EDITORIAL

New Targets of Medical Treatment in Psychiatric Disorders

K. Yui

A broader palette of safe and better-tolerated agents is available for treating people suffering from chronic schizophrenia, depressive disorders, anxiety disorder, autism spectrum disorders. However, current medical treatments are still only partially effective, and highly-prevalent psychiatric disorders continue to represent a huge personal and socio-economic burden. Most pharmacological agents sometimes induce a variety of severe movement disorders, including dystonia or dyskinesia, with an acute, subacute or more chronic time course. More extensive cerebral condition, such as the neuroleptic malignant syndrome or the serotonin syndrome may be induced by antipsychotics or selective serotonin reuptake inhibitors (SSRI). Medications commonly involve dopamine receptor blockers, antidepressants and anti-epileptics, among many others. Mechanisms underlying drug-induced movement disorders involve blockade, facilitation or imbalance of dopamine, serotonin, noradrenaline and cholinergic neurotransmission in the basal ganglia [1]. The traditional and atypical neuroleptics sometimes induce dystonic reactions, akathisia, parkinsonism, neuroleptic malignant syndrome, serotonin syndrome, tremor, hyperkinesia and movement disorders [1]. A better understanding of the impact of these drug-induced adverse effects may provide new strategies to develop novel neuroleptics with less adverse metabolic effects and to develop complementary medical therapies to patients treated with antipsychotic medication [2]. The lack of success in discovering more effective pharmacotherapy has contributed, together with many other factors, to a relative few useful findings on new drug targets for neuropsychiatric disorders.

Among partially effective or treatment-resistant psychiatric symptoms, treatment–resistant aggressive behavior, anhedonia, chronic schizophrenia with cognitive dysfunction, and social impairment of autism spectrum disorders (ASD) are important topics for new targets of neuro-pharmacological therapy. Here, we reviewed new drug targets of these refractory psychiatric disorders.

With respect to treatment-resistant aggression, Catechol O-methyltransferase (COMT) has been found to be associated with aggression, attention deficit/hyperactivity disorder (ADHD), and other psychiatric disorders [3]. In this review, Zai and Kennedy *et al.* (Canada) evaluated single nucleotide polymorphisms (SNPs) in COMT with the phenotype of high aggression in children with a possible role for the COMT marker in callous-unemotional (CU) desposition, which includes reduced empathy and remorse and shallow affect and are associated with more severe, persistent, and treatment refractory externalizing behaviors [4]. As the important role in CU despositioin in antisocial behavior, further investigation of COMT is needed.

An accumulating evidence supports a role for the central cholinergic system in the pathophysiological factors of schizophrenia and mood disorders. Muscarinic receptors (CHRMs), understanding their role in CNS functioning and in synthesizeing drugs can specifically target each of the 5 CHRMs. Dysfunction in the cholinergic muscarinic receptors has been considered as the pathophysiological factor in bipolar disorder and major depressive disorder [5]. The finding on the association between decreased CHRM3 receptor expression and bipolar disorder suggests that bipolar and major depressive disorder differs in the underlying mechanism of dysfunction of cholinergic systems [5]. In this review (Jeon *et al.*, Australia), the pan-CHRM antagonist, scopolamine, produces rapid-acting antidepressant effects on individuals with both major depressive disorder (MDD) or bipolar disorder (BPD), and thus novel drugs that selectively target CHRMs with negligible effects on the peripheral nervous system might produce more rapid and robust clinical improvement in patients with BPD and MDD

The endocannabinoid system modulates inflammatory processes, demonstrating beneficial effects on severity and symptoms of disease [6]. Moreover, the endocannabinoid system decreases mTOR signaling in the hippocampus to depressive-like behaviors [7]. Oleoylethanolamide (OEA) is known as an endocannabinoid analog belonging to endogenous acylethanolamides. Accumulating evidence suggests that OEA may act as an endogenous neuroprotective factor in the control behavior of psychiatric disorder [8]. The OEA's antidepressive effects may be related to the regulation of brain-derived neurotrophic factor (BDNF) in the hippocampus and prefrontal cortex, and the antioxidant defenses in the hypothalamic-pituitary-adrenal axis (HPA) [8]. The serine hydrolase monoacylglycerol lipase (MAGL), which combines with the endocannabinoid and eicosanoid systems, provide the arachidonic acid (AA) precursor for pro-inflammatory eicosanoid synthesis. MAGL inhibitors elicit anti-nociceptive, anxiolytic, and attenuate withdrawal symptoms in addiction paradigms *via* enhancement of endocannabinoid signaling [9]. MAGL inhibitors have also been shown to exert anti-inflammatory action in the brain and protect against neurodegeneration through lowering arachidonic related eicosanoid production [9]. Palmitoylethanolamide (PEA), which is an endogenous fatty acid amide belonging to the N-acylethanolamines (NAEs), decreases the inflammatory degree [10]. In this review, Ogawa and Kunugi (Japan) presented that the endocannabinoid and related molecules including oleoylethanolamide and pulmitoylethanolamide may be a new perspective on antidepressants. Additionally, inhibitors of fatty acid amide hydrolase and monoacylglycerol lipase have antidepressant-like effects on animal studies (Ogawa S and Kunugi H, Japan). Moreover, Ogawa and Kunugi (Japan) presented that MAGL inhibitors may reduce inflammatory responses through activation of cannabinoid receptor type 2.

