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Review Article

The "Holy Grail" of Neuropsychiatric Medicine: Challenges for Disease-Modifying Therapy

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Abstract

In recent years, there has been a growing trend in the field of CNS medicine toward disease-modifying therapy (DMT), which directly treat the underlying causes of disease. In the field of epilepsy, the limitations of conventional anti-seizure pharmacotherapy have raised a trend toward DMT aimed at anti-epileptogenicity, and efforts to prevent or modify the onset and progression of epilepsy in tuberous sclerosis, post-traumatic epilepsy, and post-stroke epilepsy have been made. In the area of dementia, after longstanding challenges and failures, the recent reports of Aducanumab and Lecanemab may provide an opportunity for significant progress in DMT for Alzheimer's disease. In multiple sclerosis, the advent of various lymphocyte-targeted agents, antibody drugs, as well as interferon beta, has led to remarkable therapeutic advances. In neurodegenerative diseases such as Parkinson's disease and amyotrophic lateral sclerosis, DMT may also become possible in the future due to advances in iPS cells and other technologies. In psychiatric disorders, the pathophysiology that needs to be corrected must first be clarified, and the glutamate hypothesis and ¹H-MRS findings in treatment-resistant schizophrenia might provide key evidence for that. Beyond the conventional symptomatic treatment, advances in DMT may lead to a cure of neuropsychiatric

disorders in the future. In this article, based on a symposium held at the 118th Annual Meeting of the Japanese Society of Psychiatry and Neurology, we discuss the current status and potential of DMT in neuropsychiatry.

Keywords: disease-modifying therapy, neuropsychiatry, neurodegenerative diseases, epilepsy, dementia

Introduction

Current neuropsychiatric practice primarily focuses on treatments aimed at symptom relief and remission. However, this is fundamentally symptomatic treatment and does not equate to a complete cure of the disease. To overcome the limitations of symptomatic treatment, there has been growing interest in recent years in the field of CNS medicine in disease-modifying therapy (DMT), which targets the fundamental causes of a disease. This paper discusses the current status and potential of DMT in psychiatric and neurological medicine, based on a symposium held at the 118th Annual Meeting of the Japanese Society of Psychiatry and Neurology.

I. Conventional Psychiatric and Neurological Medicine and Disease-modifying Therapy (DMT)

Psychotropic drugs improve psychiatric symptoms, antiepileptic drugs suppress epileptic seizures, and conventional dementia treatments slow

the progression of degenerative dementia. Furthermore, L-DOPA preparations used for Parkinson's disease help alleviate neurological symptoms. However, there are limits to symptom suppression and improvement, and the current reality is that situations where a cure can be expected for neuropsychiatric disorders are limited. In contrast, DMT is based on the principle of acting on and modifying the fundamental disease process. While it does not necessarily mean a cure at this point, it is a treatment that ultimately aims for a cure. In 2021, the U.S. Food and Drug Administration (FDA) granted limited approval for aducanumab, which targets amyloid beta plaques, for Alzheimer's disease patients. The introduction of DMTs is also emerging as a major paradigm shift in other fields of CNS medicine.

II. DMTs in Epilepsy

1. Changes in the Nomenclature of Antiepileptic Drugs

In recent years, there has been a movement to change the term “anti-epileptic drugs” (AEDs). This is because while traditional AEDs suppress seizures, they do not treat epilepsy itself (at least their efficacy in doing so has not been proven). Therefore, the term “anti-epileptic” is considered inaccurate, and “anti-seizure medications” (ASMs) is considered more appropriate.¹¹⁾ However, for convenience, this paper will continue to use the term “anti-epileptic drugs.” Over the past 20 to 30 years, numerous anti-epileptic drugs have been developed⁴³⁾ and marketed in Japan. Although problems such as side effects and drug interactions have been significantly resolved, seizure control is achieved in only about 60-70% of cases. Furthermore, therapeutic effects become increasingly difficult to achieve, particularly with the third or subsequent drugs. This situation has remained virtually unchanged for the past 20 years.³⁾²⁶⁾ Against this backdrop, the limitations of conventional AED therapy and efforts to overcome them have been proposed.

