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EDITORIAL HIGHLIGHT

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Hippocampal hyperglutamatergic signaling matters: Early targeting glutamate neurotransmission as a preventive strategy in Alzheimer's disease

An Editorial Highlight for "Riluzole attenuates glutamatergic tone and cognitive decline in AβPP/PS1 mice" on https://doi.org/10.1111/jnc.15224.

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Abstract

This Editorial highlights a remarkable study in the current issue of the Journal of Neurochemistry in which Hascup and coworkers provide novel data showing that riluzole, an anti-glutamatergic drug, may be a promising early intervention strategy for Alzheimer's disease (AD), aimed at restoring glutamate neurotransmission prior to amyloid beta (Aβ) plaque accumulation and cognitive decline. The mice APP/PS1, a model of AD, initially are cognitively normal but have elevated glutamate release in the hippocampus at 2–4 months of age. They begin showing cognitive decline and Aβ plaque accumulation at approximately 6–8 months of age, and show obvious AD neuropathology and cognitive impairment at 10–12 months. The riluzole treatment over 4 months (at 2–6 months of age) targeting early changes in glutamatergic neurotransmission prevents cognitive decline observed at 12 months of age and restores glutamatergic neurotransmission. This is one of the most convincing preclinical evidence supporting the idea of targeting glutamate neurotransmission in patients at risk for AD and to use riluzole for this purpose.

KEYWORDS

Alzheimer's disease, APP/PS1 mice, glutamate neurotransmission, hippocampus, riluzole

1 | INTRODUCTION

> It occurred to me that at one point it was like I had two diseases—one was Alzheimer's, and the other was knowing I had Alzheimer's. Terry Pratchett

Alzheimer's disease (AD) is the most prevalent age-related neurodegenerative disease associated with progressive memory loss and decline of higher cognitive function. Postmortem, neuritic plaques containing amyloid ß (Aβ) peptide and neurofibrillary tangles containing phospho-tau protein are evident in the diseased brain. Despite the huge amount of effort to develop an effective cure, pharmacological treatment of AD still represents an unresolved problem. Currently, approved anti-dementia drugs have limited efficacy providing neither a stop of disease progression nor a significant delay. Decades of clinical trials did not bring any efficient disease-modifying therapeutics to market, still giving no hope to AD patients and people at risk for AD. Obviously, an innovative hypothesis regarding the understanding AD pathogenesis is wanted for an effective novel strategy for this devastating disease.

Abbreviations: AD, Alzheimer's disease; APP/PS1 mice, double transgenic mice expressing the amyloid precursor protein (Mo/HuAPP695swe) and Presenilin 1 (PS1-dE9) genes; Aβ, amyloid ß peptide Glu, glutamate; α7nAChR, alpha-7 nicotinic acetylcholine receptor.

2 | GLUTAMATERGIC NEUROTRANSMISSION AS A TARGET, RILUZOLE AS A MEANS

A promising ideological shift in this field may be related to new and encouraging experimental results indicating that glutamate (Glu) pathway may play a substantial role in the pathogenesis of AD, in particular at the early stages of the disease. Chronic excess of extracellular Glu may result in excitotoxicity because of an over-activation of ionotropic Glu receptors. Excitotoxicity has been hypothesized to be implicated in various neurodegenerative diseases including amyotrophic lateral sclerosis, AD, and Huntington's disease as well as focal brain damage (stroke, traumatic brain injury) (Wang & Reddy, 2017). Chronically elevated Glu levels may attenuate the detection of physiological signals and thus inhibit memory and retrieval associated with excitotoxicity-mediated neurodegeneration observed in AD. The inability of existing drugs targeting the glutamatergic system (e.g., memantine) to significantly slow disease progression may be related to their modulating post-synaptic N-methyl-D-aspartate (NMDA) receptors rather than Glu release or clearance (Hascup, Broderick, et al., 2019). Hyperexcitability of the hippocampus is a commonly observed phenomenon in the period preceding a diagnosis of AD. It has been suggested that a dysregulation in Glu neurotransmission may mediate this hyperexcitability (Hunsberger et al., 2015).

