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Invited review

Mouse pharmacological models of cognitive disruption relevant to schizophrenia

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ABSTRACT

Schizophrenia is a debilitating cognitive disorder. The link between cognitive debilitation and functional outcome in patients with schizophrenia has prompted research to develop procognitive therapies. It is hoped that by improving cognition in these patients, their functional outcome will also improve. Although no established treatments exist as yet, progress has been made toward understanding how to evaluate putative compounds in the clinic. Genetic mouse models and pharmacological rat models of cognitive disruption are being developed that may help to evaluate these putative compounds pre-clinically. Considering the increased number of genetic mouse models relevant to schizophrenia, there is a need to evaluate pharmacological manipulations on cognition in mice. Here we review the current literature on mouse pharmacological models relevant to schizophrenia. In this review, we discuss where different pharmacological effects between rats and mice on cognitive tasks are observed and assess the validity offered by these models. We conclude that the predictive validity of these models is currently difficult to assess and that much more needs to be done to develop useful mouse pharmacological models of cognitive disruption in schizophrenia.

This article is part of a Special Issue entitled 'Schizophrenia'.

1. Introduction

1.1. Cognitive dysfunction in schizophrenia

Kraepelin (1896) first described as *dementia praecox* the disorder now known as schizophrenia. Schizophrenia carries a lifetime risk of 1% (Cannon and Jones, 1996), and has both a genetic and environmental etiology (lifetime risk for a dizygotic twin of a patient with schizophrenia is ~40% (Klaning, 1999; van Os and McGuffin, 2003). Traditional diagnosis of schizophrenia has been based on characterized positive and negative symptoms (Andreasen et al., 1997; Pearlson, 2000). Cognitive deficits are also observed in these patients however and are recognized as core to the disorder, correlating most closely with functional outcome (Green, 1996, 2006). Current treatments for schizophrenia are primarily efficacious at treating positive symptoms, with limited if any efficacy at treating negative or cognitive symptoms (Carter, 2005; Harvey and Keefe, 2001; Keefe et al., 2007; Mintz and Kopelowicz, 2007). Given the link between cognitive functioning and functional outcome, research has begun focusing on developing drugs to improve cognition in schizophrenia patients (Floresco et al., 2005; Green, 1996, 2006).

To address this great 'unmet therapeutic need' in schizophrenia, the United States National Institute of Mental Health sponsored several initiatives. These initiatives include: 1) the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) group (Marder, 2006; Marder and Fenton, 2004); 2) the Treatment Units for Research on Neurocognition in Schizophrenia (Buchanan et al., 2007); and 3) the Cognitive Neuroscience Treatment to Improve Cognition in Schizophrenia project (Carter and Barch, 2007). The MATRICS group developed a consensus clinical test battery (MCCB) in which positive data for a test compound could be approved as a procognitive treatment in schizophrenia by the Food and Drug Administration. TURNS was designed to select and evaluate potential procognitive candidates in the MCCB across several sites. CNTRICS was and is currently developing novel tasks from the field of cognitive neuroscience to be used in clinical neuroscience. Because these initiatives have focused primarily on assessing cognition in humans, while recognizing the need for animal models (Barch et al., 2009; Floresco et al., 2005; Geyer, 2010; Young et al., 2007, 2009), there has been little consensus from a preclinical perspective on developing animal models relevant to schizophrenia.

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1.2. Assessing the predictive validity of animal models of cognitive disruption in schizophrenia

