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Current Neuropharmacology, **2015**, *13*, **793-801**

New Pharmacotherapy Targeting Cognitive Dysfunction of Schizophrenia via Modulation of GABA Neuronal Function

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Abstract: Schizophrenia is considered a neurodevelopmental and neurodegenerative disorder. Cognitive impairment is a core symptom in patients with the illness, and has been suggested a major predictor of functional outcomes. Reduction of parvalbumin (PV)-positive γ-aminobutyric acid (GABA) interneurons has been associated with the pathophysiology of schizophrenia, in view of the link between the abnormality of GABA neurons and cognitive impairments of the disease. It is assumed that an imbalance of excitatory and inhibitory (E-I) activity induced by low activity of glutamatergic projections and PV-positive GABA interneurons in the prefrontal cortex resulted in sustained neural firing and gamma oscillation, leading to impaired cognitive function. Therefore, it is important to develop novel pharmacotherapy targeting GABA neurons and their activities. Clinical evidence suggests serotonin (5-HT) 1A receptor agonist improves cognitive disturbances of schizophrenia, consistent with results from preclinical studies, through mechanism that corrects E-I imbalance *via* the suppression of GABA neural function. On the other hand, T-817MA, a novel neurotrophic agent, ameliorated loss of PV-positive GABA neurons in the medial prefrontal cortex and reduction of gamma-band activity, as well as cognitive dysfunction in animal model of schizophrenia. In conclusion, a pharmacotherapy to alleviate abnormalities in GABA neurons through 5-HT_{1A} agonists and T-817MA is expected to prevent the onset and/or progression of schizophrenia.

Keywords: cognitive dysfunction, GABA, glutamate, 5-$HT1_A$ agonist, neuroprotection, schizophrenia, T-817MA.

1. INTRODUCTION

Schizophrenia is a relatively common and often debilitating neuropsychiatric disorder. The illness typically starts in late adolescence or early adulthood, and in most cases, persists throughout life. Patients manifest positive and negative symptoms, as well as impairments in cognitive function. Long-term disability and social decline is most closely associated with deficits in cognition, which also determines treatment outcome [1-3]. Currently, the disease is treated mainly with antipsychotic drugs through the actions on various neurotransmitter receptors, such as dopamine (DA) receptors. However, the effect of the majority of established pharmacological therapies is mainly limited to the reduction of positive symptoms, while negative symptoms and cognitive impairments may often persist throughout life, in spite of treatment with existing antipsychotics [4, 5]. These lines of evidence lead to the concept that brain morphological changes induced by response to neurotoxic stress is a primary pathophysiology of schizophrenia.

Schizophrenia is considered as both a "neuro-degenerative" [5, 6] and "neurodevelopmental" [7, 8] disorder. While these two concepts may appear contradictory, they are, in fact, neural processes to explain the patho-physiology of the illness, if coupled with the temporal factor. Each process may predominate at different stages of schizophrenia, which may contribute to the variety of symptoms [9]. Given accumulating neuroimaging evidence for progressive volume changes occurring early in psychosis, neurodegeneration is likely to be associated with neuro-chemical dysregulation that can lead to the onset of the illness [5, 10]. Progressive cortical atrophy has been considered to be related to histological abnormalities, such as a smaller somal volume and decreased spine density, dendritic length and terminals, without gliotic reactions. It is postulated that these findings represent neurodegeneration induced by apoptosis, not necrosis [11]. The apoptotic processes, such as synaptic apoptosis and layer-specific neuronal and/or glial apoptosis, occur during the prodromal phase of schizophrenia [9, 11, 12].

Dysfunction of γ-aminobutyricacid (GABA) interneurons, particularly those containing the calcium-binding protein parvalbumin (PV), has been suggested to be associated with the pathophysiology of schizophrenia, as the result of an *imbalance* between excitation and inhibition in the cerebral cortex [13-15]. In fact, levels of glutamate decarboxylase (GAD) 67, the enzyme that synthesizes GABA, mRNA and protein have been found consistently to be lower in the frontal cortex of subjects with schizophrenia [16-18]. There is histological evidence for the reduction of PV-positive GABA interneuron density in the frontal cortex [19, 20]. It is suggested that a developmental deficit of

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1570-159X/15 $58.00+.00

inhibitory GABA interneurons may underlie neuro-degeneration through the exaggerated activation of gulutamatergic neurons [21]. Therefore, efforts to identify more effective approaches, for example, the application of neuroprotective and/or neuroregenerative compounds, as well as neuromodulators, are needed.

