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Review Article

GABAergic inhibitory neurons as therapeutic targets for cognitive impairment in schizophrenia

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Abstract

Schizophrenia is considered primarily as a cognitive disorder. However, functional outcomes in schizophrenia are limited by the lack of effective pharmacological and psychosocial interventions for cognitive impairment. GABA (gamma-aminobutyric acid) interneurons are the main inhibitory neurons in the central nervous system (CNS), and they play a critical role in a variety of pathophysiological processes including modulation of cortical and hippocampal neural circuitry and activity, cognitive function-related neural oscillations (*eg*, gamma oscillations) and information integration and processing. Dysfunctional GABA interneuron activity can disrupt the excitatory/inhibitory (E/I) balance in the cortex, which could represent a core pathophysiological mechanism underlying cognitive dysfunction in schizophrenia. Recent research suggests that selective modulation of the GABAergic system is a promising intervention for the treatment of schizophrenia-associated cognitive defects. In this review, we summarized evidence from postmortem and animal studies for abnormal GABAergic neurotransmission in schizophrenia, and how altered GABA interneurons could disrupt neuronal oscillations. Next, we systemically reviewed a variety of up-to-date subtype-selective agonists, antagonists, positive and negative allosteric modulators (including dual allosteric modulators) for α5/α3/α2 $GABA_A$ and $GABA_B$ receptors, and summarized their pro-cognitive effects in animal behavioral tests and clinical trials. Finally, we also discuss various representative histone deacetylases (HDAC) inhibitors that target GABA system through epigenetic modulations, GABA prodrug and presynaptic GABA transporter inhibitors. This review provides important information on current potential GABA-associated therapies and future insights for development of more effective treatments.

Key words: schizophrenia; cognitive impairment; GABA; GABA prodrug; HDAC inhibitor; positive allosteric modulator; negative allosteric modulator; GAT-1 inhibitor; $GABA_B$ receptor antagonists

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Introduction

Schizophrenia is a devastating psychiatric disease that affects approximately 1% of the population worldwide. This disorder is characterized by a heterogenous combination of symptoms that can be divided into positive symptoms including delusions and hallucinations, negative symptoms of impaired motivation, social withdrawal and affective flattening, and cognitive deficits such as impairments in attention, reasoning, processing speed as well as verbal and working memory[1, 2]. The onset of psychosis typically occurs in late adolescence or early adulthood, but there are rare cases in which symptoms emerge during childhood or old age. A decline in cognitive ability or prodrome often precedes the onset of the first psychotic episode[3]. Cognitive symptoms persist throughout the course of the illness, and are the most important factors in long-term functional outcomes in schizophrenia[1, 2, 4, 5].

Although schizophrenia is typically classified as a psychotic disorder[1, 5], some suggest that it should be "considered primarily and foremost as a cognitive disorder"[1]. Current pharmaceutical treatments are partially effective in reducing positive symptoms, but not for negative and cognitive symptoms. Therefore, functional outcomes in schizophrenia are limited by the lack of effective pharmacological and psychosocial interventions for cognitive impairment[1, 2, 6].

γ-Aminobutyric acid (GABA) interneurons are the main inhibitory neurons in the central nervous system (CNS), and they play a critical role in a variety of physiological processes including modulation of cortical and hippocampal neural circuitry and activity[7, 8], cognitive function-related neural oscilla-

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tions (*eg* gamma oscillations)[9] and information integration and processing[10]. Multiple lines of evidence strongly support that the GABAergic system is a major convergence point for both genetic and environmental risk factors of schizophrenia[11]. For instance, a recent large genome-wide association study (GWAS) involving 11 355 schizophrenia patients and 16 416 controls identified copy number variations (CNVs) enriched in genes related to GABA neurotransmission[12]. Duplications were strongly enriched for components of $GABA_A$ receptor complexes, where the most highly associated genes were α5, β3, and δ receptor subunits. It is known that excessive α5-GABA receptor signaling can contribute to cognitive impairment of schizophrenia (discussed below), thereby providing strong support for the view that tonic inhibition mediated by α5 and δ subunits-containing $GABA_A$ receptors could be disrupted in schizophrenia[12]. Mutations in schizophrenia-linked genes such as *DISC1*[13], *NRG1* and *ERBB4*[14] can lead to disrupted GABA interneuron development, perturbed GABA circuitry and impaired synchrony of neural oscillations. Environmental factors such as prenatal infection and hypoxia, stress, smoking and cannabis use, when interacting with risk genes, can also contribute to schizophrenia[15, 16]. Dysfunctional GABA interneuron activity can disrupt the excitatory/inhibitory (E/I) balance in the cortex[17], which could be a core pathophysiological mechanism underlying cognitive dysfunction in schizophrenia. In this review, we will discuss evidence from postmortem and animal studies for abnormal GABA neurotransmission in schizophrenia, and how altered GABA interneurons could disrupt neuronal oscillations underlying cognitive impairment in schizophrenia. We will also discuss potential therapeutic targets and pharmacological treatments for cognitive deficits, with a focus on selective $GABA_A$ and $GABA_B$ receptor modulators, epigenetic modulations, GABA prodrug and presynaptic GABA transporter inhibitors.

GABA system and cognitive dysfunction in schizophrenia

Reductions in parvalbumin and GAD67 expression are associated with alterations in GABA transmission in schizophrenia

Several markers of GABA neurotransmission are altered in cortical regions of patients with schizophrenia. The most conserved and consistent finding from multiple imaging, animal and postmortem studies is the reduction in mRNA and protein levels for the 67 kDa isoform of glutamic acid decarboxylase (GAD67). This enzyme is responsible for synthesizing the majority of cytosolic and vesicular GABA[18] in the dorsal lateral prefrontal cortex (DLPFC), which is responsible for working memory and selective attention[19–21]. Decreased GAD67 mRNA is selectively observed in a subpopulation of prefrontal cortex (PFC) GABA neurons that express the calcium-binding protein parvalbumin (PV)[19, 22]. Around 45% of PV-mRNA positive neurons have undetectable levels of GAD67 mRNA and such alteration is due to reduction in PV mRNA in neurons rather than a decreased density of PV neurons. By contrast, approximately 10% of PV neurons do not express GAD67 mRNA in healthy controls[22–24]. Furthermore, since the reduction in PV mRNA is also found in non-medicated schizophrenia patients and PV mRNA is not altered in the PFC of primates treated long-term with antipsychotics[22–24], alterations in PV mRNA are unlikely to be due to antipsychotic drugs.

Parvalbumin functions as a slow calcium buffer, and can influence GABA release. Genetic elimination of this protein leads to various alterations in GABA neurotransmission. Taken together, these findings support the hypothesis that the capacity of PV neurons to synthesize and release GABA is impaired in the cortex of patients with schizophrenia[25]. The reduction in GAD67 mRNA, however, does not necessarily mean that the GABA concentration is decreased in schizophrenia, because the reduced GAD67 mRNA may also be associated with slower GABA metabolism[26]. Interestingly, a recent study found that the cerebrospinal fluid concentration of GABA analyzed by high-performance liquid chromatography was significantly reduced in first-episode psychosis patients compared with healthy controls, and patients with low GABA concentrations tend to have poor attention. Therefore, this study provides clinical evidence for a potential role of GABA in an early-stage schizophrenia[27].

GABA inhibitory circuit deficits lead to impaired neural oscillations in schizophrenia

Many important brain functions depend on the coordinated activity of large populations of neurons within one region or across brain regions. Neural oscillations in the gamma frequency range (30–80 Hz) in the PFC have been studied extensively because of their strong relationship with complex cognitive functions, and because disruption of gamma oscillations could be an important mechanism underlying cognitive deficits in schizophrenia[28]. Functionally, gamma-band oscillations in the human PFC increase in proportion to working memory load[29]. Compared to healthy controls, schizophrenia patients have a marked decrease in the amplitude and phase synchronization of gamma oscillations in the frontal cortex, and they tend to perform poorly on executive and working memory tasks[28, 30]. These deficits in gamma oscillations are observed in schizophrenia patients, independently of antipsychotic medication treatment[30, 31].

