GLUTAMATERGIC DRUGS IN TREATMENT OF SCHIZOPHRENIA

A report on relevance

1. Abstract / resumé

2. Introduction
   - Epidemiology and disposition to schizophrenia: Environmental factors
   - Disposition to schizophrenia: Genetic factors
   - Diagnosis
     - Endophenotypes in diagnosis
   - The dopaminergic system in the CNS
   - The glutamatergic system in the CNS
     - GABA in the glutamatergic system
   - Altered transmitter systems related to the pathophysiology of schizophrenia
     - the dopamine hypothesis
     - the glutamate hypothesis

3. Methods
   - Search criteria and keywords
   - Articles chosen

4. Results
   - Presentation of glutamatergic drugs in the pipeline and their targets

5. Discussion

6. Conclusion

7. Reference list
1. Abstract

*Purpose:* There is still work to do in order to reach a satisfactory treatment of schizophrenia, since the currently existing antipsychotics have little or no effect on negative symptoms and cognitive deficits. Besides, dopaminergic dysfunction, in general, accounts poorly for symptom classes in schizophrenia other than positive symptoms associated with schizophrenia (Javitt and Zukin 1991). Thus, alternative approaches to treatment are needed. The purpose of the current thesis is to describe and discuss the rational for interfering with the glutamatergic system in the central nervous system. Which glutamatergic drugs are in the pipeline? Are they effective enough, considering the diffuse glutamatergic system in the brain?

*Method:* A literature study reviewing existing data on the subject. The PubMed database was searched using different profiles, and the *advanced search* function filtered out articles that were not relevant to the subject.

*Result:* As no glutamatergic drugs have yet reached the market, no unambiguous results of treatment with these are available. Research with glutamatergic drugs in treatment of symptoms points in three directions; 1) lack of improvement of symptoms, 2) worsening of symptoms and 3) positive results of trials have been published.

*Discussion:* The complexity of schizophrenia with many transmitter systems involved complicates an absolute treatment of symptoms. Just treatment of symptoms is the best offer as long as the genetic basis for development of disease has not yet been mapped. In reverse, because of the complexity there are many receptors, transporters etc. to interfere with pharmacologically. The selection of glutamatergic drugs covers a broad range of target receptors.

*Conclusion:* All in all, glutamatergic drugs seem promising for treatment in the future. The drugs show some effectiveness in treatment of negative and cognitive symptoms, and future research with larger cohorts will prove relevance of glutamatergic drugs.

**Resumé**

*Formål:* Der er stadigvæk arbejde at gøre for at opnå en tilfredsstillende behandling af skizofreni, siden de gængse eksisterende antipsykotika har ringe eller ingen effekt på negative symptomer og kognitive defekter. Desuden dækker dopaminerg dysfunktion utilstrækkeligt over symptomklasser i skizofreni ud over positive symptomer associeret med skizofreni (Javitt and Zukin 1991).

Således behøves alternative tilgange til behandlingen.

Formålet med nærværende opgave er at beskrive og diskutere racionalet for at påvirke det glutamaterg system i centralnervesystemet. Hvilke glutamaterg stoffer er under udvikling? Er de effektive nok, hjemens diffuse glutamaterg system taget i betragtning?

*Metode:* Et litteraturstudie med overblik over eksisterende data på området. PubMed-databasen var gennemsøgt ved at bruge forskellige profiler, og *advanced search*-funktionen filtrerede artikler fra, som ikke var relevante for emnet.

*Resultat:* Da ingen glutamaterg stoffer endnu har nået markedet, er der ingen entydige resultater fra behandling med disse. Forskning med glutamaterg stoffer i symptombehandling peger i tre retninger; 1) mangel på forbedring af symptomer, 2) forværring af symptomer og 3) positive resultater fra forsøg er publiceret.

*Diskussion:* Kompleksiteten ved skizofreni, med mange transmittersystemer involveret, komplicerer en fuldstændig symptombehandling. Netop symptombehandling er det bedste tilbud, så længe den genetiske basis for
Glutamatergic drugs in treatment of schizophrenia. A report on relevance

Konklusion: Alt i alt virker glutamaterge stoffer lovende for fremtidig behandling. Stofferne udviser nogen effektivitet i behandling af negative og kognitive symptomer, og fremtidig forskning med større kohorter vil bevise glutamaterge stoffers relevans.