2. COGNITIVE DYSFUNCTION IN SCHIZOPHRENIA

2.1. Behavioral Symptoms

Schizophrenia has been characterized by positive symptoms (*e.g.*, delusions, hallucination, thought disorder) and negative symptoms (*e.g.*, psychomotor retardation, blunted affect, social withdrawal). Patients with the illness also demonstrated about a 1-2.5 SD decline in neuro-psychological performance, *e.g.* several types of memory, executive function, attention/information processing, verbal fluency, and motor function [22]. For example, working memory impairment is thought to be a core feature of schizophrenia, because it consists of several processes including storage buffers for different domains of information and a central executive component for the manipulation of information within the storage buffers [23]. It is considered that cognitive dysfunction is a major determinant of outcome, including quality of life and social function [24].

2.2. Relation to the Abnormality of GABA Neurons

Cognitive performance relies on coordinated activities of several brain regions, including the dorsolateral prefrontal cortex (DLPFC) [25]. Gamma frequency (30-80 Hz) oscillations in DLPFC neural networks are thought to provide a key neural substrate for cognition. Fast-spiking PV-positive GABAergic interneurons and pyramidal glutamatergic neurons seem to act as a basic unit of synchronous oscillatory activity, and this high frequency gamma band activity may underlie basal cognitive processes, especially working memory [26].

It is assumed that an *imbalance* of excitatory and inhibitory (E-I) activity induced by low activity of glutamatergic projections and PV-positive GABA interneurons in the prefrontal cortex resulted in sustained neural firing and gamma oscillation, leading to impaired working memory in schizophrenia [15, 27-29]. An upstream GAD 67 deficit in PV-positive GABA interneurons has been reported in the PFC of rats treated with MK-801, which is related to *N*-methyl-$_D$-aspartate (NMDA) receptor hypofunction in these neurons, leading to disinhibition of pyramidal cells [30]. Postmortem studies report reductions in the number of PV-positive GABA interneurons in the PFC of patients with schizophrenia [13]. Moreover, the concentration of cortical GABA and the activity of GAD67 has been shown to be decreased [31, 32]. These observations led to the "GABA hypofunction" theory [33].

3. STRATEGY FOR THE DEVELOPING NOVEL PHARMACOTHERAPY IN SCHIZOPHRENIA

The first antipsychotic drugs were not prospectively designed but rather discovered serendipitously [21]. Since chlorpromazine was found in the early 1950s to alleviate agitation and hallucinations, a large amount of research has been directed to the molecular mechanisms (usually neurotransmitter receptors) underlying the effects of first-generation antipsychotic (FGA) or psychotomimetic drugs [34]. The pathophysiology of schizophrenia remains unclear; however, some promising hypotheses have been postulated. One convincing hypothesis is dysregulation of dopaminergic neurotransmissions in limbic brain regions [35], because all antipsychotic drugs are dopamine D_2 receptor antagonists [36]. Specifically, there is a linear relationship between clinical potencies of antipsychotic drugs and their affinity for D_2 receptors in the brain [37-39]. However, FGAs have relatively little influence on cognitive and negative symptoms, and elicit adverse side effects, such as extrapyramidal motor symptoms, tardive dyskinesia, weight gain, and sedation [1, 2, 40].

Recently, second-generation antipsychotics drugs (SGAs) have been used as first-line medication to treat patients with schizophrenia. It has been indicated that SGAs elicit a partial effect on improving cognitive dysfunction, which may be related to their relatively high affinity for serotonin (5-HT)-$5HT_{2A}$ receptors compared with DA-D_2 receptors [41, 42]. However, about one-third of patients are resistant to treatment with existing SGA [4].

As a next step to develop novel psychotrophic compounds to treat negative symptoms and cognitive deficits, correcting the "E-I imbalance" (low activity of glutamatergic projections and PV-positive GABA interneurons) may be important to enhance cognitive performance in schizophrenia [29, 43, 44]. Several pharmacological approaches in this line are currently under study; these include agonists at the glycine site of NMDA receptor, DA-D_1 receptor, metabotropic glutamate receptor (mGluR; type-2/3 or 5), or 5-HT_{1A} receptors [45, 46].

On the other hand, there is evidence for a progressive volume loss of gray matter and reduced growth of white matter in schizophrenia, particularly in cases with multiple exacerbations [47]. Histological evidence demonstrated the reduction of PV-positive GABA interneuron density in the frontal cortex [19, 20]. These volumetric changes may be a challenge for pharmacological treatments [45]. Therefore, it is important to develop a novel paradigm targeting those morphological abnormalities Fig. (**1**).

In the following sections, we will discuss data on the effects of 5-HT_{1A} agonists and of T-817MA, a novel neurotropic agent, on cognitive deficits and changes of PV-positive GABA interneurons.