In the hippocampus, gamma-band oscillations originating in the CA3 and CA1 regulate network activity that promotes the encoding of spatial information and formation of episodic memories[32]. Slow theta-frequency oscillations (4-8 Hz) are complementary to gamma oscillations, and are especially important for episodic memory formation. Both gamma and theta oscillations are observed independently in the cortex and hippocampus but they are also coupled to each other[9]. Aberrant theta-gamma coupling can affect cognitive function in schizophrenia, such as visuospatial working memory[33]. In addition, ketamine, a pharmacological agent often to create animal models of schizophrenia, has been shown to alter gamma-theta oscillatory coupling in the hippocampus[34]. Taken together, these findings support the view that disrupted functional connectivity of cortical and hippocampal neural networks is a core mechanism underlying cognitive impair-

ment in schizophrenia[31].

It has been suggested that GABAergic inhibitory circuits play a crucial role for the generation of gamma oscillations and synchrony[28]. Despite the presence of many cortical interneuron subtypes, only some contribute to the generation of gamma oscillations. Several lines of evidence have linked disturbances in the subset of perisomatic-targeting, fast-spiking, PV-expressing (FS PV) neurons to impaired gamma oscillations and working memory deficits in schizophrenia. The synchronous activity of FS PV neurons can generate gamma oscillations in mice *in vivo*. Optogenetic stimulation[35, 36] and inhibition[35] of FS PV neurons selectively enhances and suppresses gamma oscillations *in vivo*, respectively. A subset of the FS PV interneurons, namely the parvalbumin-containing basket neurons (PVBC) that synapse on the somas of target pyramidal neurons and mediate fast, strong and shunting inhibition, are primarily responsible for gamma oscillations[37]. Networks of these basket neurons connected by gap junctions have been shown to produce large synchronous inhibitory postsynaptic potentials (IPSPs) to pyramidal neurons, thus exerting precise inhibitory control over the temporal coding of information in pyramidal neurons[25, 37]. PV interneurons are also important for intrinsic theta rhythm generation in the hippocampus[38]. Detailed neuronal mechanisms by which PV neurons mediate neural oscillations have been reviewed elsewhere[25, 26, 28, 37, 39–42].

The reduced expression of GAD67 and PV in schizophrenia is accompanied by disinhibition of cortical excitatory neurons and diminished neuronal oscillation and synchrony. For example, GAD67[26] and PV[43] protein levels are lower in PVBC boutons in DLPFC of human postmortem brain tissues[43], and downregulation of these two proteins in PV neurons probably reduces gamma oscillatory activity[44] in PFC. In addition, by conditionally knocking out one allele of the *Gad1* gene (the gene encoding for GAD67) in PV neurons in rats, Lazarus *et al* found that the decrease in GAD67 mRNA reduced PV-neuron synaptic output[45]. This in turn, disinhibited local pyramidal neurons in the DLPFC[45]. Other subtypes of interneurons such as parvalbumin-expressing chandelier cells (PVChCs) and cholecystokinin-expressing (CCK) interneurons also promote gamma synchronization *in vivo*[46]. As a whole, these findings suggest that reduced PV neuron output could result from decreased GABA synthesis and calcium buffering. This could be the cause of impaired gamma oscillations and working memory deficits in schizophrenia. Restoring the activity of GAD67 and PV within PV neurons, in particular PVBC, could be a promising strategy for improving cognitive deficits in schizophrenia[43].

Furthermore, interneurons that innervate the perisomatic regions of the targeted pyramidal neurons such as axo-somatic PV basket neurons, axo-axonic PV chandelier neurons and CCK-containing neurons, also appear to be essential for generating and maintaining the fast oscillations (*eg*, gamma oscillations) and slow theta-frequency oscillations in the hippocampus, which play a critical role in different aspects of episodic memory[47].

Alterations in other GABA genes related to GABA neurotransmission

In addition to GAD67 and PV, the expression of other key proteins in GABAergic pathways such as GABA transporter type 1 (GAT-1), REELIN (which is encoded by the gene *RELN* in humans), NMDA receptor subunits (*eg*, NR2A, NR3A), nicotine acetylcholine receptor (nAChR) α4 and α7 subunits, and brain-derived neurotrophic factor (BDNF)[48] are reduced in the brains of schizophrenia patients[49, 50].

Reelin is essential for regulating the growth, maturation, synaptic plasticity[51] and positioning of interneurons in the developing and adult brain[52], and hence plays a crucial role in the pathophysiology of schizophrenia[51]. The decreased number of dendritic spines observed in postmortem brains of schizophrenia patient is likely due to a deficit in reelin[51]. At the molecular level, reelin can enhance GABA inhibitory signals through inhibition of GAT-1 internalization and increase KCC2 (potassium chloride cotransporter 2) expression[53]. Hypermethylation of the *RELN* promoter can result in silencing of reelin[54], with reduced transcription[53, 54].

As molecular alterations of these proteins have been implicated in the pathophysiology of prefrontal cortex dysfunction, they are potential targets for novel pharmacological interventions.

The $GABA_A$ receptor as a therapeutic target in schizophrenia

The $GABA_A$ receptor is a heteropentameric ligand-gated chloride channel, widely distributed in the mammalian CNS, that mediates synaptic and extrasynaptic inhibition. These receptors are also the site of action of a number of clinically important drugs, including benzodiazepines (BZs), barbiturates, and anesthetics[55]. $GABA_A$Rs consist of five different subunits, composed of 19 known subtypes (α1-6, β1-3, γ1-3, δ, ε, π, θ and ρ1–3), although three subunits (ρ1–3) are also thought to form the $GABA_C$ receptor[56]. Figure 1(A) depicts the structure and GABA/benzodiazepine binding sites of $GABA_A$ receptors, whereas (B) depicts phasic *vs* tonic inhibition of the postsynaptic membrane mediated by synaptic *vs* extrasynaptic $GABA_A$ receptors, respectively.

Benzodiazepine-like ligands for the treatment of cognitive defects in schizophrenia and other neuropsychiatric disorders

In general, the sedative and addictive effects of classical non-selective $GABA_A$ receptor benzodiazepines have limited their usefulness in treating psychosis and cognitive impairments in schizophrenia. Consequently, a $GABA_A$ receptor subtype-selective compound could overcome these limitations of the classical BZDs without unwanted side effects. Compared to full agonists or antagonists, allosteric modulators like BZDs that possess selective affinity and/or efficacy for different $GABA_A$ receptor subtypes have been widely used for various purposes in schizophrenia[67]. Despite some positive reports, there is no consistent evidence of efficacy of BZDs as adjunctive treatment for positive symptoms in schizophrenia[67]. Convincing evidence for long-term cognitive benefits is also lacking[56].

