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Role of Glycine in Schizophrenia

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1. INTRODUCTION

The glutamate (GLU) hypothesis of schizophrenia was first published in 1980 and was based on reduced Glu levels in the cerebrospinal fluid (CSF) of schizophrenic patients *(1)*. Although it took a while, this negative correlation between Glu levels and schizophrenic symptoms has recently been confirmed *(2)*. Further evidences are also in concert with a hypoactive glutamatergic system as one but not solely underlying mechanism in schizophrenia (*see* Chapter 7 by Bleich and Kornhuber) and one of these major findings is going back to the late 1950s when schizophrenia-like symptoms were described after administration of phencyclidine (PCP) in humans *(3)*. However, a link between PCP-induced effects and the glutamatergic system was drawn not earlier than 20 years later when an interaction of PCP with the GluR and more specifically with the *N*-methyl-D-aspartate (NMDA) receptor was shown *(4–6)*. Further antagonists that block the NMDA receptor in a competitive or noncompetitive manner induce schizophrenia-like symptoms as well when they are given to humans and also to animals *(7–11)*. More support for the GLU hypothesis derived from postmortem studies showing an increase of NMDA receptor density in several brain areas *(12–13)* most probable as a consequence of lowered GLU release in these regions although differences regarding the NMDA subunits can be seen *(14–15)*. Adaptation in the density of other GluRs as α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA), kainate-, and metabotropic receptors has also been described, but the findings are less concise and depend on the respective subunit of the receptor and on the anatomical structures *(14,16–17)*.

The glycine-binding site is one of several other binding sites (i.e., polyamine, zinc, magnesium, and noncompetitive) that are expressed in the NMDA receptor complex (*see also* Chapter 4). Altogether they modulate the function of the NMDA receptor and depending on the composition of the NMDA receptor complex the pharmacological characteristics of the whole complex change significantly.

Glycine binds to the glycine-binding site as a coagonist and is a positive modulator of the NMDA receptor complex. The presence of glycine is prerequisite for the activation of the NMDA receptor through GLU or NMDA (*18–22*; for review, *see* ref. *24*). Interest in the glycine-binding site in schizophrenia came up when Ishimaru et al. *(12)* described lower levels of glycine-binding sites in the cortex of schizophrenic patients and when

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therapeutic consequences were drawn from the GLU hypothesis. Because a therapeutic approach via direct GluR-agonists is not feasible owing to the risk of neurotoxicity, stimulation of a hypoactive glutamatergic system through the coagonistic glycine-binding site that bears no risk of neurotoxicity seemed therefore to be smarter from the functional point of view.

There are at least two opportunities to increase glycinergic transmission and by this to induce functional GLU agonism:

1. The glycine site can be modulated directly through agonists and indeed several agonists have been described. Variations that lead to modified chemical structures are limited and are very often accompanied by the loss of agonistic properties because glycine itself is a very small molecule. Although this approach does not bear the risk of neurotoxicity, it bears the risk of tolerance development in a chronic treatment schedule. However, many studies in humans and animals indicate that pathophysiological conditions can be improved by the direct agonists (*see* Section 3).
2. The glycine site can be modulated indirectly via blockade of the glycine transporter (GlyT). This transporter is located in the vicinity of glycinergic transmission and controls the glycine concentration in the synaptic cleft. Two subtypes have been described, GlyT1 (with three isoforms) and GlyT2 (two isoforms). GlyT2 is present in presynaptic elements in spinal cord and brainstem and regulates the strychnine-sensitive glycinergic transmission *(24)*, whereas GlyT1 is present in glia cells in frontal cortex, hippocampus, striatum, thalamus, and also on the level of brainstem and spinal cord. This latter one is colocalized with the NMDA receptor complex and controls the glycine concentration in the NMDA receptor complex *(25)*. Blockade of the GlyT1 would therefore extend the time of glycine available in the synaptic cleft after release from its storage sites. Moreover, this approach is without any interaction with the glycine site itself and without a risk of tolerance development and neurotoxicity. Indeed, an increase of glycine concentration in a schizophrenia-related structure (ventral hippocampus) has recently been shown in rats treated with the GlyT1 inhibitor ORG 24598 *(26)*. To evaluate the role of glycine in schizophrenia, behavioral effects of glycine site antagonists and agonists are summarized in the following paragraphs. If an impaired glutamatergic transmission is one underlying mechanism in schizophrenia, (1) glycine site antagonists should have behavioral effects resembling to those of NMDA receptor antagonists and (2) glycine site agonists or GlyT 1 inhibitors should improve schizophrenic symptoms in animals and patients.