4. 5-HT_{1A} AGONISTS IN THE TREATMENT OF COGNITIVE DYSFUNCTION

4.1. Clinical Evidence for the Role for 5-HT_{1A} Receptors in Cognition

Disturbances of cognitive function, evaluated by psychological and neurophysiological methods, have been shown to predict social outcome in patients with schizophrenia [3, 42]. Particularly, interests are given to the

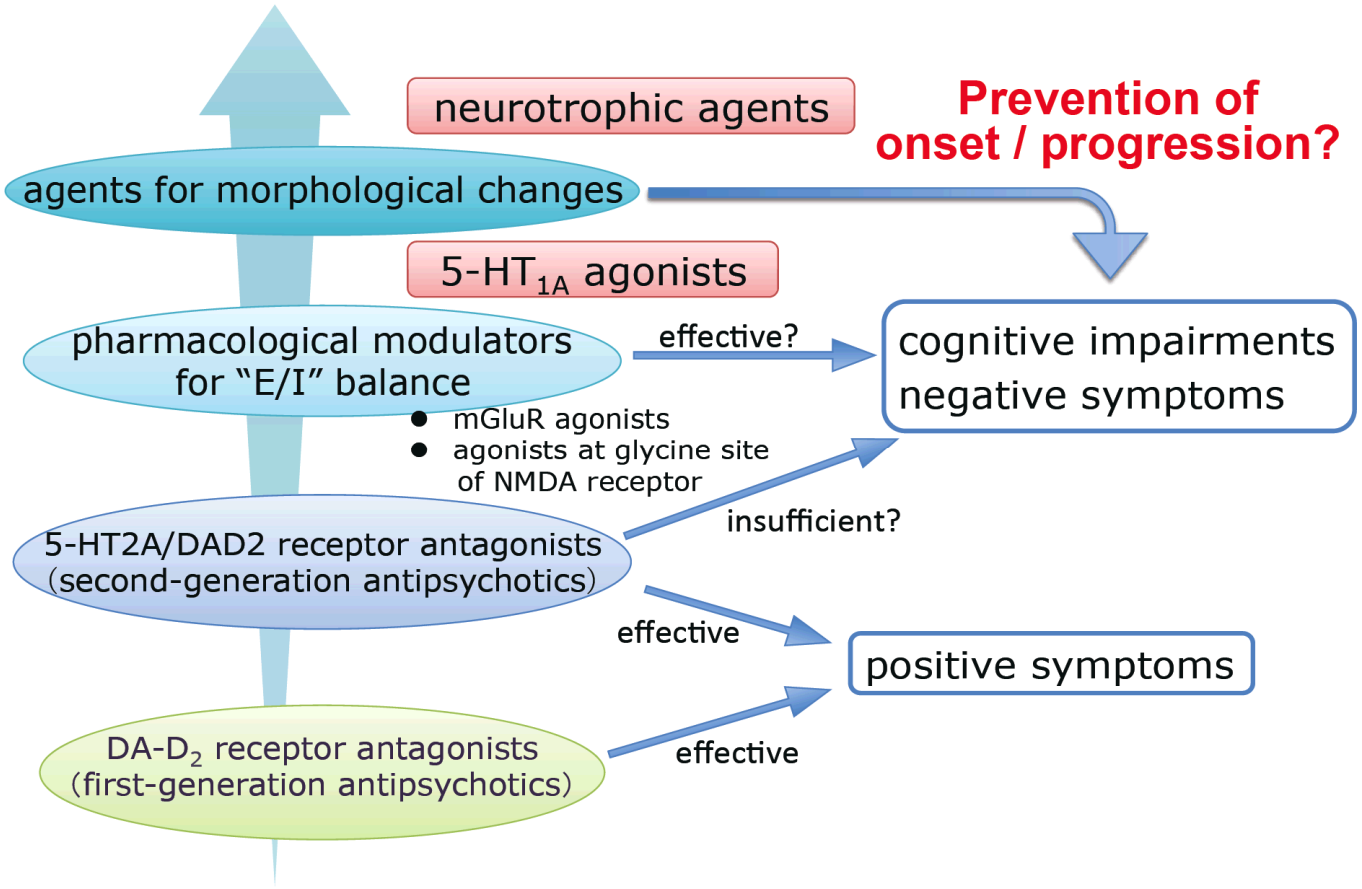

Fig. (1). The strategy for developing new pharmacotherapy in schizophrenia.

role of psychotropic compounds acting on 5-HT receptors in alleviating cognitive impairment of the disease. Among the 5-HT receptor subtypes, the 5-HT_{1A} receptor has been a focus as a potential target for enhancing cognition [48-51]. We have carried out a series of clinical trials to determine whether 5-HT_{1A} agonists improve cognitive function in patients with schizophrenia [52-54]. The addition of tandospirone (30 mg/kg) to typical antipsychotic drugs taken (mainly haloperidol) for 4-6 weeks, was found to improve verbal memory, memory organization, and executive function [52, 54]. Furthermore, in a randomized, double-blind, placebo-controlled study, the addition of buspirone (30 mg/kg) outperformed the placebo in improving attention/information processing in patients treated with SGAs, such as olanzapine and risperidone [53]. These findings provided the basis for the ability of 5-HT_{1A} receptor stimulation to enhance cognition, a therapeutic approach that has promoted the development of novel antipsychotic drugs [48-50, 55].