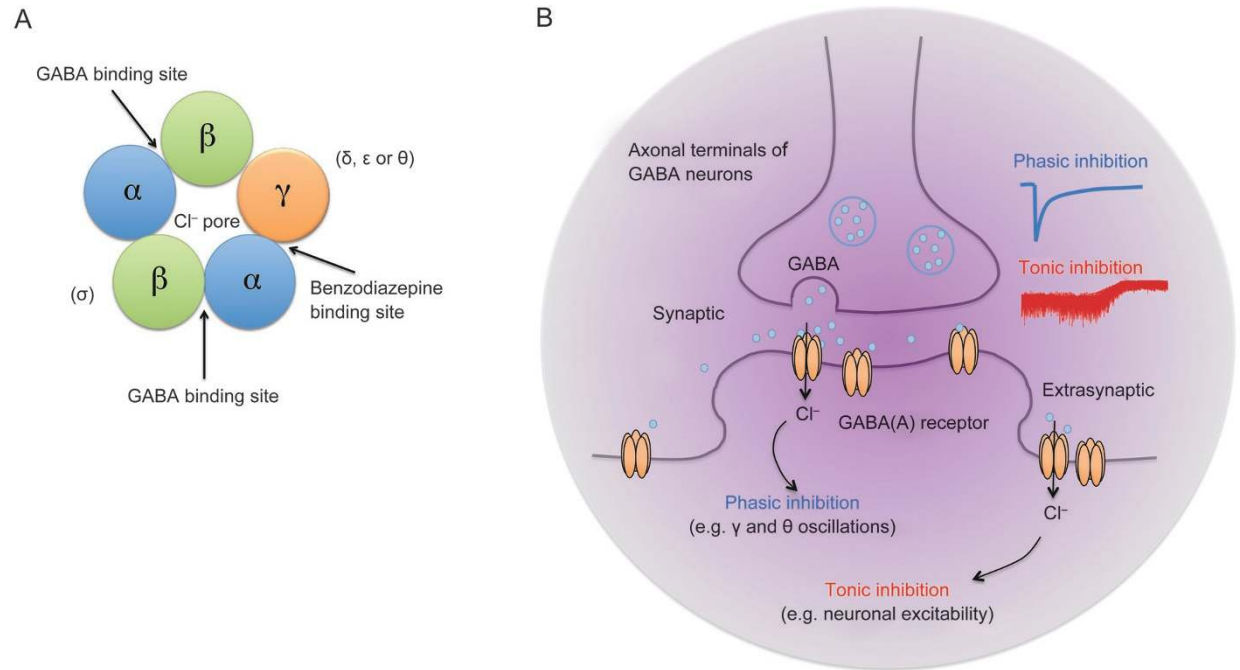

Figure 1. (A) The $GABA_A$ receptor generally contains two α, two β and one γ subunit that are arranged in a αβαβγ fashion, of which the γ subunit may be replaced by either an δ, ε or θ subunit, and the β subunit may be replaced by σ[57]. Benzodiazepines enhance the action of the neurotransmitter GABA at $GABA_A$ receptors by interaction with their allosteric modulatory benzodiazepine binding site (BZ site) that is formed by one of the α subunits (α1-3 and α5) and γ2 subunit [56]. The BZ site is distinct from the endogenous ligand GABA binding site that occurs at the interface of the α and β subunits[56, 58]. The α subunit is of importance in determining the pharmacological properties of the benzodiazepine drugs. (B) GABA-induced chloride ion influx hyperpolarizes postsynaptic neurons, generating inhibitory postsynaptic potentials (IPSPs)[56]. $GABA_A$ receptors mediate two distinct effects on the postsynaptic membrane: synaptic $GABA_A$ receptors containing the α1-, α2- and α3- subunits and the ubiquitous γ2 subunit [59] have been shown to possess a low affinity for GABA and mediate fast but short-lasting phasic inhibition, whereas extrasynaptic $GABA_A$ receptors with a high-affinity for GABA that contain the relatively rare subunits α4, α5, α6, and δ mediate slow but long-lasting tonic inhibition[56, 59, 60, 61, 62]. The function of phasic inhibition is critically dependent on the synaptic location of the subunit and the IPSP timing. One crucial role of phasic inhibition is to provide timing-based signaling for setting the temporal window of neuron networks firing[63], therefore it is important for the generation and regulation of gamma (γ) or theta (θ) oscillations and synchrony[64]. In contrast, tonic inhibition is responsible for generating about 75% of the total inhibitory conductance received by hippocampal neurons[65] and regulates neuronal excitability through its effects on the magnitude and duration of the postsynaptic excitatory postsynaptic potential (EPSP)[66].

$GABA_A$ receptors containing the α1 subunit are the most prevalent BZDs-sensitive $GABA_A$ receptors in the brain[68]. There is insufficient evidence that selective allosteric agonists at α1 subunit-containing $GABA_A$ receptors could improve cognition in schizophrenia[68]. Two such compounds, triazolam and zolpidem, impair cognition in adult rhesus monkeys in the object retrieval with detours (ORD) task of executive function[69]. Furthermore, $GABA_A$ receptors containing α3 subunits inhibit the dopamine system[70], and reduction in α3 subunit expression could contribute to a hyperdopaminergic state in schizophrenia[71]. Partial positive agonists at α3 subunits (*eg*, ELB139) could thus be potential antipsychotics[70].

Reduction in α5-$GABA_A$ receptor signaling might indirectly contribute to increased dopamine signaling in schizophrenia[72, 73]. Therefore, selective allosteric α5 subunit activators could also have potential as antipsychotic medications. Multiple lines of evidence implicate $GABA_A$ receptors containing α2 and/or α3 and α5 subunits in cognition. The following sections will focus on these two $GABA_A$ subtypes and how selective modulators at these subtypes can improve cognition in neuropsychiatric disorders such as schizophrenia, Alzheimer's disease and Down syndrome.

Role of α5 $GABA_A$ receptor in cognitive function

The α5 subtype constitutes 5%–10% of total brain $GABA_A$ receptors, but 25% in the hippocampus[55]. The α5-$GABA_A$ receptor is mainly localized in the dendritic regions of the CA1–CA3 hippocampal areas[55, 74], where they can modulate excitatory glutamatergic input[75]. α5 subunits are also expressed in olfactory bulb, amygdala, hypothalamus and neocortex (layer V and VI) but to a lesser extent[55, 74].

Studies in rodents have confirmed the role of α5-$GABA_A$ receptors in cognition through a variety of genetic and pharmacological approaches[55, 59, 76]. For example, mice deficient for α5 subunits ($\alpha5^{-/-}$) had better spatial learning in the water maze[55]. Moreover, α5 (H105R) mutant mice with reduced α5 $GABA_A$ receptors on hippocampal pyramidal neurons had stronger trace fear conditioning, but not in hippocampal-independent delay or contextual fear conditioning[59].

The α5 $GABA_A$ receptor subunit mediates tonic inhibition

in hippocampal neurons[77], and regulated gamma oscillations[77, 78]. Genetic knock-down or pharmacological inhibition, negative modulation of α5-$GABA_A$ receptors promotes hippocampal gamma oscillations[77], long-term potentiation (LTP), and learning[79]. For example, genetic reduction of α5 and δ subunits blocks tonic inhibition in CA3 pyramidal neurons, and produces spontaneous gamma oscillation *in vitro*. Together, these results suggest that reducing α5-GABA signaling could improve hippocampus-based cognitive functions. However, other studies involving genetic reduction of α5 subunit expression found behavioural abnormalities related to schizophrenia, arguing against the potential therapeutic value of this approach. For example, α5 (H105R) mutant mice also display attenuated prepulse inhibition (PPI), increased spontaneous locomotor activity[72] and latent inhibition (LI) deficits.

α5 subtype selective ligands as nootropic drugs

α5 negative allosteric modulators

Inverse agonists at α5-$GABA_A$ receptors could have potential to enhance cognition. Several α5 $GABA_A$ receptor-selective ligands have tested in animal models. Non-selective BZD inverse agonists may enhance cognitive function in rodents (*eg*, β3-CCM facilitated spatial learning)[80] but can cause anxiety-like behavior (*eg*, β3-CCM; FG 7142)[79, 80, 81] and seizures (*eg*, DMCM and FG 7142)[58, 80, 82, 83] and cause increased vigilance. These side effects prevent these compounds from being clinically useful[79]. Reduced expression of α5 $GABA_A$ receptors can enhance cognition in some contexts, while α1 subunit inverse agonists can promote seizures. Hence $GABA_A$ receptors containing the α5 subunit would appear to be more promising as a target for the development of cognition-enhancing compounds.

The imidazo-benzodiazepine L-655,708 (also known as FG-8094) has weak inverse agonist efficacy at all four GABA receptor subtypes, but a 50–100-fold higher selectivity for the α5 subunit. This drug enhances performance in normal rats in both the learning and recall phases of the water maze, at a dose previously shown to not be pro-convulsant. Unfortunately, the pharmacokinetic profile of this compound makes it unsuitable for further development as a drug. Other similar α5 selective compounds, including RY-023, RY-024 and RY-080, can promote seizures, which obviously precludes them from clinical use[79].

To address the side effects associated with targeting $GABA_A$ receptors containing the α1 subunit, some have investigated compounds with selectivity at the α5 receptor[84]. One example of this is RO4938581, an imidazo-triazolo-benzodiazepine with both binding and functional selectivity at the α5 receptor. This compound reversed scopolamine-induced working memory impairment in the delayed match-to-position task (DMTP task) and diazepam-induced spatial learning impairment in the water maze. More importantly, RO4938581 did not produce anxiety or seizures at ~30% occupancy of hippocampal $GABA_A$ α5-receptors[84, 85]. RO4938581 improved performance in a prefrontal cortex-mediated executive function task in monkeys[84]. This compound also improved cognitive deficits in rats induced by sub-chronic and neonatal administration of phencyclidine (PCP) (a NMDAR antagonist) in novel object recognition (NOR) and intradimensional/extradimensional attentional set-shifting (ID/ED) task, respectively[86].

