels in a variety of brain regions but not the caudate nucleus, olfactory tubercle, or nucleus accumbens. Paradoxically, while the dopamine D1 receptor agonist, SKF81297, caused a dose-dependent increase in locomotor activity in wild-type mice, it had no effect or actually decreased activity in D1 transgenics.[70] The effect of amphetamine and cocaine was not altered in the transgenic mice. These results were interpreted as indicating the presence of 2 types of D1 receptors, one inhibiting activity and overexpressed in the transgenic mice and the other decreasing activity. Alternatively, behavior in the transgenic mice could have been altered by an imbalance between D1 and D2 receptor–mediated effects.[70]

Dopamine D2 Receptors Initial reports on the behavioral phenotype of dopamine D2 receptor knockouts described these animals as severely bradykinetic.[71] Later studies found several aspects of behavior of these animals to be essentially normal, but there was a profound loss of responsiveness to the behavioral activation by treatment with a D2 receptor agonist.[72] A parallel D2 receptor knockout was developed which did not display severe bradykinesia[73] and showed a diminished locomotor hyperactivity response to acute treatment with methamphetamine, cocaine, or MDMA.[74–76] These data (table 1) and other findings[77] are another example of how compensatory changes in the density or coupling of other receptors may mask some of the phenotypic changes in a particular receptor mutant and emphasize that appropriate pharmacological challenges should be part of behavioral phenotyping.[77,78] A dopamine D2 receptor transgenic line has also been developed,[79] but as yet, these mice have not been tested for drug-induced locomotor hyperactivity or PPI disruptions.

Further studies focused on selective deletion of either the "long" or "short" form of the D2 receptor. Thus, D2long knockouts showed normal baseline and novelty-induced locomotor activity compared with wild-type controls.[80–82] Dopamine D2 expression in the brain of these mice was normal, suggesting an upregulation of D2short expression in the absence of the D2long isoform.[82] However, these animals showed no cataleptic effect of haloperidol treatment, similar to the knockout of both isoforms.[80,82] Similarly, these animals had absent or markedly reduced responses to treatment with apomorphine or D1 receptor agonists. Thus, it was concluded that the D2long isoform synergistically interacts with D1 receptors in locomotor activity regulation, whereas the D2short isoform may functionally oppose the D1 receptor.[80]

PPI and startle were normal in D2 receptor knockout mice. However, the effect of amphetamine to disrupt PPI was completely abolished in these animals.[68,83] The effect of cocaine on PPI was partially attenuated,[69] whereas the effects of apomorphine, SKF81297, or MK-801 on PPI were not significantly altered in D2 receptor knockouts.[68]

In D2long knockouts, baseline PPI and the effects of amphetamine and apomorphine were not altered.[81] These results suggest a critical role of the D2short form in mediating the action of amphetamine on PPI.

Dopamine D3, D4, and D5 Receptors. Compared with the D1 and D2 receptors, less is known about the effect of mutation of the D3, D4, and D5 receptor on locomotor behavior and PPI. Several laboratories have generated D3 receptor knockout lines.[84–87] Generally, the mice displayed mild-to-moderate baseline locomotor hyperactivity.[84–86] The effect of amphetamine or cocaine to induce locomotor hyperactivity was also greater in these mice compared with wild-type controls, particularly at moderate doses.[86,88,89] In contrast, the effect of the NMDA receptor antagonist, MK-801, was markedly reduced in D3 knockout mice.[90] These results are consistent with a role of the D3 receptor as a postsynaptic inhibitory dopamine receptor, but the importance of this role appears to differ depending on the pharmacological stimulus used.

Dopamine D4 receptor knockout mice were moderately hypoactive in the open field but showed hyperresponsiveness to the effects of cocaine,[91,92] methamphetamine,[91] and amphetamine.[93] However, a more recent report suggested that D4 knockouts show dose-dependent changes in the locomotor hyperactivity response to amphetamine and no difference in the acute effect of cocaine.[94] These discrepancies with earlier studies were explained by the use of lower doses of amphetamine and cocaine. It was suggested that the higher doses of these psychostimulants in the earlier studies in fact revealed serotonergic compensatory changes in D4 knockouts.[94]

Dopamine D5 receptor knockout mice showed reduced effects of the dopamine D1/D5 receptor agonist, SKF81297, to increase behavioral activity. However, there was no genotype difference in the effect of the D1/D5 antagonist, SCH23390, to decrease activity.[95] The acute effect of cocaine to induce locomotor hyperactivity was reduced in D5 knockouts in one study[96] but unchanged in another.[97] Several other psychotropic drugs have not been tested for their effects on locomotor activity in D3, D4, and D5 mutant mice (table 1).

There were no changes in baseline PPI in either D3 or D4 knockouts[83] or D5 knockouts.[95] The effect of amphetamine on PPI was not altered in D3 or D4 receptor knockouts.[83] The effect of the dopamine D1/D5 receptor agonist, SKF81297, to disrupt PPI tended to be reduced in D5 knockouts.[95] Taken together with the locomotor activity observations (see above), these findings led the authors to conclude that "the results support the interpretation that the D5 receptor subtype plays a minor functional role, complementary to the D1 receptor, in dopaminergic pathways mediating behavior."[95] However, further studies are needed to assess the effect of other drugs, particularly the mixed D1/D2 agonist, apomorphine, and NMDA receptor antagonists, such as MK-801 or phencyclidine, on PPI in these mutant mice (see table 1).

Dopamine Transporter. Knockout of the dopamine transporter has been shown to severely disrupt regulation of extracellular dopamine levels,[98,99] an effect which was more pronounced with the mutation on a DBA/2 genetic background compared with a C57BL/6 background.[100] Dopamine transporter mice were highly hyperactive in a novel environment and showed no effect of either amphetamine or cocaine on locomotor activity.[99] Treatment with dopamine D1 and D2 antagonists attenuated the locomotor hyperactivity in dopamine transporter knockout mice,[101] but the NMDA receptor antagonist, MK-801, increased locomotor activity to a greater extent than in controls.[102] Furthermore, PPI was significantly disrupted, an effect which could also be reversed by treatment with dopamine D2 receptor antagonists.[101,103] A multitude of other behavioral, neurochemical, and molecular changes have been described in these animals (for references, see Gainetdinov[98] and Gainetdinov and Caron[104]), and it was suggested that these hyperdopaminergic animals could be a novel model for psychotic symptoms in schizophrenia.[99] It should be noted, that the reduced activity of amphetamine in this mouse model is in contrast to enhanced effects of this drug in schizophrenia.[23] Furthermore, the chronic nature of the profoundly elevated extracellular dopamine levels in the dopamine transporter knockout mouse, different from the more phasic upregulation of dopaminergic activity in schizophrenia, induced considerable compensatory responses in other transmitter systems.[98,99,104]

Instead of a complete knockout, a "knockdown" mutant displayed a 90% reduction of dopamine transporter expression.[105] These animals were hyperactive in a novel environment,[105,106] and this hyperactivity could paradoxically be *reduced* by amphetamine and apomorphine, which induced hyperactivity in wild-type control mice.[105] In contrast, the effect of cocaine to induce locomotor hyperactivity was enhanced in these mice.[107] These differential effects of the dopamine transporter knockdown on the action amphetamine vs cocaine once again reveal fundamental differences in the neuropsychopharmacological mechanism of action of these drugs and the compensatory mechanisms they recruit in the brains of genetically modified mice. Baseline PPI was normal in these mice.[106]

Glutamate

Similar to hyperdopaminergia as a contributing mechanism to psychosis, in the literature, there has been extensive focus on the "hypoglutamatergic hypothesis" of schizophrenia. It is therefore not surprising that there

are a large number of studies on mutant models of glutamate function, including glutamate receptor subtype mutants.[108] Of the ion channel subfamily of glutamate receptors, the NMDA receptor has received most attention. Of the G-protein–coupled metabotropic subfamily of glutamate receptors, most work has been done with mGluR5 mutants. Studies have furthermore addressed other components of glutamate function in the brain, such as glycine or excitatory amino acid transporters (EEATs).

