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Review

Regulation of cognition and symptoms of psychosis: Focus on $GABA_A$ receptors and glycine transporter 1`

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ABSTRACT

Adaptive purposeful behaviour depends on appropriate modifications of synaptic connectivity that incorporate an organism's past experience. At least some forms of such synaptic plasticity are believed to be mediated by NMDA receptors (NMDARs). Complementary interaction with inhibitory neurotransmission mediated by $GABA_A$ receptors, and upstream control of the excitability of NMDARs by glycine availability can greatly influence the efficacy of NMDAR mediated neuroplasticity, and thereby exert significant effects on cognition. Memory, selective attention or sensorimotor gating functions can be modified in mice with a reduction of α_5GABA_A receptors in the hippocampus or a selective deletion of glycine transporter 1 (GlyT1) in the forebrain. Both genetic manipulations altered the formation or persistence of associative links leading to distinct phenotypes on trace conditioning, extinction learning, latent inhibition, working memory, and object recognition. Behavioural assays of latent inhibition, prepulse inhibition, working memory, and sensitivity to psychostimulants in particular suggest that α_3 and α_5 subunit-containing $GABA_A$ receptors as well as GlyT1 are potential sites for ameliorating psychotic-like behaviour. Taken together, these results qualify distinct GABA-A receptor subtypes and GlyT1 as molecular targets for the development of a new pharmacology in the treatment of cognitive decline and psychotic symptoms.

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1. Introduction: GABAergic control of neuronal rhythms

Various brain functions, such as sensory perception, cognition, emotion and memory, are linked to oscillatory activity of neuronal networks. The disruption of neural oscillations may contribute to brain dysfunctions, including psychiatric disorders. The spike timing of principal cells and the sculpting of neuronal rhythms are largely governed by GABAergic interneurons. To ensure adequate response characteristics of the target neurons, the brain has a bewildering array of inhibitory interneurons at its disposal (Somogyi and Klausberger, 2005) which is complemented by a correspondingly extensive multiplicity of $GABA_A$ receptors. By their strategic positioning in the neuronal networks the $GABA_A$ receptor subtypes affect distinct input–output patterns. The functional analysis of a particular $GABA_A$ receptor subtype is therefore expected to relate to a particular network activity which subserves a particular behaviour. $GABA_A$ receptor subtypes are precision targets for the functional analysis of neuronal circuits in normal and diseased brain.

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A case in point is a comparative high-frequency EEG analysis of a visual perception task in normal controls and in schizophrenics (Spencer et al., 2004). Visual Gestalt stimuli elicited a γ-band oscillation generated in the visual cortex. The fact that this oscillation was elicited by the Gestalt pattern and was phase-locked to the reaction time suggests that it could reflect the neuronal mechanism involved in linking the elements of the illusory square into a coherent percept. The occipital response-locked oscillation could be the most direct manifestation of visual feature-binding processes on the macroscopic EEG level. While both controls and schizophrenics display γ-band oscillations in visual Gestalt recognition, the frequency of the oscillation is lower in schizophrenics than in healthy individuals. This pattern may reflect impairments in the formation of neural assemblies, which use γ-band oscillations as a mechanism for synchronization. Although synchronization must occur for the perception of the Gestalt, it occurs at a lower frequency in schizophrenics. The neuronal networks are apparently not able to support high-frequency synchronization. If the disruption of fast neuronal oscillations indeed reflects a basic pathophysiological mechanism in schizophrenia, a greater understanding of the functional role of these brain oscillations in information processing may provide a background upon which to design and test new pharmacological therapeutic interventions (Whittington et al., 2000). γ-Oscillations are known to require the input of particular GABAergic interneurons (Somogyi and Klausberger, 2005) and it is also known that cortical inhibitory neurons are strongly impaired in schizophrenia (Lewis et al., 2005; Benes et al., 2007). On the molecular level, the pathology of GABA neurons is accompanied by a compensatory upregulation of α_2GABA$_A$ receptors on the cortical pyramidal target neurons (Lewis et al., 2005). In addition, a deficit in GABAergic transmission may also contribute to the dopaminergic hyperactivity, which is typical of schizophrenia. Dopamine neurons are under inhibitory control through α_3GABA$_A$ receptors (see below). Thus, enhancing GABAergic transmission at α_2 and α_3GABA$_A$ receptors would be expected to rectify at least some of the pathophysiological deficits in schizophrenia. It is therefore encouraging that MK-0777, a partial agonist acting at α_2 and α_3GABA$_A$ receptors, is presently being tested clinically as a potential therapeutic for schizophrenic patients, especially with regard to cognitive deficits. This example of the development of a new therapeutic strategy illustrates the contribution of GABA$_A$ receptor research to the understanding and therapy of mental disorders.