NOR and ID/ED tasks are two preclinical behavioral assays that are related to cognitive tests used to evaluate patients with schizophrenia, such as the MATRICS (measurement and treatment research to improve cognition in schizophrenia) and CNTRICS (cognitive neuroscience treatment research to improve cognition in schizophrenia) test packages[61, 86–90].

RO4882224, a functional selective inverse agonist for the α5-$GABA_A$ receptor from Roche, is another imidazo-triazolo-benzodiazepine. RO4882224 enhanced hippocampal LTP and reversed scopolamine-induced working memory impairment in the DMTP task in rodents[85]. One derivative of RO4938581, Basmisanil (RG1662 or RO5186582), failed at Phase II clinical trial for the treatment of cognitive impairments in Down syndrome[91] and schizophrenia. There is an ongoing Phase II clinical trial with Basmisanil for treating cognitive deficits in schizophrenia (NCT02953639). Other compounds, such as the thiophene MRK-536, enhanced performance in a Morris water maze of spatial memory[92] without pro-convulsant effects.

PWZ-029 is another compound with binding selectivity and moderate functional selectivity at α5-containing $GABA_A$ receptors. It enhanced encoding and consolidation of memory in normal rats tested with the passive avoidance task at doses that did not cause anxiety-like effects or seizure[93], but had no effect in the active avoidance task. Moreover, PWZ-029 attenuated scopolamine-induced impairment of pavlovian fear-conditioned contextual memory in mice[94], and reversed scopolamine-induced deficits in novel object recognition, but not the water maze[95]. PWZ-029 also improved cognitive deficits induced by MK-801 in rodents tested on novel object recognition in the water maze. PWZ-029 did not improve deficits in social recognition memory[96]. An important caveat with studies of $GABA_A$ α5 drugs in animal models is the difficulty in translating the results to schizophrenia, since many features are difficult to accurately reproduce or measure in animals[97].

Another compound, α5IA, is a triazolophthalazine with an equivalent affinity for $GABA_A$ receptors-containing either an α1, α2, α3 and α5 subunit but with greater inverse agonist efficacy than L-655,708 at the α5 subtype (40% for a5IA *vs* 17% for L-655,708)[79, 92, 98]. α5IA enhances LTP, and improves encoding and recall in the DMTP task, without producing anxiety-like effects or seizure[98–99]. In addition, α5IA can reverse ethanol-induced memory impairment in healthy volunteers[100]. However, α5IA actually worsened some cognitive impairments in elderly people[98]. This drug also has a nephrotoxic metabolite that prevents long-term clinical use in humans. The structurally similar compound α5IA-II has improved oral bioavailability and efficacy selectivity but has pro-convulsant effects[92]. Another compound MRK-016 (pyrazolotriazine) with high efficacy selectivity at the α5 subtype had promising cognitive effects in animal models but was poorly tolerated in humans[92, 101].

In summary, inverse agonists at α5 $GABA_A$ receptors have

cognition-enhancing effects in pre-clinical studies. However, many of these drugs have side effects such as anxiety or seizure, and there is the potential for them to amplify psychotic symptoms since they can impair PPI and latent inhibition in animals.

Dual allosteric modulators of α5 $GABA_A$ receptors and α7 nAChRs

The α7 neuronal nicotinic-acetylcholine receptor (α7 nAChR) has been investigated as a valid therapeutic target for treating cognitive deficits in schizophrenia[102]. Genome-wide association studies have linked deletion of a genetic locus containing the α7 nAChR to increased risk for schizophrenia[103]. In addition, linkage studies have strongly associated variants in the α7 nAChR gene with deficient P50 auditory gating in schizophrenic patients[104]. Emerging evidence suggests that P50 sensory gating deficits reflect various cognitive (*eg*, executive functioning) and perceptual dysfunctions in schizophrenia[105].

Interestingly, individuals diagnosed with schizophrenia have among the highest rates of cigarette smoking[106]. Reduction of α7 nAChR function or expression has been identified as a potential mechanism for elevated tobacco use in schizophrenia[107]. Moreover, multiple studies have found that nicotine, the major psychoactive component of tobacco, can improve cognitive function (*eg*, attention and spatial working memory) in schizophrenic patients[106, 108] by activating α7 nAChRs. Enhancing the activity of α7 nAChRs is a potential strategy for ameliorating cognitive impairment in schizophrenia.

α7 nAChRs are densely expressed in the hippocampus, especially in interneurons where the density of α7 nAChRs is decreased in schizophrenia[109]. Given the preferential expression of α7 nAChRs in interneurons, the effects of α7 nAChR on hippocampal neurotransmission is mainly mediated by activation of GABA interneurons[110]. Pre-synaptic α7 receptors facilitate the release of glutamate and GABA[102], whereas postsynaptic α7 receptors can regulate $GABA_A$ receptor signaling[109]. α7 nAChR selective positive allosteric modulators (PAMs) are able to preserve the temporal integrity of neurotransmission[111] and can improve cognitive deficits in animal models[102].

522-054, a novel "dual modulator" that acts both as an α5 $GABA_A$ receptor negative allosteric modulator (NAM) and a selective α7 nAChR PAM, was able to restore scopolamine-disrupted deficits in the five-choice serial reaction time test (5-CSRTT) and the eight-arm radial arm maze (RAM). 5-CSRTT is a behavioral test that measures the visual attention and impulsivity in rodents. The test chamber has five holes on one wall, and a reward dispenser on the opposite wall. The task requires the animals to detect a briefly illuminated light presented in one of the five holes and identify the correct spatial location of the hole with nose pokes in order to obtain reward[112]. The accuracy of visual stimulus discrimination reflects the attentional capacity of the animals[112]. Intraperitoneal injection of 522-054 in the rats can significantly improve the baseline performance of scopolamine-treated (1.25 mg/kg, ip) animals at a dose of 0.003 mg/kg, suggesting beneficial effects on attention.

The eight-arm RAM task evaluates hippocampus-based spatial learning and memory in rodents. Animals must find the food reward at the end of four randomly chosen maze arms based on spatial navigation cues. At a dose of 0.03 mg/kg, 522-054 had a trend towards reversing the acquired short-term and long-term memory impairments caused by scopolamine (1 mg/kg, ip) in rats.

Flumazenil (an α_1- and α_5-subunit-selective antagonist) and methyllycaconitine (a selective α7 nAChR antagonist) blocked the effect of 522-054 on scopolamine-induced attentional and cognitive deficits, suggesting that simultaneous allosteric modulation of different receptors mediating related functions can have synergistic effects on cognition[111]. It is possible that compounds with relatively low specificity and moderate potency could be effective[113].

α5 positive allosteric modulators

α5-$GABA_A$ receptors mediate the majority of tonic inhibition in hippocampal neurons, and some have suggested that reduced GABA inhibitory input could lead to hyperactivity in the ventral hippocampal dopamine system[114]. Neural activity in the PFC can synchronize with the neural oscillations in ventral hippocampus, so it is possible that PAMs at α5 $GABA_A$ receptors could restore dopamine tone by selectively reducing vHPC output and vHPC-PFC oscillatory activity, with positive effects on cognition[115]. PAMs selective for $GABA_A$ α5 receptors improve hippocampal-dependent memory in a rodent model of age-related memory impairment where CA3 neurons have excess firing rates[116]. In contrast, other α5-selective PAMs can worsen cognition.