One of the greatest difficulties in developing animal models of cognitive disruption in schizophrenia is that no drugs have been approved for treating these symptoms (Floresco et al., 2005; Geyer, 2010). Therefore, assessing the pharmacological predictive validity of an animal model of cognitive disruption in schizophrenia is problematic. The primary treatments for schizophrenia are antipsychotics, which primarily reduce psychotic symptoms. The effects of antipsychotic treatment on cognition continue to be debated. First generation antipsychotics (FGA) share a primary dopamine D2 receptor antagonist mechanism (Richelson and Souder, 2000) and have traditionally been thought to impair cognition in patients with schizophrenia (see review; Cassens et al., 1990). FGA-induced cognitive disruption may have contributed to studies suggesting the superiority of second generation antipsychotics (SGA), which have diverse actions on dopamine D2, 5-HT2A, and other receptors (Richelson and Souder, 2000). While some studies report no effects of FGA or SGA on cognition (Kunitachi et al., 2009; Nagai et al., 2009; Thomsen et al., 2009; Wang et al., 2007), other clinical trials (Harvey et al., 2003, 2004; Kern et al., 1998; Kern et al., 1999; Purdon et al., 2001; Velligan et al., 2002, 2003) and meta-analyses (Harvey and Keefe, 2001; Keefe et al., 1999) reported superiority of SGA over FGA for treating cognitive symptoms in schizophrenia. Lack of cognitive improvement from FGAs could be related to co-administration of anti-cholinergic drugs (Keefe et al., 1999; Paulsen et al., 1995; Spohn and Strauss, 1989), used to counter the extra-pyramidal side-effects of FGA, because cholinergic antagonists can impair cognitive performance (see below). Moreover, it has been suggested that the effects reported in some studies may have been biased by industry support (Heres et al., 2006), or methodological weaknesses (Harvey and Keefe, 2001). Other studies (Crespo-Facorro et al., 2009; Green et al., 2002; Harvey et al., 2005; Keefe et al., 2006; Rollnik et al., 2002) and meta-analyses (Mishara and Goldberg, 2004) have supported similar efficacy for FGA and SGA at improving cognition in schizophrenia. Several large-scale studies have reported the equal efficacy of FGA and SGA for treating cognitive disruption in schizophrenia (Jones et al., 2006; Keefe et al., 2007; Lewis et al., 2006). Several investigators and clinicians have questioned the real-term gains and clinical relevance of these significant effects of FGA and SGA on cognition (Heinrichs, 2007). For example, FGA and SGA improved patients ability to recall a 12-word list by a only a tenth of a word in these large-scale studies (Keefe et al., 2007). Such low effect sizes may have contributed to the lack of FDA approval for these antipsychotics being indicated as procognitive. While basic science studies in animal models related to schizophrenia have assessed the effects of FGA or SGA, rarely have the authors discussed the relevance of the low to moderate effects of these drugs in patients (Martinez and Sarter, 2008). This approach becomes a problem when the animal models show full reversals of cognitive disruptions with antipsychotics – drugs that show minimal improvement in cognitive symptoms in patients. While testing antipsychotics in mouse models of cognitive disruption is a valid approach, ideally the model would better predict the dose effect function for low levels of cognitive enhancement at lower doses of antipsychotics and cognitive-disrupting effects at higher doses (i.e. an inverted U-shaped dose function), as well as the lack of full reversals of cognitive impairment. Models showing low to moderate effects of antipsychotics on cognition may represent a "real life" scenario and enable the evaluation of add-on therapies with putative cognitive enhancers. This review will highlight studies on mouse pharmacological animal models of cognitive disruption in schizophrenia; paying particular attention to differential effects of FGAs and SGAs in the models, as well as when such treatments result in a full reversal of the cognitive deficits in the model. The predictive validity of such models will be evaluated (Geyer, 2006; Meyer et al., 2005; Young et al., 2009) in light of the low to moderate effects of these drugs in patients.

Acetylcholinesterase inhibitors (AChEIs) constitute another class of drugs that have mixed degrees of efficacy for improving cognition in schizophrenia. Several small-scale, open-label studies reported positive effects of AChEIs on cognition in schizophrenia (Bora et al., 2005; Buchanan et al., 2003; Mendelsohn et al., 2004; Stryjer et al., 2003), supported by some randomized double-blind trials (Buchanan et al., 2008; Schubert et al., 2006). The majority of larger double-blind randomized placebo designs (Chouinard et al., 2007; Fagerlund et al., 2007; Ferreri et al., 2006; Keefe et al., 2008; Lee et al., 2007; Mazeh et al., 2006; Risch et al., 2007; Sacco et al., 2008; Sharma et al., 2006) reported no improvement of cognition in patients with schizophrenia. In a meta-analysis, it was suggested that AChEIs may improve short-term memory and attention in patients with schizophrenia (Ribeiz et al., 2010). Given that a third of the studies in the meta-analysis were from small-scale, open-label trials, useful meta-analysis focused on large double-blind controlled studies would provide greater information on the effects of AChEIs on cognition in patients with schizophrenia. These studies are further complicated by the use of AChEIs as add-ons to FGA and SGA treatment. Further clarity on the effects of AChEIs on cognition in schizophrenia would aid the assessment of animal models of cognitive abnormalities in schizophrenia. In the present review, we will include animal models that have utilized AChEIs to assess the validity of the model. Hence, although the positive predictive validity of an animal model for cognitive deficits in schizophrenia cannot be assessed clearly based on the effects of AChEIs, it is possible to comment on the putative validity of some models. Until the first treatments for cognitive deficits in schizophrenia are developed, nicotine could also be used to assess the predictive validity of animal models because it can improve cognition in normal subjects as well as in patients with schizophrenia (for review see; Levin et al., 2006), especially for attention/vigilance (Smith et al., 2006). Without a clear pharmacological tool to assess positive predictive validity, however, 1) basing the manipulation used in the animal model on clear clinical evidence of pathology (e.g. decreased frontocortical area predicting working memory span capacity deficits in schizophrenia patients; Gutierrez-Galve et al., 2010); or genetic risk, and 2) using tasks with cross-species construct validity (Sarter, 2006) will be crucial to the refinement of animal models of cognitive disruption in schizophrenia (Floresco et al., 2005).