2. EVIDENCE FROM ANIMAL STUDIES

Schizophrenia is characterized by positive symptoms with hallucinations, delusions, attention deficits, loose associations, disorganized thoughts, and psychomotor stimulations, and by negative symptoms with flat affect, social impairment, and impaired memory and cognition (*see also* Chapter 6). In animals schizophrenia-like symptoms can be induced by pharmacological or by neurodevelopmental manipulations (i.e., neonatal hippocampus lesion, isolated rearing, neonatal PCP administration), however only particular aspects of behavioral dysfunctions can be generated (i.e., psychomotor stimulation with perseverative behavioral aspects like hyperlocomotion, stereotyped behavior, and head weaving; attention or sensory gating deficits with deficits in prepulse inhibition (PPI) and latent inhibition; social impairment; and cognitive disturbances).

2.1. Psychomotor Stimulation

In parallel to NMDA receptor antagonists, glycine site antagonists induce psychotomimetic effects although less pronounced and sometimes less concise between the individual compounds. For example, systemic administration of the partial agonist

(R,+)-HA-966—which acts predominantly as an antagonist—or of the full antagonists L-701,324, MRZ 2/576, and ACEA 1021 do not increase locomotor behavior but rather induce sedation in higher doses when given to rodents *(27–33)*. In contrast, stereotyped sniffing behavior and head weaving can be induced by systemic administration of (R,+)-HA-966, L-687,414, L-701,324, and ACEA 1021. The latter one has, however, a tight dose–response relationship although the induced behavior can be blocked by the glycine site agonist DCS *(28,30,34,35)*. The overall intensity of the psychotomimetic effects induced by these substances is lower than that of direct NMDA receptor antagonists. This is supported by the finding that glycine site antagonists do not substitute for the discriminative stimuli of noncompetitive NMDA receptor antagonists *(36,37)*.

The dichotomy of the effects of glycine site antagonists on locomotion and stereotyped behavior is also reflected by studies investigating the antagonist 7-chlorokynurenate (7-CLKYN), which does not penetrate the blood–brain barrier and needs to be administered directly into the brain. Infusion of 7-CLKYN into the third ventricle of rats dose-dependently enhances stereotyped sniffing behavior but has no effect on locomotion *(38,39)*. In parallel to systemic applications, higher doses generate sedation and strong muscle relaxation and by this reduce motor activity *(39)*. When 7-CLKYN is infused into the dorsal striatum or the nucleus accumbens—structures that are directly involved in stereotyped behavior and locomotion—the same results are obtained. The antagonist induces stereotyped sniffing behavior after infusion into both structures but dose-dependently only after infusion into the dorsal striatum. However, locomotor behavior is once again not affected by this antagonist *(40)*.

Thus, blockade of the glycine-binding site induces at least some psychomotor stimulatory symptoms that are described for direct NMDA receptor antagonists. The symptomatology is less pronounced after systemic administration of the glycine site antagonists. However, it resembles to the symptomatology of the noncompetitive NMDA-antagonists after local infusion into structures directly linked to the respective symptom. As mentioned earlier, a low brain penetration and/or bioavailability of glycine receptor antagonists may be reasons behind the differences.

Glycine agonists have been less intensively characterized. So far no effect on sniffing behavior and locomotion has been found after administration of D-serine and glycine *(41)*. Also, the partial agonist DCS with an agonistic profile in doses up to 20–30 mg/kg also does not modulate sniffing behavior and locomotion in rats *(29,31,42,43)*.

Other partial agonists such as (R,+)-HA-966, ACPC, L-687,414, cycloleucine, and S18841 with an intrinsic activity between 10 and 92% *(23)* are in vivo mainly characterized by antagonistic effects even when they have a high intrinsic activity in vitro. They are commonly used as antagonists.

