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Muscle Relaxant Dantrolene Repurposed to Treat Alzheimer's Disease

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Abstract : Failures of developing new drugs primarily based on the amyloid pathology hypothesis after decades of efforts internationally lead to changes of focus targeting alternative pathways of pathology in Alzheimer's disease (AD). Disruption of intracellular Ca2+ homeostasis, especially the pathological and excessive Ca2+ release from the endoplasmic reticulum (ER) via ryanodine receptor (RyRs) Ca2+ channels, has been considered an upstream pathology resulting in major AD pathologies, such as amyloid and Tau pathology, mitochondria damage and inflammation, etc. Therefore, dantrolene, an inhibitor of RyRs that reduces the pathological Ca2+ release from ER and a clinically available drug for the treatment of malignant hyperthermia and muscle spasm, is expected to ameliorate AD multiple pathologies synapse and cognitive dysfunction. Our own studies indicated that dantrolene ameliorated impairment of neurogenesis and synaptogenesis in neurons developed from induced pluripotent stem cells (iPSCs) originated from skin fibroblasts of either familiar (FAD) or sporadic (SAD) AD by restoring intracellular Ca2+ homeostasis. Intranasal administration of dantrolene significantly increased its passage across the blood-brain barrier (BBB) and, therefore its brain concentrations and durations. This can render dantrolene a more effective therapeutic drug with fewer side effects for chronic AD treatment. This review summarizes the potential therapeutic and side effects of dantrolene and repurposes intranasal dantrolene as a disease-modifying drug for future AD treatment.

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