4.2.Preclinical Evidence

The advantage of 5-HT_{1A}agonism for cognitive function is also suggested by animal studies. Thus, treatment with perospirone [56] or aripiprazole [57], 5-HT_{1A} partial agonists [58, 59], dose-dependently alleviated phencyclidine (PCP)-induced cognitive deficits in mice. This effect was abolished by pretreatment with the selective 5-HT_{1A}antagonist WAY-100635. Moreover, tandospirone, a partial 5-HT_{1A} receptor agonist, dose-dependently improves impaired memory performance as evaluated by the Novel Objects Recognition Test in PCP-induced rat models. This effect was also abolished by pretreatment with WAY 100635 [60]. These findings provide further support for the concept that cognitive disturbances of schizophrenia are ameliorated by stimulation of 5-HT_{1A} receptors [50, 60].

We have examined the effects of tandospirone on extracellular lactate concentration (eLAC) as an indicator of brain energy metabolism using a microdialysis technique [61]. Lactate production was hypothesized to supply energy substrates and reflect neural activity, whose metabolism depends on glutamatergic activity [61]. Specifically, activation of postsynaptic NMDA receptors or glutamate transporters on astrocyte enhance lactate production [61, 62]. Our investigation revealed that the acute administration of tandospirone increased eLAC in the medial prefrontal cortex (mPFC) of naïve adult rats [63], while chronic treatment ameliorated abnormal lactate metabolism in the mPFC of a rat model of schizophrenia [64, 65]. These data on brain energy metabolism support the hypothesis that 5-HT_{1A} agonism can improve cognitive deficits of schizophrenia [55, 66].

4.3. Mechanisms Underlying Cognitive Enhancement by 5-HT$_{1A}$ Receptors

Sumiyoshi *et al.* postulated a putative neural network involving glutamate, GABA, 5-HT and DA associated with the ability of 5-HT$_{1A}$ agonists to enhance cognition in schizophrenia [50, 51, 55] Fig. (**2**). Systemic administration of 8-OH-DPAT, a 5-HT$_{1A}$ agonist, decreases action potentials of GABA neurons. This leads to disinhibition of glutamate neurons [50, 67] and activation of meso-cortical dopamine neurons [68]. For example, administration of clozapine increases extracellular DA concentrations in the prefrontal cortex through activation of 5-HT$_{1A}$ receptors [68]. Findings from electrophysiological studies are consistent with the concept that cognitive benefits of 5-HT$_{1A}$agonism are mediated by glutamate and GABA neurons [67, 69].

Altogether, clinical and animal studies provide evidence for the benefits of 5-HT$_{1A}$agonism on cognitive function in schizophrenia and the mechanism is possibly involved in resetting the E-I imbalance.

It is noteworthy that activation of 5-HT$_{1A}$ receptors exerts a neuroprotective effect in animal models of ischemia. 5-HT$_{1A}$ agonists have been shown to moderate cerebral damage induced by focal cerebral ischemia in rats and mice [70]. Moreover, stimulation of 5-HT$_{1A}$ receptor induces neuroprotection against NMDA-induced apoptotic cell death in cell cultures [71]. Although the cellular mechanisms underlying the neuroprotective effect of 5-HT$_{1A}$ receptor activation remain unclear, it is assumed that 5-HT$_{1A}$ receptor stimulation can modulate NMDA-receptor-induced Ca^{2+} influx and facilitate the antiapoptotic effect of neurotrophin brain-derived neurotrophic factor (BDNF) [70]. Further studies are warranted to determine the ability of 5-HT$_{1A}$ receptor agonism to ameliorate morphological abnormalities in schizophrenia.

5. NEUROTROPHIC AGENTS AND MORPHOLOGICAL ABNORMALITIES

While some debate exists as to whether schizophrenia is entirely neurodevelopmental in nature, there is evidence supporting a progressive and neurodegenerative disease process as well. The pathophysiological processes possibly begin in the prodromal stage of the illness, and continue after the onset of the illness [5, 9, 10]. The underlying mechanisms may include apoptosis (a.k.a. programmed cell death). Progressive volume reduction of the brain, especially the prefrontal cortex, is found in individuals at high genetic risk of schizophrenia who later develop schizophrenia [72].