2. Dissecting GABA$_A$ receptor functions

Receptors containing the α_1, α_2, α_3 or α_5 subunit in combination with any of the β subunits and the γ_2 subunit are most prevalent in the brain, with the major subtype being $\alpha_1\beta_2\gamma_2$. These receptors are sensitive to benzodiazepine modulation. The pharmacological relevance of GABA$_A$ receptor subtypes for the spectrum of benzodiazepine effects was recently identified based on a highly selective genetic approach (Rudolph et al., 1999; Löw et al., 2000; McKernan et al., 2000; Whiting et al., 2000; Rudolph et al., 2001; Crestani et al., 2002; Möhler et al., 2002; Whiting, 2003b; Möhler and Rudolph, 2004; Rudolph and Möhler, 2006; Möhler, 2007a,b). Experimentally, the GABA$_A$ receptor subtypes were rendered diazepam-insensitive by replacing a conserved histidine residue with an arginine residue in the benzodiazepine binding site of the respective α subunit gene of mice [α_1(H101R), α_2(H101R), α_3(H126R) and α_5(H105R)] (Rudolph et al., 1999; Löw et al., 2000; Crestani et al., 2002). A deficit of behavioural drug action in the corresponding mutant mouse pointed to the functional role of the respective GABA$_A$ receptor subtype. This strategy permitted the allocation of benzodiazepine drug actions to the α_1, α_2, α_3 and α_5GABA$_A$ receptor subtypes (Rudolph et al., 2001; Crestani et al., 2002). In addition, by visualizing GABA$_A$ receptor subtypes immunohistochemically, the neuronal networks mediating the corresponding drug actions became apparent. This genetic approach to GABA$_A$ receptor subtype functions was complemented by a medicinal-chemistry approach. Ligands which differentiate between receptor subtypes by efficacy and/or affinity became available for direct behavioural testing (McKernan et al., 2000; Whiting, 2003a,b). Thus, both genetics and the medicinal-chemistry, led to a unified concept of a new CNS pharmacology based on GABA$_A$ receptor subtypes as novel targets (see Table 1).

3. Behavioural correlates of GABA$_A$ receptor subtypes: separating sedation from anxiolysis

Among α_1-, α_2- and α_3-point-mutated mice only the α_1(H101R) mutants were resistant to the depression of motor activity by diazepam or zolpidem (Rudolph et al., 1999; Löw et al., 2000; McKernan et al., 2000; Crestani et al., 2000) while pentobarbital or a neurosteroid remained as effective in α_1(H101R) mice as in wild-type mice in inducing sedation. Clearly, diazepam-induced sedation is linked to α_1GABA$_A$ receptors and ligands with preferential affinity for α_1 receptors comprise common hypnotic drugs (Table 1).

In contrast, the anxiolytic-like action of diazepam is attributed to the modulation of α_2GABA$_A$ receptors as shown by the lack of tranquillizing action of diazepam in α_2(H101R) mice (elevated plus maze; light/dark choice test) (Löw et al., 2000). The α_2GABA-A receptors, which comprise only about 15% of all diazepam-sensitive GAA-A receptors, are mainly expressed in the amygdala and in principal cells of the cerebral cortex and the hippocampus with particularly high densities on their axon initial segments (Nusser et al., 1996; Fritschy et al., 1998a,b). Thus, the control of the amygdala and the inhibition of the output of these principal neurons appear to be a major mechanism of anxiolysis. In keeping with this notion, the ligand L-838417 with partial efficacy at α_2, α_3 and α_5 but not on α_1GABA$_A$ receptors, was anxiolytic in wild-type rats in the absence of sedation (McKernan et al., 2000) (Table 1). Similar findings applied to TPA023, a partial agonist acting at α_2 and α_3GABA$_A$ receptors (Atack et al., 2006). Thus, a neurobiological basis was discovered for the development of daytime anxiolytics which are