Some more interest was given to the effects of glycine agonists in pathophysiological models such as pharmacologically or environmentally induced hyperlocomotion and stereotyped sniffing behavior via PCP, (+)MK-801, amphetamine, apomorphine, or impaired neurodevelopment (neonatal hippocampus damage, isolated rearing).

Neonatal ventral hippocampal damaged rats are characterized by one prominent symptom that they share with schizophrenic patients; they show a postpupertal onset of symptoms especially a hypersensitivity to PCP, (+)MK-801, and amphetamine, and also changed responses to novelty *(46–49)*. Glycine itself is able to attenuate the effects on novelty- and amphetamine-induced hyperlocomotion *(46)*.

However, glycine site agonists give controversial results in pharmacologically induced models. Whereas amphetamine- or apomorphine-induced hyperlocomotion cannot be antagonized by glycine or the GlyT1 inhibitors (GDA and its derivates, ORG 24461, NFPS) *(50–52)*, the effects on PCP- and (+)MK-801-induced psychotomimetic effects are less clear. In several studies alanine, D-serine, D-cycloserine (DCS), glycine, and GlyT1 inhibitors (ORG 24461, NFPS) are able to attenuate PCP-mediated behavior *(50–55)*, (+)MK-801-induced effects are however potentiated by DCS *(42,56)* and antagonized by D-serine *(57)*. Although this latter finding looks puzzling, there is a previous study pointing to a false-positive effect of D-serine. *(42)*. In this study, it is found that (+)MK-801-induced locomotion was reduced by coadministration of DCS; sniffing stereotypy was however increased at the same time *(42)*. Thus, in the combination of (+)MK-801 and DCS there is a shift in the behavioral dominance toward a focused hyperactivity, a shift that is precisely described for higher doses of (+)MK-801 and also for amphetamine; hyperlocomotion over a large area of the cage at low doses and hyperactivity in one location of the cage with stereotyped sniffing at higher doses *(58,59)*. Thus, a decrease of (+)MK-801-induced behavior after coadministration of D-serine *(57)* seems to be the result of a focused stereotypy and in this respect, (+)MK-801-mediated psychotomimetic actions are not antagonized but rather potentiated by glycine site agonists. Even surprising on the first view, it can be explained by the functional interaction of the glycine-binding site and the noncompetitive binding site at the NMDA receptor complex. From electrophysiological experiments, it is well known that activation of the glycine-binding site enhances the binding affinity of the NMDA receptor although it increases the frequency of the channel openings *(21,60)*. Because the binding of noncompetitive NMDA receptor antagonists like PCP and (+)MK-801 strictly depends on an open state of the ion channel, the activation of the glycine-binding site increases the binding probability of the noncompetitive NMDA receptor antagonists and potentiates the behavioral effects of these antagonists. Thus, the potentiated behavior of noncompetitive NMDA receptor antagonists supports the benefit of glycine site agonists as functional GLU agonists even if it is indirect.

2.2. *Sensorimotor Gating and Glycine*

Apart from psychomotor stimulation, attention or sensory gating deficits can also be observed in schizophrenic patients and animals pharmacologically stimulated or impaired in neurodevelopment. The sensory gating deficit can be measured as a PPI deficit. It is widely accepted as a model with excellent predictive, face, and construct validity *(61,62)*. More recently, however, reports of inhomogeneous presence of PPI deficits in schizophrenics and relatives took some of the convincing power of this model in schizophrenia. In fact, a PPI deficit does not solely predict the latent or manifested presence of schizophrenia, a PPI deficit does not appear in all schizophrenics, and nor does the intensity of a PPI deficit correlate with the intensity of negative and positive symptoms *(62–66)*. Moreover, PPI deficits can also be found in other psychiatric and neurodegenerative diseases, like obsessive compulsive disorder, Huntington's disease, noctural enuresis, attention deficit disorder, Tourette syndrome, blepharospasm, nonepileptic seizure, and to a lesser extent posttraumatic stress disorder *(62)*. Thus, a PPI deficit has some convincing associations and correlations to schizophrenia but it cannot be taken as the ultimate indicator for this disease.