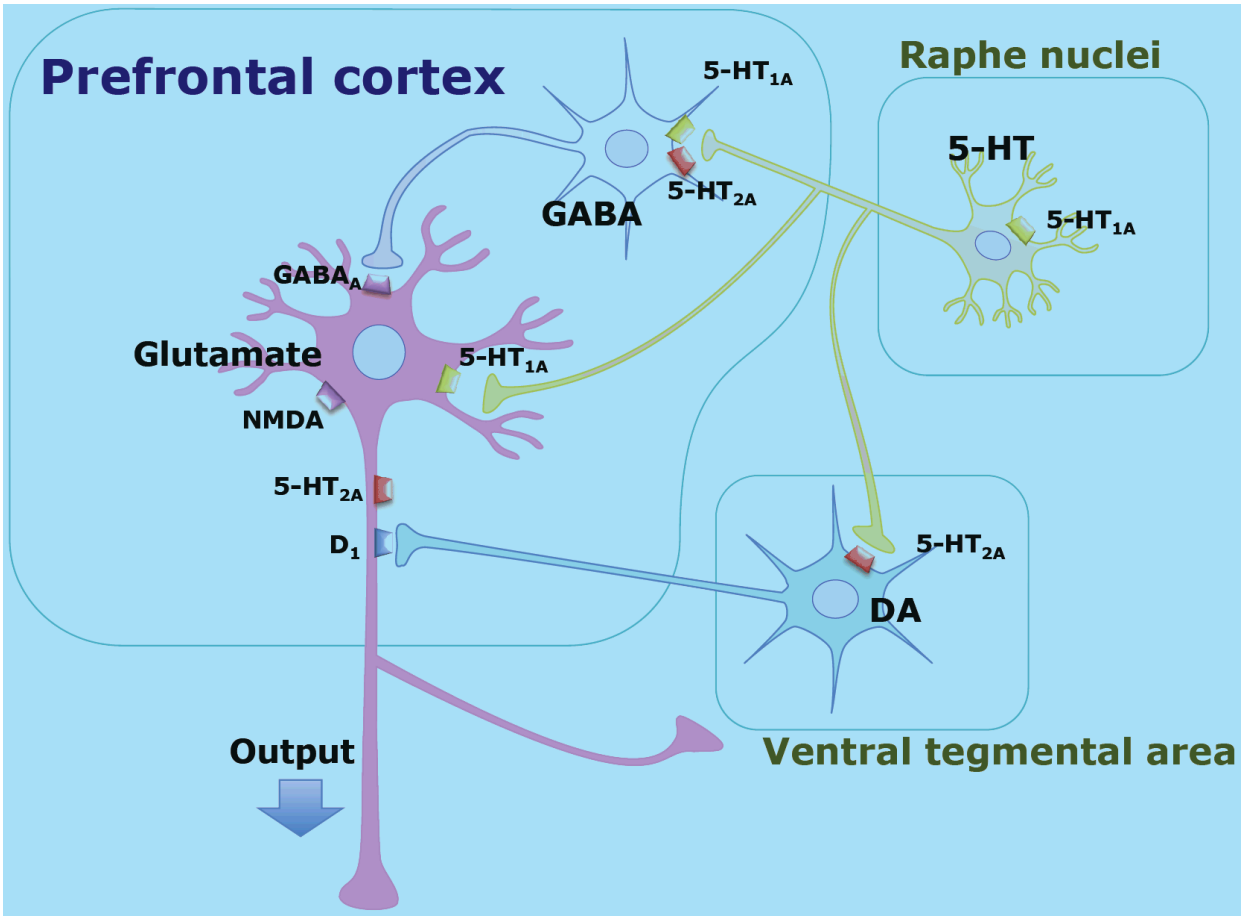

Fig. (2). The putative mechanisms underlying cognitive enhancement by 5-HT$_{1A}$ receptors and Neural network in the prefrontal cortex involving glutamate, GABA, 5-HT and DA neurons. Part of the effect of 5-HT$_{1A}$ agonists on cognition and negative symptoms is thought to be mediated by 5-HT$_{1A}$ receptors located on GABAergic interneurons regulating glutamatergic pyramidal neurons [50, 51, 55].

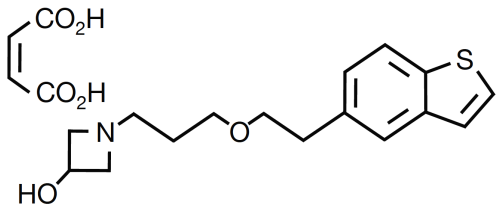

Fig. (3). Chemical structure of T-817MA [1-{3-[2-(1-benzothiophen-5-yl) ethoxy]propyl} azetidin-3-ol maleate] [78].

The vulnerability of neurons to pro-apoptotic insults (pro-apoptotic triggers) would lead to selective dendritic and synaptic losses observed in subjects with schizophrenia [11]. The number of spines on the dendrites of pyramidal neurons in the frontal association cortex is largely reduced in schizophrenia, while neurons themselves are reduced in size and packed more densely without any change in number [73, 74]. In the promotion of apoptosis, several stimuli have also been suggested to play a role, including 1) glutamatergic excitotoxicity, 2) excess synaptic calcium flux, 3) oxidative stress, and 4) reduced neurotrophin levels (for example, BDNF, neurotrophin-3; NT-3) [11, 75].

