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Research report

Chronic minocycline treatment improves social recognition memory in adult male Fmr1 knockout mice

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HIGHLIGHTS

- Fragile X syndrome (FXS) patients are associated with social behavioral deficit.
- FXS mice display intact social interaction, but impaired social recognition memory.
- Minocycline treatment improved social recognition memory in FXS mice.
- Minocycline could be effective in treating FXS with social behavioral deficit.

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ABSTRACT

Fragile X syndrome (FXS) is caused by a mutation in the *Fmr1* gene that leads to silencing of the gene and a loss of its gene product, Fragile X mental retardation protein (FMRP). Some of the key behavioral phenotypes for FXS include abnormal social anxiety and sociability. Here we show that Fmr1 knock-out (KO) mice exhibit impaired social recognition when presented with a novel mouse, and they display normal social interactions in other sociability tests. Administering minocycline to Fmr1 KO mice throughout critical stages of neural development improved social recognition memory in the novel mouse recognition task. To determine if synaptic changes in the prefrontal cortex (PFC) could have played a role in this improvement, we examined PSD-95, a member of the membrane-associated guanylate kinase family, and signaling molecules (ERK1/2, and Akt) linked to synaptic plasticity in the PFC. Our analyses indicated that while minocycline treatment can enhance behavioral performance, it does not enhance expression of PSD-95, ERK1/2 or Akt in the PFC.

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1. Introduction

FXS is the most common form of inherited intellectual disability and one of the leading causes of autism in humans. It results from a loss of the Fmr1 gene product, FMRP, which regulates synaptic protein synthesis in an activity-dependent manner [2]. Although numerous therapies have been proposed for FXS, minocycline, a broad spectrum tetracycline antibiotic, is currently the only pharmaceutical agent that is routinely prescribed as a treatment for patients with FXS [1]. Clinical studies have indicated that minocycline treatment can lead to significant improvements in several behavioral deficits related to FXS including anxiety, mood, language and social communication skills [3–5]. The use of minocycline in children and adolescents when FXS is first identified appears to be particularly effective in significantly improving a number of behaviors [3].

Understanding the impact of FXS on the brain and cognition has proven a difficult challenge. Animal studies indicate that FXS can be associated with dendritic spine abnormalities and reduced synaptic plasticity in some areas of the brain [6–9]. Many of the impairments in learning and memory can be linked to hippocampal dysfunction, where we and others have recently shown that there are significant deficits in NMDA-receptor functioning, neurogenesis and synaptic plasticity [7,8,11,12]. Synaptic spine abnormalities, decreased neural activity, and decreased levels of synpatic plasticity-related proteins including PSD-95 and NMDA receptors subunits have also been shown in the prefrontal cortex (PFC) of Fmr1 KO mice [6]. Brain imaging studies have suggested that the medial PFC is linked to social cognitive processing [13]; whether these deficits in the PFC may contribute to social behavioral deficits presented in FXS is still unexplored.

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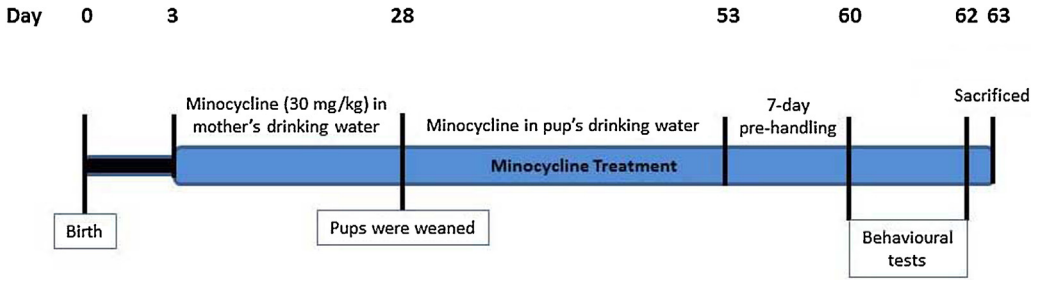

Fig. 1. The treatment timeline. Minocycline was administered to the pups through the drinking water of the mother starting at post-natal day 3, until day 28 when pups were weaned and the minocycline was administered into the drinking water of the pups at 30 mg/kg/day until they were sacrificed. Seven days before the behavioural tests, pups were pre-handled. Behavioural tests began at 2 months of age and sacrificed the following day.