2. Introduction

Epidemiology and disposition to schizophrenia: Environmental factors
The severity of schizophrenia becomes evident when considering a lifetime prevalence and incidence of 0.30–0.66% and 10.2–22.0 per 100 000 person-years, respectively (van Os and Kapur 2009) and usually the disease manifests early with a first-episode psychosis in the 2nd or 3rd decade of life (Coyle and Tsai 2004; Keshavan 1999) with several environmental correlations and triggers; The significant impact of urbanicity and migrant status on prevalence and distribution of schizophrenia (McGrath, Saha, Welham et al., 2004) suggest a geographically varying incidence, where countries with larger urban areas and a high number of immigrants show higher incidences of schizophrenia. The urban environmental risk factor is underlined when revealing a higher incidence of schizophrenia in cities compared to mixed urban/rural catchment areas (McGrath et al. 2004). Also more direct environmental triggers are enhancing development of the disease: Cannabis abuse is confounded with an increased risk of developing psychosis and subsequently schizophrenia (Moore et al. 2007). LSD and amphetamine, too, have proven to induce psychosis-like conditions with hallucinations and delusions (Paparelli et al. 2011).

Disposition to schizophrenia: Genetic factors
Vulnerability for schizophrenia is partly genetic. Twin studies suggest that the syndrome has heritability estimates of as much as 80% (van Os and Kapur 2009). Besides, men generally have a higher risk of developing schizophrenia compared to women, the rate ratio being 1.4:1 (McGrath et al. 2004).

Despite genetic association, the identification of specific molecular genetic variation has not been easy. Unclear diagnostic criteria and uncertainty about the natural phenotype of psychosis are likely to contribute to slowing the process. The high heritability (80%) of schizophrenia is not only due to genetic influences but also to environmental effects moderated by genes in a gene–environment interaction (van Os and Kapur 2009), for instance an immigrant with a perception of being socially excluded combined with a genetic vulnerability of developing schizophrenia (Morgan et al. 2008).

The precise genetic disposition to schizophrenia still remains a mystery, however, significant correlations exist between rare genetic microdeletions, so-called copy number variations (CNVs) and development of schizophrenia related to psychosis (Stefansson et al. 2008). Identified CNVs associated with schizophrenia may point the way towards underlying pathogenic pathways in the disease, and even though the CNVs only account for a very small fraction of the genetic risk of schizophrenia, it is a step towards further investigation (Stefansson et al. 2008).

Many other gene variants are involved in brain development with influence on ubiquitous brain transmitters such as glutamate or γ-aminobutyric acid (GABA) (Shi et al. 2008). The poor statement, that can be made today, is that while a number of genetic associations have been identified, none of them account for the majority of schizophrenia, and the functional relevance of most of them is not known. This view of schizophrenia genetics then reemphasizes a critical role for other interacting factors - particularly the environmental risk factors for schizophrenia (Shi et al. 2008; Stefansson et al. 2008).

Diagnosis
Schizophrenia is a serious mental disorder with characteristic of psychosis with hallucinations and delusions. Today schizophrenia is internationally diagnosed on basis of the International Classification of Diseases version 10 (ICD-10...
Glutamatergic drugs in treatment of schizophrenia. A report on relevance

index) by WHO and the Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV). Both systems are based on the clinical evaluation of symptoms, and according to DSM-IV the symptoms can be described as either positive or negative. Positive symptoms, such as hallucination, delusion and racing thoughts, reflect an excess or distortion of normal functions while negative symptoms, such as apathy, loss of fluency and productivity of thought and speech and poor social functioning, symptoms reflect a diminution or loss of normal functions. Another key component of schizophrenia is cognitive dysfunction including early sensory and perceptual information processing, impaired working memory, attention, and social cognition. Profound cognitive deficits are central in patients with schizophrenia (Joyce and Roiser 2007; van Os and Kapur 2009).

A rating system of schizophrenic positive and negative symptoms can be made with the Positive And Negative Syndrome Scale (PANSS) to evaluate a patient’s development of symptoms (Kay et al. 1987). PANSS is thus relevant in evaluating medication, and it is used in clinical trials testing drugs in the pipeline, see Table 1.

Antipsychotics

Psychosis is not unique to schizophrenia and is not always present (van Os and Kapur 2009), but it is an important symptom in patients with schizophrenia, since the presence of psychotic symptoms arguments for treatment of schizophrenia today as antipsychotics are commonly prescribed. Today we discriminate between 1st and 2nd generation antipsychotics:

The generations of antipsychotics differ in the target of the drug, since first generation antipsychotics (FGAs) have high affinity for antagonizing dopamine 2 (D2) receptors in the brain affecting the nigrostriatal as well as the mesolimbic dopaminergic system, the nigrostriatal system causing serious motor side effects, so-called extrapyramidal side effects (EPS) when given in large doses. Therefore second generation antipsychotics (SGAs) tend to have a wider spectrum of receptor targets; 5-HT receptors, histamine receptors, and a reduced affinity for D2 receptors to avoid the comprehensive motor side effects (Leucht et al. 2009).

Even though the SGAs are effective in treating positive symptoms with a reduced burden of motor side-effects, the promise of efficacy against negative and cognitive symptoms has not been borne out (Leucht et al. 2009). Additionally, the SGAs with their altered receptor profile tend to induce a high incidence of metabolic side-effects such as weight gain, increased triglycerides and cholesterol, hyperglycemia (Newcomer and Haupt 2006), and metabolic syndrome (Leucht et al. 2009).