DMT in epilepsy is defined as the prevention or modification of the onset and progression of epilepsy, with effects that are not solely attributable to the anticonvulsant action; it is also referred to as “anti-epileptogenesis.”¹⁵⁾ Efforts aimed at achieving anti-

epileptogenesis/DMT include the following:

2. Tuberous Sclerosis and mTOR Inhibition

The mechanistic target of rapamycin (mTOR) is one molecule constituting a cellular signaling pathway. Upstream molecules of mTOR are phosphoinositide 3-kinases (PI3Ks) and protein kinase B (Akt), which together form the mTOR pathway. Between Akt and mTOR lie TSC2 and TSC1 genes, causative for tuberous sclerosis.²⁵⁾ Molecular targeted therapy using mTOR inhibitors for tuberous sclerosis have already demonstrated tumor-shrinking effects under conditions like subependymal giant cell astrocytoma (SEGA) and angiomyolipoma (AML). Consequently, therapeutic efficacy became anticipated for epilepsy, which frequently co-occurs with tuberous sclerosis. Indeed, the mTOR inhibitor everolimus demonstrated seizure control in phase III trials for epilepsy in tuberous sclerosis that was refractory to conventional antiepileptic drugs (AEDs),¹⁰⁾ marking a significant step forward in DMT for epilepsy. Epilepsies involving the mTOR pathway are not limited to tuberous sclerosis but also include certain cases of hemimegalencephaly and focal cortical dysplasia, for which molecular targeted therapies are also anticipated.²⁵⁾

3. Post-traumatic Epilepsy (PTE), Post-stroke Epilepsy, and Their Prevention

Seizures occurring more than 7 days after head trauma are diagnosed as post-traumatic epilepsy (PTE). The risk of epilepsy onset increases 16-fold with severe trauma, and up to 53% of penetrating injuries result in PTE.⁸⁾ Unlike symptomatic seizures seen in the acute phase of head injury, PTE is considered a state of acquired chronic epileptogenicity, a process involving neuroinflammation, neuronal cell death, and synaptic changes. Research into the anti-epileptogenesis effects of existing antiepileptic drugs (AEDs) for preventing PTE onset has been conducted, but none have shown efficacy. Currently, AED use is recommended only for suppressing seizures in the early post-injury period.⁸⁾

Similarly, delayed seizures occurring 1–2 weeks or later after stroke are considered a result of acquired chronic epileptogenicity. The mechanisms involved are considered to include gliosis, disruption of neural networks followed by neuronal excitation, or, in the case of hemorrhagic strokes, hemosiderin deposition.⁷⁾ Regarding the preventive effect of AEDs on post-stroke epilepsy, randomized controlled trials are currently underway,³⁵⁾ but efficacy has yet to be established. Therefore,

prophylactic medication is generally not recommended.⁷⁾

4. Epilepsy Surgery

Epilepsy surgery is an established and widely accepted treatment for drug-resistant epilepsy. It can achieve high rates of seizure freedom, particularly in cases where epileptogenic lesions are resectable.³⁹⁾⁵⁵⁾ In addition to achieving seizure freedom, it frequently alleviates adverse events, such as psychiatric complications, and reduces mortality.¹⁵⁾ Epilepsy surgery addresses and corrects the fundamental cause of the disease; in this sense, it is arguably the only widely available and established DMT currently in clinical use.¹⁵⁾ Limitations of epilepsy surgery include the fact that only about 5% of drug-resistant epilepsy patients are ideal candidates with high expectations for seizure freedom, thus limiting its applicability.