Table 1
Behavioural endophenotypes of selective GAB-A$_A$ receptor subtype knock-in and knock-out mice

Mutant	Paradigm	Major results	References
α_1(H101R)	Open field, elevated plus maze,	Lack of the depression of motor activity by diazepam	Rudolph et al. (1999);
	light–dark choice test	Retention of the tranquilizing effect of diazepam	Crestani et al. (2000);
			McKernan et al. (2000)
α_2(H101R)	Elevated plus maze	Lack of tranquilizing effect of diazepam	Löw et al. (2000)
	Light/dark choice test	Lack of tranquilizing effect of diazepam	Löw et al. (2000)
α_3 knockout	Open field	Increased spontaneous locomotion in novel environment	Yee et al. (2005)
	Prepulse inhibition	Impaired, and can be reversed by haloperidol pretreatment	Yee et al. (2005)
α_5 knockout	Water maze	Enhanced working memory	Collinson et al. (2002)
α_5(H105R)*	Associative learning	Facilitated trace conditioning	Crestani et al. (2002);
			Yee et al. (2004)
		Reduced Latent inhibition effect	Gerdjikov et al. (2008)
		Impaired extinction of a conditioned fear response	Yee et al. (2004)

Summary of the behavioural endophenotypes associated with selective GABA$_A$ receptor subtype mutant mice.
* This point mutation is associated with a partial knock-down of the α_5 GABA-A receptors.

devoid of drowsiness and sedation. This is the more encouraging as these α_1-sparing ligands show a much reduced dependence liability compared to classical benzodiazepines (Ator, 2005).

It had previously been postulated that the anxiolytic action of diazepam is based on the dampening of the reticular activating system which is mainly represented by noradrenergic and serotonergic neurons of the brain stem. These neurons express preponderantly α_3GABA$_A$ receptors. The analysis of the α_3-point-mutated mice [α_3(H126R)] indicated that the anxiolytic effect of benzodiazepine drugs was unaffected (Löw et al., 2000). The reticular activating system therefore does not appear to be a major contributor to anxiolysis. Nevertheless, the α_3-selective ligand TP003 showed anxiolytic activity, at least at high receptor occupancy (Dias et al., 2005). Thus, under these conditions of α_3GABA-A receptors to anxiolytic activity may have to be considered.

4. Associative learning and memory

The acquisition of spatial and temporal memory is associated with excitatory synaptic plasticity involving hippocampal NMDA receptors (Morris et al., 1986; Davis et al., 1992; McHugh et al., 1996; Tsien et al., 1996; Tang et al., 1999; Huerta et al., 2000; Nakazawa et al., 2002). This process was found to be amenable to molecular regulation in vivo. By manipulating genetically either the inhibitory GABAergic control or the role of the co-transmitter glycine, striking behavioural alterations in learning and memory were found. They point to α_5GABA$_A$ receptors and to the neuronal glycine transporter 1 as promising targets for improving cognitive behaviour.

4.1. α_5GABA$_A$ receptors and cognition

In α_5(H105R) mice, the content of α_5GABA$_A$ receptors was reduced by 30–40% exclusively in the hippocampus (Crestani et al., 2002). This is presumably due to an effect of the mutation on receptor assembly or insertion. There was no indication for adaptive changes of other GABA$_A$ receptors expressed in the same pyramidal cells. Behaviourally, the partial deficit of hippocampal α_5GABA$_A$ receptors resulted in an improved performance in trace fear conditioning, a hippocampus-dependent memory task (Crestani et al., 2002). These results pointed to a role of α_5GABA$_A$ receptors in the function of temporal memory. When the α_5GABA$_A$ receptors were deleted in the entire brain by targeting the α_5 subunit gene (Whiting, 2003a; Collinson et al., 2002) a significant improvement in working memory performance in a water maze spatial learning test was observed. These findings were accompanied by a decrease of the amplitude of hippocampal IPSCs and an increase of the paired-pulse facilitation of field EPSPs amplitudes. These data strongly suggest that α_5GABA$_A$ receptors play a crucial role in cognitive processes of hippocampal learning and memory. Indeed, a partial inverse agonist acting at α_5GABA$_A$ receptors enhanced the performance of wild-type rats in the water maze test (Chambers et al., 2004).

