Chapter 11
Amino Acids in Schizophrenia – Glycine, Serine and Arginine

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Abstract In recent years, there has been increased interest in the possible role of amino acids in the etiology and pharmacotherapy of schizophrenia. Much of this research has focused on glutamate and γ-aminobutyric acid (GABA), and these are the subjects of other chapters in this book. However, there have also been interesting findings reported with glycine, serine (particularly D-serine) and arginine, and this chapter provides a brief overview of those findings. Glycine and D-serine are coagonists at the NMDA glutamate receptor and lower plasma levels of these two amino acids have been reported in schizophrenia compared to controls. Combinations of glycine with antipsychotics or glycine transport inhibitors have been reported to be useful in treatment of schizophrenia, and increased glycine serum levels have been reported in schizophrenia patients responsive to antipsychotics. Behavioural studies in mutant mice in which D-serine levels are altered by manipulating catabolic or anabolic enzymes suggest that inhibitors of D-amino acid oxidase (DAO), particularly in combination with D-serine, may represent a useful future therapeutic approach to the treatment of schizophrenia. Arginine, a precursor to nitric oxide (NO) is also of interest in schizophrenia, although at present there is evidence for both hypo- and hyperfunction of this amino acid in schizophrenia and further clarification is required.

Keywords Glycine · Serine · Arginine · Glutamate · Schizophrenia · Antipsychotics · Transport inhibitors

Abbreviations

DA	Dopamine
DAO	D-amino acid oxidase

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fMRI	functional magnetic resonance imaging
GABA	γ-Aminobutyric acid
GTI	Glycine transport inhibitor
HPLC	High performance liquid chromatography
5-HT	5-Hydroxytryptamine
L-NAME	Nitro-L-arginine methyl ester
MWM	Morris water maze
NMDA	N-methyl-D-aspartic acid
NMDAR	NMDA receptor
NO	Nitric oxide
PCP	Phencyclidine
PFC	Prefrontal cortex
PLP	Pyridoxal 5-phosphate
PPI	Pre-pulse inhibition

Introduction

Despite more than a half decade of intensive searching, the biochemical basis of schizophrenia remains uncertain. For over 30 years, the catecholamine dopamine (DA) has been studied extensively [1–4]. The dopamine hypothesis, which suggests that there is dopaminergic hyperfunction in the mesolimbic system and dopaminergic hypofunction in the mesocortical system, has certainly contributed to our understanding of the functions of DA in the brain and has been useful for screening potential new antipsychotic drugs. Several of the "atypical" or "second generation" antipsychotics are also relatively potent 5-HT_2 receptor antagonists, suggesting that 5-hydroxytryptamine (5-HT serotonin) may also play an important role in the etiology of schizophrenia. Despite advances made in schizophrenia research and drug development based on our knowledge of DA and 5-HT, the currently available drugs for this disorder are disappointing with regard to the speed of action, their overall efficacy and their adverse side effect profile, all of which contribute to decreased medication adherence by patients. It seems obvious that other neurochemical systems must be contributing to the symptoms and that we must have an increased knowledge of the effects of these other neurochemicals if we are to advance in the treatment of this devastating disorder.

In recent years, there has been a great deal of interest in the possible involvement of amino acids in the etiology and pharmacotherapy of schizophrenia. The focus of this research has been on the excitatory amino acid glutamate [5–10] and, to a lesser extent, the inhibitory amino acid γ-aminobutyric acid (GABA) [11–13]. Comprehensive reviews of the literature on these two amino acids are provided in other chapters in this book, but several other amino acids are also of interest in this regard (glycine, serine and arginine; Fig. 11.1), and they will be the topics of this chapter.

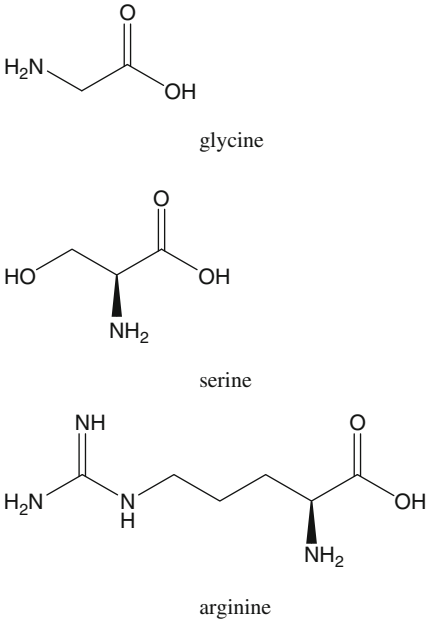

Fig. 11.1 Structures of the amino acids that are the topic of this chapter

Glycine

Glycine is an amino acid that has inhibitory effects in the spinal cord and lower parts of the brain but acts as a coagonist at the glutamate NMDA receptor (NMDAR) in some other parts of the brain. Given the interest in glutamatergic dysfunction in schizophrenia, the possible involvement of glycine in the etiology and/or pharmacotherapy of schizophrenia has been the subject of considerable research interest in recent years. Genetic and pharmacologically-induced deficiencies in glycine binding in mice produce behavioural changes which appear to model the negative and cognitive symptoms of schizophrenia [14].