Ion Channel Glutamate Receptors. Based on the "hypoglutamatergic hypothesis" of schizophrenia, an NMDA receptor hypomorph was generated which expressed only 5%–10% of the NR1 subunit common to all NMDA receptor isoforms.[109] In contrast to complete knockout of this subunit, which is lethal,[110] these mice were viable and markedly hyperactive at baseline. Acute treatment with phencyclidine, at a dose which induced marked hyperactivity in wild-type controls, had no effect in the NR1 hypomorphs. Studies with antipsychotic drug pretreatment or microdialysis[109,111] revealed that reduced NMDA receptor function in these mice was not associated with enhanced dopaminergic activity.

These NR1 hypomorphic mice also showed disrupted PPI at rest[7–9] and other sensory gating deficits,[112,113] again similar to the effect of NMDA receptor antagonists in this species.[17] In contrast to the locomotor hyperactivity, however, treatment with both typical (haloperidol) and atypical antipsychotic drugs (olanzapine, risperidone, quetiapine, or clozapine) had similar effects in NR1 hypomorphs and wild-type controls.[111,114,115] Treatment with amphetamine reduced the already lower PPI in NR1 hypomorphs even further and at doses lower than those effective in wild-type mice, suggesting a hypersensitivity to dopaminergic disruption of PPI in these mice.[116]

In addition to the NR1 hypomorphic model, which had already generated substantial insight into the role of NMDA receptors in locomotor hyperactivity and PPI, other, more region-specific approaches were also used. Mice with specific ablation of the NR1 subunit in striatum by CreLox conditional gene targeting developed normally until postnatal day (pnd) 12.[117] After that, the mice developed abnormal gait and failed to grow, eventually dying at around pnd 21. At pnd 16, but not pnd 9, the pups showed marked locomotor hyperactivity. Surprisingly, treatment with both a dopamine D1 receptor agonist (SKF81297) or a D2 receptor agonist (bromocriptine) at this age reduced the hyperactive phenotype of these mice, with the opposite occurring in wild-type controls, ie, an expected increase in locomotor activity.[117] The authors discussed these paradoxical results in terms of a possible interaction of dopamine D1 and D2 receptors with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors in these mutant mice.[117] These almost complete but striatum-specific knockouts of NMDA receptor function contrast with other regionally specific models where little effect on motor function was observed. For example, using a complex combination of 4 genetic modifications, a region-specific (cortex, hippocampus and striatum), inducible and reversible NR1 knockout could be produced.[118] These animals showed normal locomotor activity in the open field.[118] A more regionally specific, but not inducible knockout similarly showed approximately 65% reduction of NR1 expression in the striatum but similarly no changes in locomotor activity in the open field.[119] Further cellular specificity was achieved by restricting the expression of mutated NR1 to dopamine D1 receptor–expressing cells only.[120] These mice showed no change in baseline locomotor activity or the locomotor hyperactivity induced by treatment with amphetamine or cocaine.[120] The relative lack of overt phenotype in these mice,[120] when compared with more complete striatum knockout mice[117] could be due to a lower extent of NMDA receptor hypofunction or its restriction to D1 receptor–expressing neurons.

Mice with mutations in members of the NR2 subunit group showed varying levels of altered behavior. For example, mice lacking the ε1 subunit (NR2A) were hyperactive in an open field, and this effect could be attenuated by treatment with the typical antipsychotic, haloperidol, or the atypical antipsychotic, risperidone.[121] In contrast, a mutation in the ε4 member of the NR2 subunit (NR2D) resulted in hypoactivity and reduced rearing in the mice.[122] Mice lacking the ε3 subunit (NR2C) appeared to have no behavioral phenotype.[123] However, compensatory upregulation of the expression of other subunits could play a role in this apparent lack of effect. For example, combined deletion of both the NR2A and NR2C subunit resulted in motor incoordination, where the single mutations had no such effect.[124]

A comprehensive comparison of NR2 mutant mice revealed changes in startle amplitudes and PPI depending on which subunit was targeted.[125] Startle was markedly increased in NR2B (ε2) heterozygous mice, but only a moderate increase was observed in NR2A (ε1) and NR2D (ε4) knockout mice, whereas NR2C (ε3) mutants showed no change in startle.[125] PPI was moderately increased in NR2B (ε2) heterozygous mice, with no change observed in the other NR2 subunit mutants.[125]

Compared with the NR1 and NR2 subunits of the NMDA receptor, much less is known about the NR3 subunit which is able to form a glycine-sensitive binding site in combination with the NR1 subunit (for references, see Brody et al[126]). There were no differences in PPI between double-transgenic, inducible NR3A overexpressing mice and wild-type controls PPI.[126] In NR3A knockouts, baseline PPI was significantly increased in males, but not females, at 3 weeks of age, when PPI is low in wild-type and heterozygous mice. With age, PPI in the controls and heterozygotes increased and a genotype

difference disappeared.[126] The sex specificity of the effect in NR3A knockouts may be related to an interaction of estrogen with PPI regulation and NMDA receptor function.[126]

Another way to indirectly affect NMDA receptor function is to specifically target glycine-mediated binding mechanisms on the NR1 subunit. Two different point mutations in the glycine site on the NMDA receptor resulted in a 5-fold and 86-fold reduction of glycine binding.[127] Mutant mice with the modest reduction showed no overt changes in locomotor activity, stereotypy or PPI, but increased startle. In contrast, mice with the large reduction of glycine binding died within 48 h after birth.[127] Compound heterozygous mice, which carried one allele of each mutation and showed an approximately 90% reduction of glycine affinity, were behaviorally hyperactive.[128] MK-801 treatment caused no further increase in these double mutants, but the effect of amphetamine tended to be reduced. The antipsychotics, haloperidol and clozapine, had no effect in the hyperactive double mutants.[128] These mice may represent a model of severe NMDA receptor hypofunction which is resistant to pharmacological inhibition.[128]

Extracellular glutamate concentrations are tightly regulated by glutamate transporters on glial cells. Therefore, in the context of enhanced glutamatergic tone associated with the hypoglutamatergic model of schizophrenia, mice with disrupted glutamate transporter function may be a promising experimental and drug development tool. Specifically, mice deficient in the glial glutamate and aspartate transporter (GLAST, also known as EEAT1) showed locomotor hyperactivity in a novel open field but not in the home cage.[129,130] This genotype effect could be blocked by haloperidol and the mGlu2/3 receptor agonist, LY379268, at doses which had no effect in wild-type controls.[129] MK-801 treatment induced enhanced locomotor hyperactivity in GLAST knockout mice.[129] Startle amplitudes were reduced, but PPI was not significantly different to controls.[130]

Compared with the NMDA receptor, far less is known about ''psychosis-like'' behavioral changes in mice with genetic modification of AMPA function. One extensive study characterized AMPA knockout mice in a battery of tests[131] and found the animals to be hyperactive in a novel environment but not in the familiar home cage. MK-801 treatment had no effect on locomotor activity in AMPA knockouts. Finally, these mice showed normal startle amplitudes but moderately reduced PPI.[131] These data extended previous observations in these animals (for references, see Wiedholz et al[131]) and confirmed a range of functions of the AMPA receptor.

