Differential Alterations of Neocortical GluN Receptor Subunits in Patients with Mixed Subcortical Ischemic Vascular Dementia and Alzheimer’s Disease

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Abstract

Background: Glutamatergic deficits are well-established neurochemical findings in Alzheimer’s disease (AD) and are thought to underlie both cognitive and behavioral symptoms of the disease. However, it is unclear whether subcortical ischemic vascular dementia (SIVD) and mixed SIVD/AD (MixD) manifest similar changes in the glutamatergic system.

Objective: To measure the immunoreactivities of NMDA receptor GluN1, GluN2A, and GluN2B subunits in SIVD and MixD.

Methods: Postmortem neocortical tissues from a cohort of well-characterized, longitudinally followed-up patients with SIVD and MixD, together with age-matched controls, were processed for immunoblotting with GluN subunit-specific antibodies.

Results: There was a significant reduction of GluN1 only in MixD, while significant increases of GluN2A and GluN2B were found only in SIVD. Furthermore, GluN1 loss and GluN2A/2B upregulation was associated respectively with higher Braak stages and lacunar infarct scores.

Conclusions: Our data suggest that the differential alterations of GluN subunits in SIVD and MixD may result from separate, interacting disease processes, and point to the potential utility of glutamatergic approaches for pharmacotherapy.

Keywords: Alzheimer’s disease, GluN receptors, mixed dementia, neurochemistry, subcortical ischemic vascular dementia

INTRODUCTION

Although Alzheimer’s disease (AD) remains the most common cause of dementia in people aged 65 years or older, stroke and related cerebrovascular disease are increasingly recognized as important contributors to dementia in the form of vascular dementia (VaD), which has become the second most prevalent form of neurodegenerative dementia [1]. While AD is characterized by amyloid plaques and neurofibrillary tangles, VaD features prominent stroke- or hypertension-related cerebrovascular disease and relatively low plaque and tangle burden [1]. VaD can