In animal studies the predictive validity of PPI experiments is more concise and this model is commonly used to identify new antipsychotic drugs and to elucidate the underlying mechanism of sensory gating under normal and maladapted conditions. The glycine site antagonists (R,+)-HA-966, L-701,324, ACEA 1021, MRZ 2/576, and MDL 105,519 have, in contrast to noncompetitive NMDA receptor antagonists, no effect on PPI when they are given systemically in rats *(30,32,67–72)*. The antagonists also have no synergistic or inhibitory effects on PCP- or apomorphine-induced PPI deficits *(32,68)*.

The situation differs when the glycine site antagonists 5,7-diCLKYN or 7-CLKYN are applied into the third ventricle or nucleus accumbens, respectively *(73,74)*. Both antagonists show a marked PPI deficit and that of 7-CLKYN can be attenuated by a glycine site agonist *(74)*. Although this behavioral modulation via the nucleus accumbens should be surprising considering the negative effects on locomotion *(40)*, a later study suggests that a PPI deficit is mediated via an anatomical pathway different from that of locomotion *(75)*. The higher local concentration of the antagonists in structures directly linked to PPI may be the reason why these antagonists are able to disrupt PPI after local but not systemic administration.

Studies of glycine site agonists on PPI are rare; DCS and glycine have been studied but they have no effect on PPI themselves *(70,74)*. However, in a neurodevelopmental approach *(44,76)* where the animals develop a PPI deficit postpuperal, glycine itself and the GlyT1 inhibitor ORG 24598 attenuate the lesion-induced deficit *(26)*. Thus, sensory gating seems to be sensitive to a manipulation of the glycine-binding site.

2.3. Cognitive Deficits and Glycine

Cognitive deficits in schizophrenia are dominated by strategic sequencing and planning deficits and working memory deficits that are subserved in the dorsolateral part of the prefrontal cortex *(77)*. In healthy volunteers, the noncompetitive NMDA receptor antagonist ketamine induced deficits resembling those of schizophrenics using, for example, the Wisconsin Card Sorting Test and delayed word-recall tests *(11,78–80)*. Moreover, these symptoms can be exacerbated in stable schizophrenic patients by treatment with ketamine *(79,81)*. In animals, not only NMDA receptor antagonists but also the glycine site antagonists; (R,+)-HA-966 *(83)* and its less selective racemate (±)-HA-966 impair working memory in a PFC-related operant delayed matching-to-position task *(84)*. In contrast, ACEA 1021 has no effect in a delayed nonmatching -to-sample task *(85)*. Up to now glycine site agonists or antagonists have not yet been tested on schizophrenia-like cognitive deficits in neurodevelopmental and pharmacological models. Interestingly, DCS treatment is able to improve cognitive impairments in Alzheimer's patients when given for 4 wk *(86)*, as well as in hippocampal-damaged rats when given acutely *(87)*.

2.4. Transgenic Mice and Glycine

Pharmacological manipulations are commonly used to characterize a particular transmitter or modulator system. The respective drugs, however, are administered acutely and the behavioral outcome after this approach does not reflect the pathophysiological situation where a system is in a chronic maladapted condition. To circumvent this missing correlation, transgenic animals with a permant overexpression or downregulation of particular genes are closer to the situation of chronic diseases like schizophrenia. However, missing genetic information can induce compensatory mechanisms during the embryonic and

postembryonic development with an unknown outcome on the whole transmitter balance. To bypass this uncertain situation, "induceable" transgenic animals that develop an overexpression or downregulation during adulthood can be used. They are free of a developmental compensation but are not easy to create and are less commonly used. Nevertheless, the results available from transgenic animals are valuable and they may give a deeper insight into chronic conditions, although they very often confirm data that have been previously established with respective antagonists (e.g., *see* refs. *88* and *89*). Thus, it is necessary to keep in mind that results from transgenic animals as well as those from pharmacological studies are excellent tools but they have limits.

