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Potential target pathway may pave the way for new therapeutic approaches for fragile X syndrome and autism

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Scientists at VIB and KU Leuven have discovered that the protein APP plays a significant role in the development of fragile X syndrome (FXS) at young stages. They identified an unexpected biological pathway as a promising target to ameliorate deficits associated with FXS and autism. The results have recently been published in *Neuron*, one of the most influential journals in the field of neuroscience.

FXS is the most common inherited cause of intellectual disability worldwide, and the most frequent cause of autism spectrum disorders (ASDs). The syndrome is a consequence of the absence or incorrect production of the fragile X mental retardation protein (FMRP). So far, no cure has been discovered for FXS.

Early neuronal development

The study, led by Dr. Emanuela Pasciuto in the laboratory of Prof Claudia Bagni (VIB/KU Leuven/University of Rome Tor Vergata), has identified the molecular mechanism that leads to increased levels and maturation of the protein APP in the FXS mouse model.

The scientists revealed how the absence of FMRP leads to an excessive production of the protein APP and its processing enzyme ADAM10. In turn, this dysregulation affects neuronal development and behavior. Importantly, the APP-ADAM10 pathway is unbalanced in FXS during

the crucial period of synaptogenesis – the period in which an infant's brain synapses are formed and remodeled.

Using a therapeutic agent developed by Prof Monica Di Luca (University of Milan) to target ADAM10 activity in an FXS mouse model, the team managed to significantly reduce molecular, cellular and behavioral deficits associated with FXS and autism.

Claudia Bagni (VIB/KU Leuven):

"While a dysregulation of the protein APP is known to play an important role in the development of Alzheimer's disease, a neurodegenerative disorder in people of old age, the discovery that it might also contribute to FXS, a neurodevelopmental disorder occurring at a young age, is remarkable. Additionally, the discovery that the APP-ADAM10 pathway dysregulation occurs only at the crucial developmental window coinciding with synaptogenesis strengthens the therapeutic potential of targeting this pathway at an early, postnatal stage.

These findings open new avenues towards the development of non toxic agents, as the one used in this study, that can be designed with the potential to ameliorate FXS and neurodevelopmental diseases such as autism at specific developmental postnatal stages."

More information: "Dysregulated ADAM10-Mediated Processing of APP during a Critical Time Window Leads to Synaptic Deficits in Fragile X Syndrome." DOI: dx.doi.org/10.1016/j.neuron.2015.06.032

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