The dopaminergic system in the CNS

Dopamine is one of the brain’s monoaminergic transmitters. The dopamine producing cells are relatively sparse and concentrated in substantia nigra pars compacta and ventral tegmental area (VTA), from where axonal projections spread across cerebrum innervating the rest of central nervous system (CNS). The nucleus of interest in schizophrenia is the VTA with projections to limbic structures at the base of the forebrain, prefrontal cortex and temporal lobe, which is why dopaminergic system can be separated into a nigrostriatal system and a mesolimbic system. The first performs motor functions, while the latter primarily is involved in limbic functions and thus also schizophrenia when pathologic. The anatomy of the system leads to a general assumption, that the neurotransmitters are released as a ‘spill-over’ from the synapse from where they diffuse and spread to function on monoamine receptors on surrounding neurons (volume transmission), thus contrasting specific synaptic transmission via synaptic clefts. The diffuse spread of transmitter, incl. dopamine, suggests a modulating effect on function of other neurons (Carlsson 2006) rather than individual functions of dopamine itself. As a transmitter dopamine must act on a set of receptors:

Dopaminergic receptors are separated into a D1 family (of D1 and D5 receptor subtypes) and a D2 family (of D2, D3, and D4 receptor subtypes). The D1 family has been associated with cognitive disturbances in animal studies where a D1 agonist has shown to reverse induced cognitive disturbances in rats (Fletcher et al. 2005; McLean et al. 2009), whereas the D2 family is linked to positive psychotic symptoms and some early information processing disturbances in relation to schizophrenia (Glenthøj et al. 2008). D2 receptors are also the targets of antipsychotics, since studies
reveal a connection between antipsychotic effect and striatal D2 blockade. This blockade also reduces the risk of neutral stimuli being inappropriately registered of value, so-called salience disturbances (Kapur 2003). In line with salience disturbances it is proposed that in psychosis there is a dysregulated dopamine transmission that leads to stimulus-independent release of dopamine. This neurochemical aberration takes over the normal salience attribution and leads to aberrant assignment of salience to external objects and internal representations. Thus, dopamine, which under normal conditions is a mediator of contextually relevant saliences, in the psychotic state becomes a creator aberrant ones (Kapur 2003).

The glutamatergic system in the CNS

Glutamate is the main excitatory neurotransmitter in the CNS. Unlike dopamine with its anatomically concentrated dopamine-producing cells in the brain stem, the glutamatergic system seems disorganized and impossible to delineate. The functions of glutamate are numerous, including the early information processing considering its influence on the cortico-striato-thalamo-cortical circuit illustrated in Fig. 2.

In spite of a diffuse glutamate system, the transmitter acts on a well-defined set of receptors: Glutamatergic receptors are divided into two main groups based: 1) ionotropic ligand-gated ion channels and 2) metabotropic G-protein coupled glutamate receptors.

The ionotropic glutamate receptors mediate the vast majority of excitatory neurotransmission in the brain (Dingledine et al. 1999) including all cortico-cortical connections and cortical efferents (Moghaddam 2004). The three pharmacologically defined classes of ionotropic glutamate receptors were originally named after reasonably selective agonists; N-methyl-D-aspartate, NMDA (NMDA receptor = NMDAR), alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA, (AMPA receptor = AMPAR), and kainate (Dingledine et al. 1999), but for reasons of space the latter will not be described further in the thesis.

Metabotropic glutamate receptors, mGluRs, are of subtypes yielding two subfamilies relevant to schizophrenia: Group one consisting of mGluR1 and mGluR5, while group two is mGluR2 and mGluR3 (Moghaddam 2004). The first group increase presynaptic glutamate release, while the second group inhibits presynaptic glutamate release (Moghaddam 2004), which is a simplified statement, sine the response of a neuron depends on the ligand connected to its receptor.
Glutamatergic drugs in treatment of schizophrenia. A report on relevance

The NMDAR is an ion channel responsible for influx of Ca$^{2+}$ and Na$^+$ with a primary glutamate binding site and an allosteric glycine binding site (Gray and Roth 2007). An observation of interest is that both transmitters must be present to open the ion channel, and it can be modulated by Mg$^{2+}$, polyamines and other protons at various allosteric sites, thus suggesting a line of targets to reach pharmacologically (Javitt 2004). In the presence of glutamate and glycine the channel is open exposing PCP binding sites inside the channel. The channel is blocked when PCP enters the channel and bind (Dingledine et al. 1999; Javitt 2010).

