Available online at www.sciencedirect.com
ScienceDirect
Neurobiology of Learning and Memory 90 (2008) 90–102
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Olfactory discrimination learning in mice lacking the fragile X mental retardation protein

John Larson *, Daniel Kim, Roseanne C. Patel, Christina Floreani

Psychiatric Institute, Department of Psychiatry (M/C 912), College of Medicine, University of Illinois at Chicago, 1601 W. Taylor Street, Chicago, IL 60612, USA

Received 22 October 2007; revised 2 January 2008; accepted 8 January 2008
Available online 4 March 2008

Abstract

An automated training system was used to compare the behavior of knockout (KO) mice lacking the fragile X mental retardation protein with that of wild-type (WT) mice (C57Bl/6 strain) in the acquisition and retention of olfactory discriminations. KO and WT mice did not differ in the acquisition of a four-stage nose poke shaping procedure. In two separate experiments, mutant mice required substantially more training to acquire a series of novel olfactory discrimination problems than did control mice. The KO mice required significantly more sessions to reach criterion performance, made significantly more errors during training, and more often failed to acquire discriminations. Both KO and WT mice showed similar error patterns when learning novel discriminations and both groups showed evidence of more rapid learning of later discriminations in the problem series. Both groups showed significant long-term memory two or four weeks after training but WT and KO mice did not differ in this regard. A group of well-trained mice were given training on novel odors in sessions limited to 20–80 trials. Memory of these problems at two day delays did not differ between WT and KO mice. Tests using ethyl acetate demonstrated that WT and KO mice had similar odor detection thresholds.
© 2008 Elsevier Inc. All rights reserved.

Keywords: *Fmr1*; FMRP; Odor discrimination; Olfaction; Olfactory learning; Memory

1. Introduction

The most prevalent inherited form of mental retardation is the fragile X syndrome (FXS), a disorder caused by mutations of the fragile X mental retardation 1 (*FMR1*) gene (O'Donnell & Warren, 2002). In nearly all cases, the mutations involve a trinucleotide (CGG) repeat expansion in the 5′ untranslated region of the gene that leads to DNA methylation and transcriptional silencing. As a result, the *FMR1*-encoded protein, the fragile X mental retardation protein (FMRP) is absent in individuals affected by FXS. In some rare cases, point mutations within the protein-coding sequence or deletions of *FMR1* also result in FXS, indicating that the syndrome is indeed caused by absence of functional FMRP (Hoogeveen & Oostra, 1997). A mouse model for FXS has been developed by targeted mutation of the *Fmr1* gene; these *Fmr1* knockout (KO) mice lack expression of functionally intact FMRP (Bakker et al., 1994).

FMRP is an RNA binding protein that in brain is localized to neurons and is found in dendrites; the protein appears to regulate translation by binding to mRNAs in large messenger ribonucleoprotein particles (O'Donnell & Warren, 2002). An increasingly large body of evidence implicates FMRP in synaptic function (Antar & Bassell, 2003; Antar, Afroz, Dictenberg, Carroll, & Bassell, 2004; Antar, Li, Zhang, Carroll, & Bassell, 2006; Greenough et al., 2001; Muddashetty, Kelic, Gross, Xu, & Bassell, 2007; Nakamoto et al., 2007). Dendritic spines on neurons in brains from FXS patients exhibit immature morphology, suggesting that the protein is necessary for normal spine development and/or adult spine plasticity (Irwin, Galvez, & Greenough, 2000); these spine abnormalities are also

* Corresponding author. Fax: +1 312 413 4569.
E-mail address: jrlarson@uic.edu (J. Larson).

1074-7427/$ - see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2008.01.002

seen in *Fmr1* KO mice (Comery et al., 1997; Irwin et al., 2002). In isolated synaptoneurosome preparations, stimulation of metabotropic glutamate receptors (mGluRs) increases FMRP synthesis by activating its local translation (Muddashetty et al., 2007; Todd, Mack, & Malter, 2003; Weiler et al., 1997). Similar effects have been observed in cultured neurons (Todd et al., 2003) where mGluR stimulation also induces translocation of FMRP and *Fmr1* mRNA to dendrites and FMRP away from synapses (Antar et al., 2004) and induces the synthesis of PSD-95, a postsynaptic scaffolding protein, *via* an FMRP-dependent mechanism (Todd et al., 2003). Finally, mice lacking FMRP show enhanced long-term depression (LTD) in hippocampus (Huber, Gallagher, Warren, & Bear, 2002) and impaired long-term potentiation (LTP) in several cortical areas (Larson, Jessen, Kim, Fine, & du Hoffmann, 2005; Li, Pelletier, Perez Velazquez, & Carlen, 2002; Wilson & Cox, 2007; Zhao et al., 2005). However, LTP in hippocampus appears to be normal in the KO mice (Godfraind et al., 1996; Larson et al., 2005; Lauterborn et al., 2007; Li et al., 2002; Paradee et al., 1999).

