Research Report

Muscarinic M1 Receptor Coupling to G-protein is Intact in Parkinson’s Disease Dementia


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Abstract

Background: Postsynaptic cholinergic deficits, including reduced cortical muscarinic M1 receptor coupling to G-proteins, are neurochemical findings postulated to underlie the limited efficacy of presynaptically-targeted cholinergic replacement therapies in Alzheimer’s disease (AD). While the loss of M1-G-protein coupling has been associated with β-amyloid (Aβ) burden in AD, the status of M1 coupling to G-proteins in Parkinson’s disease-related or mixed dementias is unclear.

Objective: To test the hypothesis that M1 receptor uncoupling is correlated with Aβ burden, we aimed to study muscarinic M1 neurochemical parameters in neurodegenerative dementias characterized by low and high Aβ loads.

Methods: M1 receptors, M1 coupling to G-proteins as well as Aβ were measured in postmortem frontal cortex of a cohort of longitudinally assessed patients with Parkinson’s Disease Dementia (PDD, low Aβ load) and AD with significant subcortical cerebrovascular disease (AD + CVD, high Aβ load).

Results: We found unchanged levels of M1 receptors in both dementia groups, while M1 coupling was reduced only in AD + CVD (p < 0.01). Furthermore, Aβ concentration was significantly increased only in AD + CVD, and correlated negatively with M1-G-protein coupling in the dementia groups.

Conclusions: Our study suggests that loss of M1 coupling to G-proteins may be a neurochemical feature of neurodegenerative dementias with high cortical Aβ burden, and that cholinergic replacement therapies may be more efficacious for PDD due to low Aβ burden.

Keywords: Parkinson’s Disease Dementia, Alzheimer’s Disease, cerebrovascular disease, muscarinic M1 receptors, G-protein coupling, β-amyloid

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