**AMPA receptors** are ionotropic ligand-gated ion channels generating excitatory post synaptic potentials (EPSP) from influx of cations, such as Ca$^{2+}$ and Na$^+$ (Black 2005; Marenco et al. 2002a). AMPAR help to activate NMDAR while NMDAR are required for proper incorporation of AMPAR into the postsynaptic membrane, a process involved in synaptic plasticity allegedly involved in memory formation in the CNS (Black 2005). Direct AMPA receptor agonists rapidly desensitize AMPA receptors limiting their therapeutic utility, therefore, allosteric potentiators of AMPA receptor function, a class of compounds termed ampakines, are being studied as potential treatments for schizophrenia (Black 2005). Ampakines are able to enhance glutamatergic transmission, facilitating long term potentiation, learning and memory in rodents and may avoid the desensitization frequently seen with direct AMPA agonists (Black 2005). In a pilot study of patients with schizophrenia medicated with the atypical antipsychotic clozapine, co-administration of the ampakine CX516 yielded significant improvements in memory and attention (Goff et al. 2001), however, a trial of CX516 as monotherapy in schizophrenia showed no clear beneficial effects (Marenco et al. 2002a), as did the add-on trial of CX516 by Goff (Goff et al. 2008) (see Table 1).

**GABA in the glutamatergic system**

$\gamma$-amino-butyric acid (GABA) is the major inhibitory transmitter in the CNS. It is usually released from inhibitory interneurons serving to modulate the activity of other neurons, for example the glutamatergic ones (Moghaddam and Javitt 2011). One example of GABAergic influence is the feed-forward inhibition where the effect of afferent excitation on a pyramidal neuron is decreased by co-activation of GABA interneurons that synapse onto the same pyramidal neuron. Thus, increased discharge of an interneuron results in decreased discharge of pyramidal neurons. That is, processes that inhibit the GABA excite or ‘disinhibit’ pyramidal neurons (Moghaddam and Javitt 2011). Hypofunction of NMDA receptors on local GABAergic interneurons might play a role in dysfunction of neuron ensembles, leading to disturbances of certain firing frequencies known as gamma-oscillations, that may be the foundation for optimizing cortical function (Gonzalez-Burgos and Lewis 2008).

**Altered transmitter systems related to the pathophysiology of schizophrenia**

Postmortem pharmacological findings illustrate schizophrenia as an illness arising from deficits in several of the transmitter systems of the brain (Shapiro 1993) also manifesting itself from anatomical-structural changes in the brain; global atrophy of grey matter, ventricular enlargement, alterations especially located to fronto-temporal regions with volume reductions in temporal structures, the superior temporal gyrus and inferiorly in the frontal cortex in the affected patients (Nickl-Jockschat et al. 2011). The structural changes may be visible to the human eye, while the functional changes and deficits of the neuronal circuits involving the basal ganglia are not.

**Basal ganglia:** In the CNS the term ‘ganglia’ refers to concrete telencephalic structures; substantia nigra, caudate nucleus, lentiform nucleus and subthalamic nucleus. The primary function of the basal ganglia is processing information from cortex and thalamus, the information being limbic, cognitive or motoric. The information then travels via parallel circuits through the basal ganglia before it reaches thalamus or cortex, which allows the basal ganglia’s participation in information processing, assumably functioning as a filter for information, inhibiting inappropriate information while facilitating beneficial information. The thalamus is viewed as a higher-order relay station, since signals run cumulatively through the relevant thalamo-cortical loops, as conscious awareness becomes more refined and sophisticated (Min 2010).
Glutamatergic drugs in treatment of schizophrenia. A report on relevance

Research and health sciences have revealed deficits in the transmitter systems of the brain of patients with schizophrenia, most importantly the dopamine system related to positive psychotic symptoms and disturbances in early information processing. Schizophrenia as a complex disease also includes disturbances in norepinephrine, serotonin, histamine, and cholinergic systems, but for reasons of space they will not be mentioned further. Motor and cognitive alterations are few of the many changes relevant for diagnosis and are thus relevant in determining the pathophysiology of schizophrenia (van Os and Kapur 2009). The dopamine circuit is central for motor alterations, and the disease results partly from an altered and exaggerated dopamine synthesis (Abi-Dargham et al. 2000; Keshavan 1999; Lisman et al. 2008; McGowan et al. 2004; Meyer-Lindenberg et al. 2002; van Os and Kapur 2009), release, and effect (van Os and Kapur 2009).

Current hypotheses of schizophrenia suggest positive symptoms such as delusions, hallucinations, grandiosity and paranoia reflect a hyperfunction, that is, an exaggerated synthesis/release/receptor binding of dopamine with origin in the basal ganglia. On the contrary, negative symptoms like social withdrawal, difficulties in abstract thinking, lack of spontaneity and flow in conversations arise from hypofunction of the glutamatergic system (Lisman et al. 2008), which also seems to be the case for cognitive impairments (van Os and Kapur 2009).

