Fragile X Syndrome

A Novel Pharmacological Treatment

This article is a review of the following research: Berry-Kravis, E. M., Harnett, M. D., Reines, S. A., Reese, M. A., Ethridge, L. E., Outterson, A. H., Michalak, C., Furman, J., & Gurney, M. E. (2021). Inhibition of phosphodiesterase-4D in adults with fragile X syndrome: a randomized, placebo-controlled, phase 2 clinical trial. *Nature Medicine*, 10.1038/s41591-021-01321-w. Advance online publication.

Fragile X syndrome (FXS) is an inherited disorder that is often linked with autism. Those with FXS often have severe intellectual disabilities, social deficits, behavior difficulties, anxiety, and challenges with daily function. The behaviors seen in children with FXS are often similar to those found in individuals with autism spectrum disorder (ASD) and FXS is one genetic cause of autism. Studies show that about two percent of individuals diagnosed with autism actually have fragile X syndrome.[1,2] They also show that about 60 percent of children with fragile X syndrome have co-occurring ASD.[1,3]

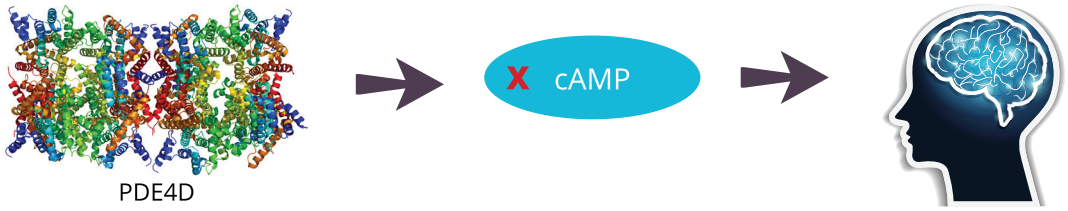
FXS affects one in every 4,000 males and about one in every 8,000 females.[1] FXS occurs when there is a genetic mutation to the *FMR1* gene, which is located on the X chromosome. Although the *FMR1* gene is expressed in most body tissues, the most severe impact of the genetic mutation is on the brain.[1] Currently there are no pharmacological treatments to improve the symptoms of patients living with fragile X. Children and adults with FXS are usually enrolled in a wide range of therapies to help with their challenges, often with varying degrees of success.

Previous studies have shown that humans with FXS have a decrease in cyclic adenosine monophosphate (cAMP) in multiple cell types.[4,5] Further to these investigations, scientists have shown that mice with FXS have a decrease in cAMP in the brain.[6] cAMP is a signaling molecule that is primarily involved in memory function and learning. It is mainly controlled by the enzyme phosphodiesterase-4D (PDE4D).[7] In a typically functioning system, PDE4D breaks down cAMP as too much of it could cause heart complications, such as an increased heart rate or irregular heart contractions.[8]

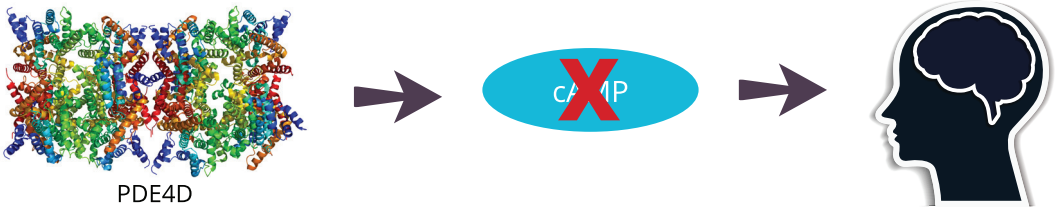
Scientists wondered if preventing PDE4D from breaking down cAMP in FXS patients would improve memory, learning and cognitive function.

A team of researchers, led by Dr. Berry-Kravis (Rush University Medical Center), tested a drug developed by Tetra Therapeutics, on fragile X patients. The drug, BPN14770, inhibits PDE4D and allows increased production of cAMP, which in turn is thought to improve memory and cognitive function.

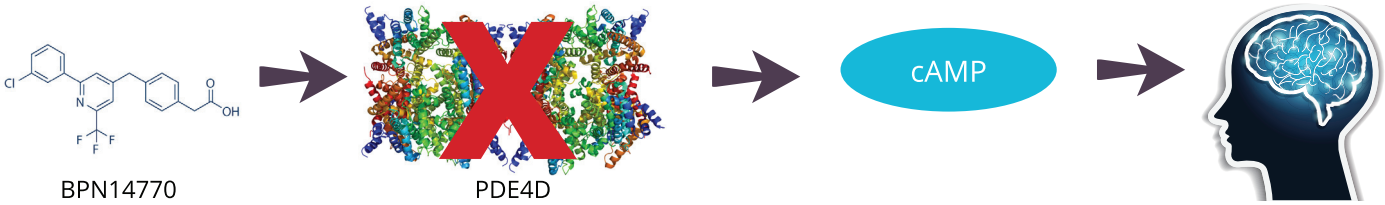
Typical: In typical individuals, PDE4D breaks down cAMP to ensure there is not an overproduction, which could cause heart complications.



Fragile X: Patients with fragile X syndrome have a decrease in cAMP in the brain, which affects memory and cognitive function.



Research Study: BPN14770 inhibits PDE4D and allows increased production of cAMP, which in turn improves memory and cognitive function in individuals with FXS.



Study

- Thirty men with fragile X syndrome, aged 18-41, were enrolled in the study.
- The participants were divided into two groups. Group 1 received the medication for 12 weeks and then the placebo for 12 weeks. Group 2 received the placebo for 12 weeks and then the drug for 12 weeks.
- Each participant was given an oral dose of BPN14770 (25 mg) or placebo, twice daily.
- Participants were assessed at the start of the study and every six weeks during the study. During these assessments, participants completed cognitive assessments, and parents/caregivers rated the change in the men's language, daily function and anxiety.

Results

- Results showed statistically significant improvements in daily function and cognition, especially in the area of language, after 12 weeks of receiving BPN14770. The results were seen in both the cognitive assessments and the ratings given by parents/caregivers.
- The researchers note that the improvements continued for at least 12 weeks following the last dose of BPN14770.

Conclusions

Currently there are no approved pharmacological treatments that successfully improve the symptoms of fragile X syndrome. The results of this study showed that there can be improvements in language, cognition and daily function for those living with FXS. This is very important as intellect and cognition are imperative for independence. If this treatment can improve the intellectual disability seen in many fragile X patients even by a small margin, it could translate into enormous strides for those living with FXS.

This study is very promising as the results were shown in adults. Children tend to be more susceptible to changes and improvements if therapies are started when they are young. The results of a trial like this could be even more dramatic if it were to involve child participants.

This therapeutic is still in clinical trials, and many other tests and trials must occur to show it works in larger groups of people with FXS. Additional data will also be needed for it be approved by the FDA and made widely available. Many questions remain. Is it safe for children? Are there side effects? Can it be used on individuals with a partial mutation (mosaic) of the *FMR1* gene? In the near future, studies using this treatment will include women and children with FXS and will help answer some of these questions.

Researchers and scientists continue to dedicate their lives and careers to discovering more about autism and FXS. This study is yet another example of the positive changes that are possible, and of the steps that are being taken to improve the quality of life for loved ones.

Written By Autism Advocate Parenting Magazine

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