There is further evidence to suggest that the role of α_5GABA$_A$ receptors in the hippocampus extends to the modulation of associative learning in the form of selective attention. The hippocampus together with its allied structure entorhinal cortex plays a crucial role in the expression of a form of selective learning called latent inhibition (Gray et al., 1996). Latent inhibition refers to the retardation of conditioning to a CS that has previously been pre-exposed without consequence in comparison to the conditioning to a novel CS (Lubow and Moore, 1959; Lubow, 1989). A neutral stimulus with a history of non-reinforced exposures would be perceived as less salient and command less attention (Mackintosh, 1973, 1974, 1975). Hence, conditioning to a pre-exposed CS typically proceeds more slowly. Partial deficit of hippocampal α_5GABA$_A$ receptors has been shown to disrupt latent inhibition (Gerdjikov et al., 2008). First, this indicates that a partial reduction in neuronal inhibition normally mediated by hippocampal α_5GABA$_A$ receptors is associated with enhanced associative learning under condition that normal animals tend not to learn. This is in line with the result on trace conditioning demonstrated previously (Crestani et al., 2002; Yee et al., 2004). Second, the loss of the latent inhibition under reduced hippocampal α_5GABA$_A$ receptors suggests a role of these receptors in normal selective attention. Effective and adaptive learning obviously requires the ability to decide when an association ought to be formed and when not. Indeed, loss of latent inhibition has been reported in schizophrenia patients (Baruch et al., 1988; Gray et al., 1992), and it has been suggested that this may contribute to the emergence of some positive symptoms in schizophrenia ((Gray et al., 1991) also see further discussion below).

In support of the hypothesis that α_5GABA$_A$ receptors in the hippocampus may assume a general role in the control of the selectivity of learning and expression of learned behaviour, relevant findings have been reported in extinction learning. In Pavlovian conditioning, extinction training involves the repeated presentations of the CS without the antecedent US. This leads to the cessation of conditioned responding and is an active learning process implying the acquisition of new information (instead of "un-learning"). Partial deficit of hippocampal α_5GABA$_A$ receptors impairs extinction of a conditioned fear response, leading to persistent conditioned responding despite that the CS is no longer predictive of US occurrences (Yee et al., 2004). This confirms the suggestion that the interplay between GABAergic and glutamatergic activities determines the efficacy of extinction training (Davis and Myers, 2002; Myers and Davis, 2002, 2007). The extent to which the formation and persistence of such learned association may result in pathological conditions, e.g., in PTSD patients suffering from traumatic memory, would point to a potential therapeutic use of α_5-selective agonist in treating such anxiety-related disorders.

In summary, α_5GABA$_A$ receptors in the hippocampus are in a pivotal position to modulate activity of hippocampal principle neurons, which are assumed to be central to various mnemonic functions. While glutamatergic neurotransmission via NMDA receptors in these neurons is widely believed to mediate long-term potentiation (LTP) that sustains memory functions, inhibitory modulation via α_5GABA$_A$ receptors may regulate the acquisition of new associations and/or the expression learned associations. This gatekeeping function is essential for flexible and adaptive learned behaviour and is a hallmark of higher cognition that goes beyond the conception of memory as a passive registry of past experiences. This is in line with the observation, mentioned above, that in the water maze, it is working memory rather than reference memory that has been reported to be enhanced by either whole-brain α_5GABA$_A$ receptors knockout (Collinson et al., 2002) or α_5GABA$_A$ receptors an inverse agonist ligand (Chambers et al., 2004; Collinson et al., 2006). Indeed, the mammalian memory system has exploited multiple avenues, other than GABAergic inhibition, to allow additional control over NMDA receptor-mediated synaptic plasticity. Another such control is achieved through the regulation of the obligatory co-agonist of NMDA receptors — glycine.

4.2. Neuronal glycine transporter 1 and cognition

Glycine is an obligatory co-agonist of glutamate at NMDA receptors and its binding to the NMDA receptor glycine site (glycine-B-site) is necessary for ion channel opening (Johnson and Ascher, 1987; Verdoorn et al., 1987). The concentration of glycine in the vicinity of NMDA receptors is normally maintained at sub-saturation levels by glycine transporter 1 (GlyT1) (Smith et al., 1992; Supplisson and Bergman, 1997; Bergeron et al., 1998). An elevation of the synaptic availability of glycine constitutes a potent means to enhance the efficacy of NMDA receptor-mediated neurotransmission and neural plasticity (Igartua et al., 2007). This can be achieved effectively by the inhibition or down-regulation of GlyT1 activity, either by means of pharmacological blockade (e.g. Depoortere et al., 2005; Sur and Kinney, 2007; Walter et al., 2007) or molecular deletion of the transporter (Tsai et al., 2004a; Yee et al., 2006) (see Table 2). In particular, deletion of neuron-associated GlyT1 in the

