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Predictive validity of a MK-801-induced cognitive impairment model in mice: Implications on the potential limitations and challenges of modeling cognitive impairment associated with schizophrenia preclinically

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ABSTRACT

Cognitive impairment associated with schizophrenia (CIAS) is a major and disabling symptom domain of the disease that is generally unresponsive to current pharmacotherapies. Critically important to the discovery of novel therapeutics for CIAS is the utilization of preclinical models with robust predictive validity. We investigated the predictive validity of MK-801-induced memory impairments in mouse inhibitory avoidance (MK-IA) as a preclinical model for CIAS by investigating compounds that have been tested in humans, including antipsychotics, sodium channel blocker mood stabilizers, and putative cognitive enhancers. The atypical antipsychotic clozapine, as well as risperidone and olanzapine (see Brown et al., 2013), had no effect on MK-801-induced memory impairments. For sodium channel blockers, carbamazepine significantly attenuated memory impairments induced by MK-801, whereas lamotrigine had no effect. Nicotine, donepezil, modafinil, and xanomeline all significantly attenuated MK-801-induced memory impairments, but the magnitude of effects and the dose–responses observed varied across compounds. Clinically, only acute administration of nicotine has demonstrated consistent positive effects on CIAS, while inconsistent results have been reported for lamotrigine, donepezil, and modafinil; atypical antipsychotics produce only moderate improvements at best. A positive clinical signal has been observed with xanomeline, but only in a small pilot trial. The results presented here suggest that the MK-IA model lacks robust predictive validity for CIAS as the model is likely permissive and may indicate false positive signals for compounds and mechanisms that lack clear clinical efficacy for CIAS. Our findings also highlight the potential limitations and challenges of using NMDA receptor antagonists in rodents to model CIAS.

1. Introduction

Schizophrenia is a heterogeneous and complex psychiatric illness that affects roughly 1% of the worldwide population (Rossler et al., 2005). Patients who suffer from this debilitating disorder display psychopathologies that can be characterized by three broad symptom domains: positive symptoms, negative symptoms, and cognitive deficits. The last symptom domain, cognitive impairment associated with schizophrenia (or CIAS), is highly prevalent, affecting about 75–80% of patients (Meltzer et al., 1996), and has been suggested to be a better predictor of functional outcome and quality of life than the presence or severity of positive symptoms (Alptekin et al., 2005; Green et al., 2000; Velligan et al., 2000). Schizophrenia patients typically perform 1–2 standard deviations below healthy populations on measures of executive function, working and long-term memory, and attention (Harvey and Keefe, 2001; Heinrichs and Zakzanis, 1998; Keefe et al., 2011). There are currently no drugs with regulatory approval for CIAS, although numerous pharmaceutical and biotech companies are actively engaged in discovery and development efforts spanning a diverse set of targets in hopes of identifying novel therapeutic agents.

Crucial to the development of novel and efficacious drugs to treat CIAS, particularly in the early phase of drug discovery, is the identification of preclinical animal models that demonstrate robust pharmacological predictive validity. Predictive validity, one of the cornerstones in characterizing a model's validity (in addition to construct and face validity), can be defined as the ability of a model to accurately identify drugs with therapeutic effects in the targeted human patient population. Animal models that fail to demonstrate sufficient predictive validity, such that they wrongly predict false positive (type I errors) or false

Abbreviations: CIAS, cognitive impairment associated with schizophrenia; IA, inhibitory avoidance; MK-IA, MK-801 inhibitory avoidance; NMDA, N-methyl-D-aspartate; FDA, U.S. Food and Drug Administration; PCP, phencyclidine; IP, intraperitoneal; CNS, central nervous system; DHEA, dehydroepiandrosterone; Naive-IA, naive inhibitory avoidance; PANSS, Positive and Negative Syndrome Scale.

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negative (type II errors) results, are a detriment to the drug discovery process. False positive signals may lead to the costly development of compounds that ultimately fail in the clinic; false negative signals may lead researchers to abandon compounds that may hold therapeutic potential. While very few if any animal models can prospectively predict clinical efficacy of drugs with absolute accuracy, especially for complex psychiatric disorders like schizophrenia that are inherently difficult to model in non-human species, the ultimate goal is to utilize only those models that have demonstrated robust predictive validity.

A major obstacle to comprehensively evaluate the predictive validity of animal models for CIAS is that there is currently no FDA-approved drug available for this indication. Although a therapeutic standard is presently absent, available clinical results from controlled trials enable some assessment of the predictive validity of preclinical models, if only preliminarily. Atypical antipsychotics are the current standard pharmacotherapy for schizophrenia, and though they are effective in improving positive symptoms in most patients, they have only moderate effects on cognition at best (Crespo-Facorro et al., 2009; Keefe et al., 2007a, 2007b). Many mood stabilizers, like the sodium channel blockers lamotrigine and carbamazepine, are also frequently used off-label in schizophrenia patients as adjunctive treatments (Hosak and Libiger, 2002), particularly in those subjects who do not adequately respond to neuroleptics. Carbamazepine has not been empirically investigated for CIAS, but improvements on cognitive function in patients have been reported for lamotrigine (Goff et al., 2007; Zoccali et al., 2007). In addition to mood stabilizers, multiple classes of putative cognitive-enhancing or nootropic drugs have been clinically investigated for CIAS. These include wake-promoting agents like modafinil and H_3 receptor antagonists, as well as cholinergic modulators like donepezil, nicotine, and xanomeline. Of these examples, only nicotine has demonstrated consistent positive effects on CIAS across multiple clinical trials (Barr et al., 2008; Depatie et al., 2002; Hong et al., 2011; Quisenaerts, 2012; Smith et al., 2002, 2006), while mixed results have been reported for modafinil (for review, see Scoriels et al., 2013) and donepezil (see Thakurathi et al., 2013 for review). A positive signal for improvement in cognition in schizophrenic subjects has been reported for xanomeline, but only in one double-blind, placebo-controlled pilot study with a small sample size (Shekhar et al., 2008).