Reduced plasma levels of glycine have been reported in schizophrenia patients, and these reduced levels seem to correlate with severity of negative symptoms [15–17] and response to clozapine [18]. Hones et al. [17] found the lower serum levels of glycine to be associated with an increased intensity of negative symptoms but to have no relationship with positive or cognitive symptoms in schizophrenic patients. In a study comparing treatment-responsive and non-responsive schizophrenia patients to healthy controls, Cunha et al. [19] found increased serum levels of glycine in the responsive group and increased serum glutamate in the treatment resistant patients.

Several studies have tested the effects of combining glycine with certain antipsychotics or using glycine transport inhibitors (alone or in combination with glycine) as possible treatment approaches for schizophrenia and obtained promising results

[20–26]. Glycine transport inhibitors (GTIs) indirectly activate the glycine modulatory sites on NMDA receptors, increasing their functional capacity, and also prevent glycine from being removed from the synaptic cleft, thereby elevating glycine levels [26, 27]. When glycine is administered concurrently with GTIs, lower drug doses of glycine are required [27].

In conclusion, there is evidence supporting the administration of glycine and GTIs in order to enhance NMDA receptor-mediated neurotransmission for treatment in schizophrenia. However, further research is still needed since study results are inconsistent [27]. Further testing is also necessary to identify the level of glycine reuptake inhibition needed to produce effective results in treating schizophrenic patients [27].

D-Serine

Although currently prescribed antipsychotics successfully alleviate the positive symptoms of schizophrenia, they either do not or only mildly improve negative symptoms and cognitive deficits, and it is necessary to develop effective treatments with greater symptom coverage for this disease. In recent years, D-serine, a potent co-agonist at the NMDA receptor site, has been receiving a great deal of attention in research studies. For NMDA receptor channels to open, glutamate must bind to one receptor site (NR2), and either D-serine or glycine must activate the other (NR1) [27]. D-Serine has a high affinity for the glycine receptor site and is more permeable to the blood-brain barrier than glycine. Therefore, in comparison to each other as treatment approaches, a smaller dose of D-serine should be more effective than an equal amount of glycine [27]. According to current literature, D-serine is the main NMDA receptor co-agonist and it potentiates NMDA receptor function [27]. Increased activation of the hippocampus has been observed using functional magnetic resonance imaging (fMRI) following D-serine administration [28]; improvements in learning processes, enhancement of long term potentiation, and an increase in field potential occurred as a result [28].

Waziri et al. [29, 30] reported increased levels of serine in the blood and brains of schizophrenics and Macciardi et al. [31] also reported increased serum levels of serine in schizophrenics. Neither of these groups separated the D- and L-serine, but their studies probably represent changes in levels of L-serine since it is much more abundant in blood and brain than D-serine. The literature about L-serine continues to be confusing since several groups have reported abnormal serine levels in schizophrenia [16, 18, 31–34] while others have reported no differences from control values [19, 35, 36]. Using high performance liquid chromatography (HPLC), Hashimoto et al. [36] found lower serum levels of D-serine in schizophrenia patients than controls. These results suggest that the enzymatic activity of serine racemase, which converts L-serine to D-serine in the presence of a pyridoxal 5-phosphate (PLP) co-factor, could be reduced in individuals with schizophrenia or that there could be overactivity of D-amino acid oxidase, the enzyme that catalyzes catabolism of D-serine. Ohnuma et al. [37] reported that D-serine levels and the D-/L-serine ratio increased markedly in schizophrenia patients as clinical symptoms

improved. Loss of serine racemase in mutant mice dramatically reduces brain levels of D-serine, and these mice display schizophrenia-related behaviours (impairments in prepulse inhibition, sociability and spatial discrimination) [38].

Daily administration of large quantities of glycine or D-serine alone or use of either as an adjunct to atypical antipsychotics has been reported to result in improvement of schizophrenic symptoms [25 for review]. Duffy et al. [39] reported that administration of D-serine to mice resulted in augmented cognitive flexibility. Heresco-Levy et al. [40] reported that D-serine added to risperidone or olanzapine resulted in improvements in negative, positive, cognitive and depressive symptoms in treatment-refractory schizophrenics. Lane et al. [41] found that the GTI sarcosine was a more effective add-on treatment than D-serine in acute exacerbation of schizophrenia. Tsai et al. [42] reported that when D-serine was given with clozapine, neither positive, negative, nor cognitive symptoms improved.