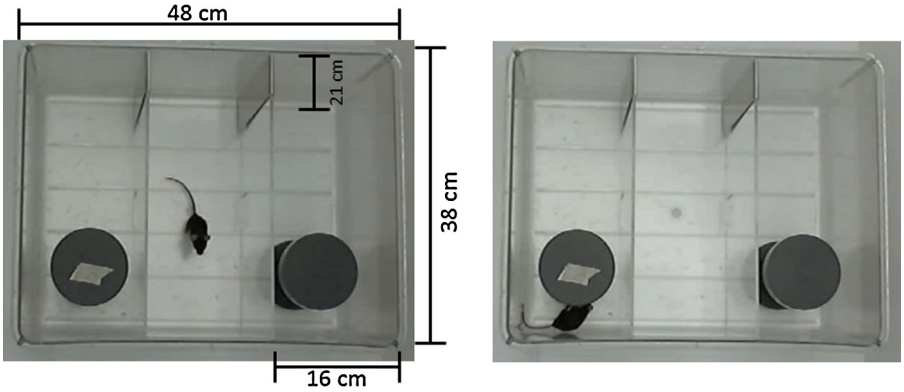

Fig. 2. The social behavior test chamber. The apparatus was divided into three chambers. Mice could enter adjacent chambers through the doorways in the dividing walls. The stimulus mice were restrained in the wire enclosures.

Recently, animal studies have also demonstrated that chronic minocycline treatment can improve ultrasonic vocalizations for facilitating mating behavior [10] and improve dendritic spine maturation and cognitive performance in Fmr1 knockout (KO) mice [9]. Moreover, when mice are treated with minocycline early in life, these improvements in behavior persist even after the cessation of treatment. Conversely, adult Fmr1 KO mice require continuous minocycline treatment to exhibit improved behavioral performance [14]. These studies indicate that treatment with minocycline at an early developmental stage is a more effective strategy for providing prolonged therapeutic effects in FXS patients. In the present study, we explored the effects of minocycline treatment on social behavior in Fmr1 KO mice, and examined signaling molecules related to synaptic plasticity in the brain regions thought to be involved in social behaviours. The intent of the study was to provide evidence that changes in synaptic plasticity might underlay the benefits of minocycline.

2. Materials and methods

2.1. Animals

All experiments followed the international standards on animal welfare and guidelines set by the Canadian Council of Animal Care and the Animal Care Committee at the University of Victoria. Adult male Fmr1 KO mice (n = 28) with a C57Bl/6J genetic background and their wildtype littermates (n = 31) were used. Mice were generated by breeding Fmr1 heterozygous females with WT males. Experimenters were blind to the genotype of the animals throughout the experiment and data collection. Stimulus animals and test animals were housed in the same room, with stimulus mice (2-month old ovariectomized female) housed individually and test animals housed with one or two littermates. Mice were maintained in a 12 h light/dark cycle with standard mouse chow in ventilated racks. Animal groups for behavioral tests included: 1) Non-treated WT (n = 8); 2) Non-treated Fmr1 KO (n = 8); 3) Minocycline-treated WT (n = 9); 4) Minocycline-treated KO (n = 6). All behavioral testing was conducted in the light phase. A separate cohort of animals was used for Western blot analysis so as to avoid the influence of behavioral testing on the expression of synaptic plasticity-related signaling molecules (n = 7 per group).

2.2. Genotyping

Genotype of the animals was determined by using the polymerase chain reaction (PCR) to detect a neomycin cassette insertion into the Fmr1 gene. The primers used to probe for the Fmr1 KO allele were M2 = 5′ ATCTAGTCATGCTATGGATATCAGC-3′ and N2 = 5′-GTGGGCTCTATGGCTTCTGAGG-3′, while S1 = 5′-GTGGTTAGCTAAAGTGAGGATGAT-3′ and S2 = 5′-CAGGTTTGTTGGGATTAACAGATC-3′ were the primers used to probe for the WT allele. The amplified fragments were 800 base pairs for the Fmr1 KO allele and 465 base pairs for the WT allele. The cycling parameters for PCR were denaturation for 5 min at 94 °C, followed by 35 cycles of 60 s at 94 °C, 90 s at 65 °C and 150 s at 72 °C.

2.3. Minocycline treatment

Minocycline (30 mg/kg mincycline hydrochloride, MP Biomedicals Inc.) was administered daily to newborn mice through the mother's drinking water, starting at three days after birth as previously described [9,15]. After weaning, the mice were weighed every three days, and the dose of minocycline was adjusted daily based on the water consumption and body weight. The minocycline treatment was administered to the mice until they were sacrificed.

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