The objective of the studies presented here was to evaluate the predictive validity of using MK-801-induced cognitive impairments in mouse inhibitory avoidance (IA) as a preclinical model for CIAS. NMDA receptor antagonists, like PCP and ketamine, are known to elicit schizophrenia-like behaviors and cognitive impairments in healthy humans and exacerbate symptoms in schizophrenic patients (Ghoneim et al., 1985; Javitt and Zukin, 1991; Krystal et al., 1994; Lucy et al., 1959; Malhotra et al., 1997). In rodents, NMDA receptor antagonists produce behavioral disturbances suggested to mimic schizophrenia, including impaired sensorimotor gating (for review, see Geyer et al., 2001), reduced social interaction (for review, see Sams-Dodd, 1999), and importantly for CIAS research, neurocognitive deficits (for review, see Large, 2007). The memory-impairing effects of MK-801, a potent non-competitive NMDA receptor antagonist, in IA (MK-IA) are well documented (Benvenga and Spaulding, 1988; Brown et al., 2013; Jones et al., 1990; Parada-Turska and Turski, 1990; Venable and Kelly, 1990), yet the pharmacological predictive validity of the model for CIAS has not been thoroughly investigated nor established. We sought to systematically test the effects of atypical antipsychotics, sodium channel blocker mood stabilizers, and putative cognitive-enhancing drugs which have been tested clinically for effects on cognition in schizophrenia patients in MK-IA to enable an empirical assessment of the predictive validity of the model. Furthermore, no mood stabilizers have been investigated in this model, nor has donepezil, modafinil, or xanomeline (to the best of our knowledge). We also compared the effects of these drugs in the MK-IA model against those reported in the naive-IA paradigm (i.e., non MK-801-challenged) to better understand if the pharmacological-induced disease model (MK-IA) provides greater sensitivity with respect to predictive validity compared to the non-disease model (naive-IA).

2. Materials and methods

2.1. Animals

Male CD1/ICR mice (Charles Rivers Laboratories, USA), weighing between 30 and 40 g at the time of testing, were used. Mice were group-housed 10 per cage (24 cm W × 47 cm L × 15 cm H, equipped with standard bedding and nesting material) in climate-controlled rooms and maintained on a 12 h light/dark cycle (lights on from 6:00 to 18:00 h). Food and water were available ad libitum. All experiments were approved by the AbbVie, Inc. Institutional Animal Care and Use Committee and conducted in a facility accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care.

2.2. Drugs

(+)-MK-801 hydrogen maleate, clozapine, carbamazepine, (−)-nicotine hydrogen tartrate salt, and donepezil hydrochloride monohydrate were obtained from Sigma-Aldrich (St. Louis, MO, USA). Lamotrigine and xanomeline oxalate were obtained from Tocris (Bristol, UK). Modafinil was obtained from Sequoia Research Products (Oxford, UK). (+)-MK-801 hydrogen maleate, (−)-nicotine hydrogen tartrate salt, donepezil hydrochloride monohydrate, and xanomeline oxalate were prepared in sterile water. Lamotrigine and modafinil were prepared in 5% dimethyl sulfoxide/95% Cremophor EL (20% v:v in sterile water). Carbamazepine was prepared in 5% dimethyl sulfoxide/95% (2-hydroxypropyl)-β-cyclodextrin (45% w:v in sterile water). Clozapine was prepared in 0.3% tartaric acid and pH adjusted to 4.0–5.0 with NaOH. All compounds were administered in solution and dosed at a volume of 10 ml/kg body weight.

2.3. Inhibitory avoidance

Mice were trained and tested in the MK-801 step-through inhibitory avoidance paradigm as described previously (Brown et al., 2013). Experiments were conducted across two consecutive days: mice were trained on the first day (training day) and then tested 24 h later for memory retention (test day). Mice that did not transfer within 60 s during the training trial were excluded from experiments (training day cut-off criterion). Shock intensity was set at 0.3 mA, 1 s duration. During the test session, a latency cut-off criterion was set at 180 s. Mice that did not cross within this pre-specified time period where given a maximal transfer latency of 180 s.

Clozapine (0.1, 0.3, 1 mg/kg), lamotrigine (3, 10, 30 mg/kg), carbamazepine (12.5, 25, 50 mg/kg), nicotine (0.3, 1, 3 μmol/kg), donepezil (0.25, 0.5, 1 mg/kg), modafinil (16, 32, 64 mg/kg), and xanomeline (5, 10, 20 mg/kg) were administered i.p. 40 min before the training session. Doses were chosen based on those reported in the literature to have either procognitive or antipsychotic-like effects in rodent preclinical models. Mice were then challenged with MK-801 (0.1 mg/kg, administered i.p.) 20 min later (or 20 min pre-training). MK-801 was given pre-training only, and not both pre-training and pre-test, as a prior internal experiment (data not shown) did not indicate that the drug-induced impairment was due to state-dependency. The dose of MK-801 used produced a robust and consistent impairment in memory retention while having minimal motoric effects (e.g., hyperactivity). It is understood that appreciable drug-induced changes in activity level during the test session (e.g., hyper or hypoactivity) can confound the interpretation of results in the IA test due to non-cognitive factors. In the studies presented here, drugs were given pre-training only (or 24 h pre-test), so it is highly unlikely that sufficient drug concentrations would still be present during the test session to confound transfer latencies due to motoric side-effects.