Metabotropic Glutamate Receptors. The group I metabotropic glutamate receptors includes mGluR1 and mGluR5 and has received considerable interest because of their possible role in schizophrenia.[132] The first study on mGluR1 knockout mice revealed a severe motor coordination deficit.[133,134] Despite this, spontaneous locomotor activity was normal, but the mice showed significantly increased responding to amphetamine treatment.[135] These mice showed disrupted baseline PPI, but no significant changes in startle amplitude or habituation.[136] The PPI disruption was not affected by pretreatment with the dopamine D2 receptor antagonist, raclopride, but the mood stabilizer, lamotrigine, tended to increase PPI more in mGluR1 knockouts than in wild-type controls.[136] This was interpreted as indicating a potential role of the mGluR1 in bipolar disorder rather than schizophrenia.

Mice with mutations in the mGluR5 receptor did not show the same motor coordination deficits as mGluR1 knockouts and were normally active at baseline.[137] However, cocaine at doses which induced locomotor hyperactivity in controls had no effect in mGluR5 knockouts.[137] PPI showed a modest disruption in mGluR5 knockout mice in one study[138] but a more severe deficit in another study.[139] Parametric studies investigated the influence of different experimental conditions on the severity of the PPI deficit in these mice.[139–141] Thus, a similar extent of disruption was observed in mGluR5 knockouts on either a C57BL/6 or 129Sv genetic background, and startle amplitude was significantly increased in both cases, despite the C57BL/6 mice showing higher baseline PPI and lower startle than 129Sv mice.[139] The earlier PPI study in mGluR5 knockout mice was done with animals on a CD-1 outbred genetic background, which may explain the more moderate disruption observed.[138] Indeed, a more robust disruption of PPI was attained when the mutation on a CD-1 background was backcrossed onto a C57BL/6 background.[142] In this line of mGluR5 knockouts, MK-801 had no effect on PPI at doses which reduced PPI in wild-type controls to levels even lower than those seen in the knockouts.[142] Further parametric analysis revealed that the genotype difference in PPI was similarly seen using different PPI modalities (eg, light or tactile stimuli) and was not caused by altered responses of the mutants to the prepulse nor by changes in the prepulse-pulse temporal relationship or deficits in hearing.[139]

Surprisingly, when mGluR5 knockout mice were tested after acute pretreatment with the typical antipsychotic, raclopride, the atypical antipsychotic, clozapine, the mood stabilizer, lamotrigine, or the 5-HT2A receptor antagonist, M100,907, none of the treatments appeared to have any effect, despite being used at doses which reversed pharmacological disruptions of PPI in control experiments.[140] However, in a later study, it was shown that chronic treatment with clozapine could ameliorate the PPI deficit.[143] In that study, the mGluR5 knockouts showed a modest locomotor hyperactivity at baseline and were hypersensitive to the effect of MK-801. Chronic

clozapine treatment also reversed the baseline locomotor hyperactivity.[143]

Compared with mGluR1 and mGluR5 mutants, much less is known on behavioral changes in mice with modifications of other metabotropic glutamate receptors. mGluR2 receptor knockout mice showed normal startle and PPI[144] but were slightly hyperactive in a novel open field.[144] The acute effect of cocaine on locomotor activity was approximately doubled in mGluR2 knockouts compared with controls.[144] Much of the other available work on mGluR2 and mGluR3 receptor knockouts has been done in the context of development of mGluR2/3 receptor agonists which may be beneficial in schizophrenia by counteracting hyperglutamatergia caused by reduced NMDA receptor function.[145] For example, amphetamine and phencyclidine (PCP) dose dependently induced locomotor hyperactivity with little difference between mGluR2 knockouts and C57BL/6 wild-type controls.[146] The novel mGluR2/3 receptor agonist, LY379268, dose dependently reduced spontaneous locomotor activity only in wild-type mice but not mGluR2 knockouts.[146] In addition, LY379268 reduced both amphetamine- and PCP-induced locomotor hyperactivity in wild-type mice but not in mGluR2 knockouts.[146] The possibility was discussed that mGluR2/3 agonist drugs exert their effects essentially by a generalized reduction of locomotor activity, both at the level of baseline activity and PCP-induced hyperactivity and, thus, have the potential of significant side effects.[146,147]

Comparison of mGluR2[148] and mGluR3 receptor knockout mice[149] showed that the latter receptor was not involved in the action of the mGluR2/3 receptor agonist drugs.[146] Interestingly, however, the mGluR3 knockout mice showed a number of behavioral changes. For example, unlike mGluR2 knockouts, mGluR3 knockouts were slightly hyperactive at baseline and had a reduced response to treatment with PCP but not amphetamine.[146] In contrast, the direct effect of the mGluR2/3 agonist was greater in mGluR3 knockout mice than in wild-type controls. These differences in the pharmacology of behavior between mGluR2 and mGluR3 knockout mice could be related to the cellular localization of the 2 receptors, with mGluR2 receptors being directly involved in presynaptic modulation and dampening of excessive glutamate release but mGluR3 receptors being localized more distinctly and potentially not involved with negative feedback regulation.[146]

A comprehensive parallel study on the action of another novel mGluR2/3 receptor agonist, LY404039, compared mGluR2, mGluR3, and mixed mGluR2/mGluR3 knockouts.[150] There was no significant difference in baseline activity or the effect of a high 7.5-mg/kg dose of PCP between wild types and any of the knockouts. The increase in ambulation induced by this dose of PCP was attenuated by the mGluR2/3 agonist in wild-type mice and mGluR3 knockouts but not in mGluR2 knockouts and combined mGluR2/mGluR3 knockouts.[150] Treatment with clozapine or risperidone also blocked the effect of PCP, but this effect was similar in wild-type and combined double knockouts, suggesting that these antipsychotics acted independently from mGluR2 or mGluR3 receptors.[150] It should be noted that the effect of these high doses of antipsychotics on baseline behavior was not reported, and therefore, a generalized sedative effect in this experiment cannot be excluded. LY404039 also inhibited the hyperlocomotion induced by amphetamine.[150] Interestingly, in mGluR2 and particularly mGluR2/mGluR3 double knockouts, the effect of amphetamine appeared to be reduced.

