Fmr1-KO Mice, a Suitable Tool to Study Core and Secondary Symptoms of Autism Spectrum Disorders

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BACKGROUND

The mutation of the *FMR1* (fragile X mental retardation 1) gene, leading to Fragile X syndrome (FXS), is known as a monogenic cause of autism spectrum disorders (ASD). Modeling FXS using the genetically modified mouse model *Fmr1* Knock-Out (KO) is a fundamental and valuable approach to studying ASD and assessing the efficacy of new pharmacological compounds targeting core behavioral abnormalities of social impairment and repetitive behaviors as well as secondary symptoms of hyperactivity and anxiety. In the current study, we behaviorally characterized and compared the *Fmr1*-KO mouse model with C57BL/6JRj (control) mice and evaluated the efficacy of a widely used GABAergic drug, R-Baclofen, on behavioral abnormalities in *Fmr1*-KO mice.

MATERIAL & METHODS

Male B6.129P2-*Fmr1*^{tm1Cgr}/J (*Fmr1*-KO) mice were allocated to two groups and intraperitoneally treated once with either R-Baclofen or vehicle. Additionally, C57BL/6JRj (B6) mice received vehicle only. Open field, elevated plus maze, self-grooming, and ultrasonic vocalization (USV) emission recording tests were conducted at the ages of 7-10 weeks.

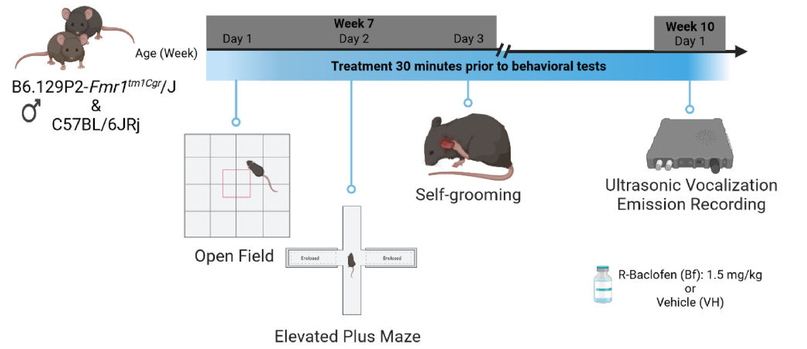

Figure 1: Experimental time schedule. Created with BioRender.com

RESULTS

In the **Open Field** test, *Fmr1*-KO mice presented higher locomotor activity, moved a longer distance, and showed hyperactivity compared to B6 mice. In addition, the strain showed lower anxiety compared to B6 mice, observed by a slightly higher rearing activity and significantly lower thigmotaxis. *Fmr1*-KO mice also spent more time in the center of the Open Field box. R-Baclofen treatment did not affect these parameters in *Fmr1*-KO mice.

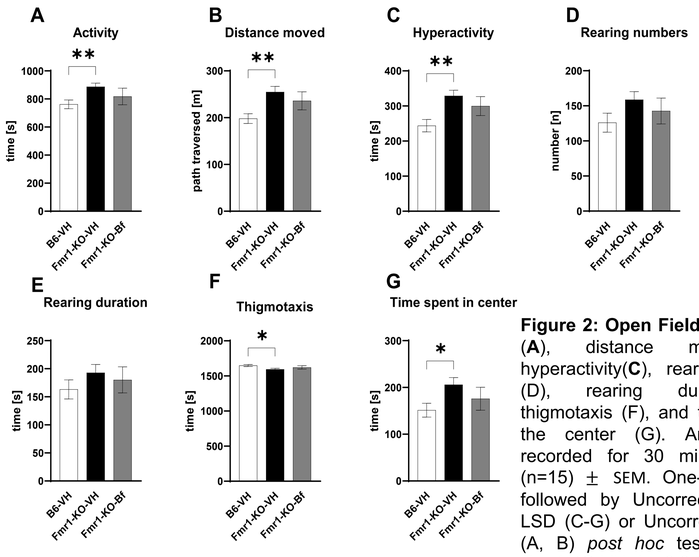

Figure 2: Open Field test. Activity (**A**), distance moved (**B**), hyperactivity(**C**), rearing numbers (D), rearing duration (E), thigmotaxis (F), and time spent in the center (G). Animals were recorded for 30 minutes. Mean (n=15) ± SEM. One-way ANOVA followed by Uncorrected Fisher's LSD (C-G) or Uncorrected Dunn's (A, B) *post hoc* test; all versus *Fmr1*-KO-VH; *p<0.05, **p<0.01.