Table 2
Behavioural endophenotypes of GlyT1 mutant mice

Mutant	Paradigm	Results	References
Whole brain heterozygous GlyT1 deletion	Water maze	Enhanced retention of spatial reference memory	Tsai et al. (2004a)
	PPI	Restoration of amphetamine induced PPI disruption Potentiation of MK-801-induced PPI disruption	
Homozygous GlyT1 deletion selectively in forebrain neurons	Conditioning	Facilitated conditioning in conditioned tone freezing and active avoidance learning	Yee et al. (2006)
	Latent inhibition	Enhanced LI in conditioned tone freezing, active avoidance learning and conditioned emotional response	
	Locomotor response to psychostimulant drugs	Attenuation of MK-801-induced hyperlocomotion (see Fig. 1) Attenuation of PCP-induced hyperlocomotion Delayed motor stimulant effect of amphetamine	
	Recognition memory	Enhanced recognition memory for the identity and the spatial location of objects	Singer et al. (2007)

Summary of the behavioural endophenotypes associated with Glyt1 mutant mice.

forebrain has recently been shown to be sufficient to enhance NMDA receptor current and is effective in inducing enhanced mnemonic functions (Yee et al., 2006; Singer et al., 2007).

Unlike a partial deficit of hippocampal α_5GABA_A receptors, forebrain neuronal specific deletion of GlyT1 has been found to facilitate Pavlovian conditioning across a variety of paradigms including conditioned freezing, active avoidance learning, and conditioned taste aversion learning (Yee et al., 2006). Moreover, forebrain neuronal GlyT1 deletion enhances the latent inhibition effect (Yee et al., 2006), which is precisely opposite to the effect of hippocampal α_5GABA_A receptors deficiency (Gerdjikov et al., 2008). These apparent contradictory outcomes may reflect the differing functional modulations exerted by glycine/GlyT1 and α_5GABA_A receptors on NMDA receptor activity.

One parsimonious interpretation is that forebrain neuronal GlyT1 deletion enhances the formation of associative links, not only between CS and an unconditioned stimulus (US), but also the formation of [CS → nothing] association as a result of CS alone presentations during the pre-exposure (prior to CS–US pairing) stage of a latent inhibition experiment. Latent inhibition emerges because of the two opposing associative links: ([CS → nothing] vs [CS → US]) compete with each other over the control of behaviour in response to the CS (Kraemer and Spear, 1991, 1993). The response by animals that have not received CS pre-exposure would be totally governed by the [CS → US] association and therefore is stronger than in animals having been through CS pre-exposure. Hence, forebrain neuronal GlyT1 deletion leads to the expression of latent inhibition when the amount of pre-exposures is insufficient to generate latent inhibition in control littermates; and at the same time it also facilitates the expression of conditioned responding in the non-pre-exposed condition relative to control mice. In contrast, hippocampal α_5GABA_A receptors deficiency abolishes the latent inhibition effect (Gerdjikov et al., 2008), because the inhibition mediated by hippocampal α_5GABA_A receptors normally suppresses the formation of the [CS → US] associative link and/or the expression of the [CS → nothing] associative link. A partial deficit in hippocampal α_5GABA_A receptors therefore biases the competition over behavioural control towards [CS → US] leading to an attenuation of the latent inhibition effect. Thus, while glycine (controlled by GlyT1) may represent an upstream control over NMDA receptor function, extrasynaptic α_5GABA_A receptors in the hippocampus may assume a downstream control. Normal cognitive function relies on their coordinated interplay to yield optimal learning performance. Indeed, this may be a widespread strategy adopted by other brain structures, as it has been shown that an extinction deficit of emotional memory induced by intra-amygdala infusion of the $GABA_A$ agonist muscimol can be reversed by the administration of the partial glycine-B site agonist D-cycloserine (Akirav, 2007).

