Neurodegeneration and Excitotoxicity: The Interplay of Ischemic Stroke and Alzheimer's Disease

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Key points:

- Introduction
- Pathophysiology of Stroke and Alzheimer's Disease
- Preventive strategies and treatment approaches
- Conclusion

Introduction

Ischemic stroke and AD represent two of the most prevalent neurological disorders among aging populations. Stroke remains a leading cause of mortality and disability, while Alzheimer's Disease (AD) contributes significantly to cognitive decline and dementia. Despite their differences in onset and progression, these conditions exhibit overlapping mechanisms, primarily involving excitotoxicity, disrupted calcium homeostasis, and neuroinflammation[1]. Recent research suggests that individuals with AD have an increased risk of ischemic stroke and vice versa[2]. Understanding their interplay is essential for developing effective preventive and therapeutic strategies.

Pathophysiology of Stroke and AD:

- **Excitotoxicity in Ischemic Stroke and Alzheimer's Disease:**

Excitotoxicity results from excessive activation of NMDARs, leading to intracellular Ca2+ overload and subsequent neuronal damage. In ischemic stroke, reduced cerebral blood flow triggers massive glutamate release, causing acute excitotoxicity and rapid neuronal necrosis. Conversely, in AD, chronic excitotoxicity due to sustained Ca2+ dysregulation contributes to progressive neurodegeneration over the years.[1]

- **NMDAR-Mediated Calcium Dysregulation:**

NMDAR activity plays a pivotal role in synaptic plasticity and cognitive function. However, excessive activation of extra synaptic NMDARs leads to neurodegeneration. Stroke-induced excitotoxicity causes immediate Ca2+-mediated neuronal death, whereas in AD, prolonged yet mild disruptions in Ca2+ homeostasis contribute to gradual neurodegeneration. The GluN3A subunit of NMDARs has been identified as a neuroprotective agent, modulating Ca2+ influx and preventing excitotoxic damage. Recent studies have further supported the neuroprotective.[1]

- **Amyloid Pathology and Stroke:**

Amyloid-β (Aβ) accumulation is a hallmark of AD. Studies suggest that stroke-induced excitotoxicity can exacerbate Aβ pathology, accelerating cognitive decline. Moreover, ischemic stroke patients often develop Aβ deposits in cerebral vasculature, further linking these conditions. Emerging research from 2023-2025 indicates that vascular contributions to cognitive impairment and dementia (VCID) play a crucial role in post-stroke cognitive decline, reinforcing the need for targeted therapeutic interventions.[2]

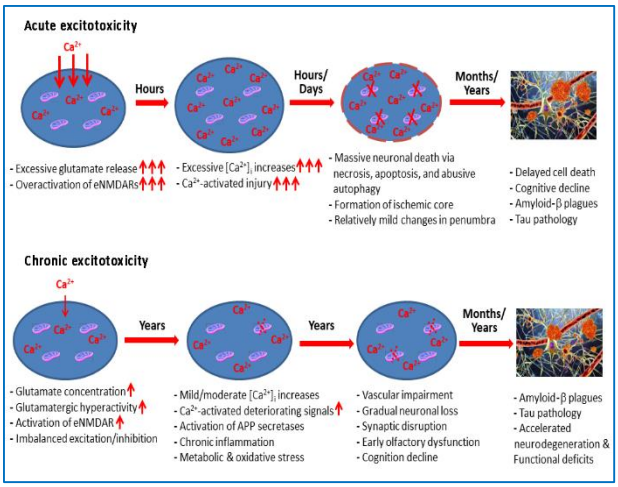

Figure 1: *Acute and chronic excitotoxicity in ischemic stroke and late-onset AD.* [6]

Neuropsychological Assessments in Cognitive Impairment Diagnosis

Neuropsychological assessments are crucial for early diagnosis and differentiation between stroke-induced cognitive impairment and AD. Standardized cognitive testing evaluates memory, executive function, and processing speed, aiding in clinical decision-making. Early detection allows for timely interventions, improving patient outcomes. New assessment methodologies, incorporating AI-driven cognitive tests, have shown promise in enhancing diagnostic accuracy.[3]

Preventive Strategies and Treatment Approaches

Given the shared pathophysiological mechanisms between ischemic stroke and Alzheimer's disease (AD), targeting NMDAR hyperactivity has emerged as a promising therapeutic strategy. Research in 2024 explored neuroprotective approaches in stroke and it highlighted the leading role of excitotoxicity in ischemic neuronal death, a mechanism also implicated in AD [4]. Memantine, an NMDAR antagonist approved for AD, has demonstrated efficacy in reducing excitotoxic neuronal injury in both conditions. Early administration of NMDAR modulators may act as a form of neuroprotective preconditioning, enhancing cerebral resilience against ischemic insults while potentially slowing neurodegeneration. Furthermore, complementary therapeutic strategies such as sigma-1 receptor (S1R) activation—shown to modulate neuroinflammation and promote neuronal survival—have also gained traction. Repurposed S1R-targeting drugs, including amantadine and fluvoxamine, are being explored for their neuroprotective roles in AD and other neurodegenerative diseases [5]. Recent clinical trials have further supported the utility of NMDAR and S1R modulation in mitigating neurodegenerative effects. [4,5]

Conclusion

The interplay between ischemic stroke and AD underscores the importance of understanding excitotoxicity in neurodegeneration. Targeting NMDAR-mediated Ca2+ dysregulation presents a viable approach for mitigating neuronal damage[4,5]. Furthermore, integrating neuropsychological assessments into clinical practice enhances early detection and intervention [1]. Future research should explore combination therapies addressing both acute and chronic excitotoxicity to improve outcomes for individuals at risk of stroke and AD [4,5]. The latest research from 2023 to 2025 highlights the growing potential of multimodal approaches that combine pharmacological, cognitive, and lifestyle interventions for better long-term outcomes.[1,4,5]

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