In the **Elevated Plus Maze** test, anxiety evaluations revealed lower levels of this behavior in *Fmr1*-KO mice compared to B6 mice. *Fmr1*-KO mice spent more time in the open arms and entered them more frequently. The time spent and the number of entries to the closed arms were comparable in *Fmr1*-KO and B6 mice; however, *Fmr1*-KO mice entered the center of the maze more frequently.

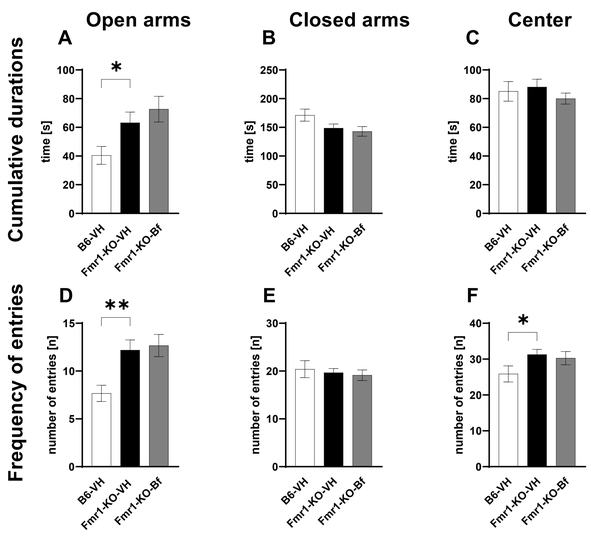

Figure 3: Elevated Plus Maze test: Cumulative durations in open and closed arms and the center of the maze (A-C), frequency of entries into open and closed arms, and the center (D-F) of the Elevated Plus Maze. Total test duration 5 min. Mean (n=15) ± SEM. One-way ANOVA followed by Uncorrected Fisher's LSD *post hoc* test; all versus *Fmr1*-KO-VH; *p<0.05, **p<0.01.

In the **Self-grooming** test, *Fmr1*-KO mice showed higher repetitive behavior compared to B6 mice. Acute R-Baclofen treatment reversed this behavior.

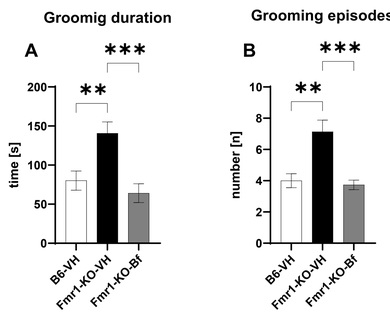

Figure 4: Self-grooming test. Grooming duration (A) and grooming episodes (B). Animals were recorded for 10 minutes. Mean (n=15) ± SEM. One-way ANOVA followed by Uncorrected Fisher's LSD (A) or Uncorrected Dunn's (B) *post hoc* test; all versus *Fmr1*-KO-VH; **p<0.01, ***p<0.001.

In the **USV recording** test, *Fmr1*-KO mice emitted significantly fewer calls with a slightly more delayed initiation than B6 mice. R-Baclofen did not affect these parameters.

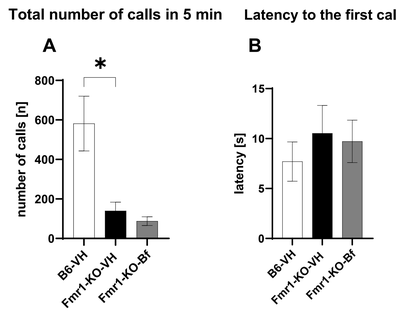

Figure 5: Ultrasonic Vocalization Emission Recording test: Number of vocalizations (A), latency to the first call (B). The recording was performed for 5 minutes. Mean (n=15) ± SEM. One-way ANOVA followed by Uncorrected Dunn's *post hoc* test; all versus *Fmr1*-KO-VH; *p<0.05.

CONCLUSION

Increased activity, hyperactivity, repetitive behavior, and impaired social communication were observed in *Fmr1*-KO mice. Acute R-Baclofen treatment could alleviate repetitive behavior of grooming in *Fmr1*-KO mice. In conclusion, these data propose that the *Fmr1*-KO mouse model can be a valuable tool for investigating core and secondary symptoms of ASD. Therefore, the *Fmr1*-KO strain could be used to design and test novel therapeutic approaches against ASD.

Contact for more information about the models:
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