5.1. T-817MA as a Novel Neurotrophic Agent

Neuroprotection refers to the relative preservation of the structural integrity and normal functioning of the central nervous system against a pathological process and consequent neurobiological stress [75]. T-817MA [1-{3-[2-(1-benzothiophen-5-yl) ethoxy]propyl} azetidin-3- ol maleate] is a newly synthesized agent that was developed for the treatment of neurodegenerative disorders, such as Alzheimer's disease (Fig. **3**). It (1) exerts neuroprotective effects against neurotoxicity caused by intracerebroventricular infusion of amyloid-β(Aβ) [76, 77], (2) facilitates neurogenesis, such as neuron proliferation, neurite outgrowth, and synaptogenesis [78], and (3) improves cognitive impairment in rats receiving intracerebroventricular infusion of Aβ [76, 77] or expressing FTDP17 human P301L mutant tau [79]. In particular, this agent elicits neuroprotective effects against H_2O_2-induced neurotoxicity [78] through attenuation of reactive oxygen species (ROS) production in mitochondria [80]. These data suggest that T-817MA exerts neurotrophic potency on the central nervous system, but precise mechanism of action remains unclear, for example, whether this agent itself has neurotrophic effects or leads to enhance neurotrophic factors.

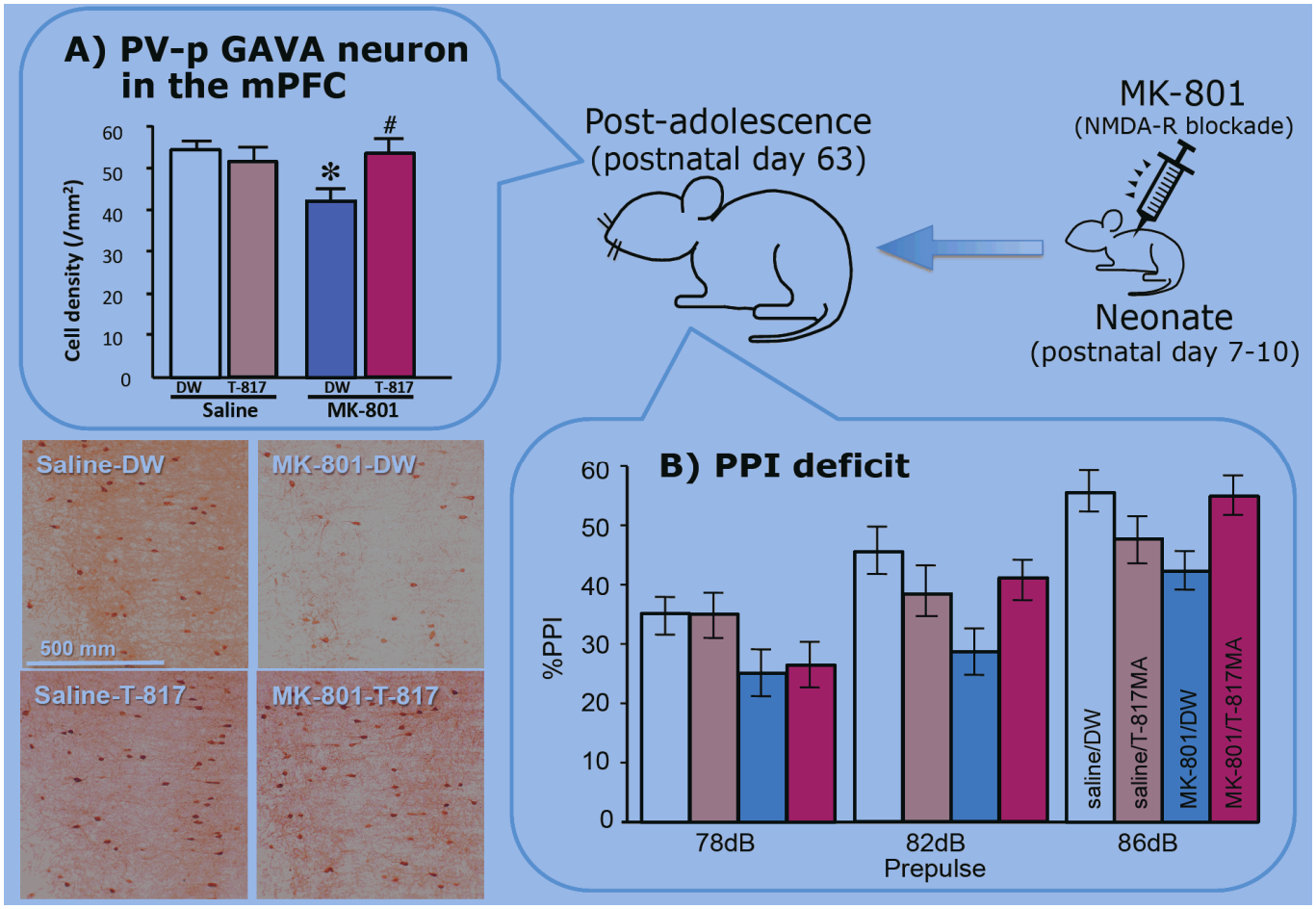

Fig. (4). The schema of effects of T-817MA on (A) decreased number of parvalbumin positive GABA interneurons (PV-p GAVA neuron) in the medial prefrontal cortex (mPFC) and (B) prepulseinhibiton (PPI) deficit in animal model of schizophrenia. Rats were received MK-801 (0.2 mg/kg/day, s.c.) neonatally (postnatal days 7-10) [85].

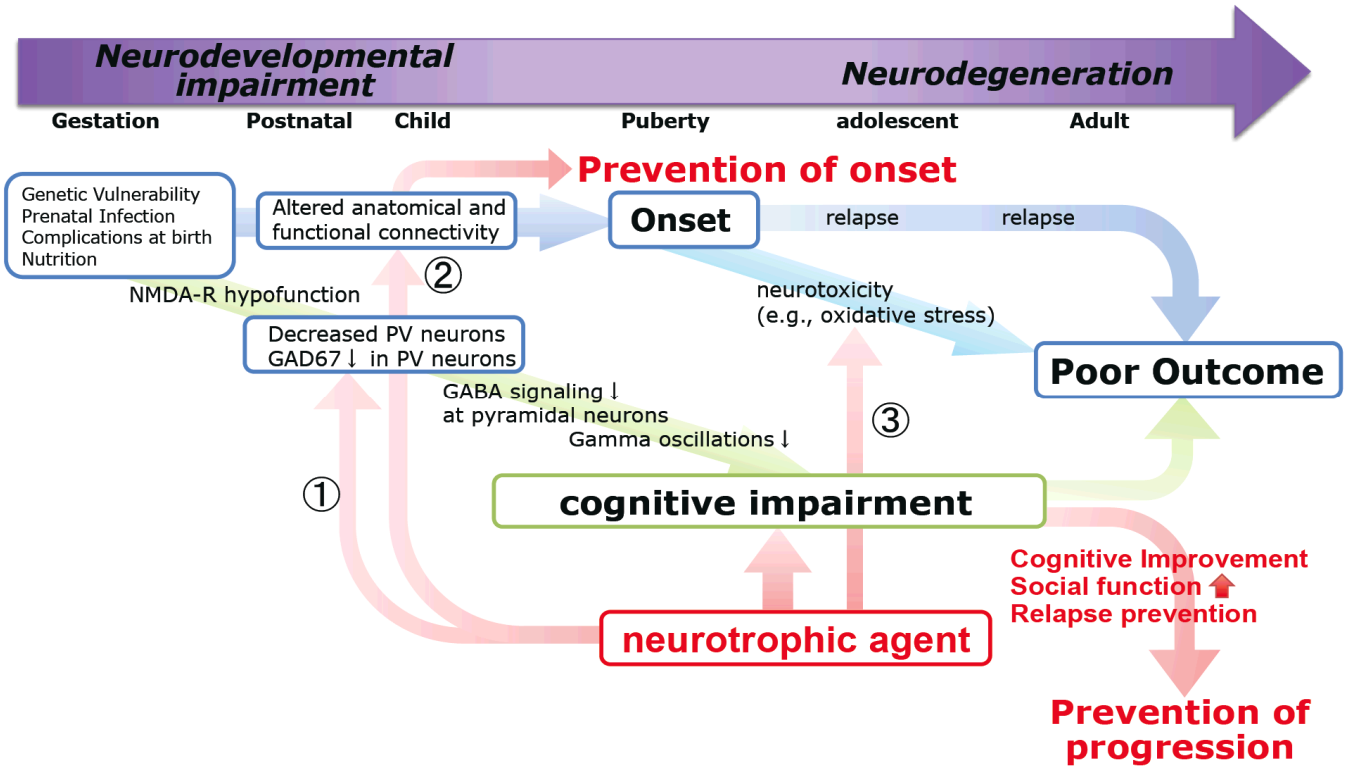

Fig. (5). The schema of T-817MA efficacy to prevent the onset or progression of schizophrenia. T-817MA have shown the ability *in vivo* or animal models of schizophrenia to ①reverse the decrease in the number of parvalbumin (PV) -positive GABAergic interneurons in the mPFC and hippocampus, ②facilitate neurogenesis, such as neuron proliferation, neurite outgrowth, and synaptogenesis, through the increase of neurotrophic factors and ③elicit neuroprotective effects against H_2O_2-induced neurotoxicity through attenuation of reactive oxygen species (ROS) production in mitochondria.