One theory to explain symptoms involves the cortico-striato-thalamo-cortical circuit which controls early information processing:

![Cortico-striato-thalamo-cortical circuits related to schizophrenia](image)

**Fig. 2**: Cortico-striato-thalamo-cortical circuits related to schizophrenia, GABA: γ-aminobutyric acid; VTA: ventral tegmental area of substantia nigra; GPe: globus pallidum externa; GPI: globus pallidum interna; STN: sub-thalamic nucleus (with inspiration from (Carlsson 2006))

In Fig. 2 the cortico-striato-thalamo-cortical circuit, one of the basal ganglia circuits, is illustrated with its three transmitters; glutamate excitatory, GABA inhibitory, while dopamine modulates the effects of glutamate and GABA. Glutamate is released from cortex via neurons to striatum located in mesencephalon. The direct pathway (upper projection from striatum on Fig. 2) transmits via GABAergic neurons directly from striatum to the internal globus (GPI), while the indirect pathway (lower projection from striatum on Fig. 2) leaves striatum continuing through the external globus pallidus (GPe) with GABAergic neurons and via other GABAergic neurons to the subthalamic nucleus (STN), finally projecting glutamatergic neurons to GPI. Both pathways continue with GABAergic neurons to thalamus, and the circuit is completed with excitatory glutamatergic transmission from thalamus back to cortex. The circuit is then modulated by dopamine released from ventral tegmental area of mesencephalon acting on D2 receptors in the striatal complexes (Carlsson 2006), but also on D1 receptors of putamen as part of striatal complexes (Javitt 2010; Perreault et al. 2010).
Considering function of the circuit in healthy individuals, the striatum is excited to inhibit globus pallidus’ inhibiting neurons, thus elevating excitatory impulses back to cortex from thalamus and enhancing information processing with help and promotion from dopamine (Carlsson 2006). Other studies suggest that dopamine modulation of D1 receptors results in excitation of the excitatory direct pathway, because of increased activity of excitatory D1 receptors. Reversely, dopaminergic modulation of D2 receptors has inhibitory effect on the inhibitory indirect pathway because of increased activity of the inhibitory D2 receptor. These parallel processes result in increased thalamic impulses to cortex (Carlsson 2006).

In psychotic schizophrenic patients with exaggerated dopamine effect, the modulating effect of the cortico-striato-thalamo-cortical circuit is out of balance. As mentioned, the striatal complex usually has an inhibiting effect on thalamus via GABAergic neurons. The thalamus can thus act as a filter of sensory information (Carlsson 2006). D2 receptors in striatal neurons inhibit their inhibitory output projecting to the thalamus. The result is a hyperactive thalamus overstimulating the cortex manifesting as positive symptoms.

The striatal complex is controlled via inhibition by the brain stem and activation from the glutamatergic neurons of cortex. Strong inhibition of the inhibitory GABA neurons by hyperactivated D2 receptors as well as reduction of glutamatergic input to striatal neurons may reduce inhibition of the thalamus, so the main problem underlying development of positive symptoms is an exaggerated dopamine release and an opening of the thalamic filter.

The dopamine hypothesis

The dopamine hypothesis of impairment in dopaminergic neurotransmission is the most accepted hypothesis of positive symptoms of schizophrenia. According to this hypothesis, schizophrenia psychotic episodes are triggered specifically by the activation of dopamine receptors.

The dopamine hypothesis does not cover the spectrum of symptoms in schizophrenia, and other transmitter systems can be helpful in explaining other symptoms than the positive ones.

Psychoactive drugs acting on other systems may indirectly act on the dopaminergic system by potentiating dopamine release caused by other effects. This has been shown for the NMDA blocker ketamine, which has been found to increase amphetamine-induced dopamine release in healthy humans to the levels seen in schizophrenia. These new data therefore indicate that even psychoactive drugs that do not directly act on the dopamine system are linked to the dopaminergic system, thus illustrating an interconnection between transmitter systems.

The glutamate hypothesis

In the 1990s, an alternative to the commonly accepted dopamine hypothesis of schizophrenia was proposed on basis of the observation that phencyclidine (PCP) and ketamine acted psycho-mimetically by blocking NMDAR, producing the key symptoms of schizophrenia; the positive symptoms of psychosis and negative symptoms (Javitt 2010; Carlsson 2006), but also neurocognitive disturbances similar to those of schizophrenia. Other findings of lower levels of glutamate (by about 50%) in cerebrospinal fluid samples from patients with schizophrenia compared to controls added to the rise to the glutamate hypothesis of schizophrenia (reviewed in (Paparelli et al. 2011)). The observation led to the idea that schizophrenic symptoms might reflect dysfunction or dysregulation of NMDA receptors and their neurotransmission (Javitt 2004; Javitt 2010; Moghaddam 2004). The effect of the glutamatergic system becomes clearer when studying glutamatergic drugs in the pipeline. Ongoing research using glutamatergic drugs is, though, an attempt to relieve negative symptoms and cognitive deficits.
3. Methods

Search criteria and keywords
The database of use was PubMed.

