The quest for targeted therapy in fragile X syndrome

For many years we believed that most hereditary diseases were untreatable. However, hopes for a cure were raised following the discovery of genetic causes and better understanding of disease mechanisms. This elucidated new targets for therapy. The development of targeted treatment for fragile X syndrome (FXS), is a striking example of this process.

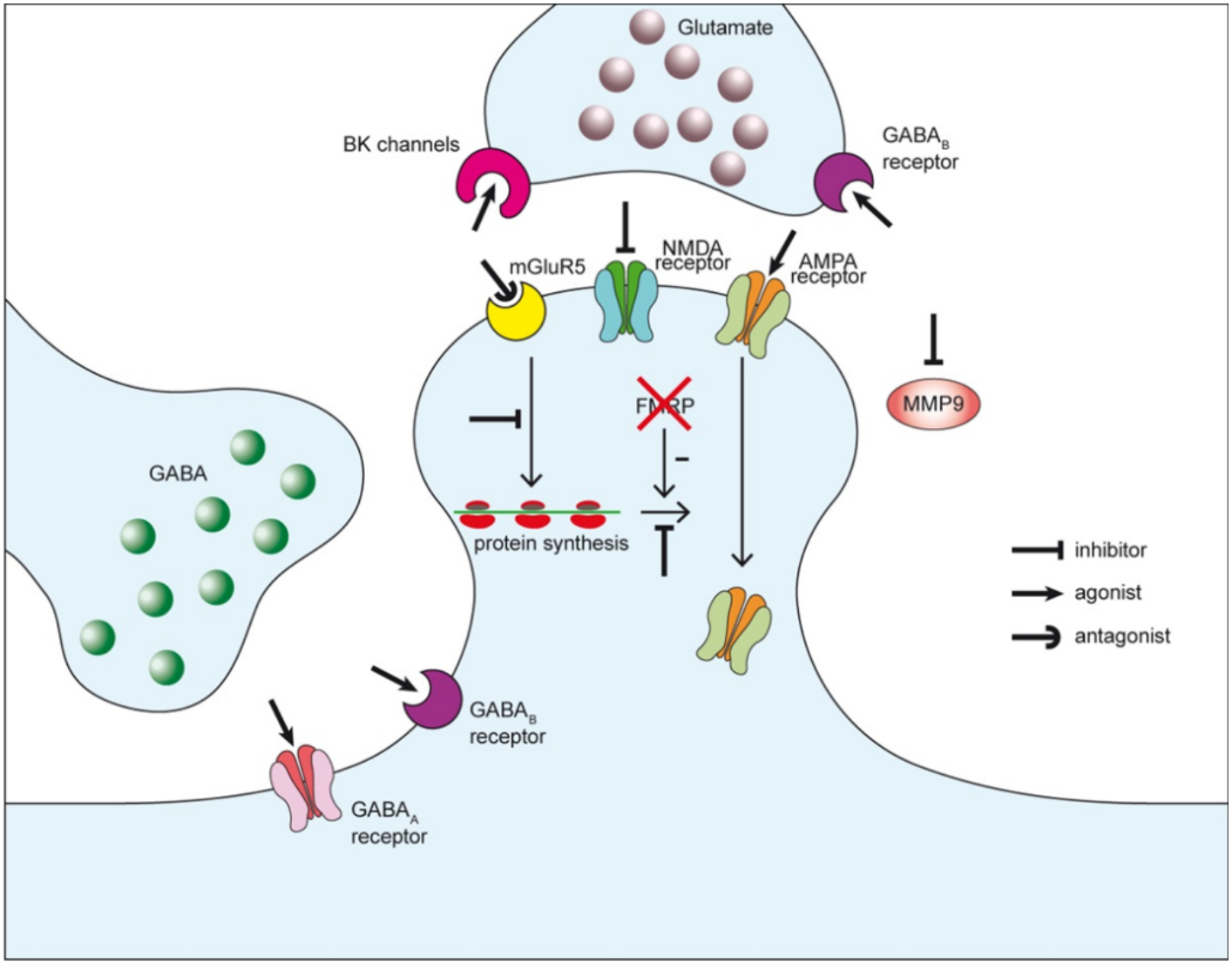
FXS is a common inherited genetic cause of intellectual disability, autistic features and behavior problems. FXS is caused by mutations in the *FMR1* gene, leading to lack of the *FMR1* protein (FMRP) in the brain.

What do we know about the function of FMRP?

Research in the past decades revealed much about the mechanisms involved in FXS. This knowledge could be used for identification of targets for specific therapy. FMRP is involved in important cellular processes in the brain, namely in synaptic function. The synapse connects neurons in the brain, which need this contact for learning, memory formation and behavior. We continuously learn and adapt to the environment. These contacts, the synapses, are changing constantly. This is termed synaptic plasticity. Lack of FMRP results in aberrant synaptic plasticity. A complex balance of signaling pathways in the neuron assures a correct function of the synapse. In FXS many parts of these signaling pathways are disturbed.

Intervention seems possible

Most research was done in the FXS mouse model, that lacks FMRP and has features similar to FXS patients. Research also showed us that we can interfere in these mechanisms and successfully improve many FXS features in mice. With great enthusiasm human clinical trials started. However, the encouraging results of the mouse-studies, were not confirmed in patients. Many clinical trials were stopped without positive results. Mice share many cellular processes with humans, so what went wrong in translating positive results from mice to human? There are several causes we can suggest.



Possible targets for therapy for FXS syndrome (from: The quest for targeted therapy in fragile X syndrome. Zeidler S, Hukema RK, Willemsen R. Expert Opin Ther Targets. 2015)

Mice are not human

First of all, mice are not human. Mice in research have no genetic and environmental variation, while patients with FXS are all different. Many results of mice studies are contradicting and approaches are different. Obviously, mostly success stories are published, which perhaps makes a positive effect seem stronger than in real-life.

How do we measure?

Effects of therapy need to be measured somehow; the outcome measures. Outcome measures in mice are often not applicable in humans. Most of the used outcome measures for people are possibly not sensitive enough to measure subtle improvements and effect of targeted therapy. Many outcome measures are subjective, which can cause substantial placebo-effects that disguise real effects. We certainly need new robust, reliable and feasible outcome measures in the search for a treatment for FXS.

Other problems concern the right timing, age of onset of treatment, dosing and duration of treatment. We are not sure when we should start treating a developmental disorder like FXS to be able to see an effect. And obviously, the most severe patients, who might benefit from treatment the most, cannot participate in intensive clinical trials.

Complex balance

Plasticity in the brain is a very complex balance. Most research is focused on only one small part. It is reasonable to assume that several parts of the processes will need to be targeted simultaneously to restore this balance. Perhaps using a cocktail of several targeted drugs, a combinational therapy, may finally lead us to treatment options for FXS.

We definitely won't give up on finding an effective treatment. It is important to learn from our previous experiences. Hopefully the coming years will be more fruitful in our quest for a targeted treatment for FXS.

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