1.3. Rat and mouse models related to schizophrenia: species differences in pharmacological response?

Previously, we reviewed rat and mouse pharmacological and genetic models of disrupted cognition in schizophrenia with a specific focus on reviewing tasks with putative translational validity for the MCCB (Young et al., 2009). A species disparity is evident in approaches toward developing animal models of cognitive deficits in schizophrenia insofar as few pharmacological models are established for mice while few rat genetic models have been developed. This disparity has been discussed in other reviews of rodent cognitive testing and/or animal models related to schizophrenia (Brigman et al., 2010a; Neill et al., 2010; Robbins, 2002). While it has proven difficult to develop mutant genetic rat models, pharmacological models can be developed readily in either species. Species differences in pharmacological effects indicate that one cannot necessarily predict drug effects in mice based on the rat pharmacological literature (or vice versa), suggesting that more

emphasis needs to be placed on understanding the behavioral pharmacology of CNS drugs in mice, particularly for cognition. Mouse pharmacological studies will aid in drug discovery since a combined approach of molecular genetics and pharmacology will likely be required for drug development in schizophrenia. The proportion of one-to-one orthologues within G-protein-coupled receptors (GPCR) superfamily – which contain many targets for cognitive enhancement in schizophrenia – is only 70% between rat and mouse, with greater similarity between mouse and human (86%) compared to rat and human (79%) (Gloriam et al., 2007). Acknowledging and working around such differences in receptor characteristics between rats and mice would assist in CNS drug discovery (Geerts, 2009). These differences can manifest as different binding affinities, where for example the binding profile of amphetamine is similar in mice and man, but less so when compared to rats (Han and Gu, 2006). The behavioral effects of these differences can also be observed. A widely used cross-species test of sensorimotor gating in schizophrenia is prepulse inhibition (PPI) of startle, where a pulse-induced startle reflex is reduced if preceded immediately by a non-startling pulse (Braff and Geyer, 1990; Graham et al., 1975). Mice are less sensitive to the PPI-disruptive effect of dopamine D2 receptor agonists than are rats (Ralph-Williams et al., 2003, 2002; Ralph and Caine, 2005) while the D1 receptor plays a more important role in the modulation of PPI in mice compared to rats (Halberstadt and Geyer, 2011; Powell et al., 2003). Effects of other neurotransmitter systems on PPI also vary by species. For example, indoleamine hallucinogens such as psilocin and 5-MeO-DMT that act primarily on the serotonergic system increase PPI in mice (Halberstadt and Geyer, 2011) while decreasing PPI in rats (Krebs-Thomson et al., 2006). Further behavioral pharmacological differences are described elsewhere for PPI (Powell et al., 2009; Halberstadt and Geyer, 2011).

These species differences are less well understood for cognitive tasks pertinent to schizophrenia research, primarily because fewer pharmacological studies have been conducted in mice compared to rats. Thus, the potential pharmacological differences between rats and mice performing cognitive tasks should be considered when generating pharmacological mouse models of cognitive disruption in schizophrenia. For example, subchronic phencyclidine (PCP) administration to rats consistently produces deleterious effects on performance of the attentional set-shifting task (ASST) that are specific to the extra-dimensional (ED) shifting stage (Egerton et al., 2005; Goetghebeur and Dias, 2009; Goetghebeur et al., 2010; Rodefer et al., 2005). Subchronic PCP in mice (0.63 and 1.3 mg/kg, 5 days with testing occurring immediately after administration), however, impaired simple discrimination and reversal learning as well as ED shifting (Laurent and Podhorna, 2004). Although the mouse data are confounded by the lack of intradimensional (ID)/ED differences, perhaps because of the limited ID shifts used (see; Young et al., 2009), the differences in ASST performance with subchronic PCP between rats and mice indicate that further effort is required to assess pharmacological effects on mouse cognition. In the present review, we provide an overview of mouse pharmacological models of impaired cognition related to schizophrenia in order to outline what has been done to date and suggest directions for future pharmacological studies in mice.

2. Pharmacological mouse models of cognitive dysfunction in schizophrenia

Psychotomimetic drugs induce hallucinations and psychotic states, and exacerbate symptoms in patients with schizophrenia (Geyer and Vollenweider, 2008; Javitt and Zukin, 1991; Krystal et al., 1994; Malhotra et al., 1997a, 1997b). These drugs include dopaminergic agonists (e.g. amphetamine), glutamatergic antagonists (e.g. PCP), and cholinergic antagonists (e.g. scopolamine) and are often used in pharmacological rodent models of schizophrenia. For example, the glutamate hypothesis of schizophrenia is derived from evidence that acute administration of N-methyl-D-aspartate (NMDA) antagonists, including PCP and ketamine, produces schizophrenia-like symptoms in healthy humans (Javitt, 2004; Javitt and Zukin, 1991). Ketamine has since been used to induce a model of psychosis in normal volunteers (Abel et al., 2003; Krystal et al., 1994; Malhotra et al., 1996; Oranje et al., 2002), and to exacerbate symptoms in patients with schizophrenia (Malhotra et al., 1997a, 1997b). While the effects of psychotomimetics described above occur following acute treatment, subchronic or sensitizing regimens of drug treatment are also used to assess behavior after a washout period while drug is not on board, avoiding putative drug by drug interaction confounds (Jentsch et al., 1998; Jentsch and Roth, 1999; Martinez and Sarter, 2008; Neill et al., 2010; Young et al., 2009). Acute, subchronic, chronic, and sensitizing regimens of psychotomimetic administration will be covered below.