5. Other DMT Candidates

Research is also being conducted on anti-epileptogenesis effects of anti-inflammatory and antioxidant actions, with a particular focus on targeting epilepsy types involving marked cytokine release (e.g., FIRES, NORSE).⁴⁶⁾⁴⁹⁾

However, a recent randomized controlled trial using natalizumab, a drug for relapsing-remitting multiple sclerosis expected to have anti-

inflammatory effects, for refractory epilepsy failed to demonstrate efficacy.

¹²⁾ Gene therapy as DMT also presently remains at the research stage.⁵⁷⁾

6. DMTs in Epilepsy: Summary

Conventional antiepileptic drug therapy for seizure control is symptomatic and has limitations in actual clinical practice. Advances such as mTOR inhibition represent progress toward DMTs aiming at anti-epileptogenesis, and further developments are anticipated.

III. DMTs in Dementia

1. History of Alzheimer's Disease Research

Among neurodegenerative diseases causing dementia, Alzheimer's disease (AD) is the most prevalent. Regarding the history of AD research, the acetylcholine hypothesis was established in the 1970s based on neurotransmitter studies, leading to the development of cholinesterase inhibitors, which were introduced in the 1990s. Currently, four therapeutic drugs are marketed in Japan: donepezil, galantamine, rivastigmine, and memantine. These drugs were developed at that time and belong to symptomatic therapies that act on neurotransmitters to improve dementia symptoms. Meanwhile, molecular biology research in the 1990s led to the

proposal of the amyloid cascade hypothesis, which posits that amyloid- β (A β) protein deposition represents the earliest pathological change in the disease process.¹⁸⁾ At this point, AD established its position as a model for degenerative diseases encompassing molecular-pathology-syndrome.

Development of DMTs targeting proteins centered on A β to inhibit the progression of causative pathological changes became active from the 2000s.

2. History of A β Vaccine Therapy

The first DMT to gain attention for AD was A β vaccine therapy. Immunization of amyloid- β precursor protein (APP) transgenic mice with A β 42 and an adjuvant was reported to prevent the formation of senile plaques.⁴⁴⁾ A muscle injection formulation (AN 1792) consisting of synthetic A β 1-42 and an adjuvant, was developed and underwent Phase II trials in Europe. However, meningoencephalitis occurred as a side effect in approximately 6% of the 280 patients in the active drug group, resulting in discontinuation of the trial in 2002. Autopsy brains revealed infiltrating CD4-positive T cells, suggesting autoimmune encephalitis. Subsequent follow-up of participants continued until recent years. Results showed that while A β and senile plaques were generally cleared,

cognitive decline progressed.¹⁶⁾²⁰⁾³⁴⁾ These findings highlighted the critical issue of treatment timing, prompting a shift toward diagnosing and treating protein pathology before symptom onset.

3. Further Challenges and Failures in DMTs for AD

Regardless of the failure of AN 1792, drug development based on the amyloid cascade hypothesis continued. Development directions included vaccine therapies avoiding lymphocyte stimulation; passive immunotherapy using humanized anti-A β antibodies (e.g., aducanumab, solanezumab, gantenerumab); γ -secretase inhibitors/modulators (e.g., semagacestat) targeting the enzyme that cleaves A β from APP; β -secretase cleavage enzyme inhibitors (e.g., verubecestat, lanabecestat, elenbecestat); and A β aggregation inhibitors (e.g., tramiprosate). Additionally, anti-tau therapeutics, among others, were attempted from the 2000s to 2010s, although the details are not presented here. However, most of these drugs did not achieve success.²⁸⁾ Several reasons can be cited for the failure of these trials, primarily the issue of the accuracy of the clinical diagnosis of AD. The sensitivity and specificity of clinical AD diagnostic criteria have been reported as 71–87 and 44–71%, respectively.¹⁾ This

suggests that early trial participants may have included those without pathological evidence of AD. Furthermore, as mentioned earlier, the timing of treatment initiation is a significant issue. There is a time lag of approximately 15 years between the onset of A β accumulation and emergence of clinical symptoms.⁴²⁾ Consequently, clinical trials are shifting toward preclinical diagnosis using amyloid imaging and preclinical treatment for familial cases. However, this raises new challenges: the need to recruit preclinical individuals outside the standard healthcare system, high cost and limited availability of amyloid imaging facilities, and necessity of screening large numbers of subjects, all of which significantly increase the barriers to conducting trials.