Search profiles
Many specific searches on authors and articles included in reviews have been made, but these were primary search profiles using advanced search:

“Schizophrenia AND glutamate OR glutamatergic drugs AND treatment”

“Schizophrenia AND negative symptoms AND cognitive impairments OR cognitive deficits AND treatment”

Articles chosen
To the widest possible extent newer publications (year 2000 +) were used as references, but deviations have been made. Reviews have been cited, where primary articles were not accessible.

4. Results

The term ‘glutamatergic drug’ is used to describe drugs with effect on the glutamatergic system. Table 1 lists the ways of action; glutamatergic drugs can interfere directly with glutamate receptors (NMDA, AMPA, kainate or mGluRs) as agonists, antagonists, or allosteric modulators or indirectly affect the glutamatergic system by increasing synaptic amount of glycine by inhibiting reuptake of the allosteric modulator glycine, thus leading to endogenous increase in cerebrospinal fluid (CSF) levels of glycine, facilitating glutamatergic signaling.

Presentation of glutamatergic drugs in the pipeline and their targets
To answer the question ‘Which glutamatergic drugs are in the pipeline?’ a table below presents the different approaches in reversing glutamatergic dysfunction. Drugs are separated into a group of either NMDA interaction or mGluR interaction. Since many drugs are in the pipeline or in phase II and phase III studies, the side effects are not fully mapped and therefore not listed.

Table 1

<table>
<thead>
<tr>
<th>Category of drug</th>
<th>Target</th>
<th>Example of drug name</th>
<th>Action</th>
<th>Benefits on symptoms</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1: NMDA interactions (direct or indirect)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agonist, naturally occurring amino acid</td>
<td>NMDAR</td>
<td>Glycine</td>
<td>Full agonist on glycine modulatory site(^1,2)</td>
<td>Studies with full agonists combined with SGA show 15% reduction of neg. symp. and significant improvement of cognition and positive symp(^1), but no effect of glycine(^3) or D-serine(^4) in combination with clozapine</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td></td>
<td>D-serine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allosteric modulator and partial agonist, anti-tuberculosis drug, ‘stabilizer’ with 60% occupancy</td>
<td>NMDAR</td>
<td>D-cycloserine</td>
<td>Partial agonist at glycine-site on NMDAR(^11), cross-reacts with NMDA glycine site(^2)</td>
<td>D-cycloserine + conventional AP reduce neg. symptom, but no change in cognition(^11)</td>
<td>Least effective agonist.(^11) Worsen symptoms when co-administered</td>
</tr>
</tbody>
</table>

\(^1\) Reference 1
\(^2\) Reference 2
\(^3\) Reference 3
\(^4\) Reference 4
\(^11\) Reference 11
| **Glutamatergic drugs in treatment of schizophrenia. A report on relevance** |
|---|---|---|---|
| **GTI** | GlyT1 | Sarcosine, low affinity GTI | Inhibits PCP-induced behavioral hyperactivity in rodents. High significant reduction in negative symp. and significant reduction in positive and cognitive symp. when added to antipsychotics. No improvement when added to clozapine |
| **GSH-precursor** | Redox-senstive site of NMDAR, modulated by oxidized form of GSH | N-acetylcysteine | Total decrease in PANSS and negative symptoms |
| **Ampakine / AMPAR-modulator** | AMPAR | CX516 | Pilot study showed significant improvement of memory and attention when added to clozapine, whereas an add-on trial showed no improvement of cognition or pos. and neg. symptoms when added to SGAs. Another study shows no effect when given as monotherapy. Examples of transient increased liver enzymes and leucopenia in monotherapy. Generally well tolerated, but examples of insomnia, fatigue and gastric discomfort. |
| **NMDA antagonist, non-competitive** | Memantine (anti-Alzheimer’s drug) | Based on the concept, that hyper-glutamatergic neurotoxocity causes cognitive deficits. Memantine blocks the excessive influx of calcium ions through the channel of the activated NMDA receptor of GABAergic interneurons in PFC. Needs more investigation, poor outcome so far. |

### 2: mGluR2/3 interaction:

<table>
<thead>
<tr>
<th>mGluR2/3 agonist</th>
<th>Prodrug</th>
<th>The agonists compensate for a decreased glutamate level in the synapse, leaving the mGluR2/3 in an active conformation. LY354770 acts on mGluR2/3 in prefrontal cortex.</th>
</tr>
</thead>
<tbody>
<tr>
<td>LY354740 Prodrug</td>
<td>LY544344</td>
<td>Reverse PCP-effect and ketamine effects in human volunteers.</td>
</tr>
<tr>
<td>LY404039 Prodrug</td>
<td>LY2140023</td>
<td>Decrease PANSS. Oral LY2140023 in acutely relapsing patients: Beneficial effects like olanzapine in early study. A phase II study shows no effect in relation to placebo. LY2140023 given as monotherapy in one phase II study showed reduced metabolic side effects compared to clozapine.</td>
</tr>
</tbody>
</table>
**Glutamatergic drugs in treatment of schizophrenia. A report on relevance**