Importantly, GlyT1 deletion enhances cognition without compromising the selectivity in learning. Indeed it enhances selectivity by promoting the acquisition of relevant events (or non-event) associated with a given environmental stimulus. In contrast, deficiency of hippocampal α_5GABA_A receptors result in inflexible learning performance as outlined previously: (i) reduced sensitivity to the insertion of a CS–US trace interval, (ii) retarded extinction when the CS is no longer followed by the US, and (iii) insensitivity to CS pre-exposure effect leading to a loss of the latent inhibition effect.

Recently, the promnesic effects of GlyT1 deletion have been extended to learning beyond Pavlovian conditioning. Singer et al. (2007) showed that object recognition memory as well as memory of the spatial location associated with specific objects is enhanced following forebrain GlyT1 neuronal deletion. These findings are encouraging because object recognition memory is believed to be mediated largely by rhinal cortices with hippocampus playing a more critical role only when the spatial location of specific objects becomes relevant. Manipulations targeted at GlyT1 may therefore provide a means to modulate multiple memory systems: from the hippocampus to the neocortex.

While the deletion of GlyT1 restricted to forebrain neurons is associated with some clear promnesic effect as described above, brain-wide constitutive heterozygous disruption of GlyT1 only leads to limited and marginal enhancing effect on spatial reference memory learning in the water maze (Tsai et al., 2004a). This may reflect a gene dosage effect due to the heterozygosity of the mutation. Alternatively, GlyT1 disruption restricted to forebrain neurons — and therefore selective inhibition of the neuronal subset of GlyT1 — is somehow functionally more effective than a whole-brain approach. Unfortunately, currently available GlyT1 inhibitors cannot discriminate between glial- and neuron-associated GlyT1. We are therefore in the process of evaluating these two alternative accounts by generating mice with both neuronal and glial GlyT1 deletion in the forebrain. If neuronal specificity is a critical property, this would have important implications with respect to the development of GlyT1 inhibitors as potential cognitive enhancing agents or therapeutics for cognitive impairments in schizophrenia and other relevant psychiatric conditions.

The strategy to inhibit or delete GlyT1 and extrasynaptic α_5GABA_A receptors activity is ultimately to enhance NMDA receptors excitability, and thereby to boost NMDA receptor mediated neural plastic events that underlie learning and memory. However one potential caveat of this approach may be excitotoxicity in the longer term. Chronic and sustained elevation of NMDA receptors activity may lead to cell death and eventual deterioration of function instead of enhancement. Indeed, it has been argued that such approach might exacerbate, rather than ameliorate, conditions like Alzheimer's disease (Javitt, 2004). We have preliminary data now to suggest that at least some of the promnesic effects associated with forebrain neuronal GlyT1 deletion can be demonstrated still in mice over 2 years old (P Singer, D Boison, H Möhler, J Feldon, BK Yee, unpublished data). Examination of the brains of these animals for the presence or absence of excessive neurotoxic damage is now underway.

5. Ameliorating psychotic symptoms: role of $GABA_A$ receptors and neuronal glycine transporter 1

A deficit in GABAergic inhibitory control is one of the major hypotheses underlying the symptomatology of schizophrenia (Lewis et al., 2005; Benes et al., 2007). A potential contribution of $GABA_A$ receptor subtypes was therefore investigated with regard to the functional hyperactivity of the dopaminergic system, considered to be a major factor in the genesis of schizophrenia symptoms, especially positive symptoms.

The dopaminergic system in animals and humans is under GABAergic inhibitory control mainly via α_3-containing $GABA_A$ receptors (Fritschy and Möhler, 1995; Pirker et al., 2000; Waldvogel et al., 2008). In mice lacking the α_3 subunit gene no adaptive changes in the expression of α_1, α_2 and α_5 subunits was observed (Studer et al., 2006) and anxiety-related behaviour was normal (Yee et al., 2005). However, the mice displayed a marked deficit in prepulse inhibition of the acoustic startle reflex, pointing to a deficit in sensorimotor information processing (Yee et al., 2005). This deficit in prepulse inhibition was normalized by administration of the antipsychotic dopamine D2 receptor antagonist haloperidol, suggesting that the phenotype is linked to hyperdopaminergia (Yee et al., 2005).