Riluzole (2-Amino-6-(trifluoromethoxy)benzothiazole) is a well-known benzothiazole anticonvulsant with neuroprotective effects. The mechanism of riluzole action involves the inhibition of pathologic glutamatergic transmission in neuronal synapses via sodium channel blockade, though other, still unclear, mechanisms may be also involved (Bellingham, 2011). Riluzole inhibits persistent and fast Na^+ currents, voltage-gated Ca^{2+} and K^+ currents, repetitive firing, and neurotransmitter release, while it potentiates Ca^{2+}-dependent K^+ current and Glu transporters, promotes neuronal survival and expression of growth factors (Figure 1). A high-affinity neuron-specific glutamine transport system inhibited by riluzole is described in developing and mature neuron-enriched hippocampal cultures (Erickson, 2017). Riluzole is approved by FDA for clinical use in patients with amyotrophic lateral sclerosis and is promising for spinal cord injury (both preclinical evidence, and clinical data are available) as a safe and well-tolerated neuroprotective treatment (Zhou et al., 2019). Riluzole is also discussed as a potential therapeutic drug for spinocerebellar ataxia type 3 (Schmidt et al., 2016).

Previous publications have demonstrated amelioration of glutamatergic hyperactivity immediately following cessation of riluzole treatment in 5XFAD transgenic mice harboring amyloid β precursor protein (APP) and presenilin mutations and demonstrating early Aβ accumulation (Okamoto et al., 2018) as well as in the rTg(TauP301L)4,510 mouse model of AD (Hunsberger et al., 2015). Recent data also indicate that riluzole attenuates $A\beta_{42}$-mediated increases in CA1 spike frequency and restores the hippocampal glutamatergic/GABAergic imbalance induced by $A\beta_{42}$ (Yang et al., 2020). These findings suggest that riluzole has the potential to ameliorate cognitive deficits during different stages of AD progression. However, long-term effects of riluzole in AD models have not been studied.

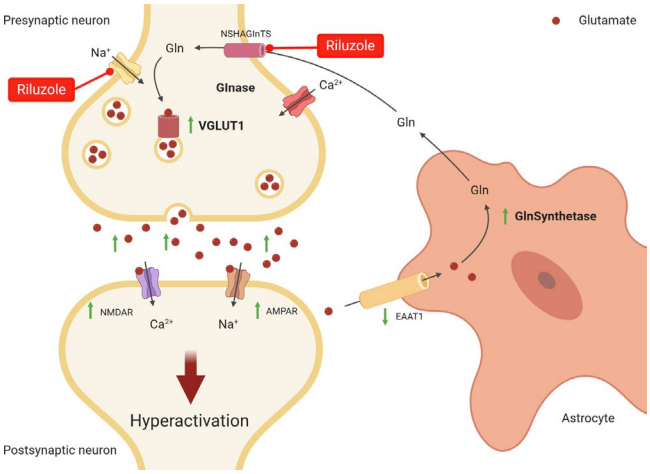

FIGURE 1 Early alterations to the glutamatergic system developing throughout disease progression in AβPP/PS1 murine model of AD contribute to hyperactivation, extracellular glutamate accumulation, and resulting excitotoxicity. Riluzole blocks sodium channels and neuron-specific, activity-regulated, high-affinity glutamine (Gln) transport system (NSHAGlnTS). Green arrows show the direction of changes. Other abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; EAAT1, excitatory amino acid transporter 1; Glnase, glutaminase; GlnSynthetase, glutamine synthetase; NMDAR, N-methyl-D-aspartic acid receptor; VGLUT1, vesicular glutamate transporter 1