2.1. Pharmacologically induced disruption in learning and memory

Several paradigms exist with which to assess learning and memory in mice. Previously we assessed the validity of novel object recognition tasks, the Morris water maze (MWM), and the Barnes maze for assessing this domain in mice (Young et al., 2009). In the present review we will examine pharmacologically induced disruptions in additional tasks that may have some relevance to learning and memory. For example, NMDA antagonists have been evaluated in tests of step-down latency (long-term fear-related memory), as well as spatial and non-spatial object recognition (short- and long-term memory). Acute administration of the non-competitive NMDA receptor antagonist MK-801 (0.25 mg/kg) to mice impaired their ability to remember to refrain from stepping down from a platform onto a grid that had delivered a shock 24 h previously (Dall'Igna et al., 2003; de Oliveira et al., 2005). MK-801-induced hyperactivity at this dose may have confounded the step-down behavior of these mice, although these behaviors may be dissociable because chronic caffeine treatment (1 mg/ml in drinking water for 7 days) reversed the hyperlocomotor but not step-down latency (memory) effects of MK-801 (Dall'Igna et al., 2003). When administered at lower doses in another study however, MK-801-induced (0.01 mg/kg) disruption in step-down latencies was also attenuated with subchronic caffeine treatment (de Oliveira et al., 2005), complicating whether these activity/memory effects are dissociable. Further details are required to specifically address the dissociation of drug-induced effects on activity and memory in this paradigm.

Mandillo et al. (2003) examined the effects of subchronic (5 days) MK-801 treatment (0.3 and 0.6 mg/kg) in a novel task designed to assess both spatial and non-spatial object recognition. Consistent with subchronic PCP (5 and 10 mg/kg) and amphetamine (2.5 and 5 mg/kg), MK-801 impaired object recognition during a spatial, but not non-spatial challenge (Mandillo et al., 2003). The effects of these drugs were assessed the day after treatment cessation; hence it is unclear whether these effects on spatial memory were due to the animals going through withdrawal or a fundamental change in their cognitive capabilities induced by the drug. Another novel task to assess the effects of subchronic PCP (3 mg/kg on days 1–5, and 8–12 with a 3-day washout period) on spatial recognition memory was used by Thomsen et al. (2009). Subchronic PCP treatment impaired spatial recognition memory as measured by increased time spent in a previously unvisited arm with 0 min between forced sample arm and choice of arms. This effect was reversed by the novel α7 nicotinic acetylcholine receptor (nAChR) partial agonist (SSR 180711) and attenuated by the

antipsychotics clozapine and haloperidol (Thomsen et al., 2009). While additional dose–response studies may be needed to further validate this novel task and replicate these findings, the data from this study are compelling.

Two laboratories have demonstrated on several occasions that non-spatial long-term (24 h) object recognition performance was impaired following subchronic PCP (10 mg/kg for 10–14 days) administration in mice even after a 3-day washout period (Hashimoto et al., 2007; Kunitachi et al., 2009; Nagai et al., 2009; Wang et al., 2007). This subchronic PCP-induced deficit in performance was reversed via several mechanisms including treatment with the SGA aripiprazole but not the FGA haloperidol (Nagai et al., 2009), and the AChEI donepezil but not physostigmine (Kunitachi et al., 2009). Interestingly, a sigma-1 receptor agonist (SA4503) (Hashimoto et al., 2007) also reversed the subchronic PCP-induced deficit, while the sigma-1 receptor antagonist NE-100 blocked donepezil-induced improvement (Kunitachi et al., 2009). This administration regimen also impaired long-term (24 h) spatial memory for a single location, which was subsequently reversed by treatment with the AChEI galantamine and SGA risperidone, both of which were blocked by the dopamine D1 receptor antagonist SCH23390 (Wang et al., 2007). Interestingly SCH23390 and the serotonin 5-HT1A receptor antagonist WAY100635 blocked aripiprazole-induced reversal of the long-term memory deficit, but the dopamine D2 receptor antagonist raclopride did not (Nagai et al., 2009). Thus, dopamine D1 and serotonin 5-HT1A receptors may contribute to antipsychotic- and or AChEI-induced reversal of PCP-induced impairment of 24 h single item memory, while sigma-receptors may be important for AChEI treatment effects. Given that direct activation of sigma receptors also reversed this PCP-induced deficit, donepezil may be acting via this receptor. Evidence for direct cholinergic agonist-induced improvement in long-term memory also exists, via the α7 nicotinic acetylcholine receptor (Hashimoto et al., 2006). One problem with the interpretation of these studies however, is that neither the vehicle- nor PCP-treated mice in exhibited a preference (thus memory) for the novel object in several studies when compared with chance. Thus, with no evidence of a memory trace, it is unclear what the cognitive relevance would be of a significant difference between subchronic PCP and vehicle-treated mice. As discussed previously, neither risperidone nor AChEIs fully reverse memory deficits in schizophrenia, raising the possibility that these models may produce false positive results. The discrepancy between these preclinical data and the clinical data could exist however, because the novel object recognition paradigm utilized may not be assessing the same aspect of memory that is assessed in patients with schizophrenia (see below). Alternatively, the possibility remains that floor and/or ceiling effects may limit the opportunity to observe modest improvements in performance. The difference of FGA- and SGA-induced effects could reflect doses used, because low doses may be more efficacious for improving cognitive symptoms in patients with schizophrenia (Green et al., 2002). That said, the data on subchronic PCP administration and object recognition deficits in mice are promising by virtue of the number and consistency of observed effects.