4. The Aducanumab Frenzy

Against this backdrop, aducanumab, a human monoclonal antibody utilizing passive immunotherapy, was reported in 2016 to slow the decline in CDR-SB (Clinical Dementia Rating Sum of Boxes) and MMSE (Mini Mental State Examination) scores in patients with mild cognitive impairment (MCI) and mild AD,⁴⁵⁾ administered via monthly intravenous infusion, and Phase III clinical trials commenced. Although the trials were initially halted in March 2019 based on the Independent Data

Monitoring Committee's judgment, a report in October of the same year stated: "Additional analyses showed the high-dose group significantly suppressed clinical symptom deterioration compared with placebo, achieving the primary endpoint." This led to a reversal, with approval application subsequently announced and submitted to FDA in July 2020. Although the advisory committee expressed the view that the evidence was insufficient, FDA stated that it was "an accelerated approval based on the reduction of amyloid beta plaques in the brain as a surrogate endpoint" and granted conditional approval in June 2021, contingent upon conducting new clinical trials. Conversely, it was not approved in EU, and in December 2021, Japan also placed its review on hold. This sequence of events made the situation very complicated, affecting both society and the market.

5. The Impact of Lecanemab

Although this article was written after the June 2022 symposium, there has been significant progress in the field of DMTs for dementia. Results from the large-scale global Phase III confirmatory trial of lecanemab, an anti-A β protofibril antibody, were released in November 2022.⁵²⁾ According to these results, in the large-scale global Phase III confirmatory trial,

the mean change in CDR-SB at 18 months was -0.45 in the lecanemab group compared with placebo, indicating a 27% slower progression of deterioration ($P = 0.00005$), achieving the primary endpoint. This finding is important because it demonstrated a slowing of cognitive decline rather than merely a reduction in A β , potentially dispelling doubts about the previously weakening A β hypothesis. Furthermore, the side effect of amyloid-related imaging abnormalities (ARIA) was weak, with an ARIA-E (edema) incidence rate of 2.8%. However, several issues remain unresolved: whether a 27% reduction in progression is perceptible to patients and their families; the lack of demonstrated long-term efficacy; the importance of infrastructure development since the drug is not widely accessible; and numerous unresolved healthcare economic and ethical issues previously mentioned.

6. Insights from the History of DMTs in Dementia

The series of developments described thus far raises a critical question: Is the strategy of targeting accumulated proteins, using AD as a disease model, truly valid? Should accumulated proteins be regarded as the gold standard: the holy grail? As the involvement of other age-related

changes in AD pathogenesis and issue of complex pathology gradually become clearer, the very model of AD as a disease is beginning to weaken.

IV. DMTs and iPS Cells in Neurology

1. Neurological Diseases and DMTs

When considering DMTs in neurological diseases, a primary example is interferon beta (IFN β) therapy for multiple sclerosis (MS), which prevents relapses and slows disease progression. It has also been demonstrated that early initiation and continuation of IFN β therapy are critical for improving the long-term prognosis associated with MS.²⁾¹⁷⁾ Recently, the emergence of various lymphocyte-targeted drugs, including antibody drugs, alongside IFN β , has led to marked advances in the treatment of MS, including secondary progressive forms.²⁹⁾ However, what is the current situation regarding DMTs in neurodegenerative diseases (NDDs), such as Alzheimer's disease (AD), Parkinson's disease (PD), or amyotrophic lateral sclerosis (ALS)?

