**INTRODUCTION**

Fragile X Syndrome (FXS) is the leading monogenetic cause of intellectual disabilities and autism spectrum disorder (ASD). Epilepsy, sensory hypersensitivities, and several other neuropsychiatric symptoms are also common in FXS and ASD. FXS is caused by a >200 CGG-repeat on the FMR1 gene, located on the X-chromosome, that silences its transcription, preventing expression of the protein, FMRP. Possessing a single X-chromosome, FXS females typically have more severe clinical symptoms than females with FXS. For example, males are more than twice as likely to have epilepsy. Genetic mosaicism (X-inactivation) in females with FXS is the presumed mechanism, occurs more frequently in males than females. Males with FXS and/or sexually dimorphic brain systems—could be involved.

**RESULTS**

Increased whole brain expression of 5-HT<sub>1A</sub>Rs in adult Fmr1 KO male mice

Left: Representative saturation binding isotherms showing increased expression of brain 5-HT<sub>1A</sub>Rs in an adult, male Fmr1 KO mouse. Right: Representative data showing 5-HT<sub>1A</sub>R expression differences between a WT and Fmr1 KO mouse were blocked by the selective 5-HT<sub>1A</sub>R antagonist, WAY-100635 (10 µM). Thus, whole brain 5-HT<sub>1A</sub>R expression is higher in adult, male Fmr1 KO mice.

**CONCLUSIONS and DISCUSSION**

During preclinical testing of Fmr1 knockout mice, we observed a statistically significant, higher prevalence of audiogenic seizures in juvenile, male Fmr1 KO mice (100%) compared to juvenile, female Fmr1 KO mice (50%). These observations closely parallel clinical data. Males with FXS have a higher incidence of epilepsy than females with FXS. The reason for this clinical, sex difference is purportedly that females with FXS have one functioning X-chromosome, whereas males do not. Importantly, however, female Fmr1 KO mice are homozygous for the Fmr1 gene, and therefore, do not express FMRP, thus suggesting sex hormones or sexually dimorphic brain systems could be involved in protecting females from seizures. Our preclinical data challenge the presumption that reduced frequency of FXS and symptom severity in males suggests that targeting 5-HT<sub>1A</sub>Rs might be therapeutic for FXS or ASD with epilepsy.

**REFERENCES**


**Sex Differences in an Fmr1 Knock-out Mouse Model of Fragile X Syndrome**

Jessica L. Armstrong, Yiming Chen, Tanishka S. Saraf, Clinton E. Canal

Mercer University College of Pharmacy, Atlanta, Georgia

**METHODS**

Subjects. FVB:129P2-Pde6b<sup>–/–</sup> <sup>Tyr<sub>49</sub>-Asp</sup> Fmr1<sup>–/–</sup> (Fmr1 KO mice) and FVB:129P2-Pde6b<sup>–/–</sup> <sup>Tyr<sub>49</sub>-Ala</sup> (WT mice) were purchased from Jackson Laboratories to develop a colony. Genotyping of litters was based on established protocols. KO males are hemizygous and females are homozygous for the knock-out Fmr1 gene.

Audiogenic Seizure (AGS) Susceptibility. Fmr1 KO male and female juvenile (P23-P25) mice were given IP injections 30 minutes prior to testing of vehicle (MilliQ water). Mice were exposed to a 120 dB alarm (Radioshack) for 5 min, and responses, including wild running and jumping (WRJ), tonic-clonic seizure, respiratory arrest and subsequent death, were recorded.

Radioligand Saturation Binding. The saturation binding assay was performed using cell membranes of brain tissue collected from adult (≥60) male and female WT and Fmr1 KO mice, as previously described (Canal et al., 2011; PMID: 20165943). <sup>[3H]</sup>5-CT (PerkinElmer) with cold ligands were added to block off-targets were used to label 5-HT<sub>1A</sub>Rs.