For example, in methylazoxymethanol acetate (MAM)-treated rats, the α5-selective partial agonist SH-053-2'F-R-CH3 impaired cognitive performance[58] but normalized the aberrant increase in the number of spontaneously firing dopamine neurons in the VTA to levels comparable to saline-treated rats, and reduced locomotor response to amphetamine[117]. SH-053-2'F-R-CH3 has no effect on visual recognition and spatial working memory in rhesus monkeys[118]. Similarly, in an immune-neurodevelopmental model of schizophrenia, the S-isomer of SH-053-2'F-R-CH3 (SH-053-2'F-S-CH3) has detrimental effects on both cognitive function and social interaction[119]. In contrast, SH-053-2'F-S-CH3 reduces amphetamine-induced hyperactivity[119]. These findings suggest that α5-selective PAMs are not suitable for treating cognitive deficits in schizophrenia. However, positive modulation at α5 $GABA_A$ receptors could be a promising adjunctive treatment for targeting positive symptoms in schizophrenia.

Cognitive enhancement through α2 and/or α3 $GABA_A$ receptor modulation

$GABA_A$-α2 receptor and schizophrenia

$GABA_A$ receptors containing α2 subunits comprise 15%–20% of all $GABA_A$ receptors[120]. Within the cortex, α2-containing $GABA_A$ receptors are enriched on the axon-initial segments (AIS) and perisomatic region of pyramidal neurons that are opposed to PVChC and CCK-basket cell (CCK-BCs) terminals, respectively[121]. PVChCs have arrays of boutons (cartridges)

immunoreactive for the GABA membrane transporter 1 (GAT-1) that innervate the AIS of postsynaptic target neurons[122]. PVChCs are important for facilitating synchronization of large populations of pyramidal neurons and are thus critical for working memory[122]. In addition, animal studies have supported an important role for α2-containing $GABA_A$ receptors in schizophrenia-related cognitive impairment. For example, mice with down-regulated α2 subunits in the frontal cortex have PPI deficits, reduced gamma oscillations, and impairments in working memory[121].

Postmortem and animal studies have reported that the density of PVChC axon cartridges appears to be reduced in DLPFC layer 2-4 in schizophrenia[26, 122–123]. Moreover, the immunoreactivity for the $GABA_A$ receptor α2 subunit is markedly elevated in schizophrenia, while the density of α2-labeled AIS is negatively correlated with the density of PVChCs cartridges[124]. These findings may be interpreted as compensatory responses to the diminished presynaptic GABA input[25, 120]. Based on this interpretation, one would predict that augmenting GABA neurotransmission from chandelier neurons through $GABA_A$ receptors containing the α2 subunit could restore gamma-frequency synchronized neuronal activity required for working memory[125–126]. Therefore, a positive allosteric modulation of α2 subunit-containing $GABA_A$ receptors could be a promising therapeutic strategy in schizophrenia.

$GABA_A$ α2/ α3 positive allosteric modulators

MK-0777 (also known as TPA-023 or L-830982) is a selective partial positive allosteric modulator at α2 and α3 subtypes. MK-0777 can improve performance on several cognitive tasks in patients with schizophrenia. Moreover, MK-0777 improved frontal gamma band power [127]. However, a subsequent larger clinical trial (n=60) failed to replicate these promising findings[128]. Since MK-0777 is a partial agonist of α2 subunits, a more selective agonist with a greater potency at the $GABA_A$ receptor-containing α2 subunit might work better[128].

There are questions about the role of PVChCs as neural substrates for the reduced frontal gamma oscillations in patients with schizophrenia[26]. PVChCs may depolarize cortical pyramidal neurons rather than hyperpolarizing them, and so PVChCs may be a potent source of a slow depolarizing current that mimics the type of slow, NMDA-like depolarization of pyramidal cells[26]. Moreover, the slow kinetics of α2 $GABA_A$ receptors does not appear to meet the requirement for the strong and fast inhibition required for gamma-band neural oscillations[26, 129, 130]. In contrast, other studies have indicated that α2 $GABA_A$ receptors are strongly coupled to theta oscillations[26, 131]. Consequently, the compensatory effects or lower presynaptic GAT-1 and higher postsynaptic $GABA_A$ α2 receptors, in response to decreased GABA neurotransmission may in fact increase EPSCs at the AIS. This could be a way to increase excitation and restore the E/I imbalance in schizophrenia[26].

$GABA_B$ receptor ligands as cognitive enhancers

$GABA_B$ receptors and schizophrenia

$GABA_B$ receptors are G-protein-coupled receptors consisting of GABBR1 and GABBR2. Unlike $GABA_A$R, $GABA_B$Rs are found outside the synapse and have high affinity for GABA[132]. They are widely distributed in the brain and regulate neuronal network activity[133], neurodevelopment[134] and synaptic plasticity[135]. Given their prevalence and widespread distribution in the CNS, it is not surprising that dysfunctions of $GABA_B$ receptors have been implicated in numerous CNS disorders such as major depression[136], schizophrenia[137], bipolar disorder[138] and seizures.

Multiple lines of evidence implicate $GABA_B$ receptors in the pathophysiology of schizophrenia[139]. $GABA_B$ receptors are markedly reduced in the cerebellum[139], hippocampus[140], entorhinal cortex, inferior temporal cortex[141] of patients with schizophrenia compared with healthy controls. $GABA_B$ receptors in the entorhinal cortex and hippocampus are important for memory[142]. Agonist activation of $GABA_B$ inhibits neuronal excitation and gamma oscillations[143], while antagonists promote theta and gamma oscillations[144]. Inhibition of postsynaptic $GABA_B$ receptors can enhance LTP by lengthening NMDA receptor-mediated currents[145]. Inhibition of presynaptic $GABA_B$ receptor enhances GABA release, thereby decreasing calcium conductance and subsequent GABA release[146].

$GABA_B$ receptor antagonists

$GABA_B$ receptor antagonists can improve cognition[145]. Proposed mechanisms include facilitating synaptic plasticity and LTP[147–148] and entraining neuronal oscillations[144, 149]. For example, intrahippocampal infusion of the antagonist 2-OH saclofen can markedly reverse scopolamine-induced impairments in LTP and Y-maze performance[148]. Similarly, the antagonists CGP 55845 and CGP 52432 enhance impaired LTP in the dentate gyrus of Ts65Dn mice, a genetic mouse model of Down Syndrome[147]. Moreover, CGP 55845 significantly increased gamma and theta oscillations in rat brain slices[149]. Another antagonist SCH 50911 was also found to increase gamma power[150].

So far, a variety of $GABA_B$ receptor antagonists have displayed cognition-enhancing effects in animal models of psychiatric disorders. Representative $GABA_B$ receptor antagonists and their effects on cognition are summarized in Table 1. CGP 36742 (also known as SGS742) was the first[151] and the only antagonist tested in clinical trials for mild cognitive impairment. SGS742 enhances cognition in animal models and in clinical phase II trials (Table 1) (For a comprehensive review, see[145, 151]). However, no current data are available with regards to treating cognitive deficits in schizophrenia using SGS742.

Despite evidence for cognitive enhancing effects of $GABA_B$ receptor antagonists, few studies have examined these compounds in animal models of schizophrenia. For example, in a recent apomorphine-susceptible (APO-SUS) young rat model displaying schizophrenia-relevant features[146], the level of GAD67 and the density of GAD67-positive cells were reduced. However, basal synaptic input to pyramidal neurons was unaltered. In contrast, the paired-pulse ratio (PPR) at lon-

Table 1. Effects of representative GABA(B) receptor antagonists on cognition in preclinical/clinical trials.

