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Friday

Anti-GluA3 antibodies in Frontotemporal Dementia: an *in vivo* approach

Maria Italia, Diego Scheggia, Elisa Zianni, Michela Salvadè, Filippo La Greca, Antonella Alberici, Alberto Benussi, Silvana Archetti, Alessandro Padovani, Barbara Borroni, Monica Di Luca, Fabrizio Gardoni

State of the art: Frontotemporal dementia (FTD) is a common type of presenile dementia that presents as a clinically and neuropathologically heterogeneous disorder. Recently, autoantibodies directed against the GluA3 subunit of AMPA-type glutamate receptors (AMPARs) have been identified in 20% to 25% of FTD patients. Data from patients and in vitro/ex vivo studies indicate that anti-GluA3 IgG negatively affect glutamatergic neurotransmission.
Methodology: We developed a chronic mouse model of autoimmunity in FTD to study whether and how the chronic presence of anti-GluA3 IgG triggers synaptic dysfunction and neurodegenerative process in mice and the association between these events and the appearance of FTD-related neuropathological and behavioural signature. Specifically, we infused mice with anti-GluA3 IgG isolated from FTD patients for one month through an intracerebroventricular cannula. The model was used to perform morphological and biochemical analyses and behavioural tasks. What is more, we treated mice with a well-validated AMPAR positive allosteric modulator (PAM, CX-1632) as a possible rescue strategy to counteract the detrimental effects mediated by anti-GluA3 IgG.
Results: Data showed that chronic anti-GluA3 IgG administration led to the appearance of FTD-related neuropathological markers and to dendritic spine loss in mice prefrontal cortex. In addition, we identified alterations in sociability and cognition that partially reflect those deficits proper of FTD GluA3+ patients. Some of these alterations were rescued by PAM administration.
Conclusion: Our model allowed to identify the specific contribution of anti-GluA3 autoantibodies to FTD neuropathology and was instrumental to the development of a putative therapeutic strategy for GluA3+ patients.

Conflicts of interest

N/A