In addition to providing clues about the pharmacological mechanism of novel antipsychotic compounds, these studies have also described behavioral changes in mGluR2 and mGluR3 receptor knockouts. A recent report showed that dopamine D2 receptor signalling was upregulated in these mice by 67-fold and 17-fold, respectively, as measured by a GTPγS assay. This was associated with a marked elevation of dopamine D2 receptors in the high-affinity state in both mutant lines and could explain some of the altered responses to psychotropic drug stimuli, such as amphetamine and PCP.[151]

Taken together, studies on behavioral changes in mice with disruption of specific components of dopaminergic and glutamatergic neurotransmission, have shown the complexity of seemingly simple behaviors such as baseline locomotor activity levels or PPI and provided important clues to begin to unravel these regulatory pathways.

Schizophrenia "Risk" Gene Models of Psychosis

A large number of previous studies have suggested many risk genes in schizophrenia. However, recent meta-analyses have produced a more limited list, including 24 variants in 16 genes (*APOE*, *COMT*, *DAO*, *DRD1*, *DRD2*, *DRD4*, *DTNBP1*, *GABRB2*, *GRIN2B*, *HP*, *IL1B*, *MTHFR*, *PLXNA2*, *SLC6A4*, *TP53*, and *TPH1*).[1,152] Of these, 4 were proposed as having a "strong degree of epidemiological credibility (*DRD1*, *DTNBP1*, *MTHFR*, and *TPH1*)."[1] Dopamine D1 receptors and other dopamine receptors (*DRD1*, *DRD2*, and *DRD4*) have been discussed in previous sections of this review. Dysbindin (*DTNBP1*) is described below (the "Dysbindin" section). *MTHFR* encodes for 5,10-methylenetetrahydrofolate reductase which is indirectly involved in homocysteine metabolism and methylation processes and may be involved in negative symptoms of schizophrenia.[153] However, as yet, mice with mutations in this pathway have not been tested for locomotor hyperactivity or PPI disruption. Finally, with respect to tryptophan hydroxylase 1 (*TPH1*), the identified polymorphism does not appear to have a functional effect.[1] Moreover, while this isoform of the enzyme may play a role in PPI

regulation in early neurodevelopment,[154] several studies have shown it to be nonneuronal in adulthood (eg, [155,156]) and *Tph1* knockout mice do not show changes in serotonin levels in the brain.[157]

Several other genes have been identified by genetic association studies as potentially involved in the development of schizophrenia, but it is beyond the scope of this article to review the evidence for the strength of these associations. Even if these proposed candidate genes were not included in a recent meta-analysis,[1] the often large amount of literature on mutant mouse models for these genes justified inclusion in this review.

Dysbindin

The dysbindin gene (*DTNBP1*) has been proposed as one of the most promising candidate genes in schizophrenia.[1,11,158] This protein is the receptor for dystobrevins, a family of proteins originally characterized as required for maintenance of muscle integrity and function.[159] The *sandy* (*sdy*) mouse has a deletion of 2 of the exons of the dysbindin gene[160] and has therefore emerged as a naturally occurring dysbindin knockout.[158]

Sdy mice were originally compared with DBA/2J mice for behavioral characterization and were found to be less active and with lower levels of dopamine, but not glutamate, in the cerebral cortex, hippocampus, and hypothalamus.[161] Other studies failed to find clear differences between the genotypes in psychosis-like behaviors,[162,163] including PPI (although no data were shown[160]) or reported that locomotor hyperactivity induced by acute treatment with a single 2.5-mg/kg dose of amphetamine was about 50% less than in DBA wild-type controls.[164] Altered dopaminergic and glutamatergic activity was suggested in *sdy* mice by observations on dopamine/metabolite ratios or kinetics of transmitter release.[165,166] The significance of these neurochemical findings remains to be established with more detailed drug testing in *sdy* mice, eg, the effect of NMDA receptor antagonists. Recently, the *sdy* mutation was studied after backcrossing on a C57BL/6 genetic background.[167] These animals were hyperactive in the open field, but no drug studies or PPI were reported as yet.[167]

Taken together, the *sdy* mice represent some behavioral phenotypes with relevance to schizophrenia, but in general, the data on psychotic-like behaviors are too limited to draw firm conclusions.

Neuregulin 1

Because a genome-wide scan study first identified neuregulin 1 as a candidate study for schizophrenia,[168] several mutant mouse models have been generated to investigate its role in behavior.[169,170] Neuregulins are a family of growth factor proteins which are involved in neurodevelopment at a number of levels and interact with specific tyrosine kinase receptors, the predominant one being *ErbB4*.[171,172] There are 4 neuregulin genes, and alternative splicing is able to generate several neuregulin 1 isoforms which all contain a transmembrane domain and share a common epidermal growth factor (EGF)-like signalling domain.[170–172] In addition, types I and II neuregulin 1 share an immunoglobulin domain which is not present in type III.

Although homozygous knockout of neuregulin 1 is developmentally lethal, heterozygous mice are viable and develop normally.[168] Several studies showed that mice heterozygous for a mutation in the transmembrane domain are mildly hyperactive when placed in a novel open field.[168,173–175] Pretreatment with a moderate dose of clozapine reduced this hyperactivity to the level of wild-type mice, where the treatment had no effect. The result could therefore not be explained by nonspecific sedative effects of clozapine.[168] Despite the baseline locomotor hyperactivity, the additional hyperactivity induced by amphetamine, phencyclidine, or MK-801 was not different between transmembrane domain heterozygotes and wild-type controls.[175] On the other hand, treatment with tetra-hydrocanabinol (THC), the main psychoactive component of cannabis, suppressed locomotor hyperactivity more in mutants than in controls[176] although the difference in baseline activity may be a complicating factor in the interpretation of this result. Thus, the neuregulin 1 mutants "started" from a higher baseline, but after THC treatment reached levels of locomotor activity, no different from controls.[176] Such methodological considerations do not negate an enhanced sensitivity of neuregulin 1 mutants to cannabis-like compounds, but illustrate how baseline behavioral differences between genetically modified mice and wild-type controls could be an important factor to influence the extent of drug effects observed.

Measurement of PPI in neuregulin 1 transmembrane heterozygous mutant mice showed a moderate disruption in one study[168] with only a nonsignificant tendency found in another study[176] and no difference with wild-type controls in a third, recent study.[175] Close inspection of the data reveals that the baseline PPI level in wild-type mice could play a role in the differences between these studies with a significant PPI disruption in neuregulin 1 hypomorphs (average around 48%) occurring when baseline PPI in wild-type mice was 60%–65%. In contrast, a trend for a disruption of PPI in mutants (50%–55% PPI) was found where baseline PPI was about 60% in controls and no change in hypomorphs was found where baseline PPI was 45%–50%.[168,175,176] The reasons for these baseline effects are unclear but could be due to differences in housing or handling procedures or the degree of backcrossing onto a congenic C57BL/6 background. Where observed, the disruption of PPI was not reversed by clozapine treatment.[168] Treatment of the mice with THC elicited significant increases in PPI in neuregulin 1 hypomorphs but not in wild-type controls although

the level of PPI in both genotypes was similar after treatment.[176] Thus, neuregulin 1 hypomorphs may be more sensitive to the effects of cannabis-like compounds but not to a level where they reach PPI values significantly greater than controls. Treatment with apomorphine, amphetamine, or MK-801 reduced PPI to a similar extent in neuregulin 1 hypomorphs and controls.[175] Treatment with the 5-HT1A receptor agonist, 8-OH-DPAT, induced a disruption of PPI in neuregulin 1 hypomorphs, but not in wild-type controls.[175] However, this treatment also elicited a significant reduction of startle amplitude in the mutants only, and the PPI result should therefore be interpreted with caution as sedation may have occurred. Interestingly, also THC elicited a reduction of startle in neuregulin 1 hypomorphs but not wild-type controls,[176] perhaps, pointing toward an increased sensitivity of these mice to the sedative actions of cannabinoid and/or serotonergic compounds.