“Neurodegeneration” is defined as the degeneration of neurons or their projections, accompanied by progressive neurological dysfunction.²⁴⁾ Furthermore, DMTs in NDDs are defined as interventions that bring about lasting changes in the clinical progression of NDDs by interfering with

the fundamental pathophysiological mechanisms of the disease process that cause neuronal death.⁵⁾ Two types of outcomes are considered to support DMT efficacy: (i) When a treatment intervention demonstrates a significant difference between the active drug and placebo in clinical effects, accompanied by consistent effects on biomarkers considered to reflect the fundamental pathophysiology of NDD; or (ii) When positive results are obtained in clinical trial designs using “staggered start” or “delayed withdrawal” to confirm lasting clinical course changes due to the treatment intervention. In both cases, disease progression delay based on clinical indicators is evident. From another perspective, “neuroprotection” is defined as an intervention that influences the disease process or underlying pathogenesis to have lasting, beneficial effects for patients.⁴⁰⁾⁵⁶⁾ Neuroprotection can be achieved through direct action on neurons (primary neuroprotection) or by inhibiting secondary processes that cause cell death, such as inflammation or oxidative stress (secondary neuroprotection). Therefore, neuroprotection can be considered the primary goal of disease modification.

The same principles regarding disease modification, neurodegenerative diseases, neuroprotection, and the definition of

DMTs apply to various NDDs, including AD, PD, and ALS. Many underlying molecular biological mechanisms, biomarkers, trial designs, and even therapeutic candidates/targets may be commonly applicable across NDDs.⁴⁾ In any of these NDDs, neuroprotection is essential to achieve disease modification. The persistent and beneficial changes integral to the concept of disease modification can be demonstrated through various clinical indicators and biomarkers, or by trial designs aimed at evaluating disease modification. For example, neurodegenerative-disease-related biomarkers such as neurofilament light chain (NF-L) protein are considered to reflect the direct late stages of cell death in several NDDs.¹⁴⁾ Conversely, disease-pathology-specific biomarkers, such as abnormal accumulation proteins (β -amyloid, tau, TDP-43, α -synuclein, etc.), are generally considered to reflect events in the early stages of the cascade leading to cell death. While important in drug development, they do not necessarily indicate neuroprotection.

Although basic research on NDDs is actively progressing worldwide and our understanding of their pathogenesis is gradually advancing, the translational gap between basic research findings and clinical treatment remains significant. To date, no disease-modifying therapy (DMT) has been approved for any

NDD.³²⁾³⁸⁾ For example, a large-scale staggered start trial for PD was conducted recently, but no disease-modifying effect was confirmed.⁵³⁾ Therefore, proactive efforts are essential, including: the identification of candidate molecules with potential disease-modifying effects, development of new disease models that more accurately predict efficacy in humans, refinement of clinical trial methodologies, and establishment of biomarkers that enable the assessment of disease progression.⁹⁾

2. The Role of Human iPSC Cell Models in Creating DMTs for NDDs

In 2007, Yamanaka et al. at Kyoto University successfully generated induced pluripotent stem cells (iPSCs) from human skin fibroblasts.⁴⁷⁾ This breakthrough enabled the *in vitro* differentiation of iPSCs into various human somatic cell types.³⁶⁾ When using these cells as human disease models, these cells have the potential to replicate any human cell or organ. Importantly, they retain the genetic background of the patient from whom the source cells were derived. This allows modeling of sporadic patients, addressing a major challenge in animal models.³⁷⁾ The majority of existing diseases are sporadic, suggesting that iPSC cell models are also beneficial for mental disorders in which identifying

genetic predispositions is difficult.¹⁹⁾ Using in vitro models derived from the patient enables scientific validation of the fundamental requirement for DMTs: “interfering with the underlying pathophysiological mechanisms of the disease process that cause neuronal cell death.”