<table>
<thead>
<tr>
<th>PAMs</th>
<th>mGluR2</th>
<th>Biphenyl-indanone A (BINA)</th>
<th>mGluR2 potentiators; - primary/orthosteric glutamate agonists, bind glutamate-binding site on mGluR2 extrasynaptically which allows the drug to enhance negative feedback on glutamate release, when the glutamate release is exaggerated. (^7,8)</th>
<th>BINA shown to reduce hallucinogenetic effect and head twitches of 5-HT(_{2A/2C}) agonist. (^9) The drug’s effect on cognition needs to be investigated.</th>
</tr>
</thead>
</table>
| Anti-epilepsy drug (anti-convulsant) | Voltage sensitive presynaptic \(\text{Na}^+\)-channels \(^5\) | Lamotrigine | Inhibiting presynaptic Na\(^+\)-channel-dependent glutamate release \(^9\) | Might reduce cognitive symptoms \(^9\). 
Reduction in pos. and neg. sympt. |
| | | | | Three incidences of psychotic symptoms and facial pain, one incidence of gingival infection \(^10\). |

**Notes:**

- **AMPAR =** AMPA-receptor, **AP =** antipsychotic, **CSF =** cerebrospinal fluid, **GlyT1 =** glycine transporter 1, **GSH =** glutathione, **GTI =** glycine transporter inhibitor, **NMDAR =** NMDA receptor, **PAM =** positive allosteric modulator, **PANSS =** Positive and Negative Syndrome Scale, **PCP =** phencyclidine, **PFC =** prefrontal cortex, **SGA =** second generation antipsychotics
- \(^1\) reviewed in (Javitt 2010) \(^2\) (Coyle and Tsai 2004) \(^3\) (Berk et al. 2008) \(^4\) (Goff et al. 2001) \(^5\) (Olney and Farber 1995) \(^6\) (Lieberman et al. 2009) \(^7\) (Patil et al. 2007) \(^8\) (Johnson et al. 2005) \(^9\) (Large et al. 2011) \(^10\) (Goff 2009) \(^11\) reviewed in (Gray and Roth 2007) \(^12\) (Tsai et al. 1999) \(^13\) (Evins et al. 2000) \(^14\) (Lune et al. 2006) \(^15\) (Aubrey and Vandenberg 2001) \(^16\) (Tsai et al. 2004) \(^17\) (Marenco et al. 2002b) \(^18\) (Do et al. 2000) \(^19\) (Parsons et al. 2007) \(^20\) (Kinon et al. 2011) \(^21\) (Profaci et al. 2011) \(^22\) (Benneyworth et al. 2007) \(^23\) (Goff et al. 2008)

---

**Fig. 3:** Glial glycine transporter (GLYT1) inhibition illustrated by the upper arrow crossed out. Glycine binds to glycine modulatory site of postsynaptic NMDA-receptor (blue). With inspiration from (Javitt 2010).
5. Discussion

