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Letter to the editor

Memantine treats psychosis and agitation associated with Moderna COVID-19 vaccine

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1. Introduction

Currently, mRNA-1273 COVID-19 (Moderna) vaccine is widely used to prevent the SARS-CoV-2 pandemic and shows powerful effectiveness to deter community transmission. There are common reactogenicity-related side effects such as fever, fatigue, and headache; however, rare report on the neuropsychiatric problems (Kim et al., 2021). More than 8200, 000 doses of Moderna vaccine were injected in Taiwan by April 2022. Two stable psychiatric patients complicated with acute agitation and exacerbated psychosis after getting first dose of Moderna vaccine and rescued by memantine treatment against NMDA receptor-mediated excitotoxicity. Based on the clinical course and pharmacological treatment effect, the plausible mechanism of neuroinflammation and modulation of glutamate neurotransmission by mRNA vaccine was addressed in this report.

2. Case reports

Case 1, a 46-year-old man with schizophrenia, without chronic physical disease, was admitted to our psychiatric ward for an acute episode of psychosis. The symptoms of auditory hallucinations, persecutory ideation improved with the use of olanzapine 20 mg per day for one month and were ready to transfer to our daycare center under more stable mental conditions. However, he experienced acute relapse of the psychotic symptoms within 5 h after received the Moderna vaccine. Perplexed and agitated behaviors, involuntary eye-lid twitching, self-talking and laughing, and pacing around the lounge were noted. He locked himself in the bathroom and showed treatment refractory to olanzapine 30 mg combined with chlorpromazine 25 mg for more than two weeks. Considering the symptoms triggered by vaccination and severe behavioral excitation different from previous symptoms, we use memantine under the impression of acute neuroinflammation. With the adjunctive therapy started with memantine 10 mg daily, the acute psychotic features got improved within 3 days, and we maintained the dose of 10 mg per day for 2 months.

Case 2, an 82-year-old man had been followed up at our psychiatric outpatient clinic for treatment of alcohol-related dementia after abstaining from alcohol drinking for 5 years. He has been stable and able to maintain fair daily activities and routines under alprazolam 0.5 mg as needed. In the night after received the Moderna vaccine, acute disorganized behaviors, severe restlessness, aggressive and agitated behaviors were developed. After a week of quetiapine 25 mg treatment failed, we added memantine 20 mg per day and his condition improved to his baseline in 3–5 days. The memantine 20 mg treatment was continued for 3 months and then maintained with 10 mg per day for dementia treatment.

3. Discussion

The acute psychosis and agitation were developed after Moderna vaccination and failed to previous antipsychotics. Considering the possibility of COVID-19 vaccine-induced neuroinflammation, memantine, an anti-NMDA mediated excitotoxicity, was used and showed striking effect to rescue acute psychosis. The preclinical report of Moderna vaccine demonstrated around 2–4 % of the plasma level lipid nanoparticle distributed to the brain after single-dose intramuscular injection in Sprague Dawley rats and remained measurable for over 25 h. We proposed that the nucleoside-modified mRNA could be rapidly uptake and expressed the spike-protein elicits both humoral and cellular immunity. The lipid nanoparticle delivery system protects the mRNA fragments from nuclease degradation, and its lipophilic fashion endues its capability to pass the blood-brain barrier (BBB), as well as potentially modulates the neuroinflammation. The mRNA particle may be phagocytized by microglia cells and translated to spike protein, stimulate the immune response (as shown in Fig. 1-A), which would lead to massive proinflammatory cytokine production, including tumor necrosis factor (TNF), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-12 (IL-12), reactive oxygen species (ROS), and chemokines (Haroon et al., 2017; Shabab et al., 2017).

The neuroinflammation provoked astrocytes to release excessive

Abbreviations: NMDA, *N*-methyl D-aspartate; IL-6, interleukin-6; TNF, tumor necrosis factor; ROS, reactive oxygen species.