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Anhedoniathe, which is defined as the inability of feel pleasure, has been shown to be a critical feature of a range of schizophrenia and depression [11]. Anhedoniathe sometimes persists in depressed subjects despite being on SSRI antidepressant treatment [12]. A recent epidemiological study revealed that the cortical thickness of the superior frontal gyrus and the volume of the pallidum in the left hemisphere were associated with anhedonia scores in a non-clinical sample, suggesting pathological mechanisms underlying the anhedonia in schizophrenia and other psychiatric disorders [13]. Here, Lee and Kim *et al.* (Korea) reviewed that anhedonia is related to deficit activity in reward processing systems. A further analysis into the neuroimaging findings of schizophrenia shows that the neural correlates overlap in the reward network such as ventral striatum, anterior cingulate cortex and orbitofrontal cortex. Other neuroimaging studies have demonstrated the involvement of the default mode network in anhedonia.

In spite of progress in pharmacological therapy for schizophrenia, the lack of efficacy of medical drugs for cognitive deficits is a serious burden on careers and also family members. New drug targets for cognitive deficits require appropriate neural biomarkers in model organisms, treatment response and insight into pathophysiological disease mechanisms. Recently, the 5-HT (1A) receptor has been considered a key candidate for mediating cognitive dysfunction of schizophrenia [14,15]. Preclinical studies have reported various findings regarding the effects of 5-HT (1A) partial agonists to improve cognition. However, several previous studies reported that 5-HT (1A) antagonists are effective to improve cognition. Namely, atypical antipsychotics including aripiprazole, clozapine, olanzapine, perospirone, quetiapine, risperidone and ziprasidone are either direct or indirect 5-HT (1A) agonists, and can improve cognitive function in subjects with schizophrenia [14]. 5-HT (1A) receptor partial agonists may elicit hyppocampal neurogenesis and increases prefrontal cortex dopamine [15]. In this review, according to studies of Uehara *et al.* (Japan), reduction of parvalbumin (PV)-positive γ-aminobutyric acid (GABA) interneurons has been associated with the pathophysiology of cognitive impairments of schizophrenia. It is assumed that an imbalance of excitatory and inhibitory activity induced by low activity of glutamatergic projections and PV-positive GABA interneurons in the prefrontal cortex may lead to cognitive dysfunction, suggesting novel pharmacotherapy targeting GABA neurons and their activities. 5-HT 1A receptor agonist improves cognitive disturbances through mechanism that corrects E-I imbalance *via* the suppression of GABA neural function. Thus, the new pharmacotherapy may alleviate abnormalities in GABA neurons through 5-HT_{1A} agonists and T-817MA, preventing the onset and/or progression of schizophrenia (Uehara *et al.*, Japan).

It is well known that omega-6 polyunsaturated fatty acid arachidonic acid (AA)-derived eicosanoids are a complex family of lipid signaling mediators. AA-derived eicosanoids play various modulations of brain functions. AA can be converted into biologically active compounds by cyclooxygenases (COX). The COX pathway has important role in numerous homeostatic and pathophysiological processes, including neuropsychiatric conditions, such as schizophrenia and bipolar depression. Celecoxib, which is a selective COX-2 inhibitor, has antipsychotic effects on schizophrenia. In this review, Yui *et al.* (Japan) summarized more favorable effects of celecoxib add-on therapy compared to atypical antipsychotics, such as risperidone or amisulporide. Celecoxib can be considered as an effective add-on treatment for refractory major depression and bipolar depression. The COX/PEG_2 pathway plays an important role in synaptic plasticity and may be included in pathophysiology of an ASD. Further precise clinical studies on efficacy of inhibitors of COX-2 as well as COX-1 are needed to show definitive efficacy of these inhibitors (Yui *et al.*, Japan).

SHANK3 is a synaptic protein in the postsynaptic density of excitatory synapses, and plays important role in synapse formation, maturation and maintenance [16]. Mutations in SHANK3 is a cause of autism spectrum disorder (ASD) and schizophrenia. SHANK3 causes a wide range of neuropsychiatric disorders, indicating that SHANK3 may be critical for normal brain function [17, 18]. In this review, Uchino and Waga (Japan) focused the functions and expression profile of each SHANK3 isoform in relation to synaptic dysfunction and the features of ASDs, and discussed the therapeutic potential of SHANK3 for ASD.

Finally, the new targets of these refractory symptoms will open new avenues for research in pathophysiology of central nervous system-related psychiatric disorders, and may provide useful information on novel and effective drug targets and pharmacological agents to induce remission states of these symptoms. The effort to research new drug targets may accumulate useful data for more useful psychiatric drugs development. We sincerely hope that the findings presented in this thematic issue will be helpful for all of the clinical and preclinical researchers in the field of neuropharmacology, and will stimulate further research to treat refractory psychiatric symptoms.

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Kunio Yui
(Guest Editor)
Research Institute of Pervasive Developmental Disorders
Ashiya University Rokurokusocho 13-22, 659-8511
Ashiya
Japan
Department of Pediatrics
Dokkyo Medical University Kitakobayashi 880
Mibu, 321-0293
Tochigi
Japan