A fundamental barrier to development and discovering of new drug targets exists, since the biology of schizophrenia is still not fully understood and mapped. Besides, not much time has passed, since health science began focusing on negative and cognitive symptoms, and thereto follows a long duration of drug development appropriate for treatment, keeping the process of drug testing in phase I-III studies and clinical trials in mind. On the other hand, a complex disease like schizophrenia with deficits in numerous transmitter systems allows for many targets to be modulated in order to relieve symptoms, that is, there are many places to manipulate in the brain. An interference with only the glutamatergic system might then seem as a kludge. Nevertheless the glutamatergic synapse, in spite of its wide and bulky distribution in the brain, has become one of the most prominent targets in alternative treatment strategies of schizophrenia (Javitt 2004; Moghaddam 2004). This is possible because the biological evidence supports involvement of deficient glutamate neurotransmission in the pathology of schizophrenia. Another reason is the complex architecture of the synapse containing a large number of presynaptic, postsynaptic, and regulatory proteins constituting appropriate targets for drug development (Moghaddam and Javitt 2011). D-serine and glycine are naturally occurring endogenous compounds with known effects and tolerated doses in vivo, yet Table 1 shows no efficacy when given as an adjunct to SGAs. D-serine and glycine are thus at first unsuitable for patients with psychosis. D-cycloserine is acting as a stabilizer. Generally, novel experiments with stabilizers seem like a constructive way of interfering, because a stable level of glutamate brings back some order to a system disrupted in schizophrenic patients. The contrasting agonists or antagonists might affect occupancy and thus transmission by abruptly raising or inhibiting transmission, respectively, thus risking yet another pathologic condition. The drug is, though, tested as a week agonist and mostly corrects negative symptoms while risking worsening of symptom given with clozapine. GlyT1 has widespread distribution throughout the brain, but in cerebellum and caudal parts of the CNS, GlyT1 seems to be predominantly localized on glial cells, thus involved in regulation of inhibitory glycine neurotransmission. Glial cells as a target illustrates the abstract thinking in development of new treatment strategies. The location of glial cells outside the synapse, yet in close proximity to synaptic activity and NMDARs, makes GlyT1 ideally suited to modulate their activity and stabilize transmitter concentration (Zafra and Gimenez 2008). Unfortunately the results are not impressing. N-acetylcysteine compensates for a decreased level of protective glutathione. The thesis does not go into detail with oxidative damage, but it must be mentioned that the target is promising because of reduction of negative symptoms and overall PANSS decrease without notable adverse effects. Ampakine CX516 started out as a drug of success, until later studies found no significant improvement in schizophrenic symptoms compared to placebo, and its side effects of altered liver enzymes, and involvement of leucocytes do not seem promising. NMDA antagonist Memantine is an anti-Alzheimer’s drug. The agonist effect seems as a paradox, since schizophrenia is normally associated with hypofunction of NMDAR. But schizophrenic symptoms may also be improved by NMDA receptor antagonists, as glutamatergic neurons in the prefrontal cortex are inhibited by NMDA-mediated GABA interneurons (Homayoun and Moghaddam 2007), so by blocking GABAergic NMDAR, the inhibitory output to glutamatergic neurons in prefrontal cortex, increasing glutamatergic outflow in the cortex output while restoring normal functioning. The mGluR2/3 agonists or mGluR2 PAMs acting on metabotropic G-protein coupled receptors suggest a long-term stabilizing effect on symptoms and Table 1 shows an overall improvement of positive, negative, and cognitive symptoms. The PAMs of mGluR2 are meant to rebuild a deficient extrasynaptic glutamate receptor that normally functions as a provider of negative feedback. In schizophrenic patients showing with excessive glutamate release, administration of PAMs will reestablish a normalized level of glutamate, thus relieve negative and cognitive symptoms. More research is needed to confirm its efficacy. Administering the anti-convulsant Lamotrigine demands an exaggerated synthesis and release of glutamate because of its presynaptic target. Few studies have been made, but the reduction of positive symptoms might be worth investigating in spite of facial and gingival side effects.

So are the glutamatergic drugs effective enough, considering the diffuse glutamatergic system in the brain? To what extent do we believe in the drugs, and what is the relevance of the suggested targets? Should we not expect a range of side effects when interfering with a ubiquitous system? In order to reach the market the glutamatergic drugs must
Glutamatergic drugs in treatment of schizophrenia. A report on relevance

prove to have benefits justifying the costs/side effects. The drugs in the pipeline with published side effects show examples of serious side effects; 1) D-cycloserine with worsening of symptoms, 2) LY2140023 with examples of convulsions, and 3) incidences of psychotic episodes with Lamotrigine. Nevertheless, the drugs generally do not cause that many adverse effects. Side effects can be related to doses, and the absence of negative outcomes might reflect a small given dose, which can also explain the inefficiency of a list of drugs when given as an adjunct to clozapine. The lack of effect in co-administration with the SGA suggests the glutamatergic drugs be used to patients without positive symptoms. Considering the large glutamatergic system, some drugs show surprising reductions of symptoms, most of these being of the negative and cognitive symptoms. The GSH precursor N-acetylcysteine and the positive allosteric modulator BINA show promising results, but more research must be made to reach satisfactory knowledge about the side effects. Others, such as LY404039 shows contradictory results, whereas outcomes of Memantine are not impressive. It would be expected to experience a long list of side effects when interfering with the ubiquitous glutamatergic system, but surprisingly the reports on negative outcome are not striking.

6. Conclusion

It took some time for the glutamatergic hypothesis to establish on the basis of results with the psychotomimetics PCP and ketamine, who have shown to block neurotransmission via NMDA-type glutamate receptors. For decades the negative and cognitive symptoms related to schizophrenia have stood in the shadow of psychosis, but new treatment approaches based upon the glutamatergic hypothesis are getting to closer to the clinic as an alternative or adjunct to the current antipsychotics. Overall, it must be stated that the glutamatergic drugs are of great relevance, and future research with larger cohorts will map more precise benefits and costs, preparing the drugs for treatment of the many patients with schizophrenia.

7. Reference List


Glutamatergic drugs in treatment of schizophrenia. A report on relevance


Glutamatergic drugs in treatment of schizophrenia. A report on relevance