3 | EVIDENCE IN MURINE AβPP/PS1 MODEL OF AD

Deficits in Glu transporter function were reported in young AβPP/PS1 mutant transgene mice, and these deficits might contribute to early occurring pathogenic processes associated with AD (Mookherjee et al., 2011). In this AβPP/PS1 murine model of progressive cerebral amyloidosis/familial AD, hippocampal hyperglutamatergic signaling occurs prior to plaque accumulation (Hascup, Broderick, et al., 2019; Hascup, Findley, Britz, et al., 2020; Hascup & Hascup, 2015). Importantly, at advanced stages of the development, AβPP-PS1 mice exhibit a severe reduction in glutamatergic and gamma-amino butyric acid (GABA)ergic neuronal metabolic activity and neurotransmitter cycling fluxes in the hippocampus, cerebral cortex, and striatum (Patel et al., 2018). This late period of glutamatergic hypoactivation accompanying Aβ-associated depression of long-term potentiation and cognitive deficits may be the consequence of a preceding period of increased glutamatergic activity (Findley et al., 2019). Subregion and age-specific alterations in hippocampal glutamatergic activity in AβPP/PS1 mice have been reported. Elevated evoked glutamate release in the dentate gyrus and CA1 was observed at 2–4 months of age, whereas elevated basal glutamate was observed in these regions by 6 months of age (Hascup et al., 2020). These elevated levels were evident up to 12 months of age (Hascup, Broderick, et al., 2019; Hascup et al., 2019), when cognitive deficits were more pronounced. These findings are indicative of early alterations of the glutamatergic

system in the AβPP/PS1 murine model of AD and suggest that elevation of synaptic Glu levels over time may result in excitotoxicity and ultimate hippocampal atrophy observed in AD. The reported data allow to hypothesize that riluzole treatment may have long-term pro-cognitive advantages mediated by reduced glutamatergic tone in amyloidogenic AD mice.

In the current issue, Hascup and colleagues (Hascup, Findley, Britz, et al., 2020), provide data that support the concept of a critical involvement of glutamatergic hyperactivity in the cognitive deterioration in AD. Their results also give experimental confirmation for the potential use of riluzole as an early intervention strategy for AD, aimed at re-establishing Glu neurotransmission before significant Aβ plaque accumulation and cognitive decline. The group performed a prodromal treatment with riluzole of male AβPP/PS1 mice for 4 months. This treatment resulted in prolonged pro-cognitive effects (improved long-term memory assessed in Morris water maze), accompanied by restored glutamatergic tone (basal Glu concentration and evoked Glu release levels evaluated by in vivo electrochemistry) observed 6 months after discontinuing riluzole treatment. Interestingly, riluzole treatment did not affect Aβ plaque accumulation. Notably, in contrast to riluzole, treatment of AβPP/PS1 mice with LY379268, a metabotropic glutamate receptor (mGluR)2/3 agonist, failed to exert long-term pro-cognitive effects and to attenuate glutamatergic signaling (Hascup, Britz, et al., 2019).

Recently, it has been reported that soluble Aβ42 elicits glutamate release through the alpha-7 nicotinic acetylcholine receptor (α7nAChR), which may contribute to elevated levels of hippocampal glutamate first observed prior to cognitive decline in AβPP/PS1 mice (Hascup & Hascup, 2016). However, in this study, the authors were unable to find differences in α7nAChR expression across treatment groups. Immunofluorescent staining of Glu transporter 1 could not reveal differences either. Thus, no direct evidence could be provided in this study substantiating the involvement of α7nAChR expression or Glu transporter 1 in changes in Glu dynamics. However, to assuredly exclude or confirm these mechanisms, additional experimental approaches should be used. More in-depth studies are needed to elucidate the mechanism of riluzole action in this AD model, in particular, pre- and post-synaptic effects.

4 | CONCLUSION

George Carlin once joked about AD: "I think it would be interesting if old people got anti-Alzheimer's disease where they slowly began to recover other people's lost memories." However, seriously speaking, there is no doubt that awareness about a potential effective cure for AD would allow seeing the light at the end of the tunnel for thousands of patients and people at risk for AD. The data presented by Hascup and colleagues in this issue (Hascup, Findley, Britz, et al., 2020) confirm that at the early stage of AD progression, interventions targeting the glutamatergic system may exert lasting effects on disease outcome and may prevent cognitive decline. This is one of the most convincing preclinical evidence supporting the idea of targeting Glu neurotransmission in patients at risk for AD. It is assumed that since AD is the result of multiple interrelated causalities culminating in anterograde amnesia and cerebral atrophy, multiple therapeutic strategies for individual patient care are necessary (Hascup & Hascup, 2020). Riluzole therapy may be a promising approach among these strategies.

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CONFLICT OF INTEREST

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