Compound	Pharmacological properties	Species	Behavioural test/clinical trial	Effect on cognition	References
CGP 35348	Showed affinity for the	Scopolamine-induced amnesia in CD1 mice	Passive avoidance test	Amnesic effect ↓	[152]
(IC_{50}=34 μmol/L)	GABA(B) receptor only	CD1 mice	T maze footshock avoidance test	Retention memory↑	[153]
		Baclofen-treated male Sprague–Dawley rats	Novel object recognition	Recognition memory ↑	[154]
	200 and 500 times more	Streptozotocin-induced dementia in rats	Morris water maze	Recognition memory ↑	[155]
	potent than the GABA(B) receptor antagonists OH-saclofen and phaclofen, respectively [153]	Hypoxia ischemia insult induced-neonatal brain damage albino mice	Morris water maze	Spatial learning and memory M↑,F↔	[156, 157]
	Displayed higher affinity for postsynaptic *vs* presynaptic GABA(B) receptors	Streptozotocin-induced dementia in rats	Morris water maze	Retention memory↑	[155]
		Insular injection of CGP 35348 in Sprague–Dawley rats	Intellicage	Position learning, punitive learning and punitive reversal learning ↓; position reversal learning↔	[158]
CGP 36742 (SGS742)	Interacted very weakly with GABA(A) receptor (IC_{50}=500	Mice	Footshock passive avoidance test	Retention memory F↑ (male mice were not tested)	[159, 160]
(IC_{50}=36 μmol/L)	μmol/L)	Male Sprague-Dawley rats	Social recognition test	Retention memory ↑	[159, 161]
		CD1 mice	Eight arm radial maze	Spatial learning and memory ↑	[162]
		Rhesus monkeys	Conditional space-color test	Cognitive function ↑	[159]
		Baclofen- and scopolamine-induced deficits in Wistar rats	Morris water maze	Spatial learning and memory ↑	[163]
		GAERS rats	Two-way active avoidance test	Cognitive function ↑	[164]
		Long-Evans rats	Eight- and twelve-arm radial mazes	Spatial learning and memory ↑	[165]
		110 patients aged 59–85 with mild cognitive impairment (MCI) were treated for 8 weeks at dose of 600 mg t.i.d. of SGS742	Double-blind, placebo-controlled Phase IIa clinical trial	attention↑ (i.e. choice reaction time, visual information processing); working memory↑ (i.e.pattern recognition speed)	[151]
		280 patients diagnosed with mild to moderate Alzheimer's disease	Double-blind, placebo-controlled Phase IIb clinical trial (NCT00093951)	Failed to meet the efficacy end points	[166]
CGP 55845	Acted at pre- and post-	Rats	Active avoidance test	Learning and retention memory↑	[167]
(IC_{50}=5 nmol/L)	synaptic GABA(B) receptors in the hippocampus [169]	GHBL-treated rats	Active avoidance test	Learning and retention memory↑	[168]
		GHBL-treated mice	Active avoidance test	Learning and retention memory↑	[168]
		GHBL-treated rats	Passive avoidance test	Learning and retention memory↑	[168]
		GHBL-treated mice	Passive avoidance test	Learning and retention memory ↔	[168]
		Cognitively-impaired aged Fischer 344 rats	Olfactory discrimination test	Learning↑	[170]
	~1000 times more potent than CGP 35348	Ts65Dn mice	Novel place recognition	Recognition memory↑	[147]
		Ts65Dn mice	Contexual fear condioning task	Learning and memory↑	[147]
		Ts65Dn mice	Novel object recognition	Recognition memory↑	[147]
		Ts65Dn mice	T-maze	Memory and spatial learning ↔	[147]
		Hypoxia ischemia insult induced-neonatal brain damage albino mice	Morris water maze	Spatial learning and memory↔ in both M&F (1 mg/mL solvent/kg body weight)	[171]

(To be continued)

Compound	Pharmacological properties	Species	Behavioural test/clinical trial	Effect on cognition	References
CGP 62349 (IC_{50}=2 nmol/L)	The antagonists reversed the effects of an EC70 concentration of GABA (1 μmol/L) and forskolin (10 μmol/L) with the rank order of potency: CGP62349>CGP54626A> SCH 50911>phaclofen= saclofen [172]	Rats	Active avoidance test	Learning and retention memory ↑	[167]
		GHBL-treated rats	Active avoidance test	Learning and retention memory ↔	[168]
		GHBL-treated mice	Active avoidance test	Learning and retention memory ↑ (more potent than CGP 55845)	[168]
		GHBL-treated rats	Passive avoidance test	Learning and retention memory ↔	[168]
		GHBL-treated mice	Passive avoidance test	Learning and retention memory ↔	[168]
CGP 71982 (IC_{50}=8 nmol/L)	NA	Rats	Active avoidance test	Learning and retention memory↑	[167]
		GHBL-treated rats	Active avoidance test	Learning and retention memory ↔	[168]
		GHBL-treated mice	Active avoidance test	Learning and retention memory ↔	[168]
		GHBL-treated rats	Passive avoidance test	Learning and retention memory↑	[168]
		GHBL-treated mice	Passive avoidance test	Learning and retention memory ↑	[168]

Male (M) Female (F) Increase↑ Decrease↓ No effect ↔
Gamma-hydroxybutyrolactone (GHBL)
Ts65Dn mice: a genetic mouse model of Down Syndrome
Genetic absence epilepsy rats of Strasbourg (GAERS): a model of epilepsy
NA: Data not available

ger inter-stimulus intervals was decreased in APO-SUS rats, indicative of a reduced GABA release. This reduction could be caused by enhanced $GABA_B$ receptor signaling. Interestingly, the application of CGP 55845 can completely restore the level of PPR and cause a decrease in $GABA_B$ signaling. The authors showed that CGP 55845 is likely to act at presynaptic $GABA_B$ receptors rather than postsynaptic receptors. Therefore, these findings are in line with the hypothesis that inhibition of presynaptic $GABA_B$ receptors could enhance GABA release. Decreased inhibitory drive from interneurons (*eg*, PV neurons) onto their postsynaptic targeted pyramidal neurons could be a core pathophysiological feature of schizophrenia[173], and that reduced GABA neurotransmission is highly correlated to cognitive defects in schizophrenia[146]. $GABA_B$ receptor antagonists require further investigations, especially in animal models related to schizophrenia in order to determine their potential for treating cognitive impairments in schizophrenia.

$GABA_B$ receptor agonists

The prototypic $GABA_B$ receptor agonist Baclofen is currently the only marketed drug targeting $GABA_B$ receptors. Numerous studies have reported that the Baclofen and other $GABA_B$ receptor agonists impair cognition in animal models [174]. However, these results are not consistent. Baclofen can ameliorate the recognition memory impairment induced by methamphetamine [175] and the spatial working memory deficits induced by chronic cerebral hypoperfusion in rats [176] (for a more comprehensive review, see[174]). More studies need to be conducted to confirm the effects of Baclofen on cognition.

$GABA_B$ receptor allosteric modulators

The data for the effects of PAM and NAM targeting $GABA_B$ receptors on cognition is limited. In the mouse passive avoidance cognition paradigm, a selective $GABA_B$ receptor PAM GS39783 showed no deleterious effects on cognition in contrast to Baclofen (1 mg/kg), which significantly impaired cognitive performance [177]. In 2015, the novel compound **7** from Astellas Pharma, a sulfur-containing bicyclic compound functioning as a $GABA_B$ receptor PAM, was used for the prevention or treatment of cognitive disorders, schizophrenia and pain (publication number for patent application: WO2015056771)[178].

Epigenetic therapies for cognitive impairment

Alterations in epigenetic regulations in schizophrenia

Epigenetic mechanisms (*eg*, histone modification, chromatin remodeling, DNA methylation) can synergistically interact with genetics[53] to mediate GABA system abnormalities in schizophrenia. Prominent genes include *GAD1, RELN, BDNF* and *GABAB3*[53, 179]. Several excellent reviews discuss epigenetic mechanisms in the neurobiology of neuropsychiatric disorders including schizophrenia[51, 53, 180–182]. These articles highlight several key findings about epigenetic alterations in schizophrenia.

Histone modifications in schizophrenia are shifted from open chromatin (H3K4-trimethylation, which positively regu-

lates gene expression)[53] to repressive histone methylation (H3K27-methylation that negatively regulates gene expression) at GABAergic gene promoters (*eg*, *GAD1*) in PFC of some subjects with schizophrenia[51]. In addition, the expression of histone deacetylases (HDAC) such as HDAC1 that facilitate downregulation of gene expression is increased in schizophrenic brains and correlated with reduced GAD67 expression[51, 183]. Interestingly, overexpression of neuronal HDAC1 in mouse mPFC (but not in dorsal or ventral hippocampus) resulted in schizophrenia-like phenotypes such as impaired short-term memory, PPI and synaptic plasticity[184]. In fact, many CNS disorders with cognitive impairment also have reduced histone acetylation[185].