Mice with mutations in the EGF-like domain replicate the hyperactive phenotype of those with deletion of the transmembrane domain.[168,177] These animals showed reduced PPI although this difference with the controls was not significant.[177] The effect of MK-801 and amphetamine was included in these studies, but the drugs did not induce a clear disruption of PPI nor had differential effects between the genotypes.[177]

Mice heterozygous for mutations in the immunoglobulin domain were not hyperactive in an open field.[178] However, locomotor activity was reduced in the mutants, but not in wild-type mice, after treatment with 1 mg/kg of clozapine[178] (the same dose used in transmembrane domain and EGF domain mutants[168]). This result was interpreted as a greater sensitivity to the ''sedative effects'' of clozapine in the mutant mice but was also seen as evidence for the ''schizophrenia-like phenotype'' of these animals.[178] It would be interesting to test if neuregulin 1 mutants display enhanced sensitivity to other antipsychotic drugs with less sedative effects in mice than clozapine.

Mice heterozygous for deletion of type III neuregulin 1 showed normal motor activity in the open field. There were also no differences with wild-type controls in startle amplitude, but PPI was profoundly disrupted in these mice.[179] Because of the high rate of smoking in schizophrenia and because type III neuregulin 1 has been shown to be important for cholinergic function, the mice were treated chronically with nicotine. This 6-week treatment increased PPI in mutants and normalized their PPI deficit to control levels.[179]

Mutant models for the neuregulin 1 receptors, ErbB2, ErbB3, and ErbB4 are also available. Mice heterozygous for *ErbB2* or *ErbB3* showed no changes in spontaneous locomotor activity in the open field.[180] Just like neuregulin 1 transmembrane hypomorphs, the *ErbB4* heterozygous null mice tended to be hyperactive in an open field, although the difference with wild-type controls in this case was small. These mice did not have significant PPI disruption.[168] To avoid the problem of lethality due to disrupted cardiac development in homozygous mutants, a brain-specific knockout of *ErbB4* was generated by using a Nestin-Cre/Lox approach on a C57BL/6 background.[181] These mice showed spontaneous locomotor hyperactivity at 3 weeks of age but were hypoactive in the home cage and in an open field at 9–10 weeks of age.[181] However, a similar mutation on an FVB background showed no change in open field locomotor activity,[182] again showing how important methodological factors, such as background strain, may influence the results.

Proteolytic processing of neuregulin 1 can be mediated by β-site amyloid precursor protein cleaving enzyme 1 (BACE1).[169,183] Therefore, BACE1 mutant mice may potentially display psychotic-like behavior mediated by altered levels or activity of neuregulin 1. A comprehensive behavioral phenotyping study, indeed, showed that homozygous BACE1 knockouts, but not heterozygotes, display marked disruption of PPI, enhanced novelty-induced spontaneous locomotor hyperactivity, and markedly increased MK-801-induced locomotor hyperactivity.[184] Pretreatment with a moderate dose of clozapine had no effect on startle or PPI in wild-type controls and caused only a mild reduction of locomotor activity. In contrast, in BACE1 knockouts, clozapine attenuated the PPI deficit and blocked the enhanced novelty-induced locomotor hyperactivity.[184]

Another enzyme involved in neuregulin 1 cleavage is Aph1B/C-γ-secretase (Aph1BC).[185] This proteolytic enzyme was found to be expressed in high levels in frontal cortex, hippocampus, and cerebellum in adult mouse brain. *Aph1BC* knockouts showed normal baseline motor activity and startle responses but disrupted PPI.[185] Treatment with MK-801 induced an even further disruption of PPI in the knockouts, compared with much more modest effects in the wild-type controls. The disruption of baseline PPI could be blocked by treatment of the mice with either 1 mg/kg of clozapine or 1 mg/kg of haloperidol.[185] These antipsychotic results suggested altered dopaminergic activity in these mice. Indeed, amphetamine-induced locomotor hyperactivity was significantly greater in *Aph1BC* knockouts whereas dopamine turnover, as measured by HVA+DOPAC/dopamine ratio, was enhanced in the ventral striatum of these mice.[185]

The large number of neuregulin 1 isoforms and the variety of changes seen in the available mutant mice so far illustrate the wide range of brain mechanisms that neuregulin is involved in and the many different possible ways altered neuregulin expression could be contributing (or not) to the development of psychotic features. Clearly, further characterization of existing mutant models and the generation of further, more sophisticated models of altered neuregulin function, such as inducible knockouts, are needed to resolve these issues.

DISC1

After the discovery of DISC1 as a potential schizophrenia candidate gene,[186,187] some of the earliest animal studies on its potential role included the detection of natural mutations in different mouse strains. Thus, it was shown that 129S6/SvEv mice carry a 26-bp deletion in the *mDISC1* gene, leading to reduced levels of one isoform of the protein.[188] Other commonly used strains, such as the C57BL/6J, BALB/c or DBA/2J, did not show this mutation. Congenic C57BL/6, into which the mutation was backcrossed, showed deficits in a working memory task but no locomotor hyperactivity or disruption of PPI.[188] Further studies confirmed the presence of the deletion in all 129 mouse substrains,[189] an important finding as virtually all embryonic stem cell lines used for gene-targeting studies are derived from substrains of the 129 strain. Therefore, if such newly generated mouse lines are studied on their original 129 genetic background or if not backcrossed for a sufficient number of generations on a congenic background, such as C57BL/6, any possible behavioral effect would have to be interpreted taking the DISC1 mutation into account. Indeed, some of these mice could be considered models of epistatis, ie, where multiple mutations are present at the same time.