5.2. Effect of T-817MA on the Abnormality of GABA Neurons in an Animal Model of Schizophrenia

Rats administered with MK-801, a non-competitive NMDA receptor antagonist, on postnatal days (PDs) 7-10 provide an animal model of schizophrenia. These animals have been shown to elicit (1) impaired set-shifting, a measure of PFC function, in early adulthood [81], (2) disruption of prepulse inhibition (PPI), a measure of sensorimotor gating [82, 83], and (3) enhancement of methamphetamine-induced locomotor activity after puberty [83], (4) suppression of brain energy metabolism in the mPFC but not in the striatum [64], and (5) reduction of mRNA expression of mGluR3 receptors in the mPFC [84]. Moreover, the same model animals demonstrated a decreased number of PV-positive GABA interneurons in the mPFC and hippocampus [85]. These findings suggest that neonatal treatment with NMDA antagonists produces behavioral and histochemical abnormalities mimicking some features of schizophrenia.

Using rats administered with MK-801 on PD 7-10, we examined the effect of T-817MA on the number of PV-positive GABA neurons in the mPFC and hippocampus [85]. In these experiments, rats received T-817MA (10 or 20 mg/kg/day) orally. Treatment with T-817MA, at 20 mg/kg, for 14 days (from PD49 to PD62) ameliorated PPI deficits and prevented the decrease in the number of PV-positive GABAergic interneurons in the mPFC and hippocampus (mainly CA2/3 subfield) in early adulthood (PD63), while haloperidol (1.0 mg/kg/day) or risperidone (1.0 mg/kg/day) did not cause any effect Fig. (**4**).

The same effect of T-817MA has been confirmed with another rodent model of schizophrenia [86]. Mice with knockout of the platelet-drived growth factor (PDGF) receptor ß (PDGFR-ß) gene were considered as an animal model of schizophrenia [86, 87]. These animals have been shown to elicit PPI deficits, impeded social interaction, and disturbed spatial learning, indicated by the food search test, as well as reduction of gamma-band activity and the number of PV-positive GABA neurons in the mPFC [86, 87]. Nakamura *et al.* [86] have demonstrated that T-817MA (10 mg/kg/day, p.o.) for 4 weeks ameliorated these abnormalities. Importantly, sensory-evoked gamma oscillations were significantly correlated with the density of PV-positive GABA neurons in the mPFC. These results suggest that T-817MA can improve cognitive deficits in animal models of schizophrenia through ameliorating gamma oscillation generated by PV-positive GABA interneurons in the mPFC.

These results suggest that T-817MA modifies the "E-I balance" through recovery of histochemical abnormalities. The precise mechanisms underlying the effect of T-817MA on improving the cognitive dysfunction of these animal models of schizophrenia are unclear. However, this

neurotrophic agent may also have the ability to facilitate neurogenesis and neuroprotective effects against apoptosis *in vitro* as mentioned above. Taken together, T-817MA may be able to restore some morphological changes in the brain of patients with schizophrenia Fig. (**5**).

6. CONCLUSIONS

We presented the hypothesis that 5-HT_{1A} agonists improve cognitive dysfunction in patients with schizophrenia, through modulation of the activity of GABA neurons, leading to disinhibition of glutamate neurons in the PFC. Stimulation of 5-HT_{1A} receptors may also protect neurodegeneration. T-817MA, a novel neurotrophicagent, also ameliorated cognitive impairments and gamma oscillation in mPFC of some animal models of schizophrenia, as well as recovering the number of PV-positive GABA interneurons in the mPFC. Further research is needed to confirm the efficacy of this agent in clinical settings. Data from preclinical research suggest the effects of the 5-HT_{1A} receptor hyperfunction for the neurodevelopmental disability and T-817MA for the neurodegenerative disability of schizophrenia. A pharmacotherapy to alleviate abnormalities in GABA neurons through 5-HT_{1A} agonists and T-817MA is expected to prevent the onset and/or progression of schizophrenia.

CONFLICTS OF INTEREST

The authors confirm that this article content has no conflicts of interest.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the insightful comments and criticism by Prof. Y. Kawasaki in the Department of Neuropsychiatry, Kanazawa Medical University. This study was funded by grants from the Smoking Research Foundation to Takashi Uehara, as well as the Japan Society for the Promotion of Science Grant-in-Aid for Scientific Research No. 26461761 and Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP (27-1) to Tomiki Sumiyoshi.

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Received: January 20, 2015 Revised: February 24, 2015 Accepted: February 26, 2015