Transgenic mice lacking the NR1 or NR2A subunit, and therefore having a malfunction in the glycine-binding site, show the phenotype of PCP- or (+)MK-801-treated animals with hyperlocomotion, stereotypy, social withdrawal, cognitive deficits, and a hyperactive monoaminergic system in striatum and frontal cortex; effects that are sensitive to treatment with antipsychotics like haloperidol, clozapine, and risperidone *(90–92)*. Moreover, mice carrying a point mutation in the glycine-binding site of the NR1 subunit show a reduced glycine affinity instead of reduced density that is accompanied by deficits in long-term potentiation (LTP) induction, spatial learning, and an increase in startle reactivity with, however, normal locomotion and PPI *(93)*. A mouse line with a 2-point mutation in the glycine-binding site also exhibits impaired LTP induction and dopamine and serotonin hyperfunction. These mice are insensitive to (+)MK-801 treatment, are supersensitive to startle stimuli without a defect in PPI, and show prominent hyperactivity and stereotyped behavior that do not habituate. The stereotyped behavior, but not the hyperactivity, is sensitive to clozapine, haloperidol, or M100907 treatment, however only at higher doses that are already sedative in wildtype mice *(94)*. Thus, the overall more pronounced effects of mutations in the glycine site may result from the reduced function of the NMDA receptor complex in contrast to the marked loss of NMDA receptor subunit density that may induce compensatory changes and by that reduces the symptomatology (*see* ref. *94*).

3. EVIDENCE FROM HUMAN STUDIES

From clinical trials in indications where a blockade of the glutamatergic system may be of benefit (e.g., stroke, epilepsy, pain), psychotomimetic effects in volunteers are well-known results of uncompetitive and competitive NMDA receptor antagonists *(3,8,81,95–100)*. In contrast to dopamine agonists, blockade of the glutamatergic system induces positive as well as negative symptoms and more important exacerbates psychotic symptoms, most prominently those already present in the schizophrenic patients *(80,81)*. Glycine site antagonists gained interest in GLU-dependent diseases because they seem to have fewer side effects. They were tested for efficacy in stroke, head trauma, epilepsia, pain, and neuropathic pain (*see* ref. *101*). In general, the glycine antagonists are described as well tolerated and safe in humans. In clinical phase II studies on stroke and head injury, the antagonist ACEA 1021 generates in one and two out of six patients (in a medium-dose group) visual hallucinations and transient memory disturbances, respectively. Thus, for ACEA 1021 there is an ascending risk of psychotomimetic side effects with increasing doses *(100)*. In contrast, in clinical studies with the antagonist GV 15526, no psychotomimetic side effects have been reported *(102–104)*. So far, none of the glycine site antagonists has reached the market. The development of almost all glycine site antagonists discontinued because the therapeutic

window between beneficial and mechanism-related side effects was too small. Thus, from the profile of the antagonists, the glycine site in humans bears also the risk of generating psychotomimetic effects; however more clinical data are needed for a final assessment.

In schizophrenia, glycine agonism as a treatment option emerged with the GLU hypothesis. Since bioavailability and brain penetration of glycine itself are limited, high doses are needed. Nevertheless, its efficacy was tested in a couple of trials in schizophrenic patients. The most surprising outcome was that in most studies glycine and also DCS treatment mainly affect negative symptoms and leave positive symptoms unaffected *(105–117)*. Although other reports show comparable efficacy of D-serine on positive, negative, and cognitive symptoms *(118)*, the negative outcome on positive symptoms was a drawback for the therapeutic use of glycine agonism as antipsychotic. The reason behind this may be found in the co-medication used at that time. Until the late 1990s mainly classical neuroleptics were used as gold standards in schizophrenia. They are known to be more effective on positive than negative symptoms. It is therefore not surprising that patients who are already well controlled on positive symptoms may be less sensitive to a further improvement by the co-medication with glycine site agonists. An additional aspect comes from the predominance of negative symptoms induced by the GLU/glycine receptor antagonists and it seems obvious to conclude that therapeutic effects of glycine agonists are directed toward negative symptoms. These two aspects are further supported by recent studies that directed more attention to the type of co-medication. It was found that D-serine treatment is ineffective in combination with the atypical neuroleptic clozapine *(119)*, whereas the combination of glycine plus clozapine or olanzapine—another atypical antipsychotic—still ameliorates negative symptoms but with a less pronounced effect as in patients under classical neuroleptics *(120–122)*. Moreover, symptoms worsened when DCS was combined with clozapine *(112,123)* but still improved in combination with risperidone *(117,124)*, however once again less prominently as in combination with classical neuroleptics *(123,125)*. This outcome in general is not astonishing when we consider the higher efficacy of the atypical neuroleptics on negative symptoms *(111)*. Furthermore, there are studies revealing that especially clozapine acts as a functional GLU/glycine agonist since it increases serum GLU levels *(126)* and enhances NMDA receptor-mediated responses in the prefrontal cortex *(127)*.