Subchronic methamphetamine administration (1 mg/kg, 7 days with a 7-day washout period) also impaired 24 h delay long-term object recognition memory. This effect has so far been reversed by the SGA clozapine (Kamei et al., 2006), minocycline (Mizoguchi et al., 2008), the AChEI galantamine (Noda et al., 2010), and the γ-minobutyric acid (GABA)-A agonist baclofen (Arai et al., 2009), but not the FGA haloperidol (Kamei et al., 2006). In these studies, the vehicle-treated mice generally exhibited a preference for the novel object (suggestive of a memory for the familiar object) thus the methamphetamine-induced disruption in memory represents a genuine shift in behavior.

Scopolamine-induced disruption in cognition has primarily been utilized in the past as an animal model of Alzheimer's disease. Schizophrenia and Alzheimer's disease exhibit impaired cognition in overlapping domains, such as attention, memory, and executive functioning. In contrast with some PCP and methamphetamine models, acute administration is normally used in studies using scopolamine. Acute scopolamine (0.3–3.0 mg/kg) impaired novel object recognition (3 h delay) performance in Swiss mice (Dodart et al., 1997). Because methylbromide scopolamine (which does not exert CNS effects due to its blood brain barrier impermeability) did not affect novel object recognition performance (Dodart et al., 1997), it is likely that scopolamine-induced deficits were mediated centrally. Scopolamine- (0.63 mg/kg) induced deficits in novel object recognition performance (30 min delay) was attenuated with galantamine (10 mg/kg) treatment (de Bruin and Pouzet, 2006). Reversal of a scopolamine- (2 mg/kg) induced deficit in short- and long-term memory assessed in the novel object recognition task (1.5 and 24 h delay) has also been observed with caffeine (10 mg/kg) pretreatment (Botton et al., 2010). The predictive validity of scopolamine-induced deficits in this task as an animal model of schizophrenia is complex. While galantamine – and caffeine – do not necessarily improve cognition in schizophrenia, the former has been used only as an add-on therapy to FGA or SGAs. Thus, to fully explore this model, combining scopolamine with FGA or SGAs to impair novel object performance then reassessing galantamine or caffeine effects may provide a more complete model of a putative adjunctive treatment study.

While novel object recognition testing is common in part because of its rapidity of use, there are a number of potential difficulties in the interpretation of data that can limit the predictive validity of study results. As discussed here and elsewhere, novel object recognition is of course likely to assess short- (Mori et al., 2011; Niimi et al., 2008) or long-term memory (Hashimoto et al., 2007; Kunitachi et al., 2009; Nagai et al., 2009; Wang et al., 2007) depending upon the delay utilized in the protocol. Because of the possible contribution of other cognitive processes to performance however, researchers have suggested that novel object recognition specifically measures such processes, e.g. attention (Chuhan and Taukulis, 2006; Dere et al., 2008; Silvers et al., 2007), working memory (Benice and Raber, 2009; Yamada et al., 2011), episodic memory (Idris et al., 2010; McLean et al., 2010), and learning (Mori et al., 2011; Yamada et al., 2011). Thus, putting drug study results into context for human cognitive testing has been difficult and do not readily occur in other tasks such as the ASST or 5-choice serial reaction-time task (5CSRTT) discussed below that have greater established validity for specific cognitive domains (Young et al., 2009). The cause of the uncertainty over the exact cognitive process being measured may be the lack of goal-directed behavior of the animals, which is in contrast with the ASST and 5CSRTT. Although object (shape) recognition tasks exist in human procedures which require the recognition of shapes as being novel or familiar – and for which patients with schizophrenia exhibit deficits (Bozikas et al., 2006) – these human tasks have explicit instructions and thus the motivation for recognizing novel shapes is specifiable. Recognition of novel objects in the rodent version of the task is inferred by the animal spontaneously engaging with the novel object but there is no specifiable motivation for the animal to do so. The behavior is viewed as innate, thus changes to this behavior could indeed reflect memory or changes to that innate preference. Hence, pharmacological manipulations may in fact alter this spontaneous novelty preference of the animal as much as its memory for familiar objects, possibly confounding the interpretation of the data (Young et al., 2009). Nevertheless, such concerns can be addressed in novelty recognition tasks by including shorter delays, at which the animals demonstrate intact

novelty preference. With this control, an impairment at longer delays can be interpreted more confidently as being due to the delay and indicative of impaired memory (King et al., 2004; Wietrzych et al., 2005). Unfortunately few studies – and none reported here – incorporate such a control to confirm the delay-dependency of the effect. Future studies investigating animal models with relevance to schizophrenia using novelty recognition tasks would benefit from incorporating multiple measurements across different delay intervals.