The hippocampus is also believed to play an important role in the modulation of prepulse inhibition (Bast and Feldon, 2003). In the α_5 (H105R) point-mutated mice (see above) prepulse inhibition was attenuated concomitant with an increase in spontaneous locomotor activity, the latter being tested in a novel open field and a novel environment (Hauser et al., 2005). Thus, the α_5 subunit-containing $GABA_A$ receptors which are located extrasynaptically and are thought to mediate tonic inhibition (Caraiscos et al., 2004; Scimemi et al., 2005; Glykys and Mody, 2006; Prenosil et al., 2006) are important regulators of the expression of prepulse inhibition. Attenuation of prepulse inhibition is a robust phenotype of psychiatric conditions including schizophrenia. These results suggest that α_3- and/or α_5-selective agonists may constitute an effective treatment for sensorimotor gating deficits in various psychiatric conditions.

In addition, the hippocampus and the adjoining entorhinal cortex also assume a critical role in modulating the expression of latent inhibition (Gray et al., 1991, 1996; Yee et al., 1995). These structures project directly to the nucleus accumbens and make excitatory glutamatergic synaptic connections onto neurons that also receive direct dopaminergic innervations from the ventral tegmental area (nucleus A10) (Totterdell and Smith, 1989; Sesack and Pickel, 1990). Specifically, the interaction between limbic glutamatergic inputs and ascending dopaminergic inputs in the nucleus accumbens underlies the normal expression of latent inhibition (Gray et al., 1991; Weiner, 1990; Weiner and Feldon, 1997). Its disturbance is believed to be involved in the reported lack of latent inhibition in at least some subsets of schizophrenic patients (Baruch et al., 1988; Gray et al., 1992). Hence, the loss of tonic inhibition normally mediated by α_5GABA_A receptors in the hippocampus may result in a functional disturbance of the hippocampal–accumbens projection. Loss of latent inhibition represents a severe deficit in selective attention and may contribute to some of the positive and cognitive symptoms observed in schizophrenic patients. In the α_5(H105R) point-mutated mice, latent inhibition is severely attenuated. This suggests that α_5-selective agonists may represent a potential treatment for the selective attention deficits and related positive symptoms in schizophrenia. In addition, the lack of flexible learning shown by α_5(H105R) point-mutated mice in trace conditioning and extinction may also be related to the negative symptoms of schizophrenia, suggesting that α_5-selective agonists may also be effective against negative symptoms. The latter is consistent with the glutamate hypothesis of schizophrenia (Goff and Coyle, 2001; Tsai and Coyle, 2002; Coyle and Tsai, 2004; Coyle, 2006) and current findings regarding GlyT1 inhibition or deletion (Lindsley et al., 2006).

Likewise, the efficacy of GlyT1 deletion to enhance latent inhibition also suggests that blockade or inhibition of GlyT1 may possess antipsychotic potential. These findings on the behavioural paradigm of latent inhibition however emphasize in particular positive schizophrenia symptoms. Current thinking on the other hand suggests that glutamatergic (and in particular NMDA receptor) hypofunction is more closely linked to the emergence of negative symptoms (Supplisson and Bergman, 1997; Coyle and Tsai, 2004). Accordingly, the use of NMDA receptor orientated therapy, including the use of NMDA receptor co-agonists such as D-serine and glycine has been reported to improve cognition and negative symptoms in schizophrenia (Lindsley et al., 2006). Alternatively pharmacological blockade of GlyT1 by the co-administration of sarcosine in combination with conventional antipsychotic treatment has yielded some promising synergistic efficacy against both positive and negative schizophrenia symptoms (Tsai et al., 2004b; Lane et al., 2005; Heresco-Levy, 2006). Recently, synthetic GlyT1 inhibitors with enhanced specificity than the endogenous GlyT1 antagonist sarcosine have been developed (Lechner, 2006; Harsing et al., 2006), which have been shown to exhibit significant activity in preclinical model predictive of antipsychotic efficacy (Harsing et al., 2003; Depoortère et al., 2005).