Two further mouse lines with DISC1 mutations were generated by ENU mutagenesis and backcrossing onto a C57BL/6 background.[190] Both these new lines, 100P and 31L, showed disruption of PPI, although more so in 100P mice.[190] These more severely affected mice also responded to treatment with the antipsychotics, haloperidol and clozapine. The 100P mice furthermore also showed higher spontaneous locomotion and rearing in an open field.[190]

In order to study the role of reduced DISC1 function on behavior, straightforward knockout or knockdown models were considered less useful because of the multiexon nature of the *DISC1* gene and the resulting complex pattern of multiple isoforms.[191] Therefore, a transgenic approach has been used by a number of groups to generate more subtle genetic modifications similar to those observed in humans. For example, forebrain-specific expression of dominant-negative truncated DISC1 under the control of the calcium-calmodulin–dependent kinase II promoter in C57BL/6 mice resulted in hyperactivity in the open field and slower habituation but only minor differences in PPI.[191] A tamoxifen-inducible and reversible mutant line on a C57BL/6 background expressing only the C-terminal portion of DISC1 showed no changes in open field activity, but no specific psychosis testing was done.[192] Constitutive expression of the well-defined *DISC1* schizophrenia risk allele resulted in truncation of *DISC1* transcription and reduced levels of the protein in the hippocampus and prefrontal cortex.[193] These mice displayed deficits in working memory and executive functioning, but again specific psychosis-like behavioral models were not reported.[193] Another elegant inducible transgenic approach coupled to the CAMKII promoter introduced mutant human *DISC1* predominantly into forebrain neurons.[194] In these mice, expression of the mutant transgene did not result in either changes in spontaneous hyperlocomotion in the open field, in startle or in PPI. On the other hand, spontaneous locomotor activity measured over a 22-h period was markedly higher in male but not female mutants.[194] It was concluded that "Increased motor activity in male transgenic mice is an important feature of current pharmacological models of schizophrenia because hyperlocomotion has been correlated with the positive symptoms of schizophrenia."[194] However, as discussed in the "Locomotor Hyperactivity" section, in the absence of pharmacological characterization, the mechanism underlying the spontaneous hyperlocomotion in these male mutants, and the relevance of this behavioral change for psychosis, remains unclear.

Behavioral changes in DISC1 mutant mice have been suggested to be related to altered interaction in these animals of DISC1 and phosphodiesterase-4B (PDE-4B).[190,195] Indeed, PDE-4B knockout mice showed significantly reduced PPI although startle was enhanced in these mice[196] which could have influenced the result. With respect to open-field locomotor hyperactivity, PDE-4B knockouts showed a modest hypersensitivity to a high dose, but not a low dose, of amphetamine.[196] Other studies have suggested that the effects of DISC1 deficiency are mediated by the GSK3β and β-catenin signalling pathways.[197] It is then interesting to note that mice with altered expression of GSK3β showed little changes in psychosis models (see "Akt-GSK3β signaling" section). Similarly, forebrain-specific β-catenin knockout mice, which showed 60%–70% depletion in the forebrain, showed little change in spontaneous open-field locomotor activity or the effect of amphetamine.[198] β-catenin transgenic mice displayed hypolocomotion but no difference in the acute or chronic effects of amphetamine.[199]

These mutant lines generated by different genetic modification mechanisms, thus, produced a wide variety of rather subtle psychosis-like phenotypes. Unfortunately, the behavioral test battery used in the studies was dissimilar and at times incomplete, and therefore, substantial further characterization work remains to be done to determine sufficient details of behavioral alterations in these animals.

Akt-GSK3β Signaling

In addition to being a possible target for lithium treatment,[200] Akt-GSK3β signaling has been implicated in the development of schizophrenia.[3,4] PPI levels in a range of different mouse strains (C57BL/6J, C57BL/

10J, C3H/HeJ, BALB/cByJ, FVB/NJ, DBA/2J, 129/J, A/J, 129/SvJ, and AKR/J) correlated positively with GSK3 activity but not protein levels.[201] *Gsk3β*$^{+/-}$ haploinsufficient mice showed reduced exploration but normal spontaneous locomotor activity and PPI.[202–204] However, in one study, these mice showed a blunted hyperactivity response to a 1- or 2-mg/kg dose of amphetamine,[205] suggesting Akt-GSK3β as a second major signaling pathway of dopamine receptor activation in addition to adenylate cyclase/protein kinase A mechanisms.[206] However, a subsequent detailed behavioral characterization could not replicate this genotype difference.[204] These authors found no difference between *Gsk3β*$^{+/-}$ mice and wild-type controls in amphetamine-induced locomotor hyperactivity, apomorphine-induced stereotyped climbing, baseline PPI, or startle habituation.[204] The authors concluded that their results did not support a role of GSK3β as an important factor in schizophrenia or a major target for lithium action. Also other behavioral observations in the *Gsk3β*$^{+/-}$ model were not consistent between the different research groups.[202,204,205] The reason for these marked discrepancies is unclear and highlights again that small differences between experimental conditions between laboratories may result in marked variations in experimental outcome.

In contrast to *Gsk3β*$^{+/-}$ mice with reduced Akt-GSK3β signaling, transgenic mice constitutively overexpressing an active mutated form of GSK3β were hyperactive in the open field and habituated slightly slower.[207] These animals also showed higher startle responses and reduced startle habituation, although PPI was not reported.[207] Other factors involved in Akt-GSK3β signaling and lithium effects have also been studied in genetically modified mice. Mice deficient in Akt1, for which GSK3β is a substrate, did not display changes in baseline PPI or in the effect of MK-801. By contrast, treatment with amphetamine at a dose which did not affect PPI in wild-type controls, significantly disrupted PPI in *Akt1*$^{-/-}$ mice. There were no genotype effects on startle in any of the conditions.[208] These authors discussed these behavioral results in the context of a possible link of changes in Akt-GSK3β signaling with reelin (see "Other Genetically Modified Mice With Relevance to Psychotic-Like Behaviours" section) and neuregulin-1 (see "Neuregulin 1" section) in schizophrenia. Such links suggest that epistatic interactions could be important and future studies may be able to address this using double-mutant models.

Overall, the available studies show some behavioral and neuropharmacological changes in mice with altered activity of the Akt-GSK3β signaling pathway. However, the studies were sometimes inconsistent and mostly focused on lithium effects and Bipolar Disorder.[209,210] Therefore, no conclusions as to major deficits in behavioral models related to psychosis can be drawn as yet.

The 22q11.2 Deletion Syndrome and Its Associated Genes

Several studies have shown that deletion of the 22q11.2 chromosomal region (22q11.2 deletion syndrome, 22q11.2DS), which includes at least 40 genes, is associated with schizophrenia.[211–213] *Df1*/+ mice are hemizygous for deletion of a region syntenic with the human deleted region.[214] These animals show normal exploratory activity in an open field and normal startle habituation. However, average startle amplitudes were increased, whereas PPI was moderately disrupted.[214,215] The 22q11.2 chromosomal region contains several genes of interest for schizophrenia, such as catechol-O-methyltransferase (*Comt*) and proline dehydrogenase (*Prodh*). In a way, *Df1*/+ mice are a model of epistatic interaction because multiple genes which were subsequently associated with schizophrenia are deleted in these animals.[214]

The Pro/Re strain of mice display altered proline metabolism and enhanced plasma proline levels. These mice were shown to carry a missense mutation in *Prodh* which resulted in the production of a mutant Prodh protein with reduced enzymatic activity. These animals showed normal spontaneous locomotor activity and startle, but PPI was moderately disrupted.[216] However, it was argued[214] that the PPI disruption in these homozygous mice was less severe than that seen in heterozygous *Df1*/+ mice, indicating that *Prodh* was unlikely to be solely responsible for the effect of 22q11.2DS on sensorimotor gating. The same is true for mice with deletion of the transmembrane palmitoyltransferase, *ZDHHC8*, which showed a small reduction of PPI in females but not males.[217] Interestingly, these animals also showed locomotor hypoactivity and a virtual absence of an effect of a high, 0.4-mg/kg dose of MK-801, which induced locomotor hyperactivity in the wild-type controls.[217] The latter marked phenotypic change would need to be further investigated by scoring associated behaviors, such as stereotypy, and testing lower doses of MK-801 as well (see figure 1). Potentially, these results point at a novel regulatory mechanism for NMDA receptor–mediated locomotor hyperactivity.