Another task of learning and memory is the MWM. In the MWM, animals are in pool of opaque water with only one escape – a platform located just below the surface of the water. The MWM is therefore an aversively (stress) motivated spatial learning and memory task. While the MWM has several possible confounds to interpreting data including thigmotaxis (swimming near the wall) and floating behaviors (hence the need to measure path length to finding the platform as well as latency (D'Hooge and De Deyn, 2001), it has been used extensively to assess spatial learning and memory in mutant mouse models related to schizophrenia (Young et al., 2009). Fewer studies have been performed examining pharmacological challenges, however. Subchronic PCP treatment (0.5 mg/kg for 12 days) of mice in the MWM impaired spatial learning at a dose that did not affect swimming performance (although 2 and 4 mg/kg treatment did affect swimming; Beraki et al., 2008). Training in the MWM occurred during the final 4 days of treatment; hence performance may have been confounded by acute effects of PCP as well as withdrawal during probe sessions. Repeated clozapine treatment blocked the PCP-induced impairment, while haloperidol did not (Beraki et al., 2008). In a separate study, subchronic PCP (0.5–2 mg/kg for 7 days) impaired learning the MWM 24 h after PCP cessation (Beraki et al., 2009). This effect of PCP was measured as altered latencies to find the platform, however, while the path length taken by the mice did not differ. Given that 2 mg/kg adversely affected swimming performance (Beraki et al., 2008), it is possible that the increased latency was due to floating behaviors rather than impaired memory. There are now several human virtual reality versions of the MWM in which patients with schizophrenia have been tested (Folley et al., 2010; Weniger and Irle, 2008). To date the efficacy of SGA and FGA on improving performance in patients with schizophrenia have yet to be compared in such a paradigm, but such a study could prove very useful in assessing the predictive validity of the PCP/MWM model described above.

2.2. Pharmacologically induced disruption in executive functioning and attention

Many cognitive deficits apparent in patients with schizophrenia appear to be largely frontally mediated (working memory, attention, executive functioning, speed of processing), but object recognition (Yee, 2000) and MWM (de Bruin et al., 1994) performance are not frontally mediated (Barker et al., 2007; Hannesson et al., 2004a, 2004b) but rather involve the hippocampus and peri-rhinal cortex. For example, long- (24 h) but not short- (5 min) term memory assessed in mice using the novel object recognition task requires a functioning hippocampus (CA1 region; Hammond et al., 2004). Peri-post-rhinal lesions impacted both long- (24 h) and short-term (15 min) memory, although hippocampal lesions did not affect long-term memory in rats in this task (Winters et al., 2004). Lesion studies have determined that the hippocampus (Gerlai et al., 2002; Morris et al., 1982), habenula (Lecourtier et al., 2004), and fimbria-fornix (Liu and Bilkey, 2002) contribute to learning in the MWM.