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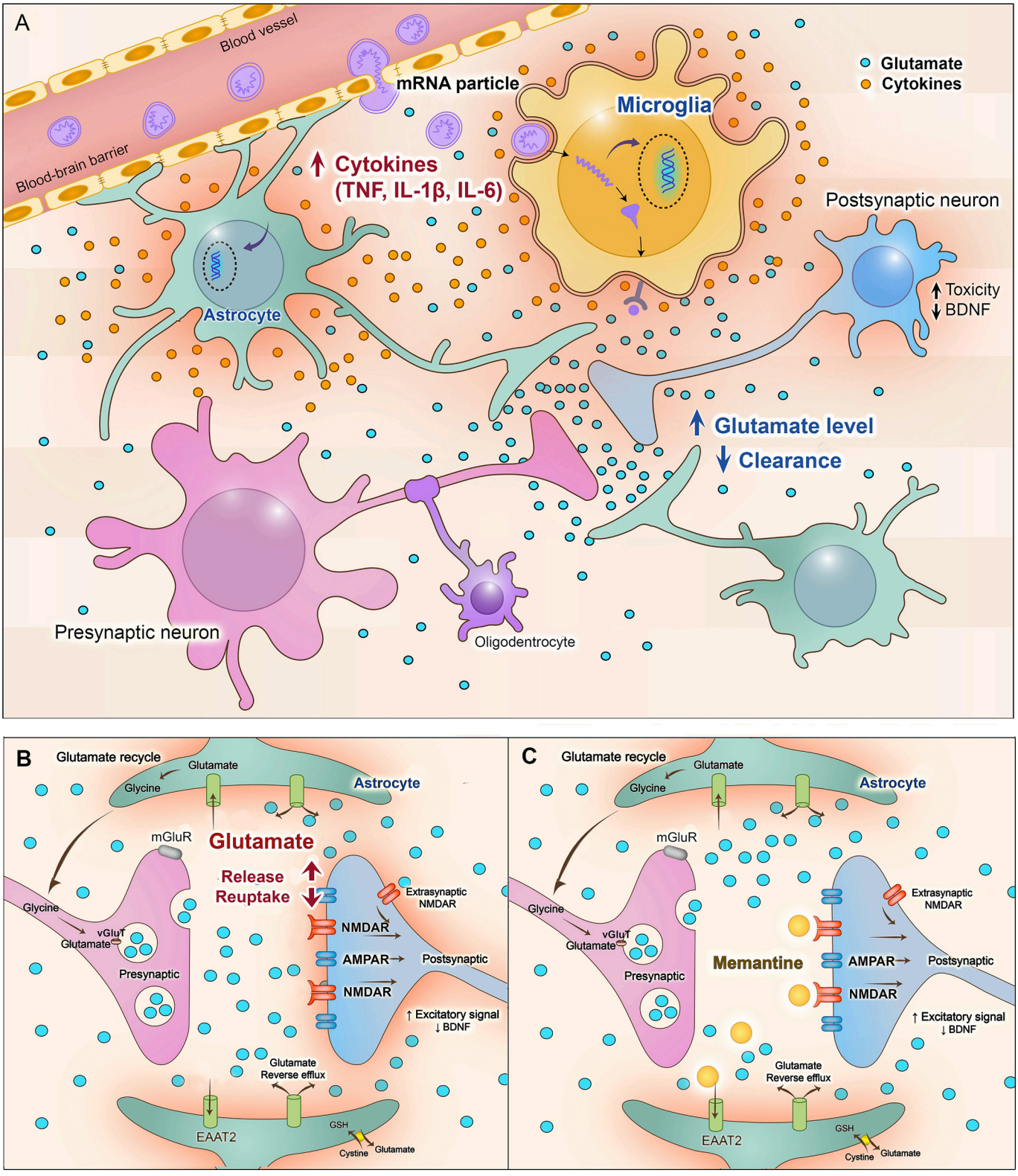

Fig. 1. Mechanism of mRNA COVID-19 vaccine and neuroinflammation.
(A) Schema of mRNA-1273 COVID-19 vaccination related neuroinflammation. mRNA particles and translated peptides activate microglia cells and produce proinflammatory cytokines including tumor necrosis factor (TNF), interleukin-1β(IL-1β), interleukin-6 (IL-6). The cascade alterations of cytokines strike astrocyte transformation and lead to massive glutamate release. (B) Glutamate neurotransmission and development of neuropsychiatric disorders. Increase synaptic glutamate level, overstimulate the ionotropic glutamate receptors, included *N*-methyl D-aspartate (NMDA) receptor, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, and moderation of glutamate reuptake via excitatory amino acid transporter (EAAT). The unbalancing glutamate levels interfere the brain neurotransmission and cause acute psychosis. (C) Memantine blocked glutamate receptors, tuning the neurotransmission and attenuating the neuropsychiatric problems. mGluR, metabotropic glutamate receptor; vGluT, vesicular glutamate transporter; BDNF, Brain-derived neurotrophic factor; GSH, Glutathione.

glutamate in the synapse and caused overstimulation of *N*-methyl D-aspartate receptor (NMDAR) related excitotoxicity. The overexcitation of glutamate neurotransmission would reduce the brain-derived neurotrophic factor (BDNF) signaling and neuroplasticity (Haroon et al., 2017). The NMDAR overactivation interferes with the balance of dopamine neurotransmission and paradoxically induces psychotic outbursts (Kayser and Dalmau, 2016), as shown in Fig. 1-B. In the two patients, the psychotic features were rescued by adding memantine, an uncompetitive NMDAR antagonist, which indirectly approved the concept. Memantine acts as an excitatory neuron modulator and effectively tones down the excessive glutamine activity thus reverse the pathological excitation (Lipton, 2006), reduces the oxidative stress (Dias et al., 2007). Its effect may also attribute to the neurotrophic factors release from astrocytes and preventing microglial activation (as shown in Fig. 1-C).

In the both cases, one with schizophrenia and the other with long-term alcohol use disorder and neurodegenerative disease, might have been more vulnerable to the mRNA vaccine-related neuroinflammation modulated by glutamate neurotransmission, and may be due to the fragile BBB in psychotic patients (Pollak et al., 2018). Otherwise, ethnical variations to the vaccine side-effect will be a noteworthy issue. The report shows mRNA-1273 vaccination was correlated with the acute exacerbated psychosis in the two psychiatric patients. The possible association effect of clinical course and pharmacological response to memantine, the adverse events may attribute to neuroinflammation and glutamate excitotoxicity after mRNA penetrated the brain. However, the therapeutic effects of memantine deserve further elucidation.

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CRediT authorship contribution statement

Chen Y.C. had the idea for the paper. Siao W.H. prepared the first draft. Chang F.Y. prepared the draft figure. WHS, FYC and YCC were involved in clinical care of the patients. All authors reviewed the manuscript for the intellectual content.

Declaration of competing interest

The authors report no conflict of interest.

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