3. iPS Cell-based Drug Discovery and Drug Repositioning (DR) for ALS

A group led by Okano at the Department of Physiology, Keio University School of Medicine, successfully differentiated iPS cells derived from familial and sporadic ALS patients into spinal motor neurons, the key cells responsible for ALS pathology. They successfully recapitulated ALS pathology, including neurite shortening, motor neuron death, mitochondrial dysfunction, increased oxidative stress, and abnormal accumulation of ALS-related proteins (TDP-43, FUS) within motor neurons. Furthermore, using these ALS motor neurons and an existing drug library, the group conducted multi-phenotypic/high-throughput drug screening (drug repositioning: DR).¹³⁾ This screening identified multiple ALS therapeutic candidates. After considering factors such as brain penetration and tolerability (including side effects), ropinirole hydrochloride was identified

as a candidate ALS therapeutic. Ropinirole hydrochloride is a dopamine D2 receptor agonist widely used in Japan for PD treatment. In vitro studies confirmed its superior efficacy in improving ALS pathology compared with existing ALS treatments, riluzole and edaravone. Furthermore, the therapeutic effects of ropinirole hydrochloride in ALS have been suggested to arise from both dopamine D2 receptor-dependent and -independent mechanisms. One dopamine D2 receptor-dependent mechanism is considered to suppress pathological hyperexcitability in motor neurons.²¹⁾

To date, in iPS cell-based drug discovery for ALS, a Harvard University group identified the antiepileptic drug ezogabine (retigabine) and Kyoto University group identified the antitumor drug bosutinib as potential therapeutic candidates.³⁶⁾ Notably, according to experimental results by Okano et al., treatment of motor neurons differentiated from iPS cells derived from multiple sporadic ALS patients with ropinirole hydrochloride showed efficacy in approximately 73% of patients' motor neurons. These findings suggest that ropinirole hydrochloride may also be effective for sporadic patients, who represent approximately 90% of ALS cases and for whom efficacy

had not previously been confirmed in animal models.

4. Physician-initiated Clinical Trial for ALS Patients (ROPALS Trial)

Results from nonclinical studies using iPS cells¹³⁾ demonstrated the efficacy of ropinirole hydrochloride for both familial and sporadic ALS patients, and consequently, a physician-initiated Phase I/IIa clinical trial (ROPALS trial), entitled: “*Phase 1/2a, Double-blind, Placebo-controlled Study with an Open-label Extension of Ropinirole Hydrochloride Extended-Release Tablets – Explorative Assessment of the Safety, Tolerability, and Efficacy after Oral Treatment in Patients with Amyotrophic Lateral Sclerosis (ALS) –*” (UMIN trial ID: UMIN000034954) was conducted at the Department of Neurology, Keio University Hospital, from December 2018 to March 2021.³⁰⁾

A key feature of the ROPALS trial was the parallel conducting of in vitro studies. The aim of these studies was to obtain proof of concept for iPS cell-based drug discovery by establishing disease-specific induced pluripotent stem (iPS) cells from all consenting participants. The studies then assessed the effects of ropinirole hydrochloride on motor neurons derived from these cells. Thus, it was a trial involving reverse translational research, including

exploration of stratification tools in sporadic patients.³⁶⁾

Although the trial included only a small number of participants, the results confirmed the safety and tolerability of ropinirole hydrochloride in ALS patients. Furthermore, the results suggested that ropinirole hydrochloride may suppress motor function decline and extend the time to respiratory failure, as well as the time to death or specific disease progression.³¹⁾

However, as mentioned above, to confirm its efficacy as DMT, clinical trial designs such as “staggered start” or “delayed withdrawal” need to be newly implemented.

5. The Role of DMTs and iPS Cells in Neurodegenerative Diseases

This section outlines DMTs for neurodegenerative diseases and the role of “iPS cells” in achieving them. The true value of iPS cell technology in DMT creation, beyond serving as a disease analysis tool, includes: (i) being the only sporadic disease model inheriting the genetic background; (ii) enabling the creation of various cell types (disease target cells in humans); (iii) allowing multi-phenotypic drug screening to ensure robustness of drug effects; (iv) enabling rapid transition to clinical trials by bypassing DR and animal model validation; and (v) contributing to

stratification and precision medicine using patient-derived iPS cells. These roles are expected to enable iPS cell technology to significantly advance the realization of DMTs for neurodegenerative diseases and mental disorders.