Following from the early studies with *Prodh* knockdown mice,[216] the same mutation was introduced into the 129/SvEv strain through backcrossing.[218] Similar to *ZDHHC8* mutant mice, these animals were hypoactive in the open field and showed reduced responding to acute treatment with a high but not a moderate dose of MK-801. In marked contrast to the result with MK-801, locomotor hyperactivity induced by a moderate or a high dose of amphetamine was significantly greater in Prodh-deficient mice.[218] It will be interesting to assess the effect of lower doses of MK-801 in these animals to confirm that the apparent hyposensitivity is not caused by the emergence of stereotyped behaviors (see figure 1).

Prodh-deficient mice showed marked upregulation of *Comt* in the cortex but not striatum.[218] Amphetamine

treatment increased dopamine release in both brain regions, but this effect was significantly potentiated in Prodh-deficient mice in the cortex but not striatum.[218] To further analyze the possible epistatic interaction between *Prodh* and *Comt*, the effect of the Comt inhibitor, tolcapone, was studied in the *Prodh* mutants. Tolcapone pretreatment potentiated the effect of a low dose of amphetamine on locomotor activity and induced a disruption of PPI in the mutants but not wild-type mice.[218] These results explain why in a number of behavioral testing paradigms, the changes in Prodh-deficient animals have been mild or inconsistent. Only if the upregulated Comt activity is also targeted, done here with tolcapone treatment, is a clear phenotype unmasked. These elegant experiments are therefore also a good example of how assessing only baseline behaviors may miss effects of genetic modifications.

In parallel to the studies on Prodh/Comt interactions, several studies have assessed the effect of mutants with altered activity of *Comt*, the gene for which is also located in the 22q11.2 region[213] and which was identified in the recent schizophrenia risk gene meta-analysis.[1] Normal frontal cortical dopaminergic activity relies strongly on intact activity of COMT, and molecular genetic studies have suggested an association of aberrant COMT activity and psychiatric illnesses.[1] Mice with deletion of *Comt* displayed a 2- to 3-fold increase in endogenous dopamine levels in the frontal cortex, but not the striatum,[219] and changes in the locomotor hyperactivity response to amphetamine dependent on the dose and time after injection.[220] The relatively small extent of behavioral changes in these mice was attributed to the presence of dopamine transporter activity which constitutes the most important mechanism to maintain extracellular dopaminergic tone. Therefore, the effects of cocaine and the dopamine transporter inhibitor, GBR12909, were investigated.[221] Both drugs induced the expected locomotor hyperactivity, but these effects were attenuated in male, but not female COMT knockout mice.[221]

To specifically study the common *Val/Met* single-nucleotide polymorphism found in several human studies, recently a transgenic mouse was generated which carries the human *COMT-Val* variant as opposed to the wild-type *COMT-Leu* mice.[222] In humans, the *Val* form leads to increased COMT activity and the *COMT-Val* transgenic mice can therefore be considered as a model of enhanced COMT function, as opposed to COMT knockout. As part of a large behavioral phenotyping study, the authors found no changes in baseline locomotor activity or in amphetamine-induced locomotor hyperactivity.[222] Startle responses were reduced, but PPI was not significantly different between transgenic animals and controls. By contrast, in COMT knockouts, startle reactivity was increased, again, however, without changes in PPI.[222]

In order to further identify the critical genes involved in 22q11.2DS and the behavioral changes in *Df1/+* mice, a series of mutants with overlapping deletions were generated.[223] Single-gene mutants were then generated to assess more specific gene modifications. It was concluded from this approach that the previously reported PPI deficits in *Df1/+* mice[214,215] could be explained by haploinsufficiency of 2 genes, *Tbx1* and *Gnb1l*,[223] with the disruption being greatest in *Tbx1* heterozygous mice.[223] However, others suggested that *Tbx1* deletion was more important for the heart abnormalities and craniofacial development defects in 22q11.2DS.[224] These latter authors found no disruption of PPI in $Tbx1^{+/-}$ mice. Instead, mice haploinsuffient for *Lgdel*, a large deletion which overlaps with the 22q11.2 deletion, showed significant disruption of PPI.[224] The reasons for these discrepancies are unclear but could be related to the different background strains used in these studies.[223,224]

Another gene which maps to the 22q11.2 region is the Nogo receptor 1 (RTN4R) which regulates axonal growth.[225] Similar to *ZDHHC8* mutants, *Rtn4r* mutant mice were hypoactive in an open field[225,226] but showed little change in PPI.[225] Despite the significant reduction of open field locomotor activity, the authors concluded that *RTN4R* was unlikely to contribute in a major way to schizophrenia.[225] Interestingly, mice deficient in Nogo-A (Rtn4), one of the ligands for Nogo receptor 1, were hyperactive in the dark phase, but not light phase, of the circadian cycle and showed a much greater amphetamine-induced locomotor hyperactivity response than wild-type controls.[227] PPI was not reported, and the relevance of these data for 22q11.2DS remains to be established.

Other Genetically Modified Mice With Relevance to Psychotic-Like Behaviors

Several other genes have been implicated in schizophrenia, related to pathophysiological aspects of the disease, neurotransmitter systems involved in antipsychotic drug action, as novel risk/susceptibility genes, or found serendipitously through random mutagenesis or chance and subsequent behavioral phenotyping, ie, a ''bottom-up'' approach.[12] This review article cannot include full details of all these additional genetic mechanisms potentially involved in schizophrenia, even though the available studies may contain important clues for future investigation.

In addition to dopaminergic involvement, a ''classical'' neuropathological mechanism in schizophrenia is represented by altered activity of gamma-aminobutyric acid (GABA) neurons in the brain.[228] Mice with genetically modified GABAergic activity show various psychosis-like behaviors,[229,230] and GABAergic drugs may be beneficial against sensorimotor gating[231] and cognitive deficits in schizophrenia.[232] Other work has focused on

the serotonin system.[233,234] Of the 14 serotonin receptors, several mutant models have shown changes in behavior with relevance to psychosis, such as altered motor activity or disruption of PPI.[50,235–240] Also the cholinergic system, particularly muscarinic receptors, has been the focus of many studies.[241,242] Knockout mice for all 5 muscarinic receptors have been investigated and have suggested important drug development targets for cognitive and psychotic symptoms of schizophrenia.[243,244]