Fmr1 KO mice are important tools for understanding how synaptic dysfunction in the absence of FMRP impairs cognitive function and cognitive development. Behavioral studies of these mice have shown deficits in aversively-motivated spatial learning and fear conditioning tasks (Brennan, Albeck, & Paylor, 2006; D'Hooge et al., 1997; Dobkin et al., 2000; Fisch, Hao, Bakker, & Oostra, 1999; Mineur, Sluyter, de Wit, Oostra, & Crusio, 2002; Paradee et al., 1999; Van Dam et al., 2000). However, the mild nature of the deficits observed in most cases suggest that either mice do not serve as ideal models of human cognition or that the tasks that have been used are not sensitive to the functional impairments caused by the absence of FMRP. It has been suggested that olfactory-guided tasks may be more appropriate tests of cognitive capacity in rodents (Otto & Eichenbaum, 1992; Slotnick, 1994; Staubli, Fraser, Faraday, & Lynch, 1987) and mutant mice in particular (Bodyak & Slotnick, 1999; Larson, Hoffman, Guidotti, & Costa, 2003; Larson & Sieprawska, 2002; Mihalick, Langlois, Krienke, & Dube, 2000). Therefore, the present study used an olfactory discrimination learning paradigm to compare learning and memory abilities in normal mice and mice lacking FMRP.

The present experiments were designed to address two main issues. First, can an appetitively-motivated olfactory discrimination paradigm be used to investigate cognitive and memory disabilities in mice lacking FMRP? With a few exceptions (Fisch et al., 1999; Moon et al., 2006; Yan, Asafo-Adjei, Arnold, Brown, & Bauchwitz, 2004), behavioral studies of cognition and learning in *Fmr1* knockout mice have used aversively-motivated tasks such as water mazes (Bakker et al., 1994; D'Hooge et al., 1997; Dobkin et al., 2000; Kooy et al., 1996; Paradee et al., 1999; Peier et al., 2000; Van Dam et al., 2000); or fear conditioning/shock avoidance (Bakker et al., 1994; Brennan et al., 2006; Dobkin et al., 2000; Paradee et al., 1999; Peier et al., 2000; Van Dam et al., 2000). The deficits that have been observed in these tasks have been subtle and some have not been readily reproducible. We show that it is possible to train *Fmr1* knockout mice on olfactory discriminations using an automated method. Second, do mice lacking FMRP differ from wild-type mice in learning olfactory discrimination problems? We find that *Fmr1* KO mice learn novel olfactory discrimination problems significantly more slowly than WT control mice. Long-term memory for the discriminations appears normal in the KO mice and their sensitivity to odors also appears similar to that of WT mice.

2. Materials and methods

2.1. Subjects

Subjects were male, *Fmr1* knockout (KO) mice (C57BL/6J background) born in our colony from stock originally obtained from Jackson Laboratories (Bar Harbor, ME) and male, age-matched, wild-type (WT; C57BL/6J) mice obtained from Jackson or born from breeders in our laboratory, all at least 2.5 months old at the onset of training. The KO mice were backcrossed at least 10 times into the C57BL/6J background. They were housed in groups of three or four in plastic cages in a climate-controlled animal colony on a normal 14:10 light:dark cycle. The mice were maintained on a water deprivation schedule with access to 1.0–2.0 mL water once per day for at least five days prior to and throughout training. This schedule reduced body weight by about 20% in the first few days but maintained the mice at a stable weight throughout the study. All testing was done during the light phase. All experiments were conducted blind with respect to genotype.

2.2. Apparatus

As described previously (Larson & Sieprawska, 2002; Larson et al., 2003; Patel & Larson, in press), the testing chamber was made of black acrylic and consisted of a straight alley 60 cm long and 10 cm wide. The two side (long) walls sloped upward and outward at an angle of 15° off vertical and were 30 cm high. The end walls were vertical. At each end ("East" and "West") of the alley were two cylindrical "sniff ports" (1.5 cm i.d.) for nose poke responses (2 cm from the floor and centered 5 cm apart) and a single small cup in the floor for water delivery. The two sniff ports at the West end of the alley were connected to individual air-dilution olfactometers for odor stimulus delivery; all of the sniff ports were equipped for photobeam detection of nose pokes. Odor and water delivery were controlled by electrically-driven, teflon-body solenoid valves (General Valve Co., Fairfield, NJ); a microcomputer (PC) detected infrared photobeam breaks and activated the valves under custom software control. The whole chamber was enclosed and the ceiling was equipped with an exhaust fan to remove odorants.

An air dilution system described previously (Larson & Sieprawska, 2002) was used to generate odorants. Bottles containing odorants (diluted to 25% in solvent) were located downstream of computer-operated control valves and flowmeters in order to minimize odorant contamination of these elements. The clean air supply (bottled zero air, AGA Gas Co., Lansing, IL) in each channel was run at 1.8 L/min; odorized air was injected into this stream at 0.2 L/min for an air dilution of 10%. The bottles and all common tubing in the system were made of teflon or glass to facilitate cleaning. The odorant bottles and tubing elements exposed to odorants were replaced as a unit when odor pairs were changed. Odorants used in these experiments were selected from a large stock of chemicals obtained from International Flavors and Fragrances (Union Beach, NJ), Aldrich Chemical Co. (Milwaukee, WI), and McCormick and Co. (Baltimore, MD).

دریافت فوری ← متن کامل مقاله

ISIArticles
مرجع مقالات تخصصی ایران

- ✓ امکان دانلود نسخه تمام متن مقالات انگلیسی
- ✓ امکان دانلود نسخه ترجمه شده مقالات
- ✓ پذیرش سفارش ترجمه تخصصی
- ✓ امکان جستجو در آرشیو جامعی از صدها موضوع و هزاران مقاله
- ✓ امکان دانلود رایگان ۲ صفحه اول هر مقاله
- ✓ امکان پرداخت اینترنتی با کلیه کارت های عضو شتاب
- ✓ دانلود فوری مقاله پس از پرداخت آنلاین
- ✓ پشتیبانی کامل خرید با بهره مندی از سیستم هوشمند رهگیری سفارشات