V. Treatment Resistance in Schizophrenia and the Potential of DMTs

1. Elucidating Schizophrenia Pathology and ¹H-MRS

In recent years, proton magnetic resonance spectroscopy (¹H-MRS), which can measure brain metabolites, has been utilized in numerous studies to elucidate the pathology of brain disorders. ¹H-MRS is a non-invasive technique that utilizes the nuclear magnetic resonance phenomenon to measure chemical substances within living organisms. In ¹H-MRS, the resonance frequency of atomic nuclei differs depending on the molecular structure and environment in the brain region of interest, allowing the identification of chemical substances from the emitted signals. The difference in the quantity of electrons in atomic nucleus orbitals is quantified, and the resulting frequency difference is called the chemical shift. Representative substances include glutamic acid (Glu) and glutamine (Gln). While much brain activity is mediated by glutamatergic

neurons, with Glu playing a crucial role as a neurotransmitter, the relationship between total Glu levels and neural transmission is not yet fully understood.

2. Limitations of the Dopamine and Glutamate Hypotheses in Schizophrenia

In schizophrenia, enhanced presynaptic dopamine function in the striatum has been shown to be associated with the pathophysiology.⁶⁾ However, the dopamine hypothesis alone cannot account for all aspects of schizophrenia. Approximately 30% of patients do not respond to antipsychotic drugs with dopamine-blocking effects; this is termed treatment-resistant schizophrenia (TRS). Furthermore, approximately 20% of schizophrenia patients and about 70% of TRS patients are resistant to drug therapy from the onset of illness.²⁷⁾

Several studies reported that presynaptic dopamine function is lower in TRS compared with treatment-responsive schizophrenia patients. Furthermore, tetrabenazine, an inhibitor of endoplasmic reticulum monoamine transporter 2, suppresses presynaptic dopamine function. However, no significant effect was observed in TRS patients compared with those receiving a placebo, suggesting that presynaptic dopamine function is not enhanced in TRS.⁴¹⁾

Furthermore, clozapine, the only drug approved for TRS, exhibits low affinity for dopamine D2 receptors. These findings suggest that TRS represents a subtype of schizophrenia with low-level involvement of the dopaminergic system.

This brings attention to the glutamate (Glu) hypothesis, which proposes that schizophrenia can be explained by abnormalities in the Glu system, located upstream of the dopaminergic system. Glu acts on N-methyl-D-aspartic acid (NMDA) receptors, activating parvalbumin-containing interneurons to inhibit pyramidal cells in the hippocampus.⁵⁴⁾ The hypothesis posits that impaired Glu input leads to disinhibition of pyramidal cells, resulting in the emergence of positive symptoms, negative symptoms, and cognitive dysfunction in schizophrenia via pathways involving the nucleus accumbens, amygdala, and prefrontal cortex. Evidence supporting this hypothesis includes reports that the NMDA receptor antagonists ketamine and phencyclidine induce schizophrenia-like symptoms in healthy individuals.⁵⁴⁾ Furthermore, PET studies and postmortem brain research in schizophrenia patients demonstrated NMDA receptor abnormalities,⁵⁴⁾ and genetic studies revealed correlations between NMDA receptor gene abnormalities and schizophrenia risk.⁵⁴⁾