There have been few pharmacological studies in mice in tasks that are putatively frontally mediated. As described above, Laurent and Podhorna (2004) assessed the effects of subchronic PCP (0.63 and 1.3 mg/kg, 5 days with testing occurring immediately after administration) in mice on the ASST. The ED shift and reversal learning components of the mouse ASST require the medial prefrontal and orbitofrontal cortices, respectively (Bissonette et al., 2008). The ASST procedure employed by the two groups differed however as Laurent and Podhorna (2004) used only one ID shift while Bissonette et al. (2008) used four, with the latter demonstrating an ID/ED shift indicating an attentional set was formed, although ID/ED shifts can be observed with one ID shift (DeSteno and Schmauss, 2008; Young et al., 2010). The lack of ID/ED shift would suggest that the PCP-induced impaired ED shifting, simple discrimination, and reversal learning in mice observed by Laurent and Podhorna (2004) may not reflect set-shifting deficits in patients with schizophrenia (Young et al., 2009), or consistency with reports on PCP-induced ED shifting deficits in rats (Egerton et al., 2005; Goetghebeur and Dias, 2009; Goetghebeur et al., 2010; Rodefer et al., 2005). While mice readily dig in bowls for a reward (as in the ASST), mice can also use visual cues and a touch-screen apparatus to perform reversal learning tasks (Bussey et al., 2001; Izquierdo et al., 2006), although ASST using this apparatus has not been successful to date (Brigman et al., 2005). Subchronic PCP (5 mg/kg twice daily for seven days with a 7-day washout period) did not affect reversal learning in this visual touch-screen paradigm (Brigman et al., 2009), which is consistent with several rat ASST studies in which no deficits in reversal learning were observed following PCP (Egerton et al., 2005; Goetghebeur and Dias, 2009; Goetghebeur et al., 2010; Rodefer et al., 2005). Reversal learning can be modulated in mice in the visual touch-screen via pharmacological or genetic inactivation of the serotonin transporter (Brigman et al., 2010b), suggesting that this assay is sensitive to detect experimental manipulations. Thus, more work is required to assess the effects of subchronic PCP in reversal learning paradigms in mice. Acute MK-801 (0.05 and 0.1 mg/kg) administration to mice impaired spatial reversal learning in a water T-maze, where the location of the escape platform was relocated to the other arm after the location was learned initially. MK-801-induced disruption of performance was reversed by the AChEIs physostigmine and donepezil, but not galantamine (Csernansky et al., 2005). These findings may relate to the primary action of physostigmine and donepezil as AChEIs because some studies suggest galantamine primarily acts as a direct nAChR agonist (Wilkinson et al., 2004). As described above, more information on the effects of FGA or SGAs on the AChEI-induced reversal of this MK-801-induced deficit would be required to fully explore this as an animal model of schizophrenia. Other tasks can be utilized to investigate NMDA-induced disruption of reversal learning including the serial reversal learning paradigm (Dickson et al., 2010).

In the 5CSRTT which assesses sustained attention (Carli et al., 1983; Humby et al., 1999), acute doses of PCP disrupted the performance of C57BL/6N (3 mg/kg) and DBA/2 (1.5 mg/kg) mice (Greco et al., 2005). The multivariate approach to measuring 5CSRTT performance enables the interpretation of pharmacologically induced changes in performance beyond that of altered attention however (Robbins, 2002). This PCP-induced impairment may have been driven by a general disruption of responding not specific to attentional processes, because premature and time-out responses were also affected. This PCP-induced effect was attenuated by administration of the metabotropic glutamate 2/3 agonist LY379268 (Greco et al., 2005), a current target for treating positive symptoms and cognitive disruption in schizophrenia (Patil et al., 2007). Acute amphetamine (1 mg/kg) also increased premature responding in C57BL/6J but not DBA/2J mice, and did not disrupt accuracy, omissions, or mean correct response latencies in either strain (Loos et al., 2010). Acute scopolamine (0.02–2 mg/kg) impaired attention in

several strains of mice (C57BL/6, DBA/2, 129/Sv, as well as C57BL/X129/Sv and C57BL/6XDBA/2 hybrids) in the 5CSRTT (de Bruin et al., 2006; Humby et al., 1999; Pattij et al., 2007). Scopolamine reduced accuracy, increased response latencies, premature responses, and omissions in second generation C57BL/6X129/Sv hybrid mice at doses as low as 0.08 mg/kg (de Bruin et al., 2006). Not all strains were identical in effect however, for example DBA/2 mice were hypersensitive to scopolamine-induced disruption in accuracy (affected at 0.1 mg/kg unlike C57BL/6 or 129/Sv mice) but their omission levels were unaffected (again unlike C57BL/6 or 129/Sv mice; Pattij et al., 2007). C57BL/6XDBA/2 hybrids were more sensitive to the scopolamine-induced detrimental effects of accuracy and omissions when compared with C57BL/6X129/Sv mice (Humby et al., 1999). These studies support evidence that DBA/2 mice may be an interesting strain to study in terms of poor cholinergic regulation for schizophrenia research (Singer et al., 2009; Stevens et al., 1996). Moreover, these studies support the notion that cholinergic antagonist-induced disruption of cognition may still be an appropriate model for deficits in schizophrenia (Friedman, 2004; Lieberman et al., 2008; Martin et al., 2004; Scarr and Dean, 2008; Terry, 2008). Interestingly, acute scopolamine (0.075 mg/kg) treatment to rats reduced accuracy and increased omissions, but did not affect premature responses or response latencies (Waters et al., 2005), although older rats exhibited slower latencies with scopolamine (0.03 and 0.075 mg/kg; Jones et al., 1995). In another study, PCP (1–3 mg/kg) affected all these measures in rats but also increased premature responding (Le Pen et al., 2003). Thus, while there are similarities between mouse and rat studies in the 5CSRTT, there are as many differences between the two species as within rat studies to date. In mice, the acute scopolamine-induced deficit in 5CSRTT performance was similar with that of PCP-induced deficit in terms of generalized disruption in performance rather than a specific effect on accuracy or omissions. Acute amphetamine selectively increased premature responding only. Thus, there have yet to be examples of pharmacological manipulations that have selectively impaired attentional measures in mice in the 5CSRTT with relevance to schizophrenia.