DNA (cytosine-5)-methyltransferase (DNMT) (*eg*, DNMT1 and 3a) expression and DNA hypermethylation are abnormally increased in gene promoters in schizophrenia, which consequently results in MecP2-mediated gene silencing of GABAergic candidate genes such *as GAD1, RELN, SOX10*[51] and *BDNF*[51, 53]. Therefore, epigenetic modulators acting in GABAergic system could remediate the epigenetic alterations observed in schizophrenia.

HDAC and DNMT inhibitors for the treatment of cognitive defects neuropsychiatric disorders

In animal models, treatment with HDAC inhibitors such as trichostatin A (TSA), valproate (VPA) and MS-275 can increase the expression of reelin and GAD67 by activating demethylation[49, 186]. In addition, co-administration of VPA with antipsychotics (*eg*, clozapine[187], olanzapine and quetiapine) can synergistically potentiate VPA-induced promoter demethylation and chromatin remodeling (see review by[49]) and enhance antipsychotic effects[188]. VPA can elevate GABA concentration via synthesis, reuptake, and metabolism. In spite of a few positive reports[189, 190], VPA is likely to be detrimental to cognition as shown in animal studies[191]. Class I HDACs play an important role in neuronal and brain development[192], and are the best-studied HDACs with respect to cognition (for comprehensive review on this topic, see[185]). HDAC inhibition/deletion facilitates upregulation of a key set of genes involved in cognitive functions and enhances synaptic plasticity and long-term memory[193, 194].

Class I HDACs HDAC 2 and 3[185, 188, 195–197] and Class II HDACs HDAC 5[198] and 6[188, 195, 197] could be potential targets for improving cognition in neuropsychiatric disorders. HDAC 1 appears to have inconsistent effects on cognition[184, 188, 195, 198–200]. Representative HDAC inhibitors that have effects on cognition in preclinical and/or clinical studies for a variety of neuropsychiatric disorders are summarized in Table 2. However, these inhibitors are also reported to cause impairment in memory, learning and cognition in some other studies[182] in a brain region- and HDAC isoform-specific manner[188]. Development of selective inhibitors may reduce undesirable side effects, while still retaining pro-cognitive effects. (For comprehensive reviews on Epigenetics in CNS diseases/cognition, see[49, 182, 185, 188, 201–202].)

Similar to HDAC inhibitors, DNMT (*eg*, DNMT1 and 3a) inhibitors such as 5AZA and zebularine are also able to restore the expression of reelin and GAD67. But the majority of these compounds or drugs are clinically used for cancer treatment (*eg*, 5AZA, zebularine, RG108, decitabine). So far, there are few reported studies of DNMT inhibitors in animal models of schizophrenia[182].

In summary, the field of epigenetic drugs for the treatment of cognitive impairment in neuropsychiatric diseases such as schizophrenia is at an early stage and development of these drugs for cognition remains a great challenge. Although HDAC and DNMT inhibitors could be of potential therapeutic value in ameliorating cognitive deficits among high-risk individuals with schizophrenia, obstacles such as the lack of subtype- or brain region-specificity[188] or capacity to cross the blood-brain-barrier (BBB)[182, 240], difficulty with the establishment of dose ranges or treatment duration in clinical trials[188], and severe toxicity[188] have hindered the translation to the clinic.

GABA prodrug with pro-cognitive and antipsychotic effects

BL-1020 (also known as CYP-1020) is being developed by Bio-LineRx. It is an ester that combines the dopamine antagonism of perphenazine (a typical antipsychotic $D_2/_5$-HT_2 antagonist drug) with GABA agonist activity[241]. This drug has promising pro-cognitive and antipsychotic effects in rodent models of schizophrenia[242–243] and phase II clinical trials for schizophrenia (NCT00480571, NCT00567710, NCT00722176)[241, 244].

Preclinical studies indicate that BL-1020 can cross the BBB[244] and is less likely to cause neurological or metabolic side effects than current antipsychotics[243, 244]. In phase II a/b clinical trials, patients with chronic schizophrenia or schizoaffective disorder treated with BL-1020 demonstrated significant improvements in cognition and psychotic symptoms. However, the most recent IIb-III clinical trial (NCT01363349) designed to compare the cognitive effects of treatment with CYP-1020 to risperidone was terminated in 2013 because CYP-1020 did not meet its standard efficacy end points. Therefore, future phase II/III clinical trials are required to determine the clinical efficacy of BL-1020 compared with the established antipsychotics such as risperidone or clozapine. Taken together, BL-1020 has shown promising signs as a novel antipsychotic and pro-cognitive compound with excellent therapeutic effects for psychosis and cognitive impairments, and produces fewer side effects that commonly occur with typical and atypical antipsychotic medications. (For review, see[244])

GAT-1 inhibitors

GAT-1, the main plasma membrane GABA transporter in brain[132], is localized almost exclusively to axon terminals[245], which mediates the uptake of extracellular GABA[132]. This activity is generally thought to terminate the synaptic effects of GABA[132]. It has been shown that GAT-1-mediated GABA transport regulates $GABA_B$ receptor electrophysiological activity through synaptic GABA[132]. Blockade of GAT-1 can enhance postsynaptic $GABA_BR$-mediated IPSPs[246] and pre-

Table 2. Summary of HDAC inhibitors and their effects on cognition in preclinical and clinical studies for neuropsychiatric disorders.

HDACi group	HDAC inhibitor	Target HDACs	Diseases targeted	Model organisms	Effects on cognition	References
Benzamide derivatives	MS-275 (Entinostat)	HDAC1, 2, 3, 9	Mood and anxiety disorders [203]	129S1/SvImJ (S1) mice; stressed Sprague Dawley male rats at the prepubertal age	Rescued extinction-consolidation deficits and temporal order recognition (TOR) memory deficits	[204,205]
			SZ	Mice suffering early life stress (i.e. maternal separation)	↑short-term memory, synaptic plasticity and PPI	[184]
	Crebinostat	HDAC1,2,3,6,8 [206]	AD	Mouse cortical primary neurons & transgenic Egr1-EGFP mice	↑associative learning, BDNF and memory-related genes; enhance synaptogenesis	[206]
	Tubastatin or Tubastatin A	HDAC6/HDAC1	AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice; rTg4510 mice	↑working memory; ↑spatial and reversal learning and memory;↓hyperphosphorylated tau and Aβ	[207]
	CI-994	HDAC1, 2, 3	PTSD	Mice model of fear extinction	Attenuated remote fear memories; upregulate a key set of neuroplasticity-related genes	[208]
Hydroxamic acids	Suberoylanilide hydroxamic acid (SAHA,Vorinostat)	Classes I, II &IV	AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice; aged mice	↑hippocampus-dependent associative learning	[189]
				Tg2576 mice	Failed to rescue memory deficits due to low brain availability; ↑ LTP and↓ LTD *in vitro*	[209]
			RTS	$CBP^{+/-}$ Mice	↑hippocampus-dependent associative learning ; enhance late phase of LTP	[210]
			?	HDAC2 over-expressed mice	↑hippocampus-dependent associative learning; enhance dendritic spine density, synaptogenesis and LTP	[200]
	Trichostatin A (TSA)	Classes I and II	RTS	$CREB^{\alpha\Delta}$ mutant mice	↑contexual fear memory	[211]
			Metabolic syndrome	High-fat diet fed mice	↑spatial learning and memory and BDNF; alleviate oxidative stress	[212]
	I-2	Class I and II	AD	hAPP 3xTg	↑spatial learning and memory; ↓tau phosphorylation and Aβ	[213]
Short chain fatty acids	Sodium butyrate (NaB)	Classes I, IIa	AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice; CKp-25 mice; aged mice	↑associative, spatial, contexual and object recognition memory; ↑dendritic spine density	[189, 214, 215, 216, 217]
			PD	6-Hydroxydopamine (6-OHDA)-treated rats	↑executive function	[218]
			Depression	Maternal deprivation and chronic mild stress treated rats	↑object recognition memory; ↑ BDNF	[219]
			ASD	Mice given prenatal exposure to VPA	↑object recognition memory; ↑ CA1 region dendritic spine density	[190]
			SZ	Quadruple blind randomized placebo controlled phase II trial (NCT03010865)	To evaluate a series of cognitive functions in patients with SZ	https://clinicaltrials.gov

(To be continued)