However, it should be noted that NMDA receptor blockade (e.g., by phencyclidine and ketamine) can also give rise to psychotic-like behaviour akin to the positive florid symptoms of schizophrenia (Farber, 2003). It has been shown that deletion of neuron-associated GlyT1 attenuates the locomotor response to phencyclidine (Yee et al., 2006). We can confirm that this effect stems primarily from a functional antagonism against NMDA receptor blockade by PCP, because neuron-associated GlyT1 deletion was similarly effective against the specific

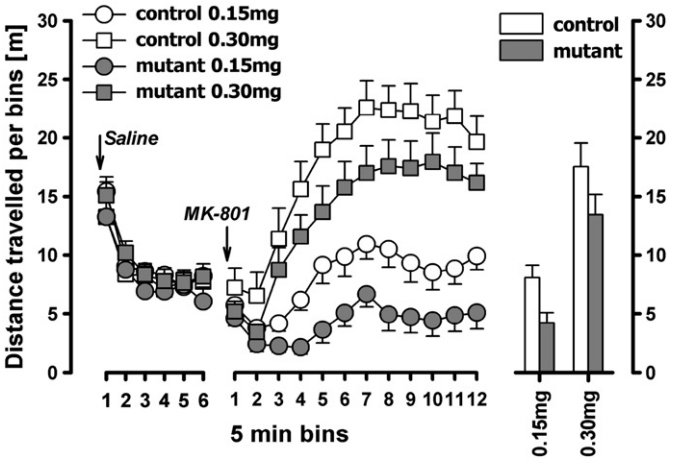

Fig. 1. Acute locomotor response to selective NMDA receptor blockade in the open field is attenuated in mice with forebrain neuron-specific deletion of glycine transporter 1 (GlyT1). Locomotor response to an acute MK-801 challenge was evaluated in the open field using a within-subjects design. First, all animals were injected with saline and exposed to the open field arena (40×40 cm) for 30 min in order to habituate them to the novel environment and to allow the assessment of baseline locomotor activity. To evaluate the motor stimulant effects of MK-801, the animals were next injected with MK-801 at either a dose of 0.15 mg/kg [mutant (n=12), control (n=16)] or 0.3 mg/kg [mutant (n=11), control (n=16)]. The animals were then observed for another 60 min. All injections were administered via the i.p. route. Locomotor activity was indexed by the distance traveled in the open field. Baseline activity in the saline phase was comparable between all groups which was supported by the absence of any group differences in a 2×2×6 (Genotype×Dose×5 min-bins) ANOVA of the distance traveled in the saline phase. A 2×2×12 (Genotype×Dose×5 min-bins) ANOVA of the distance traveled in the drug phase was carried out to asses the motor effect of MK-801. The emergence of a highly significant main effect of dose [$F(1,51)=35.94$, $p<0.001$] indicated that MK-801 enhanced locomotor activity in a dose dependent manner. However, the motor stimulant effect of MK-801 was clearly reduced in mutants relative to controls, which was observed regardless of MK-801 dosage. This impression was confirmed by the presence of a significant main effect of genotype [$F(1,51)=6.45$, $p<0.05$]. For details on the generation of the mutant mice, the biochemical and electrophysiological properties in these animals please refer to Yee et al. (2006).

NMDA receptor blockade achieved by systemic MK-801 (Fig. 1). Interestingly, GlyT1 deletion is also efficacious in delaying the motor stimulating effect of the indirect dopamine agonist and potent psychostimulant amphetamine (Yee et al., 2006). One may therefore suspect that GlyT1 can indirectly modulate glutamate–dopamine interaction at the ventral striatum, suggesting that GlyT1 blockade not only can directly counter NMDA receptor hypofunction but also dampen behavioural abnormalities due to functional hyperdopaminergia.

In summary, the full antipsychotic potential of the potential receptor sites highlighted here would require further evaluation in terms of their specific efficacy against different symptoms or clusters of symptoms. Given that the hypothesized therapeutic potentials of drugs targeting GABA-A receptor subtypes and GlyT1 are mainly derived from genetically modified animals that are not primarily created as disease models, the use of specific animals models of schizophrenia would be highly relevant here (Lipska and Weinberger, 2002; Meyer et al., 2005). This approach allows one to more directly assess whether relevant compounds possess the ability to normalize schizophrenia-related endophenotypes.

Schizophrenia is a disorder with a complex clinical manifestation involving multiple symptoms, which are most likely to involve aetiological mechanisms extending beyond one single brain region or neurotransmitter system. Hence, multiple therapeutic interventions seem necessary for the effective treatment of the disease. Various $GABA_A$ receptor sites and possibly GlyT1 may represent promising drug targets for the development of novel pharmacotherapy as well adjunctive interventions alongside conventional typical and atypical neuroleptics (Gray and Roth, 2007).

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