D-Serine is metabolized by D-amino acid oxidase (DAO) and inactivation of DAO in mice has been reported to improve behavioral deficits which are similar to the negative and cognitive symptoms in schizophrenic patients as well as improve sociability deficits, special recognition impairments, and long-term special memory disruption [43]. Since DAO breaks down D-serine, DAO inhibitors may have therapeutic potential for treatment of the disorder. There have been recent efforts to identify and characterize small molecule DAO inhibitors [44]. Some of the molecules currently under study include AS057278, CBIO, and Compound 8 [44, 45]. AS057278 is orally bioavailable, it increases D-serine in the midbrain and cortex of rats, normalizes PPI when administered acutely and chronically, and also normalizes phencyclidine (PCP)-induced hyperlocomotion when administered chronically [45]. In a recent study the coadministration of CBIO with D-serine increased the bioavailability of D-serine when administered orally, enhanced the effects D-serine had on PPI deficits, and increased D-serine extracellular concentrations in the frontal cortex [46]. This combination therapy also allowed for the administration of a lower dose of D-serine to patients in treatment [44]. Thus, treatment using DAO inhibitors, particularly in combination with D-serine, is a novel therapeutic approach worthy of further investigation.

The antipsychotic drugs chlorpromazine and risperidone have been reported to inhibit DAO [47, 48] although the contribution of this inhibition to the therapeutic efficacy of these drugs has been disputed [49]. Interestingly, the distribution of D-serine levels does not correlate well with DAO activity in adult brain, but there is a high correlation between D-serine levels and concentration of NMDA receptors in brain [50]. It has been postulated that increases in cerebellar D-serine levels by inhibition of DAO may result in antipsychotic activity through an augmentation of D-serine mediated facilitation of NMDA receptors in that brain region [49].

Arginine

In recent years, there has been considerable interest in the involvement of amino acid L-arginine, the precursor of nitric oxide (NO), in both schizophrenia and depression. Although the literature in this area is very interesting, there is evidence

suggesting both increased and decreased synthesis of NO in schizophrenia [51–53] Phencyclidine (PCP), a non-competitive antagonist of the NMDA receptor, induces very similar symptoms (including positive and negative symptoms and cognitive deficits) in humans to schizophrenia [54]. PCP mimics NMDA receptor hypofunction, and therefore, a knowledge of PCP's affects may be useful in discovering treatments for schizophrenia [54, 55]. Interfering with nitric oxide (NO) production in rodents has been reported to reverse PCP-induced effects [54]. NO is a gas synthesized in a two-step oxidation process from the amino acid L-arginine and oxygen [55]. In the prefrontal cortex, NO is also known to affect the storage, uptake, and/or release of certain neurotransmitters including glutamate, GABA, and dopamine [51]. Other evidence suggests that NO may have a role in learning and memory formation. Using a NO-sensitive microelectrocemical sensor, NO levels in awake, freely moving animals have been reported to be raised in the brain after PCP administration [54]. Pretreatment with nitro-L-arginine methyl ester (L-NAME), a nitric oxide synthase inhibitor, counteracted PCP's behavioral effects and NO levels were reduced [54]. According to the findings mentioned above, the cognitive dysfunctions seen in schizophrenia may be relieved using NOS inhibitors as a therapeutic treatment approach [56].

NMDA receptor hypofunction causes learning and memory deficits, and experimentation involving the Morris water maze (MWM) model can be used to test the PCP model of schizophrenia and how spatial memory is impacted by the administration of NMDA receptor antagonists including PCP and others [55, 57]. NOS inhibition has been shown to decrease the effects of PCP during a MWM swim test [55]. It has also been reported that the NO system is over-active in schizophrenia patients, and that NOS inhibitors block the behavioral and biochemical effects of PCP and block the disruption of PPI [52, 56].

However, there is also evidence from animal studies with PCP that underproduction of NO may be linked to schizophrenia. Some preclinical studies suggest that NO donors such as sodium nitroprusside and molsidomine can block the behavioral effects of PCP [58, 59] and improve cognitive deficits induced in animals by MK-801 [60]. A decrease in NOS activity has been reported in prefrontal cortex of brains from patients with schizophrenia [61].

Conclusions and Future Directions

In summary, although there are certainly some contradictions in the literature, it appears that the amino acids glycine, serine and arginine may play important roles in the etiology and pharmacotherapy of schizophrenia. Given the rather disappointing therapeutic efficacy and the disturbing side effect profile of currently available drugs, the possibility of new therapeutic agents based on actions on these amino acids is a promising area for continued research. It now appears that other glutamate receptors in addition to NMDA receptors may play a role in the etiology

of schizophrenia, and these receptors also appear to be involved in the actions of D-serine; these interactions and the involvement of D-serine and other amino acids should be investigated further. It is now known that glial cells play a much more important functional role in the central nervous system than was orginally thought. Given the knowledge that astrocytes and microglia can affect transport of D-serine and glycine as well as glutamate, the role of glia in schizophrenia warrants further attention. In addition, there has been increased interest in recent years in the involvement of the immune system in various psychiatric disorders, including schizophrenia, and microglia appear to be major players here. The effects of activated microglia on amino acids in the brain is an area that is underexplored. With regard to the controversy about arginine/NO hyper- or hypofunction in schizophrenia, presumably neurochemical/molecular biological studies in more areas of the brain and more comprehensive behavioural studies with drugs that affect levels of arginine and/or NO should provide clarification.

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