Molecular genetic and postmortem studies have identified several other genes which could be associated with the development of schizophrenia. For example, several studies have shown reduced levels of brain-derived neurotrophic factor (BDNF) in the frontal cortex of patients with schizophrenia (for references, see Angelucci et al[245]). Consequently, studies have addressed psychosis-like behavior of BDNF mutant mice. Cocaine-induced hyperlocomotion was markedly reduced in BDNF heterozygotes compared with wild-type controls,[246,247] but the effect of amphetamine was increased[248] or prolonged.[249] In addition to constitutive changes in BDNF expression, more regionally and temporally specific modifications have been studied. In conditional BDNF knockout mice, BDNF deletion was restricted to forebrain areas, such as the frontal cortex, amygdala, and hippocampus.[250] These Emx-BDNF knockout mice showed normal startle and PPI but *reduced* spontaneous locomotor activity.[250] Further studies used a trigenic approach to generate inducible and conditional BDNF knockouts which were found to be hyperactive.[251–253] Two additional conditional BDNF mutants, generated by crossing floxed BDNF mice with 2 different tetracyclin transactivator–induced Cre-producing lines, showed moderate or near-complete BDNF depletion in hippocampus and cortical regions.[252] Similar to previous studies with other BDNF mutants,[254,255] both the conditional mutants in this study were hyperactive in a novel environment; however, it was also shown that this phenotype was only present in male mice and not in female mice.[252] The latter is an interesting observation not only because of its potential importance for gender differences in psychiatric illness but also because many behavioral studies in mutant mouse lines appear to test only male mice, a mix of male and female mice, or not indicate the sex of the animals. In further studies, rather than full or partial genetic deletion of BDNF gene expression, a particularly elegant model of altered BDNF regulation was aimed at reproducing the Val66Met single-nucleotide polymorphism observed in clinical populations.[256] *Bdnf*^{MetMet} animals showed normal BDNF levels in the brain but dysregulated BDNF release. Baseline locomotor activity was normal, but drug-induced locomotor hyperactivity or PPI were not reported.[256] Overall, this large variety of BDNF mutant models supports a role for this neurotrophin in behavioral models with relevance to schizophrenia. However, the information is still limited and much further characterization of these mice is needed.

Reelin (RELN) is a protein involved in axon guidance, dendritic spine morphology, and neural plasticity.[257,258] In postmortem brain of patients with schizophrenia, levels of RELN and *RELN* mRNA were decreased by about 50% in cortex and hippocampus.[259] The *rl*/+ heterozygous mouse has a reduction of reelin levels similar to that seen in schizophrenia[260,261] and displays reduced sensitivity to the locomotor hyperactivity-inducing effects of metamphetamine.[262] The *rl*/+ heterozygotes also displayed reduced baseline locomotor activity, an effect which could be reversed with chronic treatment with the atypical antipsychotic, olanzapine.[263] Only *rl*/*rl*-null mutants, but not *rl*/+ heterozygotes, showed disrupted PPI and startle habituation, and the authors questioned the validity of the *rl*/+ mice as a potential animal model of schizophrenia.[264] However, another study showed an age-dependent decrease of PPI,[265] but the genotype effect appears to be sensitive to environmental modulation. For example, the significant difference in PPI between *rl*/+ mice and wild-type controls was not observed when the animals were single housed (see Tueting et al[258]). Single housing leads to disruption of PPI in mice,[266] and indeed, PPI in wild-type controls was decreased by isolation housing to the level of *rl*/+ mice where there was no further decrease (unpublished, see Tueting et al[258]). In other studies, a PPI deficit could only be demonstrated in these mice with a cross-modal PPI protocol combining acoustic startle stimuli with tactile prepulses.[267] Furthermore, where wild-type mice showed the expected inverted U-shaped relationship between ISI and levels of PPI, with optimal intervals between 40 and 80 ms, in *rl*/+ mice, this relationship was skewed toward shorter intervals of 20–60 ms.[267] Considering the large variety of PPI protocols employed in the literature, this could have marked consequences for the interpretation of a particular genetically modified mouse line like *rl*/+ mice as a valid model for sensory gating deficits in schizophrenia. Clearly, these heterozygous mice display a subtle behavioral phenotype which appears to vary between research laboratories[258,268] and is dependent on behavioral test conditions. These findings add to the growing knowledge that external conditions, such as stress, housing, and handling, may have major effects of the results of behavioral genotyping and emphasize the importance of standardization of these factors between laboratories (see ''Methodological Considerations'' section and van der Staay and Steckler[18]).

Another neurodevelopmental factor is the nucleus receptor Nurr1, which is important for development of dopaminergic neurons. Nurr1 heterozygous mutant mice show reduced brain dopamine levels and enhanced spontaneous and stress-induced locomotor hyperactivity.[269] The effect of amphetamine or MK-801 to induce locomotor hyperactivity, over and above the already

existing increased activity, was not different between Nurr1 heterozygous mice and controls,[269] a result similar to our recent findings in neuregulin 1 heterozygous mice.[175] PPI was not different at baseline between the genotypes when the animals were group housed, but post-weaning isolation induced a disruption of PPI in the Nurr1 heterozygous mice, but not the wild-type controls.[270] This is an interesting example of gene-environment interaction, similar to discussed above for reelin heterozygous mice. It again emphasizes that housing conditions can significantly impact on the results and need to be reported in detail. Parallel studies on a similar Nurr1 heterozygous model confirmed these results.[271]

The phosphatase, calcineurin, has also been implicated in schizophrenia, and forebrain-specific knockouts of calcineurin have been generated.[272] These animals showed marked spontaneous locomotor hyperactivity and disruption of PPI and were more sensitive to low doses of MK-801, but not amphetamine.[273]

Finally, genetically modified mice for a variety of other factors which have been implicated in schizophrenia, such as Regulator of G-protein Signalling-4(RGS-4), neural adhesion molecule, and the LPA1 receptor, have shown behavioral changes in the locomotor hyperactivity or PPI domain.[274–278] In addition, several genetically modified mice have been generated in the course of basic studies into neural plasticity mechanisms, addiction, neurotransmitter regulation, stress, and hormonal modulation of behavior, and in many of these animals, changes in drug-induced locomotor hyperactivity or PPI disruptions have been found. These studies include a variety of factors, eg, angiotensin-converting enzyme,[279] oxytocin,[280] estrogen,[55,281] certain G-proteins,[57,282] pituitary adenylate cyclase–activating polypeptide(PACAP),[283] and Homer1.[284] However, in the absence of consistent molecular genetic evidence, the immediate relevance of these results for schizophrenia remains to be established.

Conclusions

The studies reviewed above suggest that a multitude of genetic mechanisms are directly or indirectly involved in (drug induced) locomotor hyperactivity and PPI disruption. This complexity not only reflects the exquisite intricacy of behavioral regulation but, similarly, and perhaps consequently, the multifactorial nature of psychotic features in schizophrenia. Clearly, further studies are needed to resolve these complex mechanisms.

Genetically modified mice, ranging from straightforward knockouts to sophisticated conditional modifications, have become a standard tool in neuropsychopharmacological research into the mechanisms involved in psychosis-like behavior. Locomotor hyperactivity, either at baseline or after treatment with psychoactive drugs, such as amphetamine or MK-801, and disruption of PPI, have become widely used behavioral tools to investigate the consequences of these genetic modifications in the domain of psychosis-like behaviors. The available literature reveals variability between laboratories in terms of pharmacological and methodological details of behavioral phenotyping strategies. It will therefore be important to aim for more comprehensive testing of mouse mutant models and better standardize methods and conditions. Nevertheless, the wealth of available data has provided essential new insight and mechanistic clues which could lead to new treatments or even prevention strategies for schizophrenia.

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