3. ¹H-MRS Studies on the Glu Hypothesis in Schizophrenia

We conducted a meta-analysis of schizophrenia studies comparing the concentrations of four metabolites: Glu, Gln, Glx (glutamate + glutamine), and GABA, using ¹H-MRS, comprehensively summarizing the results for each brain region.³³⁾ A total of 134 studies were included. Subgroup analyses examined differences based on the disease stage and treatment responsiveness. Furthermore, meta-regression analyses evaluated the impact of antipsychotic medication and ¹H-MRS measurement techniques on the results. The findings showed that Glu and Glx concentrations in the basal ganglia were elevated in the schizophrenia compared with healthy control group. This increase in Glu-related metabolite concentrations tended to decrease as the disease stage progressed. In the mid-cingulate cortex, Glu-related metabolite concentrations were elevated in TRS patients but decreased in treatment-responsive schizophrenia patients. Decreased GABA concentrations in the mid-cingulate cortex and increased hippocampal Glx in untreated patients were also observed. These findings suggest that an imbalance between excitation and inhibition in the brain may contribute to the pathogenesis of schizophrenia. Notably, a contrast in

glutamatergic system abnormalities within the mid-cingulate cortex was suggested between TRS and treatment-responsive patients.

Here, we present two ^1H -MRS studies on TRS conducted by our group. The first study examined Glx concentrations in the mid-cingulate cortex and dorsal caudate nucleus in patients with severe symptomatic TRS, patients with a typical treatment response, and healthy controls.⁴⁸⁾ Specifically, by applying stricter TRS criteria, we included patients with symptom severity exceeding that reported in previous studies. The results showed that the Glx concentration in the mid-cingulate cortex was higher in the TRS group than in healthy controls, with no significant differences between patient groups. In the caudate nucleus, no group differences in Glx concentrations were observed. Furthermore, Glx concentrations in both the mid-cingulate cortex and caudate nucleus were not associated with the symptom severity or cognitive function. The second study included TRS patients receiving clozapine monotherapy, incorporating both symptomatic and asymptomatic individuals.²³⁾⁵¹⁾ Specifically, patients were divided into three groups: (i) ultra-treatment-resistant schizophrenia (URS) resistant to clozapine, (ii) clozapine-responsive schizophrenia (non-URS), and (iii)

schizophrenia responsive to non-clozapine antipsychotics. The primary objective of this study was to compare Glx and GABA concentrations in the caudate nucleus, mid-cingulate cortex, and dorsolateral prefrontal cortex (DLPFC) between groups. Results showed that the Glx concentration in the mid-cingulate cortex was higher in the URS than healthy control group, but no significant difference was found between the patient groups. The GABA concentration in the same region was higher in the non-URS than URS group. Furthermore, no associations were observed between psychiatric symptoms or cognitive function and the concentrations of these two metabolites.

4. Pathophysiology of TRS and Potential for DMT

As described above, while abnormalities in the glutamatergic system of the mid-cingulate cortex are consistently reported in TRS, a condition not fully explained by the dopamine hypothesis alone, the accuracy of distinguishing TRS from treatment-responsive schizophrenia remains limited. The treatment response in schizophrenia patients cannot be explained solely by dopaminergic or glutamatergic mechanisms. Therefore, developing DMTs for TRS requires collecting diverse biomarkers and clinical data

from individual patients, ranging from peripheral to central systems and from pre- to post-onset, in order to elucidate the underlying pathophysiology of TRS. However, while the development of Glu modulators and neuromodulation has been actively pursued, robust evidence supporting their efficacy in TRS is lacking.²²⁾⁵⁰⁾ To overcome the current impasse, data-driven biotyping based on the clinical information and biomarkers gathered in the aforementioned studies is anticipated to lead to the future of DMT. This approach involves developing closed-loop neuromodulation that targets network abnormalities specific to each biotype, using readily manageable biomarkers as therapeutic indicators.

Conclusion

Drawing on the symposium presentations, we reviewed the current status and potential of DMTs for various neuropsychiatric disorders, including epilepsy, dementia, neurodegenerative diseases, and schizophrenia. While progress and directions differ across fields, DMTs are considered promising as a new treatment modality to overcome the limitations of conventional psychiatric and neurological medicine.

No conflicts of interest exist relevant to this paper.

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