

Nrf2: a novel therapeutic target in fragile X syndrome is modulated by NNZ2566

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Abstract

Fragile X-associated disorders are a family of genetic conditions resulting from the partial or complete loss of fragile X mental retardation protein (FMRP). Among these disorders, fragile X syndrome (FXS) is the most common cause of inherited intellectual disability and autism. Progress in basic neuroscience has led to identification of molecular targets for treatment in FXS; however, there is a gap in translation to targeted therapies in humans. This study introduces a novel therapeutic target for FXS, nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a transcription factor known to induce expression of over 100 cytoprotective genes. We also show that NNZ2566, a drug that has successfully completed a phase 2 clinical trial in FXS, is effective in modulating this target in FXS, partially reversing the FXS phenotype; NNZ2566 has a therapeutic role as Nrf2 activator. Effectively, treatment with NNZ2566 normalizes the translocation of Nrf2 to the nucleus, inducing expression of numerous oxidative stress-related genes including NQO1 (NAD(P) H dehydrogenase quinone 1), GST-alpha 1 (glutathione S-transferase alpha-1) and EH (epoxide hydrolase) and has a knockdown effect on E-cadherin. In summary, the Nrf2/ARE (antioxidant response element) pathway appears to be a novel promising therapeutic target for FXS and NNZ2566 appears to be acting as an activator of the Nrf2/ARE pathway and suggests a potential benefit across multiple symptoms that could be associated with the pathobiological processes underlying FXS.

Keywords

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