Sigma-1 Receptor Agonists as Potential Treatment Options for Autism Spectrum Disorders: Pre-clinical Studies with ANAVEX 2-73 in a Fragile X Model
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Background

Autism spectrum disorders (ASD) occur in up to 2/3 of males and 1/3 of females with Fragile X syndrome (FXS). FXS is the most common form of inherited intellectual disability and the most frequent single gene cause of autism, affecting approximately 1 in 4,000 males and 1 in 6,000 females. In addition to the clinical overlap between FXS and ASD, there is likely a substantial overlap in the molecular pathology of the two disorders. Molecules aimed at targets in these shared pathways are expected to have therapeutic overlap in subsets of individuals with ASD or neurodevelopmental disorders.

The Fragile X gene FMR1 was cloned in 1991 and has been studied since then using techniques from biochemistry through genetics to model organisms in an effort to elucidate the functions of the FMR1 protein (FMRP). In the brain FMRP is highly expressed in neurons and actively transported as part of a messenger ribonucleoprotein (mRNP)-complex throughout the dendritic fields to the synaptic spines, where its main function appears to be the regulation of protein synthesis. Insufficient expression of FMRP leads to deregulated translation and a broad array of effects on cellular signaling pathways, ultimately leading to abnormalities in brain connectivity and neurodevelopmental processes (Grossman AW et al 2006, Bhakar AL et al 2012).

The sigma-1 receptor (S1R) is an intracellular chaperone protein located at the endoplasmic reticulum–mitochondria interface with important roles in inter-organellar communication. S1R is also involved in transcriptional regulation at the nuclear envelop and important roles in inter-organelle communication. S1R is also demonstrated significant improvements in an array of behavioral anticonvulsant, anti-amnesic, neuroprotective and antidepressant and gait paradigms in a mouse model for the neurodevelopmental disease Rett syndrome. In addition, ANAVEX 2-73 has exhibited dose-dependent cognitive improvements.

Experimental Procedures

Fmr1-KO2 mice (Mientjes MJ et al 2006) and wild type (WT) littermates, generated on a C57BL/6J background, were used throughout (N=10 per treatment arm). ANAVEX 2-73 was dosed at 1 mg/kg IP twice daily for 14 days. Testing was conducted on male mice that were approximately 2 months old, and the experimenters were blind to both genotype and treatment during all testing and data analyses. Drug-related safety was first assessed and then followed by a battery of 3 behavioral tests to characterize efficacy-related endpoints: open field test (hyperactivity), contextual fear conditioning ( associative learning), and marble-burying (species-specific behavior). All data were analyzed via a one-way ANOVA followed post hoc by a Tukey’s multiple comparison test.

ANAVEX 2-73 Reverses the Hyperactivity of the Fmr1 KO2 mice to Normal

Compared to the corresponding WT animals, vehicle-treated Fmr1-KO2 mice displayed an increase in total distance traveled (number of squares), a measure of general hyperactivity (**p≤0.0001). Chronic treatment with ANAVEX 2-73 significantly reduced the increased locomotor activity of the Fmr1-KO2 mice (**p≤0.0001), to the same levels observed in vehicle-treated WT mice.

ANAVEX 2-73 Normalizes the Impairment in Associative Learning Characteristic of Fmr1 KO2 mice

Under conditions of acute stress, ANAVEX 2-73 treatment rescued Fmr1 KO2 mice from the learning deficits observed in the vehicle-treated Fmr1 KO2 group (measured as % freezing during 5 min, ***p≤0.0001). Compared to the vehicle-treated WT animals, mice chronically treated with ANAVEX 2-73 exhibited a similar percentage of freezing behavior compared to the vehicle-treated WT mice in the contextual fear conditioning paradigm.

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References

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