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Researchers discover new therapy for fragile X chromosome syndrome

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Researchers at the University of the Basque Country (UPV/EHU) and the Achucarro neurosciences centre have discovered a new therapy for the fragile X chromosome syndrome. This new therapy proposes the modulation of the cerebral endocannabinoid system in order to ameliorate the symptoms of the disease. "Clearly, a cure as such is not going to be achieved, as it involves a disease of genetic origin, but the fact that, by manipulating in a certain way at a cerebral level in order to obtain an improvement in the symptoms of the disease is something highly positive", stated Ms Susana Mato, researcher at the Department of Neurosciences at the UPV/EHU and at the Achucarro centre. This scientific finding has just been published in *Nature Medicine*.

Fragile X chromosome syndrome (FXS) is the most frequent known cause of inherited mental retardation and disorders in the autistic range. It involves a genetic disease, with an incidence in Spain estimated at 1 in every 4,000 individuals. The syndrome arises from a deficit in the expression of the FMRP protein (fragile X mental retardation protein), which plays a fundamental role in the regulation of the neuronal function . Patients with FXS present mental retardation, attention deficit, anxiety, self-harming and autistic behaviour, hyposensitivity to pain and a high rate of epileptic crises. All these anomalous neuronal expressions are regulated by the endocannabinoid system.

The research, using genetically modified mice that lacked FMRP protein and that partially reproduced the symptomatology of fragile X chromosome syndrome in humans, have shown that blocking CB1

cannabinoid receptors with the Rimonabant pharmaceutical drug normalizes cognitive alterations, sensitivity to pain and epileptic crises. This finding suggests that the administration of pharmaceutical drugs that block the function of the cerebral endocannabinoid system may well be a new strategy for treating patients with fragile X chromosome syndrome.

Rimonabant pharmaceutical drug has been on the market for some time "for the treatment of obesity", explained Ms Mato. "Then, however, it was used in much higher doses and these high dosages gave rise to certain psychiatric problems, and this is why it was taken off the market". Nonetheless, it involves a drug which "has been used a lot in preclinical research into the endocannabinoid system, and its action mechanism is very well established".

The next step, Ms Mato pointed out, should be "to better characterise the action mechanism of this treatment, and test the various dosages to see what would be the optimum one to normalize the deficit. And the following stage would be the clinical trials. In fact, we believe this would be relatively feasible, because as it has already been marketed, all that preclinical stage regarding toxicity of the drug for humans has been undertaken, and it is a relatively safe pharmaceutical drug".

Although Ms Mato considers it to be a great advance that it has been shown in animal models that "the cognitive deficit caused by the disease has been normalised to a certain extent", she is aware that it could be that "the clinical trials do not produce such good results, as it is common for this to happen when developing therapies for psychiatric disorders".

More information: Busquets-Garcia, A. et al. Targeting the endocannabinoid system in the treatment of fragile X syndrome. *Nature Medicine* doi:10.1038/nm.3127

Provided by Achucarro Basque Center for Neuroscience