3. Discussion

There have been great strides accomplished in developing genetic mouse (Arguello and Gogos, 2010) and rat pharmacological models of cognitive disruption in schizophrenia (Young et al., 2009). Our understanding of mouse pharmacological models is far more limited, however (Brigman et al., 2010a). As reviewed here, although the number of studies in mice assessing pharmacological disruptions and improvements in tasks such as novel object recognition, MWM, reversal learning, and the 5CSRTT is increasing, more work needs to be done to further explore and validate these models. While it is tempting to assume there will be consistency between rats and mice in drug effects, the pharmacological and genetic differences between rats and mice in other behaviors such as PPI (described above; Geerts, 2009; Gloriam et al., 2007; Halberstadt and Geyer, 2011; Powell et al., 2009) suggest that we should be cautious with such assumptions. Thus, there is a need to understand the behavioral effects of drug manipulations in mice that produce neuropathological abnormalities consistent with schizophrenia (Behrens et al., 2008). Such knowledge will prove useful if future mouse models with susceptibility genes are combined with pharmacological or developmental models relevant to schizophrenia.

3.1. Future directions for mouse pharmacological models

In this review we describe various studies examining mouse pharmacological models of cognitive dysfunction in schizophrenia. The majority of these studies investigated the domain of visual learning and memory and assessing putative treatment effects, while there have been few studies examining the attention, reasoning and problem solving, or speed of processing domains identified by MATRICS as being impacted in schizophrenia. The procognitive efficacy of some drugs to treat these domains have been tested extensively in patients and to date have not resulted in approved medications and have yielded only low to moderate effects at best, e.g. antipsychotics at doses required to treat positive symptoms (Keefe et al., 2007; Mintz and Kopelowicz, 2007) and AChEIs as adjunctive therapy to antipsychotics (Chouinard et al., 2007; Fagerlund et al., 2007; Ferreri et al., 2006; Keefe et al., 2008; Lee et al., 2007; Mazeh et al., 2006; Risch et al., 2007; Sacco et al., 2008; Sharma et al., 2006). While we cannot assess the pharmacological predictive validity of a model directly given that no drugs have been approved for the procognitive treatment of schizophrenia, we have identified where several of these animal models were successfully treated with antipsychotic and AChEI administration (Kunitachi et al., 2009; Nagai et al., 2009; Thomsen et al., 2009; Wang et al., 2007). As discussed above, the procognitive efficacy of FGA, SGA, and AChEI drugs have been reported as weak at best. Ideally, an animal model of cognitive disruption in schizophrenia would model these weak effects, providing an opportunity for adjunctive therapies to be tested. While demonstrating weak procognitive effects of these drugs while assessing adjunctive would require large sample sizes, such studies are possible at least in rats (Horiguchi et al., 2011). From a practical viewpoint these studies may require too much effort when simply examining a mechanism of action in an animal model, but perhaps before a drug is moved into preclinical testing such larger scale studies should be completed. Thus, for many of the pharmacological mouse models described here with SGA- and AChEI-induced full reversal of cognitive deficits, further investigation is required if they are to be used to screen for procognitive drugs. Investing time and money into more complete preclinical models may offset the large cost of clinical trials to test treatment efficacy (Nolen et al., 2007).

It is important to note that animal models of cognitive disruption in schizophrenia are produced by 1) the measure (i.e. performance of a cognitive task) and 2) the manipulation (i.e. administration of drug to impair performance). The greater the cross-species translational validity the cognitive task has for measuring that domain in patients (e.g. construct validity), the higher the chances that the pharmacological effects observed in animal models will translate across species (Floresco et al., 2005; Moore, 2010; Sarter, 2004, 2006; Young et al., 2009). Moreover, the greater the validity the manipulation has to what causes impaired cognition in patients, again the higher the chances that the effects of a model will be consistent with patients with schizophrenia (Geyer and Markou, 2002; Markou et al., 2008; Moore, 2010; Young et al., 2009). Therefore, the procognitive effects of SGA and AChEIs described above could be due in part to the limited translational validity of the task (e.g. novel object recognition testing) for assessing memory as occurs in patients (Floresco et al., 2005; Moore, 2010; Sarter, 2004; Young et al., 2009). Thus, developing and validating mouse tasks with cross-species translational validity should be a priority (Moore). As mentioned previously, nicotine may be a useful tool with which to assess the predictive validity of animal models to detect improvements in cognition in normal subjects (for review see; Levin et al., 2006), and in patients with schizophrenia (Radek et al., 2010; Smith et al., 2006).

One further consideration is that a true model for cognitive disruption in schizophrenia should include treatment with a dopamine D2 receptor antagonist since it is extremely likely that cognitive treatment will be an add-on therapy to current antipsychotic medications (Buchanan et al., 2005; Marder, 2006; Young

et al., 2009). Such an inclusion of models assessing add-on therapies, in addition to combining genetic and pharmacological insults, may prove more fruitful for future tests of cognition enhancement in mice. Although a daunting experimental prospect, for applicability to the heterogeneous group of schizophrenia disorders, such studies may well be required in the future.

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