A risk of neurotoxicity obvious for direct GLU agonists is unlikely from the receptor function and was not present when glycine or DCS was given in a chronic treatment regime of 4 d to healthy subjects; there was no effect on cognition or other behavioral parameter (schizophrenic, anxiety, sadness, panic) *(128)*. A longer treatment period with high doses (1–5 mo; 1 g/kg/d or 5 g/kg/d) of glycine in rats was free of neurotoxic effects in neuronal and glia cells, but was, however, accompanied by a reduction of class B, N-type Ca2+ channels in parietal cortex and hippocampus after 3 and 5 mo of continuous treatment without functional implications *(129)*.

By summarizing the efficacy of glycine site agonists in schizophrenic patients, it is obvious that the agonists themselves as well as in combination with classical neuroleptics are mainly effective on negative symptoms whereas in combination with atypical neuroleptics they have no further benefit. A more prominent benefit for the patients may result from a fine titration of the different treatment options in relation to the preponderance of symptoms.

4. CONCLUDING REMARKS AND FUTURE DIRECTIONS

Summarizing the findings of glycine ligands in animal models of schizophrenia and in schizophrenic patients reveals that (1) downregulation of glycinergic transmission by antagonists induces symptoms associated with schizophrenia and (2) upregulation of glycinergic transmission by agonists or GlyT inhibitors ameliorates symptoms associated with schizophrenia. Thus, a dysfunction in glycinergic transmission needs to be taken into account as one mechanism involved in schizophrenia. Of course, data from additional studies indicate that schizophrenia is a multifactorial disease and that other systems than the glutamatergic/glycinergic are involved. Dopamine, serotonin, and GLU are the most frequently discussed transmitter systems in this regard. It is not clear, however, whether a single defect in one transmitter system is responsible for the disease or if defects in other transmitter systems are the consequence of an initial defect in one system. It has been discussed that a critical period for the development of schizophrenia seems to be in the neonatal phase *(49)*. Support for this comes from animals with neonatal damage in the ventral hippocampus—a region rich in glutamatergic innervation and transmission. These animals show schizophrenia-like symptoms not earlier than postpuberal *(48–49)*, a phenomenon also known from schizophrenic patients. Apart from the hippocampus other structures rich in Glu have been identified as sensitive to manipulation that leads to schizophrenic symptoms. Evidences are found for the prefrontal and frontal cortex, amygdala, and entorhinal cortex (*see* refs. *77,130,* and *131*). Because these glutamatergic efferents terminate in structures that are dopamine-driven and are involved in emotional information processing, the implications of the dopaminergic and serotonergic system are not surprising. A deficit in information processing rather than a defined anatomical or neurochemical deficit as an underlying mechanism in schizophrenia seems therefore more probable and fits with the missing neuropathology in schizophrenia.

A speculation on upcoming treatment options in schizophrenia needs to consider that family and twin studies show a role of genes in determining the susceptibility to schizophrenia. It is, however, evident that multiple gene loci are involved. Nevertheless, several candidate genes have been identified that may offer new opportunities for the development of new drugs *(132–134)*. Whether a concert of gene defects or a single gene defect in combination with other events are responsible for the development of schizophrenia is unclear for now. Interestingly, among others several genes have been identified that seem to have link to glutamatergic/glycinergic transmission. Future research is needed to show if the genes DISC-1 (disrupted-in-schizophrenia-1), dysbindin, neuregulin-1, G72, and PRODH *(132)* provide a new class of targets in drug development and if the treatment of schizophrenic patients is improved by these new approaches.

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