HDACi group	HDAC inhibitor	Target HDACs	Diseases targeted	Model organisms	Effects on cognition	References
	Phenylbutyrate/ Sodium	-	SZ	Rats with neonatal ventral hippocampus lesions	↑associative learning	[220]
	Phenylbutyrate		AD	Tg2576 mice; $A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice	↑spatial reference memory deficits; ↔$A\beta_{42/40}$ and senile plaques; ↓hyperphosphorylated tau; alleviate ER stress	[221,222]
			HD	N171-82Q mice	↑survival and ↓ gross brain and neuronal atrophy	[223]
			PD	Aged Y39C mice	↑spatial learning and memory	[224]
	Valproate/ Valproic Acid (VPA)	Classes I & IIa	ASD	Mice given prenatal exposure to VPA	↑object recognition memory, ↑ CA1 region dendritic spine density	[190]
			AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice	↑contextual memory	[189]
			Epilepsy	Patients with epilepsy	↓cognition	[225, 226]
	Sodium Valproate	Class I [227]	Epilepsy	Rats with convulsive status epilepticus (CSE)	↑spatial cognitive dysfunction of P35 CSE rats, but ↓cognition of normal P15 and P35 rats	[228]
Mercapto acetamide	W2	Class II HDACs	AD	hAPP 3xTg	↑spatial learning and memory; ↓tau phosphorylation and Aβ	[213]
Carbamide based inhibitor	BRD4884	HDAC2	neuropsychiatric diseases (*eg.* SZ/PTSD)	CKp-25 mice	Rescued memory defects in contextual fear conditioning	[197]
Urea based inhibitor	BRD6688	HDAC2	neuropsychiatric diseases (*eg* SZ/PTSD)	CKp-25 mice	Rescued memory defects in contextual fear conditioning	[197]
Carboxamide	RGFP963	HDAC1, 2 and 3	AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice	↑contexual fear memory deficits by inducing synaptogenesis and increasing hippocampal spine density	[196]
			PTSD	Male C57BL/6J mice	Enhanced consolidation of cued fear extinction	[229]
	RGFP968	HDAC1, 2 and 3	-	Primary cortical neuron	Induced synaptogenesis and increased spine density in hippocampus	[196]
	RGFP966	HDAC3	AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice	Failed to rescue contexual fear memory deficits or to stimulate synaptogenesis	[196]
			PTSD	Male C57BL/6J mice	Failed to enhance consolidation of cued fear extinction	[229]
			-	Auditory memory rat model	Enhanced memory of acoustic details associated with sound-to-reward learning; affects auditory cortical plasticity	[194]
			HD	HdhQ111 knock-in mice	↑spatial and recognition long-term memory and motor learning deficits; normalizes hippocampal expression of memory-dependent genes; ↓mutant Huntingtin oligomers	[230]

(To be continued)

HDACi group	HDAC inhibitor	Target HDACs	Diseases targeted	Model organisms	Effects on cognition	References
	RGFP136	HDAC3	-	Homozygous deletions of *Hdac3* in CA1 of the dorsal hippocampus	↑long-term memory for object recognition snd location	[231]
	Rocilinostat (ACY-1215)	HDAC6	AD	$A\beta PP^{swe}/PS1^{\Delta E9}$ (PAP) double-transgenic mice	↑non-spatial working memory; ↑ hippocampus-dependent spatial learning and memory	[207]
Quinazolin-4-one derivatives	HDACi-4b	HDAC1,3,6	HD	N171-82Q transgenic mice	↑cognitive ability in T-maze task	[232]
	EVX001688; EVX	Class I and IIb	AD	Aged rats	Had no effect on age-related spatial learning and memory	[233]
Amide of nicotinic acid	Nicotinamide (niacinamide)	SIRT1	AD	3xTg mice	↑ spatial and contextual learning; has no effect on object recognition memory	[234]
Sulfonic acid	Suramin	SIRT1	ASD/SZ?	Maternal immune activation (MIA) mice; Fragile X (Fmr1 knockout) mice	Reversed social behavior, novelty preference and metabolism deficits	[235, 236]
		-	ASD	Double-blind randonmized placebo-controlled phase I/II trial (NCT02508259)	↑in language, social interaction;↓restricted or repetitive behaviors	[237]
-	CM-414 (compound 7)		AD	Tg2576 mice	Rescued associative fear/spatial learning and memory impairment; ↑synaptic plasticity, dendritic spine density and memory-related genes; ↓Aβ and tau	[238]

Table adapted from [239]
Schizophrenia (SZ), Alzheimer's disease (AD), Post-traumatic stress disorder (PTSD), Rubinstein–Taybi syndrome (RTS), Parkinson's disease (PD)
Autism spectrum disorder (ASD), Huntington's disease (HD)
Increase↑ Decrease↓ No effect ↔
amyloid-β (Aβ)

synaptic effects (For a detailed review, see[132]). Therefore, GAT-1 inhibitors may enhance cognition.

In a lipopolysaccharide (LPS)-treated rat model which mimics the prenatal inflammation thought to contribute to schizophrenia[247], the GAT-1 inhibitor Tiagabine (TGB) (also known as Gabitril) prevents impairments in LTP and LTD (long-term depression) in male offspring but had no effect on LTD in control rats[248]. So far, several studies, including double-blind, placebo-controlled trials, have reported that TGB monotherapy or adjunctive therapy for CNS disease (*eg*, epilepsy) has no negative effects on cognitive function[249, 250]. In contrast, data for cognitive enhancing effects of this drug is lacking. Currently, a phase III clinical trial evaluating the effects of TGB on brain deficits including neurocognitive functions and clinical symptoms during early-stage schizophrenia is in progress (NCT00179465).

Conclusion

In conclusion, the literature reviewed above suggests that restoring pyramidal neuronal inhibition could normalize aberrant cortical and hippocampal neuronal oscillations in schizophrenia. This could ameliorate cognitive impairments such as episodic memory, working memory and executive function in schizophrenia and other neuropsychological disorders. Pharmacological modulation of synaptic or extrasynaptic GABAergic signaling mediated by $GABA_A$ and $GABA_B$ receptors could restore disrupted neuronal network synchronization within or between brain regions-associated with learning and memory, which can in turn restore E/I imbalance and cognitive deficits in patients with schizophrenia. Electrophysiological measurements such as electroencephalography (EEG) signals, can provide an index of functional connectivity in the brain[251], that could serve as endophenotypes for screening candidate cognitive enhancing drugs for schizophrenia.

Overall, most of the potential cognitive-enhancing pharmacological treatments targeting the GABA neurotransmitter system have shown promise in pre-clinical studies with animals. This is also true for α5 subunit-selective negative allosteric modulators. The paucity of data demonstrating therapeutic effects of these drugs in clinical studies, however, has raised questions about how valid these pre-clinical studies are for predicting clinical therapeutic effects in patients. This problem is generic to many aspects of animal models for psychiatric disease and treatment[97], and emphasizes the need for continuing development of more powerful translational animal behavioural assays with better predictive validity. One promising approach is the use of touchscreen-based cognitive tests that can deliver cognitive tests that are nearly identical for both humans and rodents[252].

Moreover, dual allosteric modulators acting at two different receptors mediating similar functions could produce synergic effects on cognition. This synergistic strategy could reduce the dosage required for achieving optimal therapeutic efficacy, reduce side effects caused by individual drugs, and potentiate the pro-cognitive effects. Therefore, deliberately targeting multiple receptors could be a promising strategy for improving the pharmacological treatment of cognitive impairment in schizophrenia and other neuropsychiatric disorders.

Finally, epigenetic therapies, in particular selective class I HDAC inhibitors, require further modifications in order to increase brain regional selectivity, capacity to cross the blood-brain-barrier, and to reduce systemic toxicity. The epigenetic machinery is difficult to manipulate with specificity, and this is especially problematic for pharmacological manipulation of higher mental functions such as cognition. However, there are examples that show promise, such as inhibiting histone methyltransferases to treat anxiety and depression[253]. Given the complexity of human cognition, and the heterogeneity of patients with schizophrenia, it is likely that targeting multiple systems and individualizing pharmacological treatment to each patient, is the way forward.

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