Neuropharmacology 62 (2012) 1168–1174

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

Reversal learning and attentional set-shifting in mice

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ARTICLE INFO

Article history:
Received 10 January 2011
Received in revised form
8 March 2011
Accepted 9 March 2011

Keywords:
Reversal learning
Mouse
Set-shifting
Orbital frontal cortex
Prefrontal cortex

ABSTRACT

Schizophrenia is a complex developmental disorder that presents challenges to modern neuroscience in terms of discovering etiology and aiding in effective treatment of afflicted humans. One approach is to divide the constellation of symptoms of human neuropsychiatric disorders into discrete units for study. Multiple animal models are used to study brain ontogeny, response to psychoactive compounds, substrates of defined behaviors. Frontal cortical areas have been found to have abnormal anatomy and neurotransmitter levels in postmortem brains from schizophrenic patients. The mouse model has the advantage of rather straightforward genetic manipulation and offers numerous genetic variations within the same species. However, until recently, the behavioral analyses in the mice lagged behind the primate and rat, especially with respect to testing of frontal cortical regions. Current reports of mouse prefrontal anatomy and function advocate the mouse as a feasible animal model to study prefrontal cortical function. This review highlights the most recent developments from behavioral paradigms for testing orbital and medial prefrontal cortical function in pharmacological and genetic models of human schizophrenia.

This article is part of a special issue entitled 'Schizophrenia'.

1. Introduction

Cognitive rigidity is a common behavior symptom of many developmental disorders, including autism, Tourette syndrome, Rett syndrome and schizophrenia, as well as neurodegenerative disorders of Parkinson's, Alzheimer's and Huntington diseases (Baddeley et al., 2001; Elliott et al., 1995; Gauntlett-Gilbert et al., 1999; Hill, 2004; Josiassen et al., 1983; Pantelis et al., 1999; Traykov et al., 2007; Verte et al., 2005). Patients that suffer frontal lobe deficiencies can easily learn and follow individual rules, but have great difficulty modifying their responses to new rules (Cools et al., 2000; Jacobs and Anderson, 2002; Shamay-Tsoory et al., 2004). For example, schizophrenic patients do not adapt normally to changes in their environments, especially in social and emotional contexts, and they exhibit an inability to modify responses in formal testing situations (Bowie and Harvey, 2006; Elliott et al., 1995; Leeson et al., 2009; Pantelis et al., 1999). Performance deficits are observed on the Wisconsin Card Sorting Test (WCST), in which the subject must sort a series of cards dependent upon changing rules, such as suit and color (Berg, 1948; Nelson, 1976). Patients can learn simple rules for sorting the cards, but they are unable to change established behavior once the relevant category changes (Egan et al., 2001; Elliott et al., 1995; Prentice et al., 2008). In addition, these patients are impaired in learning simple reversal tasks, in which the cues signaling correct and incorrect responses are switched (Leeson et al., 2009; Murray et al., 2008; Waltz and Gold, 2007). Thus, patients with different neuropsychiatric disorders display similar impairments in reversal learning and attentional set-shifting, suggesting that multiple neurotransmitters contribute to the common neural circuitry.

The components of the WCST and reversal learning employed in patient studies have been modified and adapted for research animal models. In agreement with the patient data, lesion studies in the primate and rat demonstrated that disruption in prefrontal (dorsal lateral prefrontal cortex) areas reduces the ability to shift between attentional sets (Birrell and Brown, 2000; Dias et al., 1996a, b). Similar conclusions about structural and functional analogies have been drawn about the parallel orbital frontal cortical (OFC) regions in primates and rats (Clarke et al., 2005; McAlonan and Brown, 2003; Schoenbaum and Roesch, 2005). More recently, reports on reversal and perceptual attentional set-shifting tasks in mice support analogous neural substrates in the laboratory mouse (Bissonette et al., 2010, 2008; Brigman et al., 2005; Colacicco et al., 2002; Garner et al., 2006). This review will highlight the current

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doi:10.1016/j.neuropharm.2011.03.011

literature of evaluating frontal lobe mediated cognition in the mouse, with a special emphasis on the reversal and set-shifting tasks, alterations in neural transmitters and genes associated with human schizophrenia.

Transgenic mice have provided a wealth of information about how individual genes regulate ontogeny and maintenance of the mammalian nervous system. Despite this, linking animal responses to human behavior has been challenging, invoking discussion on parallels of anatomy and behavioral testing and interpretation of the data (Gould and Gottesman, 2006; Nestler and Hyman, 2010). Whether the rodent has a prefrontal cortex has been questioned (Preuss, 1995; Uylings et al., 2003), with the consensus that analogous anatomy and function are present in rat and primate (Brown and Bowman, 2002; Groenewegen and Uylings, 2010; Kolb, 1984; Kolb and Robbins, 2003). Similar cytoarchitecture and chemoarchitecture is described for the C57BL/6J strain of the mouse (Van De Werd et al., 2010). Over the past two decades, behavioral studies in the mouse have demonstrated that although significant strain differences are present, the laboratory mouse appears capable of performing many of the cognitive tasks tested in rats and non-human primates (Owen et al., 1997; Paylor and Crawley, 1997; Rossi-Arnaud and Ammassari-Teule, 1998).

2. Reversal learning

Reversal learning in mice has been evaluated by modifying methods initially designed for the rat (see (Floresco and Jentsch, 2011) for a current review of the rat literature), including spatial learning with mazes: Morris water, T-maze (Bannerman et al., 2003) and eight-arm maze (El-Ghundi et al., 2003); with a two-choice digging task (Bissonette et al., 2008; Colacicco et al., 2002; Garner et al., 2006); and with operant learning equipment, including the go/no-go (Kruzich and Grandy, 2004; Schoenbaum et al., 2003) and delayed non-match-to-position task (Krueger et al., 2006) or visual discrimination paradigms (Brigman et al., 2005; Bussey et al., 1997b; Chudasama and Robbins, 2003). The two-choice digging task and the touchscreen visual discrimination paradigm have been most popular, especially when assessing both reversal and attentional set-shifting abilities. Both tasks rely on stimulus-reward learning, with the reward being a morsel of food for the food-deprived subject. Reversal learning involves the OFC, dorsal striatum, and amygdala, while set-shifting requires intact medial wall structures (anterior cingulate, prelimbic and infralimbic cortex), amygdala and dorsomedial striatum (Birrell and Brown, 2000; Bussey et al., 1997a, 1997b; Kim and Ragozzino, 2005; McAlonan and Brown, 2003; Ragozzino, 2007; Schoenbaum et al., 2003; Stalnaker et al., 2007; Tait and Brown, 2007, 2008). Therefore, the evaluation of reversal learning and set-shifting within the same task can provide an informative framework for testing multiple areas in the frontostriatal circuitry.

For reversal learning, the mouse must learn to discriminate between two cues. In the touchscreen task, the subject is trained to select between two images, and correct choices are rewarded (Brigman et al., 2005; Bussey et al., 1997a). Once the mouse has reached criterion, usually 85% correct choices, the cues are reversed, such that the previously rewarded image is incorrect, and the previously incorrect image is now rewarded. Perseverative errors, those that are contextually inappropriate or an unintentional repetition of the response, as defined by Crider (Crider, 1997), are used as a measure of cognitive inflexibility. Unlike maze tasks, the touchscreen method requires little movement and can be used to evaluate mice with motor deficits (Morton et al., 2006). Data from multiple mouse strains, genetic mutants and pharmacological manipulations are forming a basis to validate the test as an animal model of prefrontal cognition.

3. Automated reversal learning using a touchscreen: effects of genetic variation

Common mouse strains have known behavioral differences due their unique genetic alleles and modifiers (Crawley, 2000; Crawley and Davis, 1982). The majority of cognitive testing is performed on the C57BL/6J (B6) line or congenic mice which have been backcrossed to the B6 background for at least 10 generations (Moy et al., 2008; Nadler et al., 2006). This initial touchscreen tests reported successful reversal learning in B6 adult males (Brigman et al., 2005). When compared to the inbred DBA/2J (DBA) strain B6 mice learn more slowly, requiring 10 daily sessions (of 30 trials/session) to reach criterion (85% correct) of the discrimination task, whereas the DBA mice completed the task in 5 sessions (Izquierdo et al., 2006). The reversal task normally poses a challenge for rodents and primates, and the B6 needed about 20 sessions (a two-fold increase) to reach criterion. However, the DBA mice completed the task in 5 sessions, the same number as for the discrimination. DBA mice were generally quicker in performing the task, with shorter latency per trial. The total numbers and types of errors were not reported, but the DBA mice did have fewer correction errors. As suggested by the authors, the attributes of each mouse line can be further investigated by using the B×D recombinant inbred mouse lines in which chromosomal segments from either B6 or DBA are selectively expressed in known patterns. The choice of genetic background can greatly influence behavioral outcome and is critical when comparing across studies.

The *REELIN* gene has been implicated in schizophrenia (Guidotti et al., 2000; Torrey et al., 2005). Reelin expressing cells in the frontal cerebral cortex are GABAergic interneurons that are hypothesized to be dysfunctional in schizophrenia. Multiple variants of the null alleles are available; however mice with two mutant alleles carry motor deficits that preclude cognitive behavioral testing. Mice harboring a single mutant allele on a mixed B6C3Fe background were assessed in the touchscreen reversal discrimination task. Mice with the mutant *reelin* allele were impaired on the reversal, but had normal acquisition (Brigman et al., 2006). Error analysis did not show evidence of perseveration. The same mouse line was evaluated in an operant task with visual stimuli, and the *reelin* mutant mice were not found to differ from control mice (Krueger et al., 2006). In the operant task, two *reelin* mutant mice were unable to reach criteria, possibly due to visual deficits that accompany the retinal degeneration present in the C3Fe background strain. Disparities in age or difficulty of the task may explain the conflicting results, as may the contributions of each of the background strains.

The majority of the reports with the touchscreen assay was performed with mice on the B6 background and evaluated the effects of individual genes that were associated with cognitive impairments in humans. In addition to the GABA system, the glutamatergic system may be dysfunctional (Clinton and Meador-Woodruff, 2004; Kim et al., 1980). While mice lacking the NMDA receptor 2A subunit (NR2A, gene:*Grin2a*) mice readily learned the instrumental behavior to obtain the reward and had no differences with acquisition or extinction, the mice showed abnormal discrimination performance and impaired reversal learning on the pair discrimination task, regardless of sex (Brigman et al., 2008). Mice missing a single *Grin2a* allele were similar to wildtype (B6) control mice, showing no deficit with the hapolinsufficiency.

Increased synaptic glutamate in a mouse missing GLAST (glial glutamate and aspartate transporter, excitatory amino-acid transporter 1, gene:*Slc1a3*) led to normal learning of the pre-training parts of the touchscreen task but inability to reach the 85% criterion for the pair discrimination, regardless of sex (Karlsson et al., 2009). Wildtype (B6) mice attained criterion within 22 sessions, but *Slc1a3* null mice reached only 80% correct trials after 60 sessions (days of