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Poster 2

Modelling fragile X-associated neuropsychiatric disorders in an inducible mouse model: Increased anxiety and reduced parvalbumin-positive interneurons

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Abstract:

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that affects the carriers of fragile X premutation with 55 to 200 CGG repeats. Motor dysfunction is the hallmark of FXTAS. However, the neuropsychiatric disorders including anxiety and depression are the most common problems affecting the ~50% of premutation carriers. These neuropsychiatric disorders coincide and even precede the motor dysfunction. Despite these clinical observations, neurobiological mechanisms underlying the fragile Xassociated neuropsychiatric disorders (FXAND) have not been addressed in a FXTAS mouse model. Thus, using an early induction schedule starting from embryonic development we aimed to study the anxiety phenotype without any interference from motor deficits. Indeed, we detected a profound anxiety-like phenotype without motor dysfunction at the early stages of the disease pathogenesis. We hypothesized that physiological alterations in the amygdala together with the ventral hippocampus might underlie the pathogenesis of such anxiety phenotype. Electrophysiological analysis revealed an enhanced excitability in the lateral amygdala together with a reduction in the number of positive parvalbumin interneurons. These findings were associated to impaired synaptic plasticity in both CA3 recurrent network and medial-perforant path-to-DG synapse and a decrease in the parvalbumin+ interneurons in the ventral hippocampus. These pathological alterations were accompanied by enhanced inclusion load in the lateral amygdala and ventral hippocampus. We posit that the described neurophysiological alterations might be the underlying factors for pathological anxiety